Sleep, circadian rhythms and physical activity in depression and anxiety

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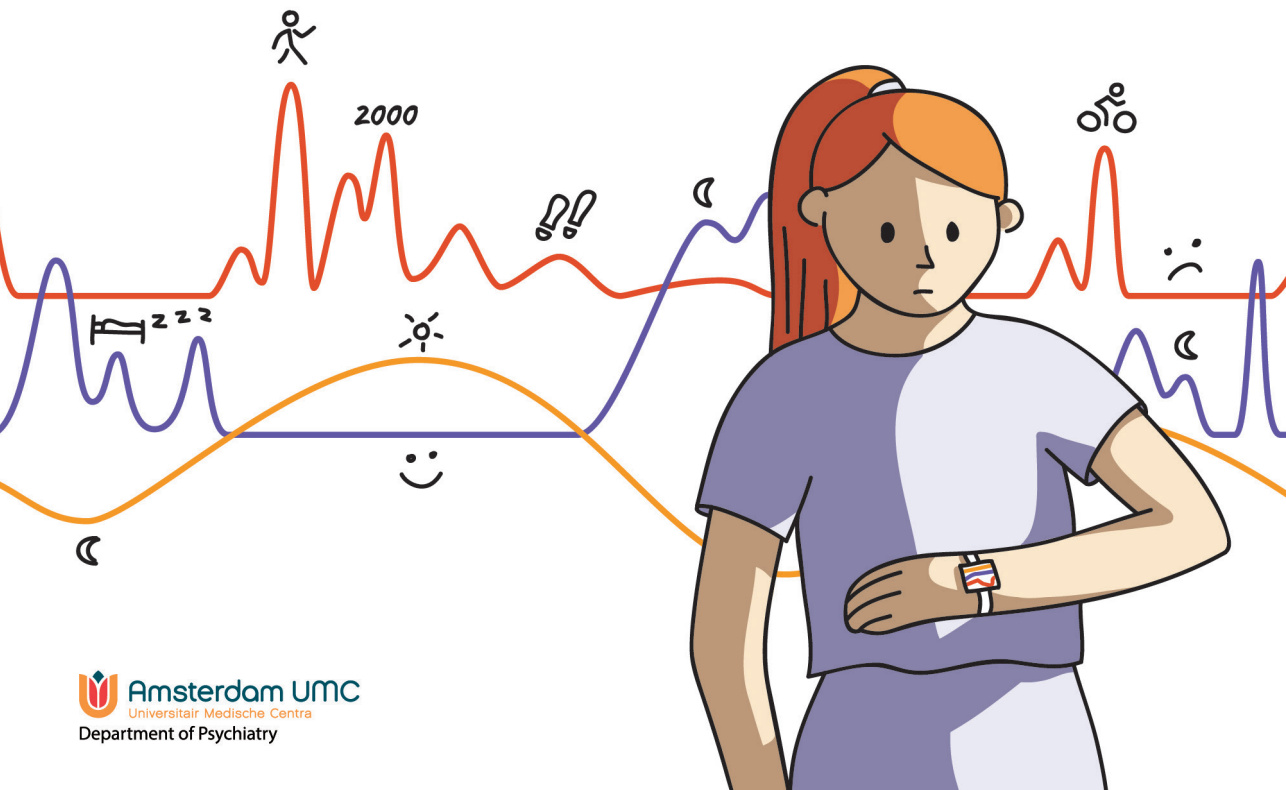
SLEEP, CIRCADIAN RHYTHMS and PHYSICAL ACTIVITY in DEPRESSION and ANXIETY

The role of ambulatory assessment tools

Sonia Difrancesco



Amsterdam UMC
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Sleep, circadian rhythms and physical activity in depression and anxiety

The role of ambulatory assessment tools

Sonia Difrancesco

COLOFON
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SLEEP, CIRCADIAN RHYTHMS AND PHYSICAL ACTIVITY IN DEPRESSION AND ANXIETY

The role of ambulatory assessment tools

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Table of Contents

1 **General introduction** 1

2 **Sleep, circadian rhythm and physical activity patterns in depressive and anxiety disorders:** 15
a 2-week ambulatory assessment study
Published in Depression and anxiety 2019, 36 (10), 975-986.

3 **Sociodemographic, Health and Lifestyle, Sampling, and Mental Health Determinants of 24-Hour Motor Activity Patterns:** 47
Observational Study
Published in Journal of Medical Internet Research 2021, 23 (2), e20700.

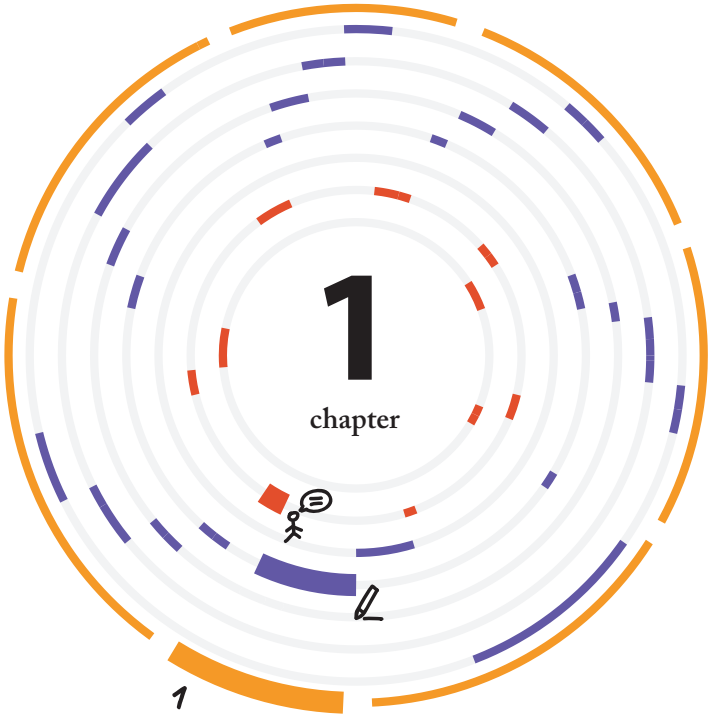
4 **The role of depressive symptoms and symptom dimensions in actigraphy-assessed sleep, circadian rhythm, and physical activity** 73
Published in Psychological Medicine 2021, 1 – 7.

5 **The day-to-day bidirectional longitudinal association between objective and self-reported sleep and affect:** 93
An ambulatory assessment study
Published in Journal of affective disorders 2021, 283, 165-171.

6 **Within-day bidirectional associations between physical activity and affect:** 117
A real-time ambulatory study in persons with and without depressive and anxiety disorders
Submitted for publication.

7 **General discussion** 145

Summary 163
Acknowledgments 167
About the author 169
Publication list 170
Dissertation series 171



General introduction

Depression and anxiety are highly prevalent psychiatric disorders (1). More than 300 million people are affected by depression and nearly the same number of people suffer from a range of anxiety disorders. Depression is ranked by the World Health Organization (WHO) as the single largest contributor to global disability, and anxiety disorders are ranked 6th.

To successfully diagnose, treat and monitor depressive and anxiety disorders, wearables/mobile technologies have become promising ambulatory assessment tools in psychiatry. Ambulatory assessment tools including wrist-worn actigraphy devices and smartphones have become widely used in psychiatric research to measure core features and symptoms of psychiatric disorders: disturbances in sleep and circadian rhythm and, physical activity alterations. However, more research is needed to understand the added value of these tools in psychiatric clinical practice. This thesis focuses on examining sleep, circadian rhythm and physical activity assessed with wrist-worn actigraphy devices in depressive and anxiety disorders.

In this general introduction, depressive and anxiety disorders will be described. This will be followed by a brief introduction of epidemiological studies on the relationship between sleep, circadian rhythm and physical activity and depressive and anxiety disorders. After that, an introduction of ambulatory assessment and literature on this topic will be described. Finally the aim and outline of the thesis will be discussed.

What are depressive and anxiety disorders?

This thesis focuses on depressive and anxiety disorders. Approximately 6% of the adult population is diagnosed with depressive disorders every year (2) and one in ten adults experience anxiety disorders every year (3).

Depressive disorders

Depressive disorders can be subdivided into Major Depressive Disorder (MDD) and dysthymia. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM, version 5) of the American Psychiatric Association, the two core symptoms of MDD are: 1) the presence of depressed mood, and 2) loss of interest or pleasure (anhedonia). Additional symptoms may be insomnia and hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, significant weight loss or weight gain (or a decreased or increased appetite), feelings of worthlessness and excessive or inappropriate guilt, loss of concentration or indecisiveness, and a death- or suicide wish attempt. To fulfill a DSM-V diagnosis of depression, five or more symptoms should be present, including at least one core symptom, for at least

two consequent weeks, almost every day and for most part of the day, resulting in marked distress or impairment. In short, a diagnosis of dysthymia is given when there is mildly depressed mood for most of the day, for more days than not, for at least 2 years.

Anxiety disorders

Anxiety disorders included in this thesis are social phobia, generalized anxiety disorder (GAD), panic disorder (with or without agoraphobia) and pure agoraphobia.

Social phobia is defined as the persistent fear of one or more social situations in which one is exposed to possible scrutiny by others or in which one could display anxiety symptoms, that will be humiliating or embarrassing.

GAD is defined as excessive anxiety and worry, occurring more days that not for at least six consecutive months, about a number of events or activities (i.e., work or school performance). Additionally, at least three or more of the following symptoms must be present: restlessness or feeling on edge, fatigue, loss of concentration, irritability, muscle tension and sleep disturbances.

The core symptom of panic disorder is recurrent panic attacks, an overwhelming combination of physical and psychological distress. During an attack several of these symptoms occur in combination: palpitations, sweating, trembling and shaking, feeling of shortness of breath, chest pain, numbness or tingling, feeling detached, fear of losing control, fear of dying.

Panic disorders may occur with agoraphobia: fear of being in situations where escape may be difficult or embarrassing, or help might not be available in the event of panic symptoms. Situations in which agoraphobia is expressed are for instance being in public transportation, standing in line or being in a crowd, being outside the home alone.

Sleep, circadian rhythm and physical activity in depressive and anxiety disorders

Epidemiological studies using traditional self-reported questionnaires

Epidemiological research on depressive and anxiety disorders has confirmed their association with a cluster of biopsychosocial and lifestyle factors (4,5). In particular, disturbances in sleep and circadian rhythm and altered physical activity have long been recognized as core features of depression and anxiety. Sleep problems, such as

experiencing insomnia or hypersomnia nearly every day is also one of the DSM-V diagnostic criteria of depressive disorders. Disturbances in sleep and circadian rhythm and altered physical activity are traditionally assessed using self-reported questionnaires; studies are summarized in this section.

Several studies reported that mental disorders are consistently associated with sleep difficulties. This seems to be especially true for depression (6,7) but it has been showed in anxiety as well (7). Sleep disturbances are characterized most frequently by insomnia, but also by hypersomnia in some individuals. Overall, sleep disturbances include reduced sleep duration, longer time to fall asleep and more awakenings during the night and lower sleep quality.

Circadian rhythm disturbances often occur in patients with depression and anxiety (8). Circadian rhythms include a range of cyclical physiological rhythms across the 24-hour period such as the sleep-wake cycle, the core body temperature and the secretion of hormones (e.g., cortisol). Studies have shown that those cyclical rhythms appear to be dampened and shifted towards later time of the day in persons with mood disorders compared to controls. Chronotype or the individual's time-of-day preference for morningness or eveningness is especially studied in persons with depression and anxiety and it is related to circadian rhythms. Evening chronotype has been linked to depressive (9) and anxiety disorders (10), depressive symptoms as reported in the meta-analysis by Au & Reece, (2017) and to comorbid depressive and anxiety disorders (9).

Depression and anxiety have also been found to be associated with altered physical activity. Altered forms of physical activity are not only limited to sedentary behavior and low daily activity levels, but psychomotor retardation, agitation and withdrawal from normal activities of daily living as well (12). Reduced physical activity level has been reported in patients with depression as shown in the meta-analysis by Schuch et al., 2018, in patients with anxiety and in patients with comorbid depressive and anxiety disorders (14). Previous studies reported more frequent sedentary behavior in mental disorders (15) and longitudinal association of low sport participation with chronicity of depression (14).

Limitations of traditional self-reported questionnaires

Sleep, circadian rhythm and physical activity are often assessed infrequently during clinical interviews with the use of static retrospective self-reported questionnaires. Although traditional self-reported questionnaires have high validity and reliability (16–18), they are often limited in detecting sudden changes in patient's symptoms. Additionally, most patients have negative and recall bias while completing assessment questionnaires and may recall their symptoms as worse than they actually pres-

ent (19). As most symptoms are not continuously tracked outside the clinical setting or between treatment sessions, there has been a recent and significant increase in research to identify novel methods to measure depressive and anxiety disorders.

Ambulatory assessment tools in psychiatry

Definition and characteristics

Ambulatory assessment covers a wide range of assessment methods to study people in their living environment, including (electronic) daily diaries, sensors to measure physiological or biological data and behavioural information (20). Mostly used ambulatory assessment tools in mental health research are actigraphy devices and Ecological Momentary Assessment methods. Actigraphy is a tool to measure objectively sleep, circadian rhythm and physical activity with the use of a wrist-worn device (21). Data are gathered continuously with the use of integrated accelerometer sensors and some algorithms are used to extract information about a person's sleep, circadian rhythm and physical activity daily measurements. Ecological Momentary Assessment measures individual's current behaviors, clinical symptoms and moods as they occur in real time and in their real-world settings (22). Persons are often asked to fill-out an electronic diary with the use of their smartphone multiple times per day for a defined time period. Studies employing actigraphy and Ecological Momentary Assessment methods have become more common in recent years in mental health research, partially spurred by the ubiquitous availability of mobile devices and wearable sensors that provide access to individuals in their living environment.

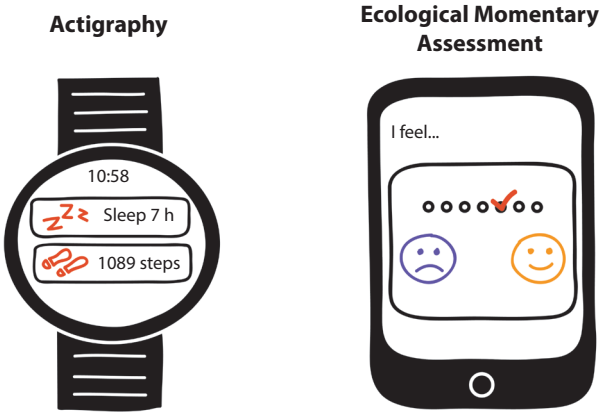


Figure 1: actigraphy and ecological momentary assessment

Many features distinctly characterized ambulatory assessment from traditional assessment approaches (20). First, ambulatory assessment is characterized by the col-

lection of data in real-world environments, gathering data that are ecologically valid and therefore results are more generalizable to real-world settings. Second, it can provide continuous measurements or individuals' current or very recent states or behaviors and collects multiple assessments of each individual over time, typically several times per day. This allows to capture fluctuations and changes over the time in patient's mental health. Third, it allows for the examination of multiple individual processes such as emotional, behavioral and psychophysiological at the same time. As a consequence the short-term, daily-life dynamics of different systems can be studied almost instantaneously.

Although more research is needed to demonstrate the clinical utility of these tools, ambulatory assessment may provide new opportunities for diagnosis, treatment and monitoring of depression and anxiety. As ambulatory assessment tools can provide a real-time and real-world measurements, they may be used to refine the diagnostic process, tailor treatment, improve the monitoring for actionable outcomes, such as identify early signs of relapse and give feedback to patients about their condition.

Actigraphy and Ecological Momentary Assessment in the study of depressive and anxiety disorders

Actigraphy has become widely available in epidemiological research to objectively study sleep, circadian rhythms and physical activity (23). Sleep quantity and quality are often assessed as sleep duration and sleep efficiency. Circadian rhythms measures can be described as circadian rhythm amplitude (i.e., the daily rhythm has a cosin shape and the difference between the min and max of the cosin function is the amplitude) and sleep midpoint which is a proxy of chronotype. Physical activity is measured as daily activity level as well as minutes spent in different levels of activity such as light and moderate-to-vigorous physical activity level.

Ecological Momentary Assessment is often used in mental health research to study affect or the underlying experience of feelings and emotions. Persons self-rate their current emotions (e.g., 'I am feeling down') on a 7-point Likert scale ranging from '1 = not at all' to '7 = very much'. Positive Affect and Negative Affect subscales are created by averaging the single scores of positive and negative emotions respectively. Ecological Momentary Assessment can also measure depressive and anxiety symptoms and, sleep quantity and quality rated by the individuals.

Several studies using actigraphy, including the systematic review of Burton (12) have shown that depressive disorders and symptoms are associated with lower daily activity (24–26) and circadian rhythm amplitude (27). The association between sleep disturbances and depression has been less confirmed when using actigraphy. Although night-time activity level appears to be higher in patients with depression (12), this

is not always reflected in actigraphy measures of sleep duration and sleep efficiency.

Research has also focused on the association of actigraphy-assessed sleep, circadian rhythm and physical activity and affect and emotions. However, only few studies have focused on the dynamics between different systems such as sleep, physical activity and their association with affect when using ambulatory assessment. Low physical activity levels assessed with actigraphy have been found longitudinally associated with subsequent sad mood assessed with Ecological Momentary Assessment (EMA) (28). EMA-based, but not actigraphy-based, sleep quality has been found bi-directionally associated with affect; better sleep quality was associated with improved subsequent affect (29–31) and improved affect was associated with subsequent better sleep quality (29).

Although several studies in mental health research have been using actigraphy and EMA, several questions on the association with psychopathology, its heterogeneity and temporal dynamics in different homeostatic systems are still open and will be addressed in this thesis.

Thesis aim

This thesis has a general aim:
To examine the associations between sleep, circadian rhythms and physical activity with depressive and anxiety disorders using ambulatory assessment tools.

Methods

The Netherlands Study of Depression and Anxiety

To address the above mentioned research aim, this thesis is mainly using data from the Netherlands Study of Depression and Anxiety (NESDA). NESDA was designed to investigate the course of depressive and anxiety disorders over a period of several years and the factors that influence the development and prognosis of such disorders. 2981 Participants were initially included at the baseline assessment in 2004-2007, and seen for the fifth time at the nine-year follow-up assessment wave (2014-2017) for a regular follow-up interview, including a psychiatric diagnostic interview. Three hundred sixty-seven siblings of a subsample of NESDA participants were (also) included by asking NESDA participants at the regular nine-year follow-up interview for their consent to approach their siblings. A sub sample from NESDA, consisting of 384 people, was selected to participate in the Ecological Momentary Assessment & Actigraphy sub-study (NESDA-EMAA). Among demo-

graphic, psychiatric and lifestyle characteristics, data from ambulatory assessment tools measuring negative and positive affect as well as actigraphy simultaneously during 2 weeks were collected at the nine-year follow-up assessment.

Thesis outline

This thesis addresses the relationship between sleep, circadian rhythms and physical activity with depressive and anxiety disorders using ambulatory assessment tools in different chapters. Figure 2 displays an overview of the chapters.

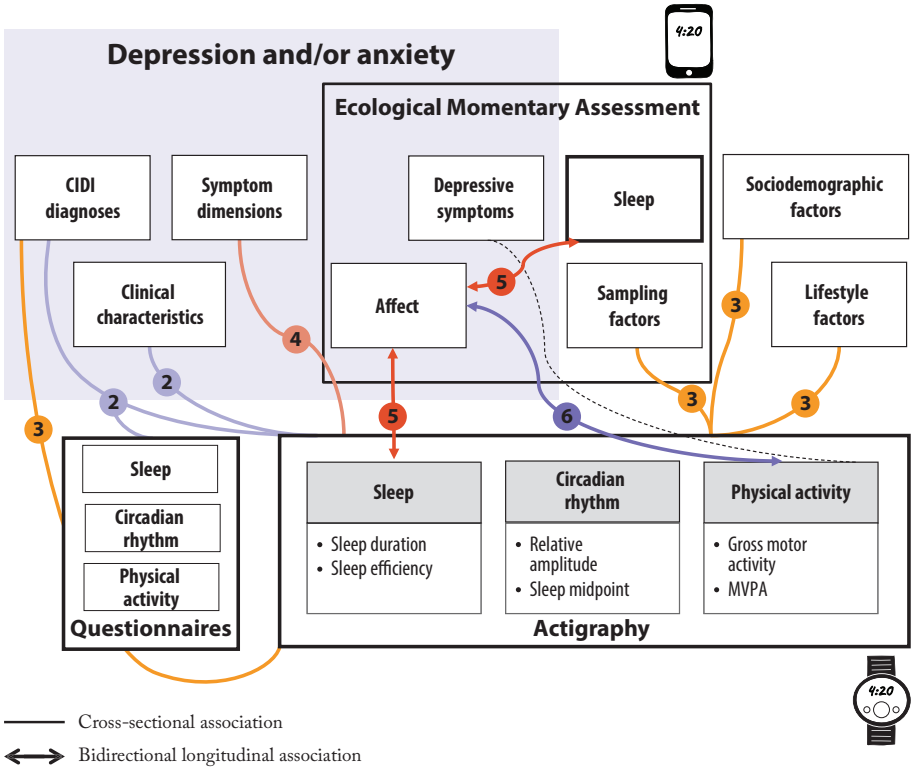


Figure 2: chapter overview of this thesis

Chapter 2 examines sleep, circadian rhythm and physical activity assessed with actigraphy and self-reported questionnaires in persons without and with depressive and anxiety disorders; it also examines the association between sleep, circadian rhythm and physical activity assessed with actigraphy and psychiatric clinical characteristics (i.e., depressive and anxiety symptom severity, number of psychiatric diagnoses, duration of depressive and/or anxiety episodes and antidepressant use).

Chapter 3 examines actigraphy-assessed daily activity patterns extracted with a data-driven technique and their association with sociodemographic, lifestyle, sampling and, mental health determinants.

Chapter 4 examines the association between sleep, circadian rhythm and physical activity assessed with actigraphy and depressive symptom dimensions (i.e., mood/cognition dimension, somatic dimension, sleep dimension).

Chapter 5 examines the daily dynamics between sleep and affect assessed with actigraphy and EMA.

Chapter 6 examines the within-person dynamics between within-day physical activity assessed with actigraphy and affect assessed with EMA every 3 hour each day.

Chapter 7 integrates findings of this thesis and discuss clinical implications as well as future research directions.

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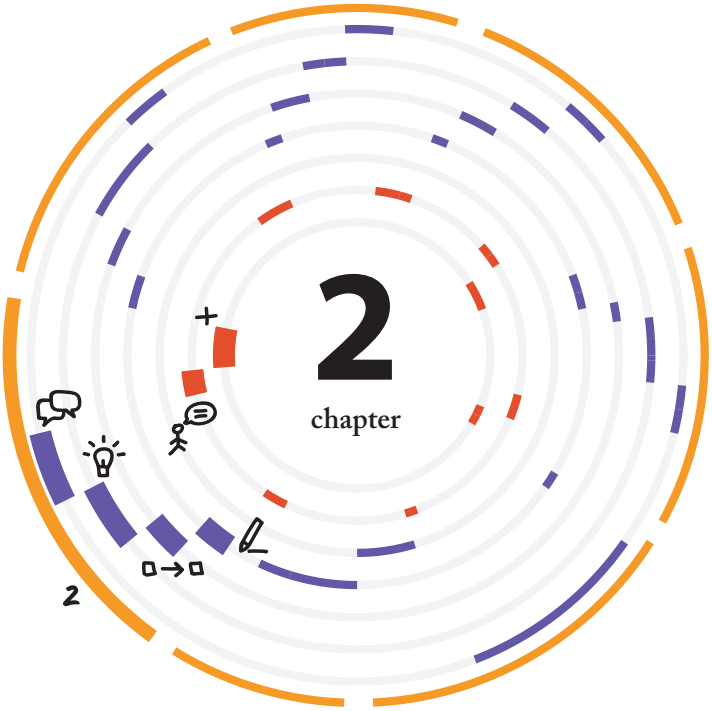

Sleep, circadian rhythm and physical activity patterns in depressive and anxiety disorders: *An ambulatory assessment study*

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Abstract

Background: Actigraphy may provide more valid assessment of sleep, circadian rhythm (CR) and physical activity (PA) than self-reported questionnaires, but has not been used widely to study the association with depression/anxiety and their clinical characteristics.

Methods: 14-day actigraphy data of 359 participants with current (n=93), remitted (n=176) or no (n=90) CIDI depression/anxiety diagnoses was obtained from the Netherlands Study of Depression and Anxiety. Objective estimates included sleep duration (SD), sleep efficiency, relative amplitude between daytime and nighttime activity (RA), Mid Sleep on Free Days (MSF), gross motor activity (GMA) and moderate-to-vigorous PA (MVPA). Self-reported measures included Insomnia Rating Scale, SD, MSF, Metabolic Equivalent Total and MVPA.

Results: Compared to controls, individuals with current depression/anxiety had significantly different objective, but not self-reported, PA and CR: lower GMA (23.83 versus 27.4 milli-gravity/day, p=0.022), lower MVPA (35.32 versus 47.64 min/day, p=0.023), lower RA (0.82 versus 0.83, p=0.033). In contrast, self-reported, but not objective, sleep differed between people with current depression/anxiety compared to those without current disorders; people with current depression/anxiety reported both shorter and longer SD and more insomnia. More depressive/anxiety symptoms and number of depressive/anxiety diagnoses were associated with larger disturbances of the actigraphy measures.

Conclusion: Actigraphy provides ecologically-valid information on sleep, CR and PA that enhances data from self-reported questionnaires. As those with more severe or comorbid forms showed the lowest PA and most CR disruptions, the potential for adjunctive behavioural and chronotherapy interventions should be explored, as well as the potential of actigraphy to monitor treatment response to such interventions.

Keywords: Actigraphy; Anxiety Disorders; Depressive Disorder; Dysthymic Disorder; Sleep; Circadian rhythm; Exercise; Comorbidity

Introduction

Depression and anxiety are highly prevalent psychiatric disorders, with largely overlapping pathophysiology (Zorn et al., 2017), high genetic correlation (Wray et al., 2018), both causing high disability (Vos et al., 2016), and sharing high degree of comorbidity (Lamers et al., 2011; Rodney et al., 1997). Sleep and circadian rhythm disturbances and altered physical activity have long been recognized as core features of depression and anxiety.

Studies have shown that insomnia and hypersomnia are more frequent among those with a diagnosis of depression (Nutt, Wilson, & Paterson, 2008; van Mill, Hoogendijk, Vogelzangs, van Dyck, & Penninx, 2010), and comorbid depression and anxiety (van Mill et al., 2010), which is not surprising as experiencing insomnia or hypersomnia nearly every day is one of the DSM-5 diagnostic criteria of depressive disorders. But more insomnia and hypersomnia have also been reported in anxiety disorders (Staner, 2003; van Mill et al., 2010). Evening chronotype has been linked to depressive (Antypa, Vogelzangs, Meesters, Schoevers, & Penninx, 2016; Norbury, 2019) and anxiety disorders (Kivelä, Papadopoulos, & Antypa, 2018), depressive symptoms as reported in the meta-analysis by Au (Au & Reece, 2017) and to comorbid depressive and anxiety disorders (Antypa et al., 2016). Reduced physical activity has been reported in patients with depression as shown in the meta-analysis by Schuch and colleagues (Schuch et al., 2017), in patients with anxiety (Hiles et al., 2017; Ströhle, 2009) and in patients with comorbid depressive and anxiety disorders (Hiles et al., 2017). These findings are mainly based on retrospective self-reported questionnaires, that summarize static estimates which are potentially biased by patient's cognitive impairments and negative perception (Sallis & Saelens, 2000).

Wrist-worn actigraphy devices can objectively assess (disturbances in) sleep, circadian rhythm and physical activity. The ecological measurement with actigraphy in patients' natural environments continuously over time may translate much more readily to potentially effective intervention (Shiffman, Stone, & Hufford, 2008). For instance, actigraphy may be used for clinical assessment to monitor treatment outcomes. Although actigraphy has become widely available in epidemiological research (Doherty et al., 2017), only few large cohort studies have studied the relationship of sleep, circadian rhythm and physical activity with depression and anxiety in a psychiatric sample using actigraphy. In addition, there is limited research studying the association of objective estimates with clinical characteristics, such as psychiatric comorbidity and chronicity of psychiatric disorders. Thus, a better understanding on the association of sleep, circadian rhythm and physical activity with psychopathology that may have important clinical implications, in particular for the clinical assessment, monitoring, and treatment of depression and anxiety.

In this study we investigate whether: (1) objective and/or self-reported estimates of sleep, circadian rhythm, and physical activity differ in persons without and with remitted or current depressive and/or anxiety disorders; and (2) objective estimates of physical activity, sleep and circadian rhythm are associated with clinical characteristics (i.e., severity of symptoms, number of psychiatric disorders, duration of psychiatric disorders, age of onset, and antidepressant use). As part of objective (1) we also explore the correlations between objective and self-reported estimates of sleep, circadian rhythm, and physical activity. This may give us insight whether the – more objective - actigraphy collection is truly providing novel information.

Method

Sample

Participants from the Netherlands Study of Depression and Anxiety (NESDA) were selected to participate in the Ecological Momentary Assessment (EMA) & Actigraphy sub-study (NESDA-EMAA). NESDA is one of the sites that is member of the Motor Activity Research Consortium for Health (m-MARCH)(Scott et al., 2017), a collaborative network on the application of objective assessment of motor activity, sleep and mood in population and clinical samples. Details about NESDA have been provided extensively before (Penninx et al., 2008). NESDA was designed to investigate the course of depressive and anxiety disorders over a period of several years and the factors that influence the development and prognosis of such disorders. Participants were initially included at the baseline assessment in 2004-2007, and seen for the fifth time at the nine-year follow-up assessment wave (2014-2017) for a regular follow-up interview, including a psychiatric diagnostic interview. Siblings of a subsample of NESDA participants were (also) included by asking NESDA participants at the regular nine-year follow-up interview for their consent to approach their siblings. Eligibility criteria were that the NESDA respondent had to meet diagnostic criteria for a depression or anxiety disorder either in the year prior to baseline or during the follow-up, participated in at least two of the four previous waves and the current regular interview, and had the same biological parents as their sibling(s). The NESDA study, including the EMAA component, was approved by the VUmc ethical committee (reference number 2003/183) and all respondents gave informed consent for both the regular interview and the EMAA component.

