GENERAL DISCUSSION

This thesis discusses the role of sleep in neurodegenerative diseases and related brain outcomes, studied from a population perspective. Here I will discuss the main findings across studies, and highlight several methodological considerations relevant for interpreting our findings.

REVIEW OF FINDINGS

Sleep in the general population

We described self-reported sleep characteristics across all ages using population-based cohorts from the Netherlands, investigated their potential determinants and compared these sleep characteristics across countries and assessment methods (see Chapter 2.1). Using the National Sleep Foundation sleep duration recommendations[1] as a benchmark, we concluded that most people sleep for an acceptable duration. More importantly, sleep complaints or impaired sleep quality were more common than deviations of self-reported total sleep time from age-appropriate recommendations, across countries. Also, sleep characteristics assessed objectively through physiologic data systematically differed from subjective assessments.

Focusing on middle-aged and elderly individuals, an increased focus of research and public health professionals to increase sleep quality, not only duration,[2] seems relevant to improve sleep, and potentially related 'cognitive, physical and emotional health problems'[1] that may arise from poor sleep. However, we found that poor subjective sleep quality did not increase the risk of dementia in an elderly population. Recent studies showed that treating insomnia symptoms in adults through digital cognitive behavioral therapy for insomnia can reduce mental health problems,[3,4] of which application to older adults should be further studied. However, findings suggest that sleep problems when assessed subjectively are not necessarily related to an increased risk of all-cause dementia or Alzheimer's disease (see Chapter 3.1). This is not to say that ameliorating insomnia symptoms, or improving sleep quality, has no value.

Although most persons report a sleep duration deemed acceptable for their age, we could not adequately address questions regarding sleep deprivation, sleep debt or chronic sleep loss at a population level. These constructs are well not captured by one measurement of self-reported sleep characteristics. But more importantly, the discrepancy between self-reported and objective measurements[5] indicates that we are probably looking at more than sleep per se when judging self-reports on a population-based scale (also see Methodological considerations, paragraph on 'Subjective versus objective measurements'). Sleep characteristics that can be quantified using physiologic data, e.g. total sleep time, may be less adequately assessed using subjective, self-reported measurements.[5,6] It suggests we need to either recalibrate the whole debate to objec-

tive measures, or shift our focus more towards the constructs that are inherently validly measured through subjective appraisal.

Further research should investigate to what extent targeting individuals that report extreme durations or time in bed for their age and sex, or certain subgroups as those identified in this chapter, may yield improvement in sleep and well-being, and in health outcomes.

Sleep and dementia

We found no association of subjective sleep quality, measured with the Pittsburgh Sleep Quality Index (PSQI), with the risk of all-cause or Alzheimer's disease dementia over 13 years of follow-up (see Chapter 3.1). Moreover, PSQI components, including the often-investigated parameters of self-reported sleep duration and efficiency, were also not related to dementia risk. We discussed that potential biases do not seem to explain our negative findings, which are, however, largely inconsistent with meta-analyzed results.[7-9] On the one hand this suggests that chance may have played a role, on the other hand meta-analysis authors have cautioned for potential publication bias.[7] Interestingly, the most recent meta-analysis showed that there was no association of poor sleep with risk of cognitive disorders including dementia when the analysis was restricted to longer follow-up studies (>10 years). This suggests reverse causation, or the effect of preclinical or prodromal dementia on sleep at baseline, may have driven the largely positive results. Repeating survival analysis across studies, using our approach of time-stratified analyses on individual-level data may be an important next step to assess such effects (see Methodological considerations, paragraph 'Reverse causation').

While self-reported sleep quality was not associated with dementia risk, we found a relation of having objectively disturbed sleep with increased dementia risk (see Chapter 3.2). Evidently, subjective and objective measurements of sleep differ. Finding only an association using actigraphy-estimated sleep suggests that some disturbances are not recognized or not experienced as problematic by participants. Presence of prodromal subtle cognitive problems may hinder recognizing poor or short sleep, or contribute to downplaying issues with sleep, possibly to avoid further enquiry.[10] Yet, we cannot exclude that participants or their spouses may be aware of sleep problems relevant to dementia risk. Beyond awareness of sleep problems, we could also not determine to what extent prioritizing sleep, or negligence of sleep, contributed to increased dementia risk.

Besides sleep, we also investigated actigraphy-estimated 24-hour activity rhythms in relation to risk of dementia, identified as a knowledge gap in Chapter 2.2.[11-13] We found no relation of fragmented or unstable 24-hour activity rhythms with incident dementia or Alzheimer's disease. Yet, we found associations of a phase advance of sleep with incident dementia only in the next 2 years of follow-up, and of a stronger association of an

earlier 'lights out' time with incident dementia in short versus longer follow-up durations. These findings suggest that underlying neurodegeneration, or concomitant behavioral or neuropsychiatric disease features disturb the 24-hour activity rhythm closely before the diagnosis, not vice versa. This is not in line with prevailing interpretations of mostly cross-sectional data in previous reviews.[11-13] We feel repeated studies similar to ours are necessary. Also, future studies may consider investigating determinants of 'lights out' time as a novel indicator of dementia risk, with the objective to determine whether this symptom is indicative of behavior choices or of underlying circadian disruption.[14]

We discussed which neurobiological correlates may potentially confound the associations of actigraphy-estimated nighttime wakefulness and higher risk of dementia, especially Alzheimer's disease (see Chapter 3.2). Here, I provide a brief background for one potentially important factor hypothesized to have a bidirectional relation with sleep disturbances: Disease-related neurodegenerative pathology.

Alzheimer's disease is characterized pathologically by plaques of beta-amyloid and tau neurofibrillary tangles. When Alzheimer's disease is clinically diagnosed, patients (or relatives) often also report sleep or circadian disturbances. Such disturbances are not only a consequence of the disease but have been hypothesized to independently contribute to development of progression or the disease.[11-13,15-17] Studies have especially focused on the role of sleep, and extended wakefulness, in beta-amyloid metabolism. Animal studies show that beta-amyloid concentrations in interstitial fluid fluctuate with sleep and wake.[18] Sleep has been hypothesized to drive beta-amyloid clearance,[19] while wakefulness drives beta-amyloid production through neuronal activity.[20,21] Human observational and experimental studies mostly confirm this regulatory role of sleep on beta-amyloid concentrations,[22-28] and also sleep's role in regulating concentrations of pathological tau proteins relevant to Alzheimer's disease pathogenesis.[29-33] The relation of sleep disturbances with Alzheimer's disease pathology is likely bidirectional.[15]

Against this background, determining an association of sleep with incident neurodegenerative disease requires accounting for neurodegenerative pathology at baseline to obtain unbiased results. We discussed the possibility of such confounding (see Chapter 3.2), and addressed it by investigating the cross-sectional relation of sleep with biomarkers of neurodegenerative disease (see Chapter 4.1). Interestingly, we found that sleep and biomarkers were unrelated. This seemed unattributable to poor validity of our biomarkers measurements, as another recent study in our cohort found that higher NfL and lower Ab-42 in plasma were associated with an increased risk of all-cause dementia and Alzheimer's disease in non-demented individuals.[34] We do not know to what extent our plasma-based measurements may have not picked up small, strategic neurodegenerative changes in sleep-wake regulating regions in brainstem and prefrontal regions.[16,35,36] Further research may focus on such local lesions using neuroimaging methods. Nevertheless, findings suggests that neurodegenerative pathologies including those related

to Alzheimer's disease were not likely a confounder, or a mediator, of the association of actigraphy-estimated sleep disturbances with dementia risk. Thus, at the same time, to explain the link between sleep disturbances and dementia risk we feel it is warranted to look beyond Alzheimer's disease pathology.[16] After all, beta-amyloid and tau pathology are not sufficient[37] causes for developing clinical Alzheimer's disease dementia.[38,39] Also, other pathophysiological processes in the brain play a role in dementia,[32,40] that may also disturb sleep. Interestingly, some of these processes have also been described to occur as a consequence of disturbed sleep, e.g. excitotoxic activity or hyperexcitability, neuroinflammation, DNA damage, oxidative stress, or impaired glucose metabolism.[41-46] This overlap argues that we further investigating these factors as potential confounders, or mediators, of the link of sleep disturbances with risk of dementia in the general population.

