Sleep and mental health in middle-aged and elderly persons

A population-based approach

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Sleep and Mental Health in Middle-aged and Elderly Persons
A population-based approach

Slaap en mentale gezondheid in personen van middelbare leeftijd en ouderen: Een populatie-gebonden aanpak

Proefschrift

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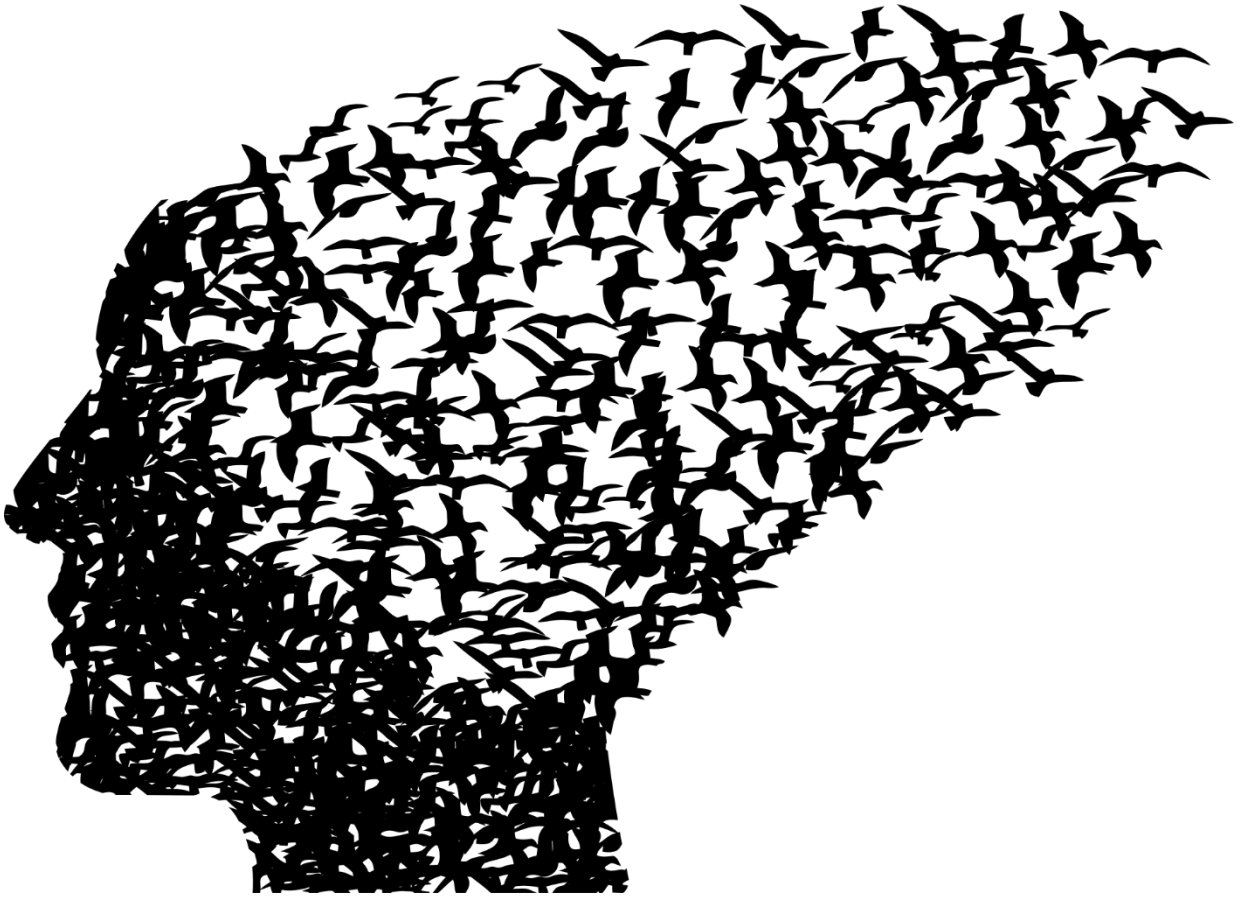

“Slapen is geen geringe kunst:
je moet er de hele dag voor wakker blijven.”

(Friedrich Nietzsche, 1844 - 1900)

Origineel: “*Keine geringe Kunst ist schlafen: es thut schon, noth, den ganzen Tag darauf hin zu wachen*.”

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TABLE OF CONTENT

1

GENERAL INTRODUCTION

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It is often when we dream that we have our best ideas and most thoughtful insights, even though we are seemingly unconscious. Some dreams even substantially changed our view on science. For example, the mapping of the Periodic Table is based on a dream of Dmitri Mendeleev, where he saw all the elements felling right into place and Einstein's theory of relativity was based on a dream about him and a farmer.[1] Besides dreams being the inspiration for several ground-breaking inventions by humans, sleep in general is one of our most important basic needs. In fact, we do understand that sleep is vital for an individual's survival,[2] but so far we we do not completely understand why.

Research so far has reported that poor sleep has a major impact on global health.[3] This is partly because poor sleep has been associated with many health outcomes, including cardiovascular disease, and neurodegenerative disease.[4,5] Even more so, sleep has been frequently associated with mental health constructs, such as depression, stress and anxiety.[5,6] In addition to a consequence of poor mental health, sleep and disrupted 24-hour activity rhythms have also been implicated as potential risk factors or early symptoms for many mental health constructs.[7,8] However, most studies so far have been based on a cross-sectional design. Randomized control trials can be used to estimate causality in the association between sleep and mental health, however these studies investigated the association in only one direction and mostly over a relative short period in time.[9,10] To be able to draw conclusions on the bidirectionality of these associations and gain insight in the function of sleep and 24-hour activity rhythms in mental health over a longer period of time, studies using repeated measures for both sleep and mental health are required.

Poor sleep and mental health problems are common in the adult population worldwide.[11,12] The high prevalence and observed associations of poor sleep with mental health problems can be an explanation for the frequent co-occurrence of mental health constructs. Comorbidity of mental health constructs can make treatment of either of these constructs substantially more complicated.[13] Following the motto '*better safe than sorry*' (voorkomen is beter dan genezen), we could speculate that prevention of mental health problems and poor sleep is just as important as treatment of comorbid psychopathology.[14] In this light, instead of focusing only on those with confirmed psychopathology, studying the full population might benefit our understanding of the role of poor sleep in onset or development of mental health problems in the general population. This could help to confirm sleep as an early risk factor for

mental health problems and support the importance of early intervention of poor sleep in the general population to prevent development of psychopathology.[15]

To further improve our understanding of the association between poor sleep and mental health problems researchers should use the opportunities of sleep research to its full potential. Sleep provides a unique opportunity to gain insight in mental health because it is possible to assess subjective sleep experience as well as to estimate objective indicators of sleep. On one hand, the subjective experience of sleep can be assessed using sleep diaries or questionnaires and reflects psychological aspects of the association of sleep with mental health.[16] On the other hand, objective sleep reflects the more physiological aspects of sleep and can improve our understanding of potential underlying biological mechanisms of sleep.[17] The current golden-standard to assess objective sleep is polysomnography (PSG), where different sensors are attached to the participants' body to measure brain waves, eye movements, muscle tone, body movements, heart rhythm, and breathing patterns during the night.[18] For example, PSG can be used to measure sleep stage durations, spectral power, and indicators of global sleep, such as total sleep time, sleep onset latency, sleep efficiency, and wake after sleep onset.[18] An alternative to estimate objective sleep that is more suitable for large samples is actigraphy, where participants continuously wear an accelerometer around the wrist for a number of days.[19] Actigraphy can be used to estimate indicators of global sleep and 24-hour activity rhythms.[19,20] Even though actigraphy is more feasible to apply on large populations, it has less detailed information on sleep when compared to PSG. Our understanding of the association between sleep and mental health has also been hampered, because so far many studies did not use the potential of PSG or actigraphy and focused mainly on total sleep time or insomnia.[6,21,22] Improving our knowledge on how different aspects of sleep are associated with different mental health outcomes could be helpful in understanding of the role of sleep in the onset or recurrence of mental health problems and potential underlying biological mechanisms. This knowledge is essential to improve treatment options for those with mental health problems that are accompanied or preceded by poor sleep.

The aim of this thesis, embedded in the Rotterdam Study,[23] is to identify the role of subjective and objective sleep in development of mental health outcomes in a population-based cohort of middle-aged and elderly persons. Within the Rotterdam Study sleep was assessed using questionnaires in all participants and using actigraphy or PSG in subsamples.[23] This allowed

us to assess the association of multiple indicators of sleep with mental health within the same population-based cohort. The long-term follow-up of the Rotterdam Study furthermore allowed us to assess the longitudinal, and even bidirectional, associations of sleep with mental health and in this way gain understanding about the role of sleep in mental health. The broad scale of measurements that was collected each round enabled us to study sleep in relation with multiple mental health outcomes and to explore new methods of studying mental health, such as network analyses.[24,25]

First, in **chapter 2** we discuss the association of sleep and 24-hour activity rhythms with health. We reviewed recent studies on 24-hour activity rhythms in elderly people and observed associations with multiple health outcomes, including mental health and neurodegenerative disease (chapter 2.1). Within the population of the Rotterdam Study, we studied the longitudinal association of objective, actigraphy-estimated, sleep with depressive symptoms (chapter 2.2) and complicated grief (chapter 2.3). In **chapter 3**, to improve our understanding of the association between tinnitus and mental health, we estimated how tinnitus is associated with subjective (chapter 3.1) and objective (chapter 3.2) sleep. To improve our understanding of the association between sleep and the stress system, in **chapter 4** we estimated how objective sleep is associated with functioning of the stress system. We assessed how actigraphy-estimated sleep (chapter 4.1) and polysomnographic sleep (chapter 4.2) were associated with functioning of the negative feedback loop of the hypothalamic-pituitary-adrenal axis, as an indicator for functioning of the stress system. In **chapter 5** we tried to unravel the complex network structure of psychosocial health factors. We assessed how symptoms of depression and anxiety are associated to other psychosocial health factors, during a lockdown (chapter 5.1). Lastly, **chapter 6** covers a general discussion of the work summarized in this thesis, discussing the key findings, methodological considerations, and implications for clinical practice and future research.

References:

1. Walsh, C. *9 inventions inspired by dreams*. 2016; Available from: https://www.bedguru.co.uk/9-inventions-inspired-by-dreams.
2. Cirelli, C. and G. Tononi, *Is sleep essential?* PLoS Biol, 2008. 6(8): p. e216.
3. Olfson, M., et al., *Insomnia and Impaired Quality of Life in the United States.* The Journal of clinical psychiatry, 2018. 79(5): p. 17m12020.
4. de Feijter, M., T.S. Lysen, and A.I. Luik, *24-h Activity Rhythms and Health in Older Adults.* Current Sleep Medicine Reports, 2020. 6: p. 76-83.
5. Gadie, A., et al., *How are age-related differences in sleep quality associated with health outcomes? An epidemiological investigation in a UK cohort of 2406 adults.* BMJ open, 2017. 7(7): p. e014920.
6. Hertenstein, E., et al., *Insomnia as a predictor of mental disorders: a systematic review and meta-analysis.* Sleep medicine reviews, 2019. 43: p. 96-105.
7. Kecklund, G. and J. Axelsson, *Health consequences of shift work and insufficient sleep.* Bmj, 2016. 355: p. i5210.
8. Luik, A.I., et al., *24-hour activity rhythm and sleep disturbances in depression and anxiety: A population-based study of middle-aged and older persons.* Depression and anxiety, 2015. 32(9): p. 684-692.
9. Gee, B., et al., *The effect of non-pharmacological sleep interventions on depression symptoms: A meta-analysis of randomised controlled trials.* Sleep medicine reviews, 2018.
10. Carney, C.E., et al., *Cognitive behavioral insomnia therapy for those with insomnia and depression: a randomized controlled clinical trial.* Sleep, 2017. 40(4): p. zsx019.
11. Bao, Y.P., et al., *Cooccurrence and bidirectional prediction of sleep disturbances and depression in older adults: meta-analysis and systematic review.* Neuroscience & Biobehavioral Reviews, 2017. 75: p. 257-273.
12. World Health, O., *Depression and other common mental disorders: global health estimates.* 2017.
13. Borsboom, D., et al., *The small world of psychopathology.* PloS one, 2011. 6(11): p. e27407.
14. Rose, G.A., K.-T. Khaw, and M. Marmot, *Rose's strategy of preventive medicine: the complete original text*. 2008: Oxford University Press, USA.
15. Buysse, D.J., *Sleep health: can we define it? Does it matter?* Sleep, 2014. 37(1): p. 9-17.
16. Buysse, D.J., et al., *Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI).* Sleep, 1991. 14(4): p. 331-338.
17. Krystal, A.D. and J.D. Edinger, *Measuring sleep quality.* Sleep medicine, 2008. 9: p. S10-S17.

18. Iber, C., *The AASM manual for the scoring of sleep and associated events: Rules.* Terminology and Technical Specification, 2007.
19. Marino, M., et al., *Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography.* Sleep, 2013. 36(11): p. 1747-1755.
20. Ancoli-Israel, S., et al., *The role of actigraphy in the study of sleep and circadian rhythms.* Sleep, 2003. 26(3): p. 342-392.
21. Itani, O., et al., *Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression.* Sleep medicine, 2017. 32: p. 246-256.
22. Grandner, M.A., *Sleep, health, and society.* Sleep medicine clinics, 2017. 12(1): p. 1-22.
23. Ikram, M.A., et al., *Objectives, design and main findings until 2020 from the Rotterdam Study.* European Journal of Epidemiology, 2020. 35(5): p. 483-517.
24. Blanken, T.F., et al., *The role of stabilizing and communicating symptoms given overlapping communities in psychopathology networks.* Scientific reports, 2018. 8(1): p. 1-8.
25. Nuijten, M.B., et al., *Mental disorders as complex networks: an introduction and overview of a network approach to psychopathology.* Clinical Neuropsychiatry, 2016. 13(4/5): p. 68-76.

2

SLEEP AND MENTAL HEALTH

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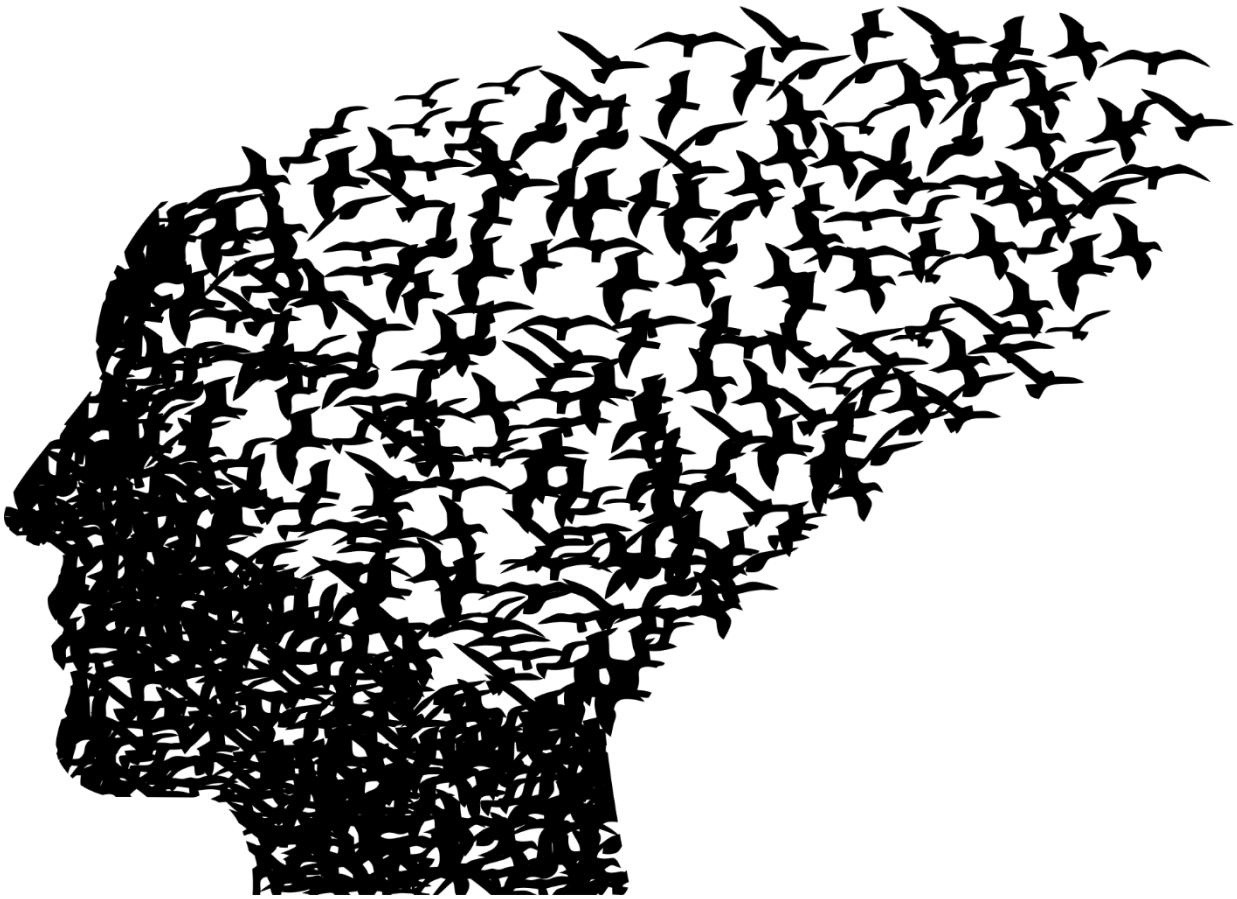

“Diepe nachten geven ons de balans van een stabiel leven.”

(Gaston Bachelard, 1884 – 1962)

Origineel: “*Les nuits profondes nous rendent à l'équilibre de la vie stable.”*

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2.1

24-h Activity Rhythms and Health in Older Adults

Maud de Feijter, Thom S. Lysen, Annemarie I. Luik

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Abstract

Purpose of Review*:* Circadian rhythms, including 24-hour activity rhythms, change with age. Disturbances in these 24-hour activity rhythm at older age have also been implied in various diseases. This review evaluates recent findings on 24-hour activity rhythms and disease in older adults.

Recent Findings*:* Growing evidence supports that 24-hour activity rhythm disturbances at older age are related to the presence and/or progression of disease. Longitudinal and genetic work even suggests a potential causal contribution of disturbed 24-hour activity rhythms to disease development. Interventional studies targeting circadian and 24-hour activity rhythms demonstrate that 24-hour rhythmicity can be improved, but the effect of improving 24-hour rhythmicity on disease risk or progression remains to be shown.

Summary*:* Increasing evidence suggests 24-hour activity rhythms are involved in age-related diseases. Further studies are needed to assess causality, underlying mechanisms, and the effects of treating disturbed 24-hour activity rhythms on age-related disease.

Introduction

The circadian rhythm is integral to physiological processes throughout the body.[1] These approximately 24-hour rhythms are regulated by the master clock located in the brain's suprachiasmatic nucleus (SCN),[2] and are shaped using endogenous and exogenous cues. Together, this ensures that our physiological functioning can be optimized and adapted to changing environmental conditions and social demands.[3]

Circadian rhythms can be observed in a range of physiological and behavioral processes throughout the body, for example fluctuations in clock gene expression, hormone levels, body temperature, and cognitive processes.[1] Although many of these fluctuations are valid and precise markers of the circadian rhythm, they are often less feasible to study when the circadian rhythm needs to be assessed over longer periods of time or in large populations. An accessible, affordable and unobtrusive alternative to measure 24-hour rhythmicity is actigraphy, also known as accelerometry. Actigraphy can measure activity continuously over multiple days, weeks or even months. Naturally, activity is under voluntary control and may therefore misrepresent some of the underlying endogenous rhythms. Yet, measuring 24-hour

activity rhythms with actigraphy has been demonstrated to be a valid method to estimate circadian rhythmicity, in both patients as well as healthy adults.[1,4] With ever increasing recording quality, better storage capacities, longer recording lengths, and the availability of open source algorithms, actigraphy has become a mainstay for studying circadian rhythms in research and clinical practice.[5,6]

Circadian rhythms, and associated 24-hour activity rhythms, are altered with increasing age.[1,7] Older age is also accompanied by an increase in the prevalence of non-communicable diseases.[8] It has been hypothesized that changes in 24-hour activity rhythms might indicate poor health or even pose a risk factor for poor health, not the least because fragmented 24-hour activity rhythms have been associated with an increased risk of mortality.[9] As modern 24/7 society puts a widespread strain on our rhythms, for example through artificial lighting and shift work, it is crucial to better understand the role of 24-hour activity rhythm disturbance in the development of age-related disease. In this review, we will briefly discuss the measurement of 24-hour activity rhythms, give a short overview of age-related changes in 24-hour activity rhythms, and discuss recent findings around 24-hour activity rhythms and some of the most common diseases in older adults.

Measuring the 24-hour activity rhythm

A range of scientific grade actigraphs, typically worn around the wrist, has become available over the past decades. Starting with relatively simple devices measuring activity on one axis, nowadays almost all actigraphs measure movement on three axes and are equipped with additional sensors measuring temperature, light and/or heart rate. Typically, only the activity data has been used to estimate the 24-hour rhythm. Multiple commercial wearables that measure activity have also become available, their value in assessing 24-hour activity rhythms remains to be determined.[10]

Several methods have been developed to derive 24-hour rhythmicity estimates from actigraphy,[4,11,12] the most used methods are based on adapted cosinor models[4,11] and non-parametric models.[12] From these models a range of 24-hour activity rhythms estimates is calculated, which are correlated to some extent.[13] Both methods come with their own set of advantages and disadvantages. For example, non-parametric measures have been suggested to better reflect 24-hour rhythms in elderly persons, because rhythms are generally less

cosine shaped in older adults.[12] In contrast, cosinor measures seem to be associated more consistently with outcomes such as cognitive functioning.[14] A description of the most commonly used cosinor and non-parametric estimates can be found in Table 1.

Table 1: Commonly used cosinor and non-parametric 24-hour activity rhythm estimates.[4,11,12]

Variable	Explanation
Cosinor	
Acrophase	Timing of maximum activity (clock time)
Amplitude	Difference between maximum and minimum value of activity (score)
Mesor	Average activity (counts/min)
Period	Time interval over which cycles repeat (hours)
Pseudo-F	Fit of activity data to the cosine function, indicating rhythm 'robustness' (score)
Non-parametric	
Interdaily Variability	Fragmentation of the rhythm relative to its 24-h amplitude (score)
Intradaily Stability	Stability of activity profiles over days (score)
Relative Amplitude	Normalized difference between most active 10 hours and least active 5 hours (score)
M10 onset	Onset of most active 10-hour period (clock time)
L5 onset	Onset of least active 5-hour period (clock time)

24-hour activity rhythms and aging

Old age is accompanied by multiple changes in the 24-hour activity rhythm, including a well-described phase advance.[13] In recent work a lower amplitude, lower mesor, earlier acrophase, and more fragmented rhythm have been described in older adults.[6,9,15-17] Daytime activity levels are also lower at old age,[18] but nighttime activity levels do not necessarily change in old age.[19] The stability of the 24-hour activity rhythm seems to remain similar across ages,[16] and has even been suggested to be higher in old age.[20] A recent study in 91,105 individuals suggested that age was not associated with relative amplitude,[21] but this study only included persons aged 73 or younger. This fits previous suggestions that 24-hour activity rhythm disturbances are most pronounced in those aged 80 years or older.[9,16]

Older and more recent studies thus both demonstrate that middle-aged and elderly persons have 'dampened' and less robust 24-hour activity rhythms,[6] similar to alterations seen in endogenous measures of the circadian rhythm at older age.[1] It is largely unknown to what extent these changes may be attributed to the aging process per se. They could also be caused by environmental changes that accompany older age, such as retirement, less physical activity, or the emergence of age-related diseases. Probably, a combination of endogenous and exogenous factors play a role in age-related changes in the 24-hour activity rhythm.[1]

24-hour activity rhythms and neurodegenerative disease

Over the last 3 years neurodegenerative disease has been the most studied disease in relation to 24-hour activity rhythms. Indeed, circadian disturbances, including disrupted 24-hour activity rhythms, are common in neurodegenerative disease.[5,22,23] These disturbances are potentially attributable to neurodegenerative processes directly affecting circadian regulatory circuits,[2,24] or indirectly through behavioral symptoms impairing daily functioning and inadequate exposure to exogenous cues. Vice versa, disturbed circadian rhythms have also been hypothesized to contribute to neurodegenerative processes.[5] In the next paragraphs, we will focus on recent findings on the role of 24-hour activity rhythm disturbances in Alzheimer's disease and other dementias, and Parkinson's disease.

Alzheimer's disease and Dementia

Dementia, of which Alzheimer's disease is the most common subtype, is characterized by progressive cognitive decline and impairment in activities of daily living.[25] Disruptions of 24-hour activity rhythms in these patients were first recorded over two decades ago,[26] and have been reviewed recently.[5,14,27] These disruptions predominantly include fragmentation and a reduced amplitude of the 24-hour activity rhythm, and behaviors such as 'sun-downing'[27] and frequent daytime napping.[28] Recent cross-sectional studies report a lower amplitude,[28-30] a lower stability,[29,31] and more fragmentation[29] in patients with dementia. More fragmented 24-hour activity rhythms were also found in persons with early-onset dementia.[32] Together these disturbances substantially impair quality of life of patients and caregivers[33,34] and are thought to be an important determinant for the institutionalization of patients.[27]

Research increasingly focuses on the pre-diagnostic phase of dementia to investigate the potential etiological or predictive role that 24-hour activity rhythm disturbances may have in

dementia. Two recent studies investigated persons with potential prodromal symptoms of dementia, but no evidence was found for an association of phase with subjective cognitive complaints[35] or of amplitude with mild cognitive impairment.[30] This was even though the latter was found to be disturbed in those with Alzheimer's disease.[30] In contrast, some earlier studies have reported a phase advance in persons with mild cognitive impairment compared to healthy controls[36,37] and a higher fragmentation and lower mesor in those with preclinical AD.[16] Data from prospective cohorts provide some further insight into the temporality of the association of 24-hour activity rhythms with dementia. An advanced acrophase was associated with an increased risk of cognitive decline in elderly men,[15] whereas in elderly women a phase delay and lower robustness of the rhythm were associated with an increased risk of dementia and mild cognitive impairment.[38] A higher fragmentation was also related with a decline in cognition measured over the prior 12 years.[39]

Associations of 24-hour activity rhythms with biomarkers of neurodegeneration in non-demented individuals have been investigated to shed further light on the link between 24-hour activity rhythms and dementia. First, fragmentation was most strongly related to a cerebrospinal fluid biomarker profile indicative of Alzheimer's disease, when compared to other disturbances.[16] Additionally, fragmentation was related to temporal lobe atrophy in cognitively unimpaired persons[29] and to loss of gray matter in parietal regions specific to early accumulation of Alzheimer's pathology.[39] Further research remains needed to determine whether 24-hour activity rhythm estimates could also serve as a valid biomarker for dementia.

Parkinson's disease

In Parkinson's disease, which has a notable association with REM sleep behavior disorder,[5] 24-hour activity rhythms disturbances have been hypothesized to occur early in the disease process and to potentially contribute to various symptoms and pathological processes specific to Parkinson's disease.[40] Patients have a higher fragmentation, lower stability, lower amplitude, and lower mesor than healthy controls.[40-42] A low stability is also associated with poorer cognitive performance in Parkinson's disease.[42] It is unclear to what extent the 24-hour activity rhythm estimates are affected by impaired motor functioning associated with the Parkinson's disease diagnosis or dopaminergic treatments for Parkinson's disease.[5]

The longitudinal relation of 24-hour activity rhythms with incident Parkinson's disease has received limited attention so far, but a recent study with 11 years of follow-up showed that daytime actigraphy-estimated inactivity, indicative of 'napping', was associated with increased risk of Parkinson's disease.[43] Longitudinal studies assessing 24-hour activity rhythms in relation to Parkinson's disease in particular, and neurodegenerative disease more broadly, are therefore highly needed.

24-hour activity rhythms and late-life psychiatric disease

Disturbances in 24-hour activity rhythms are related to a range of psychiatric disorders such as depression, anxiety, psychosis and schizophrenia,[44,45] of which some are also common in old age. Depression is of specific interest in the context of this review as a second peak in the prevalence of depression starts around the age of 60 years. Depression, characterized by a depressed mood or a loss of pleasure as a key symptom, and additionally symptoms such as weight change, changes in sleep, psychomotor agitation/ retardation, fatigue, worthlessness, cognitive complaints or suicidality,[46] has a major impact on global health.[47]

Depression

Patients diagnosed with Major Depressive Disorder have a tendency to eveningness, delayed 24-hour activity rhythms, a dampened amplitude and a lower mesor.[17, 48-51] Disturbed 24-hour activity rhythms are also related with the severity of depressive symptoms, even when symptoms are of a subclinical level, which is common in elderly persons. A cross-sectional population-based study of middle-aged and elderly persons found an association of a lower stability and higher fragmentation of the 24-hour activity rhythm with more depressive symptoms.[20,52] A preference for eveningness and a phase delay were also associated with severity of depressive symptoms.[53,54] Potentially, the association of 24-hour activity rhythms and depressive symptoms differs between men and women; in one study associations of disturbed 24-hour activity rhythms with depressive symptoms were found in men but not in women.[55]

Increasing evidence supports that disturbances in the 24-hour activity rhythm are not only apparent during the depressive episode, but might also precede depressive episodes or may persist afterwards.[49] A recent UK biobank study suggested a lower relative amplitude in those with a retrospectively determined lifetime incidence of major depressive disorder, bipolar

disorder and mood instability.[21] A longitudinal study in elderly men reported that both a late acrophase alone and the combination of an early acrophase with a dampened 24-hour activity rhythm amplitude were associated with a faster increase in depressive symptoms over time.[56] Additionally, a Genome-Wide Association Study (GWAS) including 71,500 participants reported a possible association between genetic risk of a low relative amplitude and mood disorders.[45]

It remains unclear to what extent associations between disturbances of 24-hour activity rhythms and mental health are due to medication use.[44,57] There is evidence that these associations are independent of medication use,[56] but we also know that some 24-hour activity rhythm disturbances are related to medication use. For example, eveningness and phase delay potentially hamper the efficacy of antidepressants[58,59] and ketamine might improve 24-hour activity rhythms, independent of its effect on mood.[60]

Other psychiatric disorders in late life

Bipolar disorders, in which the depressive episodes are accompanied by manic episodes, have also been related to disturbances in the 24-hour activity rhythm. Associations seem to be state-dependent, with depressive episodes being accompanied by a phase delay and manic episodes being accompanied by a phase advance.[61, 62] However, the disturbances in the 24-hour activity rhythms might not only be a state marker as the phase advance of 24-hour activity rhythms and lower mesor may persist after successful treatment of bipolar disorder.[44]

For anxiety, relatively common at older age, it was shown that more fragmented 24-hour activity rhythms were associated with higher odds of having an anxiety disorder,[52] and that lower activity levels and a lower mesor were associated with current anxiety.[48] Additionally, disrupted 24-hour activity rhythms have also been linked to more suicidal behaviors,[63, 64] but the causality of this association remains to be determined. Although actigraphy has been used in patients witch schizophrenia, 24-hour rhythmicity has not often been assessed.[65] Only one study assessed 24-hour activity rhythms and did not find an association of 24-hour rhythm estimates with positive or negative symptoms of schizophrenia.[66]

24-hour activity rhythms and other age-related diseases

Aging is accompanied by an increase in other non-communicable diseases such as type 2 diabetes, cardiovascular disease, lung disease, and cancer,[8] which have also been suggested to involve circadian and 24-hour activity rhythm disturbances.[1,50]

Cardio-metabolic disease

Cross-sectional studies reported prolonged napping,[67] a lower amplitude,[68] less stable,[20, 68, 69] and more fragmented[20] 24-hour activity rhythms in middle-aged and elderly persons with a higher Body Mass Index, a well-known risk factor for cardio-metabolic disease. Additionally, less stable 24-hour activity rhythms were associated with increased odds of metabolic syndrome and hypertension in elderly women.[69] Longitudinal work suggests that 24-hour activity rhythm disturbances might already be apparent early on. A longitudinal population-based study reported that a lower robustness of the rhythm and a lower amplitude were associated with an increased risk of overall cardiovascular disease, and that a lower mesor was associated with an increased risk of coronary heart disease.[70] It has also been repeatedly shown that shift work is a risk factor for cardio-metabolic disease, such as type 2 diabetes, obesity and coronary artery disease,[50, 71, 72] the 24-hour activity rhythm has however not been assessed in these studies. Most of these findings have been based on observational studies, making it difficult to determine the underlying mechanisms. Experimental studies in humans do however suggest that short-term circadian misalignment already affects biomarkers for metabolic disease, such as systolic blood pressure and preclinical states of diabetes.[73,74]

Cancer

Disturbed 24-hour activity rhythms are also seen in those suffering from cancer. A study in palliative cancer care reported that 24-hour activity rhythms are more disrupted towards the end of life.[75] Several recent studies also reported an association between 24-hour activity rhythm disturbance and cancer-related mortality, most prominently in lung cancer patients, where early mortality risks were up to 4 times higher in patients with disrupted 24-hour activity rhythms compared to those with robust rhythms.[76,77] More disturbed 24-hour activity rhythms were also associated with a shorter survival time in patients suffering from head and neck cancers[78] and patients receiving palliative cancer care.[75] Cancer treatment also seems to affect the 24-hour activity rhythm, a recent longitudinal study showed that several 24-hour

activity rhythm estimates, including amplitude, worsen with each cycle of chemotherapy in women with breast cancer.[79]

Research agenda

Collectively, these studies suggest that with older age, 24-hour activity rhythms are dampened, more fragmented, and more advanced. Presence of 24-hour activity rhythm disturbances are associated with various age-related diseases. Most evidence is available for dementia and depression but these have also been the most studied diseases in relation to 24-hour activity rhythms. Associations between the 24-hour activity rhythm and disease also differ per 24-hour activity rhythm estimate, which creates a complex picture. Only a minority of studies has investigated the association of 24-hour activity rhythms and health longitudinally, which limits our knowledge on the temporality of associations between 24-hour rhythm disturbances and age-related disease. Although there is some evidence for a possible causal role of 24-hour activity rhythms in disease at old age, more definitive evidence needs to be generated with sophisticated analyses methods in prospective cohort studies and intervention studies.

Studies specifically intervening on circadian rhythms that take into account the 24-hour activity rhythm remain scarce. A number of studies have reported reduced circadian disruption after bright-light therapy in patients with dementia,[80] Parkinson's Disease,[81] depression,[82] cardiovascular disease,[83] and cancer.[84] However, it is largely unknown to what extent intervening on circadian factors and, subsequently 24-hour activity rhythms, improves relevant clinical outcomes such as disease progression or mortality. So far, we do know that interventions focusing on advancing circadian timing, such as early morning bright light therapy have a positive effect on mood. Bright light therapy decreases depression severity in depressed patients,[82] and 8 weeks of dawn-dusk stimulation improved mood and reduced anxiety in elderly persons living in a care home.[85] It remains to be determined if improvement in 24-hour activity rhythms is a mediating factor.

Together, we feel that three items are essential to add to the research agenda to improve our understanding of the role of 24-hour activity rhythms in health at older age. First, implementation of actigraphy in prospective cohort studies has not only been proven feasible, it is also needed to investigate temporality. It particularly creates a unique opportunity if the

24-hour activity rhythm disturbances can be studied before the diagnosis of the disease in population-based cohorts. These studies should ideally include repeated measurements of both disease-related constructs and actigraphy to gain more insight in potentially bi-directional associations. Second, studies have reported successful improvement of circadian rhythms and mental health after interventions focused on the 24-hour rhythm, but effects on somatic conditions are largely unclear. Well-controlled intervention trials that integrate actigraphy and have longer follow-up periods will be needed to assess whether treatment of disturbed 24-hour activity rhythms can reduce disease burden or even alter disease progression or incidence. This could also provide information for any potential preventive effects of targeting 24-hour activity rhythm disturbances. Lastly, as new studies become available with high speed, well-executed meta-analyses will be needed to direct the field. For this aim, a standardized approach using the same estimates and methods between studies will be highly beneficial.

Conclusion

The 24-hour activity rhythm is disturbed in a broad range of age-related diseases. In neurodegenerative disease, psychiatric disease, cardio-metabolic disease and cancer, patients have more phase shifts, lower amplitudes, more fragmented and less stable 24-hour activity rhythms. An increasing number of longitudinal studies suggest that these disturbed 24-hour activity rhythms may also precede disease, but causality remains to be determined. The need for longitudinal observational studies remains substantial, as well as the need for investigating promising interventions for those diseases where circadian disruption could be involved in disease etiology, symptom maintenance or impaired quality of life.

References

1. Hood S, Amir S. The aging clock: circadian rhythms and later life. J Clin Invest. 2017;127[2]:437-46.
2. Swaab DF, Fliers E, Partiman TS. The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. Brain research. 1985;342[1]:37-44.
3. Aschoff J, editor Exogenous and endogenous components in circadian rhythms. Cold Spring Harbor symposia on quantitative biology; 1960: Cold Spring Harbor Laboratory Press.
4. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. Sleep. 2003;26[3]:342-92.
5. Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. Association between circadian rhythms and neurodegenerative diseases. The Lancet Neurology. 2019;18[3]:307-18.
6. Van Someren EJ, Riemersma-Van Der Lek RF. Live to the rhythm, slave to the rhythm. Sleep Med Rev. 2007;11[6]:465-84.
7. Logan RW, McClung CA. Rhythms of life: circadian disruption and brain disorders across the lifespan. Nat Rev Neurosci. 2019;20[1]:49-65.
8. Licher S, Heshmatollah A, van der Willik KD, Stricker BHC, Ruiter R, de Roos EW, et al. Lifetime risk and multimorbidity of non-communicable diseases and disease-free life expectancy in the general population: A population-based cohort study. PLoS Med. 2019;16[2]:e1002741.
9. Tranah GJ, Blackwell T, Ancoli-Israel S, Paudel ML, Ensrud KE, Cauley JA, et al. Circadian activity rhythms and mortality: the study of osteoporotic fractures. Journal of the American Geriatrics Society. 2010;58[2]:282-91.
10. Depner CM, Cheng PC, Devine JK, Khosla S, de Zambotti M, Robillard R, et al. Wearable Technologies for Developing Sleep and Circadian Biomarkers: A Summary of Workshop Discussions. Sleep. 2019.
11. Marler MR, Gehrman P, Martin JL, Ancoli-Israel S. The sigmoidally transformed cosine curve: a mathematical model for circadian rhythms with symmetric non-sinusoidal shapes. Statistics in medicine. 2006;25[22]:3893-904.
12. Van Someren EJW. Actigraphic monitoring of movement and rest-activity rhythms in aging, Alzheimer's disease, and Parkinson's disease. IEEE Transactions on Rehabilitation Engineering. 1997;5[4]:394-8.
13. Mitchell JA, Quante M, Godbole S, James P, Hipp JA, Marinac CR, et al. Variation in actigraphy-estimated rest-activity patterns by demographic factors. Chronobiology international. 2017;34[8]:1042-56.
14. Smagula S, Gujral S, Capps C, Krafty R. A systematic review of evidence for a role of rest-activity rhythms in dementia. Frontiers in Psychiatry. 2019;10:778.
15. Rogers-Soeder TS, Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Cauley JA, et al. Rest-Activity Rhythms and Cognitive Decline in Older Men: The Osteoporotic Fractures in Men Sleep Study. Journal of the American Geriatrics Society. 2018;66[11]:2136-43.

16. Musiek ES, Bhimasani M, Zangrilli MA, Morris JC, Holtzman DM, Ju Y-ES. Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease. JAMA neurology. 2018;75[5]:582-90.
17. Hori H, Koga N, Hidese S, Nagashima A, Kim Y, Higuchi T, et al. 24-h activity rhythm and sleep in depressed outpatients. Journal of psychiatric research. 2016;77:27-34.
18. Wennman H, Pietilä A, Rissanen H, Valkeinen H, Partonen T, Mäki-Opas T, et al. Gender, age and socioeconomic variation in 24-hour physical activity by wrist-worn accelerometers: the FinHealth 2017 Survey. Scientific reports. 2019;9[1]:6534.
19. Ramirez V, Shokri-Kojori E, Cabrera EA, Wiers CE, Merikangas K, Tomasi D, et al. Physical activity measured with wrist and ankle accelerometers: Age, gender, and BMI effects. PloS one. 2018;13[4]:e0195996.
20. Luik AI, Zuurbier LA, Hofman A, Van Someren EJW, Tiemeier H. Stability and fragmentation of the activity rhythm across the sleep-wake cycle: the importance of age, lifestyle, and mental health. Chronobiology international. 2013;30[10]:1223-30.
21. Lyall LM, Wyse CA, Graham N, Ferguson A, Lyall DM, Cullen B, et al. Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing, and cognitive function: a cross-sectional study of 91 105 participants from the UK Biobank. The Lancet Psychiatry. 2018;5[6]:507-14.
22. Weldemichael DA, Grossberg GT. Circadian rhythm disturbances in patients with Alzheimer's disease: a review. Int J Alzheimers Dis. 2010;2010.
23. Hatfield CF, Herbert J, van Someren EJ, Hodges JR, Hastings MH. Disrupted daily activity/rest cycles in relation to daily cortisol rhythms of home-dwelling patients with early Alzheimer's dementia. Brain. 2004;127(Pt 5]:1061-74.
24. Wang JL, Lim AS, Chiang WY, Hsieh WH, Lo MT, Schneider JA, et al. Suprachiasmatic neuron numbers and rest–activity circadian rhythms in older humans. Annals of neurology. 2015;78[2]:317-22.
25. Collaborators GBDD. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18[1]:88-106.
26. Witting W, Kwa IH, Eikelenboom P, Mirmiran M, Swaab DF. Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. Biological psychiatry. 1990;27[6]:563-72.
27. Videnovic A, Lazar AS, Barker RA, Overeem S. 'The clocks that time us'—circadian rhythms in neurodegenerative disorders. Nature Reviews Neurology. 2014;10[12]:683.
28. Weissova K, Bartoš A, Sládek M, Novakova M, Sumová A. Moderate changes in the circadian system of Alzheimer's disease patients detected in their home environment. PLoS One. 2016;11[1]:e0146200.
29. Van Someren EJW, Oosterman JM, Van Harten B, Vogels RL, Gouw AA, Weinstein HC, et al. Medial temporal lobe atrophy relates more strongly to sleep-wake rhythm fragmentation than to age or any other known risk. Neurobiology of learning and memory. 2019;160:132-8.

30. J Wams E, K Wilcock G, G Foster R, Wulff K. Sleep-wake patterns and cognition of older adults with amnestic mild cognitive impairment (aMCI): a comparison with cognitively healthy adults and moderate Alzheimer's disease patients. Current Alzheimer Research. 2017;14[10]:1030-41.
31. Saito Y, Kume Y, Kodama A, Sato K, Yasuba M. The association between circadian rest-activity patterns and the behavioral and psychological symptoms depending on the cognitive status in Japanese nursing-home residents. Chronobiology international. 2018;35[12]:1670-9.
32. Hooghiemstra AM, Eggermont LHP, Scheltens P, van der Flier WM, Scherder EJA. The rest-activity rhythm and physical activity in early-onset dementia. Alzheimer Disease & Associated Disorders. 2015;29[1]:45-9.
33. Bromundt V, Wirz-Justice A, Boutellier M, Winter S, Haberstroh M, Terman M, et al. Effects of a dawn-dusk simulation on circadian rest-activity cycles, sleep, mood and well-being in dementia patients. Experimental gerontology. 2019;124:110641.
34. Smagula SF, Krafty RT, Taylor BJ, Martire LM, Schulz R, Hall MH. Rest–activity rhythm and sleep characteristics associated with depression symptom severity in strained dementia caregivers. Journal of sleep research. 2017;26[6]:718-25.
35. Manousakis JE, Scovelle AJ, Rajaratnam SMW, Naismith SL, Anderson C. Advanced Circadian Timing and Sleep Fragmentation Differentially Impact on Memory Complaint Subtype in Subjective Cognitive Decline. J Alzheimers Dis. 2018;66[2]:565-77.
36. Ortiz-Tudela E, Martinez-Nicolas A, Díaz-Mardomingo C, García-Herranz S, Pereda-Pérez I, Valencia A, et al. The characterization of biological rhythms in mild cognitive impairment. BioMed research international. 2014;2014.
37. Zeitzer JM, Blackwell T, Hoffman AR, Cummings S, Ancoli-Israel S, Stone K, et al. Daily patterns of accelerometer activity predict changes in sleep, cognition, and mortality in older men. The Journals of Gerontology: Series A. 2017;73[5]:682-7.
38. Tranah GJ, Blackwell T, Stone KL, Ancoli-Israel S, Paudel ML, Ensrud KE, et al. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Annals of neurology. 2011;70[5]:722-32.
39. Smagula SF, Chahine L, Metti A, Rangarajan A, Aizenstein HJ, Tian Q, et al. Regional Gray Matter Volume Links Rest-Activity Rhythm Fragmentation With Past Cognitive Decline. The American Journal of Geriatric Psychiatry. 2019.
40. Videnovic A, Willis GL. Circadian system - A novel diagnostic and therapeutic target in Parkinson's disease? Mov Disord. 2016;31[3]:260-9.
41. La Morgia C, Ross-Cisneros FN, Sadun AA, Carelli V. Retinal ganglion cells and circadian rhythms in Alzheimer’s disease, Parkinson’s disease, and beyond. Frontiers in neurology. 2017;8:162.
42. Wu JQ, Li P, Stavitsky Gilbert K, Hu K, Cronin-Golomb A. Circadian Rest-Activity Rhythms Predict Cognitive Function in Early Parkinson's Disease Independently of Sleep. Movement disorders clinical practice. 2018;5[6]:614-9.

43. Leng Y, Goldman SM, Cawthon PM, Stone KL, Ancoli-Israel S, Yaffe K. Excessive daytime sleepiness, objective napping and 11-year risk of Parkinson's disease in older men. International journal of epidemiology. 2018;47[5]:1679-86.
44. Seifalian A, Hart A. Circadian Rhythms: Will It Revolutionise the Management of Diseases? Journal of lifestyle medicine. 2019;9[1]:1.
45. Ferguson A, Lyall LM, Ward J, Strawbridge RJ, Cullen B, Graham N, et al. Genome-wide association study of circadian rhythmicity in 71,500 UK Biobank participants and polygenic association with mood instability. EBioMedicine. 2018;35:279-87.
46. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association, 2013
47. World Health O. Depression and other common mental disorders: global health estimates. 2017.
48. Difrancesco S, Lamers F, Riese H, Merikangas KR, Beekman ATF, van Hemert AM, et al. Sleep, circadian rhythm, and physical activity patterns in depressive and anxiety disorders: A 2-week ambulatory assessment study. Depression and anxiety. 2019.
49. Smagula SF. Opportunities for clinical applications of rest-activity rhythms in detecting and preventing mood disorders. Current opinion in psychiatry. 2016;29[6]:389.
50. Kelly RM, Healy U, Sreenan S, McDermott JH, Coogan AN. Clocks in the clinic: circadian rhythms in health and disease. Postgraduate medical journal. 2018;94[1117]:653-8.
51. Vadnie CA, McClung CA. Circadian rhythm disturbances in mood disorders: insights into the role of the suprachiasmatic nucleus. Neural plasticity. 2017;2017.
52. Luik AI, Zuurbier LA, Direk N, Hofman A, Van Someren EJW, Tiemeier H. 24-hour activity rhythm and sleep disturbances in depression and anxiety: A population-based study of middle-aged and older persons. Depression and anxiety. 2015;32[9]:684-92.
53. Au J, Reece J. The relationship between chronotype and depressive symptoms: A meta-analysis. Journal of affective disorders. 2017;218:93-104.
54. Antypa N, Verkuil B, Molendijk M, Schoevers R, Penninx BWJH, Van Der Does W. Associations between chronotypes and psychological vulnerability factors of depression. Chronobiology international. 2017;34[8]:1125-35.
55. White KH, Rumble ME, Benca RM. Sex differences in the relationship between depressive symptoms and actigraphic assessments of sleep and rest-activity rhythms in a population-based sample. Psychosomatic medicine. 2017;79[4]:479.
56. Smagula SF, Boudreau RM, Stone K, Reynolds Iii CF, Bromberger JT, Ancoli-Israel S, et al. Latent activity rhythm disturbance sub-groups and longitudinal change in depression symptoms among older men. Chronobiology international. 2015;32[10]:1427-37.
57. Wichniak A, Wierzbicka A, Walęcka M, Jernajczyk W. Effects of antidepressants on sleep. Current psychiatry reports. 2017;19[9]:63.
58. McGlashan EM, Drummond SPA, Cain SW. Evening types demonstrate reduced SSRI treatment efficacy. Chronobiology international. 2018;35[8]:1175-8.

59. Swanson LM, Burgess HJ, Huntley ED, Bertram H, Mooney A, Zollars J, et al. Relationships between circadian measures, depression, and response to antidepressant treatment: A preliminary investigation. Psychiatry research. 2017;252:262-9.
60. Duncan Jr WC, Slonena E, Hejazi NS, Brutsche N, Kevin CY, Park L, et al. Motor-activity markers of circadian timekeeping are related to ketamine's rapid antidepressant properties. Biological psychiatry. 2017;82[5]:361-9.
61. Melo MCA, Abreu RLC, Neto VBL, de Bruin PFC, de Bruin VMS. Chronotype and circadian rhythm in bipolar disorder: a systematic review. Sleep medicine reviews. 2017;34:46-58.
62. Smagula SF, Krafty RT, Thayer JF, Buysse DJ, Hall MH. Rest-activity rhythm profiles associated with manic-hypomanic and depressive symptoms. Journal of psychiatric research. 2018;102:238-44.
63. Rumble ME, Dickson D, McCall WV, Krystal AD, Case D, Rosenquist PB, et al. The relationship of person-specific eveningness chronotype, greater seasonality, and less rhythmicity to suicidal behavior: a literature review. Journal of affective disorders. 2018;227:721-30.
64. Benard V, Etain B, Vaiva G, Boudebesse C, Yeim S, Benizri C, et al. Sleep and circadian rhythms as possible trait markers of suicide attempt in bipolar disorders: An actigraphy study. Journal of affective disorders. 2019;244:1-8.
65. Wee ZY, Yong SWL, Chew QH, Guan C, Lee TS, Sim K. Actigraphy studies and clinical and biobehavioural correlates in schizophrenia: a systematic review. Journal of Neural Transmission. 2019;126[5]:531-58.
66. Bromundt V, Köster M, Georgiev-Kill A, Opwis K, Wirz-Justice A, Stoppe G, et al. Sleep–wake cycles and cognitive functioning in schizophrenia. The British Journal of Psychiatry. 2011;198[4]:269-76.
67. Papandreou C, Díaz-López A, Babio N, Martínez-González MA, Bulló M, Corella D, et al. Long Daytime Napping Is Associated with Increased Adiposity and Type 2 Diabetes in an Elderly Population with Metabolic Syndrome. Journal of clinical medicine. 2019;8[7]:1053.
68. Feliciano EMC, Quante M, Weng J, Mitchell JA, James P, Marinac CR, et al. Actigraphy-Derived Daily Rest–Activity Patterns and Body Mass Index in Community-Dwelling Adults. Sleep. 2017;40[12].
69. Sohail S, Yu L, Bennett DA, Buchman AS, Lim ASP. Irregular 24-hour activity rhythms and the metabolic syndrome in older adults. Chronobiology international. 2015;32[6]:802-13.
70. Paudel ML, Taylor BC, Ancoli-Israel S, Stone KL, Tranah G, Redline S, et al. Rest/activity rhythms and cardiovascular disease in older men. Chronobiology international. 2011;28[3]:258-66.

71. Havakuk O, Zukerman N, Flint N, Sadeh B, Margolis G, Konigstein M, et al. Shift work and the risk of coronary artery disease: a cardiac computed tomography angiography study. Cardiology. 2018;139[1]:11-6.
72. Vetter C, Dashti HS, Lane JM, Anderson SG, Schernhammer ES, Rutter MK, et al. Night shift work, genetic risk, and type 2 diabetes in the UK biobank. Diabetes Care. 2018;41[4]:762-9.
73. Morris CJ, Purvis TE, Hu K, Scheer FAJL. Circadian misalignment increases cardiovascular disease risk factors in humans. Proceedings of the National Academy of Sciences. 2016;113[10]:E1402-E11.
74. Buxton OM, Cain SW, O'Connor SP, Porter JH, Duffy JF, Wang W, et al. Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. Science translational medicine. 2012;4[129]:129ra43-ra43.
75. Bernatchez MS, Savard J, Ivers H. Disruptions in sleep–wake cycles in community-dwelling cancer patients receiving palliative care and their correlates. Chronobiology international. 2018;35[1]:49-62.
76. Chang W-P, Smith R, Lin C-C. Age and rest–activity rhythm as predictors of survival in patients with newly diagnosed lung cancer. Chronobiology international. 2018;35[2]:188-97.
77. Kuo L-C, Chang W-P, Huang H-C, Lin C-C. Association of Time-Varying Rest-Activity Rhythm With Survival in Older Adults With Lung Cancer. Cancer nursing. 2019.
78. Cash E, Duck CR, Brinkman C, Rebholz W, Albert C, Worthen M, et al. Depressive symptoms and actigraphy-measured circadian disruption predict head and neck cancer survival. Psycho-oncology. 2018;27[10]:2500-7.
79. Sultan A, Choudhary V, Parganiha A. Worsening of rest-activity circadian rhythm and quality of life in female breast cancer patients along progression of chemotherapy cycles. Chronobiology international. 2017;34[5]:609-23.
80. Mitolo M, Tonon C, La Morgia C, Testa C, Carelli V, Lodi R. Effects of Light Treatment on Sleep, Cognition, Mood, and Behavior in Alzheimer's Disease: A Systematic Review. Dementia and geriatric cognitive disorders. 2018;46[5-6]:371-84.
81. Fifel K, Videnovic A. Chronotherapies for Parkinson's disease. Progress in neurobiology. 2019.
82. Leggett AN, Conroy DA, Blow FC, Kales HC. Bright Light as a Preventive Intervention for Depression in Late-Life: A Pilot Study on Feasibility, Acceptability, and Symptom Improvement. The American Journal of Geriatric Psychiatry. 2018;26[5]:598-602.
83. Boivin DB, James FO. Light treatment and circadian adaptation to shift work. Industrial health. 2005;43[1]:34-48.
84. Johnson JA, Garland SN, Carlson LE, Savard J, Simpson JSA, Ancoli-Israel S, et al. Bright light therapy improves cancer-related fatigue in cancer survivors: a randomized controlled trial. Journal of Cancer Survivorship. 2018;12[2]:206-15.

85. Hopkins S, Lloyd Morgan P, Jm Schlangen L, Williams P, J Skene D, Middleton B. Blue-enriched lighting for older people living in care homes: effect on activity, actigraphic sleep, mood and alertness. Current Alzheimer Research. 2017;14[10]:1053-62.

2.2

The bidirectional association of 24-hour activity rhythms and sleep with depressive symptoms in middle-aged and elderly persons

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Abstract

Background: In older populations disturbed 24-hour activity rhythms, poor sleep, and depressive symptoms are often lingering and co-morbid, making treatment difficult. To improve insights in these commonly co-occurring problems, we assessed the bidirectional association of sleep and 24-hour activity rhythms with depressive symptoms in middle-aged and elderly persons.

Methods: In 1,734 participants (mean age: 62.3±9.3 years, 55% women) from the prospective Rotterdam Study, 24-hour activity rhythms and sleep were estimated with actigraphy (mean duration: 146±19.6 hours), sleep quality with the Pittsburgh Sleep Quality Index, and depressive symptoms with the Center for Epidemiological Studies Depression scale. Repeated measures were available for 947 participants (54%) over a median follow-up of 6 years (IQR=5.6–6.3). Linear mixed models were used to assess temporal associations of 24-hour activity rhythms and sleep with depressive symptoms in both directions.

Results: High 24-hour activity rhythm fragmentation (B=1.002, 95%CI=0.641;1.363), long time in bed (B=0.111, 95%CI=0.053;0.169), low sleep efficiency (B=-0.015, 95%CI=-0.020;-0.009), long sleep onset latency (B=0.009, 95%CI=0.006;0.012), and low self-rated sleep quality (B=0.112, 95%CI=0.0992;0.124) at baseline were associated with increasing depressive symptoms over time. Conversely, more depressive symptoms at baseline were associated with an increasing24-hour activity rhythm fragmentation (B=0.002, 95%CI=0.001;0.003) and time in bed (B=0.009, 95%CI=0.004;0.015), and a decreasing sleep efficiency (B=-0.140, 95%CI=-0.196;-0.084), sleep onset latency (B=0.013, 95%CI=0.008;0.018), and self-rated sleep quality (B=0.193, 95%CI=0.171;0.215) over time.

Conclusion: This study demonstrates a bidirectional association of 24-hour activity rhythms, actigraphy-estimated sleep, and self-rated sleep quality with depressive symptoms over a time frame of multiple years in middle-aged and elderly persons.

Keywords: Actigraphy; 24-hour activity rhythm; depressive symptoms; middle-aged and elderly persons; longitudinal study; population-based

Introduction

Poor sleep and depressive symptoms are highly common,[1,2] especially in middle-aged and elderly persons.[3,4] Moreover, symptoms frequently co-occur,[1,5] and are accompanied by high physical distress and poor quality of life.[1,6] The co-occurrence of poor sleep and depressive symptoms does not merely reflect high prevalence of these disorders in old age.[7] Instead, a causal link is suggested by clinical trials showing that psychological treatment of insomnia reduces depressive symptoms[8] and conversely that psychological treatment of depressive symptoms improves sleep and insomnia.[9] Furthermore population-based studies reported poor sleep to be predictive for onset and recurrence of depression,[3,10,11] and depressive symptoms to be predictive for development and worsening of sleep disturbances.[3,12]

There are several hypotheses about what aspect of the brain could underlie these associations as a common cause or mechanism.[3,13-17] For example, deterioration of the superchiasmatic nucleus (SCN), because of its prominent role in the circadian sleep-wake cycle and functioning of the hypothalamic-pituitary-adrenal (HPA) gland.[13, 14] Additionally, the prefrontal cortex, because of its role cognitive functioning,[17] and the ascending reticular activating system, because of its role in health perception,[15] have also commonly been suggested as potentially underlying the sleep-depression link. Yet, to understand underlying mechanisms, we first need to improve our understanding of the bidirectional association between sleep and depressive symptoms within the same time-span and population.

Our understanding of the bidirectional association in is hampered because most studies use cross-sectional data or assess only one direction of the association. To estimate possible bidirectionality, it is required to investigating both directions of the association within a single study population, using similar measurements and covariates. Furthermore, research has mainly looked into the effect of sleep duration,[18] overall self-rated sleep quality,[3] or insomnia[7] when taking bidirectionality into account, neglecting other aspects of sleep, such as sleep efficiency and sleep onset latency, and 24-hour activity rhythms which may play an important role as well.[19,20] Investigating multiple aspects of sleep could provide new insights important to understand the biological mechanisms underlying the association between poor sleep and depressive symptoms, and help us to develop and improve non-pharmacological and pharmacological treatments for poor sleep and depression.

We assessed the bidirectional association of 24-hour activity rhythms, actigraphy-estimated sleep, and self-rated sleep quality with depressive symptoms to gain more insight into the temporality of these associations. Specifically, we estimated how 24-hour activity rhythms and sleep at baseline were associated with depressive symptoms over time and its change over time. Vice versa, we also assessed how depressive symptoms at baseline were associated with 24-hour activity rhythms and sleep over time and change in 24-hour activity rhythms and sleep over time. Moreover, as these associations may be dependent on several factors, we assessed whether these associations were independent of a range of factors commonly associated with poor sleep and depression. To this end, we used repeatedly collected data from the prospective Rotterdam Study, a large population-based cohort of middle-aged and elderly persons.