A flowchart of the NESDA-EMAA is provided in Figure 1. After the face-to-face nine-year interview, participants of NESDA who were eligible and willing to participate in the NESDA-EMAA sub-study were invited to one of our research facilities within one month. All participants were fully informed and given time to ask questions prior to participation. They received an instruction on the EMA

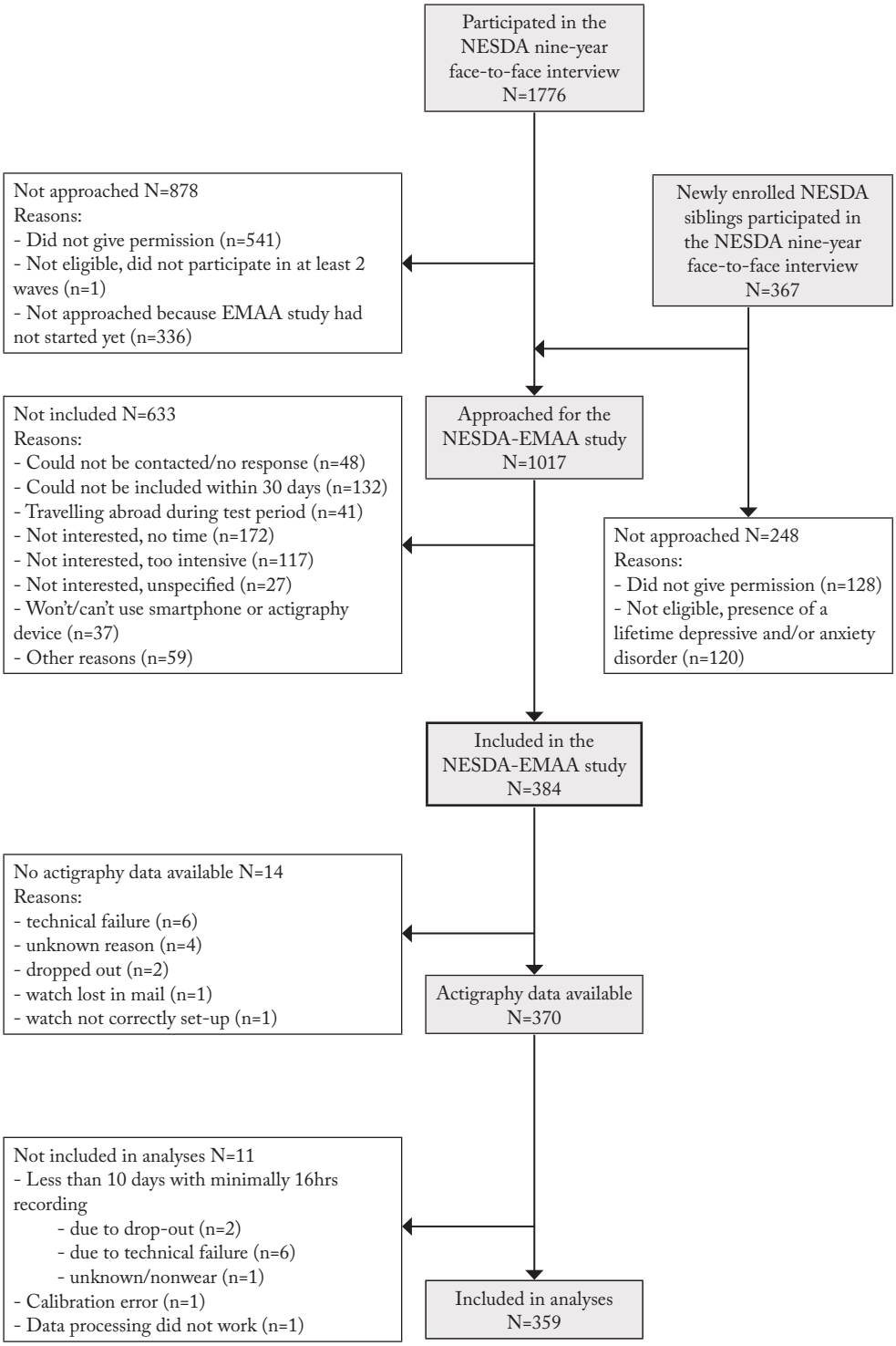

Figure 1: Flow-chart NESDA-EMAA study

and GENEActiv, and were provided with a GENEActiv device (Activinsights Ltd, Kimbolton, UK) as well as a pre-paid envelope or box to send the GENEActiv back by mail after the two-week period. Participants wore the wrist-worn GENEActiv actigraphy device and took part in the EMA assessment on a smartphone for two weeks during which they filled out questions on current mood states. If they did not have a smartphone with internet access, they could borrow one from the study. Of the 384 participants included in the NESDA-EMAA study, 14 had no available actigraphy data for several reasons, such as technical failure (see Figure 1), resulting in 370 (96.4%) participants with available data. According to previously published criteria (da Silva et al., 2014), participant's actigraphy data were included in the analyses if at least one week day and one weekend day of usable data was available, with at least 16 hours recorded per day and per night (see Supplemental material 'Raw data processing' for further details about the actigraphy data pipeline). The final sample was composed of 359 (93.5%) participants with 13.68 ± 1.26 valid days, of which 90% completed the protocol for 14 days.

Diagnosis of depression and/or anxiety disorders

As in the previous waves, at the 9-year follow-up, DSM-IV based diagnoses of depressive disorders (dysthymia and major depressive disorder) and anxiety (social anxiety disorder, panic disorder with and without agoraphobia, agoraphobia and generalized anxiety disorder) were established with the Composite International Diagnostic Interview (CIDI, version 2.1)(Wittchen, 1994). The interviews were conducted by specially trained clinical research staff. For this study, participants were divided into three groups: 1) a group with no lifetime depressive and/or anxiety disorders, 2) a group with remitted depressive and/or anxiety disorders (having a lifetime, but not current (6-month) diagnosis), and 3) a group with current depressive or anxiety disorder in the past 6 months.

Clinical characteristics

Studied clinical characteristics were: severity of depressive symptoms and severity of anxiety symptoms, number of comorbid psychiatric disorders, duration of depressive or anxiety disorders, age of onset and, medication use (i.e., antidepressant and benzodiazepines use). Severity of depressive symptoms and severity of anxiety symptoms were estimated using the 30-item Inventory of Depressive Symptomatology, self-report (IDS)(Rush, Gullion, Basco, Jarrett, & Trivedi, 1996) and the Beck Anxiety Inventory (BAI)(Beck, Epstein, Brown, & Steer, 1988), respectively. Number of psychiatric disorders was determined as a count of current depressive and anxiety diagnoses at nine-year follow-up. Duration of depressive or anxiety disorder was calculated as a count of the number of waves at which the patient reported a depression and/or anxiety diagnosis during the in-between follow-up periods (ranging from 1 waves to 5 waves). Age of onset was derived from the CIDI.

Antidepressant use and benzodiazepine use was based on drug container inspection, and medications were coded according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification. Antidepressant and benzodiazepines use was considered present if participants reported using it more than 50% of the time. Antidepressants included were selective serotonin reuptake inhibitors (SSRIs, ATC code N06AB), tricyclic antidepressant (TCA, ATC code N06AA) and other antidepressants (ATC codes N06AF, N06AG, N06AX); benzodiazepines included ATC codes N03AE, N05BA, N05CD and N05CF.

Actigraphy estimates of sleep, circadian rhythm and physical activity

Participants wore the GENEActiv watch on their non-dominant wrist for two weeks. They were instructed to wear the watch day and night and only taking it off when going to the sauna or when playing a contact sport in which wearing a wristband is unsafe. They were also instructed to press the button on the device when going to sleep and when getting up. In this study, the accelerometer was set to sample at 30 Hz and raw actigraphy data was analysed using an open source R package, GGIR (version 1.5-18, see Supplement material for further details on the raw actigraphy data cleaning processing pipeline). Sleep was assessed as total sleep duration per night [in hh:mm] and sleep efficiency per night [%]. Circadian rhythm was assessed by Mid Sleep on Free Days (MSF) [clock time] and the relative amplitude (RA) between daytime and night-time activity per day. Physical activity was assessed as gross motor activity per day [milli-gravity (mg), 1g = 9.81m/s^2] and minutes in moderate-to-vigorous physical activity per day (objective minutes in moderate-to-vigorous physical activity per day were defined as the sum of 1-min epochs in which gross motor activity was larger than 125mg, which has recently been used by others (Kim et al., 2017)). Average weekly estimates were derived for each participant. Actigraphy variables were chosen based on several reasons. First, the selected actigraphy variables are among the ones reported frequently in adult studies and have been previously linked to psychopathology (Burton et al., 2013; Hori et al., 2016; Luik et al., 2015; Lyall et al., 2018). Second, these measures cover the concepts often collected with self-reported questionnaires allowing for a comparison on their association with depressive and anxiety disorders.

Self-reported sleep, circadian rhythm and physical activity

Self-reported sleep was evaluated using the following questionnaires. Insomnia was assessed with the Women's Health Initiative Insomnia Rating Scale (IRS)(Levine et al., 2003) which consists of 5 questions on difficulties in falling asleep, disruption and quality of sleep in the past month with a total score ranging from 0 (no insomnia) to 20 (severe insomnia). Sleep duration was also assessed (i.e., ≤6 hours, 7-9 hours and ≥10 hours).

Self-reported chronotype was assessed with the Munich Chronotype Questionnaire (MCTQ)(Roenneberg, Wirz-Justice, & Merrow, 2003). The MCTQ contains 29 questions about time of waking up and falling asleep on workdays and on free days, at this moment. Chronotype was defined as the midpoint in time between falling asleep and waking up on free days (Mid Sleep on Free Days (MSF)), since it is most likely to be accurate when one's natural circadian rhythm can be observed, without the interference of work schedules and alarm clocks.

Self-reported physical activity was assessed with the International Physical Activity Questionnaire – Short Form (IPAQ)(Ainsworth et al., 2000). This seven-item questionnaire provides information on the respondent's time spent on walking and on vigorous and moderate physical activity during the last 7 days. Minutes spent in moderate to vigorous physical activity and general physical activity, expressed as metabolic equivalent total (MET, 1 MET = 1 $kcal \cdot kg^{-1} \cdot h^{-1}$) minutes per week were derived from the IPAQ. MET minutes per week were calculated as level×minutes of activity×events per week.

The reliability and validity of the used self-reported questionnaires have been shown before in large-cohort studies(IRS, Levine et al., 2003; MCTQ, Zavada, Gordijn, Beersma, Daan, & Roenneberg, 2005; IPAQ, Craig et al., 2003).

Covariates

Covariates were age at nine-year follow-up, sex and education level expressed in years. These covariates were selected as they have an established theoretical association with psychopathology and with sleep, circadian rhythm and physical activity levels, and have been regularly used in similar studies (Droomers, Schrijvers, & Mackenbach, 2001; Stamatakis, Kaplan, & Roberts, 2007).

Statistical analyses

Distributions of all variables were checked on normality with QQ plots. For descriptive statistics, participant demographics, clinical characteristics, actigraphy and self-reported estimates of sleep, circadian rhythm and physical activity were compared between the three groups (i.e., no, remitted and current depressive and/or anxiety disorders). For normally distributed continuous data ANOVA tests were used and for data that with a non-normal distribution Kruskall-wallis tests were used. Chi-squared tests were used to test differences in frequencies in the three groups. We calculated correlations between actigraphy and self-reported estimates of sleep, circadian rhythm and physical activity. Correlations were tested with Pearson's correlation or with polyserial correlation tests when the variables were continuous or nominal-continuous, respectively. This was done for the entire sample as well as stratified by the main grouping variable.

The association between actigraphy estimates and clinical characteristics (i.e., severity of depressive symptoms and severity of anxiety symptoms, number of psychiatric diagnoses, duration of psychiatric diagnoses, age of onset and antidepressant use) was tested in separate models using linear regression model corrected for covariates and with each actigraphy estimate as outcome. Analyses to study the association with number of psychiatric diagnoses, duration of psychiatric diagnoses, age of onset and antidepressant use were performed only including participants with current depressive and/or anxiety disorders. Non-normally distributed outcomes were transformed with Log-transformation or with Box-Cox transformation.

All analyses were performed with the statistical software R (version 1.0.143), a p-value < 0.05 was considered statistically significant. Post-hoc tests were performed to allow multiple comparison for actigraphy estimates with Dunn's test when the differences between the three groups, i.e. no, remitted and current depressive and/or anxiety disorders were significant. To get a more comprehensive picture, we also performed post-hoc analyses to check whether day-to-day variability in actigraphy estimates (calculated as the SD across 14 days) was associated with depressive and/or anxiety disorders.

The potential clustering of NESDA participants with their siblings was ignored, as of the 27 siblings included in the analyses, only 7 were linked to NESDA participants in this sample. Analyses were rerun without the siblings that were linked to NESDA participants, but this did not alter results (data not shown).

Results

The sample demographics and clinical characteristics are described in Table 1. Of the total sample (n = 359), 93 had current and 176 had remitted depressive and/or anxiety disorders, 90 had no current depressive and/or anxiety disorders. The current depressive/anxiety disorder group was heterogeneous: in that 38.3% had anxiety disorders only, 33.0% had depressive and anxiety disorders and 28.7% had depressive disorders only. As expected, persons with current depressive and/or anxiety disorders scored significantly higher on depressive and anxiety symptoms (both p< 0.001) and more frequently used antidepressant than both other groups, but no significant differences were found for benzodiazepine use.

When using actigraphy, persons with current depressive and/or anxiety disorders were significantly less active and had significantly lower relative amplitude between daytime and night-time activity compared to controls (p<0.05, Table 2). We did not find significant differences for objective sleep duration and sleep efficiency.

Table 1: Demographic, psychiatric, psychological characteristics and medication use in our NESDA sample (n = 359).

	Current depressive and/or anxiety disorders	Remitted depressive and/or anxiety disorders	No depressive and/or anxiety disorders	p
N	93	176	90	
Demographics				
Age, mean (SD) [a]	50.1 (11.1)	48.2 (13.4)	51.3 (12.5)	0.13
Female, n (%) [b]	58 (62.4)	120 (68.2)	50 (55.6)	0.12
Education level [years], mean (SD)	12.5 (3.4)	12.7 (2.8)	13.9 (2.9)	**<0.001**
Psychopathology				
Only depressive disorders, n (%)	26 (28.7)	46 (26.1)	-	
Only anxiety disorders, n (%)	36 (38.3)	24 (13.6)	-	
Depressive & anxiety disorders, n (%)	31 (33.0)	106 (60.2)	-	
Number of psychiatric disorders, median (IQR)	1 (1)	-	-	
Duration of psychiatric disorder/s [number of waves], median (IQR)	5 (1)	2 (2)	-	
Age of depressive disorder or anxiety onset, mean (SD)	17.2 (12.2)	21.7 (12.9)	-	
Psychological scales				
Inventory of Depressive Symptomatology (IDS), mean (SD) [a]	24.9 (13.2)	13.1 (8.9)	5.4 (3.8)	**< 0.001**
Beck Anxiety Inventory (BAI), mean (SD) [a]	13.6 (10.5)	6.1 (5.7)	1.6 (1.9)	**< 0.001**
Medication use				
Antidepressant users, n (%) [b]	35 (37.2)	34 (19.3)	2 (2.2)	**< 0.001**
Benzodiazepines users, n (%) [b]	5 (5.3)	8 (4.5)	0 (0.0)	0.10

[a] Analysis of variance (ANOVA), [b] Chi-squared test
SD, standard deviation; IQR, interquartile range

Table 2: Actigraphy (white) and self-reported (grey) estimates of physical activity, sleep and circadian rhythm (n=359)

Sleep	
Sleep duration [clock time], mean (SD) [b]	
Sleep duration [c]	
< 7 h, %	
7 ≤ h ≤ 9, %	
> 9 h, %	
Sleep efficiency [%], median (IQR) [a]	
Self-reported sleep duration [c]	
≤ 6 h, %	
7 ≤ h ≤ 9, %	
≥ 10 h, %	
Insomnia rating scale, mean (SD) [b]	
Circadian rhythm	
Relative amplitude between daytime and night-time activity level, median (IQR) [a]	
Mid Sleep on Free Days [clock time], median (IQR) [a]	
Self-reported Mid Sleep on Free Days [clock time], mean (SD) [b]	
Physical activity	
Gross motor activity [milli-gravity], median (IQR) [a]	
Moderate-to-vigorous physical activity [min/day], median (IQR) [a]	
Self-reported moderate-to-vigorous physical activity [min/day], median (IQR) [a]	
Total MET-min/week/1,000, median (IQR) [a]	

Abbreviation: SD, standard deviation; IQR, interquartile range, MET, metabolic equivalent total.
[a] Kruskal–Wallis test; [b] Analysis of variance (ANOVA); [c] Chi-squared test
[d] Dunn's test, current depressive and/or anxiety disorders versus no depressive and/or anxiety disorders, p<0.05
[e] Dunn's test, current depressive and/or anxiety disorders versus remitted depressive and/or anxiety disorders, p<0.05

Self-reported sleep, but not self-reported physical activity or circadian rhythm measures, differed significantly across groups (p<0.001, Table 2). Low to moderate correlations were observed between self-reported and objective estimates of sleep, circadian rhythm and physical activity (Table 3); objective and self-reported sleep estimates were not significantly correlated, low but statistically significant, correlations were found between objective and self-reported physical activity estimates w, and moderate and significant correlations between objective and self-reported circadian rhythm estimates were observed. When stratifying by diagnostic status (i.e., no, remitted and current depressive and/or anxiety disorders), we observed that

Table 2: (continued)

Current depressive and/or anxiety disorders	Remitted depressive and/or anxiety disorders	No depressive and/ or anxiety disorders	p
6:59 (1:08)	7:02 (0:59)	6:53 (0:58)	0.478
			0.333
33.3	27.8	25.6	
64.5	71.6	74.4	
2.2	0.6	0.0	
87.0 (8.0)	88.0 (7.0)	88.0 (6.0)	0.170
			<0.001 [d e]
40.9	19.9	13.3	
53.8	76.7	86.7	
5.4	3.4	0.0	
8.95 (4.74)	6.87 (4.46)	5.4 (3.52)	**<0.001** [d e]
0.81 (0.08)	0.83 (0.06)	0.83 (0.06)	**0.028** [d]
04:10 (01:31)	04:11 (01:17)	04:14 (01:07)	0.883
04:03 (01:10)	03:55 (01:06)	04:00 (00:52)	0.628
23.80 (9.88)	26.90 (9.47)	27.40 (10.30)	**0.021** [d]
35.14 (35.43)	45.21 (44.32)	47.39 (41.91)	**0.029** [d]
90 (139)	115 (120)	120 (120)	0.061
2.19 (3.39)	2.85 (4.28)	2.60 (2.99)	0.067

correlations for Mid Sleep on Free Days were higher in the control group compared to patients with remitted and current depressive and/or anxiety disorders (Supplemental material, Table S1). On the other hand, correlations for physical activity estimates were no longer significant in people without depressive and/or anxiety disorders compared to the other groups (Supplemental material, Table S1). Our post-hoc analyses on day-to-day variability in actigraphy estimates showed that patients with current depressive and/or anxiety disorders had significantly lower day-to-day variability in moderate-to-vigorous physical activity compared to controls (Supplemental material, Table S2).

Table 3: Correlations between self-reported and actigraphy estimates of sleep, circadian rhythm and physical activity (n=359)

	Self-reported estimates				
	Sleep (IRS)		Circadian rhythm (MCTQ)	Physical activity (IPAQ)	
Actigraphy estimates	IRS [a]	Sleep duration [b]	Mid Sleep on Free Days [a]	MET [a]	MVPA [a]
Sleep					
Sleep duration	0.076	0.019	-0.017	-0.008	0.005
Sleep efficiency	-0.082	-0.043	-0.087	0.031	0.009
Circadian rhythm					
Relative amplitude between day-time and night-time activity level	-0.179***	0.231***	-0.140**	0.235***	0.146**
Mid Sleep on Free Days	-0.078	0.075	0.582***	-0.025	-0.017
Physical activity					
Gross motor activity	-0.113*	0.105	-0.028	0.286***	0.203***
MVPA	-0.089	0.134	0.009	0.258***	0.177***

Abbreviations: IPAQ, International Physical Activity Questionnaire – Short Form; IRS, Women's Health Initiative Insomnia Rating Scale; MCTQ, Munich Chronotype Questionnaire; MET, metabolic equivalent total; MVPA, moderate-to-vigorous physical activity.
Notes: *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.
[a] Pearson's correlation
[b] Polyserial correlation

Table 4: Associations* between actigraphy-derived sleep, circadian rhythm and physical activity and clinical characteristics

	Sleep duration			Sleep efficiency		
	β	SE	p	β	SE	p
Psychological scales (n = 359)						
IDS	0.162	0.053	**0.002**	-0.084	0.053	0.115
BAI	0.141	0.053	**0.008**	-0.033	0.054	0.544
Clinical characteristics among current cases (n = 93)						
Number of psychiatric diagnoses	0.309	0.100	**0.003**	-0.038	0.104	0.714
Duration of psychiatric diagnoses [waves]	0.129	0.110	0.241	0.060	0.109	0.584
Age of onset	-0.172	0.112	0.127	-0.029	0.112	0.798
Antidepressant use	0.169	0.213	0.430	-0.198	0.210	0.348

*Linear regression model adjusted for age, sex and education. Log transformation was applied to gross motor activity and Mid Sleep on Free Days. Box-cox transformation was applied to MVPA, sleep efficiency and RA.
Abbreviations: MVPA = moderate-to-vigorous physical activity, RA = relative amplitude between daytime and night-time activity level; IDS = Inventory of Depressive Symptomatology score; BAI = Beck Anxiety Inventory score.

Having higher levels of depressive and anxiety symptoms was significantly associated with longer sleep duration, lower relative amplitude between daytime and night-time activity level, reduced gross motor activity and moderate-to-vigorous physical activity (Table 4). Looking at the smaller sized group of 93 persons with current depressive and/or anxiety disorders, number of psychiatric diagnoses was the only clinical characteristic significantly associated with longer sleep duration, lower relative amplitude between daytime and night-time activity level, lower gross motor activity and moderate-to-vigorous physical activity (Table 4). Antidepressant use was significantly associated with delayed Mid Sleep on Free Days (Table 4).

Discussion

In this study we found reduced physical activity level and daily rhythm disturbances among those with depressive and anxiety disorders compared to controls using objective measures, but not using self-reported information. By contrast, self-reported but not objective sleep measures differed between persons with depressive and anxiety disorders vs controls. Actigraphy estimates gathered in an ecologically-valid manner during continuous registration over 2-week time revealed objective differences in physical activity and circadian rhythm measures between diagnostic groups that were not captured with self-reported questionnaires. Moreover, self-reported sleep appeared to reflect the sleep misperception commonly presented in persons with depressive and anxiety symptoms (Dittoni et al., 2013). This supports the use

Table 4: (continued)

Relative amplitude			**Mid Sleep on Free Days**			**Gross motor activity**			**MVPA**		
β	SE	p	β	SE	p	β	SE	p	β	SE	p
-0.205	0.052	**<0.001**	0.132	0.054	**0.016**	-0.239	0.051	**<0.001**	-0.185	0.051	**<0.001**
-0.154	0.052	**0.003**	0.069	0.055	0.206	-0.212	0.051	**<0.001**	-0.169	0.051	**0.001**
-0.310	0.102	**0.003**	0.131	0.108	0.227	-0.383	0.099	**<0.001**	-0.305	0.100	**0.003**
-0.028	0.112	0.803	0.113	0.113	0.323	-0.106	0.112	0.346	-0.037	0.111	0.738
0.074	0.115	0.519	0.07	0.117	0.548	0.102	0.115	0.375	0.004	0.114	0.970
-0.271	0.215	0.211	0.545	0.212	**0.012**	-0.344	0.214	0.111	-0.343	0.211	0.108

of actigraphy in the assessment of physical activity, sleep and circadian rhythm disturbances in epidemiological studies and clinical practice enhancing subjective data from the traditional self-reported questionnaires. The high participation response to the study confirms the feasibility and acceptability of monitoring patients with depressive and anxiety disorders with actigraphy, which may translate to the clinical setting as well.

We found lower levels of objective physical activity (and lower day–to–day variability in objective physical activity) in persons with a current diagnosis, versus those with remitted or no diagnosis. Post-hoc analysis (data not shown) confirmed that associations for pure anxiety and pure depression cases were similar. Patients with current depression and anxiety spent on average 35 minutes per day in moderate-to-vigorous physical activity and a similar effect size has been found in the meta-analysis on depression by Schuch (Schuch et al., 2017). In terms of the association between circadian rhythm disturbances with psychopathology, we found that depressive and anxiety disorders are associated with lower relative amplitude between daytime and night-time activity level. Similarly, previous studies have shown that circadian rhythm appears to be dampened in patients with depression (Hori et al., 2016) and mood disorders (Lyall et al., 2018; Shou et al., 2017), suggesting that the lower level of daily activity is a core feature of mood disorders (Burton et al., 2013). Importantly, less research has been conducted for anxiety, however, our results showed similar effects to those in depression. Reduced daily activity level and circadian rhythm amplitude may be indicative of psychomotor retardation, withdrawal from normal activities of daily living (Burton et al., 2013) and circadian impairments (Lyall et al., 2018). As improvement in depression with antidepressant medications have been linked with greater daytime activity levels (Todder, Caliskan, & Baune, 2009) and higher relative amplitude between daytime and night-time activity (Todder et al., 2009) when using actigraphy, the continuous measurement of daily activity and circadian rhythmicity with wrist-worn actigraphy may help to monitor treatment effects (Martin & Hakim, 2011).

However, first some conditions should be met before actigraphy could play a role in monitoring of treatment response. Although it has been suggested that actigraphy could be used to follow the progression of depression treatment, it is still unclear how sensitive and specific actigraphy is for the characterisation of this change in psychological state (Martin & Hakim, 2011). Which actigraphy variables are best suited for monitoring purposes and definitions of clinically relevant improvement on these variables needs to be examined. Interpretation is also not always immediate (e.g., relative amplitude between daytime and night time activity) and clinicians may need additional training for the use of devices in the clinical practice. Wearing research devices such as a GENEActiv device, may be experienced as stigmatizing as

a patient may be asked for its use in public (Scott et al., 2019; Simblett et al., 2019). Popular commercial activity trackers are aesthetically pleasing and therefore maybe less stigmatizing, but at a cost of lower quality data – whether these devices are suitable for monitoring treatment effects is unknown (Scott et al., 2019). Currently, the majority of devices used in research settings need to be connected to a computer to download data and to extract variables with the use of specific software, resulting in a time-consuming procedure. In the future, devices with Bluetooth compatible connectivity and consumer devices are likely to become more common, allowing the real-time synchronisation of data on the patient's smartphone app and on a data visualisation dashboard. Data may become readily available and interpretable for the clinician, while for the patient real-time feedback on activity and sleep may help to adopt more healthy habits (Matcham et al., 2019). While actigraphy appeared to enhance information obtained from self-reported questionnaires, self-reported assessment can also be improved by using a daily electronic diary that is less costly and time consuming than actigraphy and it may be more personalised to individuals (Martin & Hakim, 2011). Such electronic diaries may also incorporate other questionnaires on sleep and sleep quality such as the Pittsburgh Sleep Quality Index or the Insomnia Severity Index.

Actigraphy indices of sleep were not significantly different across diagnostic groups. Moreover, while sleep duration measured with actigraphy was not associated with depression and anxiety, self-reported sleep duration was consistently associated with psychopathology in the current study and elsewhere (Luik et al., 2015). Self-reported and objectively assessed sleep duration also appeared to be poorly correlated, and this possibly indicates that perceived sleep reflects different aspects of sleep than the objective estimate. This might be due to sleep misperception, which is more common in patients with severe depressive and anxiety symptoms (Dittoni et al., 2013), and is influenced by their negative perception. It has been argued (Harvey & Tang, 2013) that this tendency to misperceive sleep does not preclude the presence of a real sleep deficit. Perhaps the increased worry associated with insomnia makes it more difficult for patients to move into the deeper stages of sleep and the lighter stages of sleep may be more likely to be perceived as wake (Harvey & Tang, 2013). It should be also mentioned that the tendency to misperceive sleep may be considered as a "prodromic or transitional state" in the development of insomnia that is characterized by a serious objective sleep deficit (Harvey & Tang, 2013). Thus, actigraphy may be used to determine whether self-reported sleep problems are not consistent with objective sleep, and the patient would potentially benefit from psychologic treatments to reverse misperception, such as cognitive behavioural therapy (Martin & Hakim, 2011).

We also found evidence for dose-response associations as those with more severe de-

pressive and anxiety symptoms were significantly less active and showed longer sleep duration and lower relative amplitude between day and night activity level. Furthermore, in the group with current depression and/or anxiety, we found that psychiatric comorbidity was associated with physical inactivity, longer sleep duration and lower relative amplitude between day and night activity level. As physical activity and circadian rhythm are modifiable factors, exercise, behavioral activation and chronotherapy may be offered as adjunctive treatments to usual care in these groups of patients (Carek, Laibstain, & Carek, 2011; Chum et al., 2017; Morgenthaler et al., 2007). The dose-response relationships provide further evidence for the ecological validity of actigraphy. Although, recent clinical trials have employed actigraphy to monitor activation therapy (Averill et al., 2019) and sleep deprivation (Arnedt et al., 2017) as adjunctive treatments to usual care, or as a tool to complement behavioral activation (Chum et al., 2017), more research is needed to clarify whether actigraphy may be used to monitor treatment outcomes of such interventions.

Sleep duration was found to be longer in persons with a greater number of depressive and anxiety symptoms. This can be explained by the fact that hypersomnia is one of the symptoms of depression and it usually characterizes patients with atypical features. Another explanation may be antidepressant use. More severe cases are more likely to use these medications and, previous research has suggested that long sleep duration can be a result of antidepressant use (Robillard et al., 2015), such as sedating tricyclic antidepressants (Wichniak & Jernajczyk, 2017). While benzodiazepine use could also be an explanation, as it is also prescribed for sleep problems, it is a less likely explanation here, as only 5 cases used benzodiazepines, and analyses excluding these cases did not alter findings (data not shown). Another possible explanation of our findings is that the used sleep detection algorithm may misclassify period of inactivity as sleep period, which may be possible since patients with depression and anxiety exhibit more sedentary behaviour.

Shifted and delayed rhythm have been previously documented in patients with depression (Hori et al., 2016) and anxiety (Robillard et al., 2015) supporting the evidence for an association between late chronotypes and psychopathology. In our sample we noticed later Mid Sleep on Free Days among current cases using antidepressant medication after covariate adjustments.. As antidepressant use may result in more daytime sleepiness and fatigue (Fava, 2003) and longer sleep duration(Robillard et al., 2015), this may possibly explain this finding.

Some limitations should be considered in the current study. Although actigraphy provides an estimate of sleep parameters such as sleep duration, sleep efficiency, it does not yield estimates of sleep stage, such as REM period that may be associated with depression. In addition, it was not possible to extrapolate actigraphy sleep es-

timates indicative of insomnia such as sleep-onset latency (i.e., time to transit from full wakefulness to sleep) and wake after sleep onset (i.e., periods of wakefulness occurring after sleep onset). Studies have also shown that actigraphy lacks the precision of the gold standard polysomnography that provides greater insight into sleep problems in people with depression or anxiety (Van Hees et al., 2015). Because sleep is inferred from a lack of movement, there may be some misclassification of sleep among those who are awake but motionless. Therefore, the technique is biased toward overestimating total sleep duration, which may lead to incorrectly minimizing the severity of sleep disturbances. Likewise, assessment of circadian rhythm with actigraphy may not reflect the underlying circadian biology and may be influenced by unmeasured demographics and other lifestyle factors (Luik, Zuurbier, Hofman, Van Someren, & Tiemeier, 2013). We also based our threshold for MVPA on that of other studies (Kim et al., 2017), but there is no consensus on these thresholds. We also used a less frequently reported measure of chronotype (Sleep midpoint on free days). Chronotype is often represented as sleep midpoint on free days corrected for sleep-debt accumulated during working days (MSFsc)(Roenneberg et al., 2003). As we did not find associations with MSF and MSF and MSFsc were previously found to be highly correlated in the NESDA sample (r=0.91, (Antypa et al., 2016)), we did not expect to find different results in our analysis and the conclusions would not change. Nevertheless, the overall chronotype (early, intermediate, and late chronotype) across a sample may influence any correlational associations leading to inconsistent associations with psychopathology (Dimitrov et al., 2018). It should also be noted that the self-reported questionnaires and the actigraphy measurement did not capture the same time period; questionnaires were filled out before actigraphy. We also used a limited number of sociodemographic covariates in this study (i.e., age, sex, education). Future analyses may take other variables into account (e.g., BMI, employment status) to study what factors may explain the association of sleep, circadian rhythm and physical activity with psychopathology. Correction for multiple testing was also not performed and may have led to finding statistical associations for chance. Strengths of the study are the inclusion of both depressive and anxiety disorder, and the ability to look in-depth at the role of clinical characteristics.

While the measures presented in this paper provide some preliminary insight into the objectively-measured physical activity, sleep and circadian rhythms and the differences therein between diagnostic groups, these measures are summaries of a much richer underlying dataset. Using studies from our collaborative Motor Activity Research Consortium for Health (m-MARCH) initiative (www.mmarch.org, Scott et al., 2017), we plan to employ more sophisticated analytical tools have been developed that can improve our understanding of these features, such as functional principal component analyses (Gershon, Ram, Johnson, Harvey, & Zeitzer, 2016), and functional scalar regression (Goldsmith, Zipunnikov, & Schrack, 2015). These

approaches will enhance the power and gain greater insight into these patterns and their relationship to depression and anxiety disorders.