This thesis further studied two such neurobiological correlates. We first determined sleep's relation with glymphatic functioning as indicated by the structural appearance of the perivascular space on magnetic resonance imaging (MRI; see Chapter 4.2). Similar to findings for plasma biomarkers, we found no consistent associations of poor sleep with higher perivascular space burden on MRI. Contrary to findings from the small number of previous studies on this topic, we found an association of higher sleep efficiency with higher perivascular space count in the centrum semiovale, i.e. an association in the opposite direction. Results could be explained by, among others, perivascular space count indicating brain physiological aspects beneficial to sleep, and we suggest further study of this surprising finding.

We also determined the association of sleep with brain functioning measured with resting-state fMRI (see Chapter 4.3). This method probes the functional organization of the brain and may represent subtle global or regional brain changes possibly relevant to neurodegeneration.[47-49] We found that longer total sleep time, measured with polysomnography and also actigraphy, was associated with a lower BOLD-signal amplitude, driven by prefrontal brain regions. The significance of this finding to risk of neurodegenerative disease remains unclear, although it seems limited as the absolute amount of actigraphy-estimated total sleep time was not associated with dementia risk (see Chapter 3.2).

Together, the neurobiological correlates investigated in chapter 4 could not explain the relation of actigraphy-estimated poor sleep with increased dementia risk (see Chapter 3.2). Further study of neurobiological correlates potentially confounding or mediating the sleep-dementia link is needed to learn what sleep characteristics, if any, contribute to risk of dementia in middle-aged and elderly persons.

Sleep and Parkinson's disease

We found that poor sleep quality and short sleep duration increase the risk of Parkinson's disease only in the first 2 years of follow-up, but not thereafter (see Chapter 3.3). Analyses over repeated measurements of sleep showed that a deterioration of sleep, i.e. a shortening of duration and a decrease in quality, was related to developing Parkinson's disease. These observations are congruent with sleep being a prodromal feature of Parkinson's disease. This interpretation also fits with neuropathological findings in the model proposed by Braak and colleagues, stating the involvement of sleep-wake regulating brain regions before onset of motor symptoms.[50-53]

We could not determine if specific sleep disorders drove our findings. Rapid eye movement sleep behavior disorder (RBD) may be considered a likely candidate as it occurs in around 30% of patients around diagnosis[54,55] and is highly specific to developing Parkinson's disease or related synucleinopathies.[56] Yet, current limited evidence suggests persons with RBD in the general population do not report their sleep as shorter or poorer than otherwise healthy individuals,[57] and may even report longer sleep durations. If, however, RBD precedes Parkinson's disease by over a decade, it could be involved in higher baseline levels of self-reported sleep duration and quality that make for steeper declines in these constructs when prodromal disease sets in. Alternatively, obstructive sleep apnea (OSA) has also been reported to precede Parkinson's disease in registry-based studies.[58] We feel further study of the involvement of OSA in the etiology of Parkinson's disease, and as driver of our findings is warranted based on several observations. First, the etiology of obstructive respiratory events strongly involves factors related to the airways, and not only central nervous system integrity. It may therefore be less susceptible to potential reverse causation effects than other sleep disorders in its relation to risk of neurodegenerative disease. Second, sequelae of OSA may potentially impact Parkinson's disease and its pathological features.[59,60] Third, a meta-analysis showed that OSA may be less prevalent in early Parkinson's disease cases versus controls,[61] which seems incongruent with Parkinson's disease as the primary cause of OSA. This has been attributed to increased rigidity in the upper airway reduces sleep-related collapse and obstructive events around the time of diagnosis.[58] However, most studies reporting a link of OSA and incident Parkinson's disease are registry-based studies which may be prone to diagnostic bias,[58] supporting the need for population-based prospective cohort studies implementing multimodal ascertainment of Parkinson's disease.

Further research into the role of sleep disturbances as marker of prodromal Parkinson's disease, or as potential risk factors to disease development seems warranted. To this end, population-based, prospective cohort studies such as the Rotterdam Study, that implement aforementioned ascertainment for incident disease as well as measurement of endophenotypes such as gait or symptoms of brady- or hypokinesia or rigidity, may well complement findings from cohort with individuals with RBD. Future studies may

also want to determine to what extent our results are generalizable to patients with early-onset Parkinson's disease.

METHODOLOGICAL CONSIDERATIONS

Sleep seems to be a highly variable phenomenon between persons and over time (see Chapter 2.1).[1,62] As hinted on in the 'General introduction' of this thesis, how normal we think sleep is contrasts sharply with how poorly we understand sleep in terms of its causes and consequences. This lack of knowledge is what makes sleep an interesting topic to study, especially in a population-based setting. At the same time, this inherently involves making several assumptions, some of which are not explicitly mentioned in the discussion sections of each chapter. The focus of this thesis was mainly on determining sleep's consequences. Here I further discuss sleep's neurobiological underpinnings and measurements, and how these are relevant to interpret the link with risk of neurodegenerative disease.

Multidimensionality of sleep

Sleep is a complex process or state, involving the orchestrated activity of diverse neuronal populations across the entire brain.[50,63,64] The dominant model for understanding how sleep and wake fluctuate at a systems level is the two-process model: Sleep depends on an interaction between a sleep homeostatic process and a circadian timing process.[65] Sleep homeostasis compensates sleep loss with extra sleep, operates throughout the brain and is indicated by slow-wave activity on the sleep electroencephalogram. Circadian timing is characterized at a cellular level by expression of proteins that inhibit their own production, fluctuating with a period of about 24-hours.[11] The master clock in the hypothalamic suprachiasmatic nucleus integrates circadian rhythms throughout the body.[66] Various brain nuclei and projections throughout the brainstem, frontal lobe and limbic system, using different neurotransmitter and hormonal systems, effectuate aforementioned processes.[50]

The approach to study this intangible process is 'multidimensional', reflected by the variety of levels, neurobiological to psychological, or characteristics on which sleep is measured.[63] Sleep can be appreciated through e.g. subjective appraisal, lack of movement, or slow-wave activity on electro-encephalography, all of which can estimate the same quantifiable characteristics such as total sleep time.[63] In line with this multidimensionality, we measured sleep using self-report, actigraphy in combination with diaries, or polysomnography, or a combination of these where deemed possible or appropriate.