Methods

Participants and design

Participants were included from the Rotterdam study, an ongoing population-based cohort of middle-aged and elderly inhabitants of Rotterdam, the Netherlands. The study started in 1990 to investigate prevalence, history and risk factors of common disease in elderly. So far 14,926 participants aged ≥45 years were included. Further details of the study design have been described elsewhere.[21]

From December 2004 until April 2007 we invited 2,614 participants to wear an actigraph for one week for our baseline assessment, 2,071 (79%) agreed. Of those that agreed, 279 participants were excluded because of incomplete or invalid baseline actigraphy (<4 complete 24-hour periods of actigraphy data or <4 complete nights of actigraphy and sleep diary). Another 20 participants were excluded because of incomplete data on depressive symptoms. Lastly, we excluded 38 participants because of a Mini Mental State Examination (MMSE)[22] score below 23 or missing score as a poor cognitive status might impair the ability to complete questionnaires validly. Therefore, a total of 1,734 participants were included at baseline.
Between February 2011 and July 2014, we aimed to follow-up these 1,734 persons. Of those, 100 persons died, 326 withdrew from the overall study or refused to participate in the actigraphy sub-study and 167 were not invited due to logistic reasons, leaving 1,141 persons that participated in the second round of the actigraphy sub-study. For 194 participants

measurements were excluded because data on 24-hour activity rhythm, sleep or depressive symptoms were incomplete or invalid at follow-up. Therefore, repeated data was available for 947 participants (55 %) with a median follow-up of 6 years (IQR=5.6–6.3). A flow diagram of the study population is presented in Supplementary Table 1.

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; http://www.trialregister.nl/trial/6645) meeting the requirements by the WHO International Clinical Trials Registry Platform (ICTRP; http://www.who.int/ictrp/network/primary-registries/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Measurement of 24-hour activity rhythms and sleep

All participants were asked to wear an actigraph on their non-dominant wrist for 7 consecutive days and nights, and complete a sleep diary at the same time. Additionally, participants were asked to press a marker button on the actigraph when they initiated sleep (time to bed) and when they got out of bed (get-up time). At baseline we used the ActiWatch, model AW4 (Cambridge Technology Ltd, Cambridge, United Kingdom), at follow-up either the ActiWatch or the GENEActiv (ActivInsight Ltd, Kimbolton United Kingdom) was used. Recordings were sampled at 32 Hz (ActiWatch) or 50 Hz (GENEActiv) and scored for each 30-s epoch, taking into account weighted scores of previous and following epochs. To distinguish sleep from wake a threshold of 20 was used for each 30-s epoch.[23] The z-axis data of the tri-axial GENEActiv data was pre-analyzed to make records comparable with ActiWatch data.[24] Actigraphy is a validated and commonly used instrument to objectively estimate sleep,[25] and 24-hour activity rhythms,[26] also in population-based samples.[27]

The 24-hour activity rhythm was estimated by analyzing actigraphy data with the nparACT R package.[28] We calculated the Interdaily Stability (IS), which indicates the stability of the rhythm over days, and Intradaily Variability (IV), which indicates the fragmentation of the rhythm relative to its 24-hour amplitude.[29]

To estimate sleep, data from the actigraphy was supplemented with information from the sleep diary or marker button. Time in Bed (TIB) was calculated as the difference between time to bed and get-up time. If time to bed or get-up time was missing from the sleep diary, information from the actigraphy marker button was used. Total Sleep Time (TST) was calculated as the total duration of epochs scored as sleep. Sleep Efficiency (SE) was defined as the proportion of time in bed spent sleeping (100% x (TST / TIB)). Sleep Onset Latency (SOL) was defined as the time it took participants to fall asleep from time to bed. Wake After Sleep Onset (WASO) was calculated as the total time of the epochs scored as wake between sleep start and sleep end.

Self-rated sleep quality was determined with the widely used Pittsburgh Sleep Quality Index (PSQI), a 19-item self-report scale on sleep quality.[30] The PSQI has also been validated for measuring self-rated sleep quality in population-based samples.[31] The total score was calculated as the sum of all items and ranges from 0 to 21, with a high score indicating poor sleep quality. For participants with 6 out of 7 valid PSQI component scores, a weighted global score was calculated by multiplying with 7/6. If less than 6 component scores were available, PSQI was set to missing.

Measurement of depressive symptoms

Depressive symptoms were assessed using Dutch version of the Center for Epidemiologic Studies Depression scale (CES-D), which consists of 20 items.[32,33] The CES-D has been validated for use in middle-aged and elderly persons[32] and population-based cohorts.[34] The total score ranges from 0 to 60, with a higher score indicating more severe depressive symptoms. A weighted score was calculated if ≥75% of the questions were completed, if less than 75% of the items was completed, CES-D was set to missing.

Other variables

Based on previous literature the following variables were assessed as possible confounders: age, sex, employment, partnership, education, smoking behavior, coffee and alcohol intake, and body mass index (BMI), and general cognitive function.[4,12] During the home interview information on employment, education, partnership, smoking behavior, and cognitive status was obtained. Education was classified as primary education (primary), lower/intermediate general education or lower vocational education (low), intermediate vocational education or higher general education (middle) or higher vocational education or university (high). Smoking behavior was classified as never, former or current smoker. Intake of coffee and alcohol were assessed in the sleep diary as cups per day after 6 PM. To calculate BMI (kg/m^2), height and weight were assessed on calibrated scales at the research center without heavy clothing and shoes.

Additionally, we determined general cognitive function by means of the g-factor.[35] The g-factor was estimated using a principal component analyses including the color-word interference subtask of the Stroop test,[36] the Letter Digit Substitution Task,[37] a verbal Word Fluency Test,[38] the delayed recall score of a 15-word Word List Learning test,[39] and Purdue pegboard test.[40]

Statistical Analyses

Descriptives are presented as number with percentage for categorical variables and mean with standard deviation (SD) for numerical data. To assess non-response at follow-up, demographic and health characteristics of participants with repeated measurements (n = 947) were compared to those with only measurements at baseline (n = 787) using chi-squared, Mann–Whitney U tests, or independent sample t-tests.

Sleep and 24-hour activity rhythms were checked for outliers, above 4 SD, were set to 4 SD from the mean in the same direction. Sleep onset latency and depressive symptom scores were log-transformed when used as an outcome. For all covariates missing values were less than 5%, these were handled using the multiple imputation MICE R package.[41] Multiple imputation resulted in 5 imputed datasets for which the pooled statistics are presented.[42] Based on 8 independent exposures, we used a Bonferroni corrected p-value = 0.00625, based on an alpha of 0.05,to account for multiple testing. For all estimates, the 95% confidence

intervals was calculated and presented. Analyses were performed in R version R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

Cross-sectional linear regression models were used to estimate the association of 24-hour activity rhythms and sleep with depressive symptoms. All associations were analyzed using three different models: in model 1 we adjusted for sex and age only. In model 2 we adjusted for above mentioned confounders, age, sex, cohort, employment, education, partnership, smoking, coffee intake, alcohol consumption, and body mass index. In model 3 we additionally adjusted for general cognitive function, which could be a confounder or mediator. For total sleep time and time in bed, analyses were repeated using quadratic terms to assess non-linear associations.

Linear mixed models were used to assess repeated measurements over time. To account for the within person correlation between measurements, a random intercept and slope were included in all linear mixed models. All linear mixed models included the baseline value of the determinant and an interaction term of the baseline determinant with time. The effect estimate of the baseline determinant describes how the determinant at baseline is associated with the outcome on average over time. The interaction term between the baseline determinant and time describes how the determinant at baseline is associated with changes in outcome over time. All associations were adjusted according the above specified models 1, 2 and 3, with all models additionally adjusted for follow-up time and type of actigraphy recorder at follow-up. For total sleep time and time in bed, analyses were repeated using quadratic terms to assess non-linear associations.

We repeated all analyses with a recalculated depressive symptoms score, excluding the question assessing problems with sleep (question 11).

Results

At baseline 1,734 participants were included with a mean age of 62.3 ± 9.3 years and 55% women (see Table 1). Valid repeated measurements were obtained for 947 participants with a median follow-up time of 6 years (IQR = 5.6 – 6.3). Participants with only baseline measurements were older ($t = 5.43$, $p < 0.001$), more often women ($\chi^2 = 8.96$, $p = 0.002$), more often without a partner ($\chi^2 = 15.17$, $p < 0.001$), lower educated ($\chi^2 = 17.65$, $p < 0.001$), more often unemployed ($\chi^2 = 6.11$, $p = 0.050$), and overall less healthy compared to participants

with repeated measurements (Supplementary Table 1). Additionally, their 24-hour activity rhythm was more disturbed and their sleep poorer (Supplementary Table 1).

Cross-sectional associations

At baseline, a fragmented 24-hour activity rhythm (B = 0.958, 95%CI = 0.581; 1.336), long time in bed (B = 0.113, 95%CI = 0.052; 0.174), low sleep efficiency (B = -0.014, 95%CI = -0.019; -0.008), long sleep onset latency (B = 0.009, 95%CI = 0.006; 0.012), and low self-rated sleep quality (where a high score reflects poor sleep quality, B = 0.116, 95%CI = 0.103; 0.129) were associated with more log-transformed depressive symptoms when adjusted for confounders (Model 2), see Table 2. When assessing quadratic association, total sleep time and time in bed were not significantly associated with depressive symptoms.

Longitudinal associations

Poor sleep at baseline was associated with more depressive symptoms over 6 years of follow-up and slower increase of depressive symptoms over time (Table 3; Supplementary Figure 2). Each 1-point higher fragmentation of the 24-hour activity rhythm was associated with 1.002 (95%CI = 0.641; 1.363) more log-transformed depressive symptoms over 6 years of follow-up when adjusted for confounders (Model 2). Similarly, a long time in bed (B = 0.111, 95%CI = 0.053; 0.169-0.017;-0.007), low sleep efficiency (B = -0.015, 95%CI = -0.020; -0.009), long sleep onset latency (B = 0.009 (95%CI = 0.006; 0.012), and high self-rated sleep quality score (where a high score reflects poor sleep quality, B = 0.112, 95%CI = 0.099; 0.124) increased depressive symptoms. When assessing quadratic associations, total sleep time and time in bed were not significantly associated with depressive symptoms. With every 1-minute longer sleep onset latency at baseline, the yearly increase of depressive symptoms was reduced with 0.001 (95%CI = -0.001; 0.000) after adjustment for confounders (Model 2). Similarly, with every 1-point higher self-rated sleep quality, the yearly increase of depressive symptoms was reduced with 0.005 (95%CI = -0.008; -0.002). In other words, long sleep onset latency (Supplementary Figure 2F) and poor self-rated sleep (Supplementary Figure 2H) at baseline were associated with a less steep increase of depressive symptoms over time.

Vice versa, having more depressive symptoms at baseline was also associated with decreased sleep over 6 years of follow-up and slower worsening of sleep over time (Table 4;

Supplementary Figure 3). A 1-point higher depressive symptoms score at baseline was associated with a 0.001 (95%CI = 0.001; 0.003) increased fragmentation of the 24-hour activity rhythm over 6 years of follow-up when adjusted for confounders (Model 2). Similarly, having more depressive symptoms was associated with increased time in bed (B = 0.009, 95%CI = 0.004; 0.015), decreased sleep efficiency (B = -0.140, 95%CI = -0.196; -0.084), increased log-transformed sleep onset latency (B = 0.013, 95%CI = 0.008; 0.018), and decreased self-rated sleep quality score (B = 0.193, 95%CI = 0.171; 0.215, a high score reflects poor sleep quality). Although total sleep time was not significantly associated with a higher intercept, with every 1-point higher depressive symptom score at baseline the yearly decrease of total sleep time was reduced with approximately 0.002 hour (95%CI = 0.001; 0.003) after adjustment for confounders (Model 2). Similar results were observed for sleep efficiency (B = 0.022, 95%CI = 0.011; 0.033) and self-rated sleep quality (B = -0.014, 95%CI = -0.019; -0.009). In other words, more depressive symptoms at baseline were associated with a less steep decrease in sleep duration (Supplementary Figure 3D), sleep efficiency (Supplementary Figure 3E) and self-rated sleep quality (Supplementary Figure 3H) over time.

Analyses adjusted for sex and age only showed similar results (data not shown) Results did not change substantially when estimates were additionally adjusted for general cognitive function (model 3, Supplementary Table 2 and 3).

Sensitivity analyses

Results did not substantially change when analyses were repeated using the depressive symptoms score without the sleep item (data not shown).

Discussion

We demonstrated a bidirectional association of 24-hour activity rhythms and sleep with depressive symptoms in a population-based cohort of middle-aged and elderly persons. For 24-hour activity rhythms, only fragmentation of the 24-hour activity rhythm was bidirectionally associated with more depressive symptoms. For sleep, we observed that long time bed, low actigraphy-estimated sleep efficiency, long actigraphy-estimated sleep onset latency and poor self-rated sleep quality were bidirectionally associated with more depressive symptoms.

Within a single study population, we demonstrated a temporal association of fragmented 24-hour activity rhythms and sleep with depressive symptoms over time, and vice versa, indicating a bidirectional association. This is in line with previous studies which have showed either direction,[7,43] but never assessed both directions using objectively estimated sleep measures in a single study population.[43,44] A bidirectional association of 24-hour activity rhythms and sleep with depressive symptoms seems plausible. On the one hand, fragmented 24-hour activity rhythms and sleep disturbances may cause depressive symptoms through internal desynchronization of 24-hour rhythms,[45] impaired REM sleep,[46] or impaired cognitive function.[47,48] On the other hand, depressed people often experience more stress and worry, potentially linked to a moor pore function of the pre-frontal cortex,[49,50] which could also lead to difficulties in falling asleep, lower sleep efficiency and poorer self-rated sleep quality.[51,52] In addition, depressed people may experience difficulties in performing daily tasks for a long period of time,[53] which could lead to less intensive activity peaks and more fragmentation of 24-hour activity rhythms. Of note, within the sleep-depression link, cognitive function is often deemed particularly relevant, as both concepts have direct relations with cognition.[17,47,49] Yet, in our study cognitive function at baseline did not affect the associations of sleep with depression or vice versa. It might be that our general indicator of cognitive function was not sufficiently able to pick up subtle changes in cognition, or that instead of general cognition, one particular construct such as executive function affects the association of sleep and depressive symptoms.

The observed bidirectional association between poor sleep and depressive symptoms could also be explained by a common cause, a third factor that explains changes in the 24-hour activity rhythm and sleep as well as depressive symptoms. One such common cause could be degeneration of the SCN, the biological clock of the brain, which is an important cause of increased fragmentation of the 24-hour activity rhythm and other sleep problems[14] and is associated with depressive disorders.[16,54] Degeneration of the SCN hampers functioning of structures that affect both sleep and mood, such as the HPA-axis.[13,55] The HPA-axis is associated with both sleep disturbances and mood disorders via elevation of cortisol levels and hyperarousal.[3] Of note, degeneration of the SCN could also reflect associated degeneration in other parts of the brain such as the diencephalon, telencephalon, which includes the previously described prefrontal cortex, and the reticular formation in the brain

stem.[56,57] This degeneration in other parts of the brain might lead to altered cognitive functioning or health perception which might in turn affect both sleep and depression.[56-58]

Our results furthermore demonstrate that poor sleep at baseline is associated with a slower increase of depressive symptoms. Vice versa, having more depressive symptoms at baseline was also associated with a slower worsening of sleep. As we only have measured sleep and depression at two time points it is difficult to explain these somewhat counterintuitive findings. It could be hypothesized that persons with poor sleep at baseline also have more depressive symptoms at baseline and therefore have less possibility for an increase of depressive symptoms or worsening of sleep. Yet this seems unlikely in our population-based sample which shows lower scores on sleep quality and depression than clinical samples. In addition, people with poor sleep at baseline still seem to have stable high depressive symptoms over time. Similarly, people with more depressive symptoms at baseline seem to have stable poor sleep over time.

Commonly, a discrepancy between objective and self-rated measures is observed for the association of sleep with depression,[59] where self-rated measures reflect more of the subjective experience and tend to be more strongly related with depressive symptoms.[43,57] Dysfunction of the reticular activating system, important for a person's consciousness and health perception,[15,60] could potentially lead to a heightened consciousness about their sleep and depressive symptoms. Based on our standardized results it seems that subjective, or self-rated, sleep indeed shows stronger temporal associations for sleep and depressive symptoms than purely objectively estimated measures such as sleep duration and sleep fragmentation. Additionally, aspects of sleep that integrate information from the sleep diary, which is self-reported, such as sleep onset latency and time in bed, also seem to be more strongly associated with depressive symptoms.

Several limitations need to be taken into account. First, we used two different actigraphy devices at follow-up. Although we have controlled for this in our analyses this might have induced measurement error. Second, our nonresponse analyses revealed differences between participants with repeated measurements and participants with only a baseline measurement, possibly introducing selection bias. Lastly, although having repeated measurements is a strength, we were only able to include two time points, 5 to 9 years apart.

We could therefore not take into account fluctuations in depressive symptoms and sleep occurring between these two time points. Third, the number of reported depressive symptoms is relatively low in our sample, about 9% of our study population reached the cut-off for clinically relevant depressive symptoms, which fits with the population-based design. Our approach however does allow us to take into account subclinical symptoms of depression which are more frequent at older ages. Lastly, the effect sizes in our study are relatively small, in part as a consequence of the population-based setting, which might limit the clinical relevance. Nevertheless, having repeated objective sleep measurements and repeated depressive symptom assessments over this period of time is unique in this field and allowed us to assess bidirectionality within one study population.

In our study population of middle-aged and elderly persons we demonstrated a bidirectional association between fragmented 24-hour activity rhythms, low actigraphy-estimated sleep efficiency, long actigraphy-estimated sleep onset latency and poor self-rated sleep quality and depressive symptoms over time. This bidirectionality in both objectively estimated aspects of sleep as well as self-rated sleep quality with depressive symptoms over time should be taken into account when assessing underlying mechanisms and when developing and improving non-pharmacological and pharmacological prevention strategies and treatments for poor sleep and depression.

References

1. Franzen, P.L. and D.J. Buysse, *Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications.* Dialogues in clinical neuroscience, 2008. **10**(4): p. 473-481.
2. Murphy, M.J. and M.J. Peterson, *Sleep disturbances in depression.* Sleep medicine clinics, 2015. **10**(1): p. 17-23.
3. Bao, Y.P., et al., *Cooccurrence and bidirectional prediction of sleep disturbances and depression in older adults: meta-analysis and systematic review.* Neuroscience & Biobehavioral Reviews, 2017. **75**: p. 257-273.
4. Luik, A.I., et al., *Stability and Fragmentation of the Activity Rhythm Across the Sleep-Wake Cycle: The Importance of Age, Lifestyle, and Mental Health.* Chronobiology International, 2013. **30**(10): p. 1223-1230.
5. Vandeputte, M. and A. de Weerd, *Sleep disorders and depressive feelings: a global survey with the Beck depression scale.* Sleep medicine, 2003. **4**(4): p. 343-345.
6. Olfson, M., et al., *Insomnia and Impaired Quality of Life in the United States.* The Journal of clinical psychiatry, 2018. **79**(5): p. 17m12020.
7. Fang, H., et al., *Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treatment.* Journal of cellular and molecular medicine, 2019. **23**(4): p. 2324-2332.
8. Gee, B., et al., *The effect of non-pharmacological sleep interventions on depression symptoms: A meta-analysis of randomised controlled trials.* Sleep medicine reviews, 2018.
9. Yon, A., et al., *Do manualized treatments for depression reduce insomnia symptoms?* Journal of Clinical Psychology, 2014. **70**(7): p. 616-630.
10. Smagula, S.F., et al., *Latent activity rhythm disturbance sub-groups and longitudinal change in depression symptoms among older men.* Chronobiology international, 2015. **32**(10): p. 1427-1437.
11. Hertenstein, E., et al., *Insomnia as a predictor of mental disorders: a systematic review and meta-analysis.* Sleep medicine reviews, 2019. **43**: p. 96-105.
12. Sun, Y., et al., *The bidirectional relationship between sleep duration and depression in community-dwelling middle-aged and elderly individuals: Evidence from a longitudinal study.* Sleep medicine, 2018. **52**: p. 221-229.
13. Asarnow, L.D., *Depression and Sleep: What has the treatment research revealed and could the HPA Axis be a potential mechanism?* Current Opinion in Psychology, 2019. **34**: p. 112-116.
14. Swaab, D.F., E. Fliers, and T.S. Partiman, *The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia.* Brain research, 1985. **342**(1): p. 37-44.

15. Brudzynski, S.M., *The ascending mesolimbic cholinergic system—a specific division of the reticular activating system involved in the initiation of negative emotional states.* Journal of Molecular Neuroscience, 2014. **53**(3): p. 436-445.
16. Vadnie, C.A. and C.A. McClung, *Circadian rhythm disturbances in mood disorders: insights into the role of the suprachiasmatic nucleus.* Neural plasticity, 2017. **2017**.
17. Beck, J.S., *Terapia cognitivo-comportamental*. 2013: Artmed Editora.
18. Zhai, L., H. Zhang, and D. Zhang, *Sleep duration and depression among adults: A meta-analysis of prospective studies.* Depression and anxiety, 2015. **32**(9): p. 664-670.
19. Luik, A.I., et al., *24-hour activity rhythm and sleep disturbances in depression and anxiety: A population-based study of middle-aged and older persons.* Depression and anxiety, 2015. **32**(9): p. 684-692.
20. de Feijter, M., T.S. Lysen, and A.I. Luik, *24-h Activity Rhythms and Health in Older Adults.* Current Sleep Medicine Reports, 2020. **6**: p. 76-83.
21. Ikram, M.A., et al., *Objectives, design and main findings until 2020 from the Rotterdam Study.* European Journal of Epidemiology, 2020. **35**(5): p. 483-517.
22. Tombaugh, T.N. and N.J. McIntyre, *The mini-mental state examination: a comprehensive review.* Journal of the American Geriatrics Society, 1992. **40**(9): p. 922-935.
23. Kosmadopoulos, A., et al., *Alternatives to polysomnography (PSG): a validation of wrist actigraphy and a partial-PSG system.* Behavior research methods, 2014. **46**(4): p. 1032-1041.
24. te Lindert, B.H.W. and E.J.W. Van Someren, *Sleep estimates using microelectromechanical systems (MEMS).* Sleep, 2013. **36**(5): p. 781-789.
25. Morgenthaler, T., et al., *Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007.* Sleep, 2007. **30**(4): p. 519-529.
26. Ancoli-Israel, S., et al., *The role of actigraphy in the study of sleep and circadian rhythms.* Sleep, 2003. **26**(3): p. 342-392.
27. Marino, M., et al., *Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography.* Sleep, 2013. **36**(11): p. 1747-1755.
28. Blume, C., N. Santhi, and M. Schabus, *'nparACT'package for R: A free software tool for the non-parametric analysis of actigraphy data.* MethodsX, 2016. **3**: p. 430-435.
29. Van Someren, E.J.W., *Actigraphic monitoring of movement and rest-activity rhythms in aging, Alzheimer's disease, and Parkinson's disease.* IEEE Transactions on Rehabilitation Engineering, 1997. **5**(4): p. 394-398.
30. Buysse, D.J., et al., *Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI).* Sleep, 1991. **14**(4): p. 331-338.

31. Mollayeva, T., et al., *The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis.* Sleep medicine reviews, 2016. **25**: p. 52-73.
32. Beekman, A.T.F., et al., *Een screeningsinstrument voor depressie bij ouderen in de algemene bevolking: de bruikbaarheid van de Center for Epidemiologic Studies Depression Scale (CES-D).* Tijdschrift voor Gerontologie en Geriatrie, 1994. **25**: p. 95-103.
33. Radloff, L.S., *The CES-D scale: A self-report depression scale for research in the general population.* Applied psychological measurement, 1977. **1**(3): p. 385-401.
34. Cosco, T.D., et al., *Reliability and validity of the Center for Epidemiologic Studies Depression Scale in a population-based cohort of middle-aged US adults.* Journal of nursing measurement, 2017. **25**(3): p. 476-485.
35. Deary, I.J., *Intelligence.* Annual Review of Psychology, 2012. **63**(1): p. 453-482.
36. Houx, P.J., J. Jolles, and F.W. Vreeling, *Stroop interference: aging effects assessed with the Stroop Color-Word Test.* Experimental aging research, 1993. **19**(3): p. 209-224.
37. Lezak, M.D., et al., *Neuropsychological assessment*. 2004, Oxford, United Kingdom: Oxford University Press, USA.
38. Welsh, K.A., et al., *The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery.* Neurology, 1994. **44**(4): p. 609-609.
39. Bleecker, M.L., et al., *Age-related sex differences in verbal memory.* Journal of clinical psychology, 1988. **44**(3): p. 403-411.
40. Tiffin, J. and E.J. Asher, *The Purdue Pegboard: norms and studies of reliability and validity.* Journal of applied psychology, 1948. **32**(3): p. 234.
41. Buuren, S.v. and K. Groothuis-Oudshoorn, *mice: Multivariate imputation by chained equations in R.* Journal of statistical software, 2010: p. 1-68.
42. Rubin, D.B., *Multiple imputation for nonresponse in surveys*. Vol. 81. 2004: John Wiley & Sons.
43. Maglione, J.E., et al., *Subjective and objective sleep disturbance and longitudinal risk of depression in a cohort of older women.* Sleep, 2014. **37**(7): p. 1179-1187.
44. Smagula, S.F., et al., *Rest–activity rhythm and sleep characteristics associated with depression symptom severity in strained dementia caregivers.* Journal of sleep research, 2017. **26**(6): p. 718-725.
45. Pandi-Perumal, S.R., et al., *Bidirectional communication between sleep and circadian rhythms and its implications for depression: lessons from agomelatine.* Progress in neurobiology, 2009. **88**(4): p. 264-271.
46. Wang, Y.-Q., et al., *The neurobiological mechanisms and treatments of REM sleep disturbances in depression.* Current neuropharmacology, 2015. **13**(4): p. 543-553.

47. Helfrich, R.F., et al., *Bidirectional prefrontal-hippocampal dynamics organize information transfer during sleep in humans.* Nature communications, 2019. **10**(1): p. 1-16.
48. Muzur, A., E.F. Pace-Schott, and J.A. Hobson, *The prefrontal cortex in sleep.* Trends in cognitive sciences, 2002. **6**(11): p. 475-481.
49. Belleau, E.L., M.T. Treadway, and D.A. Pizzagalli, *The impact of stress and major depressive disorder on hippocampal and medial prefrontal cortex morphology.* Biological psychiatry, 2019. **85**(6): p. 443-453.
50. Liu, W., et al., *The role of neural plasticity in depression: from hippocampus to prefrontal cortex.* Neural Plasticity, 2017.
51. Van Laethem, M., et al., *Day-to-day relations between stress and sleep and the mediating role of perseverative cognition.* Sleep medicine, 2016. **24**: p. 71-79.
52. Hall, M.H., et al., *Chronic stress is prospectively associated with sleep in midlife women: the SWAN sleep study.* Sleep, 2015. **38**(10): p. 1645-1654.
53. Liu, Y., et al., *The relationship between depression, daytime napping, daytime dysfunction, and snoring in 0.5 million Chinese populations: exploring the effects of socio-economic status and age.* BMC public health, 2018. **18**(1): p. 759.
54. Costa, I.C., H.N. Carvalho, and L. Fernandes, *Aging, circadian rhythms and depressive disorders: a review.* American journal of neurodegenerative disease, 2013. **2**(4): p. 228-246.
55. Murri, M.B., et al., *HPA axis and aging in depression: systematic review and meta-analysis.* Psychoneuroendocrinology, 2014. **41**: p. 46-62.
56. Musiek, E.S., et al., *Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease.* JAMA neurology, 2018. **75**(5): p. 582-590.
57. Mitrushina, M. and R. Tomaszewski, *The effect of subjective perception of cognition on emotional functioning in adults with long-term neurological and neuropsychiatric disorders.* Disability and rehabilitation, 2019: p. 1-7.
58. Leng, Y., et al., *Association between circadian rhythms and neurodegenerative diseases.* The Lancet Neurology, 2019. **18**(3): p. 307-318.
59. Van Den Berg, J.F., et al., *Disagreement between subjective and actigraphic measures of sleep duration in a population-based study of elderly persons.* Journal of sleep research, 2008. **17**(3): p. 295-302.
60. Hudson, A.J., *Consciousness: physiological dependence on rapid memory access.* Front Biosci (Landmark Ed), 2009. **14**: p. 2779-800.

Table 1

Baseline characteristics of the study population at baseline (December 2004 – April 2007), Rotterdam study

	N	(%)	M	SD
Participants	1,734			
Age (years)			62.3	9.3
Women	951	54.8		
Having a partner	1363	78.7		
Employed	608	35.1		
Education				
Primary	140	8.1		
Low	701	40.8		
Intermediate	519	30.2		
High	360	20.9		
Depressive symptoms (score) [a, b]			3.0	1 - 7
Cognitive status (score) [c]			28.0	1.6
Body mass index (kg/m^2)			27.8	4.2
Alcohol(cups/day) [a, c]			0.4	0.0 – 1.3
Coffee(cups/day) [a, c]			1.0	0.1 – 1.7
Smoking				
Non smoker	531	30.6		
Former smoker	892	51.5		
Current smoker	311	17.9		
Interdaily stability (score)			0.77	0.12
Intradaily variability (score)			0.43	0.14
Time in bed (hours)			8:12	0:50
Total sleep time (hours)			6:05	0:53
Sleep efficiency (%)			74.5	8.6
Sleep onset latency (min)			21	16
Wake after sleep onset (min)			63	26
Self-rated sleep quality (score)			4.00	3.6

Abbreviations: SD, Standard Deviation.

Sleep quality is missing for 29 participants (1.7%), partnership for 2 (0.1%), education for 14 (0.8%), alcohol and coffee intake for 36 (2.1%), BMI for 15 (0.9%), general health score for 66 (3.8%). For other variables there are no missing values.

[a] Median and Interquartile Range.

[b] Assessed using the Center for Epidemiologic Studies Depression scale.

[c] Assessed using the Mini-Mental State Exam.

[d] Alcohol and coffee intake were assessed using the actigraphy sleep dairy.

Table 2

Cross-sectional associations of 24-hour activity rhythms and sleep with depressive symptoms at baseline

	B	95%CI	β	p-value
Interdaily stability	-0.501	-0.932;-0.069	-0.056	0.023
Intradaily variability	0.958	0.581;1.336	0.125	<0.001
Time in bed (hours)	0.113	0.052;0.174	0.094	<0.001
Total sleep time (hours)	-0.043	-0.099;0.014	-0.039	0.14
Sleep efficiency (%)	-0.014	-0.019;-0.008	-0.116	<0.001
Sleep onset latency (min)	0.009	0.006;0.012	0.145	<0.001
Wake after sleep onset (min)	0.002	0.000;0.003	0.040	0.09
Self-rated sleep quality score	0.116	0.103;0.129	0.408	<0.001

Abbreviations: CI, Confidence Interval for B.

B is the effect estimate of the determinant, β the standardized effect estimate of the determinant. Effect estimates were obtained using cross-sectional linear regression models, adjusted for age, sex, cohort, actigraphy device at follow-up, employment, education, partnership, smoking, alcohol consumption, coffee intake, and body mass index (model 2). Multiple testing corrected p-value = 0.00625.

Table 3

Longitudinal association of 24-hour activity rhythms and sleep with depressive symptoms over time

	B	95%CI	β	p-value
Interdaily stability				
IS	-0.528	-0.943;-0.114	-0.059	0.012
IS*time	-0.010	-0.103;0.084	-0.001	0.84
Intradaily variability				
IV	1.002	0.641;1.363	0.131	<0.001
IV*time	-0.029	-0.109;0.051	-0.004	0.48
Time in bed				
TIB	0.111	0.053;0.169	0.092	<0.001
TIB*time	-0.007	-0.019;0.006	-0.005	0.29
Total sleep time				
TST	-0.051	-0.103;0.002	-0.046	0.06
TST*time	0.006	-0.005;0.017	0.005	0.30
Sleep efficiency				
SE	-0.015	-0.020;-0.009	-0.126	<0.001
SE*time	0.001	0.000;0.003	0.011	0.030
Sleep onset latency				
SOL	0.009	0.006;0.012	0.143	<0.001
SOL*time	-0.001	-0.001;0.000	-0.014	0.006
Wake after sleep onset				
WASO	0.002	0.000;0.004	0.049	0.034
WASO*time	0.000	0.000;0.001	0.003	0.61
Self-rated sleep quality score				
Sleep quality	0.112	0.099;0.124	0.394	<0.001
Sleep quality*time	-0.005	-0.008;-0.002	-0.019	<0.001

Abbreviations: TST, Total Sleep Time; TIB, Time In Bed; SE, Sleep Efficiency; WASO, Wake After Sleep Onset; SOL, Sleep Onset Latency; IS, Interdaily stability; IV, Intradaily variability; CI, Confidence Interval for B. B is the effect estimate of the determinant, β the standardized effect estimate of the determinant. Effect estimates were obtained using linear mixed models, adjusted for age, sex, cohort, actigraphy device at follow-up, employment, education, partnership, smoking, alcohol consumption, coffee intake, and body mass index (model 2). Estimates should be interpreted as changes on the log-transformed depressive symptoms score. Multiple testing corrected p-value = 0.00625

Table 4

Longitudinal association of depressive symptoms with 24-hour activity rhythms and sleep over time

	B	95%CI	β	p-value
Interdaily stability				
IS	-0.001	-0.002;0.000	-0.008	0.021
IS*time	0.000	0.000;0.000	-0.001	0.32
Intradaily variability				
IV	0.002	0.001;0.003	0.016	<0.001
IV*time	0.000	0.000;- 0.000	-0.002	0.025
Time in bed				
TIB	0.009	0.004;0.015	0.011	0.001
TIB*time	0.000	-0.001;0.001	0.000	0.88
Total sleep time				
TST	-0.006	-0.012;0.000	-0.006	0.06
TST*time	0.002	0.001;0.003	0.002	<0.001
Sleep efficiency				
SE	-0.140	-0.196;-0.084	-0.017	<0.001
SE*time	0.022	0.011;0.033	0.003	<0.001
Sleep onset latency				
SOL	0.013	0.008;0.018	0.018	<0.001
SOL*time	-0.001	-0.002;0.000	-0.002	0.046
Wake after sleep onset				
WASO	0.161	-0.012;0.334	0.006	0.07
WASO*time	-0.040	-0.072;-0.008	-0.002	0.015
Self-rated sleep quality score				
Sleep quality	0.193	0.171;0.215	0.056	<0.001
Sleep quality*time	-0.014	-0.019;-0.009	-0.004	<0.001

Abbreviations: TST, Total Sleep Time; TIB, Time In Bed; SE, Sleep Efficiency; WASO, Wake After Sleep Onset; SOL, Sleep Onset Latency; IS, Interdaily stability; IV, Intradaily variability; CI, Confidence Interval for B. B is the effect estimate of the determinant, β the standardized effect estimate of the determinant. Effect estimates were obtained using linear mixed models, adjusted for age, sex, cohort, actigraphy device at follow-up, employment, education, partnership, smoking, alcohol consumption, coffee intake, and body mass index (model 2). The effect estimate of the determinant*time should be interpreted as changes on the log-transformed depressive symptoms score. Multiple testing corrected p-value = 0.00625.

Supplements

Supplementary Table 1

Baseline characteristics of the study population at baseline (December 2004 – April 2007), Rotterdam study. Comparison of participants with baseline measures only to participants with repeated measures.

	Baseline	Repeated	Test-statistic	p-value
Participants	787	947		
Age (years)	63.6 ± 10.7	61.1 ± 7.6	t = 5.43	p < 0.001
Women	463 (59 %)	488 (52 %)	χ^2 = *8.96*	*p =* 0.003
Having a partner	585 (74 %)	778 (82 %)	χ^2 = *15.17*	p < 0.001
Employed	251 (32 %)	357 (38 %)	χ^2 = *6.11*	*p =* 0.013
Education			χ^2 = *17.65*	p < 0.001
Primary	79 (10 %)	61 (6 %)		
Low	335 (43 %)	366 (39 %)		
Intermediate	232 (30 %)	287 (30 %)		
High	135 (17 %)	225 (24 %)		
Depressive symptoms (score) [a, b]	3.0 (1 – 8)	3.0 (0 – 7)	U = 406150	p < 0.001
Cognitive status (score) [c]	27.9 ± 1.7	28.2 ± 1.6	U = 328480,	p < 0.001
Body mass index (kg/m^2)	27.9 ± 4.3	27.8 ± 4.2	t = 0.39	p = 0.70
Alcohol(cups/day) [a, c]	0.3 (0 – 1.1)	0.5 (0 – 1.3)	U = 327420	p = 0.004
Coffee(cups/day) [a, c]	0.9 (0.1 – 1.4)	1 (0.3 – 1.8)	U = 314260	p < 0.001
Smoking			χ^2 = *10.56*	p = 0.005
Non smoker	231 (29 %)	300 (32 %)		
Former smoker	398 (50 %)	503 (53 %)		
Current smoker	167 (21 %)	144 (15 %)		
Interdaily stability (score)	0.77 ± 0.12	0.78 ± 0.11	t = -2.75	p = 0.006
Intradaily variability (score)	0.44 ± 0.14	0.41 ± 0.12	t = 4.12	p < 0.001
Time in bed (hours)	8:17 ± 0:50	8:07 ± 0:50	t = 4.5	p < 0.001
Total sleep time (hours)	6:10 ± 0:54	6:04 ± 0:54	t = 1.94	p = 0.045
Sleep efficiency (%)	74.0 (8.5)	74.9 ± 8.4	t = -2.11	p = 0.036
Sleep onset latency (min)	22 ± 16	20 ± 16	t = 2.24	p = 0.018
Wake after sleep onset (min)	64 ± 27	61 ± 25	t = 2.38	p = 0.025
Self-rated sleep quality (score)	4.2 ± 3.7	3.8 ± 3.4	t = 2.12	p = 0.034

Abbreviations: BMI, body mass index; ADL, Activities of Daily Living; MMSE, Mini-Mental State Exam; CI, Confidence Interval.

[a] Median and Interquartile Range.

[b] Assessed using the Center for Epidemiologic Studies Depression scale.

[c] Assessed using the Mini-Mental State Exam.

[d] Alcohol and coffee intake were assessed using the actigraphy sleep dairy.

Supplementary Table 2

Longitudinal association of 24-hour activity rhythms and sleep with depressive symptoms over time, additionally adjusted for general cognitive function

	B	95%CI	β	p-value
Interdaily stability				
IS	-0.501	(-0.914;-0.088)	-0.057	0.018
IS*time	-0.010	(-0.104;0.083)	0.015	0.83
Intradaily variability				
IV	0.945	(0.583;1.307)	0.119	<0.001
IV*time	-0.029	(-0.109;0.051)	-0.007	0.48
Time in bed				
TIB	0.102	(0.043;0.160)	0.074	0.001
TIB*time	-0.006	(-0.019;0.006)	-0.005	0.867
Total sleep time				
TST	-0.053	(-0.105;0.000)	-0.038	0.048
TST*time	0.006	(-0.005;0.017)	-0.028	0.29
Sleep efficiency				
SE	-0.014	(-0.020;-0.009)	-0.102	<0.001
SE*time	0.001	(0.000;0.003)	-0.018	0.030
Sleep onset latency				
SOL	0.008	(0.006;0.011)	0.111	<0.001
SOL*time	-0.001	(-0.001;0.000)	-0.014	0.008
Wake after sleep onset				
WASO	0.002	(0.000;0.004)	0.052	0.042
WASO*time	0.000	(0.000;0.001)	-0.014	0.63
Self-rated sleep quality score				
Sleep quality	0.112	(0.100;0.124)	0.363	<0.001
Sleep quality*time	-0.005	(-0.008;-0.002)	-0.020	<0.001

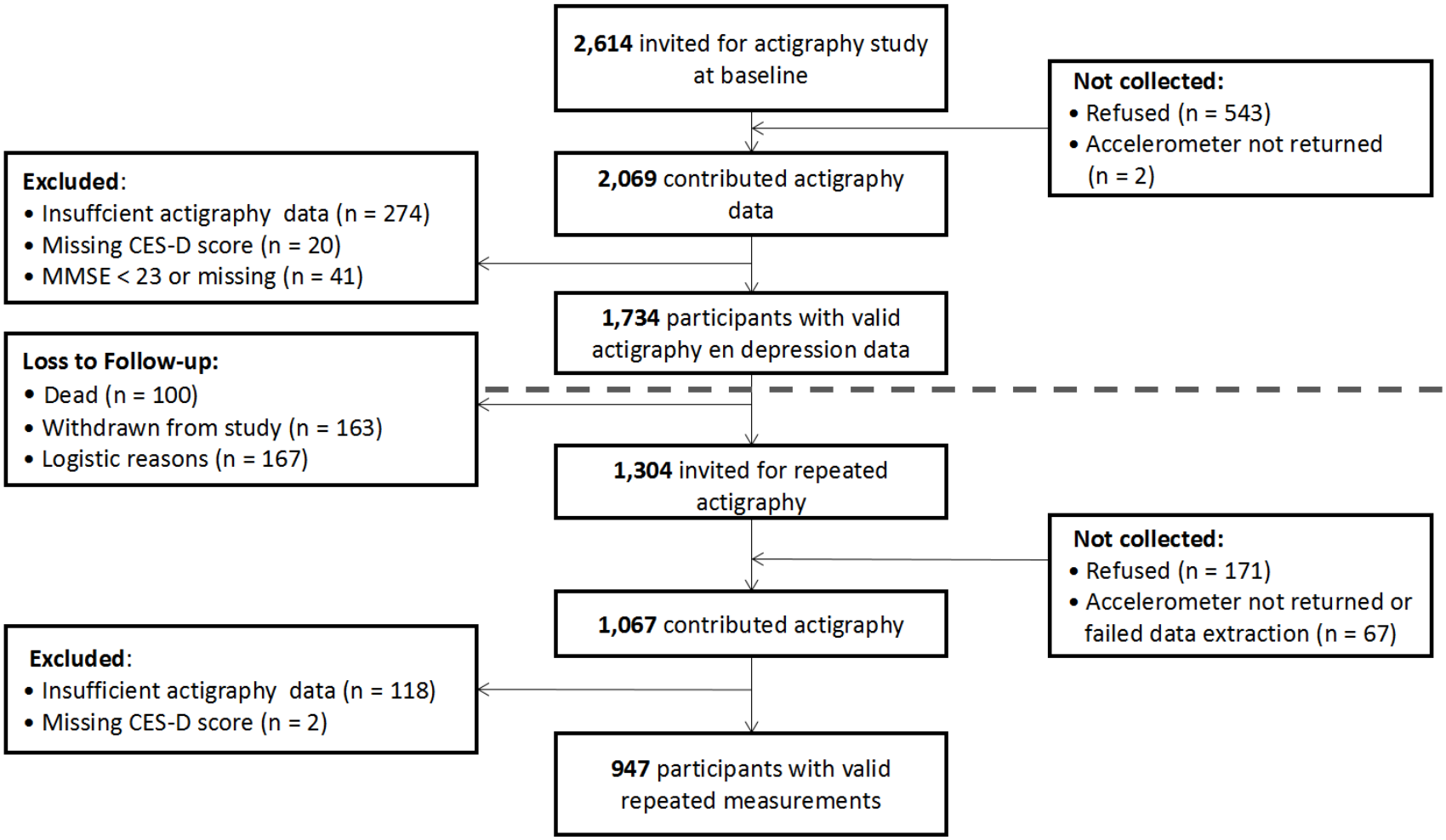
Abbreviations: TST, Total Sleep Time; TIB, Time In Bed; SE, Sleep Efficiency; WASO, Wake After Sleep Onset; SOL, Sleep Onset Latency; IS, Interdaily stability; IV, Intradaily variability; CI, Confidence Interval for B. B is the effect estimate of the determinant, β the standardized effect estimate of the determinant. Effect estimates were obtained using linear mixed models, adjusted for age, sex, cohort, actigraphy device at follow-up, employment, education, partnership, smoking, alcohol consumption, coffee intake, body mass index, and general cognitive function (model 3). Estimates should be interpreted as changes on the log-transformed depressive symptoms score. Multiple testing corrected p-value = 0.00625.

Supplementary Table 3

Longitudinal association of depressive symptoms with 24-hour activity rhythms and sleep over time, additionally adjusted for general cognitive function

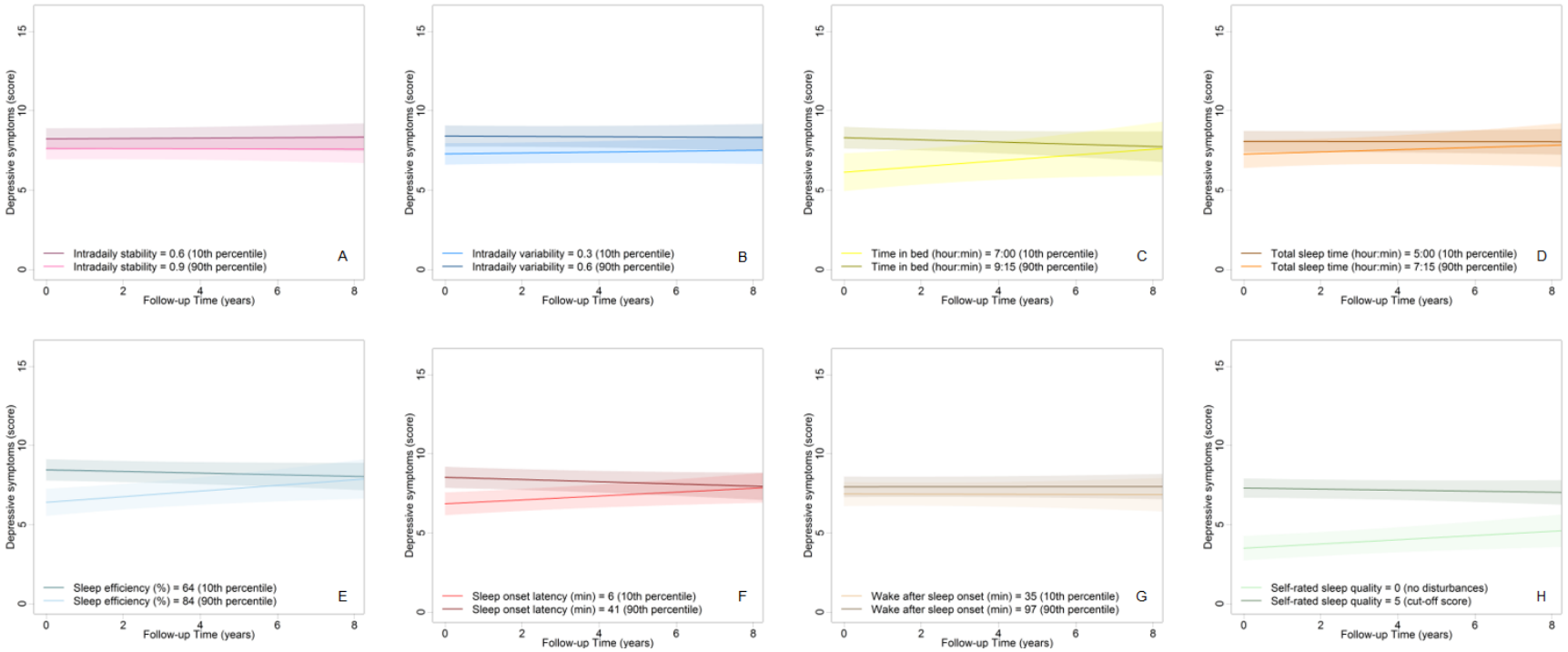
	B	95%CI	β	p-value
Interdaily stability				
IS	-0.001	(-0.002;0.000)	-0.009	0.032
IS*time	0.000	(0.000;0.000)	0.006	0.31
Intradaily variability				
IV	0.002	(0.001;0.003)	0.011	<0.001
IV*time	0.000	(0.000;0.000)	0.010	0.026
Time in bed				
TIB	0.009	(0.043;0.160)	0.010	0.002
TIB*time	0.000	(-0.001;0.001)	0.004	0.871
Total sleep time				
TST	-0.006	(-0.012;0.000)	-0.002	0.06
TST*time	0.002	(0.001;0.003)	0.007	<0.001
Sleep efficiency				
SE	-0.135	(-0.191;-0.078)	-0.011	<0.001
SE*time	0.022	(0.011;0.033)	0.005	<0.001
Sleep onset latency				
SOL	0.012	(0.007;0.017)	0.014	<0.001
SOL*time	-0.001	(-0.002;0.000)	-0.004	0.049
Wake after sleep onset				
WASO	0.152	(-0.022;0.325)	0.003	0.09
WASO*time	-0.040	(-0.072;-0.008)	0.003	0.015
Self-rated sleep quality score				
Sleep quality	0.196	(0.173;0.218)	0.049	<0.001
Sleep quality*time	-0.014	(-0.019;-0.010)	-0.003	<0.001

Abbreviations: TST, Total Sleep Time; TIB, Time In Bed; SE, Sleep Efficiency; WASO, Wake After Sleep Onset; SOL, Sleep Onset Latency; IS, Interdaily stability; IV, Intradaily variability; CI, Confidence Interval for B. B is the effect estimate of the determinant, β the standardized effect estimate of the determinant. Effect estimates were obtained using linear mixed models, adjusted for age, sex, cohort, actigraphy device at follow-up, employment, education, partnership, smoking, alcohol consumption, coffee intake, body mass index, and general cognitive function (model 3). Should be interpreted as changes on the log-transformed depressive symptoms score. Multiple testing corrected p-value = 0.00625.



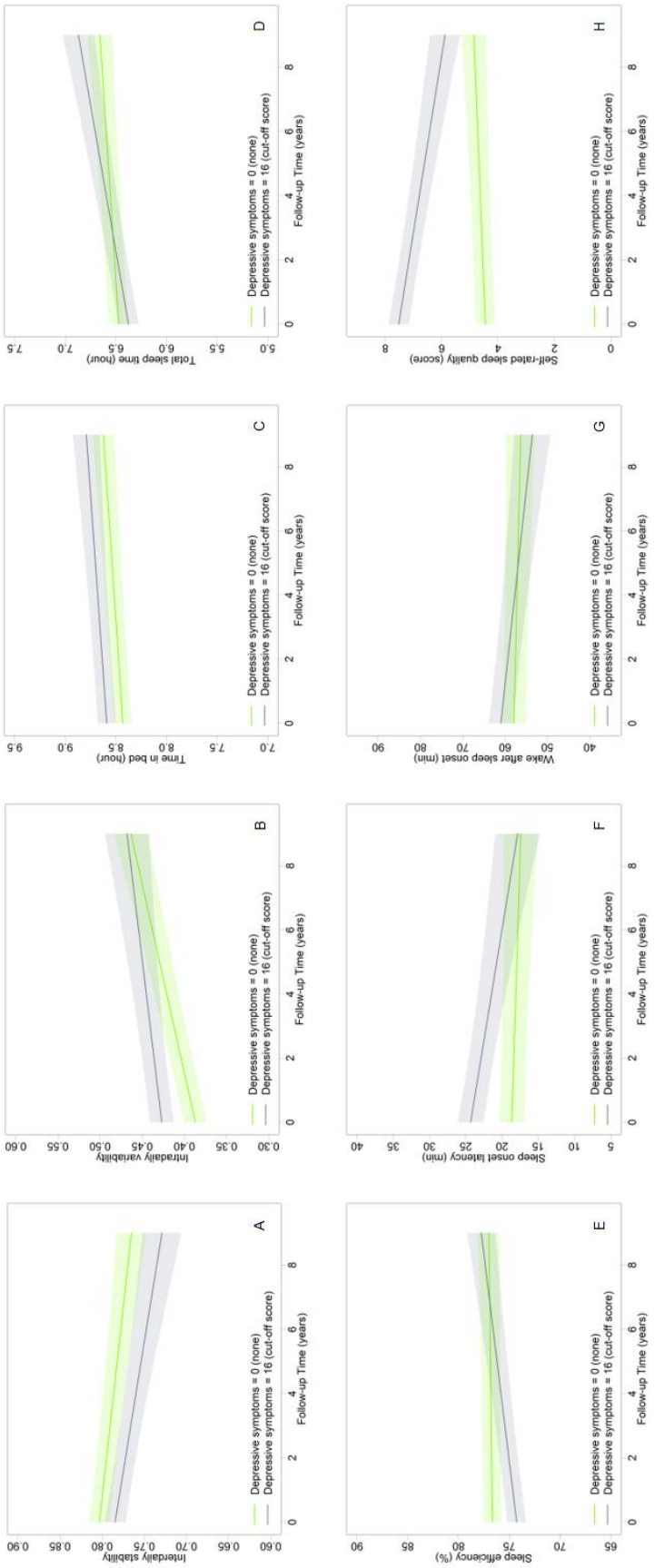
Supplementary Figure 1

Flow diagram of the study population. Valid baseline data for actigraphy and depressive symptoms was collected for 1,734 participants between 2006 and 2008. Of those, valid repeated assessment Valid baseline data for actigraphy and depressive symptoms was performed for 947 participants between 2009 and 2012..Abbreviations; CES-D: Center for Epidemiological Depression scale; MMSE: Mini-Mental State Exam.



Supplementary Figure 2

Sleep and 24-hour activity rhythms predicting depressive symptoms across time. Each plot depicts how depressive symptoms would develop over time for an average person scoring the 10th or 90th percentile for Interdaily Stability (A), Intradaily Variability (B), Time In Bed (C), Total Sleep Time (D), Sleep Efficiency (E), Sleep Onset Latency (F), and Wake After Sleep Onset (G). Darker colors indicate poor sleep, lighter colors indicate good sleep. For self-rated sleep quality (H) a line is plotted for the average person with no self-rated sleep disturbances (light green) and an average person with poor self-rated sleep quality (cut-off score, dark green).



Supplementary Figure 3

Depressive symptoms predicting actigraphy-estimated and self-rated sleep time. Each plot depicts how Interdaily Stability (A), Intradaily Variability (B), Time In Bed (C), Total Sleep Time (D) Sleep Efficiency (E), Sleep Onset Latency (F), Wake After Sleep Onset (G), and self-rated sleep quality (H) would develop over time for the average person without depressive symptoms (blue) or with clinically relevant depressive symptoms (green).

2.3

The longitudinal association of actigraphy-estimated sleep with grief in middle-aged and elderly persons

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Abstract

Most people experience grief after a loss, about 10% develop complicated grief, often accompanied by sleep complaints. Yet, the impact of objectively estimated poor sleep on grief remains unclear. We assessed cross-sectional and longitudinal associations of actigraphy-estimated sleep with grief.

We included 1,776 participants (mean age: 61.8±8.9 years, 55% women) of a prospective population-based cohort. Of 1,471 participants (83%) repeated measures of grief were available (median follow-up 6 years). At baseline, sleep was estimated using actigraphy. At baseline and follow-up, questions about significant losses and the Dutch Inventory of Complicated Grief (17 items, cut-off ≥22) were completed. At baseline 1,521 (86%) participants experienced no grief, 44 (2%) acute (<6 months, any grief score), 158 (9%) non-complicated (≥6 months, grief score<22), and 53 (3%) complicated (≥6 months, grief score≥22). In those indicating any grief (n=255), low sleep efficiency (B=-0.16, 95%CI=-0.30;-0.02), long sleep onset latency (B=0.07, 95%CI=0.01;0.14), and long wake after sleep onset (B=0.06, 95%CI=0.01;0.10) were cross-sectionally associated with more grief symptoms. Over time, those with a short total sleep time (OR=0.59, 95%CI=0.39;0.91), low sleep efficiency (OR=0.95, 95%CI=0.91;0.99), long sleep onset latency (OR=1.02, 95%CI=1.00;1.04), and long wake after sleep onset (OR=1.02, 95%CI=1.00;1.03) more often experienced complicated grief than non-complicated grief. The association of total sleep time and self-rated sleep quality remained after excluding those with grief at baseline. This study suggests that objectively estimated poor sleep is associated with grief over time. Poor sleep might not only accompany grief, but also be a risk factor for developing complicated grief after a loss.

Keywords: Actigraphy-estimated sleep; complicated grief; middle-aged and elderly persons; longitudinal; population-based

Introduction

Losing of a loved one is an ubiquitous life event, particularly with increasing age,[1] with grief as the most common response.[2] Over time, most people recover from grief, but for about 10%, grief remains unresolved and causes significant impairment in daily life, also known as complicated grief.[3,4] People suffering from complicated grief experience symptoms such as disbelief, avoidance, emotional numbness, and an adverse impact on social, work or school life.[1,5] When unresolved or complicated grief reaches the level of a clinical disorder, the term prolonged grief disorder is used in the International classification of diseases, 11th edition[6] and persistent complex bereavement disorder is used in the Diagnostic and statistical manual of mental disorders, 5th edition.[7] Of note, even though these disorders are sometimes comorbid with depressive disorders, they are distinct.[5,8,9]

One construct commonly associated with grief is poor sleep.[10-13] On one hand poor sleep during grief might be caused by worry and hyperarousal,[14] which makes it more difficult to fall asleep and more likely to awaken during the night.[15] On the other hand, poor sleep is also associated with less effective emotion regulation which may maintain or worsen symptoms of psychological disorders, such as complicated grief. A recent population-based study in middle-aged and elderly persons reported shorter self-rated sleep duration and lower self-rated sleep quality in those experiencing complicated and non-complicated grief when compared to those without grief.[10] A recent review additionally suggested that poor sleep is associated with the number of grief symptoms, and may be more severe and longer-lasting in those with complicated grief as opposed to other types of grief.[13] So far most studies have relied on self-rated indicators of sleep,[10-12,16] rather than objective estimates,[8,17,18] yet this could introduce bias due to shared variance in self-rating both grief and sleep.[19] The few studies that use a longitudinal design to assess temporality often focus on the effect of grief on self-rated sleep disturbance.[10,13,20-22] There is, however, growing evidence that sleep may be not only a symptom, but also a risk factor for developing complicated grief after a significant loss.[13,21] Yet, in many studies using self-rated measures of sleep, the association between grief and sleep has been explained by comorbid depressive symptoms.[10,11,23] Although the association could indeed be dependent on comorbidity with depressive symptoms, it could also be that a shared method bias explains these results.[24] Therefore using

objective estimates of sleep, which are thought to measure physiological sleep, can provide new insights.[19]

In order to improve our understanding of development of complicated grief, we studied the cross-sectional and longitudinal association of actigraphy-estimated and self-rated sleep with type of grief and the number of grief symptoms in a population-based cohort of middle-aged and elderly persons.

Methods

Participants & Design

This study was conducted within the Rotterdam Study, a prospective population-based cohort of middle-aged and elderly inhabitants of Rotterdam, the Netherlands. Details of the study design have been described previously.[25] The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

From December 2004 until April 2007, we invited 2,614 participants to wear an actigraph to estimate their sleep, of whom 2,071 participants (79%) agreed. Of those that agreed, 196 participants were excluded due to incomplete sleep data (including participants with <4 complete nights of actigraphy and sleep diary). Another 57 participants were excluded due to incomplete information about grief at baseline, 11 due to grieving over a pet or a sick person, and 31 due to a possible impaired cognition (Mini Mental State Examination <23 or missing).[26] Therefore, a total number of 1,776 participants were included at baseline.

For 1,501 participants of the baseline sample, information on grief was obtained for a second time between February 2011 and July 2014. This second grief assessment was performed independent of grief status at baseline. Loss to follow-up occurred because participants died (n=105) or withdrew from the study (n=163). Of those who participated, we excluded

repeated measurements for 30 participants because of incomplete or invalid data at follow-up and 7 participants because they indicated grief over a pet or sick person at follow-up. Therefore, repeated data were available for a total of 1,471 persons (83% of baseline sample).

Sleep

At baseline all participants were invited to wear an actigraph (ActiWatch, model AW4, Cambridge Technology Ltd, Cambridge, United Kingdom) for 7 consecutive days and nights on their non-dominant wrist. Additionally, participants were asked to fill out a sleep diary every day and press a marker button on the actigraph to obtain the clock times for when they initiated sleep (time to bed) and when they got out of bed (get-up time). This information is used to determine the analysis window for the actigraphy.