To conclude, we found that persons with current depression and/or anxiety exhibit reduced physical activity and more circadian rhythm disturbances than controls using actigraphy. As the correlations of actigraphy estimates with self-report measures were generally low, actigraphy monitoring was shown to provide an easy and non-invasive approach to capture objective information regarding both night time sleep and daytime activity and, sleep and circadian rhythm. In addition, persons with greater severity and, among current cases, with more psychiatric comorbidity showed lower physical activity and more circadian rhythm disturbances. Therefore, adjunctive behavioural and chronotherapy interventions in depression and anxiety may especially focus on these individuals. While this study confirms the feasibility and acceptability of monitoring patients, more research is needed to establish whether actigraphy could possibly in the future play a role in monitoring treatment response to such interventions.

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Supplemental material

Raw data processing

We used the open source R package, GGIR (version 1.5-18), for cleaning the raw actigraphy data. According to previously published methods (van Hees et al., 2014), the detailed processing pipeline included the following steps: verification of sensor calibration error using local gravity as a reference, detection of sustained abnormally high values, non-wear detection and, extraction of objective physical activity, sleep and circadian rhythm measures. Of those 370 participants with available data, one participant (0.3%) had calibration error higher than 0.02 g (1g = 9.81m/s^2), one participant (0.3%) had sustained abnormally high values, and therefore excluded. The processing pipeline implemented by GGIR failed to process data of one participant for unknown reasons.

As participants were found to inconsequently comply to the protocol to press the button when going to sleep/getting up (2 participants, 0.5%), a new method was used to calculate sleep estimates (i.e., total sleep duration per night and sleep efficiency per night) without the use of a sleep diary (van Hees et al., 2018). Inactivity periods were defined as consecutives 5-second epochs in which the arm angle relative to the horizontal plane did not change of more than 5° over at least 5 minutes (Van Hees et al., 2015). With a heuristic algorithm, a Sleep Period Time-window was identified as the time window starting at sleep onset and ending when waking up after the last sleep episode of the night (van Hees et al., 2018). Inactivity periods overlapping the Sleep Period Time-window were labelled as sleep periods. Finally, total sleep duration [clock time] was calculated as the sum of estimated sleep periods and sleep efficiency [%] was the total sleep duration divided by the time difference between sleep onset and wake-up time (i.e., time in bed).

Circadian rhythm was calculated by Mid Sleep on Free Days and the relative amplitude between daytime and night-time activity. Assuming that weekend days are most likely to be free days of the week, Mid Sleep on Free Days was calculated as the middle time point between sleep onset and wake-up time during weekend days. Relative amplitude between daytime and night-time activity was calculated according to previously published methods (Van Someren et al., 1999). Average weekly estimates were derived as [(average value for weekdays × 5 + average value for weekend days × 2) / 7], while the average was calculated for Mid Sleep on Free Days.

Physical activity was assessed as gross motor activity per day and minutes in moderate-to-vigorous physical activity per day. Objective gross motor activity was estimated by calculating the Euclidian Norm Minus One (ENMO: $\sqrt{x^2 + y^2 + z^2} - 1g$, 1g = 9.81m/s^2) with any negative values rounded up to zero and by averaging such

Table S1: Correlations between self-reported and actigraphy estimates of sleep, circadian rhythm and physical activity stratified by diagnostic status (n=359)

	No depressive and/or anxiety disorders (n =90)				
	Self-reported estimates				
	Sleep (IRS)		**Circadian rhythm (MCTQ)**	**Physical activity (IPAQ)**	
Actigraphy estimates	IRS [a]	Sleep duration [b]	Mid Sleep on Free Days [a]	MET [a]	MVPA [a]
Sleep					
Sleep duration	0.149	0.198	0.028	0.001	0.013
Sleep efficiency	-0.063	-0.067	-0.047	0.043	0.061
Circadian rhythm					
RA	-0.016	0.015	-0.380***	0.205*	0.156
Mid Sleep on Free Days	0.087	-0.063	0.638***	0.021	-0.005
Physical activity					
Gross motor activity	-0.023	0.070	-0.292**	0.163	0.126
MVPA	0.029	0.108	-0.278**	0.126	0.092

Abbreviations: IPAQ, International Physical Activity Questionnaire – Short Form; IRS, Women's Health Initiative Insomnia Rating Scale; MCTQ, Munich Chronotype Questionnaire; MET, metabolic equivalent total; MVPA, moderate-to-vigorous physical activity; RA, relative amplitude between daytime and night-time activity level.
Notes: *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.
[a] Pearson's correlation
[b] Polyserial correlation

measure over 5-second epoch (van Hees et al., 2013). Because there is no consensus on thresholds to identify moderate-to-vigorous physical activity, objective minutes in moderate-to-vigorous physical activity per day were defined as the sum of 1-min epochs in which ENMO was larger than 125mg, which has recently been used by others (Kim et al., 2017).

Table S1: (continued)

Remitted depressive and/or anxiety disorders (n=176)					Current depressive and/or anxiety disorders (n=93)				
Self-reported estimates					Self-reported estimates				
Sleep (IRS)		Circadian rhythm (MCTQ)	Physical activity (IPAQ)		Sleep (IRS)		Circadian rhythm (MCTQ)	Physical activity (IPAQ)	
IRS [a]	Sleep duration [b]	Mid Sleep on Free Days [a]	MET [a]	MVPA [a]	IRS [a]	Sleep duration [b]	Mid Sleep on Free Days [a]	MET [a]	MVPA [a]
0.076	0.022	0.039	-0.035	0.033	0.012	-0.038	-0.131	0.030	-0.062
-0.05	-0.029	-0.077	0.001	-0.001	-0.112	-0.142	-0.119	0.045	-0.059
-0.247***	0.314***	-0.110	0.261***	0.186*	-0.051	0.082	-0.054	0.180	0.013
-0.069	0.056	0.604***	0.019	0.025	-0.220*	0.174	0.508***	-0.163	-0.117
-0.187*	0.113	0.048	0.285***	0.204**	0.081	-0.005	0.024	0.379***	0.219*
-0.145	0.093	0.082	0.259***	0.182*	0.081	0.086	0.106	0.369***	0.190

Table S2: day-to-day variability in sleep, circadian rhythm and physical activity in persons with current, remitted, no depressive and/or anxiety disorders (n = 359)

	Current depressive and/or anxiety disorder(s)	Remitted depressive and/or anxiety disorder(s)	No depressive and/or anxiety disorder(s)	p
Sleep				
Sleep duration variability [clock time], mean(sd) [a]	01:05 (00:28)	01:10 (00:37)	00:59 (00:25)	**0.045** [b]
Sleep efficiency variability [%], mean (sd) [a]	0.05 (0.03)	0.05 (0.03)	0.05 (0.02)	0.234
Circadian rhythm				
Variability in relative amplitude between day and night activity, mean (sd) [a]	0.05 (0.04)	0.05 (0.04)	0.05 (0.03)	0.661
Mid Sleep on Free Daysvariability [clock time], mean (sd) [a]	00:38 (00:34)	00:41 (0:43)	00:37 (00:31)	0.297
Physical activity				
Gross motor activity variation [milli-gravity], mean (sd) [a]	4.73 (2.45)	5.1 (3.06)	5.51 (3.51)	0.197
Moderate-to-vigorous physical activity variability [min], mean (sd) [a]	18.02 (15.81)	21.46 (18.28)	25.51 (17.56)	**0.015** [c]

[a] Kruskal–Wallis test;
[b] Dunn's test, remitted depressive and/or anxiety disorders versus no depressive and/or anxiety disorders, p<0.05
[c] Dunn's test, current depressive and/or anxiety disorders versus no depressive and/or anxiety disorders, p<0.05

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Sociodemographic, Health and Lifestyle, Sampling, and Mental Health Determinants of 24-hour Motor Activity Patterns: *Observational Study*

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Abstract

Background: Analyzing actigraphy data using standard circadian parametric models and aggregated nonparametric indices may obscure temporal information that may be a hallmark of the circadian impairment in psychiatric disorders. Functional data analysis (FDA) may overcome such limitations by fully exploiting the richness of actigraphy data and revealing important relationships with mental health outcomes. To our knowledge, no studies have extensively used FDA to study the relationship between sociodemographic, health and lifestyle, sampling and psychiatric clinical characteristics and daily motor activity patterns assessed with actigraphy in a sample of individuals with and without depression/anxiety.

Objective: We aimed to study the association between daily motor activity patterns assessed via actigraphy and (1) sociodemographic, health and lifestyle, and sampling factors, and (2) psychiatric clinical characteristics (ie, presence and severity of depression/anxiety disorders).

Methods: We obtained 14-day continuous actigraphy data from 359 participants from the Netherlands Study of Depression and Anxiety with current (n=93), remitted (n=176), or no (n=90) depression/anxiety diagnosis, based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition. Associations between patterns of daily motor activity, quantified via functional principal component analysis (fPCA), and sociodemographic, health and lifestyle, sampling, and psychiatric clinical characteristics were assessed using generalized estimating equation regressions. For exploratory purposes, function-on-scalar regression (FoSR) was applied to quantify the time-varying association of sociodemographic, health and lifestyle, sampling, and psychiatric clinical characteristics on daily motor activity.

Results: Four components of daily activity patterns captured 77.4% of the variability in the data: overall daily activity level (fPCA1, 34.3% variability), early versus late morning activity (fPCA2, 16.5% variability), biphasic versus monophasic activity (fPCA3, 14.8% variability), and early versus late biphasic activity (fPCA4, 11.8% variability). A low overall daily activity level was associated with a number of sociodemographic, health and lifestyle, and psychopathology variables: older age ($p<.001$), higher education level ($p=.005$), higher BMI ($p=.009$), greater number of chronic diseases ($p=.02$), greater number of cigarettes smoked per day ($p=.02$), current depressive and/or anxiety disorders ($p=.05$), and greater severity of depressive symptoms ($p<.001$). A high overall daily activity level was associated with work/school days ($p=.02$) and summer (reference: winter; $p=.03$). Earlier morning activity was associated with older age ($p=.02$), having a partner ($p=.009$), work/school days ($p<.001$), and autumn and spring (reference: winter; $p=.02$ and $p<.001$, respectively).

Monophasic activity was associated with older age (p=.005). Biphasic activity was associated with work/school days (p<.001) and summer (reference: winter; p<.001). Earlier biphasic activity was associated with older age (p=.005), work/school days (p<.001), and spring and summer (reference: winter; p<.001 and p=.005, respectively). In FoSR analyses, age, work/school days, and season were the main determinants having a time-varying association with daily motor activity (all p<.05).

Conclusions: Features of daily motor activity extracted with fPCA reflect commonly studied factors such as the intensity of daily activity and preference for morningness/eveningness. The presence and severity of depression/anxiety disorders were found to be associated mainly with a lower overall activity pattern but not with the time of the activity. Age, working and season were the variables most strongly associated with patterns and time of activity, and thus future epidemiological studies on motor activity in depression/anxiety should take these variables into account.

Introduction

The near ubiquitous use of accelerometers in electronic devices ranging from "smartphones" to wrist-worn accelerometers provides the biomedical community with a potential richness of data that is useful to study health outcomes. Wrist-worn accelerometers have been used for more than 20 years by sleep researchers to estimate sleep and circadian activity rhythms (Ancoli-Israel et al., 2015; Martin & Hakim, 2011) and by those studying patterns of physical activity (Matthews et al., 2012). Research indicates that disruption in circadian activity rhythms, especially daily motor activity patters, correlate with poor mental (Lyall et al., 2018) and physical health (Farhud & Aryan, 2018). Burton et al., (Burton et al., 2013), and our recent results have shown that low level of daily motor activity is associated with depressive(Difrancesco et al., 2019a; Minaeva, Booij, et al., 2020) and anxiety(Difrancesco et al., 2019a) disorders. In addition, sociodemographic and lifestyle factors, especially age and body mass index (BMI), have been linked to disruptions in daily motor activity patterns. Compared to younger persons, older persons have had lower motor activity patterns (Banihashemi et al., 2016) and earlier bed and rise times, also known as early chronotype (Mitchell et al., 2017). Higher BMI has been associated with lower daytime activity level and higher night-time activity level (Cespedes Feliciano et al., 2017; Shou et al., 2017). Circadian activity rhythms are also controlled externally by environmental and social cues. For instance, light is an important synchroniser for circadian activity rhythms (Stothard et al., 2017) and has been shown to be effective in the treatment of sleep disorders (van Maanen et al., 2016) and affective disorders (Penders et al., 2016).

Despite the great interest in daily motor activity patterns and their association with health outcomes and other health factors, commonly used methodology to analyse actigraphy data are limited in the description of circadian rhythms. Often used validated methods aggregate data in daily indices (Klerman et al., 2017) losing important information that may be a hallmark of circadian impairment. The traditional approach to actigraphy data analysis employs cosinor (i.e., based on the mathematical formula of a cosine wave) or modified cosinor analyses that yield information concerning the amplitude of activity, the timing of "peak" activity, and the goodness-of-fit (how close pattern is to cosine wave) (Klerman et al., 2017). Although this is often quite useful in people with robust activity patterns, these analyses assume the presence of a particular shape of activity (i.e., a predictable pattern, such as a cosine waveform) that may be different in individuals with physical or psychological impairments. Functional data analysis (FDA) can be used to model the complete time series of actigraphy data with less restrictive assumptions (Harezlak et al., 2018). Recent studies using functional Principal Component Analysis (fPCA), a FDA technique, have shown that patterns of daily motor activity with specific shapes

are associated with psychiatric clinical characteristics (i.e., apathy (Zeitzer et al., 2013), depressive and anxiety symptoms (Zeitzer et al., 2018), objectively assessed sleep (Zeitzer et al., 2018)) in persons with Alzheimer disease. Another increasingly used FDA technique is Function-on-Scalar regression (FoSr) which analyses the relative time-varying impact of each variable of interest on the activity patters. In addition, this method yields valuable information about the time intervals in which the variables of interest have the greatest influence on activity patterns (J Goldsmith et al., 2015; Jeff Goldsmith et al., 2016). Banihashemi et al., (2016)(Minaeva, Booji, et al., 2020) have suggested that older age and higher BMI are linked to lower daytime activity levels and, higher BMI and worse symptom severity are associated with nocturnal activity patterns suggestive of sleep disturbances in a population with affective disorders. Those findings are based on first attempts using FDA and such approaches have not been explored yet in a population with depressive and anxiety disorders. In addition, no studies have extensively assessed the association of actigraphy functional curves with sociodemographic, lifestyle and sampling factors (i.e., season, working days). Functional data analysis may better capture the complexity and dynamics of daily motor activity to reveal important behavioural biomarkers. This may help to understand whether intervening on circadian rhythm or sleep (e.g. by light therapy or sleep intervention) could be useful regimen in reducing depressive and anxiety disorders.

In this study, we examine the association of daily activity patterns assessed using actigraphy and Functional Data Analysis with (1) sociodemographic (i.e., age, sex, partner status, education level), health and lifestyle (i.e., drinking, smoking, chronic diseases, BMI) and sampling factors (i.e., season, work or school day/non-work or non-school day); (2) psychiatric clinical characteristics (i.e., current/remitted depressive and anxiety disorders, severity of depressive, medication use).

Methods

Sample

Participants from the Netherlands Study of Depression and Anxiety (NESDA) were selected to enrol in the Ecological Momentary Assessment (EMA) & Actigraphy sub-study (NESDA-EMAA). NESDA is one of the sites that is member of the Motor Activity Research Consortium for Health (m-MARCH)(*MMARCH*, 2018; Scott et al., 2017), a collaborative network on the application of objective assessment of motor activity, sleep and mood in population and clinical samples. Details about NESDA have been discussed extensively before (Penninx et al., 2008). NESDA was designed to investigate the course of depressive and anxiety disorders over a period of several years and the factors that influence the development and prognosis of such

disorders. NESDA participants were initially recruited for baseline assessment between 2004-2007 (n = 2981), and seen for the fifth time at the nine-year follow-up assessment wave (2014-2017, n = 2069) for a regular follow-up interview, including a psychiatric diagnostic interview. In total, 1776 persons participated in face-to-face interviews. A total of 367 siblings of NESDA participants who met diagnostic criteria for a depression or anxiety disorder and had the same biological parents as their sibling(s) were added as participants to NESDA's nine-year follow-up assessment. At the nine-year follow-up, we conducted the EMAA substudy among 384 participants. The NESDA study, including the EMAA component, was approved by the VUmc ethical committee (reference number 2003/183) and all respondents gave informed consent for both the regular interview and the EMAA component. A flowchart of the NESDA-EMAA was previously provided in Difrancesco *et al.*, (Minaeva, Booji, et al., 2020). Eligibility criteria include: 1) they had a smartphone or were willing to use a smartphone provided by the study; 2) willing to wear a wrist-worn actigraphy device; 3) could be enrolled within one month of the NESDA interview. Siblings were invited if they did not have a current or past diagnosis of a depressive and/or anxiety disorder or another severe psychiatric disorder (such as psychotic or severe addiction disorder). Participants of the EMAA-substudy were provided with a wrist-worn GENEActiv device (Activinsights Ltd, Kimbolton, UK) and wore them for two weeks on their non-dominant wrist. The devices were initialized and set to collect raw activity measures at 30Hz frequency. They also completed questions on their current mood states using Ecological Momentary Assessment (EMA) (Schoevers et al., 2020). Here, we only report on the actigraphy component of the study. Of the 384 participants included in the NESDA-EMAA study, 14 had no available actigraphy data for several reasons, such as technical failure (more details in (Difrancesco et al., 2019a)), resulting in 370 (96.4%) participants with available data. According to previously published criteria (da Silva et al., 2014), participant's actigraphy data were included in analyses if at least one week day and one weekend day of usable data was available, with at least 16 hours recorded per day and per night. The final sample consist of 359 (93.5%) participants with 13.68 ± 1.26 valid days, of which 90% completed the protocol for 14 days.

Assessment of sociodemographic, health and lifestyle and, sampling factors

Sociodemographic, health and lifestyle factors were assessed at the nine-year follow-up. Sociodemographic factors included age, gender, education level expressed in years and partner status. Health and lifestyle factors included body mass index (BMI, kg/m^2), number of self-reported chronic diseases under treatment (heart disease, diabetes, stroke, lung disease, osteoarthritis, cancer, ulcer, intestinal problems, liver disease, epilepsy, thyroid gland disease), number of cigarettes per day and number of alcoholic drinks per day. Sampling factors were assessed at the nine-year

follow-up based on EMA and actigraphy assessment. Sampling factors included whether the actigraphy assessment was performed on a work/school day and the season in which the actigraphy assessment was performed. Work/school day was identified with information from EMA assessment. Season was determined based on the date of actigraphy assessment (e.g., 25/09/yyyy = autumn) and winter was used as reference.

Assessment of depressive and/or anxiety disorders and clinical characteristics

As in the previous waves, at the 9-year follow-up, specially trained clinical research staff conducted the diagnostic interviews. The Composite International Diagnostic Interview (CIDI, version 2.1)(Wittchen, 1994) was used to establish DSM-IV based diagnoses of depressive disorders (dysthymia and major depressive disorder) and anxiety (social anxiety disorder, panic disorder with and without agoraphobia, agoraphobia and generalized anxiety disorder). For this study, we divided participants into three groups: 1) no lifetime depressive and/or anxiety disorders, 2) remitted depressive and/or anxiety disorders defined as having a lifetime, but not current (6-month) diagnosis, and 3) current depressive or anxiety disorder diagnosed in the past 6 months.

Examined clinical characteristics were: severity of depressive symptoms , and medication use (i.e., antidepressant and benzodiazepines use). Severity of depressive symptoms was assessed with the 30-item Inventory of Depressive Symptomatology (IDS)(Rush et al., 1996). Antidepressant use and benzodiazepine use was based on drug container inspection, and medications were coded according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification. Antidepressant and benzodiazepines use was considered present if participants reported using it more than 50% of the time. Antidepressants included were selective serotonin reuptake inhibitors (SSRIs, ATC code N06AB), tricyclic antidepressant (TCA, ATC code N06AA) and other antidepressants (ATC codes N06AF, N06AG, N06AX); benzodiazepines included ATC codes N03AE, N05BA, N05CD and N05CF.

Statistical analyses

Descriptive analyses

Distributions of all variables were checked on normality with Q-Q plots. For descriptive statistics, participant sociodemographic, health and lifestyle, sampling factors and clinical characteristics were compared between the three groups (i.e., no, remitted and current depressive and/or anxiety disorders). For normally distributed continuous data, ANOVA tests were used and for data with a non-normal distribution Kruskal-Wallis test were used. Chi-squared tests were used to test differences in

frequencies across the three groups. All analyses were performed with the statistical software R (version 1.0.143), a **p** value < 0.05 was considered statistically significant.

Assessment of circadian rhythm patterns with FPCA

Raw actigraphy data was processed with open source R package GGIR (version 1.5-18) (van Hees, 2017) according to published methods (van Hees et al., 2013, 2014). Processing of data included autocalibration, non-wear detection, identification of potentially corrupted data, collapsing of raw data to epoch level and computation of missing data. Collapsing of raw data to epoch level was done by averaging 5-second data. Minute-to-minute daily actigraphy data were derived per participant by summing these 5-second data; day was defined as the 00:00 – 23:59 time interval. As days with at least 16 valid hours were included in the analyses, missing data points were replaced with participant's data from the same time of day, averaged across the other valid days to provide a person-specific informed approach.

Daily motor activity patterns were derived from minute-level actigraphy data with the R package **fda** for functional data analysis (version 2.4.8)(Ramsay et al., 2018). First, participant minute-to-minute actigraphy data was pre-smoothed as linear combinations of a set of nine Fourier basis functions to capture the major trends in daily motor activity (the same procedure was applied by Zeitzer (Zeitzer et al., 2018) and Gershon (Gershon et al., 2016)). After that, functional Principal Component Analysis (fPCA) was used for capturing the principal directions of daily variation and dimension reduction. FPCA summarized the daily-specific features as the coordinates (called principal component scores) of participant curves in the basis spanned by the principal components. The first four daily-specific features, in this paper referred to as functional principal components, were considered because they explained together at least 75% of data variability (a similar cut-off was previously used (Gershon et al., 2016)).

The association between the extracted daily functional principal components for each participant and participant sociodemographic, lifestyle, sampling factors and clinical characteristics were tested by using multiple Generalized Estimating Equation (GEE) regressions with each functional principal component as outcome. GEE was used to account for correlations between repeated days per person. Separate models were run for each clinical characteristic (i.e., current/remitted depressive and/or anxiety disorders, IDS, antidepressant use) and each model was adjusted for sociodemographic, health and lifestyle and sampling factors; this was done to avoid collinearity induced by the high correlation between psychiatric clinical characteristics. Multiple testing correction was applied by controlling the false discovery rate (FDR) (Noble, 2009).

Assessment of time-varying associations of the activity with sociodemographic, health and lifestyle and mental health determinants with Function-on-Scalar Regression

Minute-to-minute daily actigraphy data were aggregated over 10 minutes and averaged over the assessment period for each participant (similar procedure was done in (Jeff Goldsmith et al., 2016)). Function-on-Scalar regression was used to study the time-varying association of participant sociodemographic, health and lifestyle, sampling and clinical characteristics with actigraphy data as outcome (i.e., study the time-varying impact of several factors on activity patterns). For exploratory purpose, function-on-scalar regression analysis was repeated for each clinical characteristic to account for the high correlation between psychiatric clinical variables. Each model was adjusted for sociodemographic, health and lifestyle and sampling factors. Data were analysed with the R script developed by Goldsmith (Jeff Goldsmith, 2019).

Results

The sample sociodemographic, health and lifestyle, sampling and clinical characteristics are described in Table 1 (Table 1). Of the total sample (n = 359), 93 had current and 176 had remitted depressive and/or anxiety disorders, 90 had no current depressive and/or anxiety disorders. The current depressive/anxiety disorder group was heterogeneous: in that 38.3% had anxiety disorders only, 33.0% had depressive and anxiety disorders and 28.7% had depressive disorders only. As expected, individuals with current depressive and/or anxiety disorders diagnosis scored significantly higher on depressive symptoms ($p < 0.001$) and more frequently used antidepressant than both other groups, although no significant differences were found for benzodiazepine use.

Four components describing 77.4% of variability were extracted from the data with fPCA (Figure 1) and interpreted as follows. The first component was the overall daily activity level. The second component described early versus late morning activity, and could be indicative of chronotype. The third component showed a biphasic versus monophasic activity pattern, while the fourth component represented a biphasic, early versus a biphasic, late activity pattern. The biphasic pattern showed two cycles of increased activity with subsequent decreased activity. A determinant associated with a pattern marked with (+) in Figure 1 (Figure 1) has a positive β, negative otherwise.

Low overall daily activity level was associated with a number of sociodemographic, lifestyle and psychopathology variables ($p < 0.05$, Table 2): older age, higher education level, higher BMI, higher number of chronic diseases, higher number of cigarettes

Table 1: Demographic, lifestyle factors, actigraphy assessment, psychiatric characteristics and medication use (n = 359).

	Current depressive and/or anxiety disorders	Remitted depressive and/or anxiety disorders	No depressive and/or anxiety disorders	p
N	93	176	90	
Demographics				
Age, mean (SD) [a]	50.1 (11.1)	48.2 (13.4)	51.3 (12.5)	0.13
Female, n (%) [b]	58 (62.4)	120 (68.2)	50 (55.6)	0.12
Education level [years], mean (SD) [a]	12.5 (3.4)	12.7 (2.8)	13.9 (2.9)	**<0.001**
Having a partner, n (%) [b]	45 (48.4)	90 (51.1)	51 (56.7)	0.517
Lifestyle factors				
BMI, mean (SD) [a]	27.1 (5.1)	26.6 (5.2)	26 (5.4)	0.369
Chronic diseases [n], mean (SD) [a]	1.1 (1.2)	1 (1.1)	0.6 (0.8)	**0.008**
# cigarettes per day, mean (SD) [a]	3.2 (6.5)	2.9 (6.1)	0.8 (2.7)	**0.004**
# drinks per day, mean (SD) [a]	0.5 (0.8)	0.7 (1.2)	0.8 (0.8)	0.158
Actigraphy assessment characteristics				
# actigraphy days, mean (SD)	13.7 (1.0)	13.6 (1.5)	13.8 (0.7)	0.48
Measures on work/school days, n (%) [b]	398 (34.1)	769 (37.2)	467 (42.8)	**<0.001**
Season of actigraphy measurement [b]				**<0.001**
Winter days, n (%)	277 (21.8)	701 (29.3)	369 (29.7)	
Autumn days, n (%)	376 (29.5)	584 (24.4)	362 (29.1)	
Spring days, n (%)	432 (33.9)	619 (25.8)	260 (20.9)	
Summer days, n (%)	188 (14.8)	492 (20.5)	252 (20.3)	
Psychopathology				
Only depressive disorders, n (%)	26 (28.7)	46 (26.1)	-	
Only anxiety disorders, n (%)	36 (38.3)	24 (13.6)	-	
Depressive & anxiety disorders, n (%)	31 (33.0)	106 (60.2)	-	
Inventory of Depressive Symptomatology (IDS), mean (SD) [a]	28.6 (11.4)	20.9 (12.5)	6.0 (4.9)	**< 0.001**
Medication use				
Antidepressant users, n (%) [b]	35 (37.2)	34 (19.3)	2 (2.2)	**< 0.001**
Benzodiazepines users, n (%) [b]	5 (5.3)	8 (4.5)	0 (0.0)	0.10

[a] Analysis of variance (ANOVA), [b] Chi-squared test
SD, standard deviation; IQR, interquartile range

Table 2: Multivariable association* of daily motor activity patterns with sociodemographic, lifestyle, actigraphy assessment characteristics and psychopathology (n=359)

	Overall daily activity intensity		
	β	SE	p
Sociodemographic			
Age	-0.150	0.039	**<0.001**
Sex			
Female	Ref.		
Male	-0.054	0.079	0.652
Education level	-0.128	0.038	**0.005**
Has a partner			
No	Ref.		
Yes	-0.166	-0.075	0.072
Lifestyle factors			
BMI	-0.118	0.039	**0.009**
# chronic diseases	-0.109	0.040	**0.021**
Number of cigarettes per day	-0.138	0.050	**0.019**
Number of drinks per day	0.079	0.045	0.185
Actigraphy assessment characteristics			
Working/ school day			
No	Ref.		
Yes	0.171	0.060	**0.019**
Season			
Winter	Ref.		
Autumn	0.103	0.089	0.392
Spring	0.147	0.089	0.207
Summer	0.285	0.108	**0.026**
Psychopathology			
Depressive and/or anxiety disorders			
No	Ref.		
Remitted	-0.063	0.081	0.596
Current	-0.236	0.099	**0.050**
IDS	-0.143	0.039	**<0.001**
Antidepressant use			
No	Ref.		
Yes	-0.168	0.105	0.220

Note: * multivariable GEE model, multiple testing correction using false discovery rate (FDR) estimation.

Table 2: (continued)

Early vs late morning activity			Biphasic vs monophasic activity			Early vs late biphasic activity		
β	SE	p	β	SE	p	β	SE	p
0.082	0.029	**0.017**	-0.097	0.028	**0.005**	0.097	0.029	**0.005**
Ref.			Ref.			Ref.		
-0.017	0.063	0.828	-0.025	0.055	0.789	-0.071	0.055	0.339
-0.014	0.034	0.804	0.036	0.026	0.303	-0.026	0.030	0.540
Ref.			Ref.			Ref.		
0.183	-0.060	**0.009**	-0.015	-0.049	0.828	0.051	-0.054	0.496
0.048	0.030	0.219	-0.007	0.024	0.828	0.010	0.025	0.804
-0.011	0.029	0.818	-0.026	0.026	0.470	-0.047	0.025	0.145
0.029	0.034	0.545	-0.046	0.027	0.185	0.016	0.027	0.692
-0.046	0.041	0.396	-0.039	0.031	0.344	-0.009	0.033	0.828
Ref.			Ref.			Ref.		
0.284	0.049	**<0.001**	0.728	0.052	**<0.001**	0.190	0.050	**<0.001**
Ref.			Ref.			Ref.		
0.189	0.070	**0.024**	0.019	0.067	0.828	0.136	0.060	0.067
0.331	0.067	**<0.001**	0.140	0.065	0.083	0.256	0.071	**<0.001**
0.178	0.102	0.185	0.327	0.072	**<0.001**	0.243	0.076	**0.005**
Ref.			Ref.			Ref.		
-0.035	0.076	0.789	-0.046	0.065	0.641	0.077	0.067	0.392
0.019	0.077	0.831	-0.001	0.075	0.991	-0.006	0.074	0.954
-0.046	0.035	0.339	-0.015	0.026	0.698	-0.040	0.029	0.303
Ref.			Ref.			Ref.		
-0.124	0.064	0.138	-0.078	0.065	0.382	-0.106	0.079	0.325

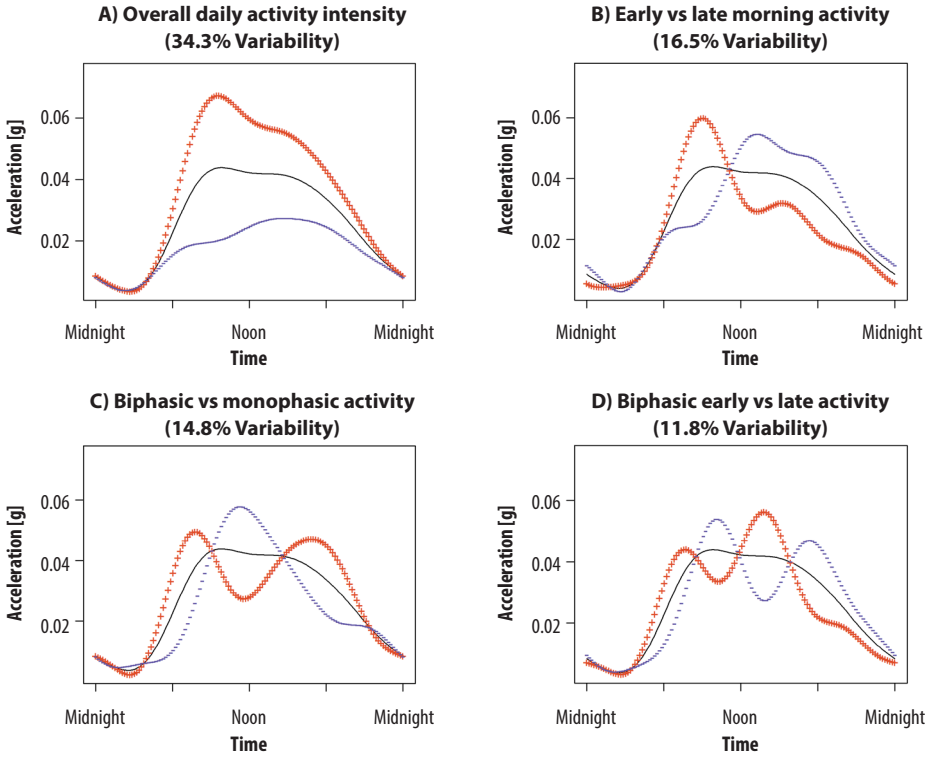

Figure 1: Patterns of daily activity explaining 77.4% of variability in the data (n=359).