Please note that our population-based measures were largely not designed to diagnose participants with sleep disorders, or in a larger sense, to identify persons with disordered

or deficient sleep versus 'normal' sleep (the 'tip of the iceberg' of sleep disturbances). Analogously, we studied sleep characteristics on a continuous scale, assuming that this conveyed information on subclinical but relevant abnormal sleep. Also, we assumed that our single measurements were to some extent stable over time and thus indicative of chronic exposure to a certain level of normal/abnormal, or good/poor, sleep.

Subjective versus objective measurements

Subjective measurements of sleep have been preferred in large-scale studies for their ease of administration and low costs. In general, subjective appraisal is inherently valuable as it expresses well-being. In sleep research, such measures are also relevant as they may drive seeking healthcare, and signal sleep problems that matter to individuals. Objectively measured sleep can only explain a part of the subjective appraisal of sleep's quality.[67,68] The role of subjective evaluation in sleep medicine, for example in insomnia diagnosis and treatment,[69] is, and remains, important regardless of increasing technological advances.

Yet, subjective quantification of sleep characteristics such as total sleep time may substantially differ from those obtained by methods taking physiological measurements, e.g. actigraphy.[6,70] This disagreement itself could of course be of interest, e.g. to assess insomnia severity.[67] Nevertheless, disagreement between methods is not random and may introduce bias.[6,71] If we are primarily interested in studying e.g. total sleep time, a characteristic best quantified physiologically, use of self-reported total sleep time means it will be misclassified and as such may introduce bias and hamper etiological inference. This issue is eloquently voiced by Bianchi and colleagues, who also highlight that using self-reported total sleep time increases the potential for confounding by unknown factors leading to systematically over- or underestimated total sleep time.[5] Especially cognition should be considered here. The importance of cognitive processes for reporting sleep is well illustrated by a study showing consistent differences for different constructs according to using a direct or indirect method of querying sleep.[72] Cognitive impairment may further reduce the validity of self-reporting sleep (see discussion of Chapter 3.1), possibly so that persons with lower cognitive functioning overstate their actigraphy-estimated sleep duration,[6] and patients with Alzheimer's disease underreport problematic sleeping in the face of evidently poor sleep estimated with actigraphy.[10] Besides cognition, affective factors are also relevant, as self-reported total sleep time is inextricably linked to mood.[6,73,74] Health-related factors as discussed by researchers from the Sleep Heart Health Study are also important to consider.[75]

We encountered inaccuracy in self-reporting time-related sleep characteristics in our meta-analysis (see Chapter 2.1), where up to 10% of individuals in some cohorts reported longer total sleep time than their time spent in bed. Moreover, this disagree-

ment in methods determined the difference in findings with regard to dementia risk in this thesis (see Chapters 3.1 and 3.2).

Some researchers respond to these inherent limitations of self-reported sleep data by carefully discussing these challenges, while others advocate we radically stop querying self-reported total sleep time.[5] We discussed possible biases and, where possible, used more objective methods to quantify sleep. Also, not knowing what determines these self-reported measures precludes actionable, preventive interventions to benefit public health when studying these measures (see paragraph "From sleep epidemiology to prevention").[76]

Reverse causation

Alzheimer's disease, the most common form of dementia, and Parkinson's disease are degenerative diseases hypothesized to be present long before diagnosis can be made.[52,53,77] Prospective cohort studies using structured repeated assessments show that subtle cognitive or motor deficits are already appreciable for up to a decade before the diagnosis in patients versus controls.[78-80] Besides typical disease-related characteristics, more non-specific neuropsychiatric symptoms may also be present in this prediagnostic phase, such as depressive symptoms,[78,81,82] or physical inactivity for Alzheimer's disease.[83,84] When such factors are investigated as potential risk factors for incident dementia in non-demented individuals followed up over time, they may temporally precede a dementia diagnosis and be labeled a risk factor when truly there is no causal relation. Instead, the temporal relation is causal but reversed, which can also be thought of as confounding by the underlying pathological processes. Sleep is also subject to this phenomenon. Neurodegenerative pathology may directly influence brain regions that generate or propagate sleep,[36,85,86] or may affect sleep and 24-hour activity rhythms through other prodromal or non-specific symptoms or signs, e.g. physical inactivity, apathy, decreased light exposure.

We examined potential reverse causation by stratifying analyses on follow-up time, simulating premature study endings. We restricted follow-up to the first e.g. 2 years after baseline, censoring all at-risk participants, and then incrementally increased follow-up from 2 years towards the duration of the overall follow-up, simulating shorter-duration studies within our own study. We did not exclude the first years of follow-up, selecting persons on not getting the outcome for the first e.g. 2 years, which has been described to potentially lead to selection bias.[87] We assumed that a decrease in strength of effect sizes with increasing follow-up time indicates preclinical or prodromal disease disturbing sleep at baseline (see Chapter 3.3).

This analytical approach to reverse causation seems worthwhile to pursue in an individual-participant data framework on sleep and incident dementia, as done by others,[83] to tease out to what extent studies suffer from reverse causation.[7-9] Importantly,

stratifying existing studies on median total follow-up time as previously performed[7,9] is a less sensible approach to examine potential reverse causation, as single risk estimates averaged over long study follow-up may still be driven only by a strong relation in the first few years of follow-up.

Please note that aforementioned approach to detect reverse causation only shows a temporal relation, and cannot prove reverse causation. This means that a typical pattern indicating reverse causation does not prove the absence of any causal effect of the exposure on the outcome. The exposure may also be a step in a multistage process that harms only in a certain opportune window. Evidence for such a multistage process, requiring accumulation of several sequential pathological 'hits', may be found in incidence data in prospective cohorts for dementia.[88] Also, a temporal relation indicative of reverse causation does not exclude the possibility of confounding of the relation of the exposure and risk of the outcome by genuine, unknown risk factors.

From sleep epidemiology towards prevention or treatment

Epidemiological studies not only aim to provide quantifiable insight into the etiology of disease but also to contribute information to prevent disease. This second step should be highlighted to show that identifying risk factors does not necessarily allow taking preventive action.[89] A difference between the two can be identified within the potential outcomes framework, or counterfactual framework, of causal inference.[90] The difference is that the sleep exposures studied by epidemiologists may differ from what is reasonably intervened upon to change that exposure.

Take the following example: Reducing high BMI may seem like a reasonable objective in public health. Yet, different interventions to reduce BMI tackle different underlying biological processes. Examples include giving lifestyle advice, prescribing diets, performing bariatric surgery, but also amputating a limb.[91,92] Amputation seems effective to reduce BMI, yet everybody would agree it would not reduce risk of cardiovascular outcomes or mortality. Why not? Clearly, the underlying biological substrates of increased BMI, its directly identifiable upstream causes, increase the risk, not necessarily BMI itself. Considering BMI as risk factor for mortality still lacks the actionable information needed to inform public health policies.

