# Sleep, Ageing, and Alzheimer's Disease: From Neural Mechanisms To Exercise Interventions.

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#### Abstract

# Sleep, ageing, and Alzheimer's disease: from neural mechanisms to exercise interventions.

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This manuscript-based thesis explores the relationships between sleep and sleep physiology during non-rapid eye-movement (NREM) sleep stages 2 and 3, brain-health, and cognition in older adults and persons with Alzheimer's Disease (AD). It provides new insights into the associations between sleep, biomarkers of neurodegeneration, and cognition in older adults. It also provides new evidence demonstrating that spindle and slow oscillation activity during NREM sleep constitute predictive and non-invasive biomarkers of neurodegeneration, cognition, and mental health in persons with AD. Sleep microarchitecture can, therefore, also provide novel therapeutic targets for preserving brain-heath and slowing AD progression. These findings extend previous evidence showing that sleep may be one of the most important modifiable risk factors for functional and cognitive decline and dementia in older adults. The thesis then explores how exercise, a promising and widely accessible intervention targeting sleep physiology, can be an effective intervention for poor sleep in healthy older adults and persons with Mild Cognitive Impairment and AD. The implications of this thesis' findings for clinical care of persons with AD, preserving brain-health and cognition in older adults, and sleep research are discussed. Our findings can serve as a springboard for future research on sleep-based strategies to preserve brain health in older adults and delay the progression of AD symptoms, with considerable potential benefits for persons with AD, their caregivers, and communities.

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Ralph Waldo Emmerson said:

"Cultivate the habit of being grateful for every good thing that comes to you, and to give thanks continuously. And because all things have contributed to your advancement, you should include all things in your gratitude."

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"... my North, my South, my East and West,

My working week and my Sunday rest,

My noon, my midnight, my talk, my song"

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"Energy and persistence conquer all things." Benjamin Franklin

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#### **Contribution of Authors**

All of the studies contained in this thesis were developed by the student, Dr. Arsenio Páez, who conceptualised the initial project and overall research program with the guidance of Prof. Thien Thanh Dang-Vu (supervisor, Concordia University). For each study and manuscript included in this thesis, Dr. Páez developed the research questions, study designs, and analytical methods, conducted the reviews of evidence, collected data (as appropriate), cleaned, processed, and curated data, extracted and analysed brain oscillation data using specialized programming scripts (chapters II and III), conducted all statistical analyses in the thesis, interpreted and synthesized results, prepared all figures and tables, wrote, revised, and submitted each manuscript (chapters II-IV) for publication, wrote and revised the thesis introduction and discussion chapter, and prepared the thesis for submission. These were completed under the scientific and academic supervision of Prof. Dang-Vu.

The brain oscillation analyses used in chapters II and II were undertaken using Python-based coding software and an in-house analysis program developed and refined at the Sleep, Cognition, and Neuroimaging Laboratory at Concordia University by Jordan O'Byrne, Dr. Nathan Cross, and Dr. Aurore Perrault.

The manuscripts in chapters II-IV were written by Dr. Páez and revised by Prof. Dang-Vu. The manuscripts in chapters II and III were also guided and revised by Dr. Gerard Piñol-Ripoll, of Unitat de Trastorns Cognitius, Cognition and Behavior Study Group, Hospital Universitari Santa Maria Universitat de Lleida, IRBLleida, Lleida, Spain the All listed co-authors in the manuscripts in chapters II-IV contributed to the interpretation of study findings and provided input on the final manuscripts.

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#### Chapter I: Introduction: Sleep, ageing, brain health, and Alzheimer's Disease

#### Chapter overview

This chapter describes the background and context for this thesis. It gives an overview of the relationships between sleep, cognition, Alzheimer's Disease and brain health, and treatments for poor sleep in older adults. It explores the associations between sleep and sleep difficulties and neurodegenerative diseases of ageing, with a specific focus on AD/ADRD. It discusses knowledge gaps, and opportunities that will be investigated in the thesis. The sections on exercise, sleep, and cognition in this chapter were published in an adapted form as "State of the Science: Exercise interventions targeting sleep in older and younger adults," a chapter in "The Cambridge University Handbook of Sleep Models and Theories." Cambridge University Press, UK, 2024 (*in press*).



Figure 1: Thesis flow diagram

Sleep is essential for health and well-being. In fact, there is a bidirectional relationship between sleep and health. Sleep disturbances can raise the risk for and increase the severity of a number of physical and mental health disorders, ranging from diabetes<sup>1</sup> and depression<sup>2</sup> to cardiovascular disease<sup>3</sup> and dementia<sup>4</sup>. Many of these disorders also result in poor sleep. For example, poor sleep is associated with up to 50% greater risk of myocardial infarct, while up to a third of persons with heart disease develop insomnia<sup>5</sup>. Similarly, poor sleep raises the risk of Alzheimer's Disease and Related Dementias (AD/ADRD), Parkinson's disease, and a range of neurodegenerative disorders of ageing. while up to two thirds of person with Alzheimer's Disease and 75% of persons with Parkinson's Disease report poor sleep<sup>6–13</sup>.