The black line represents the average daily activity, the red line represents the average daily activity + one standard deviation of PC score, the purple line represents the average daily activity – one standard deviation of PC score. A) the first component (on the upper left) represents high (+) versus low (-) daily activity intensity; B) the second component (on the upper right) shows early (+) versus late (-) morning activity; C) the third component (on the bottom left) shows biphasic (+) versus monophasic (-) activity; D) the fourth component (on the bottom right) represents biphasic early (+) versus late (-) activity. A determinant associated with a pattern marked with (+) has a positive β, negative otherwise.

per day, having current depressive/anxiety disorders, higher severity of depressive symptoms. Higher overall daily activity level was associated with working/school days, and summer (ref. winter) (all p <0.05, Table 2). Earlier morning activity was associated with older age, having a partner, work/school days, autumn and spring (ref. winter) (all p <0.05, Table 2). Monophasic activity was associated with older age (p <0.01, Table 2). Biphasic activity was associated with work/school days, summer (ref. winter) (all p <0.01, Table 2). Earlier biphasic activity was associated with older age, work/school days, spring and summer (ref. winter) (all p <0.01, Table 2).

Age, working status and season were significantly associated with motor activity in the function-on-scalar regression analyses (Figure 2, p <0.05). Older age was especially related to lower activity in the late afternoon (around 18:00hrs). Working or going to school was associated with higher activity level with a dip in activity level

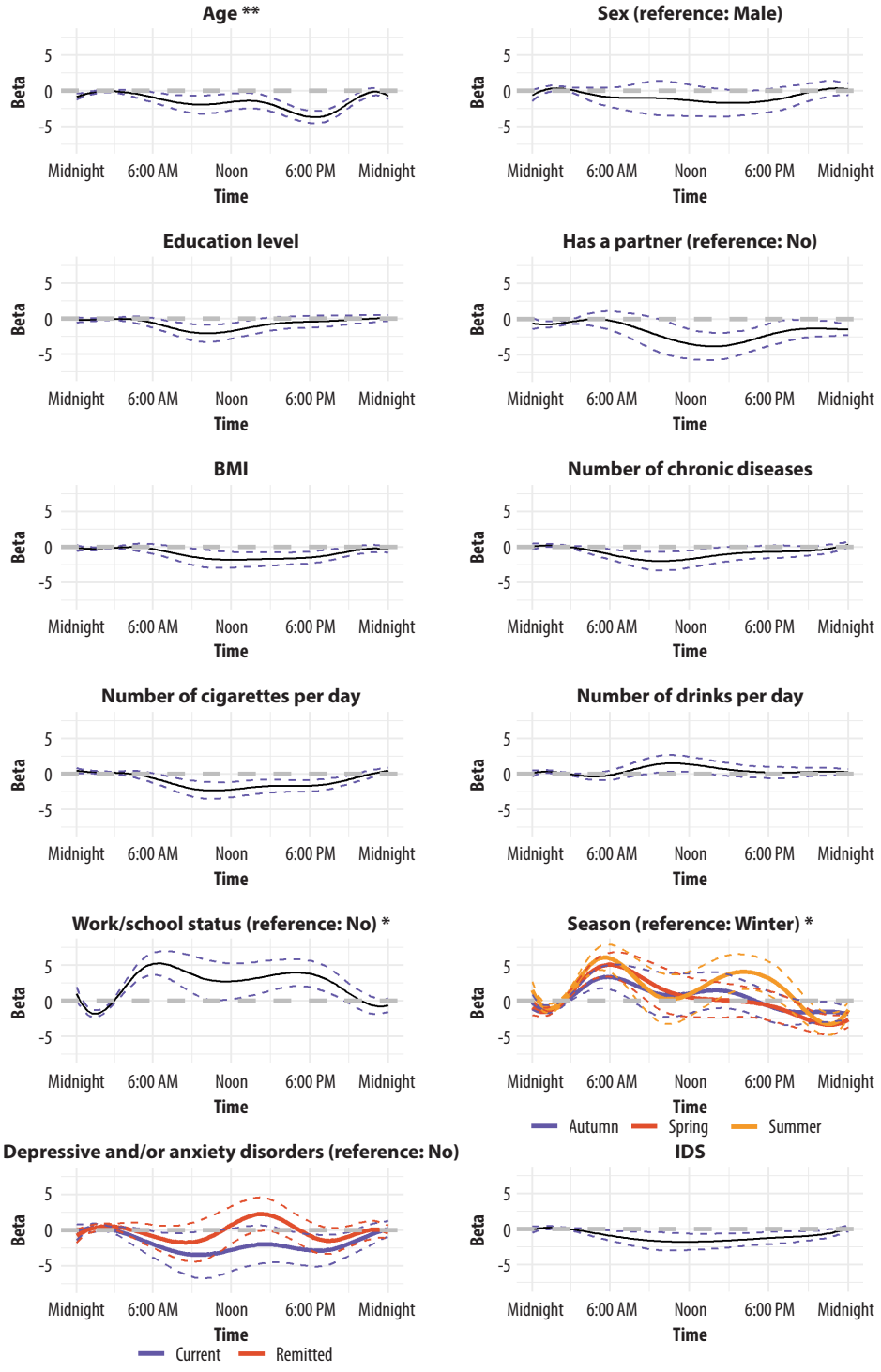

Figure 2: Effect of sociodemographic, lifestyle factors, actigraphy characteristics and clinical characteristics on time of the activity from multivariable Functional on Scalar regression. Note: *: $p < 0.05$; **: $p < 0.01$.

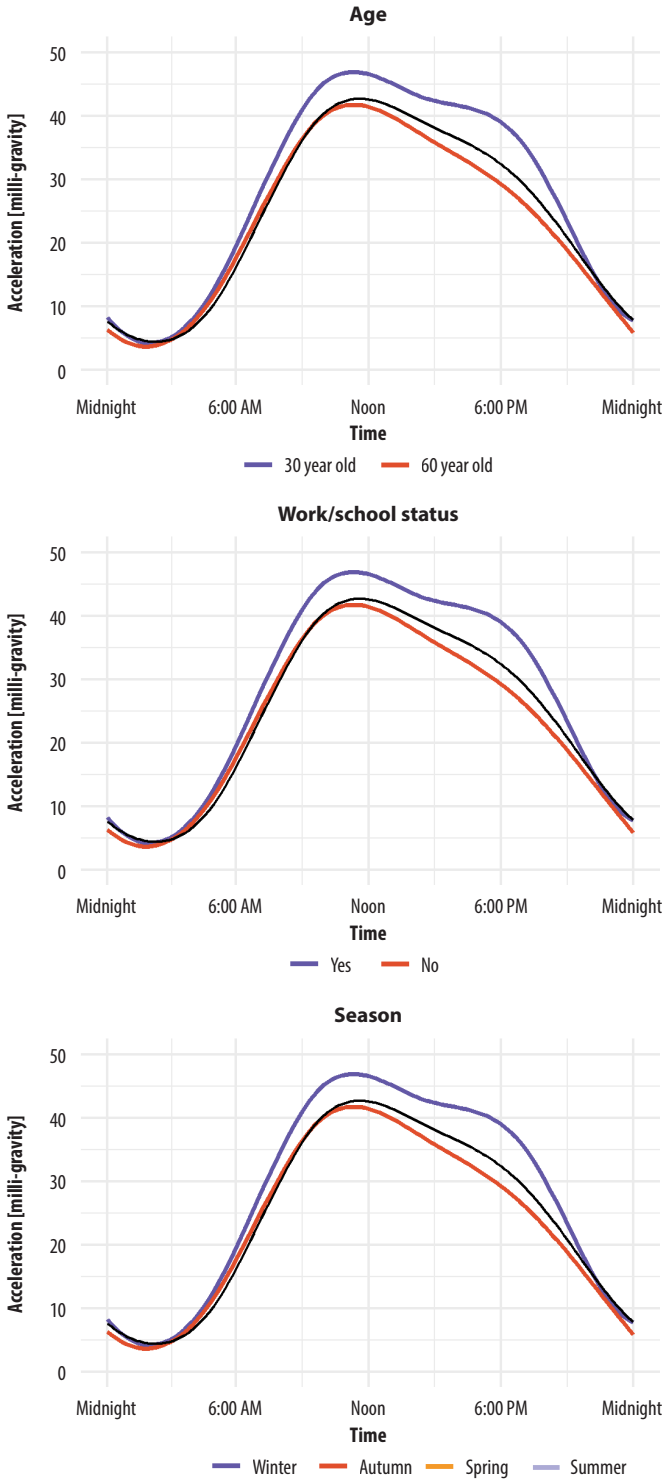

Figure 3: average daily motor activity curves by age, working status and season.

around noon compared to not working/going to school (Figure 2). Compared to those assessed in winter, those assessed in summer, spring and autumn had higher activity in the morning and those assessed in the summer had higher activity late in the afternoon (Figure 2). Average daily motor activity curves by age, working status and seasons are shown in Figure 3.

Discussion

This is the first study to study the associations of sociodemographic, lifestyle, sampling factors and psychiatric clinical characteristics with patterns of daily motor activity in a sample of people with and without depressive and anxiety disorders using functional data analysis. Patterns of daily motor activity extracted with fPCA seem to reflect commonly studied circadian activity rhythm features such as the daily activity level and the time-of-day preference for morningness or eveningness(Kivelä et al., 2018). Presence and severity of depressive and anxiety disorders were associated with overall lower activity pattern, but had no impact on time of activity. Sociodemographic, lifestyle and sampling factors were independently associated with daily motor activity patterns. Function on scalar regression analyses indicated that age, working status and season of assessment were associated with time of the activity.

Comparison with previous literature

The majority of variability (77.4 %) was explained by four principal components that reflect the complexity of activity patterns. In line with previous studies employing fPCA, the first two components indicated commonly studied actigraphy features related to circadian rhythms: overall level of physical activity (Gershon et al., 2016; Zeitzer et al., 2013, 2018)and the time-of-day preference for morningness or eveningness (Gershon et al., 2016). Interpretation of the third and fourth components was less clear. We found a monophasic versus a biphasic activity pattern, as previously reported in other studies (Gershon et al., 2016; Zeitzer et al., 2018), who suggested that a biphasic rhythm may reflect napping behavior. This monophasic pattern could also be related to the temporary drop in alertness and performance that often occurs during the early afternoon, referred to as the post-lunch dip, that reflects the 12-hour harmonic of the circadian clock (Monk, 2005). Therefore, the level of daily activity and chronotype seem to be consistent components across studies applying fPCA, demonstrating the generalizability of the extracted components and confirming that these are important features of daily activity patterns.

Sociodemographic factors, especially age, were associated with daily motor activity patterns with lower activity level. This is in line with the study byTakagi et al. (Takagi et al., 2015). This may be due to the age-related decline in physical activity

(Sallis, 2000). Aging causes changes in the organism, which leads to gradual loss of function, frailty, disease and disability (Paterson & Warburton, 2010) and therefore results in decreased physical activity and physical functioning. The sleep-wake cycle also appears to change in the aging process. Our findings showing the association between shifted earlier rhythms and increasing age are consistent with previous research that shows that aging is associated with advanced sleep timing (as reviewed by Duffy et al.(Jeanne F. Duffy et al., 2015)) and preference for morningness (as reviewed by Hood et al.(Hood et al., 2017)). The circadian phase of melatonin has also been reported to become earlier with age, as has the timing of the cortisol rhythm (Jeanne F. Duffy et al., 2015). The suprachiasmatic nucleus (SCN), which represents the biological clock of the brain, shows functional changes with age (Peters, 2007) that may be related to disturbances in circadian rhythms.

Work status and season, not surprisingly, were also very important for daily activity patterns and circadian rhythms. Circadian rhythms are controlled centrally by the SCN and influenced externally by behavioral/social cues and by the light exposure as reviewed by Duffy & Czeisler (Jean F. Duffy & Czeisler, 2009). Our findings that assessments during autumn, spring and summer days showed significantly higher level of activity and earlier morning activity compared to winter days seem to be consistent with, the systematic review of Tucker & Gilliland (Tucker & Gilliland, 2007)has shown that level of activity varies with seasonality and it is the lowest during winter. Also, other factors related to seasons can impact on daily activity such as weather conditions, which can also explain different circadian patterns across seasons. Also, on working/school days there appeared to be higher and longer daily activity and earlier morning activity compared to non-working/non-school days. Indeed, it is well known in the literature that modern life habits including night work, shift work (James et al., 2017)), jet lag (Vosko et al., 2010)), and social jet lag (Wittmann et al., 2006)), are associated with circadian rhythms disruptions.

We also found that health and lifestyle factors are linked to daily activity patterns. Our results are in line with previous research reporting the association of lower activity level with higher BMI in the NIMH Family study (Shou et al., 2017), and higher number of chronic diseases. (Durstine et al., 2013). These results may be suggestive of sedentary behavior, a factor known to relate to weight gain and disabilities. Early morning activity was associated with higher BMI. This might be due to respiration-related diseases such as apnea, which is known to be more prevalent in persons with a high BMI and can disturb sleep severely (Romero-Corral et al., 2007).

An important question of this research was to study timing of daily motor activity and psychopathology. However, we have found no association with disrupted timing of the activity. Our functional data driven-models have instead shown similar asso-

ciations to our previous analyses on NESDA data (Difrancesco et al., 2019a; Minaeva, Booji, et al., 2020) indicating that current depressive and/or anxiety disorders and more severe symptoms were associated with lower physical activity level but not with preference for eveningness. These results may suggest that perhaps the use of daily indices of motor activity is enough when studying the association with psychopathology. On the other hand, we have only evaluated group level differences; studying differences at the individual level may be important to explore. For instance, by using a idiographic approach (i.e., study associations that differ between time points or between individuals), it may be possible to study the dynamics between daily motor activity and depression/anxiety (Rosmalen et al., 2012), and help identify patients in whom activity is strongly predictive of mood. Collecting more empirical data in clinical practice is necessary to establish whether this is a promising approach.

Strengths

An important strength of this paper is the use of functional data analysis, which is a useful statistical tool for data exploration and visualization. By providing a graphical representation of motor activity and circadian rhythms, functional data analysis can help to identify specific patterns. This could help to generate new hypotheses which could in turn contribute to the improvement of treatment of circadian disturbances. Functional data analysis could also be used to predict future outcomes of treatment. For instance, the previous study of Zeitzer et al., (Zeitzer et al., 2018) has shown that low daytime activity and having a late afternoon peak extracted with fPCA are predictive of higher mortality rate in community-dwelling older men, although it remains to be investigated whether fPCA components add to the prediction over traditional actigraphy measures. Daily curves of motor activity could be potentially used also in predictive models to pick up early signs of recovery or non-response, and if predictive, could inform clinicians in monitoring treatment response or treatment planning.

Limitations

The current study was limited by several factors. Data is observational and cross sectional, and so the associations cannot be inferred to be causal. As this study is formed of individuals participating in the fifth wave of a prospective cohort, there may be a selection bias towards highly motivated individuals. Future studies may investigate whether our results may be replicated in a wider population with and without depression and anxiety. Actigraphy provides only an indirect assessment of circadian rhythm, however, has the advantage of continuously monitoring over a relatively long period of time. Not all functional components were easily interpretable. While the first two components are (possibly) indicative of the overall level of activity and the time-of-day preference for morningness or eveningness, the third and fourth components need to be replicated in order to provide a better interpretation and validity.

Conclusions

Our study showed that features of daily motor activity extracted with functional Principal Component Analysis reflect commonly studied factors such as the daily activity level and the time-of-day preference for morningness or eveningness . Age, work status and seasons were the most strongly associated with patterns of daily activity and had time-varying impact on daily motor activity. Presence and severity of depressive and anxiety disorders were associated with an overall lower activity pattern but no differences in the timing of activity. Beside psychopathology, sociodemographic, health and lifestyle, and sampling factors were independently associated with overall lower activity pattern.

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The role of depressive symptoms and symptom dimensions in actigraphy-assessed sleep, circadian rhythm and physical activity

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Abstract

Background: Considering the heterogeneity of depression, distinct depressive symptom dimensions may be differentially associated with more objective actigraphy-based estimates of physical activity (PA), sleep and circadian rhythm (CR). We examined the association between PA, sleep, and CR assessed with actigraphy and symptom dimensions (i.e., mood/cognition, somatic/vegetative, sleep).

Methods: 14-day actigraphy data of 359 participants were obtained from the Netherlands Study of Depression and Anxiety. PA, sleep, and CR estimates included gross motor activity (GMA), sleep duration (SD), sleep efficiency (SE), relative amplitude between daytime and night-time activity (RA) and sleep midpoint. The 30-item Inventory of Depressive Symptomatology was used to assess depressive symptoms, which were categorised in three depression dimensions: mood/cognition, somatic/vegetative and sleep.

Results: GMA and RA were negatively associated with higher score on all three symptom dimensions: mood/cognition (GMA: β= -0.155, $p<0.001$; RA: β= -0.116, $p=0.002$), somatic/vegetative (GMA: β= -0.165, $p<0.001$; RA: β= -0.133, $p<0.001$), sleep (GMA: β= -0.169, $p<0.001$; RA: β= -0.190, $p<0.001$). The association with sleep was more pronounced for two depression dimensions: longer SD was linked to somatic/vegetative (β=0.115, $p=0.015$) dimension, and lower SE was linked to sleep (β= -0.101, $p=0.011$) dimension.

Conclusion: As the three symptom dimensions were associated with actigraphy-based low PA and dampened CR, these seem to be general indicators of depression. Sleep disturbances appeared more linked to the somatic/vegetative and sleep dimensions; the effectiveness of sleep interventions in patients reporting somatic/vegetative symptoms may be explored, as well as the potential of actigraphy to monitor treatment response to such interventions.

Keywords: Actigraphy; Major Depressive Disorder, symptom dimensions

Introduction

Major depressive disorder (MDD) is a highly prevalent disorder, associated with high disability (Murray et al., 2012). It often has a chronic course (Verduijn et al., 2017) and a third of the patients experience poor treatment outcomes (Gaynes et al., 2009). Despite the challenges in finding consensus regarding classification, diagnosis and treatment, there has been a recent and significant increase in research to identify novel methods to measure, unravel etiology, and treat depressive disorders. Actigraphy, an ecologically valid method to objectively measure disturbances in sleep, circadian rhythm and physical activity, has become widely used in depression research.

Several studies, including the systematic review of Burton et al. (2013) and our previous work (Difrancesco et al., 2019; Minaeva et al., 2020), have shown that depressive disorders and symptoms are associated with lower daily activity (Helgadóttir et al., 2015; Hori et al., 2016; Stubbs et al., 2016) and circadian rhythm amplitude (Lyall et al., 2018). The association between actigraphy measures of sleep and depression is less clear. Although night-time activity level appears to be higher in patients with depression (Burton et al., 2013), this is not always reflected in actigraphy measures of sleep duration and sleep efficiency. Despite studies assessing sleep with self-reported questionnaires have shown that both insomnia and hypersomnia are associated with depression (Nutt et al., 2008; van Mill et al., 2010), our previous results with actigraphy have found that higher severity of depressive symptom is associated with longer (but not shorter) sleep duration (Difrancesco et al., 2019). Depression is however heterogeneous in its presentation and these results may not be generalizable to all patients.

Symptoms vary substantially in patients with depression and opposite clinical presentations occur. For instance, both insomnia and hypersomnia (Nutt et al., 2008) and psychomotor retardation and agitation (Avery & Silverman, 1984) are symptoms of depression. Considering that 1030 unique DSM-5 symptom profiles have been found among 3703 patients with MDD (Fried & Nesse, 2015), substantial symptom variation occurs among individuals who all qualify for the same DSM-5 diagnosis. Thus, as the 'depression' label provides limited information about the particular problems experienced by a patient, some researchers have moved away from traditional methods of diagnosis such as the DSM-5 and have focused on symptom dimensions (Fried, 2017). Although approaches to identify symptom dimensions vary, empirical methods such as factor analyses have been employed to identify symptoms dimensions or factor structures underlying self-reported questionnaires on depressive symptoms in a population based sample, such as the often used Inventory of Depressive Symptomatology (IDS) (Hegeman et al., 2012; Rush

et al., 1996; Wardenaar et al., 2010). Most studies illustrate the existence of three major symptom dimensions: mood/cognition, somatic and sleep symptom dimensions (Hegeman et al., 2012; Rush et al., 1996; Wardenaar et al., 2010).

Although it is clear that depression is heterogeneous, little research has focused on the role of symptoms dimensions assessed with severity measures in sleep and circadian rhythm disturbances and physical inactivity as assessed objectively with actigraphy. As cognitive impairments have been linked to sleep problems (Mantua & Simonelli, 2019) and physical inactivity has been related to somatic/energy related symptoms (Puetz, 2006), a differential association with symptom dimensions may be expected. However, this has not properly been investigated so far. A better understanding would be of benefit for the diagnosis and treatment of depression. For instance, pharmacological treatment, psychotherapy and chronotherapies to treat sleep and circadian rhythm problems can be especially administered to patients with specific symptom dimensions.

The aim of this study was to examine the association between actigraphy-based physical activity, sleep and circadian rhythm with symptom dimensions (i.e., cognition/mood, somatic, sleep). The association with individual depressive symptoms was also explored to further check on the consistency of findings for symptoms within dimensions. To address these questions, we used data from the Netherlands Study of Depression and Anxiety (NESDA) which includes persons without and with current or remitted depressive and/or anxiety disorders. As depression and anxiety are highly comorbid disorders (Lamers et al., 2011; Rodney et al., 1997) and we previously mentioned limitations in traditional diagnosis method, using the full sample gives the opportunity to investigate the associations on a larger spectrum of severity.

Method

Sample

Participants from the Netherlands Study of Depression and Anxiety (NESDA) were selected to participate in the Ecological Momentary Assessment (EMA) & Actigraphy sub-study (NESDA-EMAA). Details about NESDA have been provided extensively before (Penninx et al., 2008). NESDA was designed to investigate the course of depressive and anxiety disorders over a period of several years and the factors that influence the development and prognosis of such disorders. NESDA participants were initially included at the baseline assessment in 2004-2007 (n=2981), and seen for the fifth time at the nine-year follow-up assessment wave (2014-2017, n=1776) for a follow-up interview. At that time, also 367 sib-

lings of NESDA participants were added, bringing the 9-year follow-up sample to 2143 subjects. At this wave, 384 participants enrolled for the EMAA sub-study. The NESDA study, including NESDA -EMAA, was approved by the VUmc ethical committee (reference number 2003/183) and all respondents gave informed consent for both the regular interview and the EMAA sub-study. See for a flowchart of the NESDA-EMAA in our previous work (Difrancesco et al., 2019). Participants were eligible if they had a smartphone or were willing to use a smartphone provided by the study, and were willing to wear a wrist-worn actigraphy device. Participants to the EMAA-sub-study were provided with a GENEActiv device (Activinsights Ltd, Kimbolton, UK). Participants wore the wrist-worn GENEActiv actigraphy device for 14 days on their non-dominant wrist. Of the 384 participants included in the NESDA-EMAA study, 14 had no available actigraphy data for several reasons, such as technical failure, resulting in 370 (96.4%) participants with available data. According to previously published criteria (da Silva et al., 2014), participant's actigraphy data were included in analyses if at least one week day and one weekend day of usable data was available, with at least 16 hours recorded per day and per night. The final sample was composed of 359 (93.5%) participants with on average 13.68 ± SE 1.26 valid days, of whom 90% completed the protocol for 14 days.

Depressive symptoms and symptom dimensions

The Dutch version of the 30-item Inventory of Depressive Symptomatology, self-report (IDS) (Rush et al., 1996) was used to assess depressive symptoms (0 = no problems to 3 = severe problems) in the previous 7 days. A total sum score can be calculated (range, 0–84), with higher scores indicating higher levels of depressive symptomatology. Validity and reliability have been shown before, with Cronbach's alpha ranging from 0.92 to 0.94 (Rush et al., 1996). We used three dimensional depression symptom sum scores based in a prior factor analyses in NESDA (Wardenaar et al., 2010): mood/cognition, somatic/vegetative and sleep. The mood/cognition dimension consisted of the 16 items: feeling irritable, interpersonal sensitivity, feeling sad, diminished quality of mood, feeling anxious or tense, diminished capacity of pleasure/enjoyment, diminished reactivity of mood, diminished interest in people/activities, suicidal thoughts, future pessimism, concentration/decision making problems, self-criticism and blame, psychomotor retardation, reduced interest in sex, low energy level/fatigability, leaden paralysis. The somatic/vegetative domain included 9 items: panic/phobic symptoms, psychomotor agitation, decreased weight, increase in appetite, other bodily symptoms, decrease in appetite, increased weight, constipation/diarrhoea, aches and pains. Finally, the sleep domain included 4 items: early morning awakening, problems sleeping during the night, problems falling asleep, sleeping too much. The item 'diurnal variation (worse in the morning)' did not belong to any domain in the factor analyses and was therefore used only in our exploratory analyses with individual symptoms.

Actigraphy estimates of sleep, circadian rhythm and physical activity

In this study, the accelerometer was set to sample at 30 Hz and raw actigraphy data was analysed using an open source R package, GGIR (version 1.5-18). Actigraphy data were gathered after the depressive symptoms assessment with a median number of 23 days between the two assessments. As described before (Difrancesco et al., 2019), we used objective indicators of sleep, circadian rhythm and physical activity. Sleep was assessed as total sleep duration per night [in hh:mm] and sleep efficiency per night [%]. Circadian rhythm was assessed by the relative amplitude (RA) between daytime and night-time activity per day and sleep midpoint [clock time]. RA describes the amplitude between the activity during the day and the night; lower RA means a dampened circadian rhythm amplitude suggesting lower activity during the day and higher activity during the night. Sleep midpoint is a proxy of chronotype or preference for morningness/eveningness; later sleep midpoint means a preference for evening chronotype. Exploratory analyses showed that RA and sleep midpoint have low correlation and therefore they describe different aspects of circadian rhythm (Supplemental material Table S1). Physical activity is indexed/expressed given as gross motor activity (GMA) per day [milli-gravity (mg), 1g = 9.81m/s^2]. Daily estimates of each variable were used in the current study.

Covariates and descriptive variables

Covariates were age, sex and education level expressed in years at the time of the NESDA EMAA sub-study. These covariates were selected as they have an established theoretical association with depression and with sleep, circadian rhythm and physical activity levels, and have been regularly used in similar studies (Droomers et al., 2001; Stamatakis et al., 2007).

DSM-IV based diagnoses of depressive disorders (dysthymia and major depressive disorder) and anxiety (social anxiety disorder, panic disorder with and without agoraphobia, agoraphobia and generalized anxiety disorder) were established with the Composite International Diagnostic Interview (CIDI, version 2.1)(Wittchen, 1994). The interviews were conducted at the regular interview by specially trained clinical research staff. Participants were divided into three groups for descriptive purposes only: 1) a group with no lifetime depressive and/or anxiety disorders, 2) a group with remitted depressive and/or anxiety disorders (having a lifetime, but not current (6-month) diagnosis), and 3) a group with current depressive or anxiety disorder in the past 6 months.

Antidepressant use was based on drug container inspection, and medications were coded according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification. Antidepressant use was considered present if participants reported using it more than 50% of the time. Antidepressants included were selec-

tive serotonin reuptake inhibitors (SSRIs, ATC code N06AB), tricyclic antidepressant (TCA, ATC code N06AA) and other antidepressants (ATC codes N06AF, N06AG, N06AX).

Statistical analyses

Distributions of all variables were checked on normality with QQ plots. Non-normally distributed outcomes were transformed with Log-transformation (gross motor activity) or with Box-Cox transformation (sleep duration, sleep efficiency, relative amplitude between daytime and night-time activity level and sleep midpoint). Correlation of symptom dimensions were explored using Pearson correlation coefficient to assess the degree of intercorrelation of symptom dimensions. The association of actigraphy estimates with symptom dimensions and individual symptoms was tested in separate models using Generalized Estimating Equations (GEE) corrected for covariates and with each actigraphy estimate as outcome. GEE was used to account for correlations between repeated days per person. Separate models were ran for each symptoms dimension and each individual symptoms; each model was adjusted for age, sex and education level. As having a current/remitted diagnosis of depression and/or anxiety is highly correlated with severity of symptoms, adjustment for diagnostic groups was not performed.

All analyses were performed with the statistical software R (version 1.0.143). A p-value < 0.05 was considered statistically significant. Correction for multiple testing by using false discovery rate (FDR) was applied when testing the association with symptom dimensions adjusting for the number of outcomes (n=5) and symptom dimensions (n=3). This was not done for individual symptoms, as our aim was to visually explore overall patterns to help understand whether symptoms follow the same patterns as the dimension they belong to or not. Specifically, we visually assessed the univariate associations of individual symptoms with actigraphy measures by using a forest plot presenting the standardised coefficients and the 95% confidence intervals. In this way, it was possible to visualise whether the associations with individual symptoms followed the same direction as the dimension they belong to and whether some symptoms were outliers.

Results

Demographics and descriptive

Table 1 shows demographics and descriptive in our sample. The average age of the sample was 49.5 ± 12.6 years, of whom 63.7% was female and with a duration of education of 12.9 ± 3.1 years. Most of the persons included had a lifetime diagnosis of depressive and/or anxiety disorders: 93 (26.0%) persons had current depressive and/

Table 1: Demographics and psychopathology in the NESDA sample

	All subjects (n = 359)
Demographics	
Age, mean (SD)	49.5 (12.6)
Female, n (%)	228 (63.7 %)
Education [year], mean (SD)	12.9 (3.1)
Psychopathology	
Depressive and/or anxiety disorders	
No lifetime disorders, n (%)	90 (25.0 %)
Remitted disorder, n (%)	176 (49.0 %)
Current disorder, n (%)	93 (26. %)
IDS Score, mean (SD)	14.2 (11.7)
Mood/Cognition symptom score (IDS), mean (SD)	8.4 (7.9)
Somatic/vegetative symptom score (IDS), mean (SD)	5.1 (3.6)
Sleep symptom score (IDS), mean (SD)	3.0 (2.0)
Antidepressant use, n (%)	71 (19.7%)

or anxiety disorders, 176 (49.0%) persons had remitted depressive and/or anxiety disorders and only 90 (25.0%) persons had no depressive and/or anxiety disorders. The average severity of depressive symptoms in the sample was 14.2 ± 11.7 on the IDS total score.

Symptoms dimensions were moderately to strongly correlated (correlation ranged from 0.41 for the somatic/vegetative and sleep dimensions, to 0.75 for mood/cognition and somatic/vegetative dimensions, not tabulated and available upon request).

Association of sleep, circadian rhythm and physical activity with dimensions

14-day lower gross motor activity and relative amplitude between daytime and nighttime activity level were significantly associated with all three symptom dimensions (Table 2, all $p<0.05$). The associations with actigraphy-based sleep were more pronounced for two dimensions. Longer sleep duration was significantly associated with higher somatic/vegetative symptom dimension score (Table 2; $\beta= 0.113$, $p=0.021$) but not with mood/cognition and sleep symptom dimension scores. Lower sleep efficiency was associated with higher sleep symptom dimension score (Table 2; $\beta= -0.101$, $p=0.011$) but not with mood/cognition and somatic/vegetative symptom dimension scores.