Actigraphy recordings were sampled at 32 Hz in 30-second epochs. To estimate sleep, an averaged score was calculated for each 30-s epoch, taking into account weighted values of previous and following epochs. A threshold of 20 was used to distinguish sleep from wake.[27,28] Total sleep time was defined as nightly sleep duration and calculated as the sum in time difference of epochs scored as asleep, between sleep start and sleep end. Sleep efficiency was defined as the time sleeping whilst in bed (100*total sleep time/ time in bed), where time in bed was defined as the time difference between time to bed and get-up time (based on the sleep diary or marker button). Sleep onset latency was defined as the time it took participants to fall asleep, calculated as the time difference between time to bed and sleep start. Wake after sleep onset was defined as the total time scored as awake between sleep start and sleep end.

To assess 24-hour activity rhythms we estimated interdaily stability, intradaily variability, and L5 onset time. The nparACT R package was used to calculate interdaily stability, indicating the rhythm stability over days, and intradaily variability, indicating fragmentation of the rhythm relative to its 24-hour amplitude, and L5 onset, indicating the average clock time the 5 consecutive hours with least activity of the day started.[29,30]

The Pittsburgh Sleep Quality Index (PSQI) was used to obtain self-rated overall sleep quality.[31] A global score, ranging from 0 to 21, was calculated as the sum of 7 component scores, with a higher score indicating poorer sleep quality. If less than 6 component scores were available,

PSQI was considered missing. For participants with 6 out of 7 valid PSQI component scores, a weighted global score was calculated by multiplying with 7/6.

Grief

During the home interview, at baseline and at follow-up, all participants were asked whether they were still grieving over someone who had died in recent months or years. In case of a positive answer two follow-up questions were asked: "*When did this person die?*" and "*Who was this person?*". Additionally, grief symptoms were assessed using the Dutch version of the Inventory of Complicated Grief (ICG).[32] The Dutch version of the ICG is a 17-item self-report scale on symptoms of complicated grief,[33] questions were asked on a 5-point scale (0-never, 4-always), providing a potential score range of 0 to 68. The cut-off score for complicated grief of the Dutch version was set to 22, accounting for the smaller number of items than the original version.[32,33]

Based on the ICG score and time since the loss, participants were divided into four groups: (1) no grief, encompassing participants that indicated no grief at the time of the interview; (2) acute grief, encompassing participants with <6 months since loss irrespective of their ICG score; (3) non-complicated grief, encompassing participants with ≥6 months since loss and an ICG-score <22; and (4) complicated grief, encompassing participants with ≥6 months since loss and an ICG-score ≥22. Participants were divided into these four groups at baseline and at follow-up, and the division at follow-up was independent from the division at baseline. Thus, a person at follow up might be in the "no grief" group, even though they were in one of the grief groups at baseline, because the self-report question was whether they were still grieving over someone who had died, and not just the fact of whether someone had died.

Other Variables

Based on previous literature, the following variables were assessed as possible confounders: age, sex, depressive symptoms, education, smoking, cognitive status, and body mass index (BMI).[10] Age, sex, depressive symptoms, education and smoking behavior were assessed during the home interview. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression scale (CES-D).[34] Education was assessed at baseline as primary education (primary), lower/intermediate general education or lower vocational

education (low), intermediate vocational education or higher general education (middle), or higher vocational education or university (high). Smoking was classified as never, former, or current smoker. Cognitive status and BMI were assessed at the research center. To obtain cognitive status, participants were screened with the Mini Mental State Examination.[26] To calculate BMI (kg/m^2), height and weight were assessed on calibrated scales at the research center without heavy clothing and shoes.

Statistical Analyses

Missing values for covariates were less than 5% and handled by multiple imputation using the MICE R package.[35] Statistical analyses were performed using imputed data sets, and pooled statistics were presented.[36] Sleep variables were checked with regard to outliers, which were set to 4 standard deviations (SD) from the mean. To overcome model difficulties with small value range, we multiplied interdaily stability and intradaily variability with a factor 10. To correct for multiple testing, we used the false discovery rate (FDR) to calculate the adjusted p-values, based on 5 determinants.[37] Analyses are performed in R version R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org).

First, to estimate the association between sleep and grief at baseline, multi-nominal testing was used. These analyses provided the odds ratio (OR) of being in a certain type of grief, with each unit increase in the sleep variable under study. We selected non-complicated grief, rather than no grief, as a reference category in order to assess the effect of sleep on grief type. We did not draw comparison to the no grief group as this would have included the effect of sleep on the possibility of experiencing a loss, as this group contained both those not having experienced any loss and therefore not grieving as well as those having experienced a loss but not grieving. Second, in participants indicating any grief, we used cross-sectional linear regression models to estimate the association of sleep with the continuous number of grief symptoms at baseline. To estimate whether the association between sleep and grief differed between people suffering from acute grief (<6 months) and people who had been grieving for longer (≥6 months), we repeated the cross-sectional linear regression models, stratified for duration of grief.

To estimate the longitudinal association of baseline sleep and grief at follow-up, we used multi-nominal analyses. To overcome possible presence of grief at baseline biasing our

associations, we performed a sensitivity analysis in which we repeated the longitudinal analyses in a sample excluding participants who indicated any grief at baseline and participants who indicated grief about a loss occurring before baseline at the second grief assessment.

All associations were analyzed for total sleep time, sleep efficiency, sleep onset latency, wake after sleep onset, and self-rated sleep quality, using three models. Model 1 was adjusted for sex and age only. In model 2 we adjusted for sex, age, education, smoking, and BMI, this selection was based on previous literature. In model 3 we adjusted for all model 2 confounders and additionally depressive symptoms, to assess whether associations were independent of depressive symptomatology. In the longitudinal analyses, all models were additionally adjusted for follow-up time. As exploratory analyses, we assessed the, cross-sectional and longitudinal multi-nominal models for relations of 24-hour activity rhythms, interdaily stability, intradaily variability and L5 onset time, with grief.

Results

At baseline 1,776 participants were included with a mean age of 61.8±8.9 years and 55% women (see Table 1). At baseline 1,521 (85.6%) participants reported no grief, 44 (2.5%) acute grief, 158 (8.9%) non-complicated grief, and 54 (3.0%) complicated grief. Participants experiencing grief for a longer period of time reported grief over a partner or a child most often (Table 1). Valid repeated measurements were available for 1,471 participants with a median follow-up time of 6 years (IQR=5.6–6.3). At follow-up 1,270 (86.3%) participants reported no grief, 38 (2.6%) acute grief, 122 (8.3%) non-complicated grief, and 41 (2.8%) complicated grief.

Sleep and grief at baseline

At baseline, no significant cross-sectional associations of sleep and 24-hour activity rhythms with type of grief at baseline were found when correcting for multiple testing (Table 2, Supplementary table 1-2). In the sample of participants who indicated any grief at baseline (n=255), indicators of poor sleep were associated with the continuous number of grief symptoms (Table 3). A low sleep efficiency (B=-0.16, 95%CI=-0.30;-0.02), long sleep onset latency (B=0.07, 95%CI=0.01;0.14), long wake after sleep onset (B=0.06, 95%CI=0.01;0.10), and low self-rated sleep quality (B=0.59, 95%CI=0.30; 0.89, a high PSQI score reflects poor

sleep quality) were associated with more grief symptoms. After correcting for depressive symptoms, no associations remained significant (supplementary Table 3).

After stratification, in participants with <6 months since loss short total sleep time (B=-4.11, 95%CI=-7.41;-1.07), long sleep onset latency (B=0.18, 95%CI=0.03;0.33), and poor self-rated sleep quality (B=1.00, 95%CI=0.20;1.79) were associated with more grief symptoms (Supplementary Table 4). In participants with >6 months since loss only self-rated sleep quality was significantly associated with more grief symptoms (B=0.51, 95%CI=0.18;0.83, Supplementary Table 4).

Sleep at baseline and grief at follow-up

Over time, poor sleep at baseline was associated with increased odds on complicated grief (Table 4, Supplementary Table 5). Those with short total sleep time (OR=0.59, 95%CI=0.39;0.91), low sleep efficiency (OR=0.95, 95%CI=0.91;0.99), long sleep onset latency (OR=1.02, 95%CI=1.00;1.04), long wake after sleep onset (OR=1.02, 95%CI=1.00;1.03), and poor self-rated sleep quality (OR=1.13, 95%CI=1.03;1.23) at baseline were more likely to report complicated grief than non-complicated grief at follow-up (Table 4). For 24-hour activity rhythms, interdaily stability and intradaily variability were not associated with the odds of experiencing complicated grief compared to non-complicated grief at follow-up (Supplementary Table 5) Those with a later L5 onset time at baseline were more likely to report complicated grief than non-complicated grief at follow-up (OR=1.51, 95%CI=1.09;2.07). After additional correction for depressive symptoms, none of the associations remained significant (Supplementary Table 6).

We repeated the longitudinal analyses in a subsample (n=1,285), excluding participants who indicated any grief at baseline or who indicated at the second grief assessment any grief from a loss occurring before baseline, in order to overcome potential grief at baseline affecting our observations. The effect sizes remained similar, but only total sleep time (OR=0.39, 95%CI=0.21;0.72) and self-rated sleep quality (OR=1.26, 95%CI=1.10;1.43) reached significance in participants reporting complicated grief, opposed to non-complicated grief, at follow-up (data not shown).

Analyses adjusted for sex and age only, model 1, showed similar results to model 2 (data not shown).

Discussion

Three findings stand out from this population-based sample study of middle-aged and elderly persons. First, we found no cross-sectional association of actigraphy-estimated sleep with type of grief (i.e., none, acute, non-complicated, complicated), but self-rated poor sleep was related to type of grief. Second, in contrast, multiple indicators of poor actigraphy-estimated sleep, such as a low sleep efficiency, long sleep onset latency, long wake after sleep onset, and a poor self-rated sleep quality were cross-sectionally associated with the continuous number of grief symptoms in those that indicated any grief after the loss of a loved one. Third, baseline short total sleep time, low sleep efficiency, long sleep onset latency, long wake after sleep onset latency, poor self-rated sleep quality, and a delayed rhythm were associated with a higher chance of having complicated grief after a mean follow-up of 6 years compared to non-complicated grief. These longitudinal results remained significant for sleep duration and self-rated sleep quality after excluding participants with any grief at baseline.

We observed no cross-sectional associations between objective sleep estimates and type of grief, except for a better self-rated sleep quality in non-grieving individuals, compared to non-complicated grievers. The absence of a difference between those with non-complicated grief and those with acute grief or complicated grief in any sleep estimate seems to suggest that levels of self-rated sleep quality and objectively estimated sleep are similar in participants with grief, independent of type of grief. Overall, this is in line with previous studies assessing subjective measures of sleep,[10,13,38] but was not yet known for objective sleep measures such as actigraphy.[13] This is important as subjective sleep measures reflect psychological aspects of sleep, i.e. the experience of sleep, while objective sleep measures reflect physiological sleep abnormalities. Thus, whereas the first is important to get insight into psychological mechanisms, the latter is providing insights in the potential biological mechanisms. Yet, our work also suggests that this lack of association might be due to the categorization of grief status, as multiple indicators of objective and self-rated poor sleep were related to the number of grief symptoms in those indicating any grief. Although our study is the first to show this for actigraphy-estimated sleep, previous work has demonstrated the association of self-rated sleep, polysomnography-assessed sleep and insomnia with number of grief

symptoms,[11,18,19,38,39] suggesting that the categorization of grief can have large impact on the results. The discrepancy between the results of type of grief and number of grief symptoms could be explained by the duration criteria of type of grief. For example, sleep disturbances might be partly resolved in participants with complicated grief and non-complicated grief, due to habituation to the grief and normalization of the associated hyperarousal,[14] and only subjective feelings of poor sleep remain over time.[40] This notion is further supported by differential results between those with a less than 6 months since the loss and those with 6 months or longer since the loss.

Our work also showed that actigraphy-estimated short sleep duration, low sleep efficiency, long sleep onset latency, long wake after sleep onset, poor self-rated sleep and a more delayed 24-hr rhythm at baseline were associated with increased odds of experiencing complicated grief 6 years later. This suggests that poor sleep prior to a loss event, both self-rated and objectively measured, could potentially create a vulnerability for developing complicated grief. Although we lack power to sufficiently investigate whether this vulnerability solely depends on grief-related poor sleep (e.g., from a different loss experience), excluding those with baseline grief and those with grief at follow-up that started before baseline from our analyses, did not substantially impact our effect sizes. This may suggest that it is the poor sleep per se, and not the baseline grief, that accounts for the association between poor sleep and grief at follow-up. Mechanistically, this might be explained by the association of poor sleep with an exaggerated stress response and better memory of negative experiences.[41,42] Additionally, poor sleep has been associated with less effective emotion regulation and time spent in negative mood states,[43] which in turn could impair the individual's ability to cope with this stressful event and make one more vulnerable to develop complicated grief after a loss. These findings support the idea that people with poor sleep are more vulnerable to a range of mental health problems,[44], and the importance of an increased awareness about sleep by general practitioners, psychologists, psychiatrists and other medical specialists. Preventing or targeting poor sleep early on, could potentially help reduce psychopathology, including complicated grief, although causal pathways remain to be investigated.

The longitudinal associations of sleep with grief did not remain significant after correction for baseline depressive symptoms when taking into account multiple testing correction. Yet, the

effect sizes of the actigraphy-estimated sleep parameters remained largely the same. Complicated grief shares many symptoms with depression, including sleep disturbance,[5] and could be a confounder as well as a mediator. Although associations did not remain significant, we speculate that the relation between objectively estimated sleep and complicated grief cannot solely be attributed to their shared association with depressive symptomatology based on the stability of the effect sizes in the longitudinal associations. However, cross-sectionally effect sizes were attenuated, suggesting overlap of symptoms plays a larger role when measured grief and depressive symptoms are measured concurrently.

Several limitations should be considered when interpreting our findings. First, grief symptoms were only assessed when participants self-reported they were experiencing grief due to the death of a loved one. Thus, those who experienced a death, but not grief, were included in the non-grieving group. Second, we determined complicated grief with a questionnaire and not a clinical interview, the method required for a clinical diagnosis. Third, although having repeated measurements is a strength, we were only able to include two time points between five and nine years apart. We could therefore not take into account fluctuations in sleep or grief symptoms that occurred between these two time points. Nevertheless, having objective measures of sleep and repeated grief assessments in a population-based sample over this period of time is unique in our field of research, allowing us to assess temporal associations with actigraphy-estimated sleep for the first time.

To summarize, in our study of middle-aged and elderly persons, poor sleep was associated with more grief symptoms at baseline in those participants that indicated any grief, associations could not be fully explained by depressive symptomatology. Over time, those with poor baseline sleep were more likely to develop complicated grief after a loss, implying sleep may be a potential risk factor for developing psychopathology such as complicated grief after a loss. This study highlights that preventing or targeting sleep problems early on could help to prevent onset of psychopathology in the general population, although causality remains to be determined with regards to complicated grief.

References

1. Boelen, P.A. and H. Hoijtink, *An item response theory analysis of a measure of complicated grief.* Death Studies, 2009. **33**(2): p. 101-129.
2. Rosenzweig, A., et al., *Bereavement and late-life depression: grief and its complications in the elderly.* Annual review of medicine, 1997.
3. Nakajima, S., *Complicated grief: recent developments in diagnostic criteria and treatment.* Philosophical Transactions of the Royal Society B: Biological Sciences, 2018. **373**(1754): p. 20170273.
4. Lundorff, M., et al., *Prevalence of prolonged grief disorder in adult bereavement: A systematic review and meta-analysis.* Journal of Affective Disorders, 2017. **212**: p. 138-149.
5. Kristensen, P., K. Dyregrov, and A. Dyregrov, *What distinguishes prolonged grief disorder from depression?* Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin, ny raekke, 2017. **137**(7): p. 538-539.
6. World Health, O., *International classification of diseases for mortality and morbidity statistics (11th Revision)*. 2018.
7. Association, A.P., *Diagnostic and statistical manual of mental disorders.* 2013. **21**(Edition, Fifth).
8. Prigerson, H.G., et al., *Complicated grief and bereavement-related depression as distinct disorders: preliminary empirical validation in elderly bereaved spouses.* American journal of Psychiatry, 1995. **152**(1): p. 22-30.
9. Prigerson, H.G. and P.K. MaCiejewski, *A call for sound empirical testing and evaluation of criteria for complicated grief proposed for DSM-V.* Omega-Journal of Death and Dying, 2006. **52**(1): p. 9-19.
10. Milic, J., et al., *The Longitudinal and Cross-Sectional Associations of Grief and Complicated Grief With Sleep Quality in Older Adults.* Behavioral sleep medicine, 2019. **17**(1): p. 31-40.
11. Boelen, P.A. and J. Lancee, *Sleep difficulties are correlated with emotional problems following loss and residual symptoms of effective prolonged grief disorder treatment.* Depression research and treatment, 2013. **2013**.
12. Stahl, S.T. and R. Schulz, *Changes in routine health behaviors following late-life bereavement: a systematic review.* Journal of behavioral medicine, 2014. **37**(4): p. 736-755.
13. Lancel, M., M. Stroebe, and M.C. Eisma, *Sleep Disturbances in Bereavement: A Systematic Review.* Sleep Medicine Reviews, 2020: p. 101331.
14. Eisma, M.C., T.A. de Lang, and P.A. Boelen, *How Thinking Hurts: Rumination, Worry, and Avoidance Processes in Adjustment to Bereavement.* Clinical Psychology & Psychotherapy, 2020.

15. Bao, Y.P., et al., *Cooccurrence and bidirectional prediction of sleep disturbances and depression in older adults: meta-analysis and systematic review.* Neuroscience & Biobehavioral Reviews, 2017. **75**: p. 257-273.
16. Monk, T.H., et al., *Sleep and circadian rhythms in spousally bereaved seniors.* Chronobiology international, 2008. **25**(1): p. 83-98.
17. Monk, T.H., A. Germain, and D.J. Buysse, *The sleep of the bereaved.* Sleep and hypnosis: an international journal of sleep, dream, and hypnosis, 2009. **11**(1).
18. Reynolds, C.F., et al., *Electroencephalographic sleep in spousal bereavement and bereavement-related depression of late life.* Biological Psychiatry, 1992. **31**(1): p. 69-82.
19. Buysse, D.J., et al., *Relationships between the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and clinical/polysomnographic measures in a community sample.* Journal of clinical sleep medicine, 2008. **4**(06): p. 563-571.
20. Erlangsen, A., et al., *Association between spousal suicide and mental, physical, and social health outcomes: a longitudinal and nationwide register-based study.* JAMA psychiatry, 2017. **74**(5): p. 456-464.
21. Richardson, S.J., et al., *Sleep patterns in older bereaved spouses.* Omega-Journal of Death and Dying, 2003. **47**(4): p. 361-383.
22. Buckley, T., et al., *Prospective study of early bereavement on psychological and behavioural cardiac risk factors.* Internal Medicine Journal, 2009. **39**(6): p. 370-378.
23. Tanimukai, H., et al., *Association between depressive symptoms and changes in sleep condition in the grieving process.* Supportive Care in Cancer, 2015. **23**(7): p. 1925-1931.
24. Conway, J.M., *Method variance and method bias in industrial and organizational psychology.* 2002.
25. Ikram, M.A., et al., *Objectives, design and main findings until 2020 from the Rotterdam Study.* European Journal of Epidemiology, 2020. **35**(5): p. 483-517.
26. Tombaugh, T.N. and N.J. McIntyre, *The mini-mental state examination: a comprehensive review.* Journal of the American Geriatrics Society, 1992. **40**(9): p. 922-935.
27. Kosmadopoulos, A., et al., *Alternatives to polysomnography (PSG): a validation of wrist actigraphy and a partial-PSG system.* Behavior research methods, 2014. **46**(4): p. 1032-1041.
28. Kushida, C.A., et al., *Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients.* Sleep medicine, 2001. **2**(5): p. 389-396.
29. Blume, C., N. Santhi, and M. Schabus, *'nparACT' package for R: A free software tool for the non-parametric analysis of actigraphy data.* MethodsX, 2016. **3**: p. 430-435.
30. Van Someren, E.J.W., *Actigraphic monitoring of movement and rest-activity rhythms in aging, Alzheimer's disease, and Parkinson's disease.* IEEE Transactions on Rehabilitation Engineering, 1997. **5**(4): p. 394-398.

31. Buysse, D.J., et al., *Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI).* Sleep, 1991. **14**(4): p. 331-338.
32. Prigerson, H.G., et al., *Inventory of Complicated Grief: a scale to measure maladaptive symptoms of loss.* Psychiatry research, 1995. **59**(1-2): p. 65-79.
33. Boelen, P.A., et al., *Reliability and validity of the Dutch version of the Inventory of Traumatic Grief (ITG).* Death studies, 2003. **27**(3): p. 227-247.
34. Beekman, A.T.F., et al., *Een screeningsinstrument voor depressie bij ouderen in de algemene bevolking: de bruikbaarheid van de Center for Epidemiologic Studies Depression Scale (CES-D).* Tijdschrift voor Gerontologie en Geriatrie, 1994. **25**: p. 95-103.
35. Buuren, S.v. and K. Groothuis-Oudshoorn, *mice: Multivariate imputation by chained equations in R.* Journal of statistical software, 2010: p. 1-68.
36. Rubin, D.B., *Multiple imputation for nonresponse in surveys*. Vol. 81. 2004: John Wiley & Sons.
37. Benjamini, Y. and Y. Hochberg, *Controlling the false discovery rate: a practical and powerful approach to multiple testing.* Journal of the Royal statistical society: series B (Methodological), 1995. **57**(1): p. 289-300.
38. Szuhany, K.L., et al., *Impact of sleep on complicated grief severity and outcomes.* Depression and anxiety, 2020. **37**(1): p. 73-80.
39. Hardison, H.G., R.A. Neimeyer, and K.L. Lichstein, *Insomnia and complicated grief symptoms in bereaved college students.* Behavioral sleep medicine, 2005. **3**(2): p. 99-111.
40. Pyrke, R.J.L., et al., *Evidence-Based Design Features Improve Sleep Quality Among Psychiatric Inpatients.* HERD: Health Environments Research & Design Journal, 2017. **10**(5): p. 52-63.
41. Devine, J.K., et al., *Glucocorticoid and inflammatory reactivity to a repeated physiological stressor in insomnia disorder.* Neurobiology of sleep and circadian rhythms, 2019. **6**: p. 77-84.
42. Kim, S.Y., et al., *Interactive effects of stress reactivity and rapid eye movement sleep theta activity on emotional memory formation.* Hippocampus, 2019.
43. Watling, J., et al., *Sleep loss and affective functioning: more than just mood.* Behavioral sleep medicine, 2017. **15**(5): p. 394-409.
44. Wulff, K., et al., *Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease.* Nature Reviews Neuroscience, 2010. **11**(8): p. 589.

Table 1

Baseline characteristics of the study population at baseline, separated for type of grief.

	No grief (n=1,521) Mean±SD N (%)	**Acute grief (n=44) Mean±SD N (%)**	**Non-complicated grief (n=158) Mean±SD N (%)**	**Complicated grief (n=53) Mean±SD N (%)**
Demographics				
Age (years)	61.5±8.9	63.0±10.7	63.0±8.6	64.5±9.7
Women	798 (52.5%)	27 (61.4%)	108 (68.3%)	39 (73.6 %)
Education				
Primary	117 (7.7%)	4 (9.1%)	13 (8.3%)	6 (11.6%)
Low	614 (40.7%)	15 (34.1%)	58 (36.7%)	29 55.8%)
Intermediate	452 (30.0%)	14 (31.8%)	53 (33.5)	15 (28.8%)
High	326 (21.6%)	11 (25.0%)	34 (21.5%)	2 (3.8%)
Cognitive status (score) [a]	28.1±1.6	27.9±1.8	28.1±1.5	27.7 (1.7)
Depressive symptoms (score) [b]	3.0 (1 – 6)	7 (0 – 13)	5 (2 – 9)	8.0 (4 – 19)
Body mass index (kg/m^2)	27.7±4.2	27.2±3.9	28.2±4.0	29.6±5.4
Smoking				
Never	484 (31.8)	15 (34.1)	37 (23.4)	13 (24.5)
Former	762 (50.1)	20 (45.5)	91 (57.6)	31 (58.5)
Current	275 (18.1)	9 (20.4)	30 (19.0)	9 (17.0)
Actigraphy-estimated sleep				
Total sleep time (hour:min)	6:06±0:55	6:16±0:49	6:04±0:50	6:03±0:53
Sleep efficiency (%)	74.6±8.5	75.6±9.5	73.8±8.4	72.5±8.5
Sleep onset latency (min)	21±16	21±15	22±18	28±21
Wake after sleep onset (min)	63±26	61±30	61±24	67±27
Interdaily stability (score)	0.78±0.11	0.79±0.08	0.78±0.11	0.76±0.12
Intradaily variability (score)	0.42±0.14	0.44±0.15	0.44±0.13	0.42±0.12
L5 onset (hour:min)	1:15±2:06	1:34±2:00	1:27±2:15	1:36±2:06
Self-rated sleep				
Self-rated sleep quality (score)	3.8±3.5	4.0±3.2	4.9±3.7	6.1±4.8
Grief				
Duration since loss (months)	-	2 (0 – 3)	39 (18 – 75)	32 (16 – 67)
ICG score	-	11.0±7.6	11.6±5.3	30±6.3
Loss	-			
Partner	-	2 (4.5%)	45 (28.7%)	16 (30.2%)
Child	-	1 (2.3%)	9 (5.7%)	10 (18.7%)
Other	-	35 (79.6%)	85 (53.8%)	119 (36.0%)
>1 person	-	6 (13.6 %)	18 (11.8%)	8 (15.1%)

Variables are stated as number (percentage), mean±standard deviation, or median (inter quartile range). Missing values at baseline: Self-rated sleep quality is missing for 30 participants (1.7%), education for 13 (0.7%), depressive symptoms for 2 (0.1%) and body mass index for 16 (0.9%). For other variables there are no missing values.

[a] Assessed using the Center for Epidemiological Studies Depression scale.

[b] Assessed using the Mini-Mental State Examination.

[c] Assessed for 1,448 (95.3%) participants with no grief, 44 (100%) participants with acute grief, 149 (94.3%) participants with non-complicated grief, and 52 (98.1) participants with complicated grief.

Table 2

Cross-sectional associations of sleep with type of grief at baseline, compared to non-complicated grief (n=158).

	No grief (n=1,521)			Acute grief (n=44)			Complicated grief (n=53)		
	Adjusted Odds Ratio (95% CI)	**P-value**	**Corrected P-value**	**Adjusted Odds Ratio (95% CI)**	**P-value**	**Corrected P-value**	**Adjusted Odds Ratio (95% CI)**	**P-value**	**Corrected P-value**
Total sleep time (hour)	1.09 (0.90;1.33)	0.38	0.48	1.39 (0.93;2.10)	0.11	0.33	0.98 (0.68;1.43)	0.93	0.93
Sleep efficiency (%)	1.01 (0.99;1.03)	0.33	0.48	1.03 (0.99;1.07)	0.20	0.33	0.99 (0.95;1.02)	0.52	0.65
Sleep onset latency (min)	1.00 (0.99;1.01)	0.70	0.70	1.00 (0.98;1.02)	0.73	0.73	1.01 (1.00;1.03)	0.08	0.20
Wake after sleep onset (min)	1.00 (1.00;1.01)	0.31	0.48	1.00 (0.98;1.01)	0.72	0.73	1.01 (1.00;1.02)	0.12	0.20
Self-rated sleep quality (score)	0.95 (0.90;0.99)	0.015	0.08	0.94 (0.85;1.04)	0.20	0.33	1.07 (0.99;1.12)	0.09	0.20

Total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset were estimated using actigraphy, self-rated sleep quality was assessed using the Pittsburgh Sleep Quality Index. Effect estimates were adjusted for age, sex, education, smoking, and body mass index (model 2). None of the associations remained significant (<0.05) after correcting for multiple testing using FDR.

Table 3

Cross-sectional associations of sleep with number of grief symptoms in those participants that indicated any grief at baseline (n=255).

	Grief symptoms		
	Adjusted coefficient (95% CI)	**P-value**	**Corrected p-value**
Total sleep time (hour)	-1.403 (-2.828;0.022)	0.05	0.05
Sleep efficiency (%)	-0.158 (-0.295;-0.021)	0.024	0.039*
Sleep onset latency (min)	0.072 (0.007;0.137)	0.031	0.039*
Wake after sleep onset (min)	0.057 (0.010;0.103)	0.017	0.039*
Self-rated sleep quality (score)	0.592 (0.296;0.888)	<0.001	<0.001*

Total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset were estimated using actigraphy, self-rated sleep quality was assessed using the Pittsburgh Sleep Quality Index. Effect estimates were adjusted for age, sex, education, smoking, and body mass index (model 2).
* P-value remained significant (<0.05) after correcting for multiple testing, using FDR.

Table 4

Longitudinal associations of baseline sleep with type of grief at follow-up, compared to non-complicated grief (n=122).

	No grief (n=1,521)			Acute grief (n=44)			Complicated grief (n=53)		
	Adjusted Odds Ratio (95% CI)	**P-value**	**Corrected P-value**	**Adjusted Odds Ratio (95% CI)**	**P-value**	**Corrected P-value**	**Adjusted Odds Ratio (95% CI)**	**P-value**	**Corrected P-value**
Total sleep time (hour)	1.00 (0.79;1.26)	0.99	0.99	0.92 (0.59;1.43)	0.71	0.99	0.59 (0.39;0.91)	0.017	0.028*
Sleep efficiency (%)	1.00 (0.98;1.03)	0.92	0.99	1.00 (0.96;1.05)	0.99	0.99	0.95 (0.91;0.99)	0.007	0.023*
Sleep onset latency (min)	1.00 (0.99;1.01)	0.97	0.99	1.00 (0.97;1.02)	0.73	0.99	1.02 (1.00;1.04)	0.032	0.032*
Wake after sleep onset (min)	1.00 (1.00;1.01)	0.44	0.99	1.00 (0.99;1.02)	0.92	0.99	1.02 (1.00;1.03)	0.026	0.032*
Self-rated sleep quality (score)	1.01 (0.96;1.07)	0.72	0.99	1.01 (0.91;1.13)	0.83	0.99	1.13 (1.03;1.23)	0.009	0.023*

Total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset were estimated using actigraphy, self-rated sleep quality was assessed using the Pittsburgh Sleep Quality Index. Effect estimates were adjusted for age, sex, education, smoking, and body mass index (model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR.

Supplementary Table 1

Cross-sectional associations of sleep with type of grief at baseline additionally adjusted for depressive symptoms, compared to non-complicated grief (n=158).

	No grief (n=1,521)			Acute grief (n=44)			Complicated grief (n=53)		
	Adjusted Odds Ratio (95% CI)	**P-value**	**Corrected P-value**	**Adjusted Odds Ratio (95% CI)**	**P-value**	**Corrected P-value**	**Adjusted Odds Ratio (95% CI)**	**P-value**	**Corrected P-value**
Total sleep time (hour)	1.09 (0.89;1.33)	0.40	0.60	1.41 (0.94;2.11)	0.10	0.25	1.05 (0.72;1.52)	0.80	0.87
Sleep efficiency (%)	1.01 (0.99;1.03)	0.48	0.60	1.03 (0.99;1.08)	0.18	0.30	1.00 (0.96;1.03)	0.87	0.87
Sleep onset latency (min)	1.00 (0.99;1.01)	0.98	0.98	1.00 (0.97;1.02)	0.67	0.73	1.01 (0.99;1.03)	0.20	0.50
Wake after sleep onset (min)	1.00 (1.00;1.01)	0.25	0.60	1.00 (0.98;1.01)	0.73	0.73	1.01 (1.00;1.02)	0.20	0.50
Self-rated sleep quality (score)	0.96 (0.92;1.01)	0.12	0.60	0.91 (0.81;1.02)	0.09	0.25	1.03 (0.95;1.13)	0.44	0.73

Total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset were estimated using actigraphy, self-rated sleep quality was assessed using the Pittsburgh Sleep Quality Index. Effect estimates were adjusted for age, sex, education, smoking, body mass index, and depressive symptoms (model 3). None of the associations remained significant (<0.05) after correcting for multiple testing using FDR.

Supplementary Table 2

Cross-sectional associations of 24-hour activity rhythms with type of grief at baseline, compared to non-complicated grief (n=149).

	No grief (n=1,448)			Acute grief (n=44)			Complicated grief (n=52)		
	Adjusted Odds Ratio (95% CI)	**P-value**	**Corrected P-value**	**Adjusted Odds Ratio (95% CI)**	**P-value**	**Corrected P-value**	**Adjusted Odds Ratio (95% CI)**	**P-value**	**Corrected P-value**
Interdaily stability (score)	1.02 (0.87;1.19)	0.85	0.85	1.00 (0.96;1.03)	0.81	0.98	1.10 (0.52;2.34)	0.81	0.81
Intradaily variability (score)	0.97 (0.85;1.10)	0.61	0.85	1.00 (0.96;1.04)	0.98	0.98	1.16 (0.55;2.48)	0.70	0.81
L5 onset (hour)	0.86 (0.74;1.01)	0.06	0.018	1.00 (0.96;1.03)	0.85	0.98	1.12 (0.52;2.38)	0.77	0.81

Effect estimates were adjusted for age, sex, education, smoking, and body mass index (model 2). None of the associations remained significant (<0.05) after correcting for multiple testing using FDR.

Supplementary Table 3

Cross-sectional associations of sleep with number of grief symptoms in those participants that indicated any grief at baseline (n=255), additionally adjusted for depressive symptoms.

	Grief symptoms		
	Adjusted coefficient (95% CI)	**P-value**	**Corrected P-value**
Total sleep time (hour)	-0.834 (-2.220;0.552)	0.24	0.24
Sleep efficiency (%)	-0.118 (-0.250;0.014)	0.08	0.13
Sleep onset latency (min)	0.045 (-0.018;0.109)	0.16	0.20
Wake after sleep onset (min)	0.055 (0.011;0.099)	0.015	0.08
Self-rated sleep quality (score)	0.358 (0.027;0.688)	0.034	0.09

Total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset were estimated using actigraphy, self-rated sleep quality was assessed using the Pittsburgh Sleep Quality Index. Effect estimates were adjusted for age, sex, education, smoking, body mass index, and depressive symptoms (model 3). None of the associations remained significant (<0.05) after correcting for multiple testing using FDR.

Supplementary Table 4

Cross-sectional associations of sleep with number of grief symptoms in those participants that indicated any grief at baseline (n=255), additionally adjusted for depressive symptoms. Results are stratified based on duration since the loss, using 6 months as a cut-off.

	Grief symptoms in those with duration since loss <6 months (n=44)			**Grief symptoms in those with duration since loss ≥ 6months (n=211)**		
	Adjusted coefficient (95% CI)	**P-value**	**Corrected P-value**	**Adjusted coefficient (95% CI)**	**P-value**	**Corrected P-value**
Total sleep time (hour)	-4.109 (-7.151;-1.066)	0.010	0.037*	-0.546 (-2.155;1.064)	0.50	0.50
Sleep efficiency (%)	-0.242 (-0.497;0.013)	0.06	0.08	-0.108 (-0.266;0.050)	0.18	0.23
Sleep onset latency (min)	0.179 (0.028;0.330)	0.022	0.037*	0.050 (-0.022;0.122)	0.17	0.23
Wake after sleep onset (min)	0.060 (-0.031;0.150)	0.19	0.19	0.055 (0.000;0.110)	0.049	0.12
Self-rated sleep quality (score)	0.997 (0.204;1.791)	0.016	0.037*	0.508 (0.182;0.834)	0.002	0.010*

Total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset were estimated using actigraphy, self-rated sleep quality was assessed using the Pittsburgh Sleep Quality Index. Effect estimates were adjusted for age, sex, education, smoking, body mass index, and depressive symptoms (model 3). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR.

Supplementary Table 5

Longitudinal associations of baseline 24-hour activity rhythms with type of grief at follow-up, compared to non-complicated grief (n=119).

	No grief (n=1,216)			Acute grief (n=38)			Complicated grief (n=39)		
	Adjusted Odds Ratio (95% CI)	**P-value**	**Corrected P-value**	**Adjusted Odds Ratio (95% CI)**	**P-value**	**Corrected P-value**	**Adjusted Odds Ratio (95% CI)**	**P-value**	**Corrected P-value**
Interdaily stability (score)	1.01 (0.84;1.21)	0.94	0.94	1.16 (0.81;1.67)	0.42	0.63	0.92 (0.66;1.27)	0.60	0.60
Intradaily variability (score)	0.93 (0.79;1.10)	0.41	0.62	0.86 (0.61;1.20)	0.37	0.63	0.81 (0.58;1.14)	0.23	0.35
L5 onset (hour)	1.10 (0.92;1.31)	0.30	0.62	1.08 (0.77;1.52)	0.64	0.64	1.51 (1.09;2.07)	0.012	0.036*

Total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset were estimated using actigraphy, self-rated sleep quality was assessed using the Pittsburgh Sleep Quality Index. Effect estimates were adjusted for age, sex, education, smoking, and body mass index (model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR.

Supplementary Table 6

Longitudinal associations of baseline sleep with type of grief at follow-up additionally adjusted for depressive symptoms, compared to non-complicated grief (n=122).

	No grief (n=1,270)			Acute grief (n=38)			Complicated grief (n=41)		
	Adjusted Odds Ratio (95% CI)	P-value	Corrected P-value	Adjusted Odds Ratio (95% CI)	P-value	Corrected P-value	Adjusted Odds Ratio (95% CI)	P-value	Corrected P-value
Total sleep time (hour)	1.00 (0.79;1.26)	0.97	0.97	0.92 (0.59;1.43)	0.70	0.99	0.60 (0.40;0.92)	0.019	0.07
Sleep efficiency (%)	1.00 (0.98;1.03)	0.96	0.97	1.00 (0.96;1.05)	0.99	0.99	0.96 (0.92;0.99)	0.029	0.07
Sleep onset latency (min)	1.00 (0.99;1.01)	0.90	0.97	1.00 (0.97;1.02)	0.76	0.99	1.01 (1.00;1.03)	0.11	0.13
Wake after sleep onset (min)	1.00 (1.00;1.01)	0.43	0.97	1.00 (0.99;1.02)	0.91	0.99	1.01 (1.00;1.03)	0.040	0.07
Self-rated sleep quality (score)	1.02 (0.96;1.08)	0.56	0.97	1.02 (0.91;1.14)	0.77	0.99	1.05 (0.95;1.16)	0.34	0.34

Total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset were estimated using actigraphy, self-rated sleep quality was assessed using the Pittsburgh Sleep Quality Index. Effect estimates were adjusted for age, sex, education, smoking, body mass index, and depressive symptoms (model 3). None of the associations remained significant (<0.05) after correcting for multiple testing using FDR.

3

SLEEP AND TINNITUS

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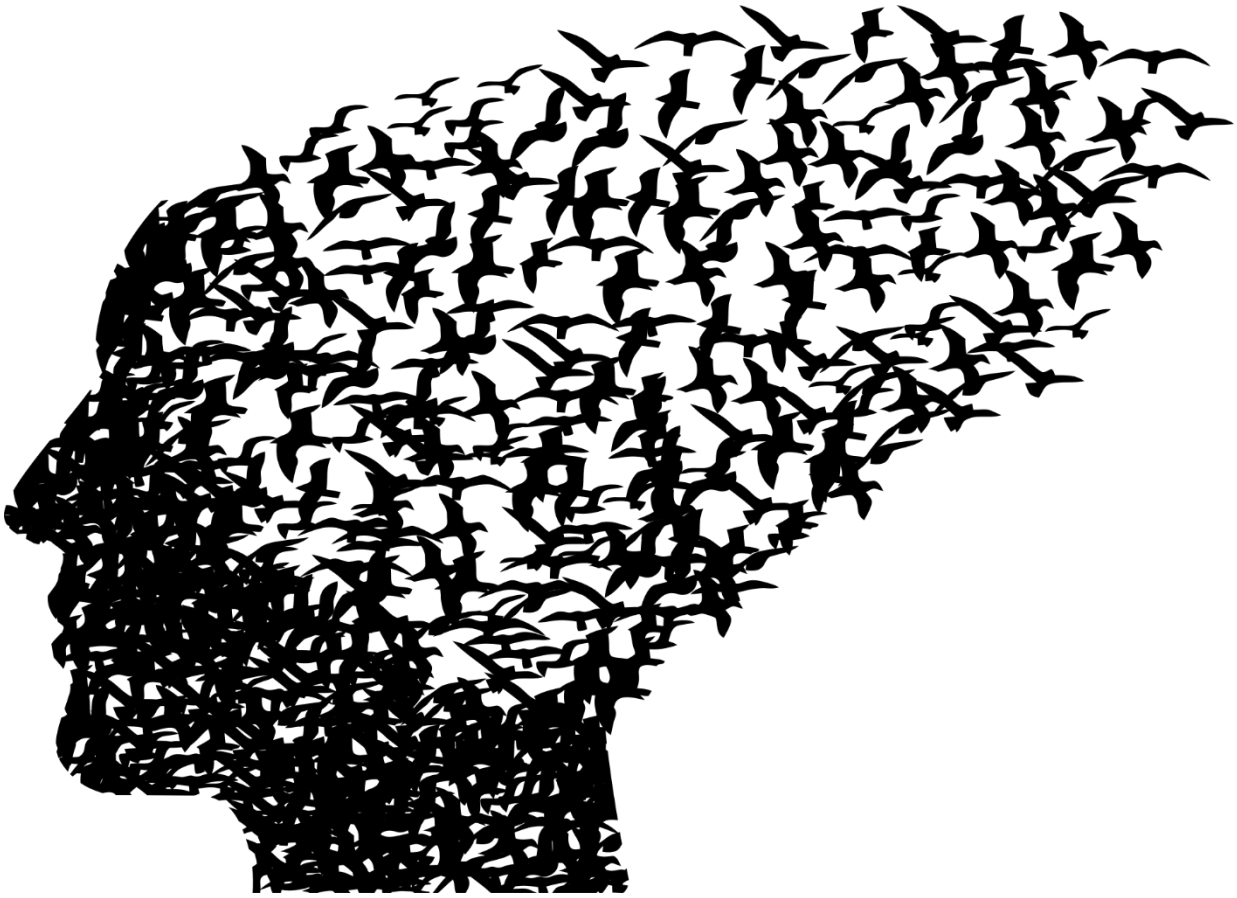

“Het dient algemeen bekend te zijn dat de bron van zowel ons plezier, onze vreugde, gelach en vermaak, als van onze smart, pijn, angst en tranen, geen ander is dan de hersenen. Het is in het bijzonder dit orgaan dat ons in staat stelt te denken, te zien en te horen e het lelijke van het schone, het kwade van het goede, het aangename van het onaangename te onderscheiden. Het zijn de hersenen ook waar zich de zetel bevindt van waanzin en krankzinnigheid, van angst en verschrikkingen die ons bestormen, dikwijls ’s nachts, maar soms zelfs overdag; daar ligt de oorzaak van slapeloosheid en slaapwandelen, van gedachten die niet willen komen, van vergeten verplichtingen en van zonderlinge verschijnselen.”

(Hippocrates, ca 460 – 370 v.Chr.)

Image by Gordon Johnson from Pixabay

3.1

Tinnitus and mental health: cross-sectional and longitudinal associations in a population-based sample of middle-aged and elderly persons

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Abstract

Importance Tinnitus is a common disorder but its impact on daily life varies largely in population-based samples. It is unclear whether this impact on daily life is directly related to mental health complaints, commonly seen in clinical populations.

Objective To investigate the association of tinnitus and its interference with daily life with complaints of depression, anxiety and a poor sleep quality in a population-based sample of middle-aged and elderly persons over a 4-year follow-up.

Design Cross-sectional and longitudinal

Setting The population-based Rotterdam Study

Participants 5,435 participants (mean age: 69.0 (SD 9.8) years, 57.3% female), of whom 975 participants (mean age: 69.0 (SD: 9.8) years, 57.3% female) had repeated measurements available

Main outcomes Tinnitus presence and interference with daily life were assessed during a home-interview. Depressive symptoms were assessed with the Center for Epidemiology Scale – Depression, anxiety symptoms with the Hospital Anxiety Depression Scale and sleep quality with the Pittsburgh Sleep Quality Index. Linear regression analyses and linear mixed models adjusted for relevant confounders were used to assess the cross-sectional and longitudinal association of tinnitus with mental health.

Results Both participants with tinnitus interfering with daily life and tinnitus not interfering with daily life reported more depressive symptoms, anxiety symptoms, and a poorer sleep quality compared to those without tinnitus. Those indicating more interference with daily life reported more mental health complaints. After an average follow up of 4 years, participants with tinnitus that interferes with daily life reported more anxiety symptoms and a poorer sleep quality than those without tinnitus.

Conclusions and relevance Tinnitus is associated with more mental health complaints in middle-aged and elderly persons from the general population, in particular when interfering with daily life but not solely. Over time, more severe tinnitus is associated with an increase in anxiety symptoms and poor sleep quality. This suggests that mental health complaints might

be part of the burden of tinnitus, even in those that do not report their tinnitus interfering with daily life.

Introduction

Tinnitus, commonly defined as a sound that is heard in absence of an objective sound-source, is a highly common condition in the general population, with a prevalence between 9 and 40%.[1] For most individuals tinnitus is not bothersome, but for about 5 to 20% of the people experiencing tinnitus the condition significantly impairs their daily life, also regarded as severe tinnitus.[1]

Tinnitus has been frequently associated with a range of psychological conditions, such as depression, anxiety, irritability, sleep disturbances, subjective distress and intense worrying.[2] These associations have been extensively researched in clinical studies,[3,4] including highly selected populations containing those with the highest tinnitus-associated burden of disease. More recently, cross-sectional epidemiological studies in population-based cohorts have confirmed associations of the prevalence of tinnitus with depression and anxiety,[5-13] as well as associations between tinnitus and sleep disorders.[14,15] As most of these studies did not take into account the interference of tinnitus on daily life, it remains unclear whether these associations are mainly driven by the high-severity tinnitus group, with high resemblance to the clinical tinnitus populations, or are also applicable to the sub-clinical tinnitus population.

Potentially, the association between tinnitus and mental health is affected by the grade of hearing loss. Hearing loss commonly co-occurs with tinnitus (43.2%[16]), is known as an accelerating factor for tinnitus[17] and has also been suggested to be associated with mental health.[18] So far, clinical studies suggest that tinnitus, hearing loss and mental health problems co-exist,[19] but no population-based studies of tinnitus have taken hearing loss into account. Lastly, due to the lack of longitudinal studies, the temporality of the association of tinnitus with mental health is still under debate. For example, tinnitus may precede mental health problems, mental health problems may precede tinnitus, or there may be a bidirectional relationship between mental health problems and tinnitus. Additionally, it is important to note that the recommended therapy for tinnitus currently is cognitive behavioral therapy, which is a psychological treatment that also entails components that may benefit mental health.[20-22]

To gain more insight into the association between tinnitus and mental health problems and the possible underlying mechanisms, we investigated the association between tinnitus and depressive symptoms, anxiety symptoms and self-rated sleep quality in a large population of middle-aged and elderly persons, focusing on its interference with daily life and the presence of hearing loss. Furthermore, we aimed to gain insight into the effect of tinnitus on the development of mental health complaints over time by analyzing longitudinal data over a period of four years.

Methods

Setting and study population

This study was embedded in the Rotterdam Study, a prospective population-based cohort of middle-aged and elderly persons. The Rotterdam Study was initiated in 1990 and investigates determinants and consequences of aging and age-related disease. The study population consists of individuals aged ≥ 40 years living in the well-defined Ommoord district of Rotterdam, the Netherlands. All participants were invited to undergo extensive examinations at study entry and subsequently every 3 to 6 years. Further details of the study have been described elsewhere.[23]

The Rotterdam Study has been approved by the medical ethics committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (www.trialregister.nl) and into the World Health Organization International Clinical Trials Registry Platform (who.int/ictrp/network/primary/en/) under shared catalog number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Tinnitus and hearing assessments were introduced into the core study protocol in 2011. Between 2011 and 2016, data on tinnitus was obtained during a home interview for at least once for 6,128 participants. Of those, we excluded participants who had no information on depressive symptoms, anxiety and/or self-rated sleep quality available from the same home interview (N=158). Additionally, because poor cognitive status might impair the ability to complete questionnaires validly, participants were also excluded if the mini mental state

examination (MMSE) score was <23 (N=143) or if missing (N=409). Of the remaining 5,418 participants, repeated data on tinnitus and mental health outcomes were obtained for 1,140 participants, with a mean follow up time 4.4 years (range: 3.5-5.1 years). Participants were excluded from the longitudinal analysis when there was incident tinnitus (N=96) or when they did not report tinnitus anymore (N=69) at follow-up. This leaves 5,418 complete-case participants for cross sectional analyses and 975 complete-case eligible participants for longitudinal analysis.

Tinnitus

Tinnitus presence was assessed during the home interview. Participants were asked if they experienced sounds in their head or in (one of) their ears, such as whizzing, beeping, or humming, without an objective external sound source being present. Possible answers to this question were: 'no, never', 'yes, less than once a week', 'yes, more than once a week but not daily', and 'yes, daily'. Reporting symptoms at least once a week was considered as tinnitus. Because of the heterogeneity and often temporary character of the complaints, having symptoms less than once a week was not considered as tinnitus. Participants who indicated experiencing tinnitus were additionally asked whether the tinnitus interfered with their daily life (yes/ no). Lastly, if participants reported daily tinnitus, independent of whether they reported interference with daily life, they were asked to complete the simplified Tinnitus Handicap Inventory (THI-s), a validated questionnaire to assess handicap in daily life caused by tinnitus. This 10-item inventory uses possible scores of 0 (no), 2 (sometimes) or 4 (yes) per item and a score of ≥16 represents a moderate/severe handicap.[24]

Based on the questions described above, we identified three groups at baseline: (1) participants without tinnitus, (2) participants with tinnitus, but not interfering with daily life (non-bothersome tinnitus), and (3) participants with tinnitus interfering with daily life (bothersome tinnitus). THI-s scores were assessed separately in anyone experiencing daily tinnitus.

Depressive symptoms

The Center for Epidemiological Studies Depression (CES-D) scale was used to assess depressive symptoms. The CES-D is a validated instrument that is widely used to estimate

self-reported depressive symptoms.[25] The CES-D is a 20-item questionnaire, where each item is scored on a four-point scale from 0 (low) to 3 (high). The cut-off value for clinically relevant depressive symptoms was set at ≥16 points.[25,26] If not all but more than 75% of the items were completed a weighted total score was calculated, if less than 75% of the questions were answered CES-D was set to missing.

Anxiety symptoms

The anxiety subscale of the Hospital Anxiety and Depression scale (HADS-A)[27] was used to assess anxiety symptoms. The HADS-A is a 7-item questionnaire, where each item is scored on a four-point scale from 0 (never) to 3 (usually). A weighted global score was calculated by multiplying by 7/6 when 6 components were available. If less than 6 component scores were available, the HADS-A was set to missing. The total score range between 0 and 21, where the cut-off value for clinically relevant anxiety symptoms was set at ≥8 points.[27]

Sleep outcomes

The Pittsburgh Sleep Quality Index (PSQI) was used to measure self-rated sleep quality. The PSQI is a 19-item questionnaire, covering sleep-associated problems. The PSQI covers 7 components, reported on a four-point scale from 0 (never) to 3 (daily).[28] A weighted global score was calculated by multiplying by 7/6 when 6 components were available. If less than 6 components were available, PSQI was set to missing. The final global score ranges between 0 and 21. The cut-off value for clinically relevant poor sleeping quality was set at ≥5 points.[28]

Other variables

Highest achieved educational level was scored using the UNESCO classification.[29] To calculate Body Mass Index (BMI) (kg/m^2), length and weight were assessed on calibrated scales at the research center without heavy clothing and shoes. Smoking data was collected through self-report and categorized into never, former, or current smoking. Alcohol consumption (glasses/day) was assessed through self-report. Pure tone audiometry was performed by a trained health care professional in a soundproof booth. Air conduction thresholds for both ears were obtained on frequencies 0.25, 0.5, 1, 2, 4, 8 kilohertz (kHz).[23] Pure tone average hearing thresholds (PTA), averaged over 0.5, 1, 2 and 4 kHz, were determined from the best hearing ear, as proposed by the WHO.[30] Hearing loss was defined as a PTA ≥25 decibel hearing

level (dB HL).[30] The Mini-Mental State Examination (MMSE) was administered during home interview to screen cognitive status.[31]

Statistical analysis

Demographic characteristics of the population were described. Descriptive statistics were used to assess and compare differences in participant characteristics in participants with and without tinnitus. For continuous variables with a normal distribution we described the mean and standard deviation (SD) and used a t-test for statistical testing. For continuous variables with a non-normal distribution we described the median and inter quartile range (IQR) and used a Mann-Whitney U test to compare groups. For categorical variables we described the number (%) and used a X^2-test to compare the groups. Depressive symptoms, anxiety symptoms, and sleep quality scores were all log-transformed (score +1) to achieve a normal distribution of the residuals.

To estimate the cross-sectional association of tinnitus with depressive symptoms, anxiety symptoms, and sleep quality at baseline we used linear and logistic regression analyses. Participants with bothersome tinnitus and participants with non-bothersome tinnitus were compared to participants without tinnitus (reference group) and with each other (non-bothersome tinnitus as reference group). To account for confounding two models were used: Model 1 was adjusted for sex and age and Model 2 was additionally adjusted for the highest achieved education, BMI, alcohol use, smoking, and hearing threshold.

Additionally, all cross-sectional regression analyses were repeated with the entire dataset stratified for hearing loss (PTA ≥25 dB HL) as this is the most important risk factor for tinnitus. In a subgroup of participants with daily tinnitus symptoms and an available THI-s score (N=625), we also assessed the associations of tinnitus handicap with mental health, comparing participants with a relevant tinnitus handicap (THI-s ≥16) to those with no tinnitus handicap (THI-s <16).

We used linear mixed models with random intercepts and slopes to explore the longitudinal association between tinnitus and depressive symptoms, anxiety symptoms and sleep quality over time. In each model, we entered follow up time in years after baseline measurement to use as time variable and added an interaction term of tinnitus and follow-up time in all models

to allow for slope differences in the relationship between mental health outcomes and time explained by the presence of tinnitus. The linear tinnitus term (intercept difference) and the interaction term between tinnitus and follow-up time (slope difference) are the main outcomes in this longitudinal analysis. Confounder adjustment performed per Model 1 and Model 2 as fixed effects. The control variables were included as fixed effects.

IBM SPSS statistics version 24.0 (IBM Corp, Armonk, NY, USA) was used for data handling and cross-sectional analyses and R statistical software version 4.0.4. Using the LME package was for longitudinal analyses. A p-value < 0.05 was considered statistically significant.

Results

Cross-sectional association of tinnitus with mental health

For the cross-sectional analyses 5,418 participants were included with a mean age of 69.0 years (SD 9.8) and 57% were women. In total 4,245 (78.4%) participants reported no prevalent tinnitus, 1,063 (19.6%) reported non-bothersome tinnitus and 110 (2.0%) reported bothersome tinnitus (Table 1). Of the participants with bothersome tinnitus 94/110 experienced tinnitus daily and 16/110 experienced tinnitus less frequently.

Participants with bothersome tinnitus scored significantly higher on depressive symptoms (difference in log (score+1): 0.20, 95%CI 0.11; 0.28), anxiety symptoms (difference: 0.15, 95%CI 0.08; 0.22), and sleep quality (difference: 0.10, 95%CI 0.03; 0.16) compared to participants without tinnitus as well as compared to participants with non-bothersome tinnitus when adjusted for confounders (Table 2). Participants with non-bothersome tinnitus also scored significantly higher on depressive symptoms (difference: 0.06, 95%CI 0.04; 0.10), anxiety symptoms (difference: 0.05, 95%CI 0.02; 0.07), and sleep quality (difference: 0.05, 95%CI 0.03; 0.08) compared to participants without tinnitus (Table 2). When using cut-offs to indicate clinically relevant symptoms for these mental health outcomes, we found effects sizes indicating similar associations (eTable 1).

As the presence of hearing loss might affect the association between tinnitus and mental health outcomes we repeated the analyses in a dataset stratified on hearing loss (≥25dB HL). These analyses suggested that associations of tinnitus with mental health were found in both groups of participants with and without hearing loss (Table 3). Yet, when using a cut-off to

distinguish between clinically relevant mental health outcomes, results were mixed, seemingly more pronounced for the group without hearing loss (eTable 2).

Information on tinnitus handicap was available in participants with daily tinnitus (N=625). Of those, 88 (13.4%) reported a relevant tinnitus handicap. Participants with a relevant tinnitus handicap, had higher scores on all three mental health outcomes compared to participants with daily tinnitus but no tinnitus handicap (Table 4, eTable 3).Median scores on all three mental health outcomes were higher per more severe tinnitus handicap category (eTable 4).

Associations of tinnitus with mental health over time

Repeated data were available for 975 participants (mean age 71.7 years (SD: 4.5), 53.2% female), with a mean follow up of 4.4 years (SD 0.2, range: 3.5-5.1 years). At baseline, no tinnitus was reported by 792 participants (81.2%), non-bothersome tinnitus by 163 participants (16.7%) and bothersome tinnitus by 20 participants (2.1%).

Participants with any tinnitus, and both bothersome and non-bothersome, had higher scores on all three mental health outcomes as compared to no tinnitus (Figure 1, eFigure 1, eTable 5). The change in mental health symptoms over the follow-up time was not significantly different for participants with tinnitus, nor were they different for bothersome and non-bothersome tinnitus, compared to participants without tinnitus.

Discussion

In this study we confirmed that both bothersome and non-bothersome tinnitus were associated with more depressive symptoms, more anxiety symptoms and a poorer sleep quality, although associations were stronger in those indicating bothersome tinnitus. Associations were present in those with and without hearing loss. Furthermore, longitudinal analysis appeared to indicate (not significantly) more depressive symptoms, anxiety symptoms and a poorer sleep quality after 4 years follow-up in participants with bothersome tinnitus.

The association of tinnitus with psychopathology is in line with previous cross-sectional studies, reporting tinnitus to be associated with depressive symptoms, anxiety and poorer sleep quality.[3-11,32,33] We found that the effect size of the association for bothersome tinnitus over non-bothersome tinnitus was nearly three times larger for depressive and anxiety

symptoms and two times larger for sleep quality as compared to no tinnitus. However, the absolute values for the difference in effect size cannot be determined from the reported values as they represent a transformed value. Moreover, we found that the daily-tinnitus group with a severe tinnitus handicap (high THI-s score) had a 2 to 4 times higher likelihood for psychopathology than the daily-tinnitus group with a mild tinnitus handicap (low/moderate THI-s score). This is in line with the results reported by Bhatt et al. 2017 who found even higher odds ratios but compared participants with tinnitus to those without tinnitus.[11] Yet, the association between tinnitus and mental health outcomes is not only driven by a small group with severe tinnitus. We also observed a similar association in the subgroup of participants with non-bothersome tinnitus. Although the effect sizes were smaller than in the bothersome tinnitus group, the associations were consistently found for each of the three investigated mental health outcomes. Mental health problems can thus also be seen in milder manifestations of tinnitus. A possible explanation for the consistent association between tinnitus and mental health outcomes, even in case of non-bothersome tinnitus, could be that people with tinnitus generally develop negative thoughts about their tinnitus, stress arousal and hyperawareness.[34] These negative thoughts and hyperawareness have been suggested to be a mechanism towards developing mental health problems.[35,36] Yet, equally, it could be speculated that mental health problems lead to a negative focus which worsens the experience of tinnitus,[37] or that a tendency towards negative thoughts, stress and hyperawareness could be a shared common cause. Further research is needed to determine the exact pathways.