Sleep also plays vital roles in maintaining brain health and is critical for cognition, learning and memory<sup>7,14–18</sup> It is important for synaptic homeostasis, neuroplasticity and neural repair<sup>6,19–24</sup>. Sleep facilitates neuroplasticity and increases during periods of greater synaptic reorganization, such as during early development<sup>19,20</sup> and recovery from neural injury<sup>2122</sup>. The brain's metabolic functions also depend on sleep, which plays vital roles in regulating the clearance of proteins such as  $\beta$ -amyloid (A $\beta$ ) and tau that are linked to neurodegeneration and neurodegenerative disorders such as AD/ADRD<sup>6,23,24</sup>.

#### Sleep architecture

Sleep is made up of two separate and distinctly different states: NREM sleep and rapid eye movement (REM) sleep. The NREM sleep state consists of light sleep stages (N1, N2) and deep sleep (N3), also referred to as slow wave sleep (SWS). Slow wave sleep is critical for

cognitive performance<sup>7</sup>, including the consolidation of declarative memories<sup>16</sup> and the recall of facts or recognition of items<sup>25,26</sup>. Early nocturnal sleep periods, which have five times more SWS and less REM than later sleep periods, enhance performance on declarative memory tasks compared to the same length of time spend asleep during the later nocturnal period<sup>27</sup>. Slow wave sleep has been also linked to a number of processes vital for brain and body health. These include immune and autonomic nervous system functions, cardio-vascular and mental health, cellular metabolism, hormone regulation, and clearance of metabolic waste products<sup>16,28–30</sup>. Loss of normal slow wave physiology has also been linked to cognitive impairment and pathophysiological changes in the brain that can precede the first cognitive symptoms of AD/ADRD by 15-20 years<sup>6,9,31–35</sup>.

During NREM sleep, brain activity is shaped by specific brainwaves that are produced by thalamocortical activity and are detectable with electroencephalography (EEG)<sup>36</sup>. These include sleep spindles and slow oscillations. **Sleep spindles** are 9–16 Hz waxing-and-waning oscillations generated within the thalamo-cortical network<sup>37</sup>. They have been consistently associated with sleep-dependent memory consolidation, cognition, and sleep continuity<sup>37</sup>. Sleep-dependent learning refers to a durable improvement of performance on a given task that occurs slowly and in the absence of continued practice and only following sleep<sup>38</sup>.

Sleep spindles are particularly involved in the transfer of information from short-term memory in the hippocampus to long-term memory in the neocortex that is critical for both declarative and procedural memory<sup>39–41</sup>. Increased sleep spindle activity during NREM sleep has been reported following learning of a variety of memory tasks<sup>42,43</sup>, including declarative memory<sup>44</sup>. Spindle activity during sleep also has enduring effects on learning and memory,

strengthening hippocampal-cortical networks and integration across memory representations<sup>45</sup>. Sleep spindle density during overnight sleep is also linked to enhanced hippocampal–cortical functional connectivity the next day, when information learned before sleep is recalled or restudied<sup>45</sup>.

Large-amplitude, low-frequency **slow-waves** (> 75 microV, 0.5-4Hz)<sup>36</sup> and slow oscillations (SO)( <1 Hz) largely arise from the prefrontal neocortex and also underlie memory consolidation during sleep<sup>46</sup>. A tight temporal correlation has been reported between hippocampal and neocortical neuronal discharges during slow-waves<sup>47</sup>. Increasing slow-wave activity with various stimulation paradigms enhances the retention of hippocampus-dependant declarative memories<sup>48,49</sup>. Weiner et al, 2023 showed that the synchronisation (cross-frequency coupling) of slow-waves and sleep spindles during NREM plays an important role in sleep-related memory consolidation in older adults<sup>50</sup>. Both SO and sleep spindles may also play other important roles in brain health and the clearance of waste material that accumulates in the brain during waking activity and is associated with neurodegeneration<sup>17,18,51,52</sup>. This is explored extensively in the studies in chapters two and three of this thesis.

Brain oscillations during NREM sleep also contribute to sleep quality and brain health by protecting the sleeping brain from external interference<sup>17,18</sup>. Sleep spindles play an important role in preserving sleep stability by filtering external information at the thalamic level during sleep, protecting the brain from disruption by sounds and other types of environmental stimulation during sleep<sup>18</sup>. For example, Dang Vu et al. (2010) investigated the relationship between spindle density and the probability of maintaining sleep continuity against sounds of

increasing intensities. At any sound intensity level, persons with higher spindle density were more likely to preserve the continuity of their sleep than those with lower spindle density<sup>18</sup>.