Table 2: Univariate association* between symptom dimensions and sleep, circadian rhythm and physical activity (n = 359)

	Physical activity		
	Gross motor activity		
Symptom dimensions	β	SE	p
Mood/Cognition	-0.163	0.043	**<0.001**
Somatic/vegetative	-0.146	0.038	**<0.001**
Sleep	-0.169	0.038	**<0.001**

*GEE model (outcomes = sleep, circadian rhythm and physical activity) adjusted for age, sex and education level. Correction for multiple testing by using false discovery rate (FDR).

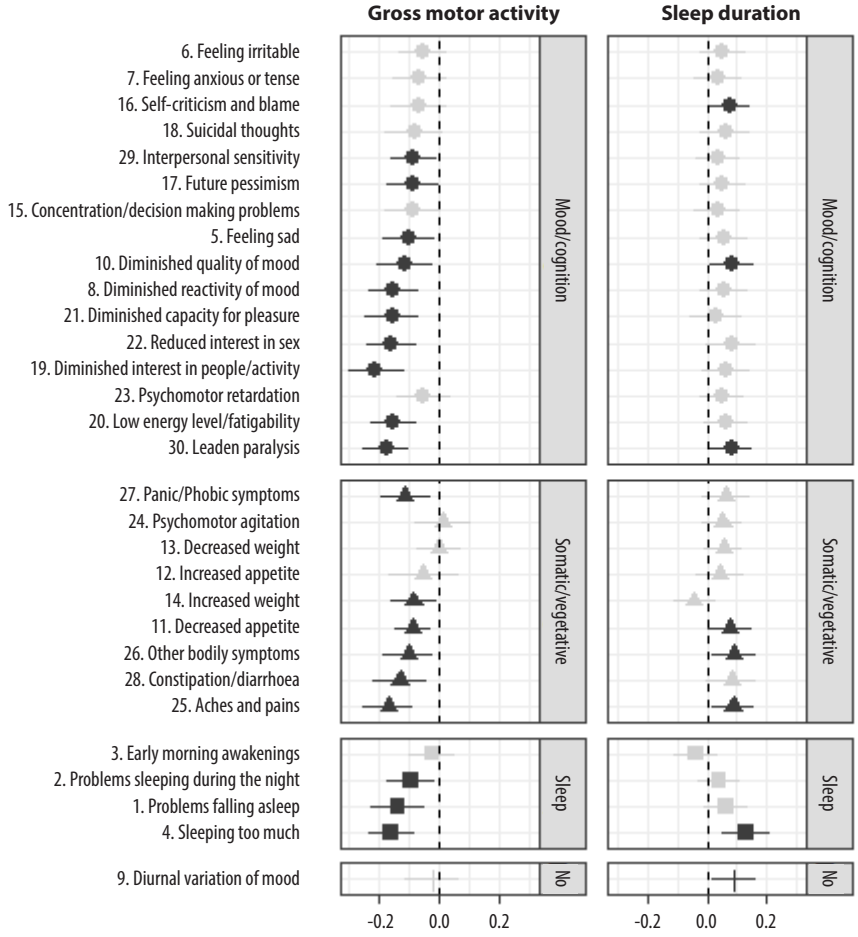

Figure 1: Univariate association between individual IDS symptoms and the actigraphy measures: physical activity (i.e., gross motor activity), sleep (i.e., sleep duration, sleep efficiency) and circadian rhythm (i.e., relative amplitude, sleep midpoint) in all sample (n = 359). Error bars represent 95% confidence intervals. Adjusted for age, sex, and education. Note: ● = mood/cognition, ▲ = somatic/vegetative, ■ = sleep, I = no dimension; black = p0<.05, grey = p>0.05.

Table 2: (continued)

Sleep						Circadian rhythm					
Sleep duration			Sleep efficiency			Relative amplitude between daytime and nighttime activity			Sleep midpoint		
β	SE	p	β	SE	p	β	SE	p	β	SE	p
0.081	0.042	0.066	-0.048	0.036	0.200	-0.122	0.036	**0.003**	0.091	0.047	0.066
0.113	0.044	**0.021**	-0.043	0.038	0.263	-0.116	0.039	**0.008**	0.090	0.046	0.066
0.078	0.039	0.066	-0.101	0.036	**0.011**	-0.190	0.039	<**0.001**	0.069	0.043	0.132

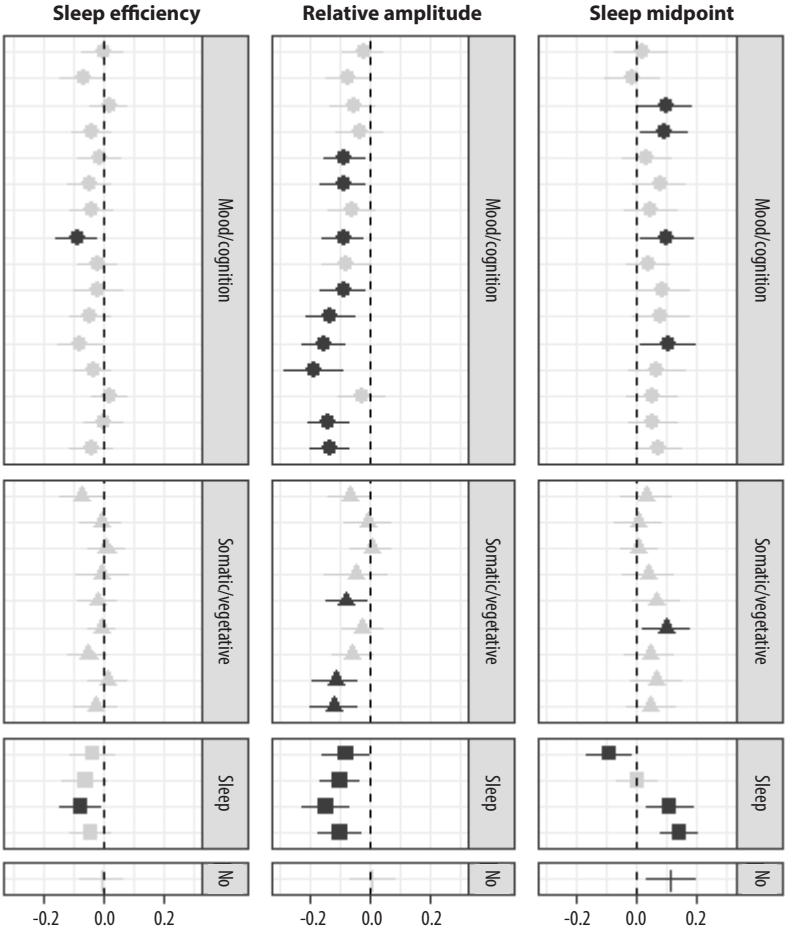

Figure 1: (continued)

Patterns of sleep, circadian rhythm and physical activity in individual symptoms

Figure 1 shows the association of individual symptoms with 14-day physical activity, sleep and circadian rhythm patterns. Associations of gross motor activity and relative amplitude between daytime and night-time activity level showed more significant associations with individual symptoms compared to other actigraphy variables.

For GMA and RA 63% (n=19) and 53% (n=16) of all individual symptoms – spread across different dimensions - were significantly associated with lower GMA and lower RA between daytime and night-time activity level. Other symptoms – although not significantly associated - followed a similar, expected negative direction in their associations with GMA and RA. By inspecting the forest plots, no differential association of GMA and RA with symptom dimensions can be confirmed.

When considering actigraphy-based sleep duration, eight of the in total thirty individual symptoms were significantly associated with longer sleep duration. Although most of somatic/vegetative symptoms followed the same direction in the association with sleep duration, 'increased weight' deviated from the overall pattern. Also, as expected 'early morning awakenings' in the sleep dimension was associated with objective shorter sleep duration.

Although not captured in the analyses using symptom dimensions, 30% (n=9) of all symptoms were associated with later sleep midpoint. Of these seven symptoms, four belong to the mood/cognition dimension and three belong to the sleep dimension. Most individual symptoms were following the same positive direction in the association with sleep midpoint, with the exception of 'early morning awakenings' that showed an – expected – negative direction. This may possibly show that there is more heterogeneity in terms of effect estimates for individual symptoms.

Only two symptoms were associated with lower sleep efficiency. As expected, all sleep symptoms were following the same negative direction in the association with sleep efficiency as shown by the sleep dimension.

Discussion

This is the first study to examine 14-day actigraphy estimates of sleep, circadian rhythm and physical activity and their relationship with symptoms and symptom dimensions of depression. As all three symptom dimensions were associated with lower and dampened 14-day physical activity and circadian patterns, it could be concluded that physical inactivity and low circadian amplitude are general indicators of depres-

sive symptom severity. However, sleep disturbances may be more specifically linked to somatic/vegetative and sleep symptom dimensions, as associations with longer sleep duration and lower sleep efficiency were more pronounced for these symptom dimensions. While exercise and behavioural activation may be used as adjunctive treatments in all patients with depression, sleep interventions may be especially effective in people with more self-reported somatic/vegetative and sleep symptoms.

While few studies have suggested that actigraphy may serve as an objective measure of psychomotor retardation in patients with depression (Krane-Gartiser et al., 2015), our results seem to support that physical inactivity is a general feature of depression (Burton et al., 2013) and symptom severity (Minaeva et al., 2020). This was also reflected in our analyses with individual symptoms, as over 60% of depressive symptoms – across different symptom dimensions - were associated with low gross motor activity with moderate effect sizes. The association between physical activity and depression has been studied before and appears to be bidirectional. Patients with depression are typically less active, and they experience a range of barriers to engaging in physical activity such as depressive symptoms, higher body mass index, physical co-morbidity, and lower self-efficacy (Vancampfort et al., 2015). Low levels of physical activity increase the risk of depression (Mammen & Faulkner, 2013) and, physical activity and exercise (i.e. structured physical activity) can improve depressive symptoms (Schuch et al., 2016). A large meta-analysis in the general population (Biswas et al., 2015) demonstrated that sedentary behaviour is associated with an increased risk of developing cardiovascular disease, type 2 diabetes, cardiovascular and all-cause mortality. As persons with depression are less active than the general population, they encounter additional risks in developing cardiovascular and chronic diseases and mortality. Physical activity and behavioural activation, predominantly through exercise, may produce an antidepressant effect through multiple biological and psychosocial pathways (Kandola et al., 2019). Neuroplasticity, neuroendocrine responses, inflammation and oxidative stress have been suggested to play a role at a biological level. Several psychosocial factors accompany, and potentially interact with, these biological changes to influence depression, such as self-esteem (Kandola et al., 2019). While there is less research into the psychosocial benefits of exercise on depression, they are likely to be of parallel importance. As we observed lower physical activity across all symptom dimensions, physical activity and behavioral activation may be of help to all patients with depression as it may produce an antidepressant effects through multiple biological and psychosocial pathways.

Similarly, dampened circadian amplitude was generally associated with all symptom dimensions, supporting previous findings on the association between dampened rhythms and mood disorders (Lyall et al., 2018). As reviewed by Vadnie and McClung (2017), multiple mechanisms can explain the association between circadian

rhythm disruptions and mood disorders including depression. One of the main theories is that disrupted circadian rhythms in the master pacemaker, or suprachiasmatic nucleus (SCN) may be the cause of mood disturbances. However, also other environmental factors, such as light, or genetic perturbations may influence mood independently from the central clock. Additionally, other studies have suggested that sleep and circadian rhythm disturbances may be symptoms of mood disorders. As dampened circadian amplitude was associated with all symptom dimensions, circadian rhythm interventions such as behavioural activation may be administered as adjunctive treatment to all patients with depression.

When studying sleep, it is important to make a clear distinction between subjective and objective sleep measures. The first provides information about a person's perception about his/her sleep quantity and quality. The latter refers to the objective measure of sleep duration and sleep efficiency with actigraphy. When assessing subjective sleep, persons diagnosed with depression often report sleep disturbances such as insomnia and hypersomnia (Nutt et al., 2008; van Mill et al., 2010). While in our previous work using actigraphy (Difrancesco et al., 2019) we have shown that depressive symptom severity is associated with longer objective sleep duration, in these follow-up analyses the association appeared to be more pronounced in patients with somatic/vegetative symptoms. We found a possible explanation for these findings. Persons with more somatic/vegetative symptoms experience more physical complains, such as aches and pains, bodily symptoms, than may directly impact on their ability to be physically active and resulting in more sleep disturbances. The sleep dimension itself may be problematic as it combines opposite clinical presentations (i.e., insomnia and hypersomnia) for which the associations with objective sleep is expected in opposite directions. However, as could be expected, lower sleep efficiency assessed objectively with actigraphy was associated with sleep symptoms assessed with self-ratings. Although in our previous work we did not find an association between objective sleep efficiency and subjective sleep assessed with the Women's Health Initiative Insomnia Rating Scale (Difrancesco et al., 2019), objective measure of sleep efficiency seems indicative of self-reported sleep disturbances assessed with the IDS. Sleep interventions may focus not only on patients reporting sleep problems, but also on those reporting somatic/vegetative symptoms. Actigraphy may be used to assess the effectiveness of such interventions.

This study has several limitations. First, although we adjusted for multiple testing, we explored several associations when looking at individual symptoms and that may lead to chance findings. However, we aimed to look more at broader patterns than to focus on specific symptoms. Second, the assessment of depression symptoms and actigraphy were not done at the same time, although there was a median number of 23 days between the two assessments. Another limitation is that sleep and circadian

rhythms are complicated concepts and actigraphy may provide only an indirect and rough estimate of them based on wrist movement, whereas polysomnography is the gold standard. In addition, sleep midpoint was evaluated during the entire period and it can be argued that chronotype is often assessed with sleep midpoint on free days corrected for the sleep debit accumulated during the working days. However, sleep midpoint measured with actigraphy provides a valid approximation of chronotype and it is moderately correlated with it as shown by Santisteban et al. (2018). Although not assessed in our study, shift work may affect sleep schedules and therefore it may influence the results on the association with sleep and circadian rhythms (James et al., 2017). While data did not show reversed activity/sleep patterns as would be expected with night shifts, early and late day shifts could have occurred and may also have an impact. Individual symptoms may fit in different symptoms dimensions, and classifications are not always consistent across studies. We based our classification on those of Wardenaar et al. (2010), in which classification, psychomotor retardation and low energy level/fatigability for instance were part of the mood/cognition dimension, but they could also be fit in the somatic/vegetative dimension. However, by looking at individual symptom patterns we found consistency as most of symptoms follow the same direction in the associations as the dimension they belong to. Although we did not investigated the role of anxiety, as Wardenaar et al. (2010) have shown that symptom dimensions were consistent across diagnostic groups (i.e., remitted depression, lifetime anxiety, healthy controls), comorbid anxiety does not seem to confound the studied associations. Important strength of the study is the attempt to investigate the heterogeneity of depressive symptoms with actigraphy in a relatively large sample. Another important strength is that on average 14 days of actigraphy data per participant were available.

To conclude, this is the first study to examine the different symptom dimensions of depression and their association with several objective indicators of physical activity, sleep, circadian rhythm gathered with wrist-worn actigraphy devices. As lower physical activity level and dampened circadian amplitude were associated with higher scores on all three dimensions, lower physical activity level and dampened circadian rhythms appeared to be general indicators of depression and depression severity. Disturbances in objective sleep were more pronounced for somatic/vegetative symptoms, suggesting that longer sleep duration may be more closely linked to this dimension. Sleep interventions may focus not only on patients reporting sleep problems, but also on those reporting somatic/vegetative symptoms. Physical activity, behavioural activation, and circadian rhythm interventions may be not limited to groups of patients based on their symptoms, but may be promoted in all patients with depression. However, clinical implementation awaits further evidence based on empirical data if indeed actigraphy may be used to monitor treatment response of such interventions.

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The day-to-day bidirectional longitudinal association between objective and self-reported sleep and affect: *An ambulatory assessment study*

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Introduction

Depressive and anxiety disorders are highly prevalent psychiatric disorders (Zorn et al., 2017), associated with high disability (Vos et al., 2016), with at least a third of patients experiencing poor treatment outcomes (Gaynes et al., 2009). Disturbances in mood and sleep are core symptoms of affective disorders and are therefore intricately linked to each other (Kahn et al., 2013).

Persons with affective disorders typically report low levels of positive affect (i.e., anhedonia) and high levels of negative affect (i.e., sad mood, guilt) on questionnaire and interview measures (American Psychiatric Association, 2013; Peeters et al., 2006). Sleep disturbances in affective disorders can entail difficulty initiating or maintaining sleep, or early morning awakening (insomnia), but also sleeping too much (hypersomnia), or both (Staner et al., 2006). As affect and sleep can fluctuate on a daily basis (Fung et al., 2014; Peeters et al., 2006), ambulatory assessments using mobile technologies (i.e., actigraphy devices and smartphones) may offer new opportunities to study the longitudinal day-to-day bidirectional associations between sleep and momentary affective states (i.e., positive and negative affect). With repeated measures throughout the day or even continuous data collection, high resolution data can be obtained that allows us to study associations within much smaller time-scales (within day or across days). Determining the extent to which sleep and affect interact on a daily level will provide additional insight and can inform on the usefulness of daily monitoring using mobile technologies and on target areas for (and timing of) user-feedback & micro-interventions.

Ecological Momentary Assessment (EMA) can provide detailed and frequent information on self-reported sleep quality and quantity, and on variations in mood and affect (Ebner-Priemer & Trull, 2009) assessed via a smartphone. This allows the examination of day-to-day bidirectional associations between self-reported sleep quality and affect. Better sleep quality has been found to predict improved affect in healthy controls as well as persons with depressive (Bouwmans et al., 2017; Bower et al., 2010; Triantafillou et al., 2019) and anxiety disorders (Triantafillou et al., 2019). Better affect has been found to be predictive of better self-reported sleep quality in both healthy controls as well as persons with depressive and anxiety disorders (Triantafillou et al., 2019).

Besides EMA, another ambulatory assessment, actigraphy, provides objective and daily measurements of a person's sleep quality and quantity in their living environments (Martin & Hakim, 2011). To date, less studies have examined the relationship between objectively assessed sleep and affect. Two studies found no bidirectional association between actigraphy-assessed sleep quality and mood in elderly (Parsey &

Schmitter-Edgecombe, 2019) and between sleep duration and mood in a sample of persons with lifetime diagnosis of unipolar and bipolar depression and healthy controls (Merikangas et al., 2019). As in our previous study using the current sample we found that self-reported sleep and actigraphy-based sleep are often poorly correlated (Difrancesco et al., 2019), passive monitoring of sleep with wrist-worn actigraphy may provide new opportunities for sleep monitoring in patients with depression and anxiety.

The aim of this study was to investigate the (1) day-to-day bidirectional longitudinal association between sleep measures and positive and negative momentary affect from ambulatory assessments using mobile technologies, and (2) whether these associations differ in persons with and without current or remitted depression and/or anxiety disorders.

Method

Sample

Participants from the Netherlands Study of Depression and Anxiety (NESDA) were selected to participate in the Ecological Momentary Assessment (EMA) & Actigraphy sub-study (NESDA-EMAA). Details about NESDA have been provided extensively before (Penninx et al., 2008). NESDA was designed to investigate the course of depressive and anxiety disorders over a period of several years and the factors that influence the development and prognosis of such disorders. NESDA participants were initially included at the baseline assessment in 2004-2007 (n=2981), and seen for the fifth time at the nine-year follow-up assessment wave (2014-2017, n=1776) for a follow-up interview. At that time, also 367 siblings of NESDA participants were added, bringing the 9-year follow-up sample to 2143 subjects. At this wave, 384 participants enrolled for the EMAA sub-study. The NESDA study, including NESDA -EMAA, was approved by the VUmc ethical committee (reference number 2003/183) and all respondents gave informed consent for both the regular interview and the EMAA sub-study. See for a flowchart and details of the NESDA-EMAA in our previous work (Difrancesco et al., 2019)(Schoevers et al., 2020).

Participants of the NESDA-EMAA study were asked to fill out the EMA assessments, an electronic diary on their smartphone, and to wear a wrist-worn actigraphy device (GENEActiv, Activinsights Ltd, Kimbolton, UK) for 14 days. In case participants did not possess a smartphone, or their phone was not suitable for participation (e.g. no internet bundle), a smartphone was provided for the duration of the study (n = 107, 27.9%). Participants of the EMA assessment completed a set of items 5 times a day (i.e. every 3 hours; fixed design). Of all sent EMA assessment invites

to 384 participants, only 8.72% were missing. EMA data of 19 participants were excluded due to various reasons such as low response rate (response rate below 50%; in line with Servaas et al. (2017)) or technical failure, resulting in 365 participants with available data. Participants wore the wrist-worn GENEActiv actigraphy device on their non-dominant wrist, day and night. Of the 384 participants included in the NESDA-EMAA study, 14 had no available actigraphy data for several reasons, such as technical failure, resulting in 370 (96.4%) participants with available data. According to previously published criteria (da Silva et al., 2014), participant's actigraphy data were included in analyses if at least one week day and one weekend day of usable data was available, with at least 16 hours recorded per day and per night. The final sample was composed of 359 (93.5%) participants with on average 13.68 ± SE 1.26 valid days, of whom 90% of participants had complete 24-h actigraphy data for 14 days.

Assessment of depressive and/or anxiety disorders

As in the previous waves, at the 9-year follow-up, DSM-IV based diagnoses of depressive disorders (dysthymia and major depressive disorder) and anxiety (social anxiety disorder, panic disorder with and without agoraphobia, agoraphobia and generalized anxiety disorder) were established with the Composite International Diagnostic Interview (CIDI, version 2.1)(Wittchen, 1994). The interviews were conducted by specially trained clinical research staff. Participants were divided into three groups: 1) a group with no lifetime depressive and/or anxiety disorders, 2) a group with remitted depressive and/or anxiety disorders (having a lifetime, but not current (6-month) diagnosis), and 3) a group with current depressive or anxiety disorder in the past 6 months.

Ambulatory assessment variables

Positive and negative momentary affect states

EMA questionnaires were assessed five times a day and had up to 31 items per time point. They contained both momentary affect state items and other items on activities, context and lifestyle. To assess momentary affect states, items covering high and low arousal, positive and negative momentary affect states were used from the Uncovering the Positive Potential of Emotional Reactivity study (Bennik, 2015). Included items were: I feel satisfied, relaxed, upset, cheerful, irritated, listless, down, energetic, enthusiastic, nervous, bored, calm, and anxious. All items were rated on a 7-point Likert scale ranging from '1 = not at all' to '7 = very much'. As used previously (Schoevers et al., 2020), a positive affect (PA) subscale was calculated by taking the average of PA items (at this moment I feel satisfied, relaxed, cheerful, energetic, enthusiastic, and calm). Similarly, a negative affect (NA) subscale was calculated by averaging all NA items (at this moment I feel upset, irritated, listless/apathic, down, nervous, bored, anxious) (Schoevers et al., 2020).

Sleep variables

Actigraphy-assessed sleep

In this study, the accelerometer was set to sample at 30 Hz and raw actigraphy data was analysed using an open source R package, GGIR (van Hees, 2017). As described before (Difrancesco et al., 2019), we used objective indicators of sleep: sleep efficiency per night [in %] and total sleep duration per night [in hh:mm]. The daily estimates were used in the current study. In short, objective sleep estimates were obtained using the GGIR package (van Hees, 2017) that uses an algorithm described extensively before (van Hees et al., 2018). This algorithm can distinguish whether inactivity periods are sleep periods without the use of sleep diaries; the algorithm has been validated on a large sample of the UK Biobank.

EMA-based sleep

Besides objectively assessed sleep duration, we also considered sleep variables collected in the EMA assessments, to get a full picture on how objective and self-reported measures relate. Self-reported sleep was assessed in each EMA questionnaire but for the purpose of this study were based on the first assessment of the day only. Included items were sleep duration ("How long did you sleep?" [in hh:mm]) and sleep quality. Sleep quality ("Did you sleep well?") was rated on a 7-point Likert scale ranging from '1 = not good' to '7 = very good'.

Covariates: age, sex and work/school days

Covariates were age, sex and work/school days at the time of the NESDA EMAA substudy. These covariates were selected as they have an established theoretical association with psychopathology and with sleep, circadian rhythm and physical activity levels, and have been regularly used in similar studies (Droomers et al., 2001; Stamatakis et al., 2007). Work/school days were identified with information from daily EMA assessment as participants were asked to document their location; if they reported their location to be at school/work at least once during a day it was counted as a work/school day.

Statistical analyses

For descriptive purpose, correlations between sleep variables were tested with Pearson's correlation.

Generalized estimating equation models (GEE) were used to test the bidirectional longitudinal association between momentary affect states assessed every three hours and self-reported/objective sleep adjusting for age, sex and work days (a summary of the performed analyses is given in Figure 1). Therefore, separate analyses were performed by first using momentary affect states (i.e., PA or NA) as outcome (Model 1) and then by using sleep variables (i.e., EMA-based sleep quality or EMA-

based sleep duration or objective sleep duration) as outcome (Model 2). Although both short and long sleep duration (defined as ≤6 hours and ≥10 hours, respectively, (Levine et al., 2003)) are often reported in persons with depression/anxiety (Nutt et al., 2008; Zhai et al., 2015), a potential relationship between short and long sleep versus normal sleep (7 ≤ hours ≤ 9) and affect was not tested. This was not done as less than 10% of our participants slept ≥10 hours in our sample (Difrancesco et al., 2019), making it impossible to have enough power to detect such effect. We therefore only used sleep duration as continuous variable in our analyses.

Data centring of momentary affect states and sleep variables was performed by within-person mean; therefore, estimates in the models indicate the effect of deviations of affect and sleep from the diurnal person-specific mean. The first-order autoregressive working correlation structure was chosen to take into account the within-person correlation over the 2-week observation period.

The same analyses were repeated to test for the moderating effect of current or remitted depressive and/or anxiety disorders. When moderation terms were significant, stratified analyses by diagnostic group were conducted to interpret and visualise the group effect.

Post-hoc analyses were performed to test the main effect and moderating effect of time of the day on the associations.

All analyses were performed with the statistical software R Studio (R Studio version 1.2.5033, R version 3.5) and the 'gee' library. A p-value < 0.05 was considered statistically significant.

Results

Demographics, ambulatory assessment variables and psychopathology

Table 1 and Figure 2 show demographics, ambulatory assessment variables and psychopathology in the NESDA EMAA subsample. The average age was 49.5 ± 12.6 years, and 63.7% were females. Of the 16920 total EMA assessments, 32.7% were on work/school days. The median momentary affect states were 5 (IQR 1.5) and 1.3 (IQR 0.9) for positive and negative affect respectively. The median sleep quality was 5 (IQR 2), while the median sleep duration was 7.5 h (IQR 1.5 h) when assessed with EMA and 7.04 h (IQR 1.7 h) when assessed with actigraphy. The median actigraphy-assessed sleep efficiency was 90% (IQR 10%). Moderate significant correlations were found between EMA-based sleep quality and EMA-based sleep duration ($r = 0.41$, $p<0.001$), and between self-reported sleep duration and

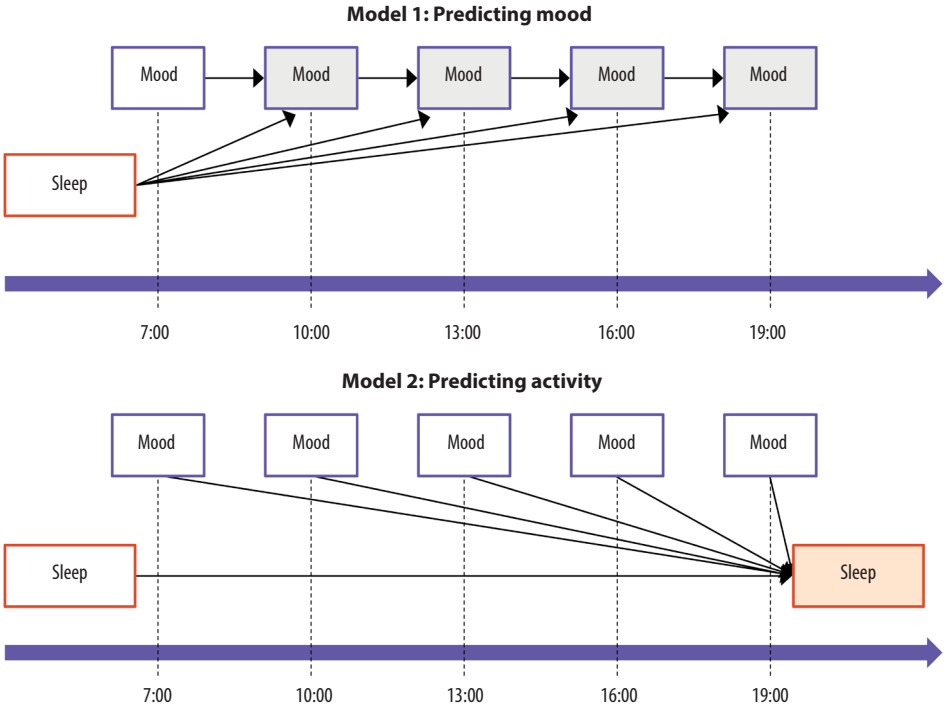

Figure 1: summary of the bidirectional longitudinal association between momentary affect states assessed every three hours and (objective and self-reported) sleep. The filled boxes indicate the outcomes. Note Model 1: as we included the previous mood rating of the same day in the model, this variable is not present for the first assessment of the day and therefore not depicted as an arrow.

Table 1: Demographics, ambulatory assessment variables and psychopathology in the NESDA sample

	Sample
N	359
Demographic and health variables	
Age, mean (SD)	49.5 (12.6)
Female, n (%)	228 (63.7 %)
Psychopathology	
Depressive and/or anxiety disorders	
No, n (%)	90 (25.0 %)
Remitted, n (%)	176 (49.0 %)
Current, n (%)	93 (25.1 %)
Antidepressant use, n (%)	71 (19.7%)

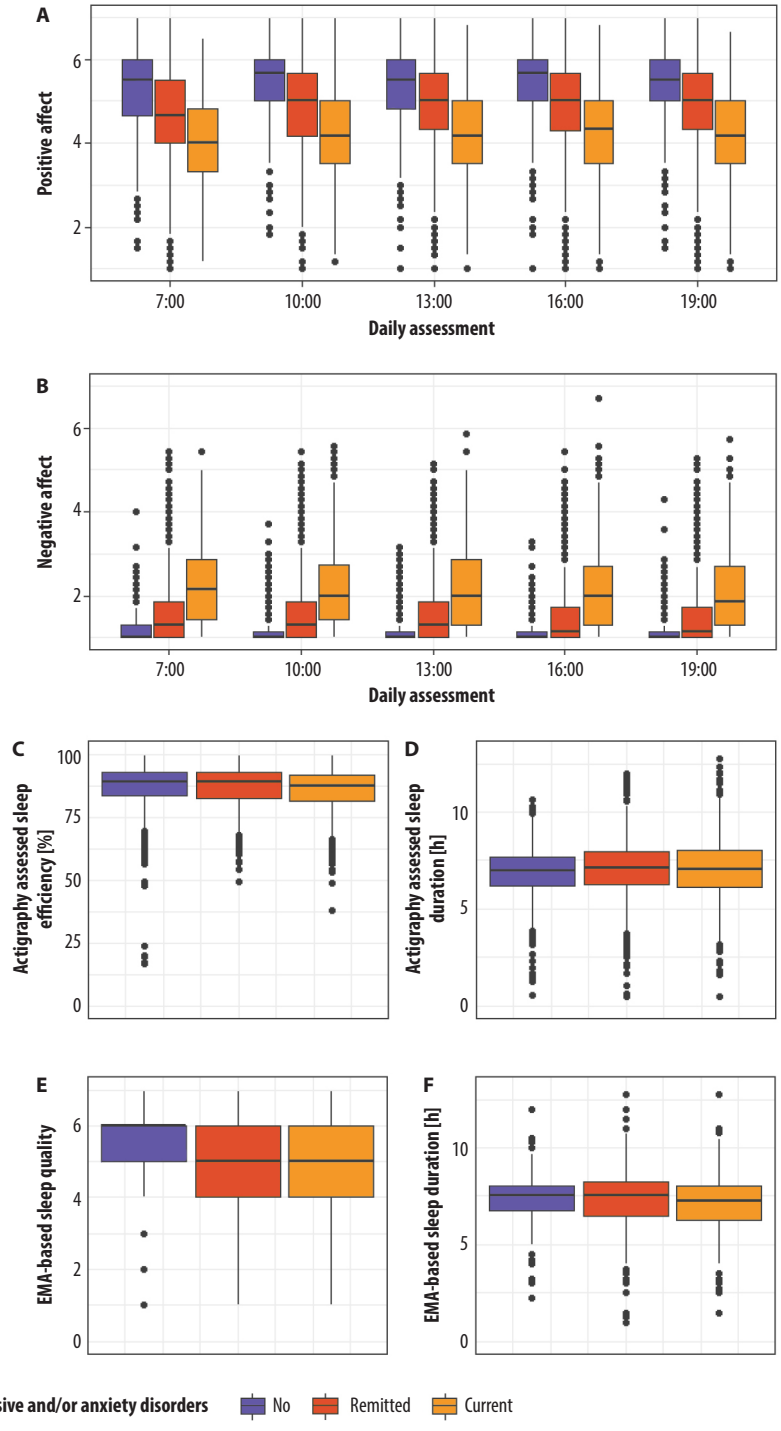

Figure 2: distribution of mood and sleep duration in the NESDA sample (n = 359): positive (A) and negative (B) affect by daily assessment and by diagnosis, actigraphy assessed sleep by diagnosis (C = sleep efficiency, D = sleep duration), self-reported sleep by diagnosis (E = sleep quality, F = sleep duration).

actigraphy-assessed sleep duration (r = 0.50, p<0.001). Weak correlation was found between EMA-based sleep quality and actigraphy-assessed sleep duration (r = 0.09, p<0.001).