Another potential cause for the association of tinnitus with mental health problems is the presence of hearing loss, as it is a strong risk factor for tinnitus[16] and also is associated with mental health problems,[18] depression in particular.[38] However, we observed associations between tinnitus and mental health outcomes in both subgroups, with and without hearing loss, suggesting that hearing loss is not a common cause that explains these associations in full. Surprisingly, we even found a higher likelihood for clinically relevant mental health problems with severe tinnitus for the subgroup without hearing loss. Even though it is counterintuitive that absence of hearing loss seems to strengthen the association of tinnitus with more psychopathology, it could be that without hearing loss different neural pathways are involved in tinnitus generation, and that these neural pathways in turn have a stronger

association with mental health problems.[39] In presence of hearing loss tinnitus pathophysiology is more likely to be initiated by hearing-related factors, whereas in absence of hearing loss it is thought that changes in the brain are responsible for tinnitus to occur.[17]

Several other causal pathways have been posed to explain the association between tinnitus and mental health.[11] To gain more insight in the directionality of the association between tinnitus and mental health problems we investigated with explorative longitudinal analyses how mental health problems evolve over time in presence or absence of tinnitus. Our results in the figure appear to suggest an increase of anxiety symptoms and poorer sleep quality over a time period of 4 years for patients due to more severe tinnitus, albeit effects did not reach statistical significance due to limited power. Additionally, as we were only able to study the effects of tinnitus on mental health, and not the other way around, we cannot infer that the direction of the effect is solely from tinnitus to mental health. The relation could also be bi-directional, where a negative vicious circle in which more severe tinnitus increases mental health problems and mental health problems induce tinnitus complaints. To the best of our knowledge there are no other longitudinal epidemiological studies devoted to the association between tinnitus and mental health over time. Future population-based studies with repeated measurements over time are therefore urgently needed.

A major strength of this study is the presence of both cross-sectional as well as longitudinal data in a relatively large population-based sample, and the large number of confounding variables taken in account, including hearing loss. Several side notes should be placed with this study. As with all tinnitus research, the lack of a uniform definition of this subjective disease hampers the ability to compare our results with other studies. Nevertheless, we used a frequently used question to assess tinnitus.[1] Additionally, we have investigated tinnitus severity both through an additional question as well as through the THI-s. Regarding our longitudinal analyses a follow-up time of four years might be too long to investigate a direct effect of the presence of tinnitus on mental health outcomes. It would also be very interesting to investigate the longitudinal association between mental health problems and incident tinnitus, however, tinnitus incidence was too low in this current study to be able to provide these results. We believe this study is of added value, as we were able to investigate cross-sectional associations between tinnitus and mental health in relevant subgroups of a large

population-based sample of middle-aged and elderly persons, and additionally explored the possible associations over time.

In conclusion, we have demonstrated that tinnitus is strongly associated with more depressive symptoms, anxiety symptoms and poor sleep quality, even when tinnitus does not interfere with daily life (non-bothersome tinnitus). Hearing loss does not seem to play a primary role in these associations. Moreover, bothersome tinnitus is associated with an increase in anxiety symptoms and poorer sleep quality over time. These results underline the importance to increase awareness of the effects of tinnitus on mental health among those affected. Primary healthcare professionals should carefully monitor mental health in tinnitus patients, even in those who do not report significant impairments to their daily life.

References

1. McCormack A, Edmondson-Jones M, Somerset S, Hall D. A systematic review of the reporting of tinnitus prevalence and severity. *Hear Res.* 2016;337:70-79.
2. Langguth B, Landgrebe M, Kleinjung T, Sand GP, Hajak G. Tinnitus and depression. *World J Biol Psychiatry.* 2011;12(7):489-500.
3. Salazar JW, Meisel K, Smith ER, Quiggle A, McCoy DB, Amans MR. Depression in Patients with Tinnitus: A Systematic Review. *Otolaryngol Head Neck Surg.* 2019;161(1):28-35.
4. Pattyn T, Van Den Eede F, Vanneste S, et al. Tinnitus and anxiety disorders: A review. *Hear Res.* 2016;333:255-265.
5. House L, Bishop CE, Spankovich C, Su D, Valle K, Schweinfurth J. Tinnitus and its risk factors in african americans: The Jackson Heart Study. *Laryngoscope.* 2018;128(7):1668-1675.
6. Nondahl DM, Cruickshanks KJ, Huang GH, et al. Tinnitus and its risk factors in the Beaver Dam offspring study. *Int J Audiol.* 2011;50(5):313-320.
7. Seo JH, Kang JM, Hwang SH, Han KD, Joo YH. Relationship between tinnitus and suicidal behaviour in Korean men and women: a cross-sectional study. *Clin Otolaryngol.* 2016;41(3):222-227.
8. Shargorodsky J, Curhan GC, Farwell WR. Prevalence and characteristics of tinnitus among US adults. *Am J Med.* 2010;123(8):711-718.
9. Stohler NA, Reinau D, Jick SS, Bodmer D, Meier CR. A study on the epidemiology of tinnitus in the United Kingdom. *Clin Epidemiol.* 2019;11:855-871.
10. McCormack A, Edmondson-Jones M, Fortnum H, et al. Investigating the association between tinnitus severity and symptoms of depression and anxiety, while controlling for neuroticism, in a large middle-aged UK population. *Int J Audiol.* 2015;54(9):599-604.
11. Bhatt JM, Bhattacharyya N, Lin HW. Relationships between tinnitus and the prevalence of anxiety and depression. *Laryngoscope.* 2017;127(2):466-469.
12. Gopinath B, McMahon CM, Rochtchina E, Karpa MJ, Mitchell P. Incidence, persistence, and progression of tinnitus symptoms in older adults: the Blue Mountains Hearing Study. *Ear Hear.* 2010;31(3):407-412.
13. Krog NH, Engdahl B, Tambs K. The association between tinnitus and mental health in a general population sample: results from the HUNT Study. *J Psychosom Res.* 2010;69(3):289-298.
14. Izuhara K, Wada K, Nakamura K, et al. Association between tinnitus and sleep disorders in the general Japanese population. *Ann Otol Rhinol Laryngol.* 2013;122(11):701-706.
15. Bhatt JM, Lin HW, Bhattacharyya N. Prevalence, Severity, Exposures, and Treatment Patterns of Tinnitus in the United States. *JAMA Otolaryngol Head Neck Surg.* 2016;142(10):959-965.
16. Oosterloo BC, Croll PH, de Jong RJB, Ikram MK, Goedegebure A. Prevalence of Tinnitus in an Aging Population and Its Relation to Age and Hearing Loss. *Otolaryngol Head Neck Surg.* 2020:194599820957296.
17. Haider HF, Bojic T, Ribeiro SF, Paco J, Hall DA, Szczepek AJ. Pathophysiology of Subjective Tinnitus: Triggers and Maintenance. *Front Neurosci.* 2018;12:866.

18. Blazer DG. Hearing Loss: The Silent Risk for Psychiatric Disorders in Late Life. *Clin Geriatr Med.* 2020;36(2):201-209.
19. Gomaa MA, Elmagd MH, Elbadry MM, Kader RM. Depression, Anxiety and Stress Scale in patients with tinnitus and hearing loss. *Eur Arch Otorhinolaryngol.* 2014;271(8):2177-2184.
20. Landry EC, Sandoval XCR, Simeone CN, Tidball G, Lea J, Westerberg BD. Systematic Review and Network Meta-analysis of Cognitive and/or Behavioral Therapies (CBT) for Tinnitus. *Otol Neurotol.* 2020;41(2):153-166.
21. Rademaker MM, Stegeman I, Ho-Kang-You KE, Stokroos RJ, Smit AL. The Effect of Mindfulness-Based Interventions on Tinnitus Distress. A Systematic Review. *Front Neurol.* 2019;10:1135.
22. Cima RFF, Mazurek B, Haider H, et al. A multidisciplinary European guideline for tinnitus: diagnostics, assessment, and treatment Multidisziplinare europaische Leitlinie fur Tinnitus: Diagnostik, Einschatzung und Behandlung. *HNO.* 2019;67(Suppl 1):10-42.
23. Ikram MA, Brusselle G, Ghanbari M, et al. Objectives, design and main findings until 2020 from the Rotterdam Study. *Eur J Epidemiol.* 2020.
24. Newman CW, Sandridge SA, Bolek L. Development and psychometric adequacy of the screening version of the tinnitus handicap inventory. *Otol Neurotol.* 2008;29(3):276-281.
25. Radloff LS. The CES-D Scale:A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement.* 1977;1(3):385-401.
26. Beekman ATF, Van Limbeek J, Deeg DJH, Wouters L, Van Tilburg W. Een screeningsinstrument voor depressie bij ouderen in de algemene bevolking: de bruikbaarheid van de Center for Epidemiologic Studies Depression Scale (CES-D). *Tijdschrift voor Gerontologie en Geriatrie.* 1994.
27. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361-370.
28. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193-213.
29. United Nations Educational SaCOU. International Standard Classification of Education (ISCED). 1976.
30. World Health Organisation W. Grades of hearing impairment. [World Health Organisation Web site]. 2015; http://www.who.int/pbd/deafness/hearing_impairment_grades/en/.
31. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198.
32. Teixeira LS, Granjeiro RC, Oliveira CAP, Bahamad Junior F. Polysomnography Applied to Patients with Tinnitus: A Review. *Int Arch Otorhinolaryngol.* 2018;22(2):177-180.
33. Loprinzi PD, Maskalick S, Brown K, Gilham B. Association between depression and tinnitus in a nationally representative sample of US older adults. *Aging Ment Health.* 2013;17(6):714-717.
34. Eysenck MW, Fajkowska M. Anxiety and depression: toward overlapping and distinctive features. *Cogn Emot.* 2018;32(7):1391-1400.
35. Harvey AG. A cognitive model of insomnia. *Behav Res Ther.* 2002;40(8):869-893.

36. McKenna L, Handscomb L, Hoare DJ, Hall DA. A scientific cognitive-behavioral model of tinnitus: novel conceptualizations of tinnitus distress. *Front Neurol.* 2014;5:196.
37. Natalini E, Fioretti A, Riedl D, Moschen R, Eibenstein A. Tinnitus and Metacognitive Beliefs-Results of a Cross-Sectional Observational Study. *Brain Sci.* 2020;11(1).
38. Blazer DG, Tucci DL. Hearing loss and psychiatric disorders: a review. *Psychol Med.* 2019;49(6):891-897.
39. Sedley W. Tinnitus: Does gain explain? *Neuroscience.* 2019.

Table 1 Demographic characteristics

	Total sample (N=5,418)	No tinnitus (N=4,245)	Bothersome tinnitus (N=110)	Non-bothersome tinnitus (N=1,063)	p-value
Age, years (SD)	69.0 (9.8)	69.0 (9.8)	68.6 (8.7)	69.3 (9.7)	0.664
Female, N(%)	3,131 (57.3)	2,476 (58.3)	59 (53.6)	561 (52.8)	0.004
Education level, N(%)					0.291
Primary	394 (7.3)	297 (7.0)	12 (10.9)	85 (8.0)	
Lower	2,103 (38.8)	1,625 (38.3)	44 (40.0)	434 (40.8)	
Middle	1,619 (29.9)	1,282 (30.2)	33 (30.0)	304 (28.6)	
Higher	1,251 (23.1)	999 (23.5)	21 (19.1)	231 (21.7)	
THI-s ≥16*, N(%)	88 (13.4)	-	41 (51.3)	47 (8.6)	<0.001
Hearing threshold, dB HL (SD)	23.6 (13.4)	22.6 (12.9)	30.8 (14.9)	26.8 (14.5)	<0.001
Hearing loss, N (%)	1,742 (32.2)	1,245 (29.3)	56 (50.9)	441 (41.5)	<0.001
Depressive symptoms					
Weighted score‡	3 (1 - 8)	3 (1 - 7)	6 (2 - 12)	4 (1 - 9)	<0.001
Clinically relevant, N(%)	500 (9.2)	371 (8.7)	17 (15.5)	112 (10.5)	0.014
Anxiety symptoms					
Weighted score‡	2 (0 - 4)	2 (0 - 4)	3 (1 - 6)	2 (0 - 5)	<0.001
Clinically relevant, N(%)	453 (8.4)	328 (7.7)	14 (12.7)	111 (10.4)	0.004
Sleep quality					
Weighted score‡	3 (1 - 6)	3 (1 - 5)	4 (2 - 7)	3 (2 - 6)	<0.001
Clinically relevant, N(%)	1,361 (25.1)	1,013 (23.9)	38 (34.5)	310 (29.2)	<0.001
Body mass index, kg/m^2 (SD)	27.5 (4.4)	27.4 (4.4)	27.8 (3.9)	27.7 (4.2)	0.297
Smoking, N(%)					0.020
Never	1,728 (31.9)	1,398 (32.9)	34 (30.9)	296 (27.8)	
Past	2,809 (51.8)	2,156 (50.8)	60 (54.5)	593 (55.8)	
Current	798 (14.7)	622 (14.7)	14 (12.7)	162 (15.2)	
Alcohol units/day, N(%)					0.603
Never	792 (14.6)	631 (14.9)	16 (14.5)	145 (13.6)	
1-2	3,526 (65.1)	2,766 (65.2)	70 (63.6)	690 (64.9)	
3-4	862 (15.9)	665 (15.7)	22 (20.0)	175 (16.5)	
>5	229 (4.2)	177 (4.2)	2 (1.8)	50 (4.7)	
MMSE‡	28 (27 - 29)	28 (27 - 29)	28 (27 - 29)	29 (27 - 29)	0.932

Values are mean (standard deviation (SD)) for normally distributed continuous variables, a t-test was used to compare groups. *% of those who filled out the THIS-s. ‡Median (interquartile range (IQR)) for non-normally distributed continuous variables, a Mann-Whitney U test was used to compare groups. Dichotomous variables are given as N, (%), a X^2-test was used to compare groups. THI-s: Tinnitus Handicap Inventory – screening version. dB HL: decibel hearing level. Hearing loss was averaged over the 0.5, 1, 2, 4 kHz frequencies in the best ear. Depressive symptoms were measured with the CES-D list, a score of ≥16 was considered clinically relevant. Anxiety symptoms were measured with the HADS- anxiety subscale, a score of ≥8 was considered clinically relevant. Sleep quality was self-reported with the PSQI, a score of ≥6 was considered as clinically relevant lower sleep quality. MMSE: Mini-Mental State Examination.

Table 2

Association between participants with tinnitus with and without interference with daily life and depressive symptoms, anxiety symptoms and self-reported sleep quality.

		Depressive symptoms	Anxiety symptoms	Sleep quality
		Difference (95% CI)	**Difference (95% CI)**	**Difference (95% CI)**
No tinnitus	Model 1	Ref	Ref	Ref
	Model 2	Ref	Ref	Ref
Bothersome tinnitus	Model 1	*0.21 (0.11, 0.28)*	*0.16 (0.09, 0.23)*	*0.09 (0.02, 0.15)*
	Model 2	*0.20 (0.11, 0.28)*	*0.15 (0.08, 0.22)*	*0.10 (0.03, 0.16)*
Non-bothersome tinnitus	Model 1	*0.07 (0.04, 0.10)*	*0.05 (0.02, 0.07)*	*0.05 (0.03, 0.07)*
	Model 2	*0.06 (0.03, 0.09)*	*0.05 (0.02, 0.07)*	*0.05 (0.03, 0.08)*

Difference represents the difference in the log-transformed (raw score +1) of the CES-D (for depressive symptoms), HADS – anxiety subscale (for anxiety symptoms) or PSQI (for self-reported sleep quality) in participants with non-bothersome or bothersome tinnitus. CI: confidence interval. Model 1: adjusted for sex and age. Model 2: additionally adjusted for highest achieved education, hearing loss, body mass index, alcohol use and smoking status. Significant effect estimates ($p<0.05$) are indicated in *italic*.

Table 3

Association between participants with tinnitus with and without interference with daily life and depressive symptoms, anxiety symptoms and self-reported sleep quality stratified analyses for hearing impairment.

		Depressive symptoms	Anxiety symptoms	Sleep quality
		Difference (95% CI)	**Difference (95% CI)**	**Difference (95% CI)**
No hearing loss (<25 dB HL), N=3,676				
No tinnitus	Model 1	Ref	Ref	Ref
	Model 2	Ref	Ref	Ref
Bothersome tinnitus	Model 1	*0.21 (0.07, 0.35)*	*0.13 (0.02, 0.24)*	0.06 (-0.04, 0.16)
	Model 2	*0.20 (0.05, 0.34)*	*0.12 (0.01, 0.24)*	0.06 (-0.04, 0.16)
Non-bothersome tinnitus	Model 1	*0.05 (0.00, 0.09)*	0.02 (-0.01, 0.06)	*0.05 (0.02, 0.09)*
	Model 2	0.04 (-0.00, 0.09)	0.02 (-0.02, 0.06)	*0.06 (0.03, 0.09)*
Hearing loss (≥25 dB HL), N=1,742				
No tinnitus	Model 1	Ref	Ref	Ref
	Model 2	Ref	Ref	Ref
Bothersome tinnitus	Model 1	*0.23 (0.12, 0.34)*	*0.19 (0.09, 0.28)*	*0.12 (0.03, 0.21)*
	Model 2	*0.22 (0.11, 0.33)*	*0.18 (0.09, 0.28)*	*0.13 (0.04, 0.21)*
Non-bothersome tinnitus	Model 1	*0.09 (0.04, 0.13)*	*0.08 (0.04, 0.11)*	*0.05 (0.01, 0.08)*
	Model 2	*0.08 (0.04, 0.13)*	*0.08 (0.04, 0.11)*	*0.05 (0.01, 0.08)*

Difference represents the difference in the log-transformed (raw score +1) of the CES-D (for depressive symptoms), HADS – anxiety subscale (for anxiety symptoms) or PSQI (for self-reported sleep quality) in participants with non-bothersome or bothersome tinnitus, stratified for hearing loss. OR: Odds ratio for the cut-off value for a clinically relevant score on either the CES-D (≥16), HADS (≥8) or PSQI (≥6). CI: confidence interval. dB: decibel. Model 1: adjusted for sex and age. Model 2: additionally adjusted for highest achieved education, hearing loss, body mass index, alcohol use and smoking status. Significant estimates ($p<0.05$) are indicated in *italic*.

Table 4

Association between participants with daily tinnitus and a relevant tinnitus handicap (vs. daily tinnitus and low tinnitus handicap) and depressive symptoms, anxiety symptoms and self-reported sleep quality.

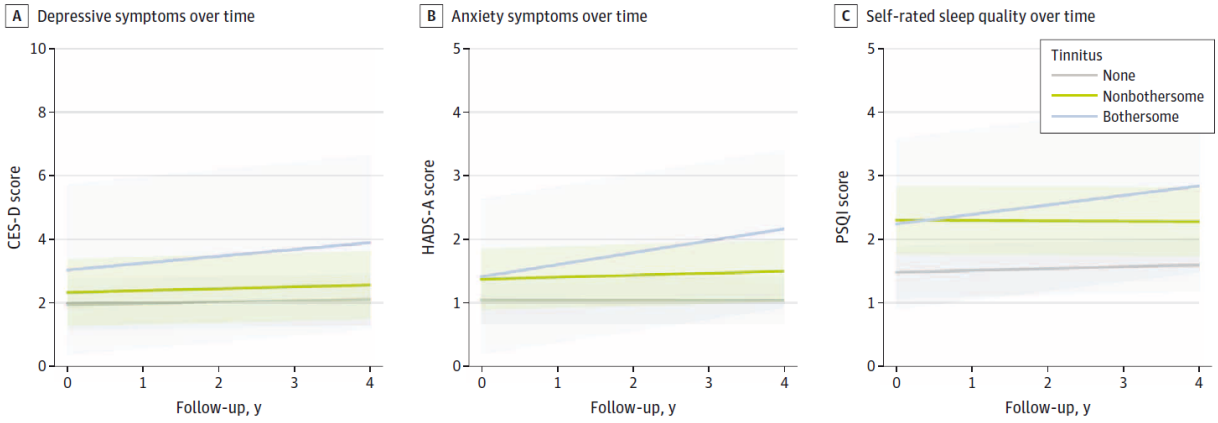
		Depressive symptoms	Anxiety symptoms	Sleep quality
		Difference (95% CI)	**Difference (95% CI)**	**Difference (95% CI)**
No relevant tinnitus handicap	Model 1	Ref	Ref	Ref
	Model 2	Ref	Ref	Ref
Relevant tinnitus handicap	Model 1	*0.22 (0.12, 0.33)*	*0.15 (0.07, 0.23)*	*0.12 (0.05, 0.19)*
	Model 2	*0.21 (0.11, 0.31)*	*0.15 (0.06, 0.23)*	*0.12 (0.05, 0.20)*

In participants with daily tinnitus (N=662), tinnitus handicap was assessed by the Tinnitus Handicap Inventory – screening version (THI-s). A relevant handicap was defined as a THI-s score ≥16. Difference represents the difference in the log-transformed (raw score +1) of the CES-D (for depressive symptoms), HADS – anxiety subscale (for anxiety symptoms) or PSQI (for self-reported sleep quality) in participants with tinnitus with and without interference with daily life. CI: confidence interval. Model 1: adjusted for sex and age. Model 2: additionally adjusted for highest achieved education, hearing loss, body mass index, alcohol use and smoking status. Significant effect estimates ($p<0.05$) are indicated in *italic*.

Figure 1 a-c

Association between participants with bothersome and non-bothersome tinnitus and depressive symptoms, anxiety symptoms and self-reported sleep quality over time.

Results of the linear mixed models, showing the average change in log (raw score+1) over time for the panel A: CES-D (for depressive symptoms), panel B: HADS – anxiety subscale (for anxiety symptoms) or panel C: PSQI (for self-reported sleep quality)



3.2

The cross-sectional association between tinnitus and actigraphy-estimated sleep in a population based cohort of middle aged and elderly persons

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Submitted

Abstract

Background: Tinnitus is a common and burdensome disease, often accompanied by complaints of poor sleep, although the associations with objectively determined sleep disturbances remain largely unknown. We assessed the association of tinnitus with sleep and 24-hour activity rhythms in a population-based cohort of middle-aged and elderly persons, using actigraphy and self-reported measures of sleep.

Methods: This study included 1,456 participants (mean age: 65.0±7.1 years, 52% women) from the population-based Rotterdam Study. Tinnitus was self-reported and in those with tinnitus, symptom severity was assessed using the Tinnitus Handicap Inventory. We used actigraphy (mean duration: 146±19.6 hours) to estimate sleep and 24-hour activity rhythms, and sleep diaries to measure self-reported sleep. Associations of tinnitus with sleep and 24-hour activity rhythms were estimated using linear regression models.

Results: Tinnitus and tinnitus severity were not associated with actigraphy-estimated sleep or 24-hour activity rhythms, but were associated with a longer self-reported sleep onset latency (adjusted $difference_{tinnitus}$=2.36, 95%CI=0.95;3.78, adjusted $difference_{tinnitus\ severity}$=0.27, 95%CI=0.013;0.54). In those with hearing loss, tinnitus was associated with longer self-reported sleep onset latency (adjusted difference=2.26, 95%CI=0.98;3.53) and less stable 24-hour activity rhythms (adjusted difference=-0.02, 95%CI=-0.04;-0.00). In those without hearing loss tinnitus was however associated with more stable rhythms (adjusted difference=0.03, 95%CI=0.01;0.05).

Conclusions: We demonstrated that tinnitus is associated with a longer self-reported sleep onset latency, but not with any actigraphy-estimated indicators of sleep, suggesting that the subjective experience of sleep may be particularly disturbed in those with tinnitus. Additionally, hearing loss modified the association of tinnitus with stability of 24-hour activity rhythms.

Keywords: actigraphy; self-reported sleep; activity rhythms; tinnitus; hearing loss; population-based.

Introduction

Tinnitus is described as a sound that is heard without an objective sound source being present.[1] With a global prevalence of 5-40%, tinnitus is a common disorder in the adult population.[2] For most people tinnitus has no a substantial impact on their life, but for 5-20% of the people that experience tinnitus, it significantly affects their functioning in daily life.[2]

Tinnitus has previously been associated with poor sleep in clinical[3] and population-based samples.[4-6] However, so far most studies assessing the association between tinnitus and sleep have focused on self-reported sleep quality or clinical diagnoses of insomnia, which are based on self-reported symptoms.[7-9] Only a few studies assessed the association between tinnitus and sleep using objective estimates of sleep, but these studies were only performed in clinical settings and showed inconclusive findings.[10] It is important to note that where self-reported sleep reflects the experience of sleep, objectively estimated sleep may more reflect the physiological aspect of sleep and may therefore provide more insights in potential underlying biological mechanisms.[11,12] As sleep is closely related to 24-hour activity rhythms, a disturbed rhythm could potentially also explain the experience of poor sleep in those with tinnitus. Knowledge about these associations could help to improve treatment or even prevention of sleep disturbances in those with tinnitus.

When studying tinnitus it is important to take a hearing loss into account, because these constructs frequently co-occur. Moreover, hearing loss is thought to be an accelerating factor for tinnitus.[13,14] Literature suggests that the origin of tinnitus between those with and without hearing loss may differ,[14] potentially also accompanied by a different association between tinnitus and sleep. So far, limited studies took hearing loss into account when studying the association of tinnitus with sleep.

In this study, we investigated the association of tinnitus and tinnitus severity with actigraphy-estimated sleep, self-reported sleep, and 24-hour activity rhythms in a population-based cohort of middle-aged and elderly persons. To gain insight in the effect of hearing loss on the association between tinnitus and sleep, we additionally stratified for hearing loss.

Methods

Participants and design

We included participants from the Rotterdam Study, a population-based cohort of middle-aged and elderly inhabitants of Rotterdam, the Netherlands. This cohort was set up in 1990 with the main aim to examine neurological, cardiovascular and other chronic age-related diseases. Details of the study design have been described by Ikram and colleagues.[15]

In 2011, tinnitus and hearing assessments were introduced to the core study protocol. Between 2011 and 2014, tinnitus was assessed in 4,839 participants during the home interview. Of those, 2,056 participants were invited to participate in an actigraphy study, 1,807 agreed. We excluded those who did not return the actigraphy device or whose data was lost (n=91), those with invalid actigraphy data (n=197), and those with less than 4 complete days of actigraphy (n=63), leaving 1,456 eligible participants for analyses (Supplementary Figure 1).

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; http://www.trialregister.nl/trial/6645) meeting the requirements by the WHO International Clinical Trials Registry Platform (ICTRP; http://www.who.int/ictrp/network/primary-registries/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Assessment of tinnitus

Tinnitus was assessed during the home interview. Participants were first asked whether they experienced sounds, such as whizzing, beeping, or humming, in (one of) their ears or in their head, without an objective external sound source being present. Answering options to this question were: ‘no, never’, ‘yes, less than once a week’, ‘yes, more than once a week but not

daily', and 'yes, daily'. If participants reported that tinnitus symptoms were present at least once a week, it was considered as tinnitus. Having symptoms less than once a week was not considered as tinnitus because of the heterogeneity and often temporary character of the complaints. If participants reported at least daily tinnitus symptoms, they were also asked to complete the simplified Tinnitus Handicap Inventory (THI). The THI is a 10-item validated questionnaire that is used to assess handicap in daily life caused by tinnitus. The total score ranges from 0 to 40, with a total score of ≥16 indicating a moderate to severe handicap.[16]

Assessment of sleep

Participants were invited to wear an actigraph on their non-dominant wrist for 7 consecutive days and only remove it when bathing or during a sauna visit. Participants were also asked to fill out a sleep diary every morning and evening during the same week. Lastly, participants were asked to press a marker button on the actigraph at the time wanted to initiate sleep (time to bed) and at the time they got out of bed (get-up time). We used the ActiWatch, model AW4 (Cambridge Technology Ltd, Cambridge, United Kingdom) or the GENEActiv (ActivInsight Ltd, Kimbolton United Kingdom). Recordings were sampled at 32 Hz (ActiWatch) or 50 Hz (GENEActiv) and scored per 30-s epoch, taking into account weighted scores of previous and following epochs. To distinguish sleep from wake a threshold of 20 was used.[17] The z-axis data of the tri-axial GENEActiv data was pre-analyzed to make records comparable with ActiWatch data.[18]

To assess sleep, actigraphy data was combined with data from the sleep diary, using validated methods that have been previously described[18] and averaged over the days with valid data available. If time to bed or get-up time was missing from the sleep diary, information from the actigraphic marker button was used. Total sleep time (hours) was estimated as the total duration of epochs scored as sleep during the night. Sleep efficiency (%) was estimated as the proportion of time spent sleeping whilst lying in bed (100% x (total sleep time/ time in bed)), with time in bed indicating the time between time to bed and get-up time. Sleep onset latency (minutes) was estimated as the duration between time to bed and sleep start. Lastly, wake after sleep onset (minutes) was defined as the total time of epochs scored as wake between sleep start and sleep end.

Additionally we estimated self-reported sleep using the sleep diaries. Total sleep time was estimated as the time participants estimated they had been sleeping that night. Sleep efficiency was the estimated time spend sleeping whilst lying in bed (100% x (total sleep time from the sleep diary/ time in bed)), where time in bed is calculated as explained earlier. Sleep onset latency was the estimated time it took to fall asleep. Lastly, wake after sleep onset was estimated as the time between self-reported sleep start and sleep end, minus the self-reported sleep duration. Each of these variables was averaged out over all nights the sleep diary was filled out.

Assessment of 24-hour activity rhythms

To assess 24-hour activity rhythms we estimated the Interdaily Stability (IS), Intradaily Variability (IV), and onset of the least active 5 consecutive hours of the day (L5) onset time. IS, indicating the stability of the sleep-wake rhythm over days, and IV, indicating fragmentation of the sleep-wake rhythm relative to its 24-hour amplitude were calculated using the nparACT R package on the actigraphy data.[19] L5 onset was estimated as the average clock time on which the least active 5 consecutive hours of the day started.[20]

Other variables

During the home interview we obtained Information on education, smoking, possible sleep apnea, and body mass index (BMI). Education was classified as primary education (primary), lower/intermediate general education or lower vocational education (low), intermediate vocational education or higher general education (middle), or higher vocational education or university (high) based on the UNESCO International Standard Classification of Education.[21] Smoking was classified as never, former, or current smoker. Possible sleep apnea was assessed as a binary variable using two questions from the Pittsburgh Sleep Quality Index.[22] Possible sleep apnea was considered present in case participants reported (1) respiratory pauses during sleep at least 1-2 nights per week or (2) loud snoring at least 2 nights per week, combined with at least occasional respiratory pauses. Alcohol and coffee intake were assessed with the sleep diary. Alcohol intake indicated the number of days per week alcoholic beverages were consumed after 6 PM Coffee intake indicated the number of days per week coffee was consumed after 6 PM. BMI (kg/m^2) and hearing loss were assessed at the research center. BMI was calculated by measuring height and weight on calibrated scales without

heavy clothing and shoes. To estimate hearing loss, pure tone audiometry data was collected by a trained health care professional in a soundproof booth. For both ears, air conduction thresholds were obtained for the frequencies 0.25, 0.5, 1, 2, 4, 8 kilohertz (kHz).[23] We determined pure tone average hearing thresholds (PTA), averaged over 0.5, 1, 2 and 4 kHz, from the best hearing ear, as proposed by the WHO.[24] Hearing loss was defined as a PTA ≥25 decibel hearing level (dB HL) in the better ear.[24] Lastly, sleep and tinnitus were not assessed at the same moment in time; therefore, we assessed the mean time between these measurements in months.

Statistical analyses

Descriptive statistics were presented as number with percentage for categorical variables and mean with standard deviation (SD) for numerical data. For our analyses, sleep and 24-hour activity rhythms variables were checked for outliers (4 SD from the mean) and set to 4 SD from the mean in the same direction. Missing values for all covariates were less than 5% and handled by using multiple imputation. The MICE R package was used with 5 imputed datasets,[25] for which we presented the pooled statistics.[26] To correct for multiple testing, we used the false discovery rate (FDR) to calculate the adjusted p-values, based on 10 determinants.[27]

First, cross-sectional linear regression models were used to estimate the association of tinnitus with actigraphy-estimated sleep, self-reported sleep, and 24-hour activity rhythms, comparing those with tinnitus to those without tinnitus. Second, to explore the effect of tinnitus severity on sleep and 24-hour activity rhythms, we used cross-sectional linear regression models to estimate the association of tinnitus severity, measured with the THI, with sleep and 24-hour activity rhythms in those experiencing tinnitus symptoms daily.

All associations were studied in a sex-age adjusted model (model 1) and a model additionally adjusted for education, smoking behavior, intake of alcohol, intake of coffee, BMI, time between sleep and tinnitus assessment and hearing loss (model 2).

To test the effect of hearing loss on the association of tinnitus with sleep, we repeated all analyses stratified for hearing loss. Furthermore, for comparison purposes, we also estimated the association of hearing loss with sleep and 24-hour activity rhythms.

Analyses were performed in R version R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org).

Results

We included 1,456 participants with a mean age of 65.0 ± 7.1 years and 52% women (Table 1). In total, 341 (23.4%) reported to experience tinnitus (Table 1). For 194 participants the tinnitus severity was assessed with the THI with a median score of 4 (IQR 0-10) (Table 1), 30 participants had clinically relevant symptoms (THI ≥16). Hearing loss was present in 664 (45.6%) of the participants, of whom 198 reported to experience tinnitus.

Tinnitus nor tinnitus severity were not associated with actigraphy-estimated sleep (Table 2). When sleep was self-reported, we observed that tinnitus was associated with a longer sleep onset latency (Table 3, adjusted difference per minute=2.36, 95%CI=0.95;3.78). Additionally we observed an association of tinnitus with lower self-reported sleep efficiency (adjusted difference per minute=-1.42, 95%CI=-2.82;-0.02), but this association did not hold after multiple testing correction. No associations of tinnitus and tinnitus severity with 24-hour activity rhythms was observed (Table 4).

After stratification for hearing loss, no associations between tinnitus and actigraphy-estimated sleep were observed in either group (Supplementary Table 1). In those with hearing loss, we did observe an association of tinnitus with long self-reported sleep onset latency (adjusted difference=2.80, 95%CI=0.91;4.70) and short self-reported total sleep time (adjusted difference=-0.19, 95%CI=-0.04;0.00, not significant after multiple testing correction) and of tinnitus severity with long self-reported wake after sleep onset (adjusted difference=2.26, 95%CI=0.98;3.53, Supplementary Table 2). In those without hearing loss no associations were found. Lastly, tinnitus was associated with a lower stability of 24-hour activity rhythms in those with hearing loss (adjusted difference=-0.02, 95%CI=-0.04;0.00), but with higher stability in those without hearing loss (adjusted difference=0.03, 95%CI=0.01;0.05) after adjustment for confounders (Supplementary Table 3). These associations did not remain significant after multiple testing correction. For comparison purposes, we also assessed the association of hearing loss with sleep and 24-hour activity rhythms, no significant associations were observed (Supplementary Table 4-6).

Discussion

Our results suggest no association of tinnitus and tinnitus severity with actigraphy-estimated sleep or 24-hour activity rhythms, but when sleep was self-reported, we did observe an association of tinnitus and more tinnitus severity with a longer sleep onset latency. After stratification for hearing loss, however, we observed an association of tinnitus with lower stability of 24-hour activity rhythms, shorter total sleep time, and longer self-reported sleep onset latency in those with hearing loss, but with a higher stability in those without hearing loss. Additionally, tinnitus severity was associated with longer self-reported wake after sleep onset in those with hearing loss, but not in those without hearing loss.

When the association between tinnitus and sleep was observed within the total study sample, we did not observe an association of tinnitus or tinnitus severity with actigraphy-estimated sleep and 24-hour activity rhythms, suggesting that tinnitus is not associated with objective disturbances of sleep and 24-hour activity rhythms. These findings might seem to contradict previous literature that observed a higher prevalence of sleep disturbances in a cohort of patients with a clinical diagnosis of tinnitus when compared to a group of healthy controls.[4,10] Yet, the burden of tinnitus and associated distress was likely substantially higher in these clinical studies as they only included persons seeking treatment for their tinnitus. Our study used a population-based approach with no pre-selection on tinnitus occurrence. The absence of an association could also be habituation to tinnitus including normalization of associated distress.[28] Potentially, distress is most prominent shortly after the onset of tinnitus. Over time, people may learn to cope with the constant noise, reducing the associated hyperarousal,[28] and consequently reducing sleep problems. Within our study, we did not assess how long the tinnitus complaints existed upon the time of the interview, participants potentially have experienced tinnitus for a longer period. Therefore, there might have been habituation to tinnitus, resulting in fewer objective sleep disturbances over time, while the subjective experience of sleep remains poor without targeted treatment.[29]

Our results indeed suggest that there is an association of tinnitus severity with longer self-reported sleep onset latency. Where previous studies mainly based self-reported sleep on a retrospective sleep questionnaires,[4,6,8] we used a prospective sleep diary. Our results therefore support that the observed findings cannot merely be explained by poorer recollection of sleep in those with tinnitus. Longer self-reported sleep onset latency in those

with tinnitus could potentially be explained by increased awareness of sleep, or worry about a lack thereof, in those with tinnitus.[12,30-32] Additionally, participants might feel it takes them longer to fall asleep, potentially because the experience of a tinnitus-related sound is unpleasant and increases the focus on how long this takes rather than an actually prolonged objective sleep onset latency. Together our results support that the experience of sleep is affected in a population-based sample of tinnitus patients, where for the majority of the people tinnitus can be classified as sub-clinical. Therefore, within this sub-clinical population with tinnitus, potentially daily life might be affected more than recognized.

Lastly, we observed substantial differences in the association of tinnitus with sleep and 24-hour activity rhythms after stratification for hearing loss. We observed an association of tinnitus with shorter self-reported total sleep time and longer self-reported sleep onset latency, and of tinnitus severity with longer self-reported wake after sleep onset in those with hearing loss, but not in those without hearing loss. Furthermore, tinnitus was associated with lower stability of 24-hour activity rhythms in those with hearing loss, but with higher stability in those without hearing loss. Of note, although those with hearing loss reported daily tinnitus more often they did not report a higher tinnitus severity. Moreover, hearing loss itself was not associated with any of the actigraphy-estimated or self-reported sleep variables. Therefore, the observed differences in associations of tinnitus with sleep and 24-hour activity rhythms are likely explained by an interaction of hearing loss with tinnitus in the association with sleep and 24-hour rhythms, implicating a different impact of the tinnitus dependent of the presence or absence of hearing loss. Tinnitus pathophysiology accompanied by hearing loss is thought to be explained more often by hearing-related factors, such as hearing damage caused by an external source.[14] Potentially these participants have an altered health perception and therefore increased focus on their health,[33] explaining the poorer subjective sleep experience. Furthermore, in those suffering from tinnitus and hearing loss, both disorders might have been induced by frequent exposure to noise at least for a subgroup of these participants.[34] We could speculate that jobs with frequent exposure to loud noise, such as in the nightlife and entertainment sector, might also be associated with less stable 24-hour activity rhythms, even after retirement. In the absence of hearing loss tinnitus pathophysiology is more likely to be explained by alterations in brain regions involved in hearing.[14] Therefore those where tinnitus is not accompanied by hearing loss might more

frequently suffer from underlying neuropathology,[33] which people might try to compensate by strong regulation their daily routine, resulting in stable 24-hour activity rhythms.[35] Potentially a different cause of tinnitus and different development of tinnitus-related sleep and 14-hour activity rhythm disturbances requires more targeted interventions. Future studies investigating these potential different groups of tinnitus patients are therefore required in order to improve treatment.

Several limitations need to be taken into account when interpreting these results. First, we were not able to draw conclusions on temporality or causality because sufficient repeated measurements were not available in our sample. Second, our measurements for tinnitus were based on self-report and not confirmed by a clinician. Third, the tinnitus burden in our population-based cohort is relatively low. Therefore, potential associations might be missed because the effects could be too small to be detected within our study sample. Last, actigraphy was collected only in a subsample of participants as an additional measurement. This might have introduced some level of selection bias as those willing to participate in the actigraphy study were more healthy and higher educated, opposed to those who refused participation. Nevertheless, studying the association between tinnitus and objective sleep estimates in a large population-based sample is unique in the field and allowed us to provide new insights in the association between tinnitus and sleep.

In conclusion, within a population of middle-aged and elderly persons we demonstrated an association of tinnitus and tinnitus severity with longer self-reported sleep onset latency, but not with actigraphy-estimated measures for sleep or 24-hour activity rhythms. These findings implicate that in a population with low tinnitus burden, tinnitus is affecting the subjective experience of sleep, but not objective measures of sleep.

References

1. Han, B.I., et al., *Tinnitus Update.* J Clin Neurol, 2021. 17(1): p. 1-10.
2. McCormack, A., et al., *A systematic review of the reporting of tinnitus prevalence and severity.* Hear Res, 2016. 337: p. 70-9.
3. Salazar, J.W., et al., *Depression in Patients with Tinnitus: A Systematic Review.* Otolaryngol Head Neck Surg, 2019. 161(1): p. 28-35.
4. Stohler, N.A., et al., *A study on the epidemiology of tinnitus in the United Kingdom.* Clinical epidemiology, 2019. 11: p. 855.
5. Wallhäusser-Franke, E., M. Schredl, and W. Delb, *Tinnitus and insomnia: is hyperarousal the common denominator?* Sleep Med Rev, 2013. 17(1): p. 65-74.
6. Oosterloo, B.C., et al., *Cross-sectional and Longitudinal Associations Between Tinnitus and Mental Health in a Population-Based Sample of Middle-aged and Elderly Persons.* JAMA Otolaryngology–Head & Neck Surgery, 2021.
7. Izuhara, K., et al., *Association between tinnitus and sleep disorders in the general Japanese population.* Ann Otol Rhinol Laryngol, 2013. 122(11): p. 701-6.
8. Bhatt, J.M., H.W. Lin, and N. Bhattacharyya, *Prevalence, Severity, Exposures, and Treatment Patterns of Tinnitus in the United States.* JAMA Otolaryngol Head Neck Surg, 2016. 142(10): p. 959-965.
9. Langguth, B., et al., *Tinnitus and depression.* The world journal of biological psychiatry, 2011. 12(7): p. 489-500.
10. Teixeira, L.S., et al., *Polysomnography applied to patients with tinnitus: a review.* International archives of otorhinolaryngology, 2018. 22(2): p. 177-180.
11. Maglione, J.E., et al., *Subjective and objective sleep disturbance and longitudinal risk of depression in a cohort of older women.* Sleep, 2014. 37(7): p. 1179-1187.
12. Mitrushina, M. and R. Tomaszewski, *The effect of subjective perception of cognition on emotional functioning in adults with long-term neurological and neuropsychiatric disorders.* Disability and rehabilitation, 2019: p. 1-7.
13. Oosterloo, B.C., et al., *Prevalence of Tinnitus in an Aging Population and Its Relation to Age and Hearing Loss.* Otolaryngol Head Neck Surg, 2020: p. 194599820957296.
14. Haider, H.F., et al., *Pathophysiology of Subjective Tinnitus: Triggers and Maintenance.* Front Neurosci, 2018. 12: p. 866.
15. Ikram, M.A., et al., *Objectives, design and main findings until 2020 from the Rotterdam Study.* European Journal of Epidemiology, 2020. 35(5): p. 483-517.
16. Newman, C.W., S.A. Sandridge, and L. Bolek, *Development and psychometric adequacy of the screening version of the tinnitus handicap inventory.* Otol Neurotol, 2008. 29(3): p. 276-81.
17. Kosmadopoulos, A., et al., *Alternatives to polysomnography (PSG): a validation of wrist actigraphy and a partial-PSG system.* Behavior research methods, 2014. 46(4): p. 1032-1041.

18. te Lindert, B.H.W. and E.J.W. Van Someren, *Sleep estimates using microelectromechanical systems (MEMS).* Sleep, 2013. 36(5): p. 781-789.
19. Blume, C., N. Santhi, and M. Schabus, *'nparACT'package for R: A free software tool for the non-parametric analysis of actigraphy data.* MethodsX, 2016. 3: p. 430-435.
20. Van Someren, E.J.W., *Actigraphic monitoring of movement and rest-activity rhythms in aging, Alzheimer's disease, and Parkinson's disease.* IEEE Transactions on Rehabilitation Engineering, 1997. 5(4): p. 394-398.
21. United Nations Educational, S.a.C.O.U., *International Standard Classification of Education (ISCED). .* 1976.
22. Buysse, D.J., et al., *Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI).* Sleep, 1991. 14(4): p. 331-338.
23. Ikram, M.A., et al., *Objectives, design and main findings until 2020 from the Rotterdam Study.* Eur J Epidemiol, 2020.
24. World Health Organisation, W. *Grades of hearing impairment*. [World Health Organisation Web site] 2015; Available from: http://www.who.int/pbd/deafness/hearing_impairment_grades/en/.
25. Buuren, S.v. and K. Groothuis-Oudshoorn, *mice: Multivariate imputation by chained equations in R.* Journal of statistical software, 2010: p. 1-68.
26. Rubin, D.B., *Multiple imputation for nonresponse in surveys*. Vol. 81. 2004: John Wiley & Sons.
27. Benjamini, Y. and Y. Hochberg, *Controlling the false discovery rate: a practical and powerful approach to multiple testing.* Journal of the Royal statistical society: series B (Methodological), 1995. 57(1): p. 289-300.
28. Simões, J.P., et al., *The progression of chronic tinnitus over the years.* Scientific reports, 2021. 11(1): p. 1-7.
29. Pyrke, R.J.L., et al., *Evidence-Based Design Features Improve Sleep Quality Among Psychiatric Inpatients.* HERD: Health Environments Research & Design Journal, 2017. 10(5): p. 52-63.
30. Leng, Y., et al., *Association between circadian rhythms and neurodegenerative diseases.* The Lancet Neurology, 2019. 18(3): p. 307-318.
31. Musiek, E.S., et al., *Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease.* JAMA neurology, 2018. 75(5): p. 582-590.
32. Riemann, D., et al., *The hyperarousal model of insomnia: a review of the concept and its evidence.* Sleep medicine reviews, 2010. 14(1): p. 19-31.
33. Langguth, B., et al., *Tinnitus: causes and clinical management.* The Lancet Neurology, 2013. 12(9): p. 920-930.
34. Henry, J.A., et al., *Tinnitus: an epidemiologic perspective.* Otolaryngologic Clinics of North America, 2020. 53(4): p. 481-499.
35. de Feijter, M., T.S. Lysen, and A.I. Luik, *24-h Activity Rhythms and Health in Older Adults.* Current Sleep Medicine Reports, 2020. 6: p. 76-83.

Table 1

Baseline characteristics of the study population at baseline. N=1,456

	N	(%)	Mean	SD
Demographics				
Age (years)			65.03	7.13
Women	755	51.9		
Education				
Primary	103	7.1		
Low	531	36.5		
Intermediate	425	29.2		
High	390	26.8		
Health indicators				
Smoking				
Non smoker	475	32.6		
Former smoker	809	55.6		
Current smoker	170	11.7		
Alcohol (units/day)			2.73	2.62
Coffee (units/day)			4.45	2.89
Body mass index (kg/m^2)			27.62	4.26
Hearing Threshold (dB HL)			26.80	13.07
Hearing loss[a]	664	45.6		
Tinnitus				
Tinnitus	341	23.4		
Tinnitus severity (score)[b,c]			4	0-10
Actigraphy-estimated sleep				
Total sleep time (hour:min)			6h14min	56min
Sleep efficiency (%)			75.94	8.36
Sleep onset latency (min)			19min	17min
Wake after sleep onset (min)			57min	27min
Self-reported sleep				
Total sleep time (hour:min)			6h 49min	56min
Sleep efficiency (%)			82.37	10.93
Sleep onset latency (min)			18min	11min
Wake after sleep onset (min)			68min	82min
24-hour activity rhythms				
Interdaily stability (score)			0.74	0.12
Intradaily variability (score)			0.46	0.15
L5 onset (24-hour clock time)			1:16	1:19
Time between measurements of sleep and tinnitus (months)[c]			3	2-5

Abbreviations: L5 onset, onset of the least active 5 consecutive hours of the day; SD, standard deviation. For categorical variables the absolute number (%) is indicated, for numeric variables the mean ± SD. Education was missing for 7 participants (0.4%), smoking for 2 (0.1%), alcohol intake for 2 (0.1%), coffee intake for 2 (0.1%), body mass index for 1 (0.1%), hearing loss for 128 (8.8%). For other variables there are no missing values.

[a] Hearing loss was defined as an average hearing level of ≥25 dB in the better ear

[b] Assessed using the tinnitus handicap inventory (n=194),

[c] median and inter quartile range were presented

Table 2

The cross-sectional association of tinnitus compared to no tinnitus and of tinnitus severity with actigraphy-estimated sleep.

	Total sleep time (min)		Sleep efficiency (%)		Sleep onset latency (min)		Wake after sleep onset (min)	
	Adjusted difference (95%CI)	**p-value**	**Adjusted difference (95%CI)**	**p-value**	**Adjusted difference (95%CI)**	**p-value**	**Adjusted difference (95%CI)**	**p-value**
Tinnitus (N=1,456)								
Model 1	0.05 (-0.06;0.16)	0.39	-0.07 (-1.09;0.95)	0.90	0.60 (-1.44;2.65)	0.56	-0.88 (-4.07;2.31)	0.59
Model 2	0.04 (-0.08;0.16)	0.54	-0.02 (-1.12;1.07)	0.97	0.22 (-1.97;2.41)	0.84	-1.74 (-5.14;1.67)	0.32
Tinnitus severity (N=194)								
Model 1	0.01 (-0.01;0.03)	0.30	0.01 (-0.15;0.18)	0.87	0.07 (-0.26;0.40)	0.68	0.02 (-0.43;0.47)	0.93
Model 2	0.01 (-0.01;0.03)	0.34	0.02 (-0.16;0.20)	0.82	0.00 (-0.35;0.35)	1.00	0.11 (-0.35;0.56)	0.65

Abbreviations: CI, Confidence Interval; Effect estimates were obtained using cross-sectional linear regression models, adjusted for sex, and age (Model 1), and adjusted for sex, age, education, smoking, alcohol intake, coffee intake, body mass index, time between sleep and tinnitus assessment, and hearing loss (Model 2).

Table 3

The cross-sectional association of tinnitus compared to no tinnitus and of tinnitus severity with self-reported sleep.

	Total sleep time (min)		Sleep efficiency (%)		Sleep onset latency (min)		Wake after sleep onset (min)	
	Adjusted difference (95%CI)	**p-value**	**Adjusted difference (95%CI)**	**p-value**	**Adjusted difference (95%CI)**	**p-value**	**Adjusted difference (95%CI)**	**p-value**
Tinnitus (N=1,456)								
Model 1	-0.08 (-0.19;0.03)	0.16	-1.13 (-2.433;0.183)	0.09	2.48 (1.15;3.81)	<0.001*	-0.29 (-11.66;11.09)	0.96
Model 2	-0.11 (-0.23;0.01)	0.08	-1.42 (-2.82;-0.02)	0.047	2.36 (0.95;3.78)	0.001*	-0.83 (-13.34;11.67)	0.90
Tinnitus severity (N=194)								
Model 1	0.00 (-0.02;0.02)	0.73	-0.17 (-0.39;0.06)	0.15	0.27 (0.02;0.51)	0.032	1.61 (0.06;3.17)	0.043
Model 2	0.00 (-0.02;0.02)	0.79	-0.16 (-0.40;0.08)	0.19	0.27 (0.01;0.54)	0.040	1.58 (-0.15;3.32)	0.073

Abbreviations: CI, Confidence Interval; Effect estimates were obtained using cross-sectional linear regression models, adjusted for sex, and age (Model 1), and adjusted for sex, age, education, smoking, alcohol intake, coffee intake, body mass index, time between sleep and tinnitus assessment, and hearing loss (Model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR.

Table 4

The cross-sectional association of tinnitus compared to no tinnitus and of tinnitus severity with actigraphy-estimated 24-hour activity rhythms.

	Intradaily stability (score)		Interdaily variability (score)		L5 onset (hour)	
	Adjusted difference (95%CI)	**p-value**	**Adjusted difference (95%CI)**	**p-value**	**Adjusted difference (95%CI)**	**p-value**
Tinnitus (N=1,456)						
Model 1	-0.01 (-0.02;0.01)	0.45	0.01 (-0.01;0.02)	0.53	0.09 (-0.07;0.25)	0.29
Model 2	0.00 (-0.02;0.02)	0.95	0.00 (-0.02;0.02)	0.92	0.08 (-0.09;0.24)	0.38
Tinnitus severity (N=194)						
Model 1	0.00 (0.00;0.00)	0.12	0.00 (0.00;0.00)	0.33	0.01 (-0.02;0.04)	0.47
Model 2	0.00 (0.00;0.00)	0.32	0.00 (0.00;0.00)	0.63	0.01 (-0.02;0.04)	0.37

Abbreviations: L5 onset, onset of the least active 5 consecutive hours of the day; CI, Confidence Interval; Effect estimates were

Supplementary Table 1

The cross-sectional association of tinnitus compared to no tinnitus and of tinnitus severity with actigraphy-estimated sleep, stratified for hearing loss.

	Total sleep time (min)		Sleep efficiency (%)		Sleep onset latency (min)		Wake after sleep onset (min)	
	Adjusted difference (95%CI)	**p-value**	**Adjusted difference (95%CI)**	**p-value**	**Adjusted difference (95%CI)**	**p-value**	**Adjusted difference (95%CI)**	**p-value**
<u>Hearing loss</u>								
Tinnitus (N=664)	0.03 (-0.13;0.187)	0.73	0.11 (-1.38;1.608)	0.88	1.54 (-1.50;4.59)	0.32	-3.46 (-8.17;1.25)	0.15
Tinnitus severity (N=120)	0.00 (-0.02;0.019)	0.82	-0.13 (-0.36;0.097)	0.26	0.11 (-0.38;0.60)	0.65	0.50 (-0.12;1.11)	0.11
<u>No hearing loss</u>								
Tinnitus (N=664)	0.04 (-0.14;0.227)	0.66	-0.20 (-1.85;1.457)	0.82	-1.81 (-5.01;1.39)	0.27	0.36 (-4.64;5.36)	0.89
Tinnitus severity (N=55)	0.03 (-0.01;0.058)	0.12	0.24 (-0.01;0.492)	0.06	-0.29 (-0.68;0.10)	0.14	-0.44 (-1.03;0.14)	0.14

Abbreviations: CI, Confidence Interval; Effect estimates were obtained using cross-sectional linear regression models, adjusted for sex, age, education, smoking, alcohol intake, coffee intake, body mass index, time between sleep and tinnitus assessment, and hearing loss (Model 2).

Supplementary Table 2

The cross-sectional association of tinnitus compared to no tinnitus and of tinnitus severity with self-reported sleep, stratified for hearing loss.

	Total sleep time (min)		Sleep efficiency (%)		Sleep onset latency (min)		Wake after sleep onset (min)	
	Adjusted difference (95%CI)	**p-value**	**Adjusted difference (95%CI)**	**p-value**	**Adjusted difference (95%CI)**	**p-value**	**Adjusted difference (95%CI)**	**p-value**
Hearing loss								
Tinnitus (N=664)	-0.19 (-0.35;-0.02)	0.026	-1.70 (-3.57;0.18)	0.08	2.80 (0.91;4.70)	0.004*	-3.95 (-18.40;10.50)	0.59
Tinnitus severity (N=120)	0.00 (-0.03;0.02)	0.79	-0.25 (-0.53;0.03)	0.07	0.23 (-0.12;0.58)	0.19	2.26 (0.98;3.53)	0.001*
No hearing loss								
Tinnitus (N=664)	-0.02 (-0.20;0.17)	0.87	-1.11 (-3.26;1.04)	0.31	1.79 (-0.37;3.95)	0.10	5.35 (-17.30;27.99)	0.64
Tinnitus severity (N=55)	-0.01 (-0.04;0.02)	0.51	-0.13 (-0.56;0.29)	0.53	0.35 (-0.06;0.75)	0.09	2.19 (-2.91;7.29)	0.39

Abbreviations: CI, Confidence Interval; Effect estimates were obtained using cross-sectional linear regression models, adjusted for sex, age, education, smoking, alcohol intake, coffee intake, body mass index, time between sleep and tinnitus assessment, and hearing loss (Model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR.

Supplementary Table 3

The cross-sectional association of tinnitus compared to no tinnitus and of tinnitus severity with actigraphy-estimated 24-hour activity rhythms, stratified for hearing loss.

	Intradaily stability (score)		Interdaily variability (score)		L5 onset (hour)	
	Adjusted difference (95%CI)	**p-value**	**Adjusted difference (95%CI)**	**p-value**	**Adjusted difference (95%CI)**	**p-value**
Hearing loss						
Tinnitus (N=664)	-0.02 (-0.04;0.00)	0.038	0.01 (-0.02;0.04)	0.42	0.08 (-0.15;0.31)	0.51
Tinnitus severity (N=120)	0.00 (-0.01;0.00)	0.27	0.00 (0.00;0.00)	0.93	0.01 (-0.03;0.05)	0.63
No hearing loss						
Tinnitus (N=664)	0.03 (0.01;0.05)	0.011	-0.01 (-0.04;0.02)	0.37	0.07 (-0.18;0.32)	0.59
Tinnitus severity (N=55)	0.00 (-0.00;0.00)	0.92	0.00 (0.00;0.01)	0.38	0.04 (-0.01;0.08)	0.11

Abbreviations: L5 onset, onset of the least active 5 consecutive hours of the day; CI, Confidence Interval; Effect estimates were obtained using cross-sectional linear regression models, adjusted for sex, age, education, smoking, alcohol intake, coffee intake, body mass index, time between sleep and tinnitus assessment, and hearing loss (Model 2). None of the p-values remained significant (<0.05) after correcting for multiple testing, using FDR.

Supplementary Table 4

The cross-sectional association of hearing loss compared to no hearing loss with actigraphy-estimated sleep

	Total sleep time (min)		Sleep efficiency (%)		Sleep onset latency (min)		Wake after sleep onset (min)	
	Adjusted difference (95%CI)	p-value	Adjusted difference (95%CI)	p-value	Adjusted difference (95%CI)	p-value	Adjusted difference (95%CI)	p-value
<u>Hearing loss (N=1,328)</u>								
Model 1	0.00 (-0.12;0.11)	0.98	0.21 (-0.84;1.25)	0.70	-0.41 (-2.50;1.69)	0.70	2.93 (-0.31;6.18)	0.08
Model 2	0.01 (-0.11;0.12)	0.89	0.36 (-0.70;1.42)	0.50	-0.99 (-3.10;1.12)	0.36	2.28 (-1.00;5.56)	0.17

Abbreviations: CI, Confidence Interval; Effect estimates were obtained using cross-sectional linear regression models, adjusted for sex, and age (Model 1), and adjusted for sex, age, education, smoking, alcohol intake, coffee intake, body mass index, time between sleep and tinnitus assessment, and hearing loss (Model 2).

Supplementary Table 5

The cross-sectional association of hearing loss compared to no hearing loss with self-reported sleep.