As discussed earlier, sleep is a process involving various neurobiological and neurotransmitter systems, and is pragmatically measured across multiple dimensions. Analogous to the BMI example, this suggest a potential for a disconnect between observational exposures and potential interventions. Let's pretend that we performed the perfect observational study on the relation of actigraphy-estimated sleep with dementia risk, and found an association of short total sleep time with increased dementia risk. How do we then increase total sleep time, and will this reduce dementia incidence? Pharmacological interventions, typically sedative hypnotics, may not necessarily mimic

naturalistic sleep.[93] Interventions such as cognitive behavioral therapies are designed to address dysfunctional thoughts or behaviors regarding sleep. This may renormalize a short total sleep time, yet problematic cognition or behavior may have not necessarily been the problem underlying short total sleep time. Moreover, behavioral changes to increase sleep, i.e. deciding to get more sleep, is only indirectly achieved by extending sleep opportunity in the hopes of getting more sleep.

Even if we studied an exposure that was more clearly defined in terms of the underlying biology, e.g. slow-wave sleep, there may still be a disconnect between observational exposure and potential interventions. Pharmacological interventions that enhance slow-wave activity and therefore slow-wave sleep, may differ in other effects that differentially relate to the outcome under study.[94] Specifically enhancing slow-wave activity during sleep may also be achieved through waking activities (meditation, cognitive activity, physical activity), sensory stimulation during sleep (acoustic, olfactory, vestibular stimuli), or non-invasive transcranial electromagnetic stimulation.[95] Interestingly, these different interventions are also associated with a better performance on cognitive tasks,[95] even in older adults,[96] supporting a key role for slow-wave activity or sleep in cognition and providing a basis for targeted treatment or prevention of cognitive impairments.

A more thorough understanding of the neurobiological determinants of sleep may help to design interventions towards preventative action. This does however not preclude that appropriate interventions may have a different effect than what was derived from observational studies.[97]

Identifying a risk factor in observational studies is a process of reasonably excluding biases and chance and then accepting that whatever remains is the causal relation of that exposure with your outcome. Aforementioned example suggests that not only is short total sleep time not defined well enough in terms of its corresponding intervention, but that this lack of specificity in its definition is hampering our ability to know to what extent our association is unconfounded.[92] This principle seems to apply not only to total sleep time but to a number of sleep exposures in epidemiological studies, including ours. It is therefore important to stress that current sleep epidemiological findings should be considered more an important first step than research efforts lacking actionable information. Epidemiologists advocating the use of well-defined interventions in the potential outcomes framework are in my opinion advocating pragmatism, and as such may understand that current population-based studies pragmatically investigate sleep through feasible measures first. If no relation exists, valuable resources are better invested elsewhere.

Threats to validity of sleep findings

Several threats, or biases, may have affected the validity of the findings in this thesis. These concern confounding, selection bias, and information bias as threats to interval

validity, and limited generalizability. We tried to account for these potential biases in the analysis phase, or discussed them, per chapter. Here, I want to briefly highlight the issues of confounding, and generalizability.

Confounding indicates that a third factor, a cause of both the exposure and outcome, distorts their relation.[98] Confounding in observational research is ubiquitous. Recognizing the potential for confounding, trying to reduce confounding or at least discuss the potential for confounding based on someone's expert knowledge is a prerequisite in any attempt to produce methodologically sound results.[99] Selection of potential confounders was informed on literature where possible.[98] Further studies on what determines our population-based measures of sleep, especially brain determinants, seems important to improve adequate control for confounding in future.

The importance of recognizing potential confounding in observational sleep research is illustrated by an example focused on the rare, neurodegenerative disease Fatal Familial Insomnia (FFI). This disease involves abnormal folding of the brain's own prion proteins, related to a specific genetic polymorphism in the gene encoding prion protein. It is characterized by a progressive, severe lack of sleep, and patients often die within a year of diagnosis. One thus observes a lack of sleep linked to a high mortality rate. While sleep disturbance can certainly impact health and well-being, and may contribute to an increased risk of dying, the apparent association of sleep disturbance in FFI with high mortality is likely confounded by the underlying neurodegenerative process. Sleep disturbances in FFI are therefore not proof that a lack of sleep is life-threatening in humans.

As a rule of thumb, one should be very critical in interpreting observational associations as causal. This is especially important as aforementioned example may lead families of patients with FFI to believe that treating sleep disturbances may have prolonged the life of their loved one, for which currently no evidence exists. I find this an interesting example as it featured in the popular book on sleep "Why We Sleep" by Matthew Walker published in 2017,[100] which evoked criticisms in the form of blogs on social media,[101,102] and a sportsman-like response by the author.[103] It is also of personal interest as I have been in personal contact with patients with prion disease and their families, during my work as physician for the Dutch National Prion Registry. Having witnessed how especially family members deal with scarce information available on these severe disorders, I find it all the more important that the information on possible treatments is accurate.

Regarding generalizability, studies embedded in the Rotterdam Study were based on predominantly individuals from European descent, with a middle-to-high income.[104] We found that subjective appraisal of sleep was poorer in the US compared to the Netherlands and the UK (see Chapter 2.1). Interestingly, meta-analyses on the relation of mostly self-reported sleep characteristics with dementia and Alzheimer's disease risk showed that results obtained from European studies were similar to those from North-American studies.[7,9] Nevertheless, cross-cultural heterogeneity in the social timing of sleep and

its role in daily life,[105] especially in aged individuals studied in this thesis, may limit the generalizability of our findings.

IMPLICATIONS

Clinical

We aimed to study sleep's role in the etiology of neurodegenerative disease, in a population-based setting, and studied sleep mostly in otherwise healthy individuals. Therefore, findings have limited implications for patients and healthcare professionals. Nevertheless, several points may be of clinical interest.

First, descriptive sleep data from our meta-analysis provides a data-driven view on extremes in sleep, e.g. through percentile curves, which may be used as an evidence-based starting point to actively screen for underlying sleep disorders. Cut-offs are applicable to the general population, and further evaluation of their accuracy and overall usefulness in more selected populations, e.g. patients visiting a general practitioner with a sleep complaint or something related, or visiting a sleep clinic, should be performed.

Our data show that sleep complaints are common, especially with increasing age in older adults, providing a potential target for sleep improvement at the population level. At the same time, the same data can be interpreted as sleep problems being something 'normal'. If indeed sleep complaints, after evaluation by a healthcare professional, are not in need of further diagnostic tests or therapeutic interventions, our data could be used to reassure individuals with sleep complaints that their problems are common.

Second, dementia patients and their families can be informed that poor sleep in late life is associated with an increased risk of dementia, or vice versa, that poor sleep may precede a diagnosis of dementia by years. This may not necessarily be reflected in subjective appraisal of sleep, although we did not investigate whether in retrospect sleep problems may be recognized. Also, our results show that typical changes in 24-hour activity rhythms that may constitute prodromal dementia features are an advance in sleep phase and earlier bedtime. Explaining these disease-related changes to patients and loved ones may help them gain a sense of understanding of, and therefore perhaps control over, the very serious problems they are faced with.

Third, patients with Parkinson's disease with questions regarding sleep could be informed that having more sleep complaints and reporting a shorter sleep duration are prodromal features of the disease that may occur on average at least two years before a diagnosis.