Most of the persons included had a lifetime diagnosis of depressive and/or anxiety disorders: 93 (26.0%) persons had current depressive and/or anxiety disorders, 176 (49.0%) persons had remitted depressive and/or anxiety disorders and only 90 (25.0%) persons had no lifetime depressive and/or anxiety disorders.

Day-to-day longitudinal association between sleep and subsequent momentary affect states

Better sleep quality was predictive of subsequent higher positive affect scores and lower negative affect scores the same day (Table 2, both p<0.001). When testing the moderating effect of current or remitted depressive and/or anxiety disorders: having a current depressive and/or anxiety disorder moderated the relationship between better sleep quality and lower negative affect score, as the interaction term was statistically significant (p=0.003, Supplemental Material, Table S1). As the interaction term was significant, we visualise group effects (Figure 3): a more pronounced negative association was observed between better sleep quality and subsequent negative affect for the groups with current and remitted depressive and/or anxiety disorders. Self-reported and objective sleep duration were not predictive of subsequent affect the same day (Table 2), nor did current/remitted depressive and/or anxiety disorders have a moderating effect (Supplemental Material, Table S1 and Table S2). When adjusting for time of the day, results did not change. Time of the day did not moderate the associations (results not shown).

Day-to-day longitudinal association between momentary affect states and subsequent sleep

Higher score on positive affect and lower score in negative affect predicted better sleep quality the next day (Table 3, both p<0.01). No interaction with current/remitted depressive and/or anxiety disorders was observed, suggesting that such associations do not depend on diagnostic group (Supplemental Material, Table S3). Affect states neither predicted self-reported and actigraphy assessed sleep duration (Table 3), nor did current/remitted depressive and/or anxiety disorders have a moderating effect (Supplemental Material, Table S3 and Table S4). When adjusting for time of the day, results did not change. Time of the day did not moderate the associations (results not shown).

Table 2: Association between sleep and momentary affect states of the following day (n = 359)

	Positive affect			Negative affect		
	β	SE	p	β	SE	p
Predictor = EMA assessed sleep quality						
Sleep quality (t-1)	0.035	0.006	**<0.001**	-0.022	0.005	**<0.001**
Mood (t-1)						
Positive affect (t-1)	0.327	0.014	**<0.001**			
Negative affect (t-1)				0.350	0.020	**<0.001**
Predictor = EMA assessed sleep duration						
Sleep duration (t-1)	0.011	0.008	0.147	-0.008	0.005	0.161
Mood (t-1)						
Positive affect (t-1)	0.334	0.014	**<0.001**			
Negative affect (t-1)				0.356	0.020	**<0.001**
Predictor = Actigraphy assessed sleep efficiency						
Sleep efficiency (t-1)	0.198	0.120	0.099	-0.078	0.071	0.273
Mood (t-1)						
Positive affect (t-1)	0.335	0.014	**<0.001**			
Negative affect (t-1)				0.357	0.021	**<0.001**
Predictor = Actigraphy assessed sleep duration						
Sleep duration (t-1)	-0.002	0.006	0.785	0.004	0.004	0.256
Mood (t-1)						
Positive affect (t-1)	0.335	0.014	**<0.001**			
Negative affect (t-1)				0.357	0.021	**<0.001**

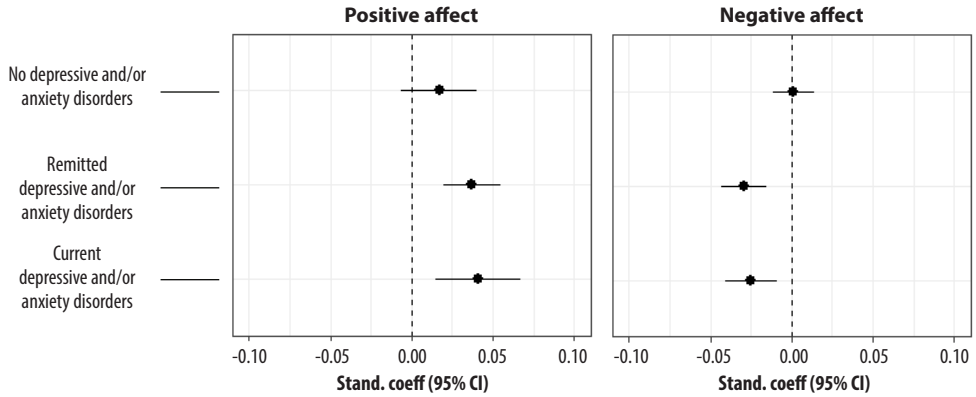

Figure 3: longitudinal association between EMA-based sleep quality and subsequent momentary assessment states stratified by diagnostic group.

Table 3: Association between momentary affect states and sleep of the following night (n = 359)

	Sleep			Sleep		
	β	SE	p	β	SE	p
Outcome = EMA assessed sleep quality						
Mood (t-1)						
Positive affect (t-1)	0.031	0.02	0.128			
Negative affect (t-1)				-0.102	0.031	**0.001**
Sleep quality (day-1)	-0.063	0.024	**0.010**	-0.066	0.024	**0.006**
Outcome = EMA assessed sleep duration						
Mood (t-1)						
Positive affect (t-1)	-0.003	0.019	0.870			
Negative affect (t-1)				-0.047	0.026	0.078
Sleep duration (day-1)	-0.085	0.021	**<0.001**	-0.086	0.021	**<0.001**
Outcome = Actigraphy assessed sleep efficiency						
Mood (t-1)						
Positive affect (t-1)	0.001	0.001	0.434	-0.001	0.002	0.523
Negative affect (t-1)						
Sleep efficiency (day-1)	-0.106	0.029	**<0.001**	-0.106	0.029	**<0.001**
Outcome = Actigraphy assessed sleep duration						
Mood (t-1)						
Positive affect (t-1)	-0.015	0.016	0.348			
Negative affect (t-1)				0.005	0.025	0.833
Sleep duration (day-1)	-0.111	0.028	**<0.001**	-0.111	0.028	**<0.001**

Discussion

This study examined the day-to-day bidirectional longitudinal association between self-reported and actigraphy-based sleep measures and momentary affect in a population with and without remitted or current depressive and/or anxiety disorders. Better self-reported sleep quality was predictive of improved affect the same day especially in persons with current depressive and/or anxiety disorders. On the other hand, better affect on the preceding day was predictive of higher self-reported sleep quality. No bidirectional longitudinal association was found between self-reported and actigraphy-based sleep duration and affect. Thus, the bidirectional associations between sleep quality and affect may highlight the potential of improving sleep quality as a target for affect improvement and regulation in patients with depression

and anxiety by breaking the vicious circle.

This study supports previous findings on the bidirectional longitudinal relationship between sleep quality and affect. Similarly to our results, better self-reported sleep quality has been linked to subsequent increased positive affect and decreased negative affect (Bouwmans et al., 2017; Triantafillou et al., 2019), and better affect has been linked to improved sleep quality (Triantafillou et al., 2019) in individuals without and with depressive and anxiety disorders when using daily (electronic) diaries and EMA. Both cognitive and biological mechanisms may explain the relationship between poor sleep quality and affect. Sleep deprivation may impact on emotions with alterations in especially the limbic system. Rapid eye movement (REM) sleep has been suggested as a modulator of affective brain processes, offering a regulatory function which restructures experiences in an emotionally adaptive manner (Kahn et al., 2013). Emotional information and memory processing may also be relevant, as a negative remembering bias has been shown, by which individuals tend to remember negative but not positive experiences following loss of sleep (Kahn et al., 2013). Finally, the cognitive-energy model (Zohar et al., 2005) suggests that sleep loss depletes energy levels, thus disrupting adaptive affective responses to stress. On the other hand, there is also data to suggest that an individual's coping style and emotion regulation strategy (e.g., avoidant emotion regulation, rumination) may moderate the relationship between low mood and sleep loss (Kahn et al., 2013)

Interestingly, in our study better sleep quality was found to improve subsequent affect especially in persons with current depression and/or anxiety. Although some studies have found that history of depression and anxiety did not mediate the relationship (Bouwmans et al., 2017; Triantafillou et al., 2019), a possible explanation of our results is that individuals with an already vulnerable emotion-regulation system may experience even more adverse effects from poor sleep quality (Harvey, 2011).

In contrast, no association was found between self-reported or actigraphy-based sleep duration and affect. These results seem to be consistent with other research which found no bidirectional association between affect and actigraphy-based sleep quality in an elderly population (Parsey & Schmitter-Edgecombe, 2019) and actigraphy-based sleep duration in a population with lifetime diagnosis of unipolar and bipolar depression (Merikangas et al., 2019). In line with our previous findings (Difrancesco et al., 2019), this study showed that the correlation between objective sleep duration and self-reported sleep quality was low and therefore objective and self-reported measures capture different aspects, enhancing the assessment of sleep.

While the current study looking at day-to-day associations did not observe associations between sleep duration and affect, sleep duration may nevertheless impact on

affect. Results from meta-analyses on prospective longitudinal studies, have shown that insomnia (Baglioni et al., 2011) and, both short and long vs normal sleep duration (Zhai et al., 2015), assessed with self-reported retrospective ratings, are longitudinally associated with increased risk of depression 6 months later. Therefore, self-reported sleep disturbances may have important long-term effects resulting in depression and worsening of depressive symptoms. More research is needed to understand the underlying biological mechanisms.

We observed bidirectional day-to-day effects between sleep quality and affect, possibly pointing to a vicious circle. A question for future studies is whether improving sleep quality may have positive outcomes on daily affect, especially in patients with depression and anxiety. As online psychological interventions have been shown to be effective for psychiatric disorders (Carlbring et al., 2018) and EMA can provide day-to-day assessments, EMA may be an add-on monitoring tool to (online) psychotherapy and Ecological Momentary Interventions (EMI). Specifically for insomnia, digital cognitive behavioral therapy (CBT-I) can be administered to patients with depression and anxiety; self-reported sleep quality may be an indicator of treatment response. Mobile technologies may also be used to monitor patients more broadly. Similarly to the biofeedback-based treatments for insomnia, integrating mobile technologies with apps summarizing affect and sleep may provide feedback to patients. This may help raise patients' awareness, and may help them to gain control.

This study has limitations. First, the observational study design can only point to areas of interest for monitoring and interventions, but does not allow us to make definitive recommendations on such interventions. Future clinical trials may further investigate the application of mobile technologies to monitor and measure treatment response. While actigraphy is feasible, it only detects sleep based on wrist movement and therefore may not be optimal to measure sleep. As restless REM sleep has been identified as a potential target for treatment of mental disorders (Wassing et al., 2019), REM sleep may be a better indicator of objective sleep disruptions. Although antidepressant use can be seen as a confounder, it is also closely associated with severity of depression and anxiety (the most severe cases use it), therefore, using it as a covariate may be seen as an overcorrection. In addition, as we have previously shown, antidepressant use is not associated with sleep duration (Difrancesco et al., 2019). Important strength of the study is the use of mobile technology to study the bidirectional day-to-day relationships between objective and self-reported indicators of sleep and affect on a relatively large sample with CIDI-based depression and anxiety diagnoses. Another strength of this study is that it strongly supports previous research on the longitudinal association between sleep quality and affect.

To conclude, this 2-week intensive ambulatory assessment study using mobile tech-

nology has shown a bidirectional association between better self-reported sleep quality and better affect, while no bidirectional association was found between self-reported and actigraphy-based sleep duration and affect. Mobile technologies may be insightful tools to provide feedback to patients about their sleep and affect. Improving sleep quality may be an important target of treatment to enhance affect in patients with depression and anxiety. Future studies may investigate whether EMA technology measuring sleep quality can be used to monitor treatment outcomes in depression and anxiety.

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Supplemental material

Table S1: Longitudinal association between EMA-based sleep and subsequent affect and moderation effect of current/remitted depressive and/or anxiety disorders compared to controls (n = 359)

	Positive affect			Negative affect		
	β	SE	p	β	SE	p
Predictor = EMA assessed sleep quality						
Sleep quality (t-1)	0.013	0.011	0.236	0.002	0.006	0.681
Mood (t-1)						
Positive affect (t-1)	0.326	0.014	**<0.001**			
Negative affect (t-1)				0.348	0.020	**<0.001**
Depressive and/or anxiety disorders						
No	Ref.			Ref.		
Remitted	-0.003	0.004	0.488	-0.002	0.002	0.365
Current	-0.004	0.005	0.393	0.001	0.003	0.873
Interactions						
Sleep quality (t-1) * No depressive and/or anxiety disorders	Ref.			Ref.		
Sleep quality (t-1) * Remitted depressive and/or anxiety disorders	0.023	0.014	0.107	-0.029	0.009	**0.001**
Sleep quality (t-1) * Current depressive and/or anxiety disorders	0.034	0.018	0.052	-0.031	0.010	**0.003**
Predictor = EMA assessed sleep duration						
Sleep duration (t-1)	0.01	0.019	0.611	0.005	0.01	0.587
Mood (t-1)						
Positive affect (t-1)	0.334	0.014	**<0.001**			
Negative affect (t-1)				0.355	0.02	**<0.001**
Depressive and/or anxiety disorders						
No	Ref.			Ref.		
Remitted	-0.003	0.004	0.459	-0.002	0.002	0.41
Current	-0.005	0.005	0.358	0.001	0.003	0.815
Interactions						
Sleep duration (t-1) * No depressive and/or anxiety disorders	Ref.			Ref.		
Sleep duration (t-1) * Remitted depressive and/or anxiety disorders	-0.007	0.021	0.734	-0.014	0.013	0.253
Sleep duration (t-1) * Current depressive and/or anxiety disorders	0.017	0.024	0.487	-0.017	0.014	0.207

Table S2: Longitudinal association between actigraphy assessed sleep and subsequent affect and moderation effect of current/remitted depressive and/or anxiety disorders compared to controls (n = 359)

	Positive affect			Negative affect		
	β	SE	p	β	SE	p
Predictor = actigraphy assessed sleep efficiency						
Sleep efficiency (t-1)	-0.076	0.221	0.731	-0.103	0.085	0.223
Mood (t-1)						
Positive affect (t-1)	0.335	0.014	**<0.001**	0.357	0.021	**<0.001**
Negative affect (t-1)						
Depressive and/or anxiety disorders						
No	Ref.			Ref.		
Remitted	-0.003	0.004	0.434	-0.001	0.002	0.442
Current	-0.005	0.005	0.319	0.001	0.003	0.779
Interactions						
Sleep efficiency (t-1) * No depressive and/or anxiety disorders	Ref.			Ref.		
Sleep efficiency (t-1) * Remitted depressive and/or anxiety disorders	0.389	0.287	0.175	0.062	0.147	0.674
Sleep efficiency (t-1) * Current depressive and/or anxiety disorders	0.332	0.312	0.287	-0.006	0.165	0.973
Predictor = actigraphy assessed sleep duration						
Sleep duration (t-1)	-0.009	0.012	0.462	0.009	0.006	0.165
Mood (t-1)						
Positive affect (t-1)	0.335	0.014	**<0.001**			
Negative affect (t-1)				0.357	0.021	**<0.001**
Depressive and/or anxiety disorders						
No	Ref.			Ref.		
Remitted	-0.004	0.004	0.397	-0.001	0.002	0.534
Current	-0.005	0.005	0.335	0.001	0.003	0.765
Interactions						
Sleep duration (t-1) * No depressive and/or anxiety disorders	Ref.			Ref.		
Sleep duration (t-1) * Remitted depressive and/or anxiety disorders	-0.005	0.014	0.709	0.002	0.008	0.791
Sleep duration (t-1) * Current depressive and/or anxiety disorders	0.032	0.018	0.076	-0.018	0.011	0.094

Table S3: Longitudinal association between affect and subsequent EMA-based sleep and moderation effect of current/remitted depressive and/or anxiety disorders compared to controls (n = 359)

	Sleep			Sleep		
	β	SE	p	β	SE	p
Outcome = EMA assessed sleep quality						
Mood (t-1)						
Positive affect (t-1)	0.046	0.036	0.204			
Negative affect (t-1)				-0.106	0.101	0.293
Sleep quality (t-1)	-0.063	0.024	**0.010**	-0.066	0.024	**0.006**
Depressive and/or anxiety disorders						
No	Ref.			Ref.		
Remitted	0.031	0.013	**0.018**	0.031	0.013	**0.019**
Current	0.021	0.014	0.135	0.021	0.014	0.133
Interactions						
Mood (t-1) * No depressive and/or anxiety disorders	Ref.			Ref.		
Mood (t-1) * Remitted depressive and/or anxiety disorders	0.008	0.046	0.860	-0.012	0.11	0.916
Mood (t-1) * Current depressive and/or anxiety disorders	-0.053	0.052	0.302	0.021	0.111	0.853
Outcome = EMA assessed sleep duration						
Mood (t-1)						
Positive affect (t-1)	-0.040	0.043	0.350			
Negative affect (t-1)				0.020	0.137	0.883
Sleep duration (t-1)	-0.085	0.021	**<0.001**	-0.087	0.021	**<0.001**
Depressive and/or anxiety disorders						
No	Ref.			Ref.		
Remitted	-0.007	0.013	0.604	-0.007	0.013	0.593
Current	0.001	0.016	0.991	0.001	0.016	0.987
Interactions						
Mood (t-1) * No depressive and/or anxiety disorders	Ref.			Ref.		
Mood (t-1) * Remitted depressive and/or anxiety disorders	0.042	0.051	0.404	-0.088	0.142	0.533
Mood (t-1) * Current depressive and/or anxiety disorders	0.046	0.052	0.370	-0.057	0.14	0.684

Table S4: Longitudinal association between affect and subsequent actigraphy assessed sleep and moderation effect of current/remitted depressive and/or anxiety disorders compared to controls (n = 359)

	Positive affect			Negative affect		
	β	SE	p	β	SE	p
Predictor = actigraphy assessed sleep efficiency						
Mood (t-1)						
Positive affect (t-1)	0.001	0.003	0.830			
Negative affect (t-1)				-0.002	0.005	0.729
Sleep efficiency (t-1)	-0.106	0.029	**<0.001**	-0.106	0.029	**<0.001**
Depressive and/or anxiety disorders						
No	Ref.			Ref.		
Remitted	0.001	0.001	0.460	0.001	0.001	0.464
Current	0.001	0.001	0.587	0.001	0.001	0.588
Interactions						
Mood (t-1) * No depressive and/or anxiety disorders	Ref.			Ref.		
Mood (t-1) * Remitted depressive and/or anxiety disorders	0.001	0.003	0.819	0.001	0.005	0.964
Mood (t-1) * Current depressive and/or anxiety disorders	0.001	0.003	0.880	0.001	0.005	0.830
Outcome = actigraphy assessed sleep duration						
Mood (t-1)						
Positive affect (t-1)	-0.077	0.041	0.058			
Negative affect (t-1)				0.052	0.11	0.638
Sleep duration (t-1)	-0.111	0.028	**<0.001**	-0.111	0.028	**<0.001**
Depressive and/or anxiety disorders						
No	Ref.			Ref.		
Remitted	-0.005	0.014	0.729	-0.005	0.014	0.717
Current	0.005	0.018	0.766	0.005	0.018	0.774
Interactions						
Mood (t-1) * No depressive and/or anxiety disorders	Ref.			Ref.		
Mood (t-1) * Remitted depressive and/or anxiety disorders	0.068	0.046	0.141	-0.049	0.115	0.671
Mood (t-1) * Current depressive and/or anxiety disorders	0.080	0.050	0.111	-0.052	0.117	0.657

Within-day bidirectional associations between physical activity and affect: *A real-time ambulatory study in persons with and without depressive and anxiety disorders*

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Abstract

Background: Ambulatory assessments offer opportunities to evaluate dynamics of physical activity and affect using mobile technologies. This study examines – at the group and at the person level - bidirectional associations between activity level and affect in a 3-hour timeframe using mobile monitoring, and evaluates whether these associations differ between people with and without current or remitted depression/anxiety.

Methods: Two-week ecological momentary assessment (EMA) and actigraphy data of 359 participants with current (n = 93), remitted (n = 176), or no (n = 90) CIDI depression/anxiety diagnoses were obtained from the Netherlands Study of Depression and Anxiety. Positive affect (PA) and negative affect (NA) were calculated from affect states assessed by EMA 5 times per day. Average activity levels between EMA assessments were calculated from actigraphy data.

Outcomes: At the group level, a bidirectional longitudinal association was found between activity level and affect. Higher activity level predicted affect 3 hours later (higher PA: b=0.109, p<0.001; lower NA: b= -0.043, p<0.001), while affect predicted higher activity level 3 hours later (higher PA: b=0.066, p<0.001; lower NA: b= -0.053, p<0.001). Current depression/anxiety disorders moderated the association between higher activity level and subsequent lower NA; it was stronger for patients than controls (p=0.01). At the person level, analyses revealed heterogeneity in within-person associations.

Interpretation: Higher physical activity may improve affect, especially among patients with current depression/anxiety. However, the relationships vary largely from person to person. Mobile technologies may help identify who would benefit from behavioural interventions.

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Keywords: Actigraphy; Ecological Momentary Assessment; Depressive disorders, Anxiety disorders

Introduction

Physical activity has gained importance in the management of affective disorders (Zschucke et al., 2013), as an effective (add-on) treatment (Schuch et al., 2016) and preventive factor for a new onset (Hu et al., 2020). Physical activity may also play a role in maintaining mood homeostasis. A potential mechanism is that mood homeostasis, e.g. stabilization of one's mood through engaging in mood-modifying activities such as physical activity or exercise, is thought to be impaired in depression (Taquet et al., 2020). Mobile technologies such as actigraphy devices and smartphones offer new opportunities to study the bidirectional longitudinal association between momentary assessed physical activity and mood states (i.e., positive and negative affect) on a fine-grained time scale in patients' daily environment. This may increase our understanding of the role physical activity in mood homeostasis, especially relevant in persons with affective disorders.

Actigraphy, which measures physical activity using a wrist-worn device, provides objective and high-density measurements of a person's physical movement in their living environments (Martin & Hakim, 2011). Studies have shown that low physical activity level assessed with actigraphy is linked to affective disorders (Burton et al., 2013), including depression and anxiety (Difrancesco et al., 2019). Ecological Momentary Assessment (EMA) provides detailed and frequent information on daily variations in mood and affect (Aan het Rot et al., 2012) that could influence systems that regulate physical activity. Studies employing EMA have shown that persons with a current depression disorder diagnosis have higher instability of negative and positive affect than persons without a diagnosed disorder (Aan het Rot et al., 2012; Schoevers et al., 2020). However, the association between physical activity and positive and negative affect with mobile technology has not often been investigated. Merikangas et al., 2019 (Merikangas et al., 2019) have found a negative unidirectional association between physical activity and subsequent sad mood and the association was stronger in persons with lifetime diagnosis of bipolar I disorder versus healthy controls. The study was, however, limited by a relatively small sample size of 91 persons with depressive disorders who were lifetime rather than current cases, making it impossible to distinguish trait vs state effects.

Another advantage of mobile technologies is that they allow to study the within-person association between physical activity and affect and their relationships at the individual level (also known as idiographic approach). Studies using ambulatory assessment tools and idiographic methods have shown that patterns in the association between physical activity and affect (Rosmalen et al., 2012) and between physical activity and stress (Burg et al., 2017) may differ widely across persons. As a consequence, not all persons may benefit of physical activity to improve their mood

and to lower their stress level. As recent personalised approaches in psychiatry have shown that smartphone-based micro-interventions can elicit short-term mood changes (Meinlschmidt et al., 2016), the use of mobile technologies can play a role in personalising treatment via direct feedback of actigraphy devices and apps assessing positive and negative affect.

The aim of this study was to investigate the bidirectional longitudinal association – at the group and individual level - between physical activity and affect assessed using mobile technologies, and whether these associations differ in persons without and with current or remitted depression and/or anxiety disorder diagnoses.

Method

Enrolment, intake and ambulatory assessment

Participants from the Netherlands Study of Depression and Anxiety (NESDA) were selected to participate in the Ecological Momentary Assessment (EMA) & Actigraphy sub-study (NESDA-EMAA). Details about NESDA have been provided extensively before (Penninx et al., 2008). NESDA was designed to investigate the course of depressive and anxiety disorders over a period of several years and the factors that influence the development and prognosis of such disorders. NESDA participants were initially included at the baseline assessment in 2004-2007 (n=2981), and seen for the fifth time at the nine-year follow-up assessment wave (2014-2017, n=1776) for a follow-up interview. At that time, also 367 siblings of NESDA participants were added, bringing the 9-year follow-up sample to 2143 subjects. At this wave, 384 participants enrolled for the EMAA sub-study. The NESDA study, including NESDA -EMAA, was approved by the VUmc ethical committee (reference number 2003/183) and all respondents gave informed consent for both the regular interview and the EMAA sub-study. See for a flowchart and details of the NESDA-EMAA in our previous work (Difrancesco et al., 2019; Schoevers et al., 2020). NESDA is also one of the sites that is member of the Motor Activity Research Consortium for Health (m-MARCH)(Scott et al., 2017). Participants of the NESDA-EMAA study were asked to fill out the EMA assessment, which is an electronic diary, on their smartphone and wore a wrist-worn actigraphy device (GENEActiv, Activinsights Ltd, Kimbolton, UK) for 14 days. In case participants did not possess a smartphone, or their phone was not suitable for participation (e.g. no internet bundle), a smartphone was provided for the duration of the study (n=107, 27.9%). Participants of the EMA assessment completed a set of items 5 times a day (i.e. every 3 hours; fixed design). Participants wore the wrist-worn GENEActiv actigraphy device on their non-dominant wrist, day and night.

Assessment of depressive and/or anxiety disorders and antidepressant use

As in the previous waves, at the 9-year follow-up, DSM-IV based diagnoses of depressive disorders (dysthymia and major depressive disorder) and anxiety (social anxiety disorder, panic disorder with and without agoraphobia, agoraphobia and generalized anxiety disorder) were established with the Composite International Diagnostic Interview (CIDI, version 2.1)(Wittchen, 1994), a highly reliable

and valid instrument for assessing depressive and anxiety disorders.. Participants were categorized into three groups: 1) a group with no lifetime depressive and/or anxiety disorders, 2) a group with remitted depressive and/or anxiety disorders (having a lifetime, but not current (6-month) diagnosis), and 3) a group with current depressive or anxiety disorder in the past 6 months.

Antidepressant use was based on drug container inspection, and medications were coded according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification. Antidepressant use was considered present if participants reported using it more than 50% of the time. Antidepressants included were selective serotonin reuptake inhibitors (SSRIs, ATC code N06AB), tricyclic antidepressant (TCA, ATC code N06AA) and other antidepressants (ATC codes N06AF, N06AG, N06AX).

Ambulatory assessment variables

Positive and negative momentary affect states

EMA questionnaires were assessed five times a day and had up to 31 items per time point. They contained both momentary affect state items and other items on activities, context and lifestyle. To assess momentary affect states, items covering high and low arousal, positive and negative momentary affect states were used from the Uncovering the Positive Potential of Emotional Reactivity study (Bennik, 2015). Included items were: I feel satisfied, relaxed, upset, cheerful, irritated, listless, down, energetic, enthusiastic, nervous, bored, calm, and anxious. All items were rated on a 7-point Likert scale ranging from '1 = not at all' to '7 = very much'. A positive affect (PA) subscale was calculated by taking the average of PA items (at this moment I feel satisfied, relaxed, cheerful, energetic, enthusiastic, and calm). Similarly, a negative affect (NA) subscale was calculated by averaging all NA items (at this moment I feel upset, irritated, listless/apathic, down, nervous, bored, anxious).

Physical activity

Raw actigraphy data was processed with open source R package GGIR (version 1.5-18) (van Hees, 2017). Minute-to-minute daily actigraphy data were derived per participant by summing 5-second data. The average physical activity (in milli-gravity

units) between EMA assessments was calculated for each day and for each participant.

Minutes spent in sedentary behaviour (physical activity level < 30 milli-gravity (Rowlands et al., 2014)), light physical activity (physical activity level between 30 and 125 milli-gravity) and moderate-to-vigorous physical activity (physical activity level > 125 milli-gravity (Kim et al., 2017)) between EMA assessments were also calculated for each day and for each participant.

Covariates: age, sex and work/school days

Covariates were age, sex and work/school days at the time of the NESDA EMAA substudy. These covariates were selected as they have an established theoretical association with psychopathology and with physical activity levels. Work/school days were identified with information from daily EMA assessment as participants were asked to document their location; if they reported their location to be at school/work at least once during a day it was counted as work/school day.

Statistical analyses

Data cleaning and missing data

Data cleaning steps including handling of missing data were previously described for both EMA (Schoevers et al., 2020) and actigraphy (Difrancesco et al., 2019) data and are further reported in the Supplemental Material. The final sample was composed of 359 (93.5%) participants with on average 64.5 ± SD 6.7 valid EMA observations and 13.68 ± SD 1.26 valid actigraphy days.

Statistical testing

The distribution of physical activity and momentary affect states observations stratified by diagnostic groups were visualised with a box plot. As the distribution of observations were skewed, Kruskall-Wallis test was used to test differences between diagnostic groups.

Generalized estimating equation models (GEE) were used to test – at group level - the bidirectional longitudinal association between momentary affect states assessed every three hours and the between assessments average physical activity adjusting for age, sex and work days (A summary of the analyses is shown in Figure 1). Therefore, analyses were performed by first using momentary affect states as outcome (Model 1) and then by using physical activity as outcome (Model 2). Physical activity was log transformed to take account of the skewed distribution. Data centring of momentary affect states and physical activity was performed by within-person mean; therefore, estimates in the models indicate the effect of changes in affect and physical activity from the diurnal person-specific mean. The first-order autoregres-

sive working correlation structure was chosen to take into account the within-person correlation over the 2-week observation period.

The same analyses were repeated to test for the moderating effect of current or remitted depressive and/or anxiety disorders. When moderation terms were significant, stratified analyses by diagnostic group were conducted to interpret and visualise the group effect. Specifically, for each diagnostic group, the longitudinal associations between minutes spent in sedentary behaviour, light physical activity and moderate-to-vigorous physical activity and momentary assessment states were tested with GEE adjusting for age, sex and work days. The longitudinal associations were then graphically displayed with a forest plot for interpretation of the results. In addition, the moderating effect of antidepressant use on the longitudinal association between physical activity and subsequent momentary affect states in patients with current depressive and/or anxiety disorders was explored.

For this analyses the moderating effect of time of the day on the bidirectional longitudinal association between momentary affect states and physical activity was also explored.

At the individual level, an analysis was performed to visually explore the heterogeneity in the within-person bidirectional longitudinal associations between physical activity and momentary affect states. A linear regression model was run for each participant and within-person slopes were graphically represented in a forest plot as done before by Burg et al (Burg et al., 2017).