	Total sleep time (min)		Sleep efficiency (%)		Sleep onset latency (min)		Wake after sleep onset (min)	
	Adjusted difference (95%CI)	**p-value**	**Adjusted difference (95%CI)**	**p-value**	**Adjusted difference (95%CI)**	**p-value**	**Adjusted difference (95%CI)**	**p-value**
Hearing loss (N=1,328)								
Model 1	0.06 (-0.06;0.17)	0.33	1.09 (-0.25;2.43)	0.11	0.21 (-1.14;1.56)	0.76	-4.77 (-16.85;7.32)	0.44
Model 2	0.03 (-0.09;0.15)	0.58	0.90 (-0.45;2.25)	0.19	0.31 (-1.06;1.67)	0.66	-4.57 (-16.84;7.70)	0.47

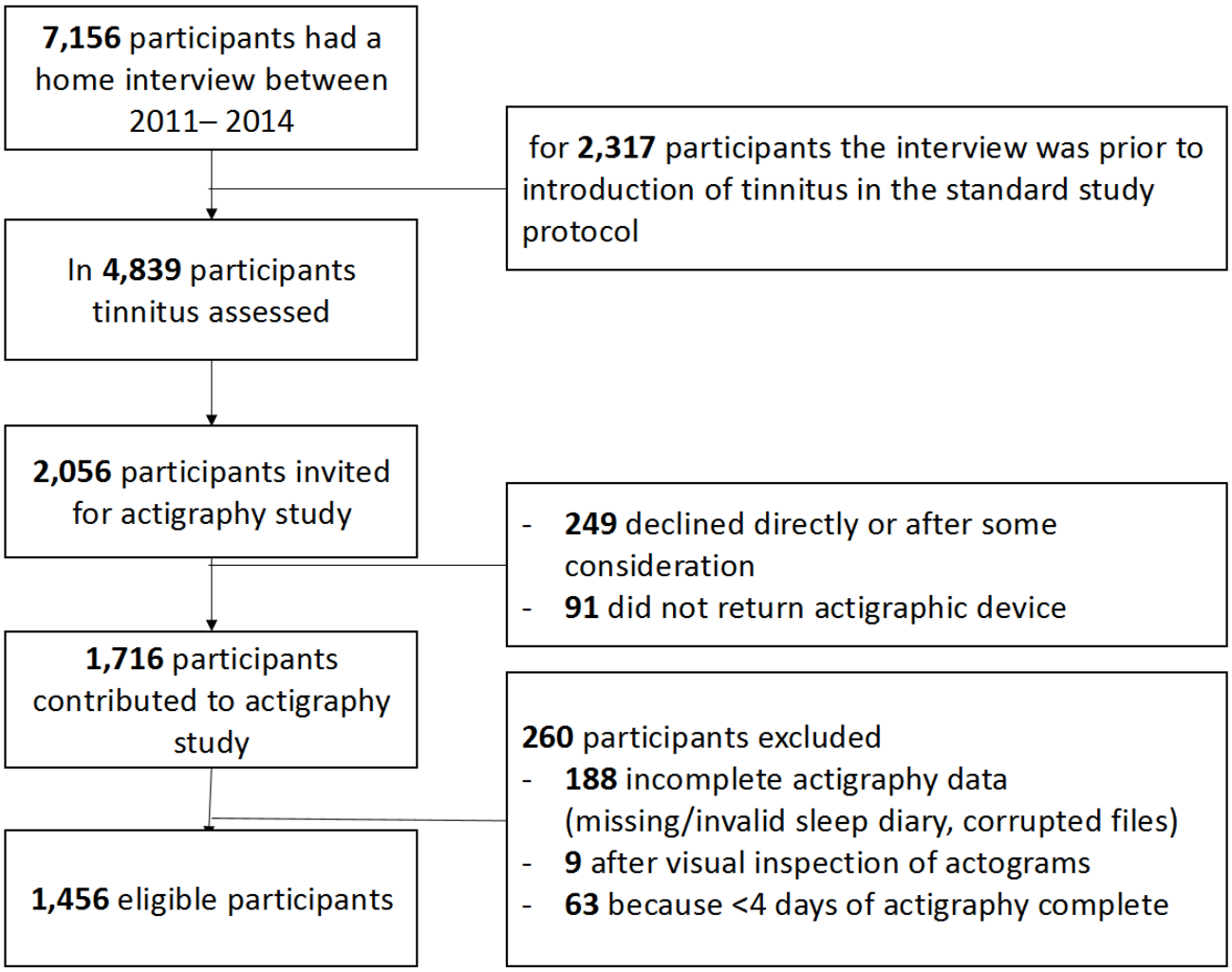
Abbreviations: CI, Confidence Interval; Effect estimates were obtained using cross-sectional linear regression models, adjusted for sex, and age (Model 1), and adjusted for sex, age, education, smoking, alcohol intake, coffee intake, body mass index, time between sleep and tinnitus assessment, and hearing loss (Model 2).

Supplementary Table 6

The cross-sectional association of hearing loss compared to no hearing loss with actigraphy-estimated 24-hour activity rhythms.

	Intradaily stability (score)		Interdaily variability (score)		L5 onset (hour)	
	Adjusted difference (95%CI)	**p-value**	**Adjusted difference (95%CI)**	**p-value**	**Adjusted difference (95%CI)**	**p-value**
Hearing loss (N=1,328)						
Model 1	0.00 (-0.01;0.02)	0.60	-0.01 (-0.02;0.01)	0.62	0.12 (-0.04;0.28)	0.15
Model 2	0.01 (-0.01;0.02)	0.34	-0.01 (-0.03;0.01)	0.31	0.09 (-0.07;0.25)	0.27

Abbreviations: L5 onset, onset of the least active 5 consecutive hours of the day; CI, Confidence Interval; Effect estimates were obtained using cross-sectional linear regression models, adjusted for sex, and age (Model 1), and adjusted for sex, age, education, smoking, alcohol intake, coffee intake, body mass index, time between sleep and tinnitus assessment, and hearing loss (Model 2).



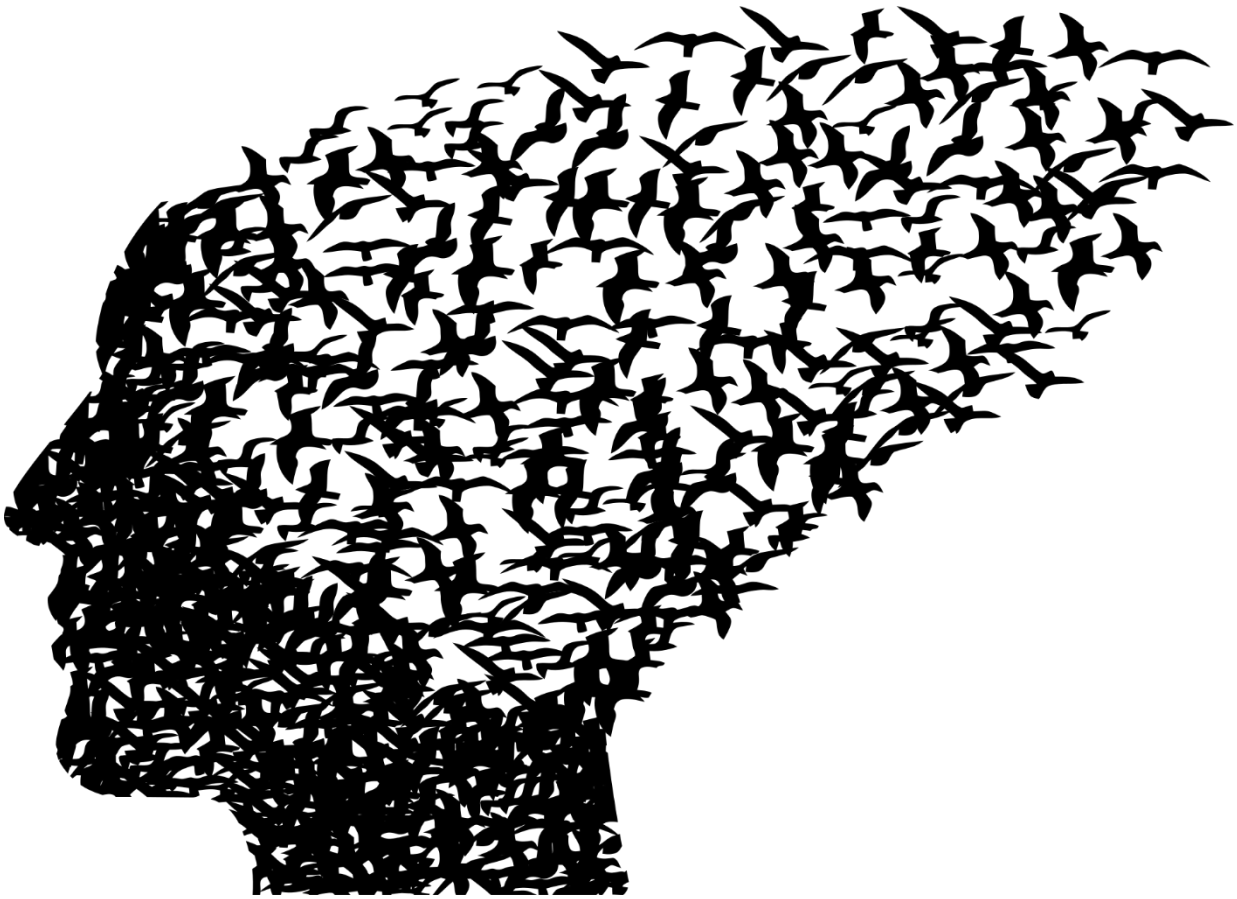
Supplementary Figure 1

Flow diagram of the study population with actigraphy data available. Valid data for tinnitus and actigraphy was collected for 1,456 participants between 2011 and 2014.

4

SLEEP AND THE STRESS SYSTEM

Image by CDD20 from Pixabay



“Slaaptekort is de meest voorkomende hersenafwijking .”

(William Charles Dement, 1928-2020)

Origineel: “*Sleep deprivation is the most common brain impairment*.”

Image by Gordon Johnson from Pixabay

4.1

The longitudinal association of sleep and 24-hour activity rhythms with cortisol response to a very low-dose of dexamethasone

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Submitted

Abstract

Objectives: Poor sleep is common in the general population, with hyperarousal and stress often suggested as causal factors. Conversely, sleep might also affect the stress response, in which the hypothalamic-pituitary-adrenal (HPA) axis plays a key role. We assessed the longitudinal association of sleep and 24-hour activity rhythms with functioning of the negative feedback loop of the HPA axis, as indicated by the cortisol response to a very low-dose of dexamethasone.

Design: Longitudinal cohort

Setting: Population-based

Participants: This study included 410 participants (mean age: 56.1±5.5 years, 59% women) from the Rotterdam Study. For 217 participants, the cortisol response to dexamethasone was assessed again after a median follow-up of 5.7 years (IQR=5.5–5.8).

Measurements: Between 2004 and 2007, sleep and 24-hour activity rhythms were estimated with actigraphy (mean duration: 146±19.6 hours) and sleep quality with the Pittsburgh Sleep Quality Index. To assess the negative feedback loop of the HPA axis we measured cortisol before and after the intake of a very low-dose of dexamethasone (0.25mg).

Results: Unstable (B=1.64, 95%CI=0.78;2.50) and fragmented (B=-1.31, 95%CI=-2.17;-0.45) 24-hour activity rhythms, and a poor self-rated sleep quality (B=-0.02, 95%CI=-0.04;0.00) were associated with an enhanced cortisol response to dexamethasone over time, also in those without clinically relevant depressive symptoms and those not using psychoactive medication.

Conclusions: This study demonstrates a longitudinal association of disturbed 24-hour activity rhythms and poor self-rated sleep quality with an enhanced cortisol response to dexamethasone, i.e. stronger suppression of cortisol.

Keywords: actigraphy; sleep; cortisol; HPA-axis; population-based; dexamethasone suppression test.

Statement of significance: This study shows that disturbed 24-hour activity rhythms and a poor self-rated sleep quality are associated with functioning of the negative feedback loop over a period of years.

Introduction

Poor sleep, such as a short sleep duration and self-rated poor sleep quality, has been hypothesized to be associated with a deregulated stress response.[1,2] Key to regulating the response to stress is the hypothalamic-pituitary-adrenal (HPA) axis.[3] One of the its' functions is to stimulate the secretion of cortisol in response to a stressor, which is required for a quick response of the body, but also triggers a negative feedback loop to inhibit further secretion of cortisol.[3] Both a diminished function of this negative feedback loop as well as an enhanced function have been associated with poor health.[4,5] For example, a weak suppression of cortisol by the negative feedback loop of the HPA axis has been associated with major depressive disorder and panic disorder,[4] while a strong suppression has been associated with schizophrenia and post-traumatic stress disorder.[4,6]

Previous studies have reported that both self-rated and objectively estimated poor sleep, and also closely related 24-hour activity rhythm disturbances, are associated with a dysregulated stress response,[7] including altered functioning of the HPA axis and its negative feedback loop.[8,9] Yet, results for the association of sleep with functioning of the HPA axis have been non-cohesive.[7,10] For example, sleep deprivation and insomnia have been associated with HPA axis hyperactivity,[11] but excessive daytime sleepiness, which can be a symptom of nighttime sleep problems, with a diminished activity of the negative feedback loop.[7] This suggests that different aspects of sleep might relate differently to the HPA axis, although these differences might also in part be explained by differences in methodology.[7]

So far, the association between sleep and the HPA axis has been mainly studies in small sample sizes.[7,12] This can partly be explained because the most frequently used experimental test to assess the HPA axis, the Trier Social Stress Test,[13] is less suitable for larger populations due to the required resources. A pharmacological alternative for assessing the function of the negative feedback loop of the HPA axis in larger populations uses dexamethasone as a pharmacological stressor.[14] High doses of dexamethasone often completely suppress cortisol secretion in healthy persons, but a very low dose (0.25 mg) allows assessing the continuum of cortisol suppression within the HPA axis.[21] Comparing cortisol levels before and after intake of a very low-dose of dexamethasone therefore allows estimating the functioning of the negative feedback loop of the HPA axis.[14]

In the current study, embedded in the population-based Rotterdam Study, our objective was to gain insight into the association of sleep and 24-hour activity rhythms with the functioning of the negative feedback loop of the HPA axis over time in a population-based sample of middle-aged and older adults. Both sleep and the negative feedback loop were assessed by objective measurements, employing actigraphy and a very low-dose dexamethasone suppression test. Based on previous research we hypothesized that markers of poor sleep and 14-hour activity rhythms were associated with an enhanced cortisol response of the negative feedback loop, i.e. a stronger suppression of cortisol, over time.

Methods

Participants and design

We analyzed data from participants from the Rotterdam Study,[15] a population-based cohort of middle-aged and older persons. The cohort was set up in 1990 and now includes 17,931 participants. In 1990, 2000, 2006 and 2008 all persons meeting the age criteria and living in the district of Ommoord, Rotterdam, the Netherlands were invited to participate, no exclusion criteria were used. Every 3–6 years participants are seen for a follow-up visit, which consists of a home interview and several visits to a dedicated research center. The main aim of the Rotterdam Study is to examine neurological, cardiovascular and other chronic age-related diseases. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

In 2006, a new cohort of inhabitants of the district of Ommoord, Rotterdam, the Netherlands, aged 45 and over was added to the study (RS-III-1, n=3,932). There were no exclusion criteria. Of this sample, 3,247 participants who previously agreed to collect saliva, were invited to participate in a very low-dose dexamethasone suppression test and 2,076 agreed (63.9%), data of 1,377 participants could be used for analyses (Figure 2). Between 2009 and 2012, after

median follow-up of 5.7 years (IQR=5.5–5.8), cortisol data was assessed a second time for 884 participants (64.2%) and valid for 606 participants.

Of the 1,377 participants with cortisol data at baseline, a random selected sample of 475 persons was invited for actigraphy, of those 451 agreed. After exclusion of participants with incomplete (<4 complete 24-hour periods, <4 complete nights, or shift work, n=37) or invalid (abnormalities after visual inspection, n=4) baseline actigraphy, data was available for 410 participants. Of those, repeated cortisol data was available for 217 participants (Figure 2).

The assessment of self-rated sleep quality is part of the standard research procedure in the Rotterdam Study and therefore also available for a larger sample (n=1,331 at baseline, n= 719 with repeated measures, see Figure 3).

Actigraphy-estimated sleep and 24-hour activity rhythms

Participants were asked to wear an actigraph on their non-dominant wrist for 7 consecutive days and only remove it when bathing. Participants were also asked to press a marker button on the actigraph when they initiated sleep (time to bed) and when they got out of bed (get-up time). Lastly, participants were asked to keep a sleep diary during the whole period. We used the ActiWatch, model AW4 (Cambridge Technology Ltd, Cambridge, United Kingdom). Recordings were sampled at 32 Hz (ActiWatch) and scored for each 30-s epoch, taking into account weighted scores of previous and following epochs. To distinguish sleep from wake a threshold of 20 was used for each 30-s epoch.[16]

Sleep estimates were calculated using the method previously described by Lindert and colleagues,[17], where actigraphy data was supplemented with information from the sleep diary or if missing, the marker button. We defined total sleep time as the total duration of epochs scored as sleep in hours. Sleep efficiency was defined as the proportion of time in bed spent sleeping (100% x (total sleep time/ time in bed)), where time in bed was defined as the time between time to bed and get-up time in hours. Sleep onset latency was defined as the time in minutes between time to bed and sleep start. Lastly, wake after sleep onset was defined as the total time of the epochs scored as wake between sleep start and sleep end in minutes.

To estimate 24-hour activity rhythms we used the Interdaily Stability (IS), which indicates the stability of the rhythm over days, and Intradaily Variability (IV), which indicates the fragmentation of the rhythm relative to its 24-hour amplitude.[18] IS and IV were calculated by using the nparACT R package on the actigraphy data.[19] A favorable 24-hour activity rhythm is indicated by high stability and low fragmentation. Additionally, as an indicator for chronotype, we assessed L5 onset time, indicating the average clock time the 5 consecutive hours with least activity of the day started.[18,19]

Measurement of self-rated sleep quality

Self-rated sleep quality was determined with the Pittsburgh Sleep Quality Index (PSQI), a 19-item self-report scale on sleep quality.[20] A total score was calculated as the sum of all items and ranges from 0 to 21, with a high score indicating poor sleep quality. For participants with 6 out of 7 valid PSQI component scores, a weighted global score was calculated by multiplying with 7/6. If less than 6 component scores were available, PSQI was set to missing.

Measurement of the negative feedback loop of the HPA-axis

The negative feedback loop of the HPA axis was assessed using a very low-dose dexamethasone suppression test, details have been described by Direk et al.[14] Briefly, participants were asked to collect a saliva sample at 8 AM and to take a very low-dose of dexamethasone (orally, 0.25 mg) at 11 PM on day 1. On day 2, participants were instructed to collect saliva again at 8 AM. Participants were asked to report the exact time of dexamethasone intake and saliva sampling. Oral and written instructions were provided on how to collect saliva samples using Salivette sampling devices (Sarstedt, Nümbrecht, Germany), with emphasis on the importance of specific timing of sampling. Until samples were analyzed at the laboratory of Biopsychology, Technical University of Dresden, Germany, the salivettes were stored at -80 °C. Cortisol concentrations in saliva were measured in nmol/l using an immunoassay with chemiluminescence detection (CLIA; IBL Hamburg, Hamburg, Germany). At follow-up, cortisol concentrations were assessed using both immunoassays and liquid chromatography-mass spectrometry (LCMS) assays, which is the current golden-standard.[21] The correlation between measures of LCMS and immunoassays was 0.98 for cortisol before dexamethasone and 0.99 for cortisol after dexamethasone. For consistency

with the baseline measurements, we only report on the immunoassay determined cortisol levels.

Other variables

During the home interview at baseline we obtained information on employment, education, smoking behavior, intake of alcohol, possible sleep apnea, depressive symptoms, and use of psychoactive medication (Anatomical Therapeutic Chemical Classification code: N05 Psycholeptics or N06 Psychoanaleptics). Employment was classified as a binary variable, based on whether the participant had paid work. Education was classified according to UNESCO standard classification as primary education (primary), lower/intermediate general education or lower vocational education (low), intermediate vocational education or higher general education (middle), or higher vocational education or university (high). Smoking behavior was classified as never, former, or current smoker. Intake of alcohol was asked as intake of different types of alcoholic beverages in units and recalculated to average grams of alcohol per day. Possible sleep apnea was assessed as a binary variable using two questions from the PSQI. We considered possible sleep apnea in case participants reported (1) respiratory pauses during sleep at least 1-2 nights per week or (2) loud snoring at least 2 nights per week, combined with at least occasional respiratory pauses.[22] Time difference was calculated as time between average wake-up time which was assessed using the question "*At what time do you usually wake up?*" from the PSQI, and the sampling time of cortisol. The Center for Epidemiologic Studies Depression scale (CES-D) was used to assess depressive symptoms.[23] At the research center, we further measured height and weight, which were assessed on calibrated scales without heavy clothing and shoes to calculate body mass index (BMI) (kg/m^2). Lastly, based on data from medical record files we assessed prevalent diabetes mellitus.

Statistical analyses

Descriptive statistics were presented as number with percentage for categorical variables and mean with standard deviation (SD) for numerical data. As cortisol levels before and after dexamethasone were not normally distributed, they were log-transformed. For sleep and 24-hour activity rhythms, variables were checked for outliers and those were set to 4 SD from the mean in the same direction. Missing values for all covariates were less than 5% and

handled by using multiple imputation. We used the MICE R package,[24] with 5 imputed datasets for which the pooled statistics are presented.[25] To correct for multiple testing, we used the false discovery rate (FDR) to calculate the adjusted p-values, based on 7 determinants; n=7 for cross-sectional linear regression models and n=14 for linear mixed models.[26] Analyses were performed in R version R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org).

Cross-sectional linear regression models were used to estimate the association of sleep and 24-hour activity rhythms with response to dexamethasone at baseline, where cortisol after dexamethasone is used as an outcome and corrected for cortisol before dexamethasone. All associations were studied in a sex-age adjusted model (model 1), a model additionally adjusted for employment, education, smoking behavior, intake of alcohol, BMI, time difference between wake-up time and cortisol sampling, depressive symptoms score, and use of psychoactive medication (model 2), and a model additionally adjusted for possible sleep apnea, and prevalent diabetes mellitus (model 3).

Linear mixed models were used to assess the association of sleep and 24-hour activity rhythms at baseline with response to dexamethasone over time. These longitudinal analyses were performed including the measures at both time points for (1) response to dexamethasone, using cortisol after dexamethasone as an outcome, corrected for cortisol before dexamethasone, or (2) cortisol before dexamethasone as an outcome. To account for the within person correlation between measurements, a random intercept and slope were included in all linear mixed models. All associations were studied all models additionally adjusted for follow-up time and with an interaction term of determinant*time. The effect estimate of the baseline determinant describes how the determinant at baseline is associated with the outcome on average over time. The interaction term indicates how the determinant at baseline is associated with changes in outcome over time. For total sleep time, analyses were repeated using quadratic terms to assess non-linear associations. Because previous literature implicates important differences in functioning of the HPA axis between men and women,[27] we additionally stratified for sex.

Longitudinal analyses on the associations of sleep and 24-hour activity rhythms with the response to dexamethasone, were repeated after exclusion of non-suppressors (participants

for whom cortisol levels did not drop), after exclusion of participants indicating clinically relevant depressive symptoms at baseline (CES-D ≥ 16), and after exclusion of participants indicating use of psychoactive medication at baseline.

Results for self-rated sleep quality were additionally analyzed in the total sample with PSQI data available, to overcome limited power of the smaller sample.

Results

At baseline, 410 participants were included with a mean age of 56.1 ± 5.5 years and 59% women (Table 1). Of those, repeated measurements on the very low-dose dexamethasone suppression test were obtained for 217 participants with a median follow-up time of 5.7 years (IQR=5.5 – 5.8).

Sleep and the cortisol response to dexamethasone at baseline

After multivariate correction, a long sleep onset latency ($B_{sleep\ onset\ latency}$=-0.01, 95%CI=-0.01;0.00), an unstable 24-hour activity rhythm ($B_{interdaily\ stability}$=1.72, 95%CI=0.80;2.64), and a fragmented 24-hour activity rhythm ($B_{intradaily\ variability}$=-1.48, 95%CI=-2.42;-0.54) were associated with an enhanced response to dexamethasone at baseline (Table 2), as the negative effect estimate indicates a lower cortisol level after dexamethasone, and therefore a stronger suppression of cortisol by the HPA axis. The association between self-rated sleep quality and the response to dexamethasone was not significant in the actigraphy study sample, but further analysis in a larger sample including all participants with self-rated sleep quality data (n=1,331) showed that poor self-rated sleep quality was significantly associated with an enhanced response to dexamethasone (where a high score reflects poor sleep quality, $B_{sleep\ quality}$=-0.03, 95%CI=-0.47;-0.01).

Sleep and the cortisol response to dexamethasone over time

Sleep at baseline was not associated with changes in response to dexamethasone over time after multivariate correction (Figure 1, Table 3), the association of sleep onset latency with response to dexamethasone over time ($B_{sleep\ onset\ latency}$=-0.01, 95%CI=-0.01;0.00) and the association of sleep onset latency with change in response to dexamethasone over time ($B_{sleep\ onset\ latency*time}$=-0.02, 95%CI=-0.0340;-0.003) did not hold after multiple testing correction.

Unstable ($B_{interdaily\ stability}$=1.64, 95%CI=0.78;2.50) and fragmented ($B_{intradaily\ variability}$=-1.31, 95%CI=-2.17;-0.45) 24-hour activity rhythms at baseline were associated with an enhanced response to dexamethasone over 5.5 years of follow-up (Table 3). Additionally, an unstable 24-hour activity rhythm was associated ($B_{interdaily\ stability}$=-0.31, 95%CI=-0.54;-0.07) with smaller change in response to dexamethasone over time. In the actigraphy study sample, self-rated sleep quality was not significantly associated with the response to dexamethasone over time ($B_{sleep\ quality}$=-0.02, 95%CI=-0.05;0.02). However, in the larger sample including all participants with self-rated sleep quality data the association was significant (n=719, $B_{sleep\ quality}$=-0.02, 95%CI=-0.03;0.00). Results did not change substantially when estimates were additionally adjusted for possible sleep apnea and diabetes mellitus (model 3, data not shown).

We performed three sensitivity analyses (Supplementary Table 1) to assess the robustness of the longitudinal results. First, after exclusion of non-suppressors, effect estimates increased for total sleep time, L5 onset time, and self-rated sleep quality, whereas effect estimates decreased for wake after sleep onset, interdaily stability, and intradaily variability. Second, after exclusion of participants with clinically relevant depressive symptoms (CES-D ≥16) effect estimates were also increased for most associations. Third, after exclusion of participants who self-reported the use psycholeptics or psychoanaleptics, results remained similar.

Lastly, we stratified for sex to observe differences between men and women (Supplementary Table 2). The association of unstable 24-hour activity rhythms with a smaller change in response to dexamethasone over time ($B_{interdaily\ stability*time}$=-0.49, 95%CI=-0.81;-0.18) was only significant in women. Furthermore, we observed higher effect estimates for total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset in women, whereas in men effect estimates for interdaily stability and intradaily variability were higher.

Associations of sleep and 24-hour activity rhythms with cortisol before intake of dexamethasone over time can be found in Supplemental Table 3.

Discussion

Our results suggest a longitudinal association of disturbed 24-hour activity rhythms and poor self-rated sleep with an enhanced cortisol response to dexamethasone, i.e. a stronger suppression of cortisol within the negative feedback loop of the HPA axis, over time. Results remained similar after exclusion of those who did not respond to dexamethasone, those with

clinically relevant depressive symptoms or those who reported to use psychoactive medication.

24-Hour activity rhythms and cortisol response to dexamethasone

Within our population-based sample of middle-aged and elderly, unstable and fragmented 24-hour activity rhythms at baseline were associated with an enhanced cortisol response to dexamethasone over time, indicating a stronger suppression of cortisol by the negative feedback of the HPA axis, in line with previous cross-sectional literature.[9] Counterintuitively, this could implicate that participants with disrupted 24-hour activity rhythms have a quicker stress response and might be able to cope with stressors more efficiently. However, a quicker stress response is not necessarily a sign of a good functioning stress system. Potentially, it is more likely that an unstable 24-hour activity rhythm is associated with malfunctioning of the HPA axis, resulting in a too strong suppression of cortisol.[1] Indeed both ends of the continuum of cortisol suppression have been associated with poor health.[4,5]

Disrupted 24-hour activity rhythms can also be accompanied by a so-called 'social jetlag,[28] a structural mismatch between internal circadian rhythms and social clocks, such as work schedule or social obligations.[28] Previous literature reported an association of chronic social jetlag with disrupted expression of clock genes in the superchiasmatic nucleus (SCN),[28] the biological clock of the brain.[29] Disrupted functioning of the SCN has in turn been associated with hampered functioning of the HPA axis, including altered negative feedback.[30,31]

Self-rated sleep quality and cortisol response to dexamethasone

Our results additionally demonstrated that poor self-rated sleep at baseline was associated with enhanced negative feedback by the HPA axis, but only when studied in a larger sample. Potentially, this association was not found in the sample that only included those who also participated in the optional actigraphy sub study because of selection bias, participants that agreed are of better health. Effect estimates in both samples were however similar and small of size, suggesting that the difference in statistical significance in the smaller sample could also be due to limited power. Moreover, the small effect estimates suggests that the clinical relevance of this association needs to be investigated further.

The association between self-rated sleep quality and functioning of the negative feedback loop of the HPA axis is in line with previous cross-sectional studies.[7,9] One explanation could be that poor self-rated sleep quality is a marker for a broad range of mental health issues,[32,33] which have also been linked to altered functioning of the HPA axis.[4,12] Yet, our results are not explained by depressive symptomatology or the intake of psychoactive medication. Rather the effect sizes get larger when excluding persons with depressive symptoms or who use of these types of medication, which is in line with previous research that suggests that the association of depressive symptoms with the negative feedback loop is most often in the opposite direction.[30] Additionally, altered functioning of the HPA axis has also been reported as a common cause[1] and a mediator[30,34] in the association of sleep with mental health, which could also explain our findings.

Sex differences

When assessing changes in effect estimates, sex seemed to modify the association of sleep with cortisol response to dexamethasone in our sample, although most associations did not reach statistical significance. Unstable and fragmented 24-hour activity rhythms seemed to have stronger effect sizes in men, whereas sleep variables showed stronger effect estimates in women. This fits the evidence for structural and functional differences between men and women in HPA axis function, the HPA axis is also mediated by gonadal steroids.[4,27] Overall, women typically exhibit a stronger cortisol response to dexamethasone than men.[14,27] Gonadal steroids do not only affect the HPA axis, but also mediate the homeostatic responses to poor sleep,[35,36] which could explain the sex differences we find.

Altogether, the direction of the effect and underlying causal mechanisms remain largely unclear for the association between 24-hour activity rhythms, self-rated sleep and the HPA axis, likely a complex network of bidirectional associations and biological mechanisms is at play. Further experimental research and longitudinal studies including repeated measures are required, also to determine the clinical relevance of the associations in light of the size of the effect estimates. This will also help to determine whether intervening on sleep and 24-hour activity rhythms can improve HPA axis function or the other way around. In particular, cognitive behavioral therapy might be of interest as they target both behavioral and cognitive aspect of sleep and stress, and have the potential to be applied at a larger scale.[37]

Limitations

Several limitations need to be taken into account. First, our measurements were 5 to 9 years apart with no measurements in between. We could therefore not take into account fluctuations in functioning of the HPA axis that occurred between these two time points. Second, we observed results for self-rated sleep quality were not significant in the actigraphy subsample. This could implicate selection bias or too little power in this sample. Third, we were not able to draw conclusions on temporality or causality due to the data availability. Fourth, the associations might have been affected by confounders that we were not able to include in our models, such as renal or kidney failure. Nevertheless, having objective sleep estimates and repeated very low-dose dexamethasone suppression tests over time in a population-based sample is unique and allowed us to assess associations over a longer period of time.

Conclusions

In our study population of middle-aged and elderly we demonstrated an association of unstable and fragmented 24-hour activity rhythms, and poor self-rated sleep quality with an enhanced cortisol response to dexamethasone over time, independent of depressive symptoms and use of medication. This suggests that robust 24-hour rhythms and good self-rated sleep quality may be needed for an optimally functioning stress response.

References

1. 1. Bao, Y.P., et al., *Cooccurrence and bidirectional prediction of sleep disturbances and depression in older adults: meta-analysis and systematic review.* Neuroscience & Biobehavioral Reviews, 2017. **75**: p. 257-273.
2. Kalmbach, D.A., et al., *Hyperarousal and sleep reactivity in insomnia: current insights.* Nature and science of sleep, 2018. **10**: p. 193.
3. Dedovic, K., et al., *The brain and the stress axis: the neural correlates of cortisol regulation in response to stress.* Neuroimage, 2009. **47**(3): p. 864-871.
4. Zorn, J.V., et al., *Cortisol stress reactivity across psychiatric disorders: a systematic review and meta-analysis.* Psychoneuroendocrinology, 2017. **77**: p. 25-36.
5. Kumari, M., et al., *Identifying patterns in cortisol secretion in an older population. Findings from the Whitehall II study.* Psychoneuroendocrinology, 2010. **35**(7): p. 1091-1099.
6. Arana, G.W., R.J. Baldessarini, and M. Ornsteen, *The dexamethasone suppression test for diagnosis and prognosis in psychiatry: commentary and review.* Archives of general psychiatry, 1985. **42**(12): p. 1193-1204.
7. van Dalfsen, J.H. and C.R. Markus, *The influence of sleep on human hypothalamic–pituitary–adrenal (HPA) axis reactivity: A systematic review.* Sleep medicine reviews, 2018. **39**: p. 187-194.
8. Riemann, D., et al., *The hyperarousal model of insomnia: a review of the concept and its evidence.* Sleep medicine reviews, 2010. **14**(1): p. 19-31.
9. Luik, A.I., et al., *Sleep and 24-h activity rhythms in relation to cortisol change after a very low-dose of dexamethasone.* Psychoneuroendocrinology, 2015. **53**: p. 207-216.
10. Chrousos, G., A.N. Vgontzas, and I. Kritikou, *HPA axis and sleep*, in *Endotext [Internet]*. 2016, MDText. com, Inc.
11. Buckley, T.M. and A.F. Schatzberg, *On the Interactions of the Hypothalamic-Pituitary-Adrenal (HPA) Axis and Sleep: Normal HPA Axis Activity and Circadian Rhythm, Exemplary Sleep Disorders.* The Journal of Clinical Endocrinology & Metabolism, 2005. **90**(5): p. 3106-3114.
12. Xia, L., et al., *Alterations in hypothalamus-pituitary-adrenal/thyroid axes and gonadotropin-releasing hormone in the patients with primary insomnia: a clinical research.* PloS one, 2013. **8**(8).
13. Allen, A.P., et al., *The trier social stress test: principles and practice.* Neurobiology of stress, 2017. **6**: p. 113-126.
14. Direk, N., et al., *The very low-dose dexamethasone suppression test in the general population: a cross-sectional study.* PloS one, 2016. **11**(10).
15. Ikram, M.A., et al., *Objectives, design and main findings until 2020 from the Rotterdam Study.* European Journal of Epidemiology, 2020. **35**(5): p. 483-517.
16. Kosmadopoulos, A., et al., *Alternatives to polysomnography (PSG): a validation of wrist actigraphy and a partial-PSG system.* Behavior research methods, 2014. **46**(4): p. 1032-1041.
17. te Lindert, B.H.W. and E.J.W. Van Someren, *Sleep estimates using microelectromechanical systems (MEMS).* Sleep, 2013. **36**(5): p. 781-789.
18. Van Someren, E.J.W., *Actigraphic monitoring of movement and rest-activity rhythms in aging, Alzheimer's disease, and Parkinson's disease.* IEEE Transactions on Rehabilitation Engineering, 1997. **5**(4): p. 394-398.

19. Blume, C., N. Santhi, and M. Schabus, *'nparACT'package for R: A free software tool for the non-parametric analysis of actigraphy data.* MethodsX, 2016. **3**: p. 430-435.
20. Buysse, D.J., et al., *Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI).* Sleep, 1991. **14**(4): p. 331-338.
21. El-Farhan, N., D.A. Rees, and C. Evans, *Measuring cortisol in serum, urine and saliva–are our assays good enough?* Annals of clinical biochemistry, 2017. **54**(3): p. 308-322.
22. Fogelholm, M., et al., *Sleep-related disturbances and physical inactivity are independently associated with obesity in adults.* Int J Obes (Lond), 2007. **31**(11): p. 1713-21.
23. Beekman, A.T.F., et al., *Een screeningsinstrument voor depressie bij ouderen in de algemene bevolking: de bruikbaarheid van de Center for Epidemiologic Studies Depression Scale (CES-D).* Tijdschrift voor Gerontologie en Geriatrie, 1994. **25**: p. 95-103.
24. Buuren, S.v. and K. Groothuis-Oudshoorn, *mice: Multivariate imputation by chained equations in R.* Journal of statistical software, 2010: p. 1-68.
25. Rubin, D.B., *Multiple imputation for nonresponse in surveys*. Vol. 81. 2004: John Wiley & Sons.
26. Benjamini, Y. and Y. Hochberg, *Controlling the false discovery rate: a practical and powerful approach to multiple testing.* Journal of the Royal statistical society: series B (Methodological), 1995. **57**(1): p. 289-300.
27. Goel, N., et al., *Sex differences in the HPA axis.* Comprehensive Physiology, 2011. **4**(3): p. 1121-1155.
28. Finger, A.M. and A. Kramer, *Mammalian circadian systems: organization and modern life challenges.* Acta Physiologica, 2020: p. e13548.
29. Swaab, D.F., E. Fliers, and T.S. Partiman, *The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia.* Brain research, 1985. **342**(1): p. 37-44.
30. Asarnow, L.D., *Depression and sleep: what has the treatment research revealed and could the HPA axis be a potential mechanism?* Current Opinion in Psychology, 2020. **34**: p. 112-116.
31. Clow, A., et al., *The cortisol awakening response: more than a measure of HPA axis function.* Neuroscience & Biobehavioral Reviews, 2010. **35**(1): p. 97-103.
32. Maglione, J.E., et al., *Subjective and objective sleep disturbance and longitudinal risk of depression in a cohort of older women.* Sleep, 2014. **37**(7): p. 1179-1187.
33. Mitrushina, M. and R. Tomaszewski, *The effect of subjective perception of cognition on emotional functioning in adults with long-term neurological and neuropsychiatric disorders.* Disability and rehabilitation, 2019: p. 1-7.
34. Murri, M.B., et al., *HPA axis and aging in depression: systematic review and meta-analysis.* Psychoneuroendocrinology, 2014. **41**: p. 46-62.
35. Hajali, V., et al., *Sex differences in sleep and sleep loss-induced cognitive deficits: The influence of gonadal hormones.* Hormones and behavior, 2019. **108**: p. 50-61.
36. Lowe, C.J., A. Safati, and P.A. Hall, *The neurocognitive consequences of sleep restriction: a meta-analytic review.* Neuroscience & Biobehavioral Reviews, 2017. **80**: p. 586-604.
37. Luik, A.I., S.D. Kyle, and C.A. Espie, *Digital Cognitive Behavioral Therapy (dCBT) for Insomnia: a State-of-the-Science Review.* Curr Sleep Med Rep, 2017. **3**(2): p. 48-56.

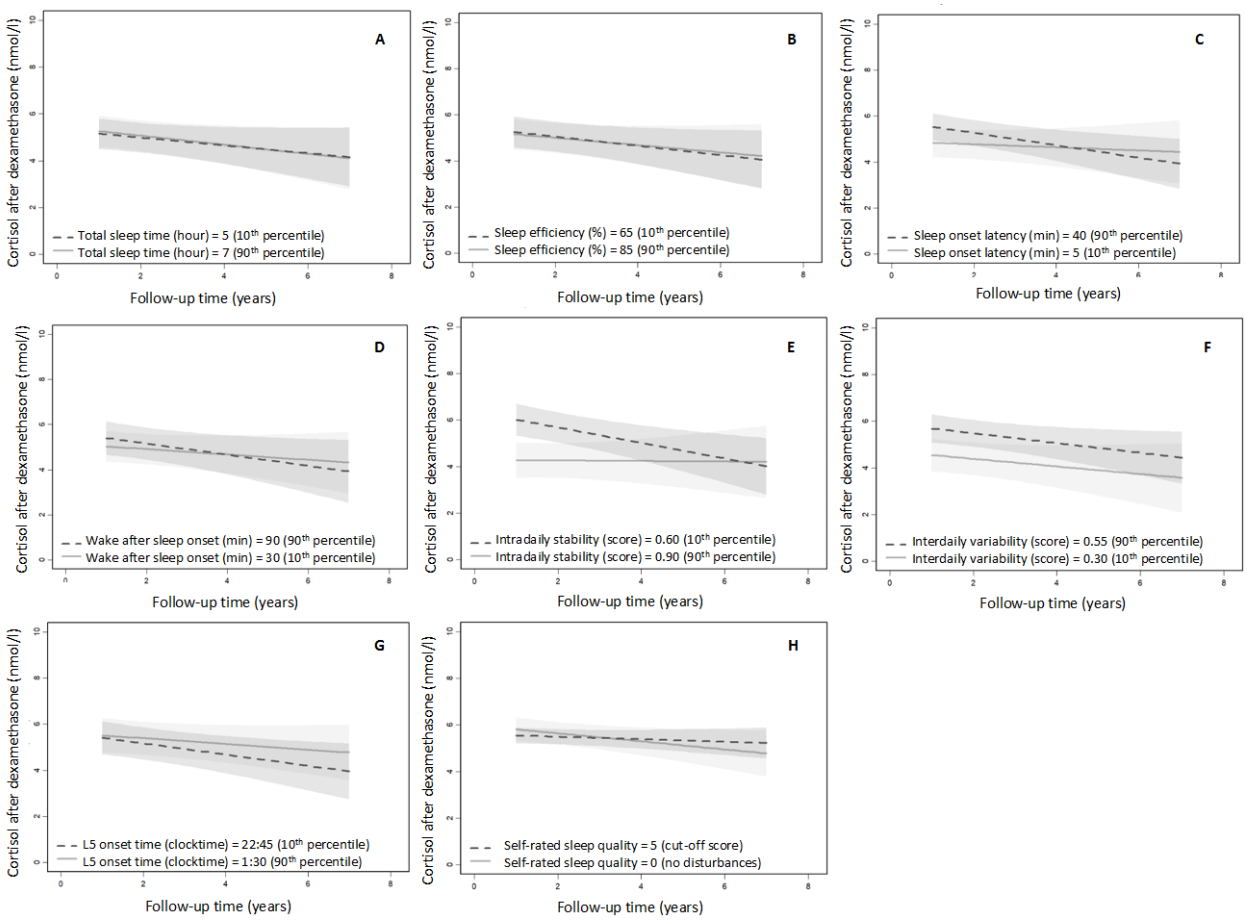

Figure 1

Sleep and 24-hour activity rhythms predicting cortisol response to a very low dose of dexamethasone over time. Each plot depicts how cortisol response after a very low-dose of dexamethasone would develop over time for a person with an average value for sex, age, education, employment, BMI, smoking, alcohol, time difference, and depressive symptoms. Lines are presented with corresponding 95% confidence interval separately for the 10th or 90th of total sleep time (A), sleep efficiency (B), sleep onset latency (C), wake after sleep onset (D), interdaily stability (E), intradaily variability (F), and L5 onset time (G). Good sleep is indicated by a solid, light grey line, poor sleep is indicated by a dashed, dark grey line. For self-rated sleep quality (H) a line is plotted indicating no self-rated sleep disturbances (solid line, light grey) and a line indicating poor self-rated sleep quality (cut-off score, dashed line, dark grey).

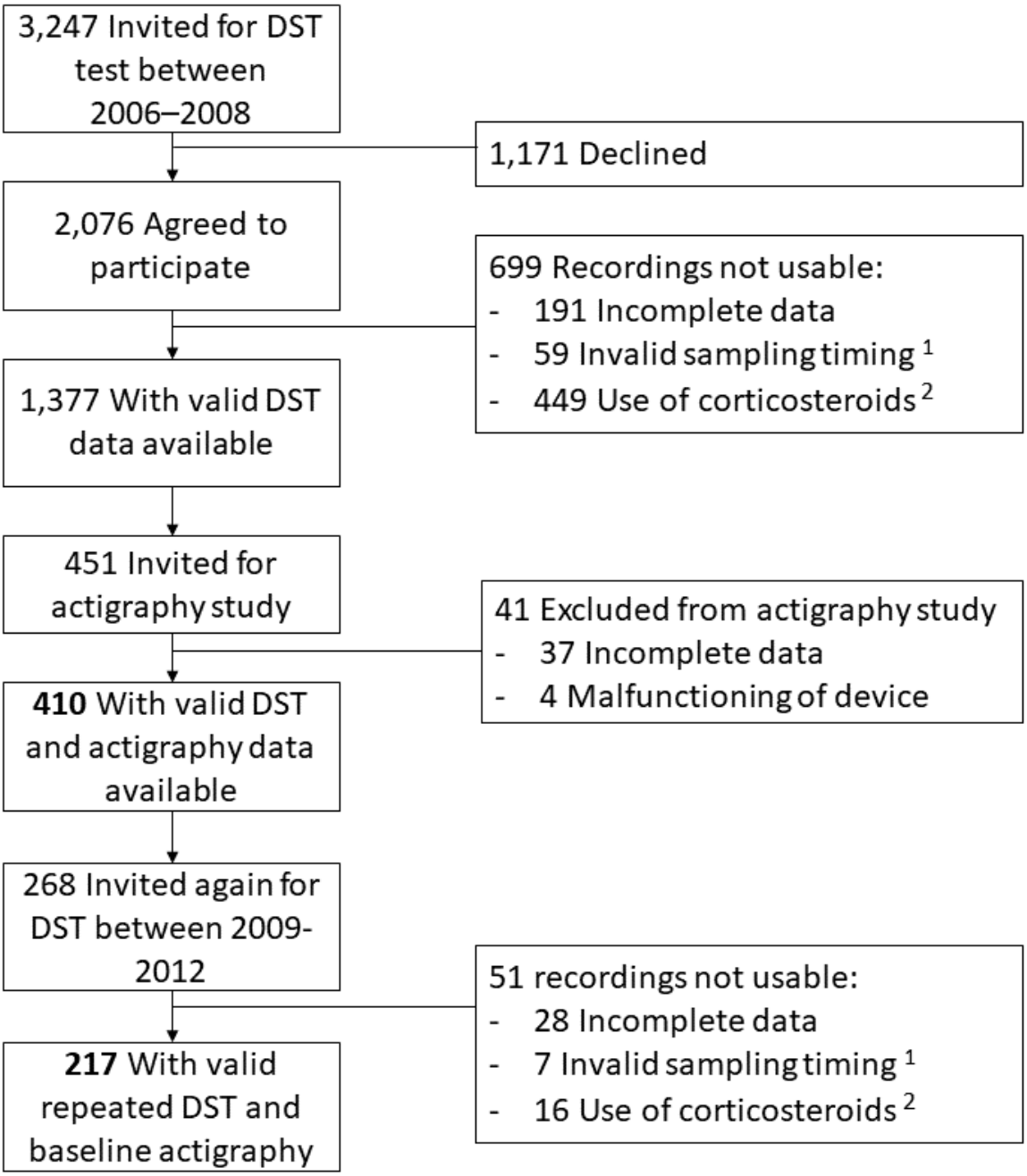

Figure 2

Flow diagram of the study population with actigraphy data available. Valid baseline data for DST and actigraphy was collected for 410 participants between 2006 and 2008. Of those, valid repeated assessment of the DST was performed for 217 participants between 2009 and 2012.

Abbreviations: DST: dexamethasone suppression test.

[1.] Incomplete sampling timing indicates a time difference between cortisol samples deviating more than 3 hours from the specified 24 hours

[2.] Use of corticosteroids indicates prescribed corticosteroids (Anatomical Therapeutic Chemical Classification code H02: oral, inhalation or dermal use) in the year before the dexamethasone suppression test or who self-reported use of corticosteroids at the time of data collection

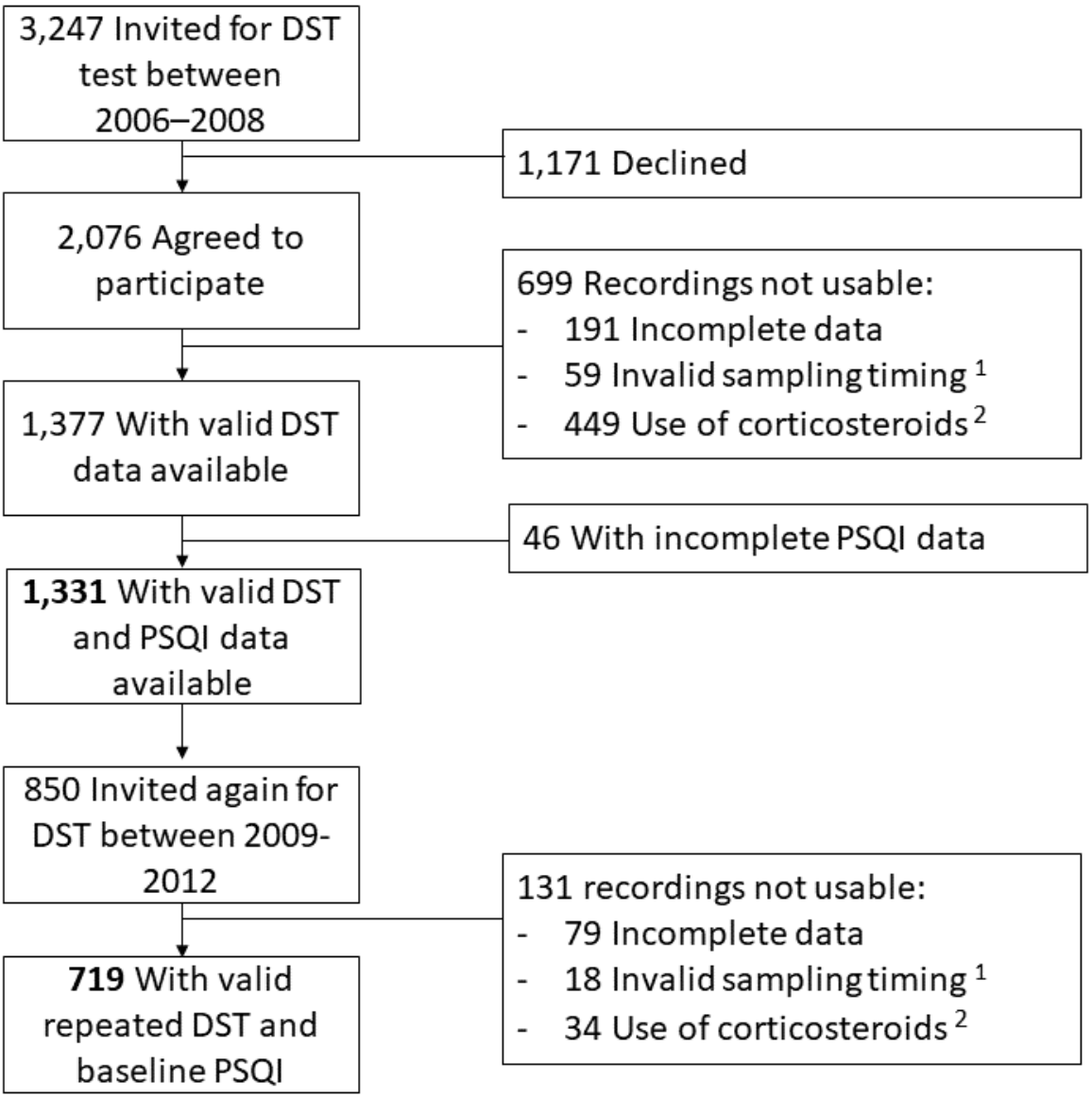

Figure 3

Flow diagram of the study population with PSQI data available. Valid baseline data for DST and PSQI was collected for 1,331 participants between 2006 and 2008. Of those, valid repeated assessment of the DST was performed for 719 participants between 2009 and 2012.

Abbreviations: DST: dexamethasone suppression test; PSQI: Pitssburgh Sleep Quality Index.
[1.] Incomplete sampling timing indicates a time difference between cortisol samples deviating more than 3 hours from the specified 24 hours
[2.] Use of corticosteroids indicates prescribed corticosteroids (Anatomical Therapeutic Chemical Classification code H02: oral, inhalation or dermal use) in the year before the dexamethasone suppression test or who self-reported use of corticosteroids at the time of data collection

Table 1

Baseline characteristics of the study population at baseline.

	N (%)	Mean ± SD Median (IQR)
Participants	410	
Demographics		
Age (years)		56.1 ± 5.5
Women	240 (58.5 %)	
Employed	232 (56.6 %)	
Education		
Primary	35 (8.6 %)	
Low	169 (41.3 %)	
Intermediate	112 (27.4 %)	
High	93 (22.7 %)	
Health Indicators		
Body mass index (kg/m^2)		27.6 ± 4.2
Alcohol (grams/day)		8.6 ± 9.3
Smoking		
Never smoker	133 (32.4 %)	
Former smoker	186 (45.4%)	
Current smoker	91 (22.2%)	
Diabetes mellitus	51 (12.4 %)	
Possible sleep apnea [a]	39 (9.7 %)	
Cognitive status (score) [b]		28.1 ± 1.7
Depressive symptoms [c, d]		3 (1 – 7)
Use of psycholeptics or psychoanaleptics	53 (12.9%)	
Cortisol		
Cortisol before dexamethasone, day 1 (nmol/L)		14.6 ± 6.3
Sampling time day 1 (clock time)		7:55 ± 0:42
Cortisol after dexamethasone, day 2 (nmol/L)		5.8 ± 6.3
Sampling time day 2 (clock time)		7:55 ± 0:34
Actigraphic sleep		
Total Sleep Time (hour:min)		6:02 ± 0:58
Sleep Efficiency (%)		74.6 ± 9.1
Sleep Onset Latency (min)		21 ± 19
Wake After Sleep Onset (min)		61 ± 24
24-hour activity rhythm		
Interdaily Stability (score)		0.76 ± 0.12
Intradaily Variability (score)		0.40 ± 0.12
L5 onset time (clock time)		1:13 ± 1:03
Self-rated sleep quality score [d]		3.0 (2 – 5)

For categorical variables the absolute number (%) is indicated, for numeric variables the mean ± SD.

[a] Assessed based on two questions from the Pittsburgh sleep quality index.

[b] Assessed using the Mini-Mental State Exam.

[c] Assessed using the Center for Epidemiologic Studies Depression scale.

[d] Median and Interquartile Range.

Table 2

The cross-sectional association of sleep and 24-hour activity rhythms with cortisol response to a very low-dose of dexamethasone baseline.

	Model 1		Model 2	
	B (95%CI)	**p-value**	**B (95%CI)**	**p-value**
Total Sleep Time (hours)	0.036 (-0.070;0.143)	0.50	0.074 (-0.043;0.192)	0.22
Sleep Efficiency (%)	0.008 (-0.003;0.019)	0.16	0.010 (-0.002;0.022)	0.10
Sleep Onset Latency (min)	-0.008 (-0.013;-0.003)	0.004*	-0.008 (-0.013;-0.002)	0.008*
Wake After Sleep Onset (min)	-0.003 (-0.007;0.001)	0.17	-0.002 (-0.007;0.002)	0.30
Interdaily Stability (score)	1.613 (0.757;2.468)	<0.001*	1.720 (0.804;2.635)	<0.001*
Intradaily Variability (score)	-1.306 (-2.146;-0.466)	0.002*	-1.483 (-2.422;-0.543)	0.002*
L5 onset time (hours)	-0.053 (-0.139;0.033)	0.23	-0.010 (-0.089;0.108)	0.85
Self-rated sleep quality (score)[a]	-0.011 (-0.041;0.019)	0.46	-0.024 (-0.059;0.011)	0.17

Abbreviations: CI, Confidence Interval. Effect estimates were obtained using cross-sectional linear regression models, adjusted for cortisol before dexamethasone, sex, and age (Model 1), and adjusted for cortisol before dexamethasone, sex, age, education, employment, BMI, smoking, alcohol, time difference, CESD, psycholeptics or psychoanaleptics (Model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR. [a] Results for self-reported sleep quality using the total population with self-rated sleep quality available (n=1,736): Model 1 (B=-0.0219, 95%CI=-0.036;-0.002, p-value=0.031), Model 2 (B=-0.028, 95%CI=-0.047;-0.009, p-value=0.004).

Table 3

The longitudinal association of sleep and 24-hour activity rhythms with cortisol response to a very low-dose of dexamethasone over time.

	Model 1		Model 2	
	B (95%CI)	**p-value**	**B (95%CI)**	**p-value**
Total Sleep Time	0.041 (-0.064;0.146)	0.45	0.073 (-0.035;0.181)	0.19
TST *time	-0.006 (-0.036;0.024)	0.68	-0.002 (-0.033;0.028)	0.87
Sleep Efficiency	0.008 (-0.003;0.019)	0.16	0.009 (-0.002;0.020)	0.11
SE *time	-0.001 (-0.004;0.002)	0.49	-0.001 (-0.004;0.002)	0.59
Sleep Onset Latency	-0.008 (-0.013;-0.002)	0.004*	-0.007 (-0.012;-0.002)	0.011
SOL*time	0.002 (0.000;0.003)	0.030	0.002 (0.000;0.003)	0.041
Wake After Sleep Onset	-0.003 (-0.007;0.001)	0.14	-0.003 (-0.007;0.002)	0.22
WASO *time	0.000 (-0.001;0.002)	0.51	0.000 (-0.001;0.002)	0.50
Interdaily Stability	1.667 (0.817;2.516)	<0.001*	1.643 (0.784;2.502)	<0.001*
IS *time	-0.333 (-0.563;-0.102)	0.005*	-0.305 (-0.541;-0.069)	0.011
Intradaily Variability	-1.358 (-2.192;-0.523)	0.001*	-1.311 (-2.168;-0.454)	0.003*
IV *time	0.093 (-0.152;0.337)	0.46	0.076 (-0.172;0.323)	0.55
L5 onset time	-0.061 (-0.147;0.025)	0.17	-0.003 (-0.092;0.087)	0.95
L5 onset time*time	-0.003 (-0.025;0.020)	0.82	-0.005 (-0.028;0.017)	0.65
Self-rated sleep quality[a]	-0.011 (-0.040;0.018)	0.46	-0.016 (-0.049;0.016)	0.32
Sleep quality*time	-0.005 (-0.013;0.003)	0.19	-0.005 (-0.013;0.003)	0.23

Abbreviations: TST, Total Sleep Time; TIB, Time In Bed; SE, Sleep Efficiency; WASO, Wake After Sleep Onset; SOL, Sleep Onset Latency; IS, Interdaily stability; IV, Intradaily variability; CI, Confidence Interval. Effect estimates were obtained using linear mixed models, adjusted for cortisol before dexamethasone, sex, and age (Model 1), and adjusted for cortisol before dexamethasone, sex, age, education, employment, BMI, smoking, alcohol, time difference, CESD, psycholeptics or psychoanaleptics (Model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR. [a] Results using the total population with self-rated sleep quality available (n=964): Model 1, self-rated sleep quality (B=-0.016, 95%CI=-0.034;-0.002, p-value=0.064) and self-rated sleep quality*time (B=0.000, 95%CI=-0.005;0.004, p-value=0.85), Model 2 self-rated sleep quality (B=-0.021, 95%CI=-0.040;-0.003, p-value=0.026) and self-rated sleep quality*time (B=-0.001, 95%CI=-0.005;0.004, p-value=0.78.

Supplementary Table 1

The longitudinal association of sleep and 24-hour activity rhythms with cortisol response to a very low-dose of dexamethasone over time after exclusion of (1) participants that did not respond to a very low-dose of dexamethasone (non-suppressors), (2) participants with clinically relevant depressive symptoms, and (3) participants that self-reported use of psycholeptics or psychoanaleptics.

	Excluding non-suppressors[a]		**Excluding participants with clinically relevant depressive symptoms[b]**		**Excluding participants indicating to use psycholeptics or psychoanaleptics[c]**	
	B (95%CI)	**p-value**	**B (95%CI)**	**p-value**	**B (95%CI)**	**p-value**
Total Sleep Time	0.099 (-0.005;0.203)	0.06	0.082 (-0.032;0.196)	0.16	0.025 (-0.092;0.142)	0.68
TST *time	-0.007 (-0.037;0.023)	0.65	0.001 (-0.031;0.033)	0.96	0.004 (-0.028;0.036)	0.83
Sleep Efficiency	0.009 (-0.001;0.020)	0.08	0.011 (-0.001;0.022)	0.07	0.004 (-0.008;0.017)	0.48
SE *time	0.000 (-0.003;0.004)	0.77	-0.001 (-0.004;0.003)	0.65	-0.001 (-0.005;0.002)	0.45
Sleep Onset Latency	-0.004 (-0.009;0.000)	0.08	-0.008 (-0.014;-0.003)	0.003*	-0.006 (-0.013;-0.000)	0.045
SOL*time	0.000 (-0.001;0.002)	0.68	0.002 (0.000;0.003)	0.033	0.002 (0.000;0.004)	0.029
Wake After Sleep Onset	-0.001 (-0.005;0.003)	0.50	-0.003 (-0.007;0.001)	0.19	-0.003 (-0.007;0.001)	0.18
WASO *time	-0.000 (-0.002;0.001)	0.47	0.001 (-0.001;0.002)	0.41	0.001 (-0.000;0.002)	0.19
Interdaily Stability	1.442 (0.635;2.250)	<0.001*	1.760 (0.834;2.685)	<0.001*	1.626 (0.703;2.549)	0.001*
IS *time	-0.390 (-0.612;-0.168)	0.001*	-0.334 (-0.586;-0.081)	0.010*	-0.320 (-0.565;-0.074)	0.011
Intradaily Variability	-1.106 (-1.944;-0.267)	0.010*	-1.310 (-2.279;-0.342)	0.008*	-1.126 (-2.085;-0.167)	0.021
IV *time	0.173 (-0.062;0.408)	0.15	0.049 (-0.219;0.318)	0.72	0.100 (-0.167;0.367)	0.46
L5 onset time	-0.026 (-0.108;0.057)	0.54	-0.006 (-0.101;0.088)	0.89	-0.029 (-0.126;0.068)	0.56
L5 onset time*time	-0.007 (-0.028;0.013)	0.48	-0.005 (-0.029;0.019)	0.67	0.005 (-0.019;0.030)	0.66
Self-rated sleep quality	-0.026 (-0.057;0.005)	0.10	-0.028 (-0.064;0.007)	0.12	-0.016 (-0.053;0.022)	0.41
Sleep quality*time	-0.002 (-0.009;0.006)	0.65	-0.004 (-0.013;0.005)	0.36	-0.004 (-0.013;0.005)	0.42

Abbreviations: TST, Total Sleep Time; TIB, Time In Bed; SE, Sleep Efficiency; WASO, Wake After Sleep Onset; SOL, Sleep Onset Latency; IS, Interdaily stability; IV, Intradaily variability; CI, Confidence Interval. Effect estimates were obtained using linear mixed models, adjusted for cortisol before dexamethasone, sex, and age (Model 1), and adjusted for cortisol before dexamethasone, sex, age, education, employment, BMI, smoking, alcohol, time difference, CESD, psycholeptics or psychoanaleptics (Model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR.