Although we could not reasonably show relations of sleep and incident outcomes that indicate a causal effect, optimizing sleep and circadian rhythms seem reasonably inexpensive secondary treatment goals, that matter to patients or caregivers. Enquiring

about perceived sleep problems seems warranted, for which Dutch healthcare professionals may find the structured *NHG-standaard* approach useful.[106]

Public health

Our meta-analysis results show what is 'normal' for different sleep characteristics, different from the expert recommendations of the US National Sleep Foundation about what constitutes 'good' sleep. This provides an alternative, more pragmatic benchmark for future sleep studies. Our findings show that sleep complaints are common and not necessarily explained by aberrant sleep times. An association of more insomnia symptoms with above-normal time in bed suggests a place for interventions to reduce the time in bed as used in insomnia disorder treatment, i.e. non-pharmacological, cognitive-behavioral interventions. Education is a key part of such interventions, so large-scale education of the public seems at first glance a potentially efficacious route to try and shift the population distribution of insomnia symptoms. Debunking false myths about sleep that have public health sleep significance[107] may be part of that approach. Possibly, as mentioned above, providing state-of-the-art cognitive behavioral therapy for insomnia via digital channels may provide a scalable alternative to effectively reduce insomnia complaints and related mental health problems.[3,4]

Important caveats that should be kept in mind is that digital health interventions may not reach elderly persons, especially the more vulnerable, cognitively impaired persons who are expected to have substantial benefit.[108,109] Nevertheless, use of smartphone in elderly persons seems to be on the rise, at least in the Netherlands,[110] and with it may come increased openness to engage with digital health solutions. Also, an important caveat in any attempt to communicate the importance of sleep to the general public is that attention to sleep equals worry about sleep, which is bad for sleep.

Future research

Designing future sleep research focused on etiology of neurodegenerative diseases may be well informed by thinking about the most optimal observational study, with infinite resources at our disposal, that may be performed to support causal claims.

Ideally, we would need a large-scale (10,000+ participants) cohort study, that from midlife onwards[111] repeatedly measures sleep with polysomnography and actigraphy, measure state-of-the-art, disease-related brain markers (CSF, blood, non-invasive neuroimaging), combined with continuous follow-up to diagnose neurodegenerative disease. Imaging approaches may focus on specific sleep-regulatory nuclei such as the locus coeruleus,[112-114] which shows Alzheimer's disease-related tau pathology early in life,[35,115] and may play a role in RBD, a sleep disorder specific to development of alpha-synucleinopathies.[116] Functional imaging approaches would need to ensure simultaneous vigilance/sleep measurement, e.g. by combining fMRI/EEG to properly assess

sleep's role in functional changes of the brain across time.[117] Measuring from mid-life onwards may help establish a potential window of opportunity for preventive action.[118] Polysomnography must include a screening approach to further evaluate persons with possible RBD. Data analysis may include implementing causal inference methods, e.g. g-methods to deal with unmeasured confounding and time-varying confounding,[119] or a 4-way decomposition analysis to deconstruct the potential interaction and mediation of sleep with Alzheimer's disease pathology on risk of dementia.[120,121]

Unfortunately, this sleep study will remain a dream. Until then, we need to investigate both determinants as well as consequences of sleep in the general middle-aged and elderly population. Important avenues to pursue are linking brain structure and function to objective sleep and 24-hour activity rhythm characteristics, and leverage genetic data to establish the biological basis of our sleep measures, for which there is increasing attention.[122] Both approaches are probably best executed in collaboration, such as the ENIGMA consortium for sleep neuroimaging studies, or setting up new collaborations to achieve large sample sizes for much-anticipated genome-wide associations studies on objective sleep and 24-hour activity rhythm phenotypes. Understanding the link of sleep and dementia may also be better achieved by using Mendelian randomization,[123] or leveraging genetic risk scores, to assess the associations of genetic correlates of certain sleep characteristics with dementia risk and vice versa. Using repeated measures of sleep to investigate what determines trajectories of sleep in aging will help elucidate relevant underlying factors in the context of slowly progressive neurodegenerative diseases. Yet, most importantly, one of the key first steps towards better understanding the potential causal role of sleep disturbances in dementia is to account for disease-related neuropathological factors. Our approach using plasma-based biomarkers is an example of a feasible design to study this in large, population-based samples.

Besides pragmatic studies on the risk of neurodegenerative disease and related neurobiological correlates, several assumptions regarding the relation of sleep and Alzheimer's disease pathology should also be addressed. These mostly concern the translation of laboratory findings to a 'real world' setting. For example, it is unclear how effects of acute sleep deprivation on pathology relate to the often less severe but chronic disturbances observed in real-life. For example, a 5-day chronic sleep restriction regime differed from acute sleep deprivation in microglia activation in mice,[44] and the history of sleep may be carried forward and help determine behavioral performance days later.[124] It is therefore unclear if a) chronic disturbances equate repeated acute disturbances, i.e. repeatedly elevate beta-amyloid levels, and if b) this leads to higher rates of plaque deposition, and if c) this leads to accelerated cognitive and functional deterioration. Acute excesses of beta-amyloid may also be adequately removed from interstitial or cerebrospinal fluid compartments,[125] and partial sleep deprivation in humans to 5 nights of 4 hours did not

elevate beta-amyloid isoforms or other biomarkers of detrimental processes in cerebrospinal fluid or plasma.[126,127]

Population-based studies may also provide insights into how sleep determines Alzheimer's disease pathology over time. Yet, so far only one study determined longitudinal changes in amyloid deposition.[128] Authors reported that excessive daytime sleepiness in non-demented individuals increased amyloid deposition over 2.2 years on average. Potential confounding was discussed but not yet taken into account in the analyses.

CONCLUSION

We conclude that sleep complaints are common in elderly persons, more so than an inadequate sleep duration. Poor sleep was associated with incident neurodegenerative disease. In the case of self-reported sleep quality and duration in relation with Parkinson's disease, patterns of associations suggest that poor sleep is a prodromal feature of the disease, whereas in the case of actigraphy-estimated nighttime wakefulness preceding all-cause dementia and Alzheimer's disease, the link seemed not explained by known potential confounders.

REFERENCES

1. Hirshkowitz M, Whiton K, Albert SM, et al. National Sleep Foundation's updated sleep duration recommendations: final report. *Sleep Health.* 2015;1(4):233-243.
2. Luyster FS, Strollo PJ, Jr., Zee PC, Walsh JK, Boards of Directors of the American Academy of Sleep M, the Sleep Research S. Sleep: a health imperative. *Sleep.* 2012;35(6):727-734.
3. Espie CA, Emsley R, Kyle SD, et al. Effect of Digital Cognitive Behavioral Therapy for Insomnia on Health, Psychological Well-being, and Sleep-Related Quality of Life: A Randomized Clinical Trial. *JAMA Psychiatry.* 2018.
4. Freeman D, Sheaves B, Goodwin GM, et al. The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. *Lancet Psychiatry.* 2017;4(10):749-758.
5. Bianchi MT, Thomas RJ, Westover MB. An open request to epidemiologists: please stop querying self-reported sleep duration. *Sleep Med.* 2017;35:92-93.
6. Van Den Berg JF, Van Rooij FJ, Vos H, et al. Disagreement between subjective and actigraphic measures of sleep duration in a population-based study of elderly persons. *J Sleep Res.* 2008;17(3):295-302.
7. Bubu OM, Brannick M, Mortimer J, et al. Sleep, Cognitive impairment and Alzheimer's disease: A Systematic Review and Meta-analysis. *Sleep.* **2017**;40(1).
8. Shi L, Chen SJ, Ma MY, et al. Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. *Sleep Med Rev.* 2017.