All analyses were performed with the statistical software R Studio (R Studio version 1.2.5033, R version 3.5) and the 'gee' library, a p-value < 0.05 was considered statistically significant.

Results

Demographics, psychopathology and ambulatory assessment variables

The total sample of 359 individuals had an average age of 49.5 ± SD 12.6 years and 63.7% were women. Of the total sample, 93 had current and 176 had remitted depressive and/or anxiety disorders, 90 had no current depressive and/or anxiety disorders. Seventy-one individuals of the total sample (19.7%) used antidepressants. Of the 16920 total EMA assessments, 32.7% were on work/school days. Figure 1 shows the distribution of the affect and physical activity observations; statistically significant differences were found between diagnostic groups ($p < 0.001$).

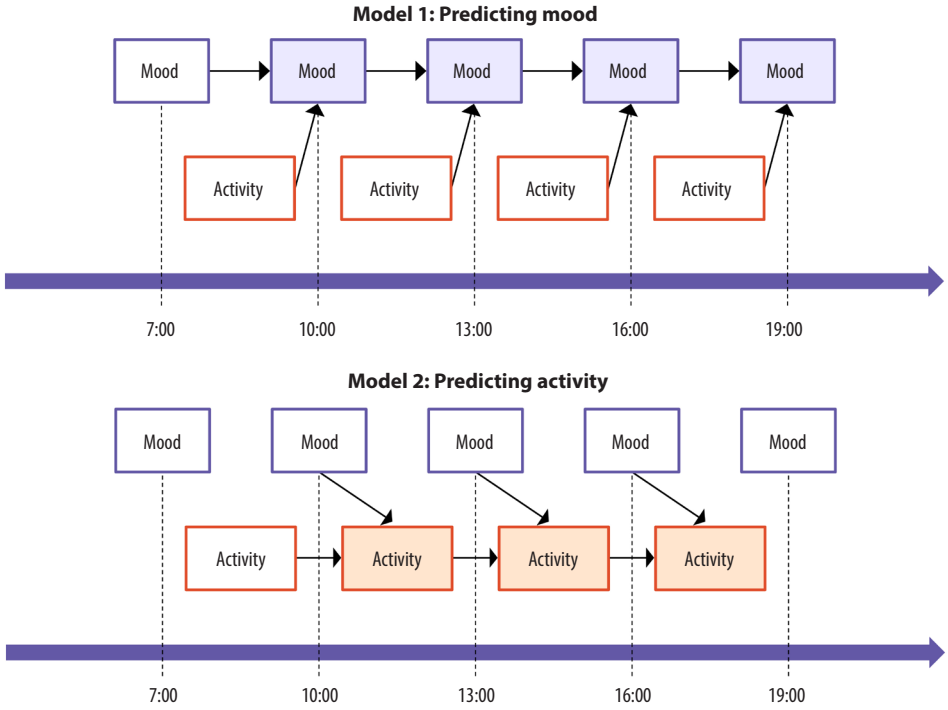

Figure 1: Summary of the bidirectional longitudinal association between momentary affect states assessed every three hours and the average physical activity between assessments. The filled boxes indicate the outcomes.

Within-day longitudinal association between physical activity and subsequent momentary affect states

Higher activity level was longitudinally associated with higher positive affect and lower negative affect scores in the following 3 hours within the same day (Table 1, Model 1, both p's<0.001). When testing the moderating effect of current or remitted depressive and/or anxiety disorders, the main effect of activity remained statistically significant. However, having a current depressive and/or anxiety disorder appeared to moderate the relationship between higher physical activity level and lower negative affect score, as the interaction term was statistically significant (p=0.010; Supplemental Material, Table S1). Having a remitted depressive and/or anxiety disorder appeared to moderate the relationship between higher physical activity level and higher positive affect score, as the interaction term was statistically significant (p=0.033; Supplemental Material, Table S1); a similar direction in the association was found in individuals with a current depressive and/or anxiety disorder (p=0.052; Supplemental Material, Table S1). As interaction terms were significant, we visualise group effects (Figure 3): a more pronounced positive association was observed between more time spent in light and moderate-to-vigorous activity level, less time spent in in sedentary behaviour and subsequent positive affect for the groups with

Table 1: Bidirectional longitudinal associations between physical activity and momentary affect states (n = 359)

	Positive affect			Negative affect		
	β	SE	p	β	SE	p
Model 1						
Activity (t-1)	0.109	0.014	**<0.001**	-0.043	0.009	**<0.001**
Affect (t-1)						
Positive affect (t-1)	0.336	0.014	**<0.001**			
Negative affect (t-1)				0.360	0.020	**<0.001**

	Activity			Activity		
	β	Se	p	β	Se	p
Model 2						
Affect (t-1)						
Positive affect (t-1)	0.066	0.008	**<0.001**			
Negative affect (t-1)				-0.053	0.011	**<0.001**
Activity (t-1)	0.068	0.013	**<0.001**	0.075	0.013	**<0.001**

Note: Model adjusted for age, sex and work/school day (details given in the method section)

current and remitted depressive and anxiety disorders. A compatible pattern was observed for negative affect in individuals with current depressive and/or anxiety disorders: less time in sedentary behaviour and more time spent in light and moderate-to-vigorous physical activity were associated with subsequent lower negative affect score. Time of the day did not moderate the relationship between physical activity level and subsequent momentary affect states (results not shown, available upon request). In the current cases, antidepressant use moderated the relationship between physical activity level and subsequent momentary affect states (Supplemental Material, Table S3, p=0.025). Higher physical activity level enhanced subsequent positive affect especially in persons taking antidepressants.

Although higher physical activity was associated with subsequent improved affect at the group level, analyses at the person level showed substantial heterogeneity in within-person associations (Figure 4). In some individuals, physical activity decreased positive affect score (within-person slope b < -0.20; 14.6% of the total sample) and increased negative affect score (within-person slope b > 0.20; 11.6% of the total sample) or had no clear effect.

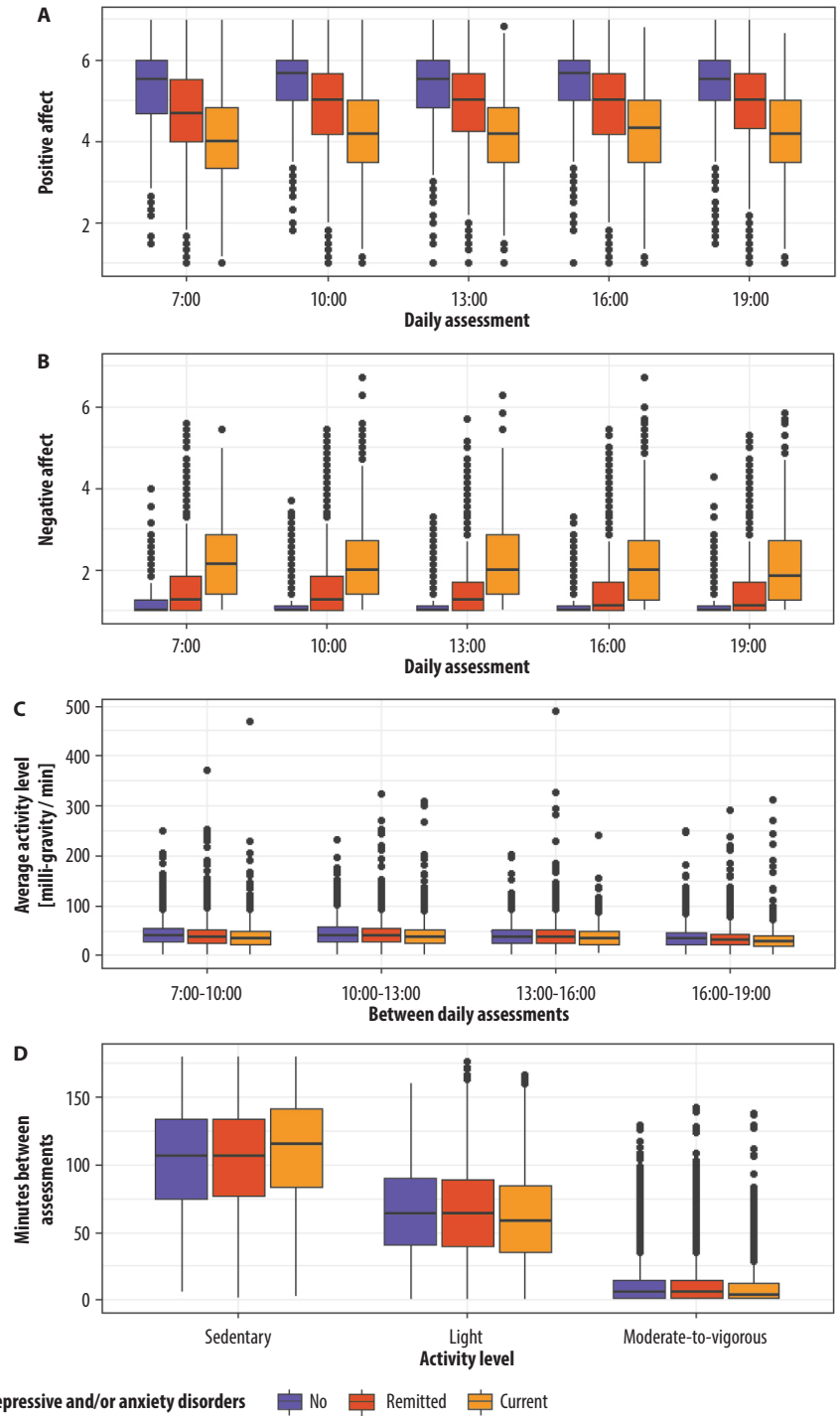

Figure 2: Distribution of affect and physical activity observations in the NESDA sample (n = 359): positive (A) and negative (B) affect by daily assessment and by diagnosis, activity level between assessments by diagnosis (C) and minutes spent in different activity levels (i.e., sedentary, light and moderate-to-vigorous) by diagnosis (D).

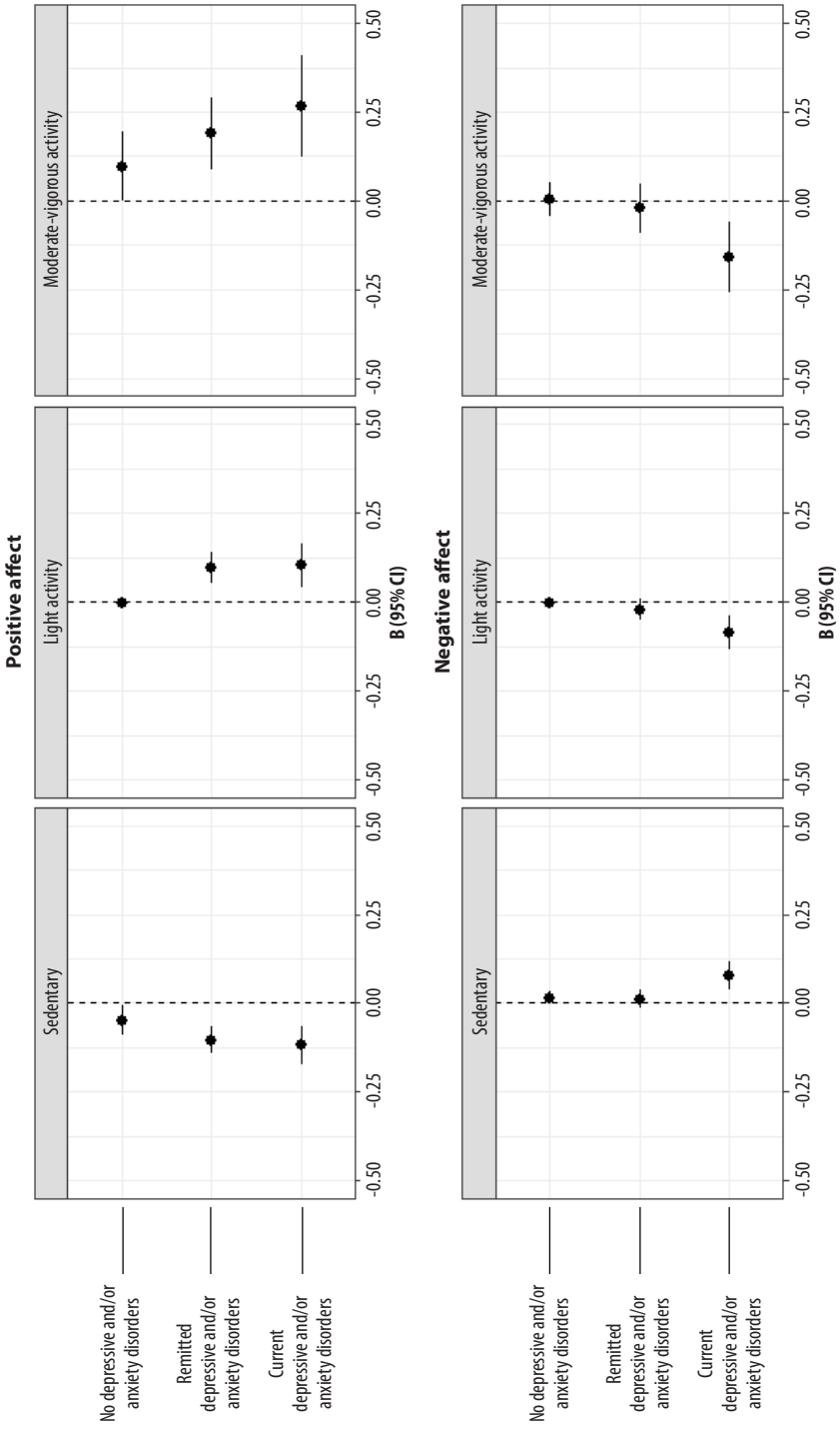

Figure 3: Longitudinal association between physical activity and subsequent affect (i.e., positive affect, negative affect) stratified by diagnostic group and by time (hours) spent at different activity levels.

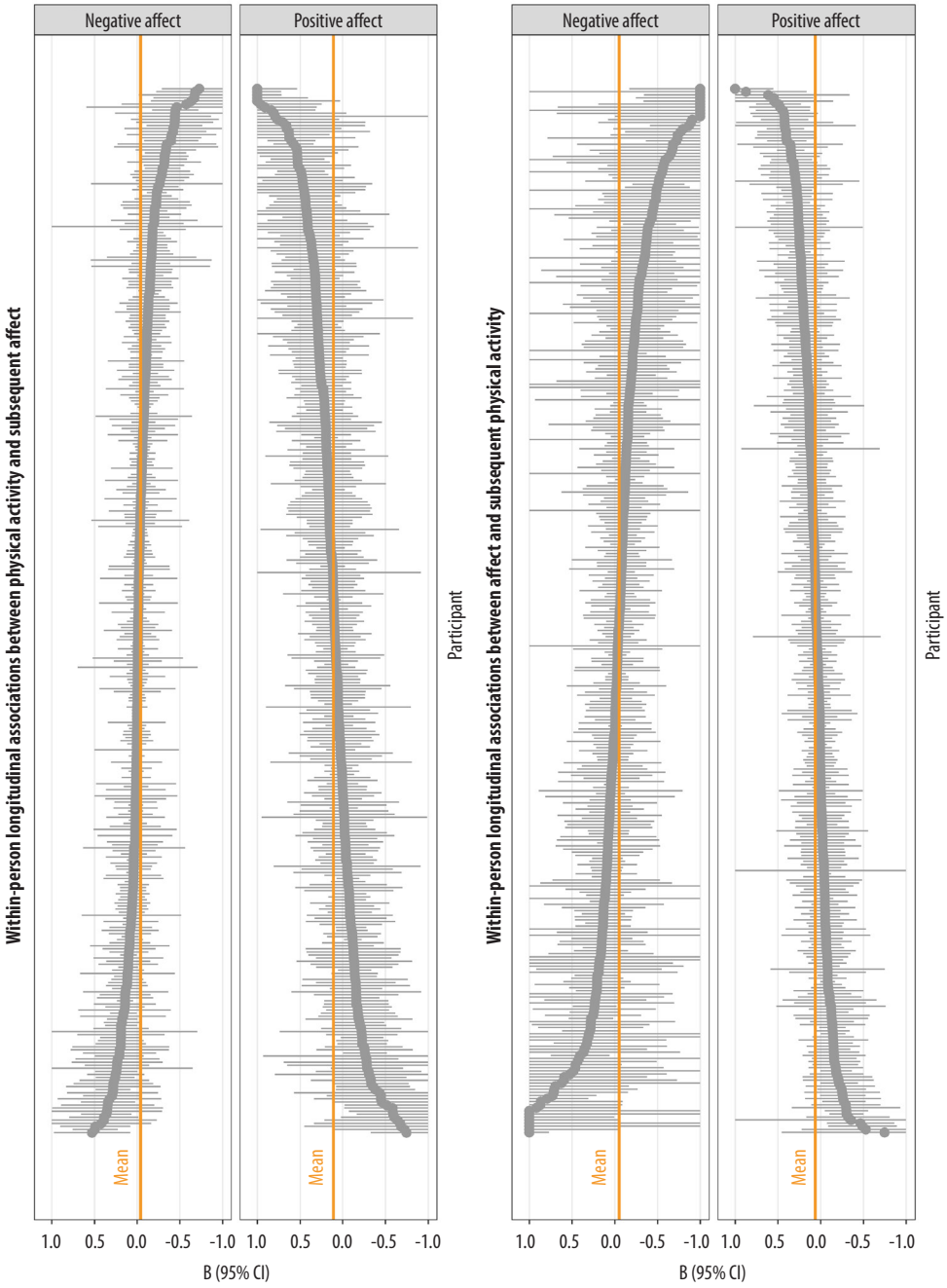

Figure 4: Within-person slopes of bidirectional longitudinal associations between physical activity and affect.

Within-day longitudinal association between momentary affect states and subsequent physical activity

Higher score in positive affect and lower score in negative affect were longitudinally associated with higher activity level in the following 3 hours (Table 1, Model 2, both $p<0.01$). Additionally, when testing the moderating effect of current or remitted depressive and/or anxiety disorders, the main effect remained significant and no interaction (all $p>0.05$; Supplemental Material, Table S2) with current or depressive and/or anxiety disorders was observed. Time of the day did not moderate the relationship between momentary affect states and subsequent physical activity level (results not shown).

Again, analyses at the person level revealed heterogeneity in within-person associations (Figure 4). In some individuals, a negative association between better positive (within-person slope $b < -0.20$; 8.5% of the total sample) and negative (within-person slope $b > 0.20$; 18.5% of the total sample) affect scores and subsequent physical activity were present or no association could be observed.

Discussion

This is one of the first studies to investigate the bidirectional within-day associations between momentary assessed daily activity and affect using mobile technology on a fine-grained time scale in a population with diagnosed current and remitted depression/anxiety disorders and controls. Higher physical activity level was longitudinally associated with improved subsequent affect with enhanced positive affect and reduced negative affect, especially in the group with current depression and/or anxiety. Better mood (i.e., higher positive and lower negative affect) was also associated with subsequent higher activity level. Thus, bidirectional associations between physical activity and affect was confirmed and, highlight the potential of physical activity as a target for mood improvement and regulation in patients with depression and anxiety by breaking the vicious circle. As variability in the within-person association between physical activity and subsequent affect was observed, physical activity may not be effective in enhancing affect in all individual. Ambulatory assessment tools may be useful to personalise physical activity interventions in patients who would benefit most from such interventions.

This study supports and extends previous findings on the bidirectional relationship between physical activity and mood. In line with our results, exercise has been linked to subsequent increased positive affect and decreased negative affect as summarised in the literature review by Chan et al., 2019 (Chan et al., 2019). Lower activity level has been linked to more sad mood in a sample with lifetime history of bipolar and

unipolar depression (Merikangas et al., 2019) using mobile technologies. However, the latter study did not find that mood was related to changes in motor activity, perhaps because of person-level differences in the study sample (Zuidersma et al., 2020). Both psychosocial and neurophysiological mechanisms have been suggested to explain such association such as self-efficacy and the distraction hypothesis, the thermogenic effects and the endorphin theory. Physical activity may lead to improved self-efficacy (i.e., an individual's belief in his or her ability to successfully carry out the necessary action required to satisfy situational demands) and psychological well-being (Barnett, 2013). According to the distraction hypothesis, exercise distracts us from stressful stimuli or offers us a break from daily routine, emancipating us from negative moods (Leith, 1994). The endorphin hypothesis suggests that exercise has a positive effect on mood due to an increased release of β-endorphins following exercise (Bender et al., 2007). The thermogenic hypothesis says that a rise in core body temperature following exercise is responsible for the reduction in symptoms of depression (de Vries, 1981).

Importantly, higher physical activity level was found to be longitudinally associated with subsequent affect improvement especially in individuals diagnosed with a current depression and/or anxiety disorder. In line with our findings, previous studies have shown that lifetime history of affective disorders moderates the association between physical activity level (Merikangas et al., 2019), daily activities (Taquet et al., 2020) and affect. Possible explanations of why current depression and/or anxiety patients have a stronger coupling of physical activity and subsequent mood than controls could be the following. Persons with depression and/or anxiety may be more sensitive to their daily context (Schoevers et al., 2020) and therefore external changes, such as in their physical activity level or daily activities (e.g., social activities), may impact their mood more strongly. In addition, it has been recently suggested that individuals with a history of depression have impaired mood homeostasis compared to controls, as they have difficulties in stabilise their mood via mood-modifying activities (Taquet et al., 2020). Physical activity and exercise may therefore be important to target affect in an effort to break a downwards spiral and thus improve mood.

However, physical activity may not be beneficial for all individuals with depression and anxiety as shown by the heterogeneity of within-person associations between physical activity and affect. While some individuals experienced a significant beneficial effect of physical activity on affect, others experienced a negative effect or no clear effect. These results may also explain why research on physical activity interventions to treat mental health disorders is often inconsistent and meta-analyses have demonstrated a range of effect sizes and large heterogeneity (Stubbs et al., 2016), and translation of research finding into clinical practice is hampered (Zuidersma et

al., 2020). Our results highlight the advantage of using ambulatory assessment tools and idiographic approaches for future research to hopefully improve on effectiveness of physical activity interventions in patients with depression and anxiety.

A question that remains for future studies is the extent to which mobile technologies may assist behavioural interventions to increase physical activity in patients with depression and anxiety. As online psychological interventions have been shown to be effective for psychiatric disorders (Carlbring et al., 2018) and mobile technologies can in real-time monitor patients, mobile technologies may be an add-on tool to online (personalized) psychotherapy. Behavioural activation may be automatically recommended by intelligent algorithms based on physical activity data collected by the wrist-worn actigraphy device of a specific individual. From a broader prospective, when proven effective, mobile technologies may be better integrated into mental health care, given their good social acceptance (Bos et al., 2019) and with relatively lower costs compared to traditional interventions (Olff, 2015). Also, feedback on affect and activity level alone may already help patients by increasing their awareness on how their physical activity and mood are related, as a first step in behavioural change.

This study has limitations. First, the observational study design does not allow to make definitive causal interpretations and to make recommendations for interventions in clinical practice. Second, implementation in clinical practice may be not as straight forward as individual differences in the associations between affect and physical activity are large. Future clinical trials may further investigate the use of idiographic approaches (i.e., individual models) and mobile technologies to provide personalised treatments. Important strength of the study is the use of mobile technology to study the bidirectional relationship between physical activity and momentary assessed affect on a relatively large sample with CIDI-based depression and anxiety diagnoses.

To conclude, this study has shown a bidirectional association between higher physical activity level and better mood. Increasing physical activity level may be an important target of treatment to improve mood by breaking the downward spiral in patients with depression and anxiety. These findings highlight the importance of mobile technologies which capture salient information about subjective experience affect and objective physical activity level in real-time. The bidirectional association between physical activity and affect can however vary from person to person. We therefore also pointed out the urge of future idiographic research to make mobile technologies useful for clinical practice. Mobile technologies may be used for real-time personalised monitoring of affect and physical activity and to provide feedback to patients. This may increase their awareness on how mood and activity are

interlinked, and perhaps increasing patient's self-management skills and support behavioural changes. As mobile technologies are widely used and accepted in patient's daily life, future online psychological interventions such as behavioural activation may integrate in such technologies to provide personalised interventions in patients with depression and anxiety.

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Supplemental material

Data cleaning and missing data

Data cleaning steps including handling of missing data were previously described for both EMA (Schoevers et al., 2020) and actigraphy (Difrancesco et al., 2019). Of all sent EMA assessments to 384 participants, only 8.72% were missing. EMA data of 19 participants were excluded due to various reasons such as low response rate (response rate below 50%; in line with Servaas et al. (2017)) or technical failure, resulting in 365 participants with available data. Of the 384 participants, 14 had no available actigraphy data for several reasons, such as technical failure, resulting in 370 (96.4%) participants with available data. According to previously published criteria (da Silva et al., 2014), participant's actigraphy data were included in analyses if at least one week day and one weekend day of usable data was available, with at least 16 hours recorded per day and per night. Missing actigraphy data points were replaced with participant's data from the same time of day, averaged across the other valid days to provide a person-specific informed approach. The final sample was composed of 359 (93.5%) participants with on average 64.5 ± SD 6.7 valid EMA observations and 13.68 ± SD 1.26 valid actigraphy days.

Table S1: Longitudinal association between physical activity and subsequent momentary affect states and moderating effect of current/remitted depressive and/or anxiety disorders compared to controls (n = 359)

	Positive affect			**Negative affect**		
	β	SE	p	β	SE	p
Activity (t-1)	0.059	0.021	**0.005**	-0.023	0.013	0.074
Mood (t-1)						
Positive affect (t-1)	0.336	0.014	**<0.001**			
Negative affect (t-1)				0.359	0.020	**<0.001**
Depressive and/or anxiety disorders						
No	Ref.			Ref.		
Remitted	-0.001	0.005	0.788	-0.002	0.002	0.322
Current	-0.005	0.006	0.359	0.004	0.004	0.318
Interactions						
Activity (t-1) * No depressive and/or anxiety disorders	Ref.			Ref.		
Activity (t-1) * Remitted depressive and/or anxiety disorders	0.064	0.030	**0.033**	-0.004	0.018	0.836
Activity (t-1) * Current depressive and/or anxiety disorders	0.073	0.038	0.052	-0.065	0.025	**0.010**

Note: Model adjusted for age, sex and work/school day

Table S2: Longitudinal association between momentary affect states and subsequent physical activity and moderating effect of current/remitted depressive and/or anxiety disorders compared to controls (n = 359)

	Physical activity			Physical activity		
	β	SE	p	β	SE	p
Mood (t-1)						
Positive affect (t-1)	0.086	0.021	**0.036**			
Negative affect (t-1)				-0.125	0.057	**0.029**
Activity (t-1)	0.068	0.013	**<0.001**	0.075	0.013	**<0.001**
Depressive and/or anxiety disorders						
No	Ref.			Ref.		
Remitted	0.003	0.006	0.619	0.003	0.006	0.592
Current	0.001	0.007	0.832	0.002	0.007	0.817
Interactions						
Positive affect (t-1) * No depressive and/or anxiety disorders	Ref.					
Positive affect (t-1) * Remitted depressive and/or anxiety disorders	-0.021	0.024	0.379			
Positive affect (t-1) * Current depressive and/or anxiety disorders	-0.028	0.025	0.262			
Negative affect (t-1) * No depressive and/or anxiety disorders				Ref.		
Negative affect (t-1) * Remitted depressive and/or anxiety disorders				0.088	0.059	0.138
Negative affect (t-1) * Current depressive and/or anxiety disorders				0.069	0.059	0.245

Note: Model adjusted for age, sex and work/school day

Table S3: Longitudinal association between physical activity and subsequent momentary affect states and moderating effect of antidepressant use within persons with current depression/anxiety (n = 93)

	Positive affect			Negative affect		
	β	SE	p	β	SE	p
Activity (t-1)	0.074	0.039	0.060	-0.056	0.023	**0.014**
Mood (t-1)						
Positive affect (t-1)	0.383	0.024	**<0.001**			
Negative affect (t-1)				0.399	0.027	**<0.001**
Antidepressant use						
No	Ref.			Ref.		
Yes	-0.010	0.010	0.340	0.007	0.008	0.385
Interactions						
Activity (t-1) * No antidepressant use	Ref.			Ref.		
Activity (t-1) * Yes antidepressant use	0.133	0.059	**0.025**	-0.076	0.046	0.103

Note: Model adjusted for age, sex and work/school day

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General discussion

This thesis extensively examined the relationships between sleep, circadian rhythms, physical activity and psychopathology using ambulatory assessment tools. Specifically, it emphasizes the role of actigraphy and Ecological Momentary Assessment (EMA) to assess sleep, circadian rhythms and physical activity in persons with depression and anxiety. The sample used in the analyses was composed of 359 participants with current (n=93), remitted (n=176) or no (n=90) CIDI depression/anxiety diagnoses; a subsample of the NESDA study. To better explain results of this thesis, Table 1 summarises the main findings.

In **Chapter 2**, we studied the relationships between sleep, circadian rhythms and physical activity with depression and anxiety by using actigraphy and self-reported questionnaires. Specifically, we found reduced physical activity level and daily rhythm disturbances among those with depressive and anxiety disorders compared to controls using actigraphy-assessed measures, but not using self-reported information. By contrast, self-reported but not actigraphy-assessed sleep measures differed between persons with depressive and anxiety disorders vs controls. In addition, we studied the associations of sleep, circadian rhythms and physical activity with clinical characteristics (i.e., severity of depressive and anxiety symptoms, number of psychiatric diagnoses, duration of depressive and/or anxiety disorders and antidepressant use). We found evidence for dose-response associations as those with more severe depressive and anxiety symptoms were significantly less active and showed longer sleep duration and lower relative amplitude between day and night activity level assessed with actigraphy.

In **Chapter 3**, we studied the associations between sociodemographic, health and lifestyle, sampling, and mental health determinants and physical activity patterns. We also explored the use of two more advanced statistical techniques also known as Functional Data Analysis methods: (a) Functional Principal Component Analysis (fPCA) was used to extract motor activity patterns assessed with actigraphy; (b) function-on-scalar regression was used to assess the association of psychopathology and other determinants with timing of activity. Specifically, we showed that data-driven features of daily motor activity extracted with fPCA reflect commonly studied factors such as the intensity of daily activity and preference for morningness/eveningness. Presence and severity of depression/anxiety disorders were found to be mainly associated with intensity of daily activity but not with timing of activity. Age, working and season were most strongly associated with overall daily activity patterns and timing of activity.

In **Chapter 4**, we explored the heterogeneity of depression in the association with sleep, circadian rhythm and physical activity assessed with actigraphy. To examine the heterogeneity of depression, individual depressive symptoms were clustered

in three symptom dimensions: mood/cognition, somatic/vegetative and sleep. We found that all three symptom dimensions were associated with actigraphy-based low physical activity and dampened circadian rhythms. Therefore, these seem to be general indicators of depression. However, sleep disturbances appeared more linked to the somatic/vegetative and sleep dimensions.

In **Chapter 5**, we studied the bidirectional longitudinal associations between actigraphy and EMA-based sleep and affect the same day. Better EMA-based sleep quality was longitudinally associated with improved affect the same day especially in persons with current depressive and/or anxiety disorders. On the other hand, better affect on the preceding day was longitudinally associated with higher EMA-based sleep quality. No bidirectional longitudinal association was found between EMA-based and actigraphy-based sleep duration and affect.

Table 1: Summary of results of this thesis. + = linear positive association, - = linear negative association, U = U-shape association, x = non-significant association, empty cell = not tested association.

			Current Depression Anxiety diagnosis	Depressive and anxiety symptoms	Duration of disorder
Sleep	Actigraphy	Sleep duration	x	+	x
		Sleep efficiency	x	x	x
	Self-report	Sleep duration	U		
		Insomnia	+		
	EMA	Sleep duration			
		Sleep quality			
Circadian Rhythm	Actigraphy	Relative amplitude	-	-	x
		Sleep midpoint	x	+	x
	Self-report	Sleep midpoint	x		
Physical activity (PA)	Actigraphy	Gross motor activity	-	-	x
		Moderate vigorous PA	-	-	x
	Self-report	Total MET	x		
		Moderate vigorous PA	x		

In **Chapter 6**, we examined the bidirectional longitudinal associations between actigraphy-assessed physical activity and affect in a 3-hour time frame. Higher physical activity level was longitudinally associated with improved subsequent affect with enhanced positive affect and reduced negative affect, especially in persons with current depression and/or anxiety. Better mood (i.e., higher positive and lower negative affect scores) was also associated with subsequent higher activity level. In addition to group-level analyses, we also explored the associations at the individual level. Heterogeneity was found in the within-person bidirectional association between physical activity and affect, indicating that the associations may differ from person to person. For instance, a positive effect of physical activity on subsequent affect was found for some people, while no clear effect or a negative effect were found for others.