[a] Included measure points: 572; 374 at baseline and 198 at follow-up.

[b] Included measure points: 571; 372 at baseline and 199 at follow-up.

[c] Included measure points: 548; 356 at baseline and 192 at follow-up.

Supplementary Table 2

The longitudinal association of sleep and 24-hour activity rhythms with cortisol response to a very low-dose of dexamethasone, stratified for sex.

	Men[b]		Women[c]	
	B (95%CI)	**p-value**	**B (95%CI)**	**p-value**
Total Sleep Time	0.061 (-0.102;0.224)	0.46	0.083 (-0.073;0.239)	0.29
TST *time	0.005 (-0.040;0.051)	0.82	0.003 (-0.042;0.047)	0.91
Sleep Efficiency	-0.002 (-0.018;0.014)	0.79	0.019 (0.003;0.035)	0.018
SE *time	0.001 (-0.004;0.005)	0.68	-0.001 (-0.006;0.004)	0.66
Sleep Onset Latency	-0.003 (-0.010;0.005)	0.49	-0.009 (-0.017;-0.002)	0.017
SOL*time	0.001 (-0.001;0.003)	0.33	0.002 (-0.000;0.004)	0.10
Wake After Sleep Onset	-0.001 (-0.008;0.005)	0.65	-0.003 (-0.009;0.003)	0.32
WASO *time	0.000 (-0.001;0.002)	0.84	0.000 (-0.001;0.002)	0.71
Interdaily Stability	1.928 (0.596;3.261)	0.005	1.309 (0.136;2.483)	0.029
IS *time	-0.094 (-0.459;0.271)	0.61	-0.494 (-0.813;-0.176)	0.002*
Intradaily Variability	-1.483 (-2.864;-0.102)	0.035	-1.088 (-2.299;0.123)	0.08
IV *time	0.198 (-0.197;0.592)	0.32	-0.010 (-0.341;0.321)	0.95
L5 onset time	0.000 (-0.135;0.134)	1.00	0.009 (-0.113;0.131)	0.88
L5 onset time*time	-0.009 (-0.048;0.029)	0.64	-0.005 (-0.033;0.023)	0.73
Self-rated sleep quality[a]	-0.014 (-0.076;0.048)	0.66	-0.012 (-0.051;0.027)	0.53
Sleep quality*time	-0.009 (-0.025;0.007)	0.28	-0.003 (-0.013;0.007)	0.52

Abbreviations: TST, Total Sleep Time; TIB, Time In Bed; SE, Sleep Efficiency; WASO, Wake After Sleep Onset; SOL, Sleep Onset Latency; IS, Interdaily stability; IV, Intradaily variability ;CI, Confidence Interval. Effect estimates were obtained using linear mixed models adjusted for cortisol before dexamethasone, age, education, employment, BMI, smoking, alcohol, time difference, CESD, psycholeptics or psychoanaleptics (Model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR.

[a] Results using the total population with self-rated sleep quality available: Men (measure points=849), self-rated sleep quality (B=-0.013, 95%CI=-0.044;.018, p-value=0.41) and self-rated sleep quality*time (B=0.001, 95%CI=-0.007;0.010, p-value=0.74), Women (measure points==1201), self-rated sleep quality (B=-0.023, 95%CI=-0.045;-0.007, p-value=0.012) and self-rated sleep quality*time (B=0.001, 95%CI=-0.005;0.007, p-value=0.75).

[b] Included measure points: 258;169 at baseline and 89 at follow-up.

[c] Included measure points: 368;240 at baseline and 128 at follow-up.

Supplementary Table 3

The longitudinal association of sleep and 24-hour activity rhythms with cortisol before a very low-dose of dexamethasone over time.

	Model 1		Model 2	
	B (95%CI)	**p-value**	**B (95%CI)**	**p-value**
Total Sleep Time	-0.020 (-0.079;0.040)	0.52	-0.015 (-0.076;0.047)	0.64
TST *time	0.001 (-0.016;0.018)	0.89	0.000 (-0.016;0.017)	0.97
Sleep Efficiency	0.001 (-0.006;0.007)	0.86	0.001 (-0.006;0.007)	0.82
SE *time	0.001 (-0.001;0.002)	0.46	0.001 (-0.001;0.002)	0.54
Sleep Onset Latency	-0.001 (-0.004;0.002)	0.69	0.000 (-0.003;0.003)	0.91
SOL*time	0.000 (-0.001;0.001)	0.80	0.000 (-0.001;0.001)	0.83
Wake After Sleep Onset	-0.002 (-0.004;0.000)	0.08	-0.002 (-0.005;0.000)	0.06
WASO *time	0.000 (-0.001;0.001)	0.82	0.000 (-0.001;0.001)	0.69
Interdaily Stability	0.739 (0.262;1.216)	0.002*	0.716 (0.233;1.200)	0.004
IS *time	0.041 (-0.091;0.172)	0.54	0.043 (-0.090;0.176)	0.53
Intradaily Variability	-0.646 (-1.118;-0.175)	0.007	-0.576 (-1.062;-0.090)	0.020
IV *time	0.169 (0.033;0.305)	0.015	0.176 (0.039;0.313)	0.012
L5 onset time	-0.059 (-0.111;-0.006)	0.028	-0.045 (-0.100;0.010)	0.11
L5 onset time*time	0.016 (0.003;0.030)	0.020	0.016 (0.002;0.030)	0.027
Self-rated sleep quality[a]	-0.008 (-0.024;0.009)	0.35	-0.012 (-0.030;0.007)	0.21
Sleep quality*time	0.003 (-0.001;0.007)	0.19	0.003 (-0.001;0.007)	0.19

Abbreviations: TST, Total Sleep Time; TIB, Time In Bed; SE, Sleep Efficiency; WASO, Wake After Sleep Onset; SOL, Sleep Onset Latency; IS, Interdaily stability; IV, Intradaily variability; CI, Confidence Interval. Effect estimates were obtained using linear mixed models, adjusted for sex, and age (Model 1), and adjusted for sex, age, education, employment, BMI, smoking, alcohol, time difference, CESD, psycholeptics and/or psychoanaleptics (Model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR.

[a] Results using the total population with self-rated sleep quality available (n=964): Model 1, self-rated sleep quality (B=-0.006, 95%CI=-0.016;0.004, p-value=0.24) and self-rated sleep quality*time (B=0.000, 95%CI=-0.003;0.003, p-value=0.97), Model 2 self-rated sleep quality (B=-0.003, 95%CI=-0.013;0.008, p-value=0.60) and self-rated sleep quality*time (B=0.000, 95%CI=-0.003;0.003, p-value=0.90).

4.2

The association between polysomnography-estimated sleep and cortisol response after a very low-dose of dexamethasone

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Submitted

Abstract

Background: Sleep and stress are highly interrelated. To improve insight into the role of sleep in functioning of the negative feedback loop of the stress system, we assessed the association between sleep and functioning of the hypothalamic-pituitary-adrenal (HPA) axis in a population-based sample.

Methods: This study included 403 participants (mean age: 62.4±5.0 years, 55% women) from the population-based Rotterdam Study. Sleep was assessed using polysomnography between 2012 and 2014. Functioning of the negative feedback loop of the HPA axis was estimated by measuring cortisol levels before and after the intake of a very-low dose of dexamethasone (0.25mg) on average 0.9±37.8 days apart from the polysomnography. Linear regression analyses adjusted for multiple confounders were used in the full sample, a sample excluding those with clinically relevant depressive symptoms and using psychoactive medicine, and a sample excluding non-suppressors.

Results: Short N2 sleep (adjusted difference=0.005, 95%CI=0.002;0.009), long N3 sleep (adjusted difference=-0.007, 95%CI=-0.010;-0.003), and short sleep onset latency (adjusted difference=0.006, 95%CI=0.001;0.011) were associated with an enhanced response to dexamethasone. However, the association of sleep onset latency did not survive multiple testing correction. All observed associations remained similar after excluding those with clinically relevant depressive symptoms and those using psychoactive medicine or exclusion of non-suppressors .

Conclusions: This study implicates that in particular more slow wave sleep is associated with a stronger suppression of cortisol within the negative feedback loop of the HPA axis. These findings provide further support that slow wave sleep is important for health.

Keywords: Polysomnography; cortisol; HPA axis; population-based; dexamethasone suppression test.

Introduction

The hypothalamic-pituitary-adrenal (HPA) axis helps us to respond to all sorts of commonly occurring stressors and regulates the stress system, for example by the secretion of cortisol.[1] Rising cortisol levels induce physiological changes required for the body to respond to the stressor. At the same time rising cortisol levels inhibit further secretion of cortisol by the HPA axis, via a negative feedback loop.[1] Correct and well-balanced functioning of the negative feedback loop is required for a healthy response to stress, as both a diminished negative feedback as well as an enhanced negative feedback of cortisol have been associated with negative health outcomes.[2,3]

Sleep is long thought to be associated with dysregulation of the stress system.[2,4,5] Poor sleep has been reported to induce dysregulation of the stress system,[6] by assessing altered functioning of the HPA axis and its negative feedback loop in insomnia patients and in relation to actigraphy-estimated habitual sleep.[7,8] Vice versa, both acute stressors and long-term stress have been reported to be associated with poor sleep.[5,6,9] It is important to note that specific aspects of sleep have been associated differently with functioning of the HPA, leading to mixed evidence so far.[6,10] For example, sleep deprivation and insomnia have been associated with hyperactivity of the HPA axis,[11] but excessive daytime sleepiness has been associated with diminished functioning of the HPA-axis.[6] Although these findings might in part be explained by differences in methodology, they could also implicate that different aspects of sleep relate differently to the HPA axis.[6]

The gold standard for assessment of sleep is polysomnography (PSG) .[12,13] Using PSG enables assessment of multiple aspects of sleep[14] and has been successfully applied in population-based cohorts. So far, research investigating the association between PSG-measured sleep and functioning of the HPA-axis was however mainly done in experimental settings, only a limited number of observational studies were performed have been done so far.[6] Observational studies are required to assess the association of sleep and the stress system in a habitual setting, more representative for daily life. Therefore, studying PSG in an observational setting could provide valuable new insights in the association between sleep and stress.

In larger study samples the functioning of the HPA axis can be relatively easy assessed with a very low-dose dexamethasone suppression test, where dexamethasone acts as a pharmacological stressor.[15] In this test, cortisol levels before and after the intake of a very low-dose of dexamethasone (0.25 mg) are compared. The difference between cortisol levels before and after dexamethasone indicate the functioning of the negative feedback loop of the HPA axis, as dexamethasone suppresses the secretion of cortisol via Adrenocorticotropic Hormone (ACTH).[15] A decrease in cortisol level is therefore expected after the intake of dexamethasone. If the decrease in cortisol is larger, the suppression of cortisol is stronger, indicating an enhanced functioning of the negative feedback loop of the HPA-axis. If the decrease in cortisol is smaller, the suppression is less, indicating a diminished functioning of the negative feedback loop.

In the current study, embedded in the population-based Rotterdam Study, we aimed to estimate the cross-sectional association between PSG-measured sleep and the functioning of the negative feedback loop of the HPA axis in a population-based sample of middle-aged and older adults. In line with previously observed hyperactivity of the HPA axis in insomnia patients,[11] we hypothesized that indicators of poor PSG-measured sleep are cross-sectionally associated with an enhanced functioning of the negative feedback loop of the HPA axis.

Methods

Participants and design

We included participants from the population-based Rotterdam Study cohort of middle-aged and elderly inhabitants of Rotterdam, the Netherlands. The cohort was set up in 1990 with the main aim to examine neurological, cardiovascular, psychiatric, and other chronic non-communicable diseases. Details of the study design have been described by Ikram and colleagues.[16]

Between 2012 and 2014, a random subsample of 1,728 participants was invited for a 1-night ambulant PSG at a regular research center visit, 929 agreed. After excluding participants of whom recordings were not usable because device malfunctioning (n=17), insufficient data (n=8), or recording failure (n=5), valid PSG data could be obtained for 899 participants. No other exclusion criteria were used. Of the 899 participants with a valid PSG, 828 participants were invited to participate in a very low-dose dexamethasone suppression test and 656

agreed during the same research center visit. After exclusion of those with incomplete data or insufficient saliva volumes (n=58), those with a time difference between samples deviating more than 3 hours from the specified 24 hours (n=10), and those who were prescribed corticosteroids (Anatomical Therapeutic Chemical Classification code H02: oral, inhalation or dermal) in the year before the dexamethasone suppression test or who self-reported use of corticosteroids at the time of data collection (n=185), valid cortisol data was available for 403 participants.

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Assessment of sleep

Sleep was measured with a 1-night ambulant PSG at the participants' home. Brain activity was assessed using six electroencephalography (EEG) derivations (F3/A2, F4/A1, C4/A2, C4/A1, O1/A2, O2/A1). Additionally, eye movement was monitored using a bilateral electrooculography (EOG) and heart rate was monitored using electrocardiography (ECG). Lastly, oximetry was used to measure the oxygen saturation in the blood and respiratory belts on the abdomen and chest, a nasal pressure sensor and an oronasal thermal sensor were used to detect the airflow and respiratory effort in the thorax and abdomen. Set-up according to the standard American Academy of Sleep Medicine set-up guidelines.[14] Participants were instructed to spend the night as normal as possible and without restrictions on bedtimes, use of alcohol, coffee or medication. Additionally, participants were asked to press a button to mark the time of when they intended to go to sleep and when they got out of bed.

A registered PSG technologist analysed the recordings to determine sleep following the American Academy of Sleep Medicine guidelines.[14] Total sleep time indicated the total time scored as sleep during the night. Sleep efficiency indicated the proportion of time in bed spent

sleeping (100% x (total sleep time/ time in bed), where time in bed was defined as the time between time to bed and get-up time in hours). Sleep onset latency indicated the time between time to bed and sleep start. Wake after sleep onset indicated the total time scored as wake between sleep start and sleep. Additionally, we determined the duration for each of the sleep stages, rapid eye movement (REM) sleep and three stages of non-rapid eye movement (NREM) sleep (N1, N2, N3).

Spectral power and spindles in the C3/A2 derivation were calculated using PRANA software (PhiTools, Strasbourg, France).[17] Spectral analysis was performed using 4-s epochs with 50% overlap, averaged over 30-s epochs. To calculate spectral power, band-pass filtering (0.125–128 Hz) and automated removal of artefacts were applied. Absolute spectral power was calculated in the delta (0.75–4.50 Hz), theta (4.50–8.50 Hz), alpha (8.50–15.50 Hz), beta (15.50–22.50 Hz) and gamma (22.50–40.00 Hz) frequency bands.

Assessment of functioning of the HPA-axis

Functioning of the negative feedback loop of the HPA axis was estimated using a very low-dose dexamethasone suppression test, as has been described previously by Direk et al.[15] In this test, we compared cortisol levels before and after intake of a very low-dose of dexamethasone (0.25 mg). Dexamethasone activates the negative feedback loop of the HPA-axis, and therefore suppresses cortisol release. A stronger suppression of cortisol by the negative feedback loop (i.e. lower levels of cortisol after intake of dexamethasone) indicates an enhanced functioning of the negative feedback loop of the HPA axis. Vice versa, a weaker suppression of cortisol by the negative feedback loop (i.e. higher levels of cortisol after intake of dexamethasone) indicates a diminished functioning of the negative feedback loop of the HPA axis. Participants received oral and written instructions on how to collect saliva samples using Salivette sampling devices (Sarstedt, Nümbrecht, Germany), emphasizing the importance of specific timing of sampling. On day 1, participants were instructed to collect saliva at 8 AM and take a very low-dose of dexamethasone (orally, 0.25 mg) at 11 PM. On day 2, participants were instructed to collect saliva again at 8 AM. Additionally, participants were asked to write down the exact time of dexamethasone intake and saliva sampling. The salivettes were stored at -80 °C, until samples were analyzed at the laboratory of Biopsychology, Technical University of Dresden, Germany. Cortisol concentrations in saliva

were measured in nmol/l using liquid chromatography-mass spectrometry (LCMS; IBL Hamburg, Hamburg, Germany), which is the current golden-standard.[18]

Other variables

Age, sex, and educational level were assessed upon inclusion of participants in the Rotterdam Study. Educational level was based on highest education achieved, classified as primary education (primary), lower/intermediate general education or lower vocational education (low), intermediate vocational education or higher general education (middle), or higher vocational education or university (high). Employment, alcohol intake, smoking behavior, depressive symptoms, use of psychoactive medicine, diabetes mellitus, and average wake-up time were obtained during the home interview. Employment was classified as a binary variable, based on whether the participant had paid work. Alcohol intake was asked as intake of different types of alcoholic beverages in units and recalculated to average grams of alcohol per day. Smoking behavior was classified as never, former, or current smoker. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression scale (CES-D).[19] Use of psychoactive medicine (Anatomical Therapeutic Chemical Classification code: N05 Psycholeptics or N06 Psychoanaleptics) was based on self-report. Diabetes mellitus was based on medical record data. Average wake-up time was assessed using the question "At what time do you usually wake up?" from the Pittsburgh Sleep Quality Index. Body mass index (kg/m^2) was calculated after measuring height and weight on calibrated scales at the research center without heavy clothing and shoes. As an indicator of sleep apnea we used the apnea–hypopnea index (AHI), which was calculated as the number of apneas and hypopneas per hour of sleep using PSG data.[14] Apneas were defined as an airflow reduction of ≥90% of baseline for ≥10 s and a hypopnea was defined as an airflow reduction of ≥30% of baseline for ≥10 s and a desaturation of ≥3% from baseline or an arousal.[13]

Statistical analyses

Descriptive statistics were presented as number with percentage for categorical variables and mean with standard deviation (SD) for numerical data. Differences in level of cortisol before and after intake of dexamethasone were assessed with a paired t-test. Cortisol levels before and after dexamethasone were log-transformed, as they were not normally distributed. Missing values for all covariates were less than 10% and handled using multiple imputation,

using the MICE R package[20] with 5 imputed datasets, pooled statistics are presented.[21] To correct for multiple testing, we used the false discovery rate (FDR) to calculate the adjusted p-values, based on 8 determinants.[22] Analyses were performed in R version R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org).

Cross-sectional linear regression models were used to estimate the association of sleep with (1) cortisol before dexamethasone and (2) response to dexamethasone corrected for cortisol before dexamethasone. All associations were studied in three models to improve our insight in potentially confounding factors. A sex-age adjusted model (model 1), a model additionally adjusted for education, employment, alcohol intake, smoking behavior, depressive symptoms score, use of psychoactive medicine, wake-up time, and body mass index, (model 2), and a model additionally adjusted for prevalence of diabetes mellitus and AHI (model 3). For sleep stage durations (N1, N2, N3, and REM), all models were additionally adjusted for total sleep time. As exploratory analyses, we additionally estimated the association between absolute spectral power and response to dexamethasone.

The associations of sleep with the response to dexamethasone were repeated in four sensitivity analyses. First, short total sleep time can have a substantial impact on all sleep estimates, we therefore reran our analyses excluding participants with a total sleep time below 5 hours. Second, we reran analyses after exclusion of participants for whom cortisol levels did not drop after a very low-dose of dexamethasone, called non-suppressors. Third, to ensure that the observed associations were not only driven by those with clinically relevant depressive symptoms, we repeated our analyses after exclusion of participants indicating clinically relevant depressive symptoms at baseline (CES-D ≥ 16) and those indicating use of psychoactive medicine.

Results

A total of 403 participants were included with a mean age of 62.4±5.0 years and 55% women (Table 1). Cortisol levels after dexamethasone intake (mean 4.0±10.8) were significantly lower than cortisol levels before dexamethasone intake (mean 11.5±8.6, t=13.76, p<0.001). Those who refused to participate in the PSG study were slightly older (t=2.12, p=0.035), more often women (χ^2=5.62, p=0.018), and lower educated (χ^2=11.52, p=0.009) compared to those who

participated. Participants who refused to participate in the dexamethasone suppression test study were more often women (χ^2=38.66, p<0.001) compared to those who participated.

Sleep and the cortisol response to dexamethasone

No PSG indicators of sleep were associated with cortisol before the intake of dexamethasone after adjustment for confounders (Supplementary Table 1). Short N2 sleep (adjusted mean difference=0.005, 95%CI=0.001;0.009) and long N3 sleep (adjusted mean difference=-0.006, 95%CI=-0.010;-0.003) were associated with an enhanced response to dexamethasone after multivariate correction (Model 2, Table 3). When estimates were additionally adjusted for diabetes mellitus and AHI, short sleep onset latency (adjusted mean difference=0.006, 95%CI=0.001;0.012) was also associated with an enhanced response to dexamethasone (model 3, data not shown), however this association did not hold after multiple testing correction. No other sleep estimates were associated with response to dexamethasone (Table 3). In addition, there was no association between absolute spectral power and response to dexamethasone (Table 4).

We performed multiple sensitivity analyses to assess the robustness of the results. First, after exclusion of participants with less than 5 hours of sleep (remaining N=360), results did not change substantially, with the exception of increased effect estimates for sleep efficiency (Supplementary Table 2). Second, after exclusion of non-suppressors (remaining N=363) short sleep onset latency (adjusted mean difference=0.005, 95%CI=0.000;0.010) and long N3 sleep (adjusted mean difference=-0.004, 95%CI=-0.008;-0.001), but not N2 sleep, were associated with enhanced response to dexamethasone. However, these results did not hold after multiple testing correction (Supplementary Table 3). After exclusion of participants with clinically relevant depressive symptoms (CES-D ≥16) and those who self-reported to use psychoactive medicine (remaining N=334), results did not change substantially. A short N2 sleep (adjusted mean difference=0.005, 95%CI=0.001;0.009) and long N3 sleep (adjusted mean difference=-0.006, 95%CI=-0.010;-0.002) were also associated with enhanced response to dexamethasone in this smaller sample (Supplementary Table 3).

Discussion

This study implicates a cross-sectional association of short N2 sleep and long N3 sleep with an enhanced response to dexamethasone (i.e. lower levels of cortisol after intake), indicating

a stronger suppression of cortisol within the negative feedback loop of the HPA axis. There was no significant association of other sleep parameters, including spectral power, and response to dexamethasone. Results remained similar after excluding those who did not respond to the very low-dose of dexamethasone, those with clinically relevant depressive symptoms and those who reported to use psychoactive medicine.

Well-balanced functioning of the stress system is important for optimal health. Both a diminished (i.e. higher levels of cortisol after intake) and an enhanced (i.e. lower levels of cortisol after intake) functioning of the negative feedback loop have been associated with negative health outcomes.[2,3] Within our study population of middle-aged and elderly adults, we observed an association of short N2 sleep and long N3 sleep with an enhanced response to dexamethasone, implicating stronger suppression of cortisol by the negative feedback loop of the HPA axis, similar as seen in stress-related disorders.[2,23] These findings are in line with previous literature reporting an association between more slow wave sleep (N3) and low cortisol levels.[24,25] Because an increase in slow wave sleep is likely at the expense of reduction in other sleep stages, including N2, we hypothesize that the association of short N2 sleep with enhanced response to dexamethasone might be explained by prolonged slow wave sleep in the same individuals. Slow wave sleep is thought to be particularly important to maintain cognitive functioning and neuronal plasticity,[26,27] suggesting implicating that more slow wave sleep is associated with better brain health. As such, the observed association between more slow wave sleep and enhanced functioning of the HPA axis might represent better functioning of the brain and therefore stress system. However, more slow wave sleep also indicates a heightened sleep pressure,[25,28] which might also indicate a sleep shortage. Indeed, sleep shortage has been related to increased cortisol levels and stress during the day,[29] as is also seen in patients with stress-related disorders.[25] However, exclusion of those with short sleep, albeit not necessarily an indicator of sleep shortage, did not change our results. We do have to note that although we found an association of more N3 sleep, of which delta waves are a key feature ,[30] we did not find an association between delta spectral power and response to dexamethasone. Potentially, this can be explained by the age of our study population, delta power during N3 sleep is significantly reduced with increasing age,[31] even within the N3 stage.

Our study also suggested a potential association of short sleep onset latency with enhanced response to dexamethasone. Previously, an association of difficulties initiating sleep have

been associated with a delayed cortisol peak.[24] Furthermore, psychological stress and difficulty falling asleep are important complaints of those with primary insomnia.[7] According to the hyperarousal model for insomnia it is the hyperarousal, or heightened stress, that maintains the insomnia. Worry and rumination, commons with stress, might induce problems with initiating sleep,[7] which is supported by our finding. Yet, we have to note that we only found this association after additional correction for diabetes mellitus and AHI. Therefore, increased worry about sleep might have a potentially stronger impact on cortisol response than in those who do not have these diabetes mellitus or sleep apnea. An explanation could be that diabetes mellitus and sleep apnea can lead to a dysregulation of cortisol levels.[32] Therefore, in these individuals, a stressor such as prolonged sleep onset latency might not disrupt the already affected regulation of cortisol as much.

One of the most common suggested explanations for the associations between sleep and altered functioning of the HPA axis is chronic stress or a shared underlying psychopathology. Chronic stress, for example induced by work or family problems, is associated with heightened cortisol levels, suggesting a disrupted function of the negative feedback loop,[33] and equally with less slow wave sleep.[34] Previous literature has also reported depressive symptoms to be associated with a dysregulated HPA axis[2,35] and poor sleep, such as less slow wave sleep and difficulties with falling asleep.[36,37] In this way, chronic stress or underlying psychopathology might be a common cause, a third factor that explains changes in sleep as well as functioning of the negative feedback loop of the HPA-axis. Yet, our findings did not substantially change after controlling for depressive symptoms or use of psychoactive medication or after exclusion of these participants. This indicates that the association between sleep and functioning of the HPA-axis is independent of depressive symptoms or medication use. This aligns with the finding that depressive disorders are typically associated with a diminished functioning of the HPA axis,[2] whereas we observed enhanced functioning of the HPA axis in relation to disturbed sleep.

When interpreting our results several limitations need to be taken into account. First, we were not able to draw conclusions on temporality or causality because repeated measurements were not available. Second, participation in the PSG study and the dexamethasone suppression test study was optional. Participants agreeing to participate in both studies likely were healthier, potentially inducing selection bias. Third, despite PSG being

the golden standard to assess sleep, a first night effects might have made our measurement less representative for a habitual night of sleep.[38] Last, environmental light is an important factor that could affect both sleep and cortisol levels. Unfortunately we were not able to obtain valid data on environmental light and therefore could not take this into account. Nevertheless, having different PSG sleep measures and the very low-dose dexamethasone suppression tests in a relatively large population-based sample is unique in the field and allowed us to assess associations between sleep and the stress system in the general population.

Altogether, in our study population of middle-aged and elderly we demonstrated an association of short N2 sleep and long N3 sleep with an enhanced response to dexamethasone over time, independent of depressive symptoms and use of medication. These results implicate that duration of slow wave sleep and potentially a longer time needed to falling asleep might play a role in altered functioning of the stress system.

References

1. Dedovic, K., et al., *The brain and the stress axis: the neural correlates of cortisol regulation in response to stress.* Neuroimage, 2009. **47**(3): p. 864-871.
2. Zorn, J.V., et al., *Cortisol stress reactivity across psychiatric disorders: a systematic review and meta-analysis.* Psychoneuroendocrinology, 2017. **77**: p. 25-36.
3. Kumari, M., et al., *Identifying patterns in cortisol secretion in an older population. Findings from the Whitehall II study.* Psychoneuroendocrinology, 2010. **35**(7): p. 1091-1099.
4. Bao, Y.P., et al., *Cooccurrence and bidirectional prediction of sleep disturbances and depression in older adults: meta-analysis and systematic review.* Neuroscience & Biobehavioral Reviews, 2017. **75**: p. 257-273.
5. Kalmbach, D.A., et al., *Hyperarousal and sleep reactivity in insomnia: current insights.* Nature and science of sleep, 2018. **10**: p. 193.
6. van Dalfsen, J.H. and C.R. Markus, *The influence of sleep on human hypothalamic–pituitary–adrenal (HPA) axis reactivity: A systematic review.* Sleep medicine reviews, 2018. **39**: p. 187-194.
7. Riemann, D., et al., *The hyperarousal model of insomnia: a review of the concept and its evidence.* Sleep medicine reviews, 2010. **14**(1): p. 19-31.
8. Luik, A.I., et al., *Sleep and 24-h activity rhythms in relation to cortisol change after a very low-dose of dexamethasone.* Psychoneuroendocrinology, 2015. **53**: p. 207-216.
9. Hall, M.H., et al., *Chronic stress is prospectively associated with sleep in midlife women: the SWAN sleep study.* Sleep, 2015. **38**(10): p. 1645-1654.
10. Chrousos, G., A.N. Vgontzas, and I. Kritikou, *HPA axis and sleep*, in *Endotext [Internet]*. 2016, MDText. com, Inc.
11. Buckley, T.M. and A.F. Schatzberg, *On the Interactions of the Hypothalamic-Pituitary-Adrenal (HPA) Axis and Sleep: Normal HPA Axis Activity and Circadian Rhythm, Exemplary Sleep Disorders.* The Journal of Clinical Endocrinology & Metabolism, 2005. **90**(5): p. 3106-3114.
12. Rundo, J.V. and R. Downey Iii, *Polysomnography.* Handbook of clinical neurology, 2019. **160**: p. 381-392.
13. Iber, C., *The AASM manual for the scoring of sleep and associated events: Rules.* Terminology and Technical Specification, 2007.
14. American Academy of Sleep, M., *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications.* Westchester, IL: American Academy of Sleep Medicine, 2007. **23**.
15. Direk, N., et al., *The very low-dose dexamethasone suppression test in the general population: a cross-sectional study.* PloS one, 2016. **11**(10).
16. Ikram, M.A., et al., *Objectives, design and main findings until 2020 from the Rotterdam Study.* European Journal of Epidemiology, 2020. **35**(5): p. 483-517.
17. Zoubek, L., et al., *Feature selection for sleep/wake stages classification using data driven methods.* Biomedical Signal Processing and Control, 2007. **2**(3): p. 171-179.
18. El-Farhan, N., D.A. Rees, and C. Evans, *Measuring cortisol in serum, urine and saliva–are our assays good enough?* Annals of clinical biochemistry, 2017. **54**(3): p. 308-322.
19. Beekman, A.T.F., et al., *Een screeningsinstrument voor depressie bij ouderen in de algemene bevolking: de bruikbaarheid van de Center for Epidemiologic Studies*

Depression Scale (CES-D). Tijdschrift voor Gerontologie en Geriatrie, 1994. **25**: p. 95-103.
20. Buuren, S.v. and K. Groothuis-Oudshoorn, *mice: Multivariate imputation by chained equations in R.* Journal of statistical software, 2010: p. 1-68.
21. Rubin, D.B., *Multiple imputation for nonresponse in surveys*. Vol. 81. 2004: John Wiley & Sons.
22. Benjamini, Y. and Y. Hochberg, *Controlling the false discovery rate: a practical and powerful approach to multiple testing.* Journal of the Royal statistical society: series B (Methodological), 1995. **57**(1): p. 289-300.
23. Arana, G.W., R.J. Baldessarini, and M. Ornsteen, *The dexamethasone suppression test for diagnosis and prognosis in psychiatry: commentary and review.* Archives of general psychiatry, 1985. **42**(12): p. 1193-1204.
24. Steiger, A., *Sleep and the hypothalamo–pituitary–adrenocortical system.* Sleep medicine reviews, 2002. **6**(2): p. 125-138.
25. Lavie, P., *Sleep disturbances in the wake of traumatic events.* New England Journal of Medicine, 2001. **345**(25): p. 1825-1832.
26. Nicolaides, N.C., et al., *HPA Axis and Sleep.* 2000.
27. Rasch, B. and J. Born, *About sleep's role in memory.* Physiological reviews, 2013.
28. Retey, J.V., et al., *A functional genetic variation of adenosine deaminase affects the duration and intensity of deep sleep in humans.* Proceedings of the National Academy of Sciences, 2005. **102**(43): p. 15676-15681.
29. Leproult, R. and E. Van Cauter, *Role of sleep and sleep loss in hormonal release and metabolism.* Pediatric Neuroendocrinology, 2010. **17**: p. 11-21.
30. Nayak, C.S. and A.C. Anilkumar, *EEG Normal Sleep.* 2019.
31. Schwarz, J.F.A., et al., *Age affects sleep microstructure more than sleep macrostructure.* Journal of sleep research, 2017. **26**(3): p. 277-287.
32. Joseph, J.J. and S.H. Golden, *Cortisol dysregulation: the bidirectional link between stress, depression, and type 2 diabetes mellitus.* Annals of the New York Academy of Sciences, 2017. **1391**(1): p. 20.
33. Mizoguchi, K., et al., *Chronic stress attenuates glucocorticoid negative feedback: involvement of the prefrontal cortex and hippocampus.* Neuroscience, 2003. **119**(3): p. 887-97.
34. Kim, E.J. and J.E. Dimsdale, *The effect of psychosocial stress on sleep: a review of polysomnographic evidence.* Behav Sleep Med, 2007. **5**(4): p. 256-78.
35. Gaffey, A.E., et al., *Aging and the HPA axis: Stress and resilience in older adults.* Neuroscience & Biobehavioral Reviews, 2016. **68**: p. 928-945.
36. Murphy, M.J. and M.J. Peterson, *Sleep disturbances in depression.* Sleep medicine clinics, 2015. **10**(1): p. 17-23.
37. Newson, J.J. and T.C. Thiagarajan, *EEG frequency bands in psychiatric disorders: a review of resting state studies.* Frontiers in human neuroscience, 2019. **12**: p. 521.
38. Byun, J.-H., et al., *The first night effect during polysomnography, and patients' estimates of sleep quality.* Psychiatry research, 2019. **274**: p. 27-29.

Table 1

Characteristics of the study population, Rotterdam study. N=403

	N (%)	Mean ± SD
Demographics		
Age (years)		62.4±5.0
Women	222 (55%)	
Employed	216 (56%)	
Education		
Primary	33(8%)	
Low	135(33%)	
Intermediate	107(27%)	
High	127(32%)	
Health Indicators		
Body mass index (kg/m^2)		27.3±4.6
Alcohol (glasses/day)		0.5±0.9
Smoking		
Never smoker	140(35%)	
Former smoker	205(51%)	
Current smoker	58(14%)	
Diabetes mellitus	47 (12%)	
Apnea-Hypopnea Index (events/hour) [a]		13.8±12.9
Depressive symptoms [b, c]		3(1-7)
Use of psychoactive medicine	51 (13%)	
Cortisol		
Cortisol before dexamethasone (nmol/L) [c]		9.4(6.0-14.4)
Sampling time day 1 (clock time)		7:59±0:43
Cortisol after dexamethasone (nmol/L) [c]		1.9(0.7-4.7)
Sampling time day 2 (clock time)		7:52±0:39

For categorical variables the absolute number (%) is indicated, for numeric variables the mean ± SD. [a] Assessed based the apnea hypopnea Index using polysomnography data. [b] Assessed using the Center for Epidemiologic Studies Depression scale. [c] Median and Interquartile Range. [d] EEG data was available for 359 (89%) of the participants

Table 2.

Sleep in the study population. N=403

	Mean ± SD
Global sleep	
Total sleep time (min)	379.7±62.9
Sleep efficiency (%)	81.2±10.4
Sleep onset latency (min)	20.6±23.0
Wake after sleep onset (min)	68.5±43.3
Sleep stage duration (min)	
N1	48.5±24.5
N2	200.0±49.8
N3	51.7±38.2
REM	79.7±24.4
Absolute spectral power ($\mu V^2/Hz$)[a]	
Alpha	12.1±8.6
Beta	3.3±2.3
Gamma	2.5±2.1
Delta	135.7±117.4
Theta	20.9±13.4

[a] Spectral EEG data was available for 359 (89%) of the participants.

Table 3

The cross-sectional association of polysomnography-estimated sleep with response to a very low-dose of dexamethasone. N=403

	Model 1				Model 2			
	Adjusted mean difference (95%CI)	**Standardized adjusted mean difference**	**p-value**	**Corrected p-value**	**Adjusted mean difference (95%CI)**	**Standardized adjusted mean difference**	**p-value**	**Corrected p-value**
Global sleep								
Total sleep time (min)	0.001 (-0.001;0.003)	0.044	0.47	0.85	0.001 (-0.001;0.003)	0.072	0.28	0.45
Sleep efficiency (%)	0.000 (-0.011;0.012)	0.004	0.95	0.95	0.000 (-0.013;0.013)	-0.001	0.99	0.99
Sleep onset latency (min)	0.005 (-0.001;0.010)	0.106	0.08	0.21	0.005 (0.000;0.010)	0.118	0.06	0.16
Wake after sleep onset (min)	-0.001 (-0.004;0.002)	-0.039	0.53	0.85	-0.001 (-0.004;0.002)	-0.040	0.57	0.76
Sleep stage duration (min)								
N1	0.001 (-0.004;0.006)	0.028	0.67	0.89	0.004 (-0.002;0.009)	0.087	0.24	0.45
N2	0.004 (0.001;0.007)	0.203	0.017	0.07	0.005 (0.002;0.009)	0.257	0.005 *	0.020
N3	-0.005 (-0.009;-0.002)	-0.193	0.005 *	0.040	-0.006 (-0.010;-0.003)	-0.241	0.001 *	0.008
REM	0.000 (-0.006;0.007)	0.006	0.94	0.95	-0.001 (-0.008;0.006)	-0.035	0.69	0.79

Abbreviations: CI, Confidence Interval; Effect estimates were obtained using cross-sectional linear regression models, adjusted for cortisol before DST, sex, and age (Model 1), or adjusted for cortisol before DST, sex, age, education, employment, BMI, smoking, alcohol, time difference, depressive symptoms, psychoactive medicine (Model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR. 3

Table 4

The cross-sectional association of polysomnography-estimated absolute spectral power with response to a very low-dose of dexamethasone. N=359

	Model 1				Model 2			
	Adjusted mean difference (95%CI)	**Standardized adjusted mean difference**	**p-value**	**Corrected p-value**	**Adjusted mean difference (95%CI)**	**Standardized adjusted mean difference**	**p-value**	**Corrected p-value**
Absolute spectral power ($\mu V^2/Hz$)[a]								
Alpha	-0.007 (-0.023;0.010)	-0.056	0.43	0.72	-0.004 (-0.022;0.013)	-0.038	0.62	0.62
Beta	0.008 (-0.053;0.069)	0.018	0.80	0.93	0.023 (-0.045;0.091)	0.052	0.51	0.62
Gamma	0.003 (-0.060;0.065)	0.006	0.93	0.93	0.042 (-0.031;0.115)	0.089	0.26	0.62
Delta	-0.001 (-0.002;0.000)	-0.130	0.07	0.33	-0.001 (-0.003;0.001)	-0.096	0.37	0.62
Theta	-0.008 (-0.019;0.002)	-0.109	0.13	0.33	-0.008 (-0.020;0.005)	-0.101	0.24	0.62

Abbreviations: CI, Confidence Interval; Effect estimates were obtained using cross-sectional linear regression models, adjusted for cortisol before DST, sex, and age (Model 1), or adjusted for cortisol before DST, sex, age, education, employment, BMI, smoking, alcohol, time difference, depressive symptoms, psychoactive medicine (Model 2). None of the P-values was significant remained significant (<0.05) after correcting for multiple testing, using FDR. [a] EEG data was available for 359 (89%) of the participants contributing to the associations with PSG-estimated sleep. [a] alpha (range: 8.50-15.50), beta (range: 15.50-22.50 Hz), gamma (range: 22.50-40.00Hz), delta (range: 0.75-4.50 Hz), and theta (range: 4.50-8.50 Hz).

Supplementary Table 1

The cross-sectional association of polysomnography-estimated sleep with cortisol before a very low-dose of dexamethasone. N=403

	Model 1				Model 2			
	Adjusted mean difference (95%CI)	**Standardized adjusted mean difference**	**p-value**	**Corrected p-value**	**Adjusted mean difference (95%CI)**	**Standardized adjusted mean difference**	**p-value**	**Corrected p-value**
Global sleep								
Total sleep time (min)	0.000 (-0.001;0.002)	0.027	0.44	0.57	0.000 (-0.001;0.001)	0.004	0.92	0.92
Sleep efficiency (%)	0.006 (0.000;0.013)	0.065	0.06	0.24	0.003 (-0.004;0.010)	0.033	0.38	0.64
Sleep onset latency (min)	-0.002 (-0.005;0.001)	-0.047	0.16	0.26	-0.001 (-0.004;0.002)	-0.032	0.35	0.64
Wake after sleep onset (min)	-0.001 (-0.003;0.000)	-0.053	0.13	0.26	-0.001 (-0.002;0.001)	-0.024	0.54	0.72
Sleep stage duration (min)								
N1	-0.001 (-0.004;0.002)	-0.021	0.57	0.57	0.000 (-0.004;0.003)	-0.012	0.77	0.88
N2	-0.001 (-0.003;0.000)	-0.070	0.15	0.26	-0.001 (-0.003;0.001)	-0.043	0.40	0.64
N3	0.002 (0.000;0.004)	0.087	0.023	0.18	0.002 (0.000;0.004)	0.062	0.12	0.64
REM	-0.001 (-0.005;0.002)	-0.028	0.53	0.57	-0.002 (-0.006;0.002)	-0.044	0.36	0.64

Abbreviations: CI, Confidence Interval. Effect estimates were obtained using linear mixed models, adjusted for sex, and age (Model 1), or adjusted for cortisol before DST, sex, age, education, employment, BMI, smoking, alcohol, time difference, depressive symptoms, and psychoactive medicine (Model 2). None of the p-value remained significant (<0.05) after correcting for multiple testing, using FDR.

Supplementary Table 2

The cross-sectional association of polysomnography-estimated sleep with response to a very low-dose of dexamethasone, after exclusion of participants with a polysomnography-estimated total sleep time shorter than 5 hours. N=360

	Model 1				Model 2			
	Adjusted mean difference (95%CI)	**Standardized adjusted mean difference**	**p-value**	**Corrected p-value**	**Adjusted mean difference (95%CI)**	**Standardized adjusted mean difference**	**p-value**	**Corrected p-value**
Global sleep								
Total sleep time (min)	0.001 (-0.001;0.004)	0.028	0.33	0.66	0.001 (-0.001;0.004)	0.093	0.32	0.51
Sleep efficiency (%)	-0.001 (-0.018;0.015)	-0.016	0.86	0.98	-0.006 (-0.023;0.012)	-0.057	0.54	0.72
Sleep onset latency (min)	0.006 (0.000;0.012)	0.128	0.07	0.19	0.006 (0.000;0.012)	0.139	0.05	0.13
Wake after sleep onset (min)	-0.001 (-0.005;0.002)	-0.051	0.51	0.79	-0.001 (-0.004;0.003)	-0.023	0.79	0.79
Sleep stage duration (min)								
N1	0.002 (-0.004;0.007)	0.037	0.59	0.79	0.004 (-0.002;0.011)	0.110	0.15	0.30
N2	0.004 (0.001;0.008)	0.222	0.012*	0.048	0.005 (0.002;0.009)	0.274	0.005*	0.020
N3	-0.006 (-0.009;-0.002)	-0.210	0.003*	0.024	-0.007 (-0.011;-0.003)	-0.263	<0.001*	<0.001
REM	0.000 (-0.007;0.007)	0.002	0.98	0.98	-0.002 (-0.009;0.006)	-0.040	0.67	0.77

Abbreviations: CI, Confidence Interval; Effect estimates were obtained using cross-sectional linear regression models, adjusted for cortisol before DST, sex, and age (Model 1), or adjusted for cortisol before DST, sex, age, education, employment, BMI, smoking, alcohol, time difference, depressive symptoms, psychoactive medicine (Model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR.

Supplementary Table 3

The cross-sectional association of polysomnography-estimated sleep with cortisol response to a very low-dose of dexamethasone, after exclusion of participants that did not respond to DST (non-suppressors), participants with clinically relevant depressive symptoms, or participants that self-reported use of psychoactive medicine.

	Excluding non-suppressors (N=363)				Excluding participants with clinically relevant depressive symptoms or indicating to use psychoactive medicine[a] (N=334)			
	Adjusted mean difference (95%CI)	**Standardized adjusted mean difference**	**p-value**	**Corrected p-value**	**Adjusted mean difference (95%CI)**	**Standardized adjusted mean difference**	**p-value**	**Corrected p-value**
Global sleep								
Total sleep time (min)	0.001 (-0.001;0.002)	0.014	0.58	0.87	0.001 (-0.001;0.003)	0.034	0.33	0.44
Sleep efficiency (%)	-0.003 (-0.014;0.009)	-0.026	0.65	0.87	-0.002 (-0.015;0.012)	-0.028	0.81	0.89
Sleep onset latency (min)	0.005 (0.000;0.010)	0.101	0.041	0.16	0.005 (-0.001;0.010)	0.116	0.10	0.22
Wake after sleep onset (min)	0.000 (-0.003;0.003)	-0.001	0.92	0.92	-0.000 (-0.004;0.003)	-0.006	0.89	0.89
Sleep stage duration (min)								
N1	0.003 (-0.003;0.008)	0.029	0.31	0.62	0.005 (-0.001;0.011)	0.069	0.11	0.22
N2	0.003 (0.000;0.006)	0.118	0.09	0.24	0.005 (0.001;0.009)	0.147	0.012 *	0.048
N3	-0.004 (-0.008;-0.001)	-0.132	0.015	0.12	-0.006 (-0.010;-0.002)	-0.162	0.003 *	0.024
REM	0.001 (-0.006;0.007)	0.032	0.84	0.92	-0.004 (-0.012;0.003)	0.016	0.27	0.43

Abbreviations: CI, Confidence Interval. Effect estimates were obtained using linear mixed models, adjusted for cortisol before DST, sex, age, education, employment, BMI, smoking, alcohol, time difference, depressive symptoms, and psychoactive medicine (Model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR. [a] use of psychoactive medicine not included as a covariate.

5

AND THEN THERE WAS COVID-19

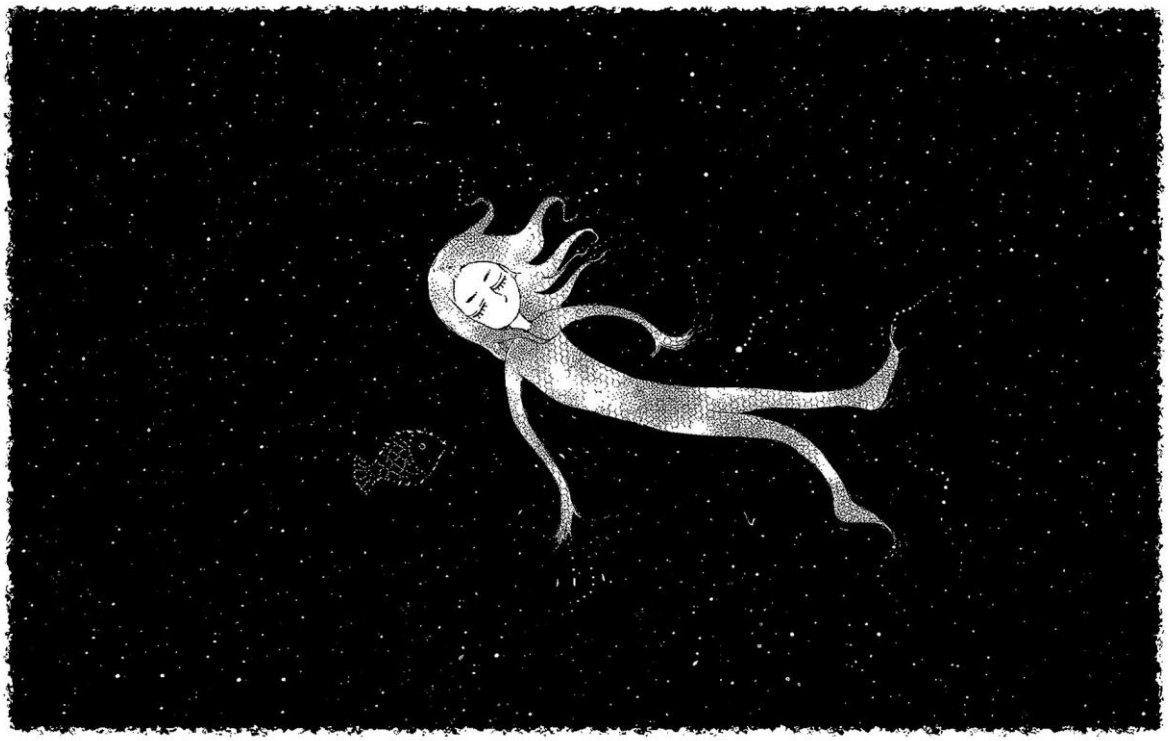
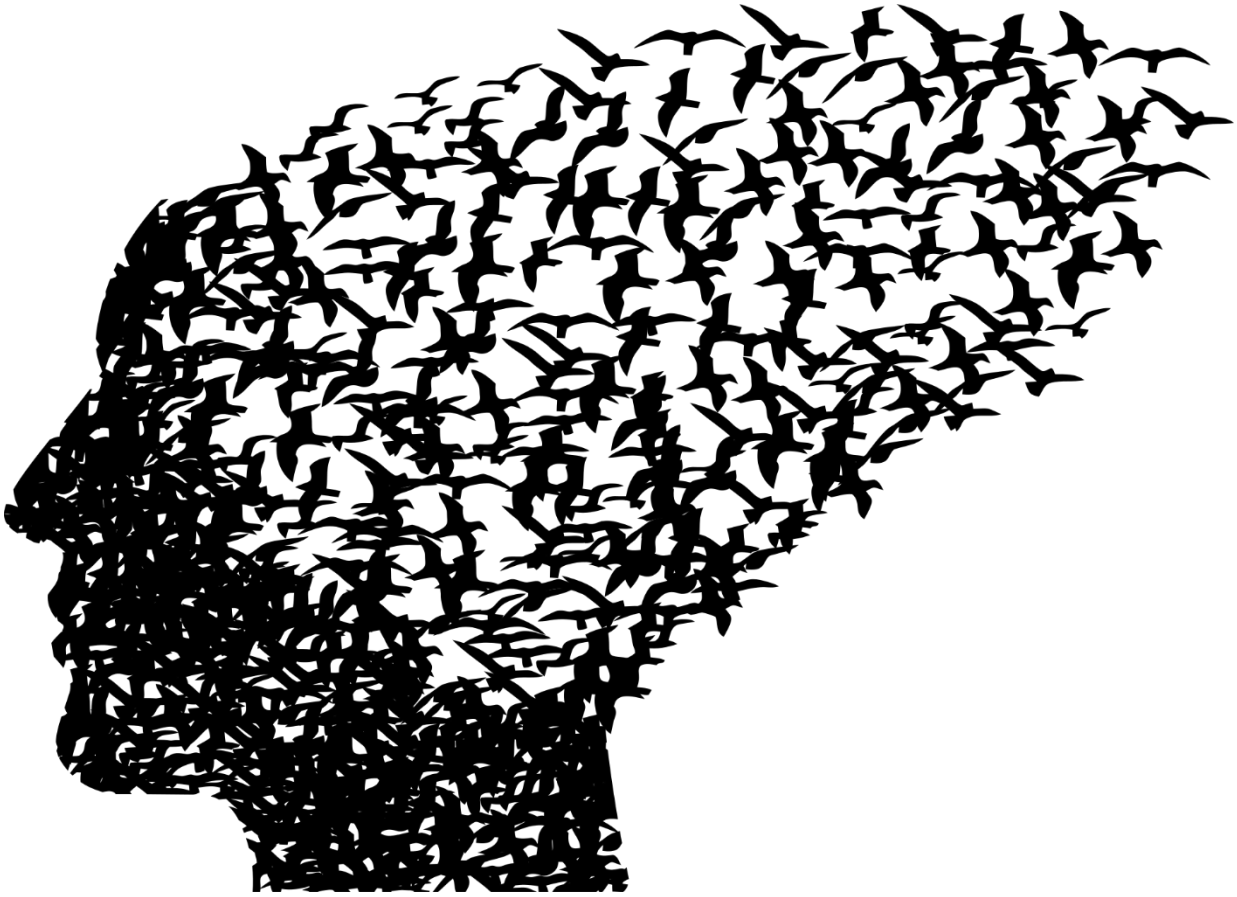


Image by CDD20 from Pixabay



“Wanneer de wereld gek wordt, moet men gekheid als gezond verstand accepteren; want geestelijke gezondheid is, inde laatste analyse, niets anders dan de waanzin waarover de wereld het eens is.”

(George Bernard Shaw, 1856 – 1950)

Origineel: “*When all the world goes mad, one must accept madness as sanity, since sanity is, in the last analysis, nothing but the madness on which the whole world happens to agree.”*

Image by Gordon Johnson from Pixabay

5.1

The network of psychosocial health during COVID-19 lockdown in middle-aged and older adults

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Submitted

Abstract

Purpose: Psychosocial health problems, such as social isolation, loneliness, depression and anxiety, have gained attention during the COVID-19 pandemic and are commonly co-occurring. We investigated the network of psychosocial health constructs during the COVID-19 pandemic.

Methods: This study included 4,553 participants (mean age: 68.6±11.2 years, 56% women) from the prospective Rotterdam Study, who filled out a questionnaire between April and July 2020, the time of the first COVID-19 wave in the Netherlands. Psychosocial health constructs included were depressive symptoms (Center for Epidemiological Studies Depression scale), anxiety symptoms (Hospital Anxiety and Depression scale), loneliness (University of California, Los Angeles loneliness scale), social connectedness (5 items) and pandemic-related worry (5 items). We estimated mixed graphical models to assess the network of items of these constructs and whether age and sex affected the network structure.

Results: Within the network of psychosocial constructs, a higher depressive symptoms score was particularly associated with items of loneliness and social connectedness, whereas overall anxiety was particularly associated with items of pandemic-related worry. Between people from different sex and age, the network structure significantly altered.

Conclusion: This study demonstrates that within the same network of psychosocial health constructs, depressive symptom score is particularly associated with loneliness and social connectedness, whereas anxiety symptom score is associated with pandemic-related worry during the first COVID-19 lockdown. Our results support that psychosocial constructs should be considered in conjunction with one another in prevention and treatment efforts in clinical care, and that these efforts need to be tailored to specific demographic groups.

Keywords: psychosocial health; lockdown; COVID-19 pandemic; network analyses; middle-aged and elderly; population-based

Introduction

Due to the COVID-19 pandemic, countries worldwide adopted prevention strategies, most including physical distancing by limiting group sizes and closing facilities.[1] These lockdown strategies have had a major impact on social lives and mental health, several studies have already reported increased prevalence of loneliness, depression and anxiety in the general population.[2-4] Social and mental health are strongly connected,[5-7] in patients with mental health problems social isolation has for example been associated with more severe symptoms. Additionally, a limited social capital, defined as the availability of social resources,[8] was associated with a hampered recovery.[5,9] We hypothesize that due to the lockdown multiple aspects of psychosocial health are affected and potentially also links between different psychosocial health constructs are rearranged.

Even though the interest in psychosocial health is growing, most studies have analyzed the impact of loneliness, social capital, and worry on mental health in separate models and as distinct psychosocial constructs.[8] Because of the overlap in symptoms, high co-occurrence and strong correlations between these constructs, growing evidence suggests it might be beneficial to study psychosocial health as a network,[10] as these constructs might also need to be targeted in conjunction rather than separately. Using network analyses the associations among psychosocial constructs are estimated in one network model, allowing the investigation of interrelationships among these constructs in the context of the full network of psychosocial health constructs. Crucially, in estimating an association between two constructs, association between the other constructs that are included in the network are taken into account, allowing the visualization of all associations at once and to distinguish direct from indirect effects.[10,11]

The structure of a psychosocial network might potentially not only be affected by the COVID-19 pandemic but also between persons of different age and sex, as lockdown measures may have impacted groups differently, for example because different advice for elderly persons.[12,13] The impact of age on the effects of the lockdown and psychosocial health remains unclear however.[2,14] Results on the impact of sex on the risk of psychiatric symptoms during the lockdown have been inconsistent. Some studies report that women had an increased risk on anxiety and depression,[2,14] whereas others suggested men had an increased risk of depression.[4]

This study aimed to identify the network of psychosocial health, by constructing a network of depressive symptoms, anxiety symptoms, loneliness, social connectedness, and pandemic-related worry in a large population-based sample of middle-aged and older adults. We added age and sex to assess differences in the network for these demographics.

Methods

Participants and design

We included participants from the Rotterdam study, an ongoing population-based cohort of middle-aged and older inhabitants of Rotterdam, the Netherlands. The study started in 1990 to investigate prevalence, history, and risk factors of common diseases later in life. So far, about 20,000 participants aged ≥40 years were included. Further details of the study design have been described elsewhere.[15,16] The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

During the COVID-19 pandemic, repeated questionnaires were sent to participants from April 20th, 2020 onwards,[16] which included questions on psychosocial health. In the current project we used data collected with the first questionnaire, which was sent out to 8,732 participants of the Rotterdam Study. This number represents all participants who were alive by April 2020, excluding participants who lived in nursing homes. The response rate for the first questionnaire was 71.5%.

Of the 6,241 participants that filled out the first questionnaire between of April, 22nd 2020 and July 16th, we excluded participants with more than one item missing for depressive symptoms or anxiety symptoms (n=566), participants with missing items for loneliness, social connectedness and/or worry (n=631), and participants who filled out the questionnaire after May 11th (n=491) as restrictions were substantially eased at this date. This resulted in a total sample of 4,553 eligible participants for analyses.

Depressive symptoms

Depressive symptoms were assessed with the shortened version of the Center for Epidemiologic Studies Depression scale (CES-D), which consists of 10 items, rated on a 0 to 3 scale.[17,18] The total score ranges from 0 to 30, with a higher score indicating more severe depressive symptoms. A weighted score was calculated if ≥9 of the questions were completed. If less than 9 of the questions were completed, CES-D was set to missing.

Anxiety symptoms

Anxiety symptoms were assessed with a 7-item, rated on a 0 to 3 scale, version of the Hospital Anxiety and Depression Scale (HADS-A) questionnaire.[19] A weighted score was calculated if ≥6 of the questions were completed, if less than 6 of the questions were completed, HADS-A was set to missing.

Loneliness

Loneliness was assessed with the 3 item University of California, Los Angeles (UCLA) loneliness scal.[20] Additionally the question "*How often do you feel alone*" was asked with the follow possible answers "*Almost never, or never*", "*Sometimes*", or "*Often*" (range 1-3). The questions were included as separate items in the network analyses.

