

# 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 6<sup>th</sup>.

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.