9. Xu W, Tan CC, Zou JJ, Cao XP, Tan L. Sleep problems and risk of all-cause cognitive decline or dementia: an updated systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry.* 2019.
10. Most EI, Aboudan S, Scheltens P, Van Someren EJ. Discrepancy between subjective and objective sleep disturbances in early- and moderate-stage Alzheimer disease. *Am J Geriatr Psychiatry.* 2012;20(6):460-467.
11. Videnovic A, Lazar AS, Barker RA, Overeem S. 'The clocks that time us'--circadian rhythms in neurodegenerative disorders. *Nat Rev Neurol.* 2014;10(12):683-693.
12. Smagula SF, Gujral S, Capps CS, Krafty RT. A Systematic Review of Evidence for a Role of Rest-Activity Rhythms in Dementia. *Front Psychiatry.* 2019;10:778.
13. Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. Association between circadian rhythms and neurodegenerative diseases. *Lancet Neurol.* 2019;18(3):307-318.
14. Vetter C. Circadian disruption: What do we actually mean? *Eur J Neurosci.* 2018.
15. Ju YE, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology--a bidirectional relationship. *Nat Rev Neurol.* 2014;10(2):115-119.
16. Mander BA, Winer JR, Jagust WJ, Walker MP. Sleep: A Novel Mechanistic Pathway, Biomarker, and Treatment Target in the Pathology of Alzheimer's Disease? *Trends Neurosci.* 2016;39(8):552-566.
17. Boespflug EL, Iliff JJ. The Emerging Relationship Between Interstitial Fluid-Cerebrospinal Fluid Exchange, Amyloid-beta, and Sleep. *Biol Psychiatry.* 2018;83(4):328-336.
18. Kang JE, Lim MM, Bateman RJ, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science.* 2009;326(5955):1005-1007.
19. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science.* 2013;342(6156):373-377.
20. Bero AW, Yan P, Roh JH, et al. Neuronal activity regulates the regional vulnerability to amyloid-beta deposition. *Nat Neurosci.* 2011;14(6):750-756.
21. Cirrito JR, Yamada KA, Finn MB, et al. Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. *Neuron.* 2005;48(6):913-922.
22. Spira AP, Chen-Edinboro LP, Wu MN, Yaffe K. Impact of sleep on the risk of cognitive decline and dementia. *Curr Opin Psychiatry.* 2014;27(6):478-483.
23. Ju YE, McLeland JS, Toedebusch CD, et al. Sleep quality and preclinical Alzheimer disease. *JAMA Neurol.* 2013;70(5):587-593.
24. Ooms S, Overeem S, Besse K, Rikkert MO, Verbeek M, Claassen JA. Effect of 1 night of total sleep deprivation on cerebrospinal fluid beta-amyloid 42 in healthy middle-aged men: a randomized clinical trial. *JAMA Neurol.* 2014;71(8):971-977.
25. Shokri-Kojori E, Wang GJ, Wiers CE, et al. beta-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci U S A.* 2018;115(17):4483-4488.
26. Lucey BP, Mawuenyega KG, Patterson BW, et al. Associations Between beta-Amyloid Kinetics and the beta-Amyloid Diurnal Pattern in the Central Nervous System. *JAMA Neurol.* 2017;74(2):207-215.
27. Ju YS, Ooms SJ, Sutphen C, et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid-beta levels. *Brain.* 2017;140(8):2104-2111.
28. Brown BM, Rainey-Smith SR, Villemagne VL, et al. The Relationship between Sleep Quality and Brain Amyloid Burden. *Sleep.* 2016;39(5):1063-1068.
29. Holth JK, Fritschi SK, Wang C, et al. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science.* 2019.
30. Zhu Y, Zhan G, Fenik P, et al. Chronic Sleep Disruption Advances the Temporal Progression of Tauopathy in P301S Mutant Mice. *J Neurosci.* 2018;38(48):10255-10270.

31. Holth J, Patel T, Holtzman DM. Sleep in Alzheimer's Disease - Beyond Amyloid. *Neurobiol Sleep Circadian Rhythms.* 2017;2:4-14.
32. Herrup K. The case for rejecting the amyloid cascade hypothesis. *Nat Neurosci.* 2015;18(6):794-799.
33. Kametani F, Hasegawa M. Reconsideration of Amyloid Hypothesis and Tau Hypothesis in Alzheimer's Disease. *Front Neurosci.* 2018;12:25.
34. De Wolf F, Ghanbari M, Licher S, et al. Plasma total-tau, neurofilament light chain and amyloid-β levels and risk of developing Alzheimer's disease: a population-based prospective cohort study *Submitted.* 2019.
35. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol.* 2011;70(11):960-969.
36. Mander BA, Marks SM, Vogel JW, et al. beta-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat Neurosci.* 2015;18(7):1051-1057.
37. Rothman KJ. Causes. *Am J Epidemiol.* 1976;104(6):587-592.
38. Glymour MM, Brickman AM, Kivimaki M, et al. Will biomarker-based diagnosis of Alzheimer's disease maximize scientific progress? Evaluating proposed diagnostic criteria. *Eur J Epidemiol.* 2018;33(7):607-612.
39. Darweesh SKL, Wolters FJ, Ikram MA, Bos D, Hofman A. Broadening the scope of epidemiologic dementia research. *Eur J Epidemiol.* 2018;33(7):617-620.
40. Tse KH, Herrup K. Re-imagining Alzheimer's disease - the diminishing importance of amyloid and a glimpse of what lies ahead. *J Neurochem.* 2017;143(4):432-444.
41. Zada D, Bronshtein I, Lerer-Goldshtein T, Garini Y, Appelbaum L. Sleep increases chromosome dynamics to enable reduction of accumulating DNA damage in single neurons. *Nat Commun.* 2019;10(1):895.
42. Irwin MR, Vitiello MV. Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. *Lancet Neurol.* 2019;18(3):296-306.
43. Cedernaes J, Osorio RS, Varga AW, Kam K, Schioth HB, Benedict C. Candidate mechanisms underlying the association between sleep-wake disruptions and Alzheimer's disease. *Sleep Med Rev.* 2017;31:102-111.
44. Bellesi M, de Vivo L, Chini M, Gilli F, Tononi G, Cirelli C. Sleep Loss Promotes Astrocytic Phagocytosis and Microglial Activation in Mouse Cerebral Cortex. *J Neurosci.* 2017;37(21):5263-5273.
45. Tsuneki H, Sasaoka T, Sakurai T. Sleep Control, GPCRs, and Glucose Metabolism. *Trends Endocrinol Metab.* 2016;27(9):633-642.
46. Spiegel K, Tasali E, Leproult R, Van Cauter E. Effects of poor and short sleep on glucose metabolism and obesity risk. *Nat Rev Endocrinol.* 2009;5(5):253-261.
47. Butz M, Worgotter F, van Ooyen A. Activity-dependent structural plasticity. *Brain Res Rev.* 2009;60(2):287-305.
48. Holtmaat A, Svoboda K. Experience-dependent structural synaptic plasticity in the mammalian brain. *Nat Rev Neurosci.* 2009;10(9):647-658.
49. Jack CR, Jr., Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol.* 2010;9(1):119-128.
50. Saper CB. The neurobiology of sleep. *Continuum (Minneap Minn).* 2013;19(1 Sleep Disorders):19-31.
51. Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. *Neuron.* 2010;68(6):1023-1042.
52. Hawkes CH, Del Tredici K, Braak H. A timeline for Parkinson's disease. *Parkinsonism Relat Disord.* 2010;16(2):79-84.

53. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging.* 2003;24(2):197-211.
54. Gagnon JF, Bedard MA, Fantini ML, et al. REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. *Neurology.* 2002;59(4):585-589.
55. Zhang J, Xu CY, Liu J. Meta-analysis on the prevalence of REM sleep behavior disorder symptoms in Parkinson's disease. *BMC Neurol.* 2017;17(1):23.
56. Galbiati A, Verga L, Giora E, Zucconi M, Ferini-Strambi L. The risk of neurodegeneration in REM sleep behavior disorder: A systematic review and meta-analysis of longitudinal studies. *Sleep Med Rev.* 2019;43:37-46.
57. Haba-Rubio J, Frauscher B, Marques-Vidal P, et al. Prevalence and Determinants of REM Sleep Behavior Disorder in the General Population. *Sleep.* 2017.
58. Al-Qassabi A, Fereshtehnejad SM, Postuma RB. Sleep Disturbances in the Prodromal Stage of Parkinson Disease. *Curr Treat Options Neurol.* 2017;19(6):22.
59. Sun HL, Sun BL, Chen DW, et al. Plasma alpha-synuclein levels are increased in patients with obstructive sleep apnea syndrome. *Ann Clin Transl Neurol.* 2019;6(4):788-794.
60. Zhou J, Zhang J, Lam SP, et al. Excessive Daytime Sleepiness Predicts Neurodegeneration in Idiopathic REM Sleep Behavior Disorder. *Sleep.* 2017;40(5).
61. Zeng J, Wei M, Li T, et al. Risk of obstructive sleep apnea in Parkinson's disease: a meta-analysis. *PLoS One.* 2013;8(12):e82091.
62. Ohayon M, Wickwire EM, Hirshkowitz M, et al. National Sleep Foundation's sleep quality recommendations: first report. *Sleep Health.* 2017;3(1):6-19.
63. Buysse DJ. Sleep health: can we define it? Does it matter? *Sleep.* 2014;37(1):9-17.
64. Vyazovskiy VV, Harris KD. Sleep and the single neuron: the role of global slow oscillations in individual cell rest. *Nat Rev Neurosci.* 2013;14(6):443-451.
65. Borbely AA. A two process model of sleep regulation. *Hum Neurobiol.* 1982;1(3):195-204.
66. Borbely AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: a reappraisal. *J Sleep Res.* 2016;25(2):131-143.
67. Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med Rev.* 2013;17(4):241-254.
68. Krystal AD, Edinger JD. Measuring sleep quality. *Sleep Med.* 2008;9; Suppl 1:S10-17.
69. Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res.* 2017;26(6):675-700.
70. Matthews KA, Patel SR, Pantesco EJ, et al. Similarities and differences in estimates of sleep duration by polysomnography, actigraphy, diary, and self-reported habitual sleep in a community sample. *Sleep Health.* 2018;4(1):96-103.
71. van den Berg JF, Miedema HM, Tulen JH, Hofman A, Neven AK, Tiemeier H. Sex differences in subjective and actigraphic sleep measures: a population-based study of elderly persons. *Sleep.* 2009;32(10):1367-1375.
72. Alameddine Y, Ellenbogen JM, Bianchi MT. Sleep-wake time perception varies by direct or indirect query. *J Clin Sleep Med.* 2015;11(2):123-129.
73. Bao YP, Han Y, Ma J, et al. Cooccurrence and bidirectional prediction of sleep disturbances and depression in older adults: Meta-analysis and systematic review. *Neurosci Biobehav Rev.* 2017;75:257-273.
74. Sun Y, Shi L, Bao Y, Sun Y, Shi J, Lu L. The bidirectional relationship between sleep duration and depression in community-dwelling middle-aged and elderly individuals: evidence from a longitudinal study. *Sleep Med.* 2018;52:221-229.

75. Silva GE, Goodwin JL, Sherrill DL, et al. Relationship between reported and measured sleep times: the sleep heart health study (SHHS). *J Clin Sleep Med.* 2007;3(6):622-630.
76. Bianchi MT, Thomas RJ, Westover MB. Response. *Sleep Med.* 2017;38:160-161.
77. Jack CR, Jr., Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol.* 2013;12(2):207-216.
78. Darweesh SK, Verlinden VJ, Stricker BH, Hofman A, Koudstaal PJ, Ikram MA. Trajectories of prediagnostic functioning in Parkinson's disease. *Brain.* 2017;140(2):429-441.
79. Verlinden VJ, van der Geest JN, de Bruijn RF, Hofman A, Koudstaal PJ, Ikram MA. Trajectories of decline in cognition and daily functioning in preclinical dementia. *Alzheimers Dement.* 2016;12(2):144-153.
80. Amieva H, Le Goff M, Millet X, et al. Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. *Ann Neurol.* 2008;64(5):492-498.
81. Mirza SS, Wolters FJ, Swanson SA, et al. 10-year trajectories of depressive symptoms and risk of dementia: a population-based study. *Lancet Psychiatry.* 2016;3(7):628-635.
82. Singh-Manoux A, Dugravot A, Fournier A, et al. Trajectories of Depressive Symptoms Before Diagnosis of Dementia: A 28-Year Follow-up Study. *JAMA Psychiatry.* 2017;74(7):712-718.
83. Kivimaki M, Singh-Manoux A, Pentti J, et al. Physical inactivity, cardiometabolic disease, and risk of dementia: an individual-participant meta-analysis. *BMJ.* 2019;365:l1495.
84. Sabia S, Dugravot A, Dartigues JF, et al. Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of Whitehall II cohort study. *BMJ.* 2017;357:j2709.
85. Murphy M, Riedner BA, Huber R, Massimini M, Ferrarelli F, Tononi G. Source modeling sleep slow waves. *Proc Natl Acad Sci U S A.* 2009;106(5):1608-1613.
86. Hogl B, Stefani A, Videnovic A. Idiopathic REM sleep behaviour disorder and neurodegeneration - an update. *Nat Rev Neurol.* 2018;14(1):40-55.
87. Hernan MA. The hazards of hazard ratios. *Epidemiology.* 2010;21(1):13-15.
88. Licher S, van der Willik KD, Vinke EJ, et al. Alzheimer's disease as a multistage process: an analysis from a population-based cohort study. *Aging (Albany NY).* 2019;11(4):1163-1176.
89. Galea S. An argument for a consequentialist epidemiology. *Am J Epidemiol.* 2013;178(8):1185-1191.
90. Hernan MA, Robins JM. Causal Inference Book - Causal Inference: What if. 2019; https://cdn1.sph.harvard.edu/wp-content/uploads/sites/1268/2019/11/ci_hernanrobins_10nov19.pdf. Accessed 20-01-2020, 2020.
91. Chiolero A. Why causality, and not prediction, should guide obesity prevention policy. *Lancet Public Health.* 2018;3(10):e461-e462.
92. Hernan MA, Taubman SL. Does obesity shorten life? The importance of well-defined interventions to answer causal questions. *Int J Obes (Lond).* 2008;32 Suppl 3:S8-14.
93. Horne JA. The substance of sleep. *Sleepfaring*. Oxford: Oxford University Press; 2007:24-27.
94. Walsh JK. Enhancement of slow wave sleep: implications for insomnia. *J Clin Sleep Med.* 2009;5(2 Suppl):S27-32.
95. Wilckens KA, Ferrarelli F, Walker MP, Buysse DJ. Slow-Wave Activity Enhancement to Improve Cognition. *Trends Neurosci.* 2018;41(7):470-482.
96. Papalambros NA, Santostasi G, Malkani RG, et al. Acoustic Enhancement of Sleep Slow Oscillations and Concomitant Memory Improvement in Older Adults. *Front Hum Neurosci.* 2017;11:109.
97. Whittemore AS, McGuire V. Observational studies and randomized trials of hormone replacement therapy: what can we learn from them? *Epidemiology.* 2003;14(1):8-10.