Social connectedness

Social connectedness was assessed an indicator for social capital, the availability of social resources.[8] In this study, social connectedness was assessed with 5 items. These items were assessed using the following statements (1) "*I feel connected to all Dutch people*", (2) "*I feel connected to my neighbors, family or friends*", (3) "*I receive the help and support that I need from my neighbors, family or friends*", (4) "*I do everything I can to help others who are infected with the coronavirus*", and (5) "*I expect others to do everything they can to help me if I become infected with the coronavirus*". Each of these statements could be answered with "*Strongly disagree*", "*Slightly disagree*", "*Not agree, or disagree*", "*Slightly agree*", or "*Strongly agree*" (range 1-5). The questions were included as separate items in the network analyses.

Pandemic-related worry

Pandemic-related worry was assessed with 5 items. These items were assessed with the following statements (1) "*I worry about contracting the virus myself*", (2) "*I worry about someone close to me contracting the virus*", (3) "*I am worried that myself or my relatives will encounter severe financial difficulties*", (4) "*I am worried about the time it will take before it is possible to return to my daily routines*", and (5) "*I am worried about not being able to visit my family or friends*". Each of these statements could be answered with "*Never*", "*Rarely*", "*Sometimes*", "*Often*", or "*Almost Continuously*" (range 1-5).The questions were included as separate items in the network analyses.

Other variables

Age and sex were self-reported within the questionnaire.

Statistical analyses

Descriptive analyses are presented as number with percentage for categorical variables and mean with standard deviation (SD) for numerical data. Analyses were performed in R version R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org).

Networks were estimated using the MGM R package,[21] and LASSO regularization was used to prevent inclusion of spurious edges.[22] Extended Bayesian Information Criterion (EBIC) was used to select the optimal tuning parameter, with the hyper parameter set to 0.25. Conditional associations between each two variables were estimated after taking into account all other variables in the network.[10,23] All variables included in a network were presented as a node. The estimated conditional direct associations were represented by edges, the thickness of the edges is scaled relative to the reference value of 0.1. This was the same for all networks, to be able to compare different networks. The relevance of all edges connected to a node was assessed using a predictability estimation for each of the variables in our network.[24] The predictability was calculated as the proportion of variance in a variable that is explained by other variables in the network that are directly connected to it and is presented as a ring around the node representing that variable. The predictability was calculated for all variables in the network. A ring that is completely filled indicates 100% of the variance of a variable can be explained by the other variables in the network that are connected to it, whereas an empty ring indicates 0% of its variance can be explained by other

variables in the network. We assessed estimated the stability of the estimated edges in the network, using the bootnet R package[22,25] using nonparametric bootstrapping with 100 bootstrap samples.

First, we estimated a network where the weighted depressive symptoms sum-score, weighted anxiety symptoms sum-score, and each of the described items for loneliness, social connectedness, and worry were included. This network provides insight in how depressive symptoms score and anxiety are conditionally associated to other items of psychosocial health during the lockdown. Given the high comorbidity between depressive symptoms and anxiety symptoms,[11] it is to be expected that these constructs will be strongly associated in the network, and explain much of the variance in one another. In order to estimate the amount in which items of loneliness, social connectedness or worry explain the variance of depressive symptoms score and anxiety symptoms score, we estimated separate networks including either depressive symptoms score or anxiety symptoms score.

Second, we aimed to identify if age and sex affected the network structure as described above. To do this we estimated a network tree using the networktree R package.[26] Using this method, the sample is split recursively based on pre-specified binary variables (i.e., age and sex in this study). The networktree function estimates whether the network structure is significantly affected by either of the specified variables. The function estimates in what order the study population should be split based on these variables, in order to maximize the differences between the network structures. For each split, the significance of the difference between the groups of that variable was presented as a p-value. In this study we used sex and age group as potential covariates, where for age group participants were categorized as either (1) the median age of 69 or below, or (2) above the median age of 69 years.

Third, the scores of depressive symptoms consist of a heterogeneous spectrum of symptoms. Therefore, we aimed to gain insight in what depression- and anxiety symptoms were most strongly associated to items of loneliness, social connectedness or worry. Furthermore, this network allows us to identify what symptoms of anxiety or depression connect these constructs to items of loneliness, social connectedness or worry, and the cluster of depression or anxiety symptoms. We estimated a network including all loneliness items, all social

connectedness items, all pandemic-related worry items, all depressive symptoms, and all anxiety symptoms separately.

For all figures, except Supplementary Figure 4, the coloring of variables in the network was presented based on the categorization in the questionnaire. Clustering of variables was further explored by using Walktrap, and Spinglass algorithms.[27]

Results

In this study, we included 4,553 participants with a mean age of 68.6±11.2 years and 56% were women. Participants reported a median depressive symptoms score of 4 (IQR=2-8) and a median anxiety symptoms score of 3 (IQR=1-5). Furthermore, 743 (16.3%) exceeded the cut-off score of 10 for clinically relevant depressive symptoms and 714 (15.7%) exceeded the cut-off score of 7 for clinically relevant anxiety symptoms. In total 483 (10.6%) participants exceeded the clinical cut-off for both depressive symptoms and anxiety symptoms score.

First, we estimated the overall network including the depressive symptoms score, anxiety symptoms score, and separate items for loneliness, social connectedness, and pandemic-related worry (Figure 1). Within the overall network we observed depressive symptoms score and anxiety symptoms score were central in the network, surrounded by clusters for items of loneliness, items of social connectedness, and items of pandemic-related worry. We observed that depressive symptoms score was positively associated with the loneliness items '*feeling left out'*, '*feeling alone'*, and '*missing company'*. Additionally, depressive symptoms score was negatively associated with the social connectedness items '*feeling connected to society'*, '*feeling connected to friends or family'*, '*receiving help'*, and '*offering help'* (Figure 1). Anxiety symptoms score was positively associated with all the pandemic-related worry items: '*worry to get infected with COVID-19'*, '*worry others will get infected with COVID-19'*, '*financial worry'*, '*worry about daily life'*, and '*worry about social life'* (figure 1). We observed the loneliness items '*feeling isolated'*, and '*missing company'*, were positively associated with the pandemic-related worry item '*worry about social contact'.* Furthermore, the loneliness items *'feeling left out'*, '*feeling isolated'*, and '*feeling alone'* were negatively associated with the social connectedness items (Figure 1). Depressive symptoms score was explained for 65% by variables in the network that were directly connected to it, for anxiety this was 64%. However, it is likely these explained variances are with a large proportion accounted by the strong

relation between depressive symptoms score and anxiety symptoms score. To account for this, we estimated separate networks including either depressive symptoms score or anxiety symptoms score. In these separate networks, 37% of the variation in the depressive symptoms score could be accounted for by variables in the network that were directly connected to it (Supplementary figure 1). When depressive symptoms score was not included in the network, explained variance for anxiety symptoms score was 35% (Supplementary figure 2). Explained variance for the loneliness items was on average 43%, for social connectedness items this was 20% and for pandemic-related worries 33%. The nonparametric bootstrap showed that the bootstrapped sampling distributions around the estimated edges in our network were generally small, indicating relatively stable estimates (Supplementary Figure 3).

Second, we assessed whether the network structure was significantly different for people of different age or sex by estimating a network tree. The observed network structure significantly differed between age and sex (Figure 2). To maximize the differences between the network structures of the groups, the population was first split based on age ($p<0.001$), separating those with an age below the median of 69 from those with an age above. In both age groups, there was a second split based on sex ($p=0.018$ in those <69 and $p<0.001$ in those ≥69) (Figure 2). In all networks we observed an association of higher depressive symptoms score with more '*feeling alone'* and less '*feeling connected with all the Dutch'*; of higher anxiety symptoms score with more *'worry to get infected with COVID-19'* and '*worry about daily life'*; and of '*missing company'* with more '*worry about inability to visit family or friends*' (Figure 2). Based on visual inspection of the networks, the association between anxiety symptoms score and *'worry to get infected with COVID-19'* seemed to be stronger in men than in women, whereas for the association between higher depressive symptoms score and less '*feeling connected with all the Dutch*' this seemed to be stronger in women than in men. Furthermore, in both middle-aged and older men, we observed an association between higher anxiety symptoms score and more '*financial worry*'. However, in women we observed an association of higher depressive symptoms score with less '*feeling connected with family or friends'*, and of more '*feeling alone'* and less '*offering help to others*' (Figure 2). In all groups except older women, there was also an association between higher depressive symptoms score and less '*currently receiving help from family or friends'*. In all groups except older men,

there was an association between higher anxiety symptoms score and more '*worry others will get infected with COVID-19'* (Figure 2). In middle-aged men and women, but not in older men and women, we observed an association between higher depressive symptoms score and more '*worry about daily life'*, and an association between more '*worry to get infected with COVID-19'* and less '*expecting help if needed in case of a COVID-19 infection'* (Figure 2).

Last, we estimated a network including all depressive symptoms and anxiety symptoms separately, and all items of loneliness, items of social connectedness and pandemic-related worry as nodes, to assess which specific depressive symptoms and anxiety symptoms most strongly connect to other aspects of psychosocial health (Figure 3). Based on the Walktrap clustering algorithm, we observed several clusters of variables; one with items of social connectedness, one with items of pandemic-related worry, and one with items of loneliness including the depressive symptom '*feeling lonely*'. Additionally, depressive symptoms and anxiety symptoms were divided over 3 clusters (Supplementary Figure 4). We furthermore observed that the depressive symptoms that were reflecting a lack of positive affect ('*feeling happy*') and loneliness ('*feeling lonely'*) connected depressive symptoms to loneliness items, whereas the depressive symptoms '*being easily bothered*, and '*feeling restless*, connected depressive symptoms to social connectedness (Figure 3). Additionally, we observed that the depressive symptoms '*feeling fearful*' and '*feeling restless',* and the anxiety symptoms '*feeling frightened something awful is going to happen*, '*feeling relaxed and at ease'*, and '*having worrying thoughts'* connected anxiety to pandemic-related worry (Figure 3).

Discussion

We demonstrated that within a network including multiple aspects of psychosocial health, a higher depressive symptoms score was specifically associated with items of loneliness and social connectedness, whereas a higher anxiety symptoms score was specifically associated with items of pandemic-related worry. Furthermore, items of loneliness were associated with items of social connectedness and items of pandemic-related worry. Second, the network structure significantly differed between age groups and sex, with for example a stronger association between anxiety symptoms score and '*worry to get infected*' and '*financial worry*' in men and an association between depressive symptoms score and '*worry about daily life*' only in middle-aged participants. Last, when including depressive symptoms and anxiety

symptoms in the network as individual items, we observed mainly depressive symptoms to connect the items of different psychosocial health constructs.

Depressive symptoms and anxiety are highly prevalent in the general population,[28] and even more often reported during the COVID-19 lockdown.[14] Our results demonstrate that when taking all variables into account simultaneously, depressive symptoms score is particularly associated with loneliness and social connectedness, while anxiety is particularly associated with pandemic-related worry. These findings are partly in line with previous literature reporting depression and anxiety both to be associated with loneliness, social connectedness, and worry.[8,9,29] An explanation for our findings could be an overlap between constructs that we observed to be associated. Loneliness, social connectedness, and depression are constructs more based on self-worth and avoidance.[30,31] People with more avoidant attachment styles or higher levels of self-disgust might be more likely to feel less socially connected, become more isolated during a lockdown, and at the same time develop a somber mood.[30,31] Worry and anxiety both are constructs that are based on hyperarousal.[32] People with more neurotic personality traits and vulnerability to hyperarousal might be more likely to worry about the COVID-19 pandemic more, and at the same time feel more anxious about it.[32,33] However, because of the strong association between depression and anxiety, comorbid symptoms are likely to occur over time.[34,35]

We observed age and sex significantly altered the network structure. First, in older men and women the network structures were less dense when compared to middle-aged men and women. A denser network indicates that change in either variable has a stronger influence on the network structure, than in a less dense network. An explanation for more dense networks for middle-aged men and women could be a bigger impact of the lockdown on their daily life. Middle-aged people are more likely to have a job and therefore experience a substantial change in their daily routines and stronger job insecurity, whereas the older people in our sample were frequently retired. Secondly, based on our findings it seems depressive symptoms and anxiety are more strongly associated with the social aspects, such as strong social connectedness, in women. In men, practical aspects like financial security seem more important. These implications are supported by gender-based personality traits.[36] Compared to men, women tend to report a lower self-esteem and the experience of more distressing emotions and thus might be more vulnerable to mood disorders and loneliness, especially in

response to stressful events such as a pandemic.[36,37] Additionally, women tend to be more focused to care for others, potentially putting them at a higher risk to experience social distress, whereas men might have a stronger focus on financial concerns.[36] However, it might well be that these differences can also be in part explained by differences in the extent to which men and women feel at ease to report these symptoms. Third, a higher anxiety symptoms score was associated with worry to get infected with COVID-19 in all groups, but this association seemed stronger in men than in women. Furthermore, we observed anxiety was associated with worry others will get infected with COVID-19 in all groups, except older men. An explanation could be that risks for severe consequences of a COVID-19 infection were reported to be specifically high in middle-aged men and older adults, causing them to feel more anxious about possible consequences and worry more about themselves and feel more anxious about possible consequences.[12,13]

When we included symptoms of depression and anxiety as separate items in the network, we observed multiple clusters of items. For most psychosocial health constructs, we observed that items within a construct indeed clustered together. Items for depression however were more spread throughout the network, suggesting that depressive symptom items connect the different constructs. Potentially, this is because in this network depressive symptoms are assessed with a substantially larger number of items than the other constructs, therefore allowing more variance. Another explanation could be that depressive symptoms cover a broader spectrum of psychosocial health complaints, because items can be classified as related to either (1) feeling depressed and lonely, (2) somatic, (3) interpersonal and connected to others, (4) positive affect and self-worth, or (5) feeling fearful.[18,38]

Several limitations need to be taken into account when interpreting these results. First, items of loneliness, social connectedness, and pandemic-related worry were only assessed during the COVID-19 pandemic. Therefore, we were not able to compare the network to a network prior to the lockdown. Second, questions on mental health were frequently missing due to non-response. Therefore, there is a possibility of selection bias as the choice to leave mental health questions unanswered is unlikely to be completely random. Lastly, exclusion of participants who responded after May 11th potentially introduced selection bias, as participants who take longer time to respond might differ from those responding earlier. Nevertheless, performing a network analysis including multiple aspects of psychosocial health

using a large population-based cohort of middle-aged and older adults is unique in this field and allowed us to assess underlying associations.

Altogether, in our study population of middle-aged and older adults we demonstrated that within a network of psychosocial factors, a high depressive symptoms score was most strongly associated with loneliness and poorer social connectedness, whereas a high anxiety symptoms score was most strongly associated with pandemic-related worry. This emphasizes that psychosocial factors should be considered in conjunction for both population-based mental health prevention efforts and treatment efforts in clinical care. Importantly, we showed that the lockdown had a stronger impact on middle-aged participants compared to older participants, women were more vulnerable to social distress, and men were more vulnerable to distress about practical issues. Efforts for prevention and treatment might therefore need to be tailored to specific demographic groups.

References

1. Hale, T., et al., *Variation in government responses to COVID-19.* Blavatnik school of government working paper, 2020. 31: p. 2020-11.
2. Smith, L., et al., *Correlates of symptoms of anxiety and depression and mental wellbeing associated with COVID-19: a cross-sectional study of UK-based respondents.* Psychiatry Research, 2020: p. 113138.
3. Smith, B.J. and M.H. Lim, *How the COVID-19 pandemic is focusing attention on loneliness and social isolation.* Public health research & practice, 2020. 30(2): p. 3022008.
4. Ozamiz-Etxebarria, N., et al., *Psychological Symptoms During the Two Stages of Lockdown in Response to the COVID-19 Outbreak: An Investigation in a Sample of Citizens in Northern Spain.* Frontiers in Psychology, 2020. 11: p. 1491.
5. Courtin, E. and M. Knapp, *Social isolation, loneliness and health in old age: a scoping review.* Health & social care in the community, 2017. 25(3): p. 799-812.
6. Ong, A.D., B.N. Uchino, and E. Wethington, *Loneliness and health in older adults: A mini-review and synthesis.* Gerontology, 2016. 62(4): p. 443-449.
7. Leigh-Hunt, N., et al., *An overview of systematic reviews on the public health consequences of social isolation and loneliness.* Public health, 2017. 152: p. 157-171.
8. Wang, J., et al., *Social isolation in mental health: a conceptual and methodological review.* Social psychiatry and psychiatric epidemiology, 2017. 52(12): p. 1451-1461.
9. Mann, F., et al., *A life less lonely: the state of the art in interventions to reduce loneliness in people with mental health problems.* Social psychiatry and psychiatric epidemiology, 2017. 52(6): p. 627-638.
10. Nuijten, M.B., et al., *Mental disorders as complex networks: an introduction and overview of a network approach to psychopathology.* Clinical Neuropsychiatry, 2016. 13(4/5): p. 68-76.
11. Blanken, T.F., et al., *The role of stabilizing and communicating symptoms given overlapping communities in psychopathology networks.* Scientific reports, 2018. 8(1): p. 1-8.
12. Park, R., et al., *Sex-bias in COVID-19-associated illness severity and mortality in cancer patients: a systematic review and meta-analysis.* EClinicalMedicine, 2020. 26: p. 100519.
13. Gao, Y.d., et al., *Risk factors for severe and critically ill COVID-19 patients: A review.* Allergy, 2021. 76(2): p. 428-455.
14. Vindegaard, N. and M.E. Benros, *COVID-19 pandemic and mental health consequences: systematic review of the current evidence.* Brain, Behavior, and Immunity, 2020.
15. Ikram, M.A., et al., *Objectives, design and main findings until 2020 from the Rotterdam Study.* European Journal of Epidemiology, 2020. 35(5): p. 483-517.

16. Licher, S., et al., *Design, Implementation and Initial Findings of COVID-19 Research in the Rotterdam Study: Leveraging Existing Infrastructure for Population-Based Investigations on An Emerging Disease.* 2021.
17. Beekman, A.T.F., et al., *Een screeningsinstrument voor depressie bij ouderen in de algemene bevolking: de bruikbaarheid van de Center for Epidemiologic Studies Depression Scale (CES-D).* Tijdschrift voor Gerontologie en Geriatrie, 1994. 25: p. 95-103.
18. Radloff, L.S., *The CES-D scale: A self-report depression scale for research in the general population.* Applied psychological measurement, 1977. 1(3): p. 385-401.
19. Hinz, A. and E. Brähler, *Normative values for the hospital anxiety and depression scale (HADS) in the general German population.* Journal of psychosomatic research, 2011. 71(2): p. 74-78.
20. Russell, D.W., *UCLA Loneliness Scale (Version 3): Reliability, validity, and factor structure.* Journal of personality assessment, 1996. 66(1): p. 20-40.
21. Yang, E., et al. *Mixed graphical models via exponential families*. in *Artificial intelligence and statistics*. 2014.
22. Epskamp, S. and E.I. Fried, *A tutorial on regularized partial correlation networks.* Psychological methods, 2018. 23(4): p. 617.
23. Borsboom, D., *A network theory of mental disorders.* World psychiatry, 2017. 16(1): p. 5-13.
24. Haslbeck, J.M.B. and L.J. Waldorp, *How well do network models predict observations? On the importance of predictability in network models.* Behavior research methods, 2018. 50(2): p. 853-861.
25. Burger, J., et al., *Reporting standards for psychological network analyses in cross-sectional data.* 2020.
26. Jones, P.J., et al., *Network Model Trees.* 2019.
27. Yang, Z., R. Algesheimer, and C.J. Tessone, *A comparative analysis of community detection algorithms on artificial networks.* Scientific reports, 2016. 6(1): p. 1-18.
28. World Health, O., *Depression and other common mental disorders: global health estimates.* 2017.
29. Kawachi, I. and L.F. Berkman, *Social ties and mental health.* Journal of Urban health, 2001. 78(3): p. 458-467.
30. Spence, R., C. Jacobs, and A. Bifulco, *Attachment style, loneliness and depression in older age women.* Aging & mental health, 2020. 24(5): p. 837-839.
31. Ypsilanti, A., et al., *Self-disgust, loneliness and mental health outcomes in older adults: an eye-tracking study.* Journal of affective disorders, 2020. 266: p. 646-654.
32. Hyde, J., K.M. Ryan, and A.M. Waters, *Psychophysiological markers of fear and anxiety.* Current psychiatry reports, 2019. 21(7): p. 1-10.
33. Hoehn-Saric, R., *Psychic and somatic anxiety: worries, somatic symptoms and physiological changes.* Acta Psychiatrica Scandinavica, 1998. 98: p. 32-38.

34. Pollack, M.H., *Comorbid anxiety and depression.* The Journal of clinical psychiatry, 2005. 66(suppl 8): p. 22-29.
35. Saade, Y.M., et al., *Comorbid anxiety in late-life depression: Relationship with remission and suicidal ideation on venlafaxine treatment.* Depression and anxiety, 2019. 36(12): p. 1125-1134.
36. Schmitt, D.P., et al., *Personality and gender differences in global perspective.* International Journal of Psychology, 2017. 52: p. 45-56.
37. Costa Jr, P.T., A. Terracciano, and R.R. McCrae, *Gender differences in personality traits across cultures: robust and surprising findings.* Journal of personality and social psychology, 2001. 81(2): p. 322.
38. Thorson, J.A. and F.C. Powell, *The CES-D: Four or five factors?* Bulletin of the Psychonomic Society, 1993. 31(6): p. 577-578.

Table 1

Demographics of the study population (N = 4,553)

	N	(%)	Median	IQR
Age (years) [a]			68.6	11.2
Women	2,556	56.2		
Psychopathology				
Depressive symptoms (score) [b]			4	2-8
Anxiety symptoms (score) [c]			3	1-5
Loneliness [d]				
Feeling left out			1	1-2
Feeling isolated			2	1-2
Feeling alone			1	1-2
Missing company			2	1-2
Social connectedness [e]				
Connected with all the Dutch			4	3-5
Connected with friends or family			5	4-5
Currently receiving help and support from family or friends			4	3-5
Currently offering help to others			3	2-4
Expecting help from others if needed in case of a COVID-19 infection			4	3-5
Pandemic-related worry [f]				
Worry to get infected with COVID-19			3	2-3
Worry others getting infected with COVID-19			3	2-3
Financial worry			2	1-3
Worry about daily life			3	2-3
Worry about inability to visit family or friends			3	2-4

Abbreviations: IQR, Inter Quartile Range; SD, Standard Deviation.

[a] Mean and SD.

[b] Assessed using the 10-item Center for Epidemiologic Studies Depression scale.

[c] Assessed using the Hospital and Depression Scale.

[d] Possible answering options were "*Almost never, or never*" = 1, "*Sometimes*" = 2, and "*Often*" = 3

[e] Possible answering options were "*Strongly disagree*" = 1, "*Slightly agree*" = 2, "*Neutral*" = 3, "*Slightly agree*" = 4, and "*Strongly agree*" = 5

[f] Possible answering options were "*Never*" = 1, "*Rarely*" = 2, "*Sometimes*" = 3, "*Often*" = 4, and "*Almost continuously*" = 5

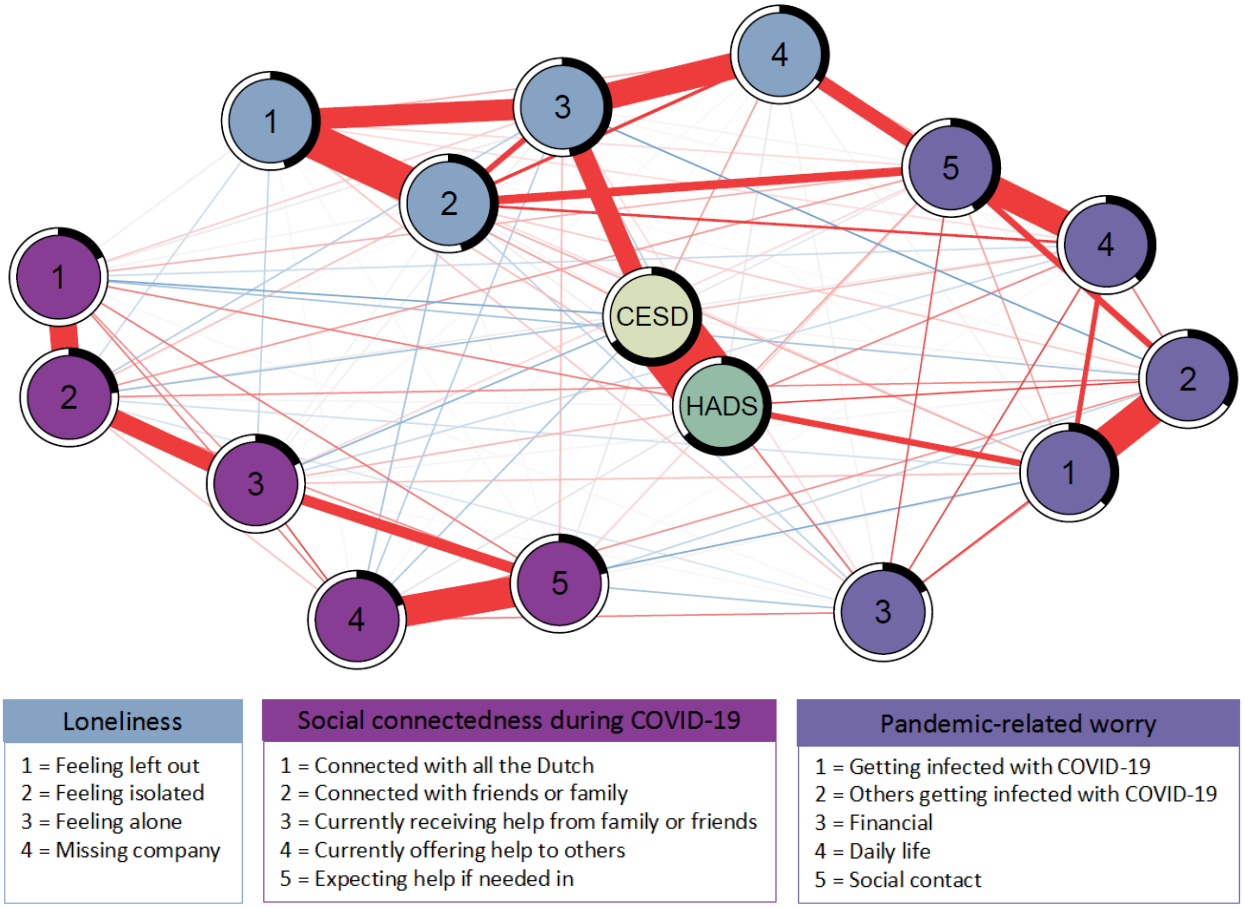


Figure 1

The estimated network of depressive symptoms score, anxiety symptoms score, and items of loneliness, social connectedness, and worry. Each variable is represented by a node in the network. Direct, conditional positive associations (red) and negative associations (blue) between variables are indicated with edges. Strength of the association is indicated by thickness of the edge, using a correlation value of 0.1 as maximum value reference point. For each node the predictability, indicating the proportion of variability that is explained by other variables in the network, is presented as a ring around the node. A completely filled ring indicates all variance of a variable can be explained by the other variables in the network, whereas an empty ring indicates none of the variance is explained.

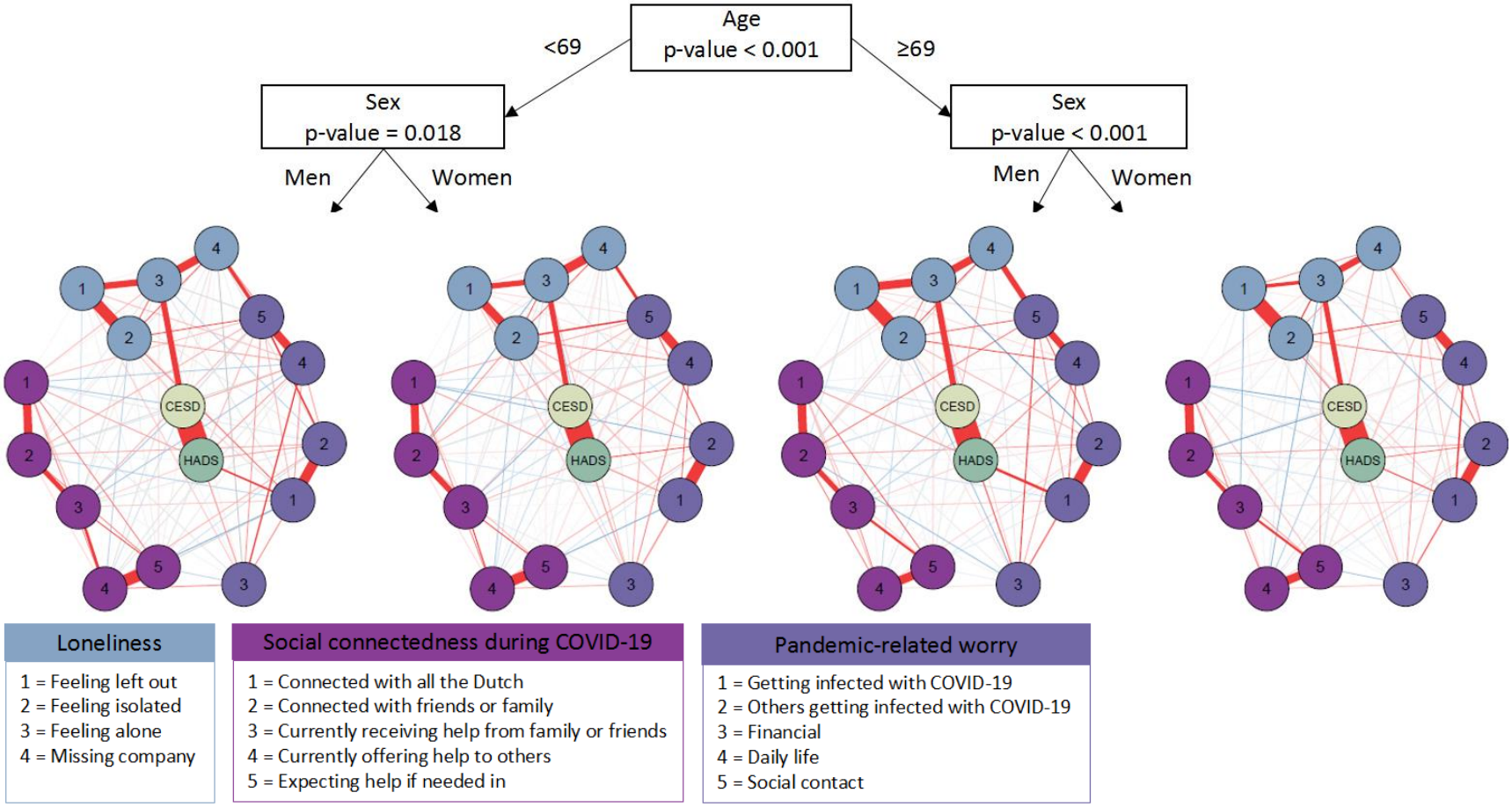


Figure 2

The estimated network tree, using age and sex as potential covariates. Each network contains depressive symptoms score, anxiety symptoms score, and items of loneliness, social connectedness, and worry, represented by a node in the network. Direct, conditional positive associations (red) and negative associations (blue) between variables are indicated with edges. Strength of the association is indicated by thickness of the edge, using a correlation value of 0.1 as maximum value reference point.

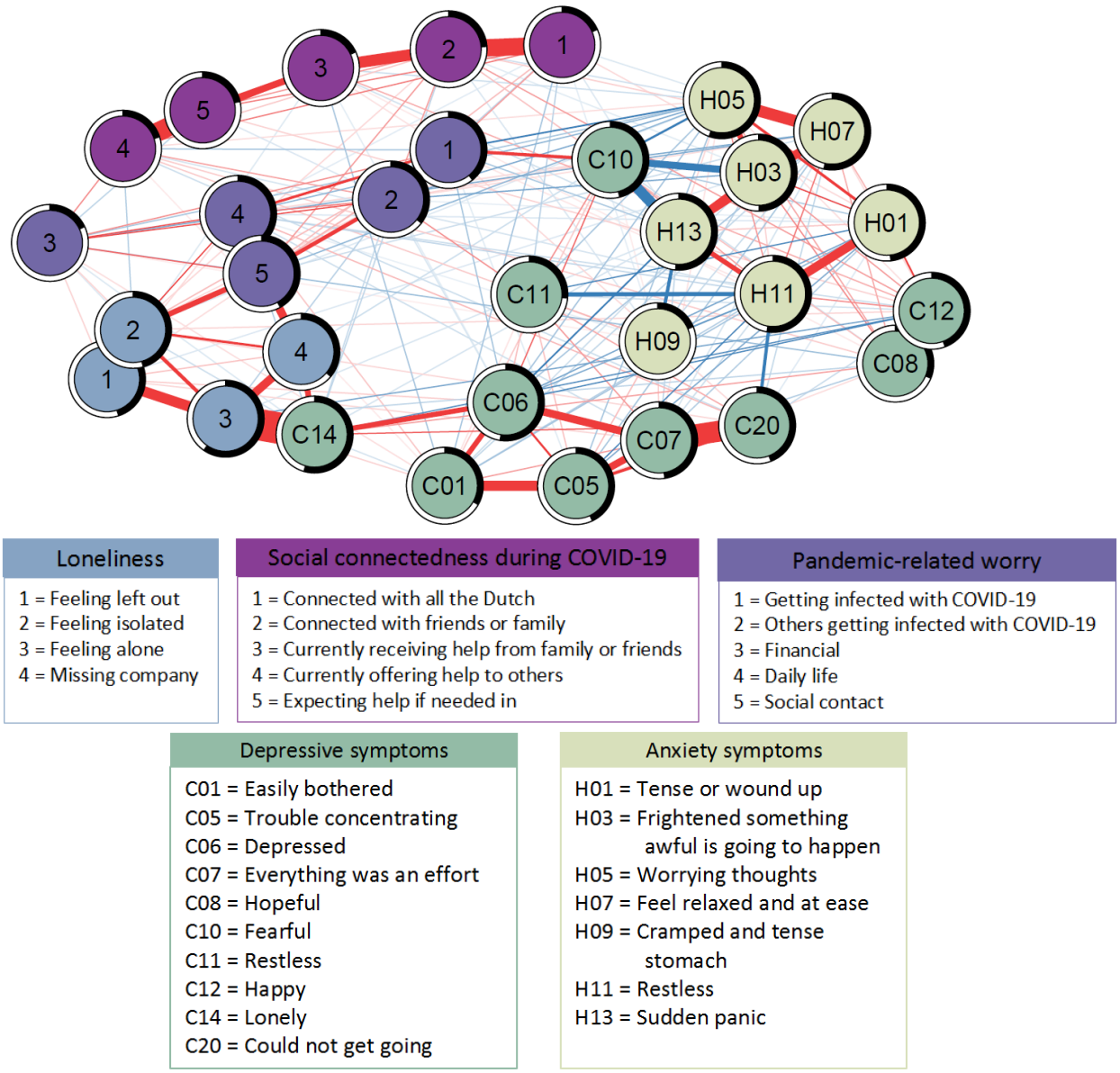
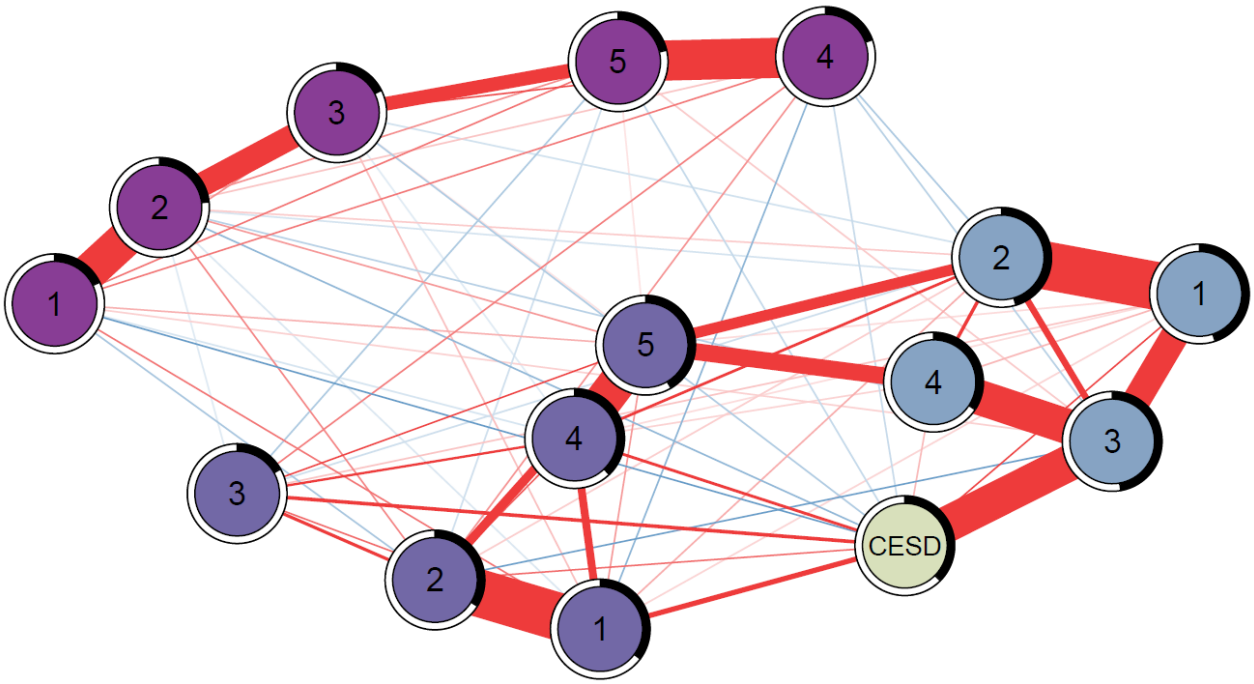


Figure 3

The estimated network of depressive symptoms, anxiety symptoms, items of loneliness, items of social connectedness, and items of pandemic-related worry. Each variable is represented by a node in the network. Direct, conditional positive associations (red) and negative associations (blue) between variables are indicated with edges. Strength of the association is indicated by thickness of the edge, using a correlation value of 0.1 as maximum value reference point. For each node the predictability, indicating the proportion of variability that is explained by other variables in the network, is presented as a ring around the node. A completely filled ring indicates all variance of a variable can be explained by the other variables in the network, whereas an empty ring indicates none of the variance is explained.

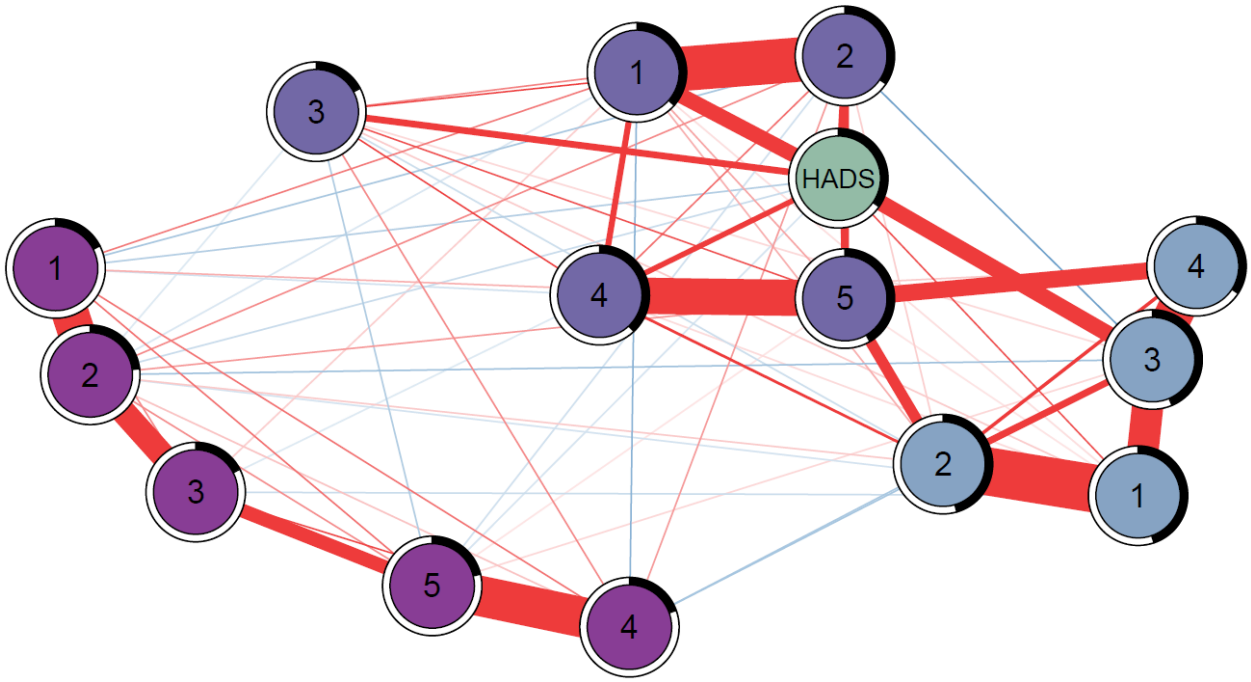
Supplements



Loneliness	Social connectedness during COVID-19	Pandemic-related worry
1 = Feeling left out	1 = Connected with all the Dutch	1 = Getting infected with COVID-19
2 = Feeling isolated	2 = Connected with friends or family	2 = Others getting infected with COVID-19
3 = Feeling alone	3 = Currently receiving help from family or friends	3 = Financial
4 = Missing company	4 = Currently offering help to others	4 = Daily life
	5 = Expecting help if needed in	5 = Social contact

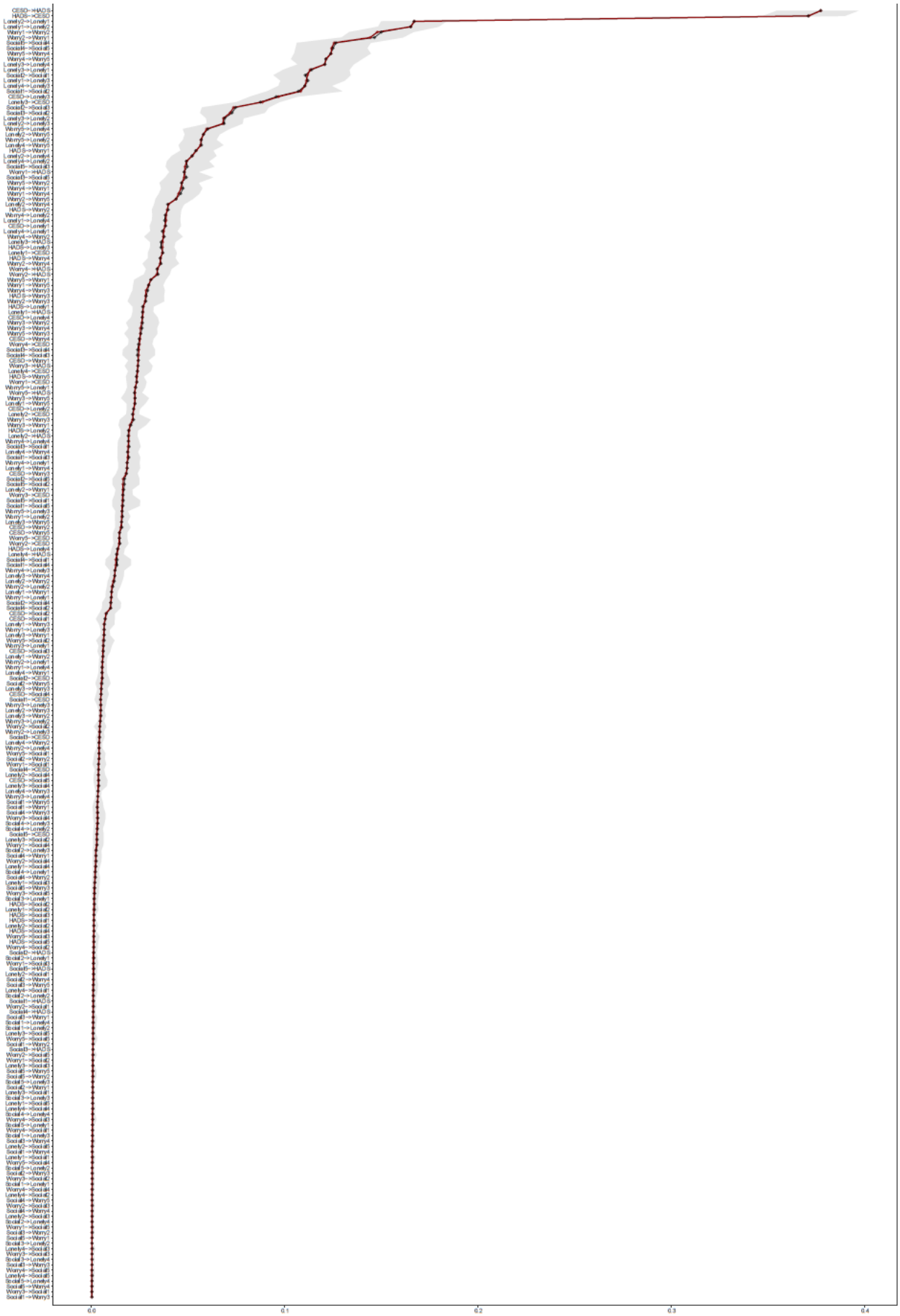
Supplementary Figure 1

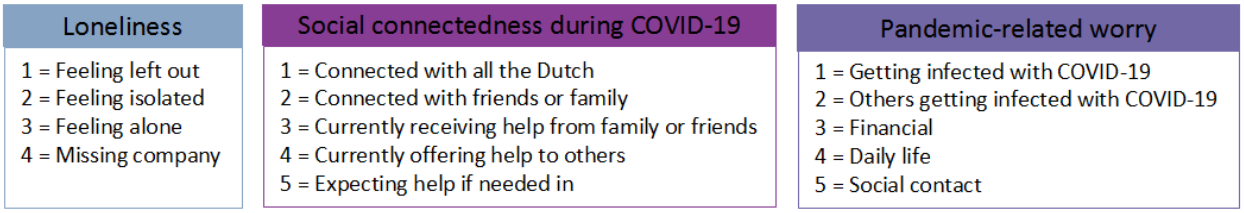
The estimated network of depressive symptoms score and items of loneliness, social connectedness, and worry. Each variable is represented by a node in the network. Direct, conditional positive associations (red) and negative associations (blue) between variables are indicated with edges. Strength of the association is indicated by thickness of the edge, using a correlation value of 0.1 as maximum value reference point. For each node the predictability, indicating the proportion of variability that is explained by other variables in the network, is presented as a ring around the node. A completely filled ring indicates all variance of a variable can be explained by the other variables in the network, whereas an empty ring indicates none of the variance is explained.



Supplementary Figure 2

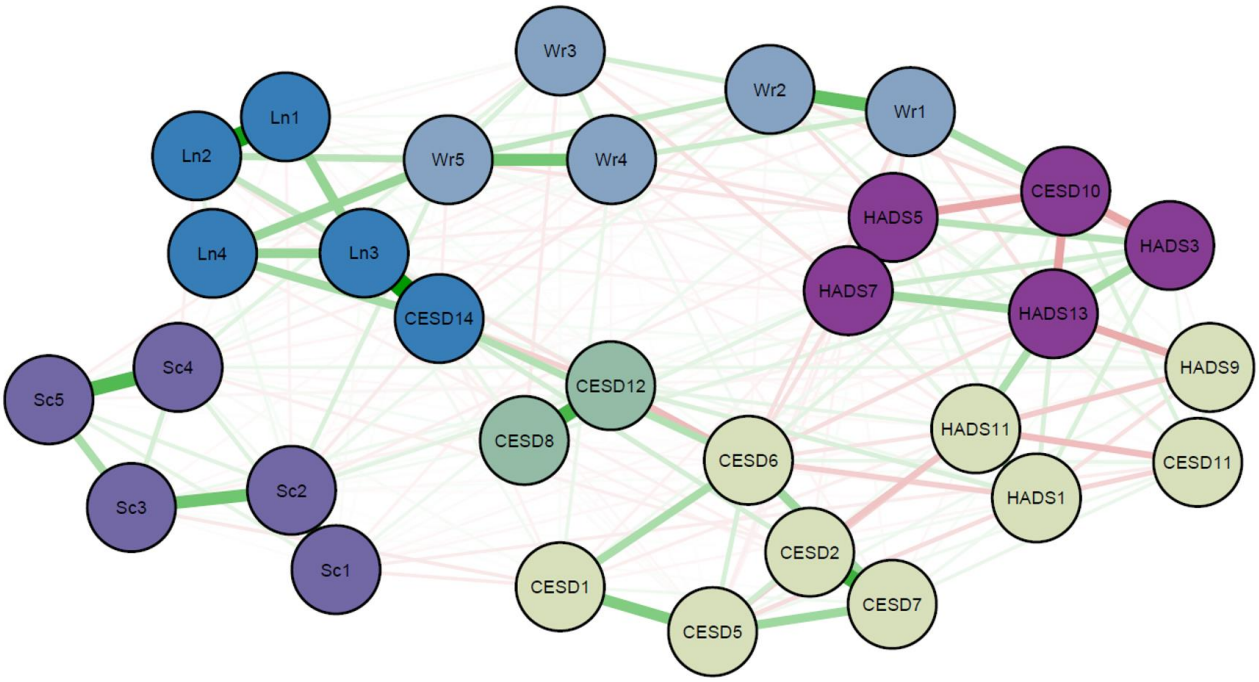
The estimated network of anxiety symptoms score and items of loneliness, social connectedness, and worry. Each variable is represented by a node in the network. Direct, conditional positive associations (red) and negative associations (blue) between variables are indicated with edges. Strength of the association is indicated by thickness of the edge, using a correlation value of 0.1 as maximum value reference point. For each node the predictability, indicating the proportion of variability that is explained by other variables in the network, is presented as a ring around the node. A completely filled ring indicates all variance of a variable can be explained by the other variables in the network, whereas an empty ring indicates none of the variance is explained.





Supplementary Figure 3

The bootstrapped confidence intervals of the estimated edge-weights in our network of depressive symptoms score, anxiety symptoms score and items of loneliness, social connectedness, and worry. The red line indicates the sample values, the black line the bootstrapped mean, and the gray area the bootstrapped CIs. The edges are ordered from the edge with the highest weight to the edge with the lowest weight.



Cluster 1

Ln1 = Feeling left out
Ln2 = Feeling isolated
Ln3 = Feeling alone
Ln4 = Missing company
CESD14 = Lonely

Cluster 2

Sc1 = Connected with all the Dutch
Sc2 = Connected with friends or family
Sc3 = Currently receiving help from family or friends
Sc4 = Currently offering help to others
Sc5 = Expecting help if needed in

Cluster 3

CESD10 = Fearful
HADS3 = Frightened something awful is going to happen
HADS5 = Worrying thoughts
HADS7 = Feel relaxed and at ease
HADS13 = Sudden panic

Cluster 4

Wr1 = Getting infected with COVID-19
Wr2 = Others getting infected with COVID-19
Wr3 = Financial
Wr4 = Daily life
Wr5 = Social contact

Cluster 5

CESD1 = Easily bothered
CESD5 = Trouble concentrating
CESD6 = Depressed
CESD7 = Everything was an effort
CESD11 = Restless
CESD2 = Could not get going
HADS1 = Tense or wound up
HADS9 = Cramped and tense stomach
HADS11 = Restless

Cluster 6

CESD8 = Hopeful
CESD12 = Happy

Supplementary Figure 4

The estimated network of depressive symptoms score, anxiety symptoms score, and items of loneliness, social connectedness, and worry. Items with the same color cluster together, as estimated using the EGA Walktrap clustering algorithm.

6

GENERAL DISCUSSION

Image by Viki B from Pixabay

Even though the association between sleep and mental health has been studied extensively, the temporality of these associations and what aspects of sleep in particular are involved remains to be determined. In this thesis I aimed to gain insight on how sleep is associated with mental health outcomes in a population-based cohort of middle-aged and elderly persons. I assessed the longitudinal association of self-reported sleep quality, actigraphy-estimated sleep, and polysomnography (PSG) measures with depressive symptoms, complicated grief, tinnitus, and functioning of the stress system. In this chapter I discuss the main findings of this thesis. Furthermore, the methodological considerations, clinical implications, and directions for future research will be addressed.

Main findings

Sleep, 24-hour activity rhythms, and mental health

For many decades poor sleep has been associated with poor mental health.[1,2] Within chapter 2.1 I showed that disturbed 24-hour activity rhythms are also associated with several mental health outcomes, including depression, anxiety and psychosis, based on reviewing recent literature. Poor sleep was long thought to be a consequence of poor mental health. However, over the past decades poor sleep and disturbed 24-hour activity rhythms have also been recognized as a potential risk factor, rather than merely a consequence of psychopathology.[3-5] To gain insight in the temporality of the association between sleep and mental health, I performed multiple longitudinal studies in a population-based setting. In chapter 2.2 I observed a longitudinal association of more fragmented 24-hour activity rhythms, long time in bed, low actigraphy-estimated sleep efficiency, long actigraphy-estimated sleep onset latency, and poor self-reported sleep quality with more depressive symptoms over time. Vice versa I observed that more depressive symptoms at baseline were associated with more fragmented 24-hour activity rhythms, long time in bed, low actigraphy-estimated sleep efficiency, long actigraphy-estimated sleep onset latency, and poor self-reported sleep quality over time. Together these findings suggest a bidirectional association of poor sleep and disrupted 24-hour activity rhythms with more depressive symptoms. In chapter 2.3 I observed a cross-sectional association of poor actigraphy-estimated sleep, including a low sleep efficiency, long sleep onset latency, long wake after sleep onset, and a poor self-reported sleep quality with more grief symptoms in those that indicated any grief after the loss of a loved one. Additionally, an association of short total sleep time, low sleep efficiency, long

sleep onset latency, long wake after sleep onset latency, poor self-reported sleep quality, and a delayed 24-hour activity rhythm at baseline with a higher risk on complicated grief compared to non-complicated grief over time was observed. The time between measuring grief symptoms and the occurrence of the loss varied substantially across participants experiencing grief, both at baseline and at follow-up. As grief can only be assessed after a loss we could not correct for grief at baseline across the analyses, persons who experienced grief at follow-up may not have experienced a loss at baseline. From an epidemiological perspective it is therefore it is debatable whether we can call these analyses truly longitudinal. We were however mainly interested to see whether sleep disturbances at baseline disrupt grief at a later point in time, independent of the cause of sleep disturbance at baseline.

These studies showed that specifically self-reported sleep quality was strongly associated with both depressive symptoms and complicated grief, based on comparison of the standardized effect estimates of different sleep measures. In line with previous literature,[6,7] an explanation for these findings is that poor sleep experience is more strongly associated with altered mental health compared to objective sleep estimates. An alternative explanation for the weaker associations of objective sleep with mental health could be habitation to the altered mental health state. Previous literature showed that, over time, people learn to cope with their mental health problem and objective sleep estimates tend to improve, whereas sleep experience remains poor.[8]

Furthermore, our results implicate that the temporal relation between actigraphy-estimated sleep and complicated grief cannot entirely be attributed to the association between complicated grief and depressive symptoms. This implication was based on stable effect sizes for the longitudinal associations between sleep and complicated grief after additional correction for depressive symptoms. This is not as was expected because depression and complicated grief share many symptoms, including poor sleep.[9] However, cross-sectional the effect sizes for the association between sleep and complicated grief were attenuated, suggesting that overlap of symptoms plays an important role when grief and depressive symptoms are measured concurrently.

Sleep, tinnitus, and mental health

A disease that has been frequently linked to poor sleep as well as poor mental health is tinnitus.[10] In order to gain more insight in the association between sleep, tinnitus, and mental health problems in those with tinnitus, I conducted two studies. In chapter 3.1 I observed a cross-sectional association of tinnitus with more anxiety symptoms, depressive symptoms, and a poor self-reported sleep quality. These associations were observed in participants who indicated tinnitus that impaired their daily life, as well as in those who indicated tinnitus did not impaired their daily life. However, effect estimates were stronger in those who indicated tinnitus impaired their daily life. Furthermore, results of an exploratory longitudinal analysis suggested that tinnitus impairing daily life at baseline was associated with more anxiety symptoms, more depressive symptoms and poorer self-reported sleep over time. However, due to limited power I was not able to draw any conclusions based on the observed longitudinal associations. In chapter 3.2 I observed tinnitus was cross-sectionally associated with longer self-reported sleep onset latency from a sleep diary, but not with actigraphy-estimated measures for sleep or 24-hour activity rhythms. Together, these studies implicate that tinnitus is associated with sleep experience, depressive symptoms and anxiety, but not with objectively estimated sleep. These findings support previous literature, stating that tinnitus has a major psychological component.[11] Poor sleep itself has been reported as a risk factor for poor mental health.[12] Therefore, in those with tinnitus poor sleep experience might even further alter mental health or vice versa, poor mental health might even further alter sleep experience. Potentially, a poor sleep experience may even act as a mediator in the association of tinnitus with depressive symptoms and anxiety. However, within the studies described in this thesis it was not possible to distinguish to what extend poor sleep was a mediator in the association of tinnitus with depressive symptoms and anxiety. Nevertheless, based on the observed results, I suggest that tinnitus treatment could benefit from early intervention on sleep experience to prevent mental health problems.

When studying tinnitus it is important to take hearing loss into account, as this is an important predictor for tinnitus and can potentially be used to identify different types of tinnitus patients.[13] To estimate the impact of hearing loss on the association between tinnitus and sleep I stratified our results for hearing loss in both studies. In chapter 3.1 I observed that in those with hearing loss, tinnitus was associated with more depressive symptoms, more anxiety, and poorer self-reported sleep quality. This applied to those for whom tinnitus

impaired daily life, as well as those who indicated tinnitus did not impaired their daily life. In participants without hearing loss, tinnitus impairing daily life was associated with more depressive symptoms and more anxiety symptoms, whereas tinnitus not impairing daily life was associated with poorer self-reported sleep quality. These findings could implicate that depressive symptoms and anxiety symptoms are experienced as interfering with daily life, but that sleep problems are interpreted as part of the disease and therefore not reported as interfering with daily life. In chapter 3.2 I observed an association of tinnitus with lower stability of 24-hour activity rhythms, shorter self-reported total sleep time, and longer self-reported sleep onset latency in those with hearing loss, but with higher stability in those without hearing loss. Furthermore, tinnitus severity was associated with longer wake after sleep onset in those with hearing loss, but not in those without hearing loss. Based on these observations I speculate that there might be different types of tinnitus patients and that hearing loss affects the association between tinnitus and poor sleep.

Sleep and the stress system

Hyperarousal and stress have been reported as a potential cause of poor sleep.[14,15] Vice versa, only few studies have been devoted to uncover whether poor sleep could also be a risk factor for deregulation of the stress system. With this study I aimed to gain insight in the association between sleep and functioning of the stress system, by analyzing a broad spectrum of sleep estimates in relation to cortisol response to a very-low dose of dexamethasone. In chapter 4.1 I observed a longitudinal association of more fragmented and less stable 24-hour activity rhythms and poor self-reported sleep quality at baseline with an enhanced response to dexamethasone, indicating a stronger suppression of cortisol. These results suggest disrupted 24-hour activity rhythms and poor self-reported sleep quality at baseline are associated with altered functioning of the Hypothalamic-Pituitary-Adrenal (HPA) axis over time. In chapter 4.2 I observed a cross-sectional association of more deep sleep, at the expense of time spent in lighter sleep, with an enhanced cortisol response to dexamethasone. After taking into account Diabetes Mellitus and the apnea-hypopnea index, also a long actigraphy-estimated sleep onset latency was associated with an enhanced response to dexamethasone.

The association between sleep and the stress system has been previously linked to depressive symptoms.[16,17] Interestingly, in this thesis the results described for actigraphy-estimated

sleep and PSG-measured sleep did not change after exclusion of those with clinically relevant depressive symptoms or those who indicated use of psychoactive medicine. These findings implicate that sleep is associated to functioning of the HPA axis, independent of depressive symptoms. In chapter 4.2, I discussed that depression might still affect the association between sleep and the stress system, but that this impact could differ between different types of depression or sleep complaints.[16] This is further supported by growing evidence stating that even though most types of depression are associated with diminished functioning of the HPA axis, some types of depression are associated with enhanced functioning of the HPA axis.[18] In this way different types of depression potentially nullify each other's impact on the association between sleep and functioning of the stress system. I was not able to confirm whether this hypothesis was supported in our studies, because in the population-based sample that was used for the studies described in this thesis the incidence of different types of depression was too low. Furthermore, previous literature has mentioned functioning of the HPA axis as a common cause[14] and a mediator[19,20] of the association between sleep and mental health, rather than a consequence of poor sleep. Altogether, the causal direction of the observed associations between sleep, functioning of the HPA axis and depressive symptoms remain largely unclear. Likely, a complex network of bidirectional associations and biological mechanisms is at play.