Table 1: (continued)

Number of diagnoses	Antidep. Use	Symptom dimension			Positive affect	Negative affect
		Mood	Somatic	Sleep		
+	x	x	+	x	x	x
x	x	x	x	-	x	x
					x	x
					+	
-	x	-	-	-		
x	+	x	x	x		
-	x	-	-	-	+	-
-	x				+	-

Discussion of the main findings

Are disturbances in sleep and circadian rhythms and altered physical activity assessed with ambulatory assessment tools associated with psychopathology?

Answer: Yes, this thesis demonstrates that disturbances in sleep and circadian rhythms and altered physical activity assessed with ambulatory assessment tools are associated with psychopathology.

Association of sleep disturbances with psychopathology

Actigraphy-based sleep measures

Although actigraphy-based sleep duration and efficiency are not associated with depressive and anxiety disorders (Chapter 2) and affect (Chapter 5), we found a dose-response association between longer sleep duration and more severe symptoms (Chapter 2). Lower actigraphy assessed sleep efficiency was also associated with the sleep dimension and longer actigraphy-based sleep duration was more specifically linked to the somatic/vegetative symptom dimension (Chapter 4). As depression and anxiety are heterogeneous conditions, objective sleep disturbances may be more linked to specific clinical characteristics and symptom dimensions.

Sleep duration was found to be longer in persons with a greater number of depressive and anxiety symptoms. As hypersomnia is one of the symptoms of depression (1), persons with more depressive symptoms may also experience more frequently longer sleep time. Another explanation may be antidepressant use. More severe cases are more likely to use these medications and previous research has suggested that long sleep duration can be a result of antidepressant use (2), such as sedating tricyclic antidepressants (3). While benzodiazepine use could also be an explanation, as it is also prescribed for sleep problems, it is a less likely explanation here, as only 5 cases used benzodiazepines.

Longer sleep duration was also found to be associated with the somatic/vegetative symptom dimension. A possible explanation is that persons with more somatic complaints, such as aches and pains and other bodily symptoms, may have more chronic or somatic diseases resulting in fatigue and increased sleepiness (4). As it could be expected, lower sleep efficiency assessed objectively with actigraphy was associated with the sleep symptom dimension. Although we did not find an association between objective sleep efficiency and subjective sleep assessed with the Women's Health Initiative Insomnia Rating Scale (Chapter 2), the objective measure of sleep efficiency seems indicative of self-reported sleep disturbances assessed with the Inventory of Depressive Symptomatology.

Ecological Momentary assessment of sleep

A bidirectional longitudinal association was found between sleep quality assessed with Ecological Momentary Assessment and affect (Chapter 5). Better self-reported sleep quality was predictive of improved affect the same day, especially in persons with current depressive and/or anxiety disorders. On the other hand, better affect on the preceding day was predictive of higher self-reported sleep quality.

Both cognitive and biological mechanisms may explain the relationship between sleep quality and affect. Sleep deprivation may impact on emotions with alterations in especially the limbic system. Rapid eye movement (REM) sleep has been suggested as a modulator of affective brain processes, offering a regulatory function which restructures experiences in an emotionally adaptive manner (5). Emotional information and memory processing may also be relevant, as a negative remembering bias has been shown, by which individuals tend to remember negative but not positive experiences following loss of sleep (5). Finally, the cognitive-energy model (Zohar et al., 2005) suggests that sleep loss depletes energy levels, thus disrupting adaptive affective responses to stress. On the other hand, there is also data to suggest that an individual's coping style and emotion regulation strategy (e.g., avoidant emotion regulation, rumination) may moderate the relationship between low mood and sleep loss (5). Interestingly, in our study, better sleep quality was found to improve subsequent affect, especially in persons with current depression and/or anxiety. A possible explanation for our results is that individuals with an already vulnerable emotion-regulation system may experience even more adverse effects from poor sleep quality (6).

Association of low circadian rhythm amplitude and physical activity with psychopathology

Associations at the group level

Low physical activity level and dampened circadian rhythm amplitude are consistently associated with psychopathology in both cross-sectional (Chapter 2, 3, 4) and longitudinal analyses at the group-level (Chapter 6). In addition, those associations were independent from several sociodemographic, lifestyle and sampling factors (Chapter 3). Low physical activity level and dampened circadian rhythms appeared to be general indicators of depression and anxiety and depression severity. A dose-response association was found (Chapter 2), as those persons with higher depressive and anxiety symptoms were less active and had reduced circadian rhythm amplitude. Therefore, it could be concluded that physical inactivity and low circadian amplitude are general indicators of depression and anxiety.

Reduced daily activity level and circadian rhythm amplitude may be indicative of psychomotor retardation, withdrawal from normal activities of daily living (7) and

circadian impairments (8). The association between physical activity and depression has been studied before and appears to be bidirectional. Patients with depression are typically less active, and they experience a range of barriers to engaging in physical activity such as depressive symptoms, higher body mass index, physical co-morbidity, and lower self-efficacy (9). Low levels of physical activity increase the risk of depression (10) and, physical activity and exercise (i.e. structured physical activity) can improve depressive symptoms (11). A large meta-analysis in the general population (12) demonstrated that sedentary behaviour is associated with an increased risk of developing cardiovascular disease, type 2 diabetes, cardiovascular and all-cause mortality. As persons with depression are less active than the general population, they thus encounter additional risks in developing cardiovascular and chronic diseases and mortality. Physical activity and behavioural activation, predominantly through exercise, may produce an antidepressant effect through multiple biological and psychosocial pathways (13). Neuroplasticity, neuroendocrine responses, inflammation and oxidative stress have been suggested to play a role at a biological level. Several psychosocial factors accompany, and potentially interact with, these biological changes to influence depression, such as self-esteem (13). While there is less research into the psychosocial benefits of exercise on depression, they are likely to be of parallel importance. As we observed lower physical activity across all symptom dimensions, physical activity and behavioral activation may be of help to all patients with depression as it may produce an antidepressant effects through multiple biological and psychosocial pathways.

As reviewed by Vadnie and McClung (2017), multiple mechanisms can explain the association between circadian rhythm disruptions and mood disorders. One of the main theories is that disrupted circadian rhythms in the master pacemaker, or suprachiasmatic nucleus (SCN) may be the cause of mood disturbances. However, also other environmental factors, such as light, or genetic perturbations may influence mood independently from the central clock. Additionally, other studies have suggested that sleep and circadian rhythm disturbances may be symptoms of mood disorders. As dampened circadian amplitude was associated with all symptom dimensions, circadian rhythm interventions such as behavioural activation may be administered as adjunctive treatment to all patients with depression.

Associations at the individual-level

As most of our analyses are performed at the group-level, these associations may be not the same for all individuals. Indeed, as we have shown in Chapter 6, the longitudinal association between physical activity and affect may differ from person to person. Although some people experienced enhanced affect in response to higher levels of physical activity, other people experienced the opposite or no clear effect. Physical activity and exercise may therefore be not be beneficial for all per-

sons with depression and anxiety. These results may also explain why research on physical activity interventions to treat mental health disorders is often inconsistent and meta-analyses have demonstrated a range of effect sizes and large heterogeneity (15), and translation of research finding into clinical practice is hampered (16). Our results highlight the advantage of using ambulatory assessment tools and idiographic approaches for future research to hopefully improve on effectiveness of physical activity interventions in patients with depression and anxiety.

Are ambulatory assessment estimates better than traditional self-reported or subjective measures of sleep, circadian rhythm and physical activity?

Answer: not always, it depends on what you want to measure. Actigraphy enhances the assessment of sleep, circadian rhythms and physical activity but it may also measure different aspects compared to self-reported questionnaires. Self-reported sleep remains an important indicator of psychopathology.

In this thesis, we often found differential associations between sleep, circadian rhythm, physical activity patterns and psychopathology when using subjective measures and actigraphy estimates. Specifically, we found reduced physical activity level and daily rhythm disturbances among those with depressive and anxiety disorders compared to controls using objective measures, but not using self-reported information (Chapter 2). In addition, while persons with current depression/anxiety reported more insomnia and both shorter and longer sleep duration compared to controls, actigraphy-based measures were not different across diagnostic groups (Chapter 2). We also found a bidirectional longitudinal association between EMA-based sleep quality and affect. Better EMA-based sleep quality was longitudinally associated with higher affect scores the following day and higher affect scores are longitudinally associated with better sleep quality the following night. However, no bidirectional association was found between actigraphy-assessed sleep and affect (Chapter 5).

The low correlations between objective/actigraphy-based measures and self-reported estimates (Chapter 2 and Chapter 5) suggest that objective and self-reported measures capture different aspects. For instance, it is well known in the literature that self-reported sleep and objective sleep are two very different concepts (17). The first provides information about a person's perception about his/her sleep quantity and quality. The latter refers to the objective measure of sleep with actigraphy or other tools such as polysomnography, the gold standard for the assessment of sleep. Self-reported sleep often reflects the sleep misperception which is more common in patients with severe depressive and anxiety symptoms (18), and is influenced by their negative perception. This tendency to misperceive sleep does not preclude the presence of a real sleep deficit (17). Perhaps the increased worry associated with insomnia makes it more difficult for patients to move into the deeper stages of

sleep and the lighter stages of sleep may be more likely to be perceived as wake (17). It should be also mentioned that the tendency to misperceive sleep may be considered as a "prodromic or transitional state" in the development of insomnia that is characterized by a serious objective sleep deficit (17). Thus, actigraphy may be used to determine whether self-reported sleep problems are not consistent with objective sleep, and whether the patient would potentially benefit from psychologic treatments to reverse misperception, such as cognitive behavioural therapy (19). It is also important to mention that the objective estimation of sleep with actigraphy may be limited and it will be discussed further in the Methodological Consideration section.

Actigraphy may therefore enhance the assessment of sleep, circadian rhythm and physical activity compared to more traditional tools. However, self-reported sleep may an important indicator of psychopathology and therefore target of psychologic treatments to reverse misperception, such as cognitive behavioural therapy.

Methodological considerations

Assessment of sleep with wrist-worn actigraphy devices

Although actigraphy provides an estimate of sleep parameters such as sleep duration, sleep efficiency, it does not yield estimates of sleep stage, such as REM period that may be associated with depression. In addition, it was not possible to extrapolate actigraphy sleep estimates indicative of insomnia such as sleep-onset latency (i.e., time to transit from full wakefulness to sleep) and wake after sleep onset (i.e., periods of wakefulness occurring after sleep onset). Studies have also shown that actigraphy lacks the precision of the gold standard polysomnography that provides greater insight into sleep problems in people with depression or anxiety (20). Because in actigraphy, sleep is inferred from a lack of movement, there may be some misclassification of sleep among those who are awake but motionless. Therefore, the technique is biased toward overestimating total sleep duration, which may lead to incorrectly minimizing the severity of sleep disturbances.

Ecological Momentary Assessment limitations

As summarized in the systematic review of Colombo et al (21), Ecological Momentary Assessment has several advantages but also has some limitations. Although studies using Ecological Momentary Assessment has shown a quite high compliance, some patients may perceive this tool as time-consuming. Patients are required to complete multiple assessments throughout a day, and protocols often last 2 or more weeks. Frequent momentary questionnaires of mental well-being may also be perceived as slightly more burdensome to the persons with affective disorders

(22) compared to persons with not disorders. In addition, although research has shown that Ecological Momentary Assessment is feasible in the short term, research assessing Ecological Momentary Assessment for prolonged time periods (e.g., 12 months) is limited and therefore compliance in the long term is still unclear. For instance, patients may engage less with Ecological Momentary Assessment after long time periods. Another important consideration is that patients taking part to this study may be highly motivated and therefore the high adherence may not be generalizable to real world settings.

Study design

The observational study design can only point to areas of interest for monitoring and interventions, but does not allow us to make definitive recommendations on such interventions. Clinical trials should be implemented to further investigate mobile technologies with their intended clinical application.

Statistical analysis

The currently used methodology in this thesis may be limited when studying longitudinal associations between sleep, physical activity and affect. As shown in Chapter 6, unique associations may be present at the individual level and new statistical methods may take that into account. For instance, Group Iterative Multiple Model Estimation (GIMME) can be used to study associations at the group-level and at the individual level from time-series. At the same time, it can be used to visualise and describe individual and personalised models of psychopathology.

Clinical implications

Can ambulatory assessment tools be used in clinical practice?

Answer: Yes, they might be used in clinical practice as complementary tools to provide more personalized psychological treatments, and monitor patients with depression and anxiety. However, they still can't be used routinely in clinical practice or as sole tool to measure sleep, circadian rhythms and physical activity. Although ambulatory assessment tools are very promising tools in psychiatry, systematic reviews (21) reveal the need of high quality clinical trials to bridge the gap between research and clinical practice.

As actigraphy and Ecological Momentary Assessment were able to capture several associations with psychopathology, this thesis confirmed the ecological validity of ambulatory assessment tools in measuring (self-reported and objective) sleep, circadian rhythms, physical activity and affect. Ambulatory assessment tools may be complementary tools to treatment that may help personalize psychological inter-

ventions and more broadly they may be used monitor patients with depression and anxiety.

Sleep interventions may be given not only to patients with sleep problems but also to patients with somatic/vegetative symptoms. Behavioral activation and physical activity interventions may be promoted in all patients with depression and anxiety. However, individual differences may play a role in the effectiveness of these interventions. As mobile technologies can in real-time monitor patients, mobile technologies may be an add-on tool to psychotherapy. Behavioural interventions, such as behavioural activation and cognitive-behavioural therapy, may be automatically recommended by intelligent algorithms based on physical activity or sleep data collected by ambulatory assessment tools. An example of this are Ecological Momentary Interventions (23), in which psychological and behavioural interventions are delivered through smartphones and personal mobile devices to elicit short-term mood changes.

Actigraphy-based physical activity level and Ecological Momentary Assessment-based sleep may be indicators of treatment response. For instance, as improvement in depression with antidepressant medications have been linked with greater daytime activity levels (24) when using actigraphy, the continuous measurement of daily activity with wrist-worn actigraphy may help to monitor treatment effects (19). Although, recent clinical trials have employed actigraphy to monitor behavioral activation therapy (25) and sleep deprivation (26) as adjunctive treatments to usual care, or as a tool to complement behavioral activation (27), more research is needed to clarify whether actigraphy may be used to monitor treatment outcomes of such interventions.

Actigraphy-based physical activity level and Ecological Momentary Assessment-based sleep may be also used to predict short-term and long-term mood changes, detect worsening of depressive and anxiety symptoms and perhaps predicting relapse. Detecting early signs of future deterioration is very important as it may help delivering timely preventive interventions. The Remote Assessment of Disease and Relapse – Central Nervous System (RADAR-CNS) study (28) is an example of the use of mobile technologies to predict early signs of depressive relapse in patients with lifetime diagnosis of depression. Future findings will tell whether mobile technologies may play a role in preventing depressive relapse.

Ambulatory assessment tools may also be very useful for patients to improve their communication with clinicians, provide educational material on psychiatric disorders as well as to provide feedback on their affect, sleep and physical activity patterns (29). Similarly to the biofeedback-based treatments for insomnia (30), integrat-

ing mobile technologies with apps summarizing affect, physical activity and sleep may provide feedback to patients. This may help raise patients' awareness, and may help them to gain control. An example of providing feedback to patients is through dashboards summarizing their sleep and physical activity patterns over a period of time. From a broader prospective, mobile technologies may be better integrated into mental health care, given their good social acceptance and with relatively lower costs compared to traditional interventions.

Barriers to clinical implementation

However, first some conditions should be met before ambulatory assessment tools could play a role in clinical practice. Although it has been suggested that actigraphy could be used to follow the progression of depression treatment, it is still unclear how sensitive and specific actigraphy is for the characterization of this change in psychological state (19). Which actigraphy variables are best suited for monitoring purposes and definitions of clinically relevant improvement on these variables needs to be examined. Interpretation is also not always immediate (e.g., relative amplitude between daytime and night time activity) and clinicians may need additional training for the use of devices in the clinical practice. Wearing research devices such as a GENEActiv device, may be experienced as stigmatizing as a patient may be asked for its use in public (31,32). Popular commercial activity trackers are aesthetically pleasing and therefore maybe less stigmatizing, but at a cost of lower quality data – whether these devices are suitable for monitoring treatment effects is unknown (31). Currently, the majority of devices used in research settings need to be connected to a computer to download data and to extract variables with the use of specific software, resulting in a time-consuming procedure. In the future, devices with Bluetooth compatible connectivity and consumer devices are likely to become more common, allowing the real-time synchronisation of data on the patient's smartphone app and on a data visualisation dashboard. Data may become readily available and interpretable for the clinician. Platforms and servers that send encrypted data only and meet all GDPR requirements are needed to ensure safe handling of the data.

Recommendations for future research

Mobile technologies appear promising ambulatory tools to monitor patients with depression and anxiety. Although the low cost and scalability of wrist-worn actigraphy devices and smartphone facilitate a potential wealth of behavioral and psychological data, clinical implementation awaits further evidence based on epidemiological and empirical data.

First, as the relationship between sleep, circadian rhythms and physical activity and

psychopathology has not been extensively studied before, more research is needed to replicate our findings in other samples. Replication may be very important to further validate our results on other samples with depression and anxiety and, understanding which variables are more consistently associated with psychopathology. This may help, for instance, to identify possible digital biomarkers of depression and anxiety (33) and to choose clinical trial outcomes (34) when assessing the effectiveness of a treatment.

Second, as this thesis has assessed the relationships over a 2-week period, several questions are still open on the association between sleep, circadian rhythms and physical activity with psychopathology. Future research using a long-term longitudinal study design (e.g., 1 or 2 years) may specifically assess the value of actigraphy and Ecological Momentary Assessment variables to predict long-term outcomes such as relapse or response to treatment. For instance, the RADAR-CNS study (28) is assessing whether data collected with mobile technologies may be a composite digital signature of depression relapse in order to early intervene and prevent worsening of symptoms.

Third, as associations at the individual-level may be different than associations at the group level, idiographic approaches may also be promoted in future research to unravel the relationships between sleep, circadian rhythm and physical activity and psychopathology at the individual level. Observational studies at the individual level may provide new insights on personalized diagnostic information about potential risk and protective factors, yielding person-tailored treatment advice and detecting psychological changes during a therapeutic process (16). Idiographic analyses may enrich and complement analyses at the group level .

Finally, future research should focus on implementing high quality clinical trials (21) to assess the use of mobile technologies to provide personalize treatments. Personalized cognitive and behavioral interventions to improve symptoms and affect in patients with depression and anxiety should be explored in future clinical trials with the use of mobile technologies. For instance, a recent randomized controlled trial has been set-up to support psychological treatment in depressed patients with personalized Ecological Momentary Assessment and actigraphy monitoring and feedback (35). However, more research is needed to translate our results to the clinical practice.

To conclude

This thesis extensively examined and demonstrated that disturbances in sleep and circadian rhythms and altered physical activity assessed with ambulatory assessment tools are associated with psychopathology. Although actigraphy-assessed sleep disturbances are not associated with depression and anxiety diagnoses, longer sleep duration assessed with actigraphy is more frequent among people with higher depressive symptoms and somatic/vegetative symptoms. In addition, higher subjective sleep quality assessed with Ecological Momentary Assessment is longitudinally associated with better affect. Low physical activity levels and dampened circadian amplitude are consistently associated with psychopathology and therefore are general indicators of depression and anxiety. However, individual differences exist and may be taken into account when providing cognitive and behavioral interventions. While more research is needed on validity, form and content of ambulatory assessments for psychiatric populations, mobile technologies are a promising to aid personalization of treatment and monitoring of treatment response. Such applications should be explored in future epidemiological and clinical studies.

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Summary

Background

Depression and anxiety are highly prevalent psychiatric disorders. More than 300 million people are affected by depression and nearly the same number of people suffer from a range of anxiety disorders. Depression is ranked by the World Health Organization (WHO) as the single largest contributor to global disability, and anxiety disorders are ranked 6th.

Disturbances in sleep and circadian rhythm and altered physical activity have long been recognized as core features of depression and anxiety. Sleep problems, such as experiencing insomnia or hypersomnia nearly every day is also one of the DSM-V diagnostic criteria of depressive disorders. Disturbances in sleep and circadian rhythm and altered physical activity are traditionally assessed using self-reported questionnaires and have been extensively studied in epidemiological studies. Several studies reported that depression and anxiety are consistently associated with sleep difficulties. Sleep disturbances are characterized most frequently by insomnia, but also by hypersomnia in some individuals. Overall, sleep disturbances include reduced sleep duration, longer time to fall asleep and more awakenings during the night and lower sleep quality. Circadian rhythm disturbances often occur in patients with depression and anxiety. Chronotype or the individual's time-of-day preference for morningness or eveningness is especially studied in persons with depression and anxiety and it is related to circadian rhythms. Evening chronotype has been linked to depression and anxiety. Depression and anxiety have also been found to be associated with altered physical activity. Altered forms of physical activity are not only limited to sedentary behaviour and low daily activity levels, but psychomotor retardation, agitation, and withdrawal from normal activities of daily living as well.

Although traditional self-reported questionnaires have high validity and reliability, they are often limited in detecting sudden changes in patient's symptoms. Additionally, most patients have negative and recall bias while completing assessment questionnaires and may recall their symptoms as worse than they present. As most symptoms are not continuously tracked outside the clinical setting or between treatment sessions, there has been a recent and significant increase in research to identify novel methods to measure depressive and anxiety disorders.

Ambulatory assessment tools including wrist-worn actigraphy devices and smartphones may provide new opportunities for diagnosis, treatment and monitoring of depression and anxiety. As ambulatory assessment tools can provide a real-time and real-world measurements, they may be used to refine the diagnostic process, tailor treatment, improve the monitoring for actionable outcomes, such as identify early

signs of relapse and give feedback to patients about their condition. Ambulatory assessment tools have become widely used in psychiatric research to measure disturbances in sleep and circadian rhythm and, physical activity alterations. However, more research is needed to understand the added value of these tools in psychiatric clinical practice.

Sample

This thesis is mainly using data from the Netherlands Study of Depression and Anxiety (NESDA). NESDA was designed to investigate the course of depressive and anxiety disorders over a period of several years and the factors that influence the development and prognosis of such disorders. 2981 Participants were initially included at the baseline assessment in 2004-2007, and seen for the fifth time at the nine-year follow-up assessment wave (2014-2017) for a regular follow-up interview, including a psychiatric diagnostic interview. Three hundred sixty-seven siblings of a subsample of NESDA participants were (also) included by asking NESDA participants at the regular nine-year follow-up interview for their consent to approach their siblings. A sub sample from NESDA, consisting of 384 people, was selected to participate in the Ecological Momentary Assessment & Actigraphy sub-study (NESDA-EMAA). Among demographic, psychiatric and lifestyle characteristics, data from ambulatory assessment tools measuring negative and positive affect as well as actigraphy simultaneously during 2 weeks were collected at the nine-year follow-up assessment.

Thesis aim

This thesis focuses on examining sleep, circadian rhythm and physical activity assessed with ambulatory assessment tools in depressive and anxiety disorders.

Important findings of this thesis

This thesis extensively examined the relationships between sleep, circadian rhythms, physical activity and psychopathology using ambulatory assessment tools. Specifically, it emphasizes the role of actigraphy and Ecological Momentary Assessment (EMA) to assess sleep, circadian rhythms and physical activity in persons with depression and anxiety.

In **Chapter 2**, we studied the relationships between sleep, circadian rhythms and physical activity with depression and anxiety by using actigraphy and self-reported questionnaires. Specifically, we found reduced physical activity level and daily rhythm disturbances among those with depressive and anxiety disorders compared to controls using actigraphy-assessed measures, but not using self-reported information. By contrast, self-reported but not actigraphy-assessed sleep measures differed between persons with depressive and anxiety disorders vs controls. In addition,

we studied the associations of sleep, circadian rhythms and physical activity with clinical characteristics (i.e., severity of depressive and anxiety symptoms, number of psychiatric diagnoses, duration of depressive and/or anxiety disorders and antidepressant use). We found evidence for dose-response associations as those with more severe depressive and anxiety symptoms were significantly less active and showed longer sleep duration and lower relative amplitude between day and night activity level assessed with actigraphy.

In **Chapter 3**, we studied the associations between sociodemographic, health and lifestyle, sampling, and mental health determinants and physical activity patterns. We also explored the use of two more advanced statistical techniques also known as Functional Data Analysis methods: (a) Functional Principal Component Analysis (fPCA) was used to extract motor activity patterns assessed with actigraphy; (b) function-on-scalar regression was used to assess the association of psychopathology and other determinants with timing of activity. Specifically, we showed that data-driven features of daily motor activity extracted with fPCA reflect commonly studied factors such as the intensity of daily activity and preference for morningness/eveningness. Presence and severity of depression/anxiety disorders were found to be mainly associated with intensity of daily activity but not with timing of activity. Age, working and season were most strongly associated with overall daily activity patterns and timing of activity.

In **Chapter 4**, we explored the heterogeneity of depression in the association with sleep, circadian rhythm and physical activity assessed with actigraphy. To examine the heterogeneity of depression, individual depressive symptoms were clustered in three symptom dimensions: mood/cognition, somatic/vegetative and sleep. We found that all three symptom dimensions were associated with actigraphy-based low physical activity and dampened circadian rhythms. Therefore, these seem to be general indicators of depression. However, sleep disturbances appeared more linked to the somatic/vegetative and sleep dimensions.

In **Chapter 5**, we studied the bidirectional longitudinal associations between actigraphy and EMA-based sleep and affect the same day. Better EMA-based sleep quality was longitudinally associated with improved affect the same day especially in persons with current depressive and/or anxiety disorders. On the other hand, better affect on the preceding day was longitudinally associated with higher EMA-based sleep quality. No bidirectional longitudinal association was found between EMA-based and actigraphy-based sleep duration and affect.

In **Chapter 6**, we examined the bidirectional longitudinal associations between actigraphy-assessed physical activity and affect in a 3-hour time frame. Higher physi-

cal activity level was longitudinally associated with improved subsequent affect with enhanced positive affect and reduced negative affect, especially in persons with current depression and/or anxiety. Better mood (i.e., higher positive and lower negative affect scores) was also associated with subsequent higher activity level. In addition to group-level analyses, we also explored the associations at the individual level. Heterogeneity was found in the within-person bidirectional association between physical activity and affect, indicating that the associations may differ from person to person. For instance, a positive effect of physical activity on subsequent affect was found for some people, while no clear effect or a negative effect were found for others.

Conclusion

This thesis extensively examined and demonstrated that disturbances in sleep and circadian rhythms and altered physical activity assessed with ambulatory assessment tools are associated with psychopathology. Although actigraphy-assessed sleep disturbances are not associated with depression and anxiety diagnoses, longer sleep duration assessed with actigraphy is more frequent among people with higher depressive symptoms and somatic/vegetative symptoms. In addition, higher subjective sleep quality assessed with Ecological Momentary Assessment is longitudinally associated with better affect. Low physical activity levels and dampened circadian amplitude are consistently associated with psychopathology and therefore are general indicators of depression and anxiety. However, individual differences exist and may be taken into account when providing cognitive and behavioural interventions. While more research is needed on validity, form and content of ambulatory assessments for psychiatric populations, mobile technologies are a promising to aid personalization of treatment and monitoring of treatment response. Such applications should be explored in future epidemiological and clinical studies.

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Sonia Difrancesco was born in Milano, Italy, on January 19th, 1990.

She completed her secondary education (scientific lyceum) at Istituto Maria Immacolata in Gorgonzola in 2009. Her education trajectory continued at the Polytechnic University of Milano where she obtained her bachelor's degree in Biomedical Engineering in 2013. During the last year of her bachelor's degree, she discovered her interest for medical informatics and analysis of biomedical signals.

Therefore, after that, she obtained her master's degree in Biomedical Engineering at the University of Pavia where she could dive deep into (medical) data science, biomedical signal processing and healthcare technologies. Her ambition and curiosity brought her to do an internship at the University of Manchester (UK) where she built an algorithm to analyze GPS data collected with smartphones in patients with schizophrenia.

In 2017, Sonia started to work as a PhD Candidate at the Department of Psychiatry of the Amsterdam University Medical Center (Amsterdam UMC), location VUmc under the supervision of prof. dr. Brenda W.J.H. Penninx and dr. ir. Femke Lamers. During the following years, she investigated the relationship between sleep, circadian rhythm and physical activity and depression and anxiety using data collected with ambulatory assessment tools including wrist-worn actigraphy devices and smartphones.

Conform to her strong interest for technological innovation in healthcare and her commitment to bring science to real-world applications, she is now working at the Dutch startup Breathomix as Quality Officer. With an enthusiastic team, she is contributing to bring a breath analyzer device for the ruling out of covid-19 infections (and many more clinical applications in the future) to the market.

Publication list

Difrancesco S, Penninx BWJH, Merikangas KR, van Hemert AM, Riese H, Lamers F. Within-day bidirectional associations between physical activity and affect: A real-time ambulatory study in persons with and without depressive and anxiety disorders. *Submitted for publication.*

Difrancesco S, Penninx BWJH, Antypa N, van Hemert AM, Riese H, Lamers F. The day-to-day bidirectional longitudinal association between objective and self-reported sleep and affect: An ambulatory assessment study. *Journal of affective disorders* 2021, 283, 165-171.

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Difrancesco S, Lamers F, Riese H, Merikangas KR, Beekman ATF, van Hemert AM, Schoevers RA, Penninx BWJH. Sleep, circadian rhythm and physical activity patterns in depressive and anxiety disorders: a 2-week ambulatory assessment study. *Depression and anxiety* 2019, 36 (10), 975-986.

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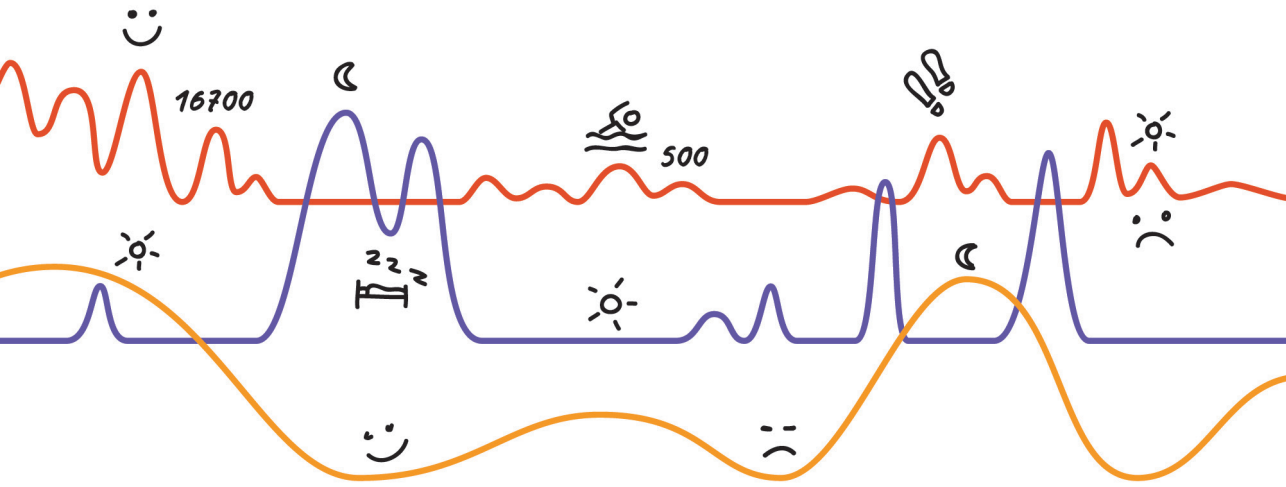
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