98. VanderWeele TJ. Principles of confounder selection. *Eur J Epidemiol.* 2019;34(3):211-219.
99. HH HA, S AS, Hofman A, Ikram MA. Amyloid-beta transmission or unexamined bias? *Nature.* 2016;537(7620):E7-9.
100. Walker MP. *Why We Sleep: Unlocking the power of sleep and dreams.* First edition ed. New York: Scribner; 2017.
101. Andrew. "Why We Sleep" update: some thoughts while we wait for Matthew Walker to respond to Alexey Guzey's criticisms. *Statistical Modeling, Causal Inference, and Social Science.* Vol 20202019.
102. Guzey A. Matthew Walker's "Why We Sleep" Is Riddled with Scientific and Factual Errors. Vol 20202019.
103. Walker MP. Why We Sleep: Response to questions from readers. *On Sleep.* Vol 20202019.
104. Ikram MA, Brusselle GGO, Murad SD, et al. The Rotterdam Study: 2018 update on objectives, design and main results. *Eur J Epidemiol.* 2017;32(9):807-850.
105. Wolf-Meyer M. Can we ever know the sleep of our ancestors? *Sleep Health.* 2016;2(1):4-5.
106. Genootschap NH. NHG-Standaard Slaapproblemen en slaapmiddelen. 2014; https://www.nhg.org/standaarden/volledig/nhg-standaard-slaapproblemen-en-slaapmiddelen. Accessed 20-01-2020, 2020.
107. Robbins R, Grandner MA, Buxton OM, et al. Sleep myths: an expert-led study to identify false beliefs about sleep that impinge upon population sleep health practices. *Sleep Health.* 2019;5(4):409-417.
108. Richard E, Jongstra S, Soininen H, et al. Healthy Ageing Through Internet Counselling in the Elderly: the HATICE randomised controlled trial for the prevention of cardiovascular disease and cognitive impairment. *BMJ Open.* 2016;6(6):e010806.
109. Davidson S. *Digital Inclusion Evidence Review 2018.* AgeUK. Love later life;2018.
110. (CBS) CBvdS. Internet; toegang, gebruik en faciliteiten. 2019; https://www.cbs.nl/nl-nl/nieuws/2020/04/steeds-meer-ouderen-maken-gebruik-van-sociale-media. Accessed 20-01-2020, 2020.
111. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet.* 2017;390(10113):2673-2734.
112. O'Donnell J, Ding F, Nedergaard M. Distinct functional states of astrocytes during sleep and wakefulness: Is norepinephrine the master regulator? *Curr Sleep Med Rep.* 2015;1(1):1-8.
113. Carter ME, Yizhar O, Chikahisa S, et al. Tuning arousal with optogenetic modulation of locus coeruleus neurons. *Nat Neurosci.* 2010;13(12):1526-1533.
114. Betts MJ, Kirilina E, Otaduy MCG, et al. Locus coeruleus imaging as a biomarker for noradrenergic dysfunction in neurodegenerative diseases. *Brain.* 2019;142(9):2558-2571.
115. Kaufman SK, Del Tredici K, Thomas TL, Braak H, Diamond MI. Tau seeding activity begins in the transentorhinal/entorhinal regions and anticipates phospho-tau pathology in Alzheimer's disease and PART. *Acta Neuropathol.* 2018;136(1):57-67.
116. Knudsen K, Fedorova TD, Hansen AK, et al. In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study. *Lancet Neurol.* 2018;17(7):618-628.
117. Tagliazucchi E, van Someren EJW. The large-scale functional connectivity correlates of consciousness and arousal during the healthy and pathological human sleep cycle. *Neuroimage.* 2017.
118. Winer JR, Mander BA, Helfrich RF, et al. Sleep as a Potential Biomarker of Tau and beta-Amyloid Burden in the Human Brain. *J Neurosci.* 2019;39(32):6315-6324.
119. Doosti-Irani A, Mansournia MA, Collins G. Use of G-methods for handling time-varying confounding in observational research. *Lancet Glob Health.* 2019;7(1):e35.

120. VanderWeele TJ. A unification of mediation and interaction: a 4-way decomposition. *Epidemiology.* 2014;25(5):749-761.
121. Lim AS, Yu L, Kowgier M, Schneider JA, Buchman AS, Bennett DA. Modification of the relationship of the apolipoprotein E epsilon4 allele to the risk of Alzheimer disease and neurofibrillary tangle density by sleep. *JAMA Neurol.* 2013;70(12):1544-1551.
122. Sleep Disorders Knowledge Portal. 2020; sleepdisordergenetics.com. Accessed 27-01-2020, 2020.
123. Noordam R, Bos MM, Wang H, et al. Multi-ancestry sleep-by-SNP interaction analysis in 126,926 individuals reveals lipid loci stratified by sleep duration. *Nat Commun.* 2019;10(1):5121.
124. McCauley P, Kalachev LV, Mollicone DJ, Banks S, Dinges DF, Van Dongen HP. Dynamic circadian modulation in a biomathematical model for the effects of sleep and sleep loss on waking neurobehavioral performance. *Sleep.* 2013;36(12):1987-1997.
125. Sadri A. Excess amyloid beta can be degraded in healthy humans. *Ann Neurol.* 2018;83(3):650.
126. Olsson M, Arlig J, Hedner J, Blennow K, Zetterberg H. Sleep deprivation and plasma biomarkers for Alzheimer's disease. *Sleep Med.* 2019;57:92-93.
127. Olsson M, Arlig J, Hedner J, Blennow K, Zetterberg H. Sleep deprivation and cerebrospinal fluid biomarkers for Alzheimer's disease. *Sleep.* 2018;41(5).
128. Carvalho DZ, St Louis EK, Knopman DS, et al. Association of Excessive Daytime Sleepiness With Longitudinal beta-Amyloid Accumulation in Elderly Persons Without Dementia. *JAMA Neurol.* 2018;75(6):672-680.