Psychosocial health during the COVID-19 lockdown

During the global COVID-19 pandemic the attention on mental health has grown. Many articles were published stating that mental health was significantly poorer as a consequence of the COVID-19 pandemic and the lockdown strategies that it was accompanied by.[21-23] This led me wondering how different psychosocial health factors are associated to one another during a pandemic-related lockdown, what factors affect our mental health the most, and whether this is different for different age groups and sexes. To be able to visualize all associations at the same time and overcome difficulties in analyzing comorbid conditions I chose to use network analyses.[24,25] In chapter 5.1 I observed that within a network of multiple aspects of psychosocial health, a higher depressive symptom score was particularly associated with items of loneliness and social connectedness during COVID-19, whereas a higher anxiety score was particularly associated with items of pandemic-related worry. These findings might be explained by similarity of constructs that I observed to be associated. For

example, loneliness, social connectedness, and depression are constructs based more on self-worth and avoidance,[26,27] whereas worry and anxiety are based more on hyperarousal.[28] When symptoms of depression and anxiety were included in the network as separate items, multiple clusters of items could be identified; a cluster for items of loneliness, a cluster for items of social connectedness, a cluster for items of pandemic-related worry, and a cluster for items of anxiety. Items for depression were less clustered, and more spread throughout the network. These observations implicate that depressive symptoms are important in connecting different constructs. Because of the strong correlation of depressive symptoms with especially anxiety symptoms,[29,30] comorbid symptoms are however likely to occur over time.

In chapter 5.1 I additionally observed that the structure of the network of psychosocial health factors significantly differed between sex and age groups. In middle-aged participants, opposed to older participants, the network structure was denser, implicating that the lockdown has a stronger impact on the psychosocial network of these middle-aged participants. Furthermore, it seemed that in women depressive and anxiety symptoms were more strongly associated with the social aspects, whereas in men practical aspects, like financial security, seemed more important. These findings could implicate that women are more vulnerable to experience social distress, whereas men are more vulnerable to experience distress about practical issues, supported by gender-related personality traits.[31] However, based on our study, I was not able to assess how the psychosocial network develops over time and determine the long-term impact of the lockdown on psychosocial health.

Methodological considerations

The value of subjective experience in sleep research

For most physiological determinants it is possible to assess objective estimates, because we are able to perform for example a blood test, analyse a saliva sample, or run an ultra-sound. In the field of psychiatric epidemiology, however, we have to rely almost completely on the self-reported experience of symptoms by study participants. Even though biological psychiatry, the science studying the biology behind mental health, has significantly improved our understanding of the nature behind psychopathology over the years, for most mental health constructs no biological markers have been identified that can be used to objectively

estimate presence of symptoms or clinical diagnosis.[25,32,33] Sleep is one of few constructs which can be estimated both subjectively, using a questionnaire or sleep diary,[34] and objectively, using actigraphy or PSG.[35-37] It is however important to keep in mind that these objective measures of sleep are possible because sleep is not solely a mental health construct, but rather a multidimensional construct cutting across specialisms.[38]

In general, using objective estimates is deemed more reliable then use of self-reported data, because self-reported estimates are more prone to bias.[39] In epidemiology there are three types of bias: selection bias, confounding bias, and information bias.[40] Selection bias is introduced if certain participants are more likely to participate in the study or in case of incomplete follow-up, confounding bias is caused by a shared cause between exposure and outcome.[40] In terms of epidemiological bias, information bias is potentially the most likely explanation for a discrepancy between self-reported and objective estimates. For one, self-reported data is accompanied by bias due to selective recollection and the way researchers ask the questions.[39,41,42] To overcome this bias, a first step might be to collect data prospectively on a day-to-day basis, for example by using a sleep diary or experience sampling methods,[43] rather than retrospectively using questionnaires asking about experience of symptoms in a specified period in time. In this way the observed findings cannot merely be explained by poorer recollection or differences in how questions were asked. However, also social desirability, mood, certain personality traits or demographic factors might induce a tendency to answer questions about health in a positive or negative way. For example, female sex and poor cognitive functioning were related to a larger discrepancy between objective and self-reported health.[41,44,45] Additionally, when a person is more aware of a particular aspect of their health, they are likely to be more conscious about other aspects of their health as well, which is called shared variance bias.[46,47] For example, a person who is suffering from a mental health problem, such as disturbed mood, is more likely to have an increased awareness about their health in general, making them for example more likely to report poor sleep.[48,49] Because the described measurement errors are more likely to occur in certain groups of participants this information bias is potentially non-random and therefore likely to induce substantial over- or underestimation of associations between self-reported mental health constructs.[40] Unfortunately information bias cannot be determined or corrected for

and should therefore be avoided by thorough study design and standardized data collection procedures.

In spite of the described information bias, it is important to note that objective sleep estimates and self-reported sleep measure different aspects of sleep and that self-reported data cannot just be replaced by or compared to objective estimates.[50] Where objective estimates reflect physiological abnormalities and provide insights in potential underlying biological mechanisms, self-reported measures may reflect more of the subjective experience of well-being.[7,47] Several studies tried to quantify measurement error of self-reported data by comparing self-reported sleep to objective sleep estimates,[45,50-52] using the objective measures as golden standard. However, by explaining all the observed discrepancy between objective and self-reported estimates to information bias, we neglect that it is plausible a discrepancy between self-reported experience and objective estimates might also be explained because different people truly experience their sleep differently. However, so far, it remains difficult to determine to what extent it is the subjective experience itself that is affected or only the way symptoms are reported.[42] We might need to accept that subjective experience does not need to be representative for objective estimates, but rather reflect a different construct. In this light, even though sleep experience differs from objectively measured sleep, this does not mean this subjective experience cannot be true or should be deemed unreliable.

Specifically in relation to mental health, the experience of sleep might be even more important than how we actually sleep. Within the Rotterdam Study sleep was assessed using PSG, actigraphy, sleep diaries, and questionnaires.[61] As this thesis was embedded in the Rotterdam Study, I was in the unique position to compare outcomes on all these different measures of sleep within the same population-based cohort of middle-aged and elderly persons. In most studies described in this thesis I particularly observed self-reported measures of sleep to be associated with other mental health outcomes. This is in line with previous literature, stating that subjective estimates tend to be more strongly related with mental health.[7] Besides the frequently confirmed association of self-reported sleep with mental health in a population-based setting,[6,53] there are also examples from clinical settings proving the importance of the subjective experience of sleep.[8,54] In relation to psychopathology, studies repeatedly reported a poor sleep experience as one of the most

important residual complaints after successful treatment, even after objective sleep estimates have improved.[8,55] This suggests that successful treatment of mental health symptoms or habituation to the mental health complaints over time are accompanied by improvement of objective sleep, but that sleep experience requires treatment to improve.[56] Also, it has been reported that some insomnia patients feel as if they sleep only a few hours per night, whereas objectively measured total sleep time was substantially longer.[54] Even though objective sleep is not disturbed, the poor sleep experience can cause substantial levels of stress and impairment of daily life in these patients.[48]

Altogether, researchers and clinicians should not forget the importance of sleep experience in relation to mental health now that objective estimates for sleep are becoming more easily accessible. Even if biological psychiatry enables researchers to use biomarkers for objective estimation of mental health in the future, we need to remember that objective sleep estimates and subjective sleep experience each assess a different aspect of sleep and therefore both are needed to get a complete understanding of sleep and how sleep is associated to other health outcomes.

The most clinically relevant way to study mental health: using a continuous scale of symptoms?

Everyone who has something to do with epidemiology has heard the story of John Snow, founder of modern epidemiological research by unravelling the source of a massive cholera outbreak in London in 1849.[57] Therefore, we can say the origin of epidemiology as we know today lays in infectious disease. For a long time epidemiological research stayed focused on how infectious disease spread through populations by comparing those who are infected to those who are not.[58,59] This scientific origin, combined with clinicians preferring a yes or no diagnosis to estimate whether therapy is required, resulted in a focus on clinical diagnoses. This clinical view on disease can be useful to estimate the incidence or prevalence of a disorder and also a diagnosis is often required to determine the most suitable therapy or to obtain reimbursement from the health insurance company. However, over time it became clear that in order to improve population health, it is important to study disease not only in a clinical setting, but also understand the biology behind sub-clinical disease.[58-60] To this cause many population-based cohorts were set-up, including the Rotterdam Study.[61] In the general

population, the number of participants with a clinical diagnosis is generally relatively small. Frequently, a much larger portion of the study population is suffering from sub-clinical symptoms. For example, in elderly the prevalence of insomnia is about 10-20%,[62,63] but up to 50% reported chronic sub-clinical sleep disturbance.[53,63] Growing evidence supports that these sub-clinical sleep disturbances could be an early symptom[1,64,65] or even a risk factor for development of psychopathology,[66] but also these subclinical problems in itself can impact quality of life. Therefore, studying the association of sub-clinical sleep disturbances with mental health outcomes could help prevention of mental health problems because it can provide valuable insights in the onset and early risk factors for psychopathology.

In a population-based setting, however, it can be difficult to obtain a correct and comparable mental health measure for all participants. Medical records often are unfit, because these records are created for clinical purposes and not for research per se. Moreover, there are substantial differences in diagnostic criteria that are used by general practitioners.[67,68] Also, because of stigma on mental health, mental health problems may not be discussed with a clinician or their general practitioner and therefore not diagnosed.[67] Frequently, because of large sample sizes, it is unfeasible to perform a clinical interview or get all participants diagnosed by a researching physician. A suitable alternative for studies with a large sample-size are questionnaires. Even though results are more prone to previously discussed information bias and cannot be used for diagnoses, use of validated questionnaires such as the Center for Epidemiological Studies Depression scale (CES-D),[69] Hospital Anxiety and Depression Scale (HADS),[70] or the Pittsburgh Sleep Quality Index (PSQI)[34] in the Rotterdam Study, enables researchers to assess comparable data for the entire cohort. The results of these questionnaires can be interpreted in two ways; (1) a weighted continuous sum-score, which is based on the number and severity of symptoms, or (2) a categorical score, based on a validated cut-off score. To determine what cut-off score can be used to identify those with clinically relevant symptoms most of these questionnaires have been validated using target populations.[71]

It might be tempting to use the cut-off score, as these categorized results are easier to interpret and seem potentially more clinically relevant. However, for most mental health outcomes the distinction between diseased and healthy can be difficult and is not without controversy.[25,71,72] Using the cut-off score implicates that there are only two groups of

participants: those with the disease and those without the disease. This is accompanied by the assumption that participants within a group are similar in terms of the mental health construct under study. In reality, however, there can be substantial differences between individuals of the same group. For example, using the CES-D to assess depressive symptoms, where the sum-score can range from 0 (no symptoms) to 60 (severe symptoms) and a cut-off score of 16 is used to define clinically relevant symptoms.[69] Both a person without any symptoms and a person with a score of 15 will be classified as "healthy". At the same time a person with relative mild symptoms, scoring 16, and a person with extremely severe complaints, scoring 60, will be classified as having the disease. Therefore, you could state that using a cut-off score reduces the required level of detail on your data. Moreover, forcing a continuous variable into a dichotomized or categorized variable introduces the risk of misclassification. This applies specifically to mental health, due to the previously described biases that are accompanied by self-reported data. Misclassification of either mental health as outcome or exposure might lead to dilution of the effect, in other words underestimation of the risk ratio.[73] Using the continuous sum-score puts data to its full potential, because all information is used and the risk on misclassification is reduced. In this way, it is possible to obtain more subtle, but not less important, insights on the association of mental health symptoms with other health outcomes across the entire spectrum. Therefore, using continuous variables allows researchers to detect smaller effects and in this way reveal potential new risk factors for mental health problems, which would have gone unnoticed by using a dichotomized score.

To summarize, thinking of mental health in terms of diagnosis can be useful in a clinical setting to determine the most suitable treatment option. However, studying mental health constructs using a continuous sum-score or even as individual symptoms enables researchers to get most value of their data and might improve our insight in the onset or recurrence of psychopathology.

Sleep as a potential biomarker for mental health

Biological psychiatry is bringing psychopathology and psychiatry closer together, by studying the biology underlying mental health. Due to recent efforts we understand more and more about the brain pathology and genetics behind multiple mental health constructs.[32,33] For

example spatial and temporal stability of the brain has been identified as potential brain biomarkers to improve our understanding of specific psychophysiological constructs.[33] Even though these studies have improved the insights in biomarkers to estimate the risk on psychopathology, biomarkers that can be used to objectively estimate presence of psychopathology or mental health symptoms are yet to be determined.[32,33]

Sleep could be a potential biomarker for psychopathology, because sleep disturbance is a symptom of many mental health disorders, as currently classified, and might even explain comorbidity.[1,4,5,74] Also, it is often said that sleep is a phenomenon that is from the brain to the brain, which is supported by changes in sleep being closely related to alterations of the brain.[75,76] Therefore, in order to improve our understanding of the biology behind mental health, and specifically the brain pathology, it would be useful to further explore sleep as a trans-diagnostic phenomenon in mental health by estimating how different aspects of sleep are associated to mental health. Due to recent efforts, as also presented in this thesis, we understand more about the association of sleep with mental health and also observed that different aspects of sleep seem to be at play for different mental health constructs.[1,5] In order to determine sleep estimates as a potential biomarker for mental health constructs we need to combine the findings of these studies. However, using conventional methods, such as regression analyses, it can be difficult to find the best way to take into account different mental health constructs and different aspects of sleep within the same model. For example, by simply adding other constructs as covariates to the model, overcorrection is likely due to the many overlapping symptoms between these constructs.[25,77] To put the knowledge on the association between sleep and mental health in a broader perspective there is need for studies using alternative methods, such as a trans-diagnostic approach. So far, several studies aimed to do so, for example by applying a meta-analyses comparing results from PSG-measured sleep in relation to several mental health outcomes, supporting disturbance of sleep continuity is a basic characteristic for mental health.[1] Another study explored the impact of sleep-based interventions on mental health outcomes in order to develop a trans-diagnostic treatment strategy.[74]

These studies however rely on the categorization of mental health constructs based on clinical observations. This view is also represented in the Diagnostic and Statistical Manual of Mental Disorders (DSM), which is currently the most used classification to diagnose

psychopathology.[78] The DSM is divided into different chapters, such as "*Bipolar and related disorders*", "*Depressive disorders*", and "*Anxiety disorders*", supporting the interpretation of mental health as distinct constructs with distinguishable, specific pathophysiology. However, there is growing skepticism towards the current classification of mental health constructs.[72,79,80] This critique is based on substantial overlap of symptoms between constructs and therefore frequently patients do not fit perfectly into one of the specified disorders or even in one of the specified constructs.[25,77] Additionally, the idea that for all people the same set of symptoms add up to a single diagnosis does not hold for most psychopathological constructs. In reality, most constructs are heterogenic and patients with the same diagnosis can have a substantially different course of disease with different symptoms.[25,72,81] Last, efforts from biological psychiatry have observed that underlying neurobiological mechanisms are not at all in line with the classification as presented in the DSM.[32,33] This emphasizes that further research to the nature behind mental health is required to develop a new biology-based classification. A first step to do so is the Research Domain Criteria (RDoC) initiative, aiming to unravel the nature behind mental health by studying varying levels of deregulation in both general psychology and biological systems.[82] This however does not mean the classification as presented in the DSM cannot be used, we only need to keep in mind that it is based on clinical observations of self-reported symptoms and not representative for psychopathology underlying mental health.[32,33]

To overcome difficulties with high comorbidity rates, overlapping symptoms, and heterogeneous disease patterns of mental health constructs in research, I speculate it might be worthwhile to study sleep in relation to mental health as a complex network of symptoms.[77,81] This trans-diagnostic approach can for example be realized by using the benefits of network analyses in future studies. Doing so could provide valuable insights of sleep estimates as a potential biomarker for specific mental health symptoms and potentially even provide directions for reclassification of mental health constructs. Network analyses allows researchers to overcome difficulties with comorbidity because it is possible to assess and visualize all associations at once within the same model and take into account all other variables in the network.[24,25] Additionally, network analyses could give insight in what symptoms are most important in relation to worsening of other symptoms by estimating what variables are most central in the network and have most connections to other variables.[25,81,83]

In this way researchers are enabled to estimate what aspects of sleep are most important in relation to specific mental health symptoms and whether sleep could be an important factor connecting clusters of symptoms from mental health constructs. Furthermore it is also possible to estimate whether the network structure is affected by other variables, such as sex, age, or educational background[84] and by plotting the same network repeatedly over time, it is also possible to determine how the network of psychological health factors evolves over time.[25] Nevertheless, results of network analyses are strongly dependent on the variables that are added to the model.[83,84] This can make it difficult to correctly take into account possible confounding bias and obtain reliable effect estimates. Therefore, in a population-based setting, this method might be specifically useful as a valuable tool to give insights in risk symptoms or sleep estimates as potential brain biomarkers for psychopathology and point out directions for further research.

Clinical implications

Based on the findings described in this thesis several implications for clinical practice and public health policies can be described. Our studies confirmed that poor sleep plays an important role in mental health in the general population. The longitudinal analyses in chapter 2.2, 2.3, and 4.1 of this thesis suggest poor sleep is not only the consequence of mental health problems, but could also be a risk factor for depressive symptoms, complicated grief, and altered functioning of the stress system in a population-based sample of middle-aged and elderly persons. These findings implicate that increased awareness of general practitioners about the importance of sleep and the potentially long-term beneficial impact of targeting poor sleep might be effective in prevention of psychopathology.

Furthermore, the findings described in this thesis implicate that subtle disturbances of sleep or 24-hour activity rhythms might be enough to significantly affect mental health. Because, even though all estimates in this thesis were based on symptoms of poor sleep in a population-based sample, and not clinical diagnosis, I still observed associations of poor sleep with mental health. Therefore I support prevention strategies where, instead of trying to treat clinical diagnosis, policy makers aim to improve sleep in the entire population. This so called ‘shifting-the-curve’ approach has its origin in Geoffrey Rose’s prevention theory[60] and might be a key step in so far unsuccessful attempts to improve mental health in the general population by targeting sub-clinical sleep disturbances.[85] Even though this approach has been

successfully applied to for example obesity prevention and for early detection of several types of cancer,[86] it has so far not been successfully implemented in mental health policies.[85] By shifting the distribution of sleep disturbances in the entire population, fewer people will be at risk for a clinical diagnosis of both sleep disorders as well as psychopathology.[60,87] Therefore, this strategy could benefit mental health in general because prevention might be easier than treatment of those with high disease burden, accompanied by complex pathology and difficulty of treating comorbid conditions.[25,85,88] A way to shift the curve could for example be promoting employers to be more flexible with office hours could be an important step towards better sleep, because people then will be able to sleep according to their own biological clock.[89] Another example is a national campaign informing about the harmful effect of using electronic devices on sleep, aiming to prevent use of these devices in the hours before bedtime or a campaign aiming to change the attitude of people towards the importance of healthy sleep, according to the health belief model.[38,90] Furthermore, increased awareness of general practitioners about the harmful effect of sub-clinical sleep disturbances, might improve treatment of these disturbances also in those without a clinical diagnosis.

Last, if we want to promote healthy sleep, it is important to acknowledge that sleep is more than only sleep duration. In sleep research there is a strong focus on total sleep time as the most important sleep construct.[91,92] However, sleep consists of many more constructs, such as sleep onset latency, wake after sleep onset, time in bed, and stability and fragmentation of 24-hour activity rhythms.[50] Based on the studies described in this thesis, combined with previous literature,[1] I suggest that different aspects of sleep are associated with different mental health constructs. This emphasizes that clinicians should be aware of the different aspects of sleep and not only focus on how long people sleep. For example, general practitioners should be more aware of the impact of prolonged sleep onset latency and disrupted 24-hour activity rhythms in development of mental health problems and in this light also take complaints such as difficulties falling asleep more serious as potential prodromal signs of psychopathology. Moreover, our studies presented in chapter 2, 3, and 4 together emphasize that sleep experience and 24-hour activity rhythms are more strongly associated with mental health opposed to objective estimates indicating how we actually sleep. These findings implicate researchers, clinicians as well as those involved in public health policy should value the sleep experience and sleep behavior in developing prevention or

intervention strategies for mental health problems. In this light the results described in this thesis support guidelines prescribing clinicians to focus on experience-based therapy, such as CBT-I,[93] mindfulness,[94] or changing sleep behavior,[95] rather than prescribe addictive sleep medication.[96]

Future directions for research

Our understanding of the role of sleep in mental health has improved substantially over the past decades.[4,12] Even though many studies have been devoted to unravel what aspects of mental health are associated to sleep, temporality and underlying biological mechanisms remain largely unclear. Within this thesis, I described several longitudinal studies, indicating sleep is associated with multiple mental health outcomes over time. However, in order to estimate causal directions and potential bidirectionality of the association between different aspects of sleep and mental health, long-term randomized control trials or longitudinal studies using at least three repeated measurements for both sleep and mental health are required.[97] These studies could additionally provide insights in potential moderation of factors such as functioning of the brain.

Our results additionally suggest that sleep experience plays an important role in other mental health constructs. However, it remains unclear to what extent the observed associations are affected by information bias or confounding. In order to overcome these types of bias we need to unravel what factors affect subjective sleep estimates and to what extent sleep experience itself is affected or only the way participants report their sleep. Studies combining in-depth interviews on sleep and sleep experience with objective measures of sleep, such as actigraphy, could be a first step to identify potential risk groups for poor sleep experience and strong disagreement between objective and subjective measures. Furthermore, estimating the experience of sleep using experience sampling methods might partly overcome information bias that is accompanied by self-reported data. These methods however have not been frequently integrated in research and require further study for validation and implementation in population-based cohorts.

We observed that for different mental health constructs it seems different aspects of sleep are at play.[1] Combined with common comorbidities of mental health constructs,[25,77] this indicates that the interaction of sleep with mental health is likely based on a complex network

of bidirectional associations,[25,81,98] which we will never be able to grasp by studying these associations in separate models. Therefore, to investigate sleep as a potential biomarker for mental health it would be helpful if more studies in a population-based setting will be conducted based on trans-diagnostic methods.[80] For example, a network approach or structural equation modeling enable researchers to study multiple associations between variables at once, taking into account overlap of symptoms and comorbidity.[24,25] These results could provide valuable insights required to unravel how different aspects of sleep are associated with mental health symptoms. In this way, we improve our understanding on what different aspects of sleep play a role in development of specific symptoms and potentially even get cues for underlying biological mechanisms of psychopathology. Furthermore, studying mental health as a network could reveal what aspects of sleep are most important in connecting other symptoms included in the network. By identifying how symptoms from different constructs are clustered in the network and what symptoms are most important in connecting clusters of symptoms, we might be able to unravel risk symptoms and thus develop interventions based on these early warning signals. Also, exploring use of sleep as a trans-diagnostic construct and the effect of sleep-based therapy in multiple psychological constructs could be useful to improve treatment efficiency and overcome difficulties of treating comorbid psychopathology.

Conclusion

While writing this thesis it became clear to me that poor sleep, specially the subjective experience of poor sleep, is a risk factor for development of mental health problems over time. Even though we still lack understanding on causal directions and potential mediation factors in the association between sleep and mental health, the findings of this thesis confirm that how we sleep objectively and, even more so, how we feel about our sleep are of great importance for a healthy life. To further improve our understanding on the role of sleep in mental health, researchers should dare to step away from conventional methods and try to focus more on early sleep disturbances in the general population and explore new methods such as network analyses. This knowledge, combined with increased awareness of clinicians and health care policy makers about the crucial role of poor sleep could be an important step in prevention of psychopathology.

References

1. Baglioni, C., et al., *Sleep and mental disorders: A meta-analysis of polysomnographic research.* Psychological bulletin, 2016. 142(9): p. 969.
2. Fredrickson, P.A., et al. *Sleep disorders in psychiatric practice*. in *Mayo Clinic Proceedings*. 1990. Elsevier.
3. Morin, C.M. and J.C. Ware, *Sleep and psychopathology.* Applied and Preventive Psychology, 1996. 5(4): p. 211-224.
4. Watling, J., et al., *Sleep loss and affective functioning: more than just mood.* Behavioral sleep medicine, 2017. 15(5): p. 394-409.
5. Wulff, K., et al., *Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease.* Nature Reviews Neuroscience, 2010. 11(8): p. 589.
6. Gould, C.E., et al., *Subjective but not objective sleep is associated with subsyndromal anxiety and depression in community-dwelling older adults.* The American Journal of Geriatric Psychiatry, 2018. 26(7): p. 806-811.
7. Maglione, J.E., et al., *Subjective and objective sleep disturbance and longitudinal risk of depression in a cohort of older women.* Sleep, 2014. 37(7): p. 1179-1187.
8. Pyrke, R.J.L., et al., *Evidence-Based Design Features Improve Sleep Quality Among Psychiatric Inpatients.* HERD: Health Environments Research & Design Journal, 2017. 10(5): p. 52-63.
9. Kristensen, P., K. Dyregrov, and A. Dyregrov, *What distinguishes prolonged grief disorder from depression?* Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin, ny raekke, 2017. 137(7): p. 538-539.
10. Langguth, B., et al., *Tinnitus: causes and clinical management.* The Lancet Neurology, 2013. 12(9): p. 920-930.
11. Cima, R.F.F., et al., *A multidisciplinary European guideline for tinnitus: diagnostics, assessment, and treatment.* Hno, 2019. 67(1): p. 10-42.
12. Hertenstein, E., et al., *Insomnia as a predictor of mental disorders: a systematic review and meta-analysis.* Sleep medicine reviews, 2019. 43: p. 96-105.
13. Haider, H.F., et al., *Pathophysiology of Subjective Tinnitus: Triggers and Maintenance.* Front Neurosci, 2018. 12: p. 866.
14. Bao, Y.P., et al., *Cooccurrence and bidirectional prediction of sleep disturbances and depression in older adults: meta-analysis and systematic review.* Neuroscience & Biobehavioral Reviews, 2017. 75: p. 257-273.
15. Kalmbach, D.A., et al., *Hyperarousal and sleep reactivity in insomnia: current insights.* Nature and science of sleep, 2018. 10: p. 193.
16. Antonijevic, I. and I. Antonijevic, *HPA axis and sleep: identifying subtypes of major depression.* Stress, 2008. 11(1): p. 15-27.
17. Asarnow, L.D., *Depression and Sleep: What has the treatment research revealed and could the HPA Axis be a potential mechanism?* Current Opinion in Psychology, 2019. 34: p. 112-116.

18. Zorn, J.V., et al., *Cortisol stress reactivity across psychiatric disorders: a systematic review and meta-analysis.* Psychoneuroendocrinology, 2017. 77: p. 25-36.
19. Murri, M.B., et al., *HPA axis and aging in depression: systematic review and meta-analysis.* Psychoneuroendocrinology, 2014. 41: p. 46-62.
20. Asarnow, L.D., *Depression and sleep: what has the treatment research revealed and could the HPA axis be a potential mechanism?* Current Opinion in Psychology, 2020. 34: p. 112-116.
21. Smith, L., et al., *Correlates of symptoms of anxiety and depression and mental wellbeing associated with COVID-19: a cross-sectional study of UK-based respondents.* Psychiatry Research, 2020: p. 113138.
22. Smith, B.J. and M.H. Lim, *How the COVID-19 pandemic is focusing attention on loneliness and social isolation.* Public health research & practice, 2020. 30(2): p. 3022008.
23. Ozamiz-Etxebarria, N., et al., *Psychological Symptoms During the Two Stages of Lockdown in Response to the COVID-19 Outbreak: An Investigation in a Sample of Citizens in Northern Spain.* Frontiers in Psychology, 2020. 11: p. 1491.
24. Blanken, T.F., et al., *The role of stabilizing and communicating symptoms given overlapping communities in psychopathology networks.* Scientific reports, 2018. 8(1): p. 1-8.
25. Nuijten, M.B., et al., *Mental disorders as complex networks: an introduction and overview of a network approach to psychopathology.* Clinical Neuropsychiatry, 2016. 13(4/5): p. 68-76.
26. Spence, R., C. Jacobs, and A. Bifulco, *Attachment style, loneliness and depression in older age women.* Aging & mental health, 2020. 24(5): p. 837-839.
27. Ypsilanti, A., et al., *Self-disgust, loneliness and mental health outcomes in older adults: an eye-tracking study.* Journal of affective disorders, 2020. 266: p. 646-654.
28. Hyde, J., K.M. Ryan, and A.M. Waters, *Psychophysiological markers of fear and anxiety.* Current psychiatry reports, 2019. 21(7): p. 1-10.
29. Pollack, M.H., *Comorbid anxiety and depression.* The Journal of clinical psychiatry, 2005. 66(suppl 8): p. 22-29.
30. Saade, Y.M., et al., *Comorbid anxiety in late-life depression: Relationship with remission and suicidal ideation on venlafaxine treatment.* Depression and anxiety, 2019. 36(12): p. 1125-1134.
31. Schmitt, D.P., et al., *Personality and gender differences in global perspective.* International Journal of Psychology, 2017. 52: p. 45-56.
32. van Praag, H.M., *Kraepelin, biological psychiatry, and beyond.* European archives of psychiatry and clinical neuroscience, 2008. 258(2): p. 29-32.
33. Fingelkurts, A.A. and A.A. Fingelkurts, *Brain space and time in mental disorders: paradigm shift in biological psychiatry.* The International Journal of Psychiatry in Medicine, 2019. 54(1): p. 53-63.

34. Buysse, D.J., et al., *Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI).* Sleep, 1991. 14(4): p. 331-338.
35. Ancoli-Israel, S., et al., *The role of actigraphy in the study of sleep and circadian rhythms.* Sleep, 2003. 26(3): p. 342-392.
36. Morgenthaler, T., et al., *Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007.* Sleep, 2007. 30(4): p. 519-529.
37. Iber, C., *The AASM manual for the scoring of sleep and associated events: Rules.* Terminology and Technical Specification, 2007.
38. Grandner, M.A., *Sleep, health, and society.* Sleep medicine clinics, 2017. 12(1): p. 1-22.
39. Althubaiti, A., *Information bias in health research: definition, pitfalls, and adjustment methods.* Journal of multidisciplinary healthcare, 2016. 9: p. 211.
40. Pearce, N., H. Checkoway, and D. Kriebel, *Bias in occupational epidemiology studies.* Occupational and environmental medicine, 2007. 64(8): p. 562-568.
41. Franz, C.E., et al., *Facets of subjective health from early adulthood to old age.* Journal of aging and health, 2017. 29(1): p. 149-171.
42. Sutin, A.R., et al., *Personality traits and the subjective and objective experience of sleep.* International journal of behavioral medicine, 2020. 27(4): p. 481-485.
43. van Os, J., et al., *The experience sampling method as an mHealth tool to support self-monitoring, self-insight, and personalized health care in clinical practice.* Depression and anxiety, 2017. 34(6): p. 481-493.
44. Kurspahić-Mujčić, A. and A. Mujčić, *The relationship between education and self-reported mental and physical health.* Medicinski Glasnik, 2019. 16(1).
45. Van Den Berg, J.F., et al., *Disagreement between subjective and actigraphic measures of sleep duration in a population-based study of elderly persons.* Journal of sleep research, 2008. 17(3): p. 295-302.
46. Hudson, A.J., *Consciousness: physiological dependence on rapid memory access.* Front Biosci (Landmark Ed), 2009. 14: p. 2779-800.
47. Mitrushina, M. and R. Tomaszewski, *The effect of subjective perception of cognition on emotional functioning in adults with long-term neurological and neuropsychiatric disorders.* Disability and rehabilitation, 2019: p. 1-7.
48. Riemann, D., et al., *The hyperarousal model of insomnia: a review of the concept and its evidence.* Sleep medicine reviews, 2010. 14(1): p. 19-31.
49. Brudzynski, S.M., *The ascending mesolimbic cholinergic system—a specific division of the reticular activating system involved in the initiation of negative emotional states.* Journal of Molecular Neuroscience, 2014. 53(3): p. 436-445.
50. Aili, K., et al., *Reliability of actigraphy and subjective sleep measurements in adults: the design of sleep assessments.* Journal of Clinical Sleep Medicine, 2017. 13(1): p. 39-47.

51. Biddle, D.J., et al., *Accuracy of self-reported sleep parameters compared with actigraphy in young people with mental ill-health.* Sleep health, 2015. 1(3): p. 214-220.
52. Buysse, D.J., et al., *Relationships between the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and clinical/polysomnographic measures in a community sample.* Journal of clinical sleep medicine, 2008. 4(06): p. 563-571.
53. Miner, B. and M.H. Kryger, *Sleep in the aging population.* Sleep medicine clinics, 2020. 15(2): p. 311-318.
54. Rezaie, L., et al., *Paradoxical insomnia and subjective–objective sleep discrepancy: A review.* Sleep medicine reviews, 2018. 40: p. 196-202.
55. Zajecka, J.M., *Residual symptoms and relapse: mood, cognitive symptoms, and sleep disturbances.* The Journal of clinical psychiatry, 2013. 74(suppl 2): p. 0-0.
56. Fava, M., *Pharmacological approaches to the treatment of residual symptoms.* Journal of Psychopharmacology, 2006. 20(3_suppl): p. 29-34.
57. McLeod, K.S., *Our sense of Snow: the myth of John Snow in medical geography.* Social science & medicine, 2000. 50(7-8): p. 923-935.
58. Frérot, M., et al., *What is epidemiology? Changing definitions of epidemiology 1978-2017.* PloS one, 2018. 13(12): p. e0208442.
59. Susser, E. and M. Bresnahan, *Origins of epidemiology.* Annals-new york academy of sciences, 2001. 954: p. 6-18.
60. Rose, G.A., K.-T. Khaw, and M. Marmot, *Rose's strategy of preventive medicine: the complete original text*. 2008: Oxford University Press, USA.
61. Ikram, M.A., et al., *Objectives, design and main findings until 2020 from the Rotterdam Study.* European Journal of Epidemiology, 2020. 35(5): p. 483-517.
62. Roth, T., et al., *Prevalence and perceived health associated with insomnia based on DSM-IV-TR; international statistical classification of diseases and related health problems, tenth revision; and research diagnostic criteria/international classification of sleep disorders, criteria: results from the America insomnia survey.* Biological psychiatry, 2011. 69(6): p. 592-600.
63. Patel, D., J. Steinberg, and P. Patel, *Insomnia in the elderly: a review.* Journal of Clinical Sleep Medicine, 2018. 14(6): p. 1017-1024.
64. Sadler, P., et al., *Cognitive behavior therapy for older adults with insomnia and depression: a randomized controlled trial in community mental health services.* Sleep, 2018. 41(8): p. zsy104.
65. Tazawa, Y., et al., *Actigraphy for evaluation of mood disorders: A systematic review and meta-analysis.* Journal of affective disorders, 2019.
66. Palmer, C.A. and C.A. Alfano, *Sleep and emotion regulation: an organizing, integrative review.* Sleep medicine reviews, 2017. 31: p. 6-16.
67. Verhaak, P.F.M., et al., *Patients with a psychiatric disorder in general practice: determinants of general practitioners' psychological diagnosis.* General hospital psychiatry, 2006. 28(2): p. 125-132.

68. Sperandeo, R., et al. *Complexity in the narration of the self A new theoretical and methodological perspective of diagnosis in psychopathology based on the computational method*. in *2019 10th IEEE International Conference on Cognitive Infocommunications (CogInfoCom)*. 2019. IEEE.
69. Radloff, L.S., *The CES-D scale: A self-report depression scale for research in the general population.* Applied psychological measurement, 1977. 1(3): p. 385-401.
70. Hinz, A. and E. Brähler, *Normative values for the hospital anxiety and depression scale (HADS) in the general German population.* Journal of psychosomatic research, 2011. 71(2): p. 74-78.
71. Taggart, F. and S. Stewart-Brown, *A Review of questionnaires designed to measure mental wellbeing.* Retrieved on, 2019. 25.
72. Kotov, R., et al., *The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies.* Journal of abnormal psychology, 2017. 126(4): p. 454.
73. Höfler, M., *The effect of misclassification on the estimation of association: a review.* International journal of methods in psychiatric research, 2005. 14(2): p. 92-101.
74. Harvey, A.G., et al., *Sleep disturbance as transdiagnostic: consideration of neurobiological mechanisms.* Clinical psychology review, 2011. 31(2): p. 225-235.
75. Bah, T.M., J. Goodman, and J.J. Iliff, *Sleep as a therapeutic target in the aging brain.* Neurotherapeutics, 2019. 16(3): p. 554-568.
76. Kondratova, A.A. and R.V. Kondratov, *The circadian clock and pathology of the ageing brain.* Nature Reviews Neuroscience, 2012. 13(5): p. 325-335.
77. Borsboom, D., et al., *The small world of psychopathology.* PloS one, 2011. 6(11): p. e27407.
78. Association, A.P., *Diagnostic and statistical manual of mental disorders.* 2013. 21(Edition, Fifth).
79. Etkin, A. and B. Cuthbert, *Beyond the DSM: development of a transdiagnostic psychiatric neuroscience course.* Academic Psychiatry, 2014. 38(2): p. 145-150.
80. Fusar-Poli, P., et al., *Transdiagnostic psychiatry: a systematic review.* World Psychiatry, 2019. 18(2): p. 192-207.
81. Borsboom, D., *A network theory of mental disorders.* World psychiatry, 2017. 16(1): p. 5-13.
82. Krueger, R.F. and C.G. DeYoung, *The RDoC initiative and the structure of psychopathology.* Psychophysiology, 2016. 53(3): p. 351-354.
83. Haslbeck, J.M.B. and L.J. Waldorp, *How well do network models predict observations? On the importance of predictability in network models.* Behavior research methods, 2018. 50(2): p. 853-861.
84. Jones, P.J., et al., *Network Model Trees.* 2019.
85. Purtle, J., et al., *Population-based approaches to mental health: history, strategies, and evidence.* Annual review of public health, 2020. 41: p. 201-221.

86. Marcotte, L.M. and D.C. Dugdale, *Prevention as a Population Health Strategy.* Primary Care: Clinics in Office Practice, 2019. 46(4): p. 493-503.
87. Murawski, B., et al., *A systematic review and meta-analysis of cognitive and behavioral interventions to improve sleep health in adults without sleep disorders.* Sleep medicine reviews, 2018. 40: p. 160-169.
88. Krawczyk, N., et al., *The association of psychiatric comorbidity with treatment completion among clients admitted to substance use treatment programs in a US national sample.* Drug and alcohol dependence, 2017. 175: p. 157-163.
89. Karatsoreos, I.N., *Effects of circadian disruption on mental and physical health.* Current neurology and neuroscience reports, 2012. 12(2): p. 218-225.
90. Irish, L.A., et al., *The role of sleep hygiene in promoting public health: A review of empirical evidence.* Sleep medicine reviews, 2015. 22: p. 23-36.
91. Itani, O., et al., *Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression.* Sleep medicine, 2017. 32: p. 246-256.
92. Irwin, M.R., R. Olmstead, and J.E. Carroll, *Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation.* Biological psychiatry, 2016. 80(1): p. 40-52.
93. Jansson-Fröjmark, M. and A. Norell-Clarke, *Cognitive behavioural therapy for insomnia in psychiatric disorders.* Current sleep medicine reports, 2016. 2(4): p. 233-240.
94. Rusch, H.L., et al., *The effect of mindfulness meditation on sleep quality: a systematic review and meta-analysis of randomized controlled trials.* Annals of the New York Academy of Sciences, 2019. 1445(1): p. 5.
95. Riemann, D., *Sleep hygiene, insomnia and mental health.* Journal of sleep research, 2018. 27(1): p. 3-3.
96. Riemann, D., et al., *European guideline for the diagnosis and treatment of insomnia.* Journal of sleep research, 2017. 26(6): p. 675-700.
97. Hernán, M.A. and J.M. Robins, *Estimating causal effects from epidemiological data.* Journal of Epidemiology & Community Health, 2006. 60(7): p. 578-586.
98. Epskamp, S. and E.I. Fried, *A tutorial on regularized partial correlation networks.* Psychological methods, 2018. 23(4): p. 617.

7

SUMMARY

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Summary

Sleep is one of our most important behaviors and is even vital for an individual's survival. Even though researchers have identified sleep to be associated with multiple health outcomes, and especially mental health, we do not exactly know why sleep is so important. It is likely sleep is not only a consequence, but also a cause for mental health problems. So far, however, only a limited number of studies have tried to identify temporality of these associations. Because poor sleep and mental health problems both frequently occur in the general population and have a major impact on global health, it is important to gain insight in the longitudinal associations between sleep and mental health in a population-based setting (**Chapter 1**). This thesis aimed to identify the role of subjective and objective sleep in development of mental health problems. To do so, we explored longitudinal associations of different indicators of sleep with mental health in a population-based cohort of middle-aged and elderly persons.

The aim of **chapter 2** was to gain insight in the longitudinal association of sleep and 24-hour activity rhythms with different mental health outcomes. **Chapter 2.1** reviewed recent studies investigating the association between 24-hour activity rhythms and health in elderly persons. Doing so, disturbed 24-hour activity rhythms were identified to be associated with multiple mental health outcomes, including depression, anxiety and psychosis. In **chapter 2.2** the longitudinal association of sleep with depressive symptoms, and vice versa, was estimated. This study confirmed a bidirectional association between more fragmented 24-hour activity rhythms, long time in bed, low sleep efficiency, long sleep onset latency, and poor self-reported sleep quality with more depressive symptoms. In **chapter 2.3** a cross-sectional association was identified of low sleep efficiency, long sleep onset latency, long wake after sleep onset, and a poor self-reported sleep quality with the number of grief symptoms in those that indicated any grief after the loss of a loved one. Additionally, short total sleep time, low sleep efficiency, long sleep onset latency, long wake after sleep onset latency, poor self-reported sleep quality, and a delayed 24-hour activity rhythm at baseline were longitudinally associated with a higher risk on complicated grief, compared to non-complicated grief, over time. Together these studies support that poor sleep and disturbed 24-hour activity rhythms are potential risk factors for development of psychopathology.

Chapter 3 focused on the association between tinnitus and sleep. First, in **chapter 3.1**, a cross-sectional association of tinnitus with anxiety symptoms, depressive symptoms, and poor self-

reported sleep quality was observed. After stratification for hearing loss, tinnitus was associated with more depressive symptoms, more anxiety, and poorer self-reported sleep quality in those with hearing loss. In participants without hearing loss, tinnitus impairing daily life was associated with more anxiety symptoms and more depressive symptoms, whereas tinnitus not impairing daily life was associated with poorer self-reported sleep quality. Second, **chapter 3.2** revealed a cross-sectional association with longer self-reported sleep onset latency from a sleep diary, but not with actigraphy-estimated measures for sleep or 24-hour activity rhythms. In those with hearing loss, tinnitus was associated with lower stability of 24-hour activity rhythms, shorter self-reported total sleep time, and longer self-reported sleep onset latency, and of tinnitus severity with longer wake after sleep onset. Whereas, in those without hearing loss tinnitus was associated with higher stability of 24-hour activity rhythms. Combined, the results of these studies suggest that specifically subjective sleep experience, rather than objective sleep estimates, are important in the association between tinnitus and sleep. Furthermore, these findings confirm that hearing loss is an important factor in the association between tinnitus and poor sleep.

Next, in **chapter 4**, the association between objective sleep and functioning of the stress system, assessed with cortisol response to a very-low dose of dexamethasone, was examined. **Chapter 4.1** confirmed a longitudinal association of more fragmented 24-hour activity rhythms, less stable 24-hour activity rhythms, and poor self-reported sleep quality at baseline with an enhanced response to dexamethasone, indicating stronger suppression of cortisol. **Chapter 4.2** identified a cross-sectional association of more deep sleep (N3), at the expense of time spent in lighter sleep, with enhanced cortisol response to dexamethasone. Together, these results implicate disrupted 24-hour activity rhythms, poor self-reported sleep quality, and more deep sleep were associated with altered functioning of the hypothalamic-pituitary-adrenal axis.

In **chapter 5** the aim was to gain insight in the complex network structure of psychosocial health factors during the first COVID-19 lockdown. Within a network including multiple aspects of psychosocial health, a higher depressive symptom score was particularly associated with items of loneliness and social connectedness. Whereas, within this same network, a high anxiety score was particularly associated with items of pandemic-related worry. Furthermore it was observed that the structure of the network of psychosocial health

factors significantly differed between sex and age groups. In middle-aged participants, opposed to older participants, we observed a denser network, suggesting the lockdown had a stronger impact on psychosocial health of middle-aged rather than older participants. Furthermore, women were more vulnerable to social distress, and men were more vulnerable to distress about practical issues. This supports that efforts for prevention and treatment need to be tailored to specific demographic groups.

Last, in **chapter 6** the main findings from these studies were summarized, methodological considerations were discussed, and implications for clinic application and future research were suggested.

Nederlandse samenvatting

Slaap is een van de belangrijkste basisfuncties. Een goede nachtrust is zelfs essentieel om te kunnen overleven. Ondanks dat onderzoekers bevestigd hebben dat slaap is geassocieerd met verschillende aspecten van gezondheid, met name mentale gezondheid, weten we niet precies waarom slaap zo belangrijk is. Het is bekend dat slechte slaap waarschijnlijk naast een gevolg, ook een oorzaak kan zijn van problemen rondom mentale gezondheid. Echter, het aantal studies dat de temporaliteit van deze associaties heeft onderzocht is beperkt. Omdat slechte slaap en problemen rondom mentale gezondheid veel voorkomen in de algemene populatie, met een grote impact op de wereldwijde gezondheid, is het belangrijk om meer inzicht te krijgen in longitudinale associaties tussen slaap en mentale gezondheid in een populatie-gebaseerde setting (**Hoofdstuk 1**). Het doel van dit proefschrift is om duidelijkheid te verkrijgen in de rol van subjectieve- en objectieve slaap in ontwikkeling van problemen met de mentale gezondheid. Derhalve zijn longitudinale associaties van verschillende aspecten van slaap met mentale gezondheid onderzocht in een populatie-gebaseerd cohort van mensen van middelbare leeftijd en ouderen.

Het doel van **hoofdstuk 2** was om inzicht te krijgen in hoe slaap en 24-uurs ritmes geassocieerd zijn met mentale gezondheid over tijd. **Hoofdstuk 2.1** is een review op basis van recente studies naar de associatie tussen 24-uurs ritmes en gezondheid in ouderen. Resultaten lieten zien dat verstoring van 24-uurs ritmes was geassocieerd met een slechtere gezondheid, waaronder mentale problemen zoals depressie, angst en psychoses. In **hoofdstuk 2.2** is de longitudinale associatie tussen slaap en depressieve symptomen onderzocht in beide richtingen. Deze studie toonde aan dat een meer gefragmenteerd ritme, langere tijd in bed, lage slaap efficiëntie, lange tijd tot inslapen, lange waak na inslapen en slechte zelf-gerapporteerde slaap bidirectioneel waren geassocieerd met meer depressieve klachten. In **hoofdstuk 2.3** werd aangetoond dat een lage slaap efficiëntie, lange tijd tot inslapen, lange waak na inslapen en slechte zelf-gerapporteerde slaap cross-sectioneel waren geassocieerd met het aantal rouwklachten in personen welke aangaven te rouwen om het verlies van een dierbare. Daarnaast werd aangetoond dat korte actigrafie-geschatte slaapduur, lange actigrafie-geschatte slaap efficiëntie, lange actigrafie-geschatte tijd tot inslapen, lange actigrafie-geschatte waak na inslapen, slechte zelf-gerapporteerde slaap cross-sectioneel, en een verlaat 24-uurs ritme op baseline longitudinaal waren geassocieerd

met een verhoogd risico op complexe rouw, ten opzichte van een niet verstoord rouwproces, over tijd. Deze studies samen bevestigen dat slechte slaap en verstoorde 24-uurs ritmes potentieel risicofactoren zijn voor het ontstaan van psychopathologie.

Hoofdstuk 3 richt zich op de associatie tussen tinnitus en slaap. Als eerst, toonde **hoofdstuk 3.1** een cross-sectionele associatie van tinnitus met angst symptomen, depressieve klachten en slechte zelf-gerapporteerde slaap. Na stratificatie voor gehoorverlies was tinnitus geassocieerd met angst symptomen, depressieve klachten en slechte zelf-gerapporteerde slaap bij personen met gehoorverlies. Bij personen zonder gehoorverlies was tinnitus waarbij het dagelijks leven was verstoord geassocieerd met meer angst symptomen en meer depressieve klachten, terwijl tinnitus zonder impact op het dagelijks leven was geassocieerd met een slechtere zelf-gerapporteerde slaap. Ten tweede, toonde **hoofdstuk 3.2**, dat tinnitus cross-sectioneel geassocieerd was met een langere zelf-gerapporteerde tijd tot inslapen uit het slaapdagboek, maar niet met actigraphy-geschatte maten voor slaap of 24-uurs ritmes. Na stratificatie voor gehoorverlies was tinnitus geassocieerd met een minder stabiel 24-uurs ritme, kortere zelf-gerapporteerde slaapduur en een langere zelf-gerapporteerde tijd tot inslapen en was de mate van tinnitus klachten geassocieerd met langere zelf-gerapporteerde waak na inslapen in personen met gehoorverlies. In personen zonder gehoorschade daarentegen was tinnitus juist geassocieerd met een meer stabiel 24-uurs ritme. Deze resultaten onderstrepen dat met name subjectieve slaap ervaring, en niet objectieve slaap, belangrijk is in de associatie tussen tinnitus en slaap. Daarnaast tonen deze bevindingen ook de belangrijke rol van gehoorverlies in de associatie tussen tinnitus en slaap.

Vervolgens werd in **hoofdstuk 4** de associatie tussen objectieve slaap en het functioneren van het stress systeem onderzocht, gemeten met cortisol reactie na een zeer-lage hoeveelheid dexamethason. **Hoofdstuk 4.1** bevestigde een longitudinale associatie van meer gefragmenteerde 24-uurs ritmes en slechte zelf-gerapporteerde slaap met een verhoogde reactie op dexamethason over tijd, wat een sterkere onderdrukking van cortisol suggereert. In **hoofdstuk 4.2** werd een cross-sectionele associatie van meer diepe slaap, ten koste van de tijd doorgebracht in lichtere slaap, met een verhoogde reactie op dexamethason aangetoond. Deze resultaten impliceren dat een verstoord 24-uurs ritme, slechte zelf-gerapporteerde slaap kwaliteit en meer tijd in diepe slaap zijn geassocieerd met een verstoorde functioneren van de hypothalamus-hypofyse-bijnier as.

In **hoofdstuk 5** was het doel om meer inzicht te krijgen in het complexe netwerk van psychosociale factoren tijdens de eerste COVID-19 lockdown. In een netwerk met meerdere aspecten van psychosociale gezondheid was de depressie somscore in het specifiek geassocieerd met aspecten van eenzaamheid en sociale verbondenheid, terwijl de angst somscore met name was geassocieerd met pandemie-gerelateerde zorgen. Ook toonde deze studie dat de structuur van het netwerk significant verschilde tussen groepen van verschillende leeftijd en geslacht. In personen van middelbare leeftijd was het netwerk compacter, ten opzichte van de netwerken in ouderen leeftijdsgroepen. Dit impliceert dat de lockdown een grotere impact heeft op personen van middelbare leeftijd dan op ouderen. Daarnaast toonde deze studie aan dat vrouwen meer vatbaar zijn voor sociale stress, terwijl bij mannen praktische zaken een grotere rol lijken te spelen. Deze resultaten ondersteunen dat preventie en behandeling aangepast moeten worden aan specifieke demografische groepen.

Ten slotte zijn in **hoofdstuk 6** de belangrijkste bevindingen van onze studies beschreven, overwegingen voor de methodiek bediscussieerd en suggesties gedaan voor toepassing van de bevindingen van dit proefschrift in een klinische setting en toekomstig onderzoek.

8

APPENDICES

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PhD Portfolio

Name PhD student: Maud de Feijter
Erasmus MC department: Epidemiology
Research school: NIHES
PhD period: July 2018 – April 2022

	Year	ECTS
MSc-program Epidemiology		
Introduction to Medical Writing	2019	2.0
Causal Inference	2019	1.4
Causal Mediation Analyses	2019	1.4
Advances in Clinical Epidemiology	2019	0.7
Social Epidemiology	2019	0.7
Fundamentals of Medical Decision Making	2019	0.7
Biostatistical Methods I: Basic principles	2018	5.7
Biostatistical Methods II: Classical Regression Models	2018	4.3
Study Design	2018	4.3
Principles of Causal Inference	2018	1.4
Principles of Research in Medicine and Epidemiology	2018	0.7
Methods of Public Health Research	2018	0.7
Introduction to Global Public Health	2018	0.7
Primary and Secondary prevention Research	2018	0.7
Elective courses, MSc		
Public Health Research: Analysis of Population Health	2019	1.9
Public Health Research: Analysis of Determinants	2019	1.9
Public Health Research: Intervention Development and Evaluation	2019	1.9
Repeated Measurements in Clinical Studies	2019	1.7
Missing Values in Clinical Research	2019	1.7
Intermediate Course in R	2019	1.4
Child Psychiatric Epidemiology	2019	0.9
Principles of Epidemiologic Data-analysis	2019	0.7
Other courses		
PhD course scientific integrity	2019	0.3
GWAS Blitz course	2019	1.0
ESRS Summer School	2019	1.4
(Inter)national conferences		
NSWO najaarssymposium, Virtual Congress	2020	0.3
SLAAP 2020, Virtual Congress	2020	1.0
ESRS 2020, Virtual Congress	2020	1.0
SLAAP 2019, Ermelo, Netherlands	2019	1.0
Kempenhaeghe, Heeze, Netherlands	2019	0.3
NSWO najaarssymposium, Amsterdam, Netherlands	2018	0.3

8.1

	Year	ECTS
Presentations		
Oral presentation: *The longitudinal association of sleep and 24-hour activity rhythms with cortisol response to a very low dose of dexamethasone* at SLAAP 2021	2021	1.0
Poster presentation: *The cross-sectional association between tinnitus and actigraphy-estimated sleep in a population-based cohort of middle aged and elderly persons* at SLAAP 2021	2021	1.0
Poster presentation: *The longitudinal association between sleep and complicated grief* at SLAAP 2020	2020	1.0
Oral presentation: *The longitudinal association between sleep and complicated grief* at ESRS 2020	2020	1.0
Poster presentation: *The bidirectional association between sleep and depressive symptoms* at SLAAP 2019	2019	1.0
Oral presentation : *The longitudinal association of sleep with depressive symptoms and complicated grief* at ESRS summer school 2019	2019	1.0
Oral presentation: *The bidirectional association between sleep and depressive symptoms* at Health Sciences Day for research departments of Erasmus MC	2019	1.0
Teaching – Supervising Master's theses		
Irash Gangapersad, Bachelor thesis, *Objective sleep and tinnitus*	2021	1.0
Athanasia Katimertzoglou, Master thesis, *Objective sleep and the stress system*	2020	2.0
Teaching – Other		
Hire and guide two bachelor student assistants for coding medical files	2019-2020	2.0
Other activities		
ERGO centrum – general tasks Rotterdam Study	2018-2022	
Data cleaning COVID-19 questionnaires	2020-2021	
Coding depression and anxiety from medical files, rater	2019-2020	
Actigraphy data cleaning	2018-2020	

List of publications and manuscripts

de Feijter M, Lysen TS, Luik AI. 24-h Activity Rhythms and Health in Older Adults. Current Sleep Medicine Reports 6, 76–83 (2020). https://doi.org/10.1007/s40675-020-00170-2

de Feijter M, O'Connor MF, Arizmendi B, Ikram MA, Luik AI. The longitudinal association of actigraphy-estimated sleep with grief in middle-aged and elderly persons. Journal of Psychiatric Research 137, 66–72 (2021). https://doi.org/10.1016/j.jpsychires.2021.02.042

de Feijter M, Kocevska D, Ikram, MA, Luik AI. The bidirectional association of 24-hour activity rhythms and sleep with depressive symptoms in middle-aged and elderly persons. Psychological Medicine, 1-8 (2021). https://www.doi.org/10.1017/S003329172100297X

de Feijter M, Tiemensma J, Ikram MA, Strickers BH, Luik AI. The longitudinal association of sleep and 24-hour activity rhythms with cortisol response to a very low-dose of dexamethasone, *submitted*

de Feijter M, Katimertzoglou A, Tiemensma J, Ikram MA, Luik AI. The association between polysomnography-estimated sleep and cortisol response after a very low-dose of dexamethasone, *submitted*

de Feijter M, Kocevska D, Blanken TF, van der Velpen IF, Ikram MA, Luik AI. The network of psychosocial health in middle-aged and older adults during the first COVID-19 lockdown, *submitted*

de Feijter M, Oosterloo BC, Goedegebure A, Luik AI. The cross-sectional association between tinnitus and actigraphy-estimated sleep in a population based cohort of middle aged and elderly persons, *submitted*

8.2

Oosterloo BC, de Feijter M, Croll PH, Baatenburg de Jong RJ, Luik AI, Goedegebure A. Tinnitus and mental health: cross-sectional and longitudinal associations in a population-based sample of middle-aged and elderly persons, JAMA Otolaryngology-Head & Neck Surgery (2021). https://doi.org/10.1001/jamaoto.2021.1049

Van der Velpen IF, de Feijter M, Raina R, Özel F, Ikram MA, Vernooij MW, Luik AI. Cortisol response after a very low-dose of dexamethasone is associated with brain structure in healthy older adults with depression or low perceived social support, *in preparation*

Mooldijk SS, Dommershuijsen LJ, de Feijter M, Luik AI, Trajectories of depression and anxiety during the COVID-19 pandemic in the general population in the Netherlands, *submitted*

Özel F, Hilal S, de Feijter M, van der Velpen IF, Direk N, Ikram MA, Vernooij MW, Luik AI. Association of neuroimaging markers with depressive symptoms over time in middle-aged and elderly persons, *submitted*

Licher S, Terzikhan N, Splinter M, Velek P, van Rooij F, Verkroost-van Heemst J, Haarman AEG, Thee EF, Geurts S, Mens MMJ, van der Schaft N, de Feijter M, Cortes L, Leening Kieboom B, Ikram MA. Design, implementation and initial findings of COVID-19 research in the Rotterdam Study: leveraging existing infrastructure for population-based investigations on an emerging disease, European Journal of Epidemiology (2021). https://doi.org/10.21203/rs.3.rs-634697/v1

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8.3

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8.4

About the author

Maud de Feijter was born on December 5, 1992 in Deventer, the Netherlands. After graduating from secondary school she started the Bachelor Biology at the Radboud University in Nijmegen, including a 3-month internship at the Donders Institute for Brain, Cognition and Behavior (supervision: prof. dr. R.J.A. van Wezel). During the bachelor she additionally obtained a teaching qualification for the subject of Biology. In 2015 she started the 2-year Master in Medical Biology. The first year focused on research, including a 9-month internship at the Donders Institute for Brain, Cognition and Behavior (supervision: dr. N. Kohn). The second year she choose to take the Science, Management and Innovation (SMI) track, including a 9-month internship at the National Institute for Public Health and the Environment (RIVM) (supervision: dr. I. van den Broek and dr. B. Knols). During the internship at the RIVM Maud developed her interest in Epidemiology. Nevertheless, she started with her job as junior data analyst/programmer at OCS Life Sciences in Den Bosch, after obtaining her Master of Science degree in 2017. After working there for 9 months she decided she wanted to go back to epidemiology. This is why she quit her job at OCS and started the work presented in this thesis in 2018 (supervision: Prof. dr. M.A. Ikram and dr. A.I. Luik). As a part of her PhD-trajectory, in 2020 she obtained a Master of Science in Health Sciences (epidemiology) at the Netherland Institute for Health Sciences (NIHES). Since April 2022, Maud is working as a scientific researcher at Lareb, pharmacovigilance centre.

Image by Ward Kleuskens