#### Sleep and ageing

Sleep quality, quantity, and architecture change throughout the lifespan, however<sup>53,54</sup>. Sleep duration decreases by an average of 27 minutes per decade after mid-life<sup>55</sup>. Sleep also becomes lighter and more fragmented<sup>53,56</sup>. Sleep latency (the length of time it takes to fall asleep), and waking after sleep onset (WASO) increase,<sup>57–59</sup> while sleep efficiency (the percentage of time we spend asleep while in bed), decreases<sup>60</sup>. Age-related changes in the brain and shifts in circadian rhythms also influence the earlier evening sleepiness and early morning waking frequently reported by older adults<sup>58,60 61</sup>. Sedentariness, comorbidities, and polypharmacy can increase with age and are also associated with poor sleep, further reducing sleep quality in later life<sup>62–64</sup>.

Sleep architecture and microarchitecture also change with increasing age. Older adults spend more time in light sleep (NREM1 and NREM2), while and SWS (NREM3) and rapid eye-movement sleep (REM), vital for many body and cognitive processes, decrease<sup>56,57</sup>. Slow wave activity (spectral power between 0.5 and 4 Hz) during NREM sleep begins to decrease as early as middle age<sup>59,65</sup>. Sleep spindle activity, including their duration, frequency and density (the number of spindles during a 30 second sleep epoch) slow wave and SO amplitude and density decrease<sup>7,39,66</sup>. Slow wave-spindle cross-frequency coupling and functional connectivity between brain regions and networks also decrease with normal

ageing and are associated with the cognitive decline and impaired memory experienced by older adults<sup>7,34,39,67,68</sup>.

These age-related changes in sleep physiology increase older adults' vulnerability to sleep disturbances such as insomnia. Sleep disorders such as insomnia become increasingly common in later life<sup>53,56</sup>. Over half of people over 60 years old have difficulty sleeping or experience insomnia symptoms (difficulty falling or staying asleep and resulting daytime impairment)<sup>69–72</sup>. Middle-aged and older adults with insomnia disorder have higher risk of poorer health outcomes and cognitive decline than older adults without sleep complaints, even after adjusting for comorbidities such as obesity, hypertension, and diabetes<sup>71–74</sup>. Insomnia also raises their risk of decreased quality of life, impaired attention and decision making, cognitive decline, and dementia<sup>70–72,75</sup>. Poor sleep is highly linked to increased risk Alzheimer's Disease (AD) and its progression, with important consequences for population health<sup>6,76–78</sup>.

#### Alzheimer's Disease and Related Dementias

Alzheimer's disease is the most common cause of dementia<sup>79</sup>. It is associated with progressive loss of memory and cognitive impairment, decreased functional capacity, institutionalization, and increased risk of mortality among older adults<sup>77,79</sup>. Alzheimer's disease is also the fifth leading cause of death among persons 65 years and older and the seventh-leading cause of death in the United States<sup>80,81</sup>. Over 51 million people currently live with Alzheimer's disease and Related Dementias (AD/ADRD) worldwide<sup>80,81</sup>. This number is expected to triple to more than 132 million by 2050, with the greatest increase expected in

low and middle-income countries, presenting profound challenges for families, communities, and societies in resource-constrained settings<sup>82,83</sup>.

Advancing age is the strongest risk factor for AD<sup>77,84</sup>. However, an interplay of genetic susceptibility, environmental, and lifestyle factors also contribute to the risk of AD<sup>77,85,86</sup>. Genetic risk factors include familial history of AD (two or more family members, alleles of the apolipoprotein E [APOE] gene<sup>87,88</sup>, or other genes associated with susceptibility to AD<sup>89,90</sup>. Environmental exposures such air pollution and toxic and heavy metals have been linked to increased risk of AD<sup>91,92</sup>. Other factors such as education, social connectedness, and leisure activity are also associated with the risk of AD<sup>4,93,94</sup>.

Lifestyle factors play an important role in the risk of AD<sup>4,86,93</sup>. Cardiovascular risk factors, including such as hypertension, hypercholesterolaemia, diabetes, and obesity, or a combination of them, increases the risk of AD in middle-aged and older adults<sup>77,95</sup>. High fat and high glycaemic diets increase the risk of obesity, type II diabetes, and cardiovascular disease, each of which are associated with increased risk of AD<sup>86</sup>. Other modifiable lifestyle factors such as smoking, physical activity, diet, and sleep are also associated with AD risk<sup>6,94,96</sup>. Regular physical activity, particularly aerobic exercise, has been shown to reduce the risk of AD<sup>94,97,98</sup>.

### Sleep and Alzheimer's Disease

There is a bidirectional relationship between sleep and AD<sup>9,10</sup>. Sleep disturbances increase the risk of cognitive decline and AD<sup>6,7,99</sup>. They can also predict or accelerate the progression

of cognitive decline and functional impairment in persons with AD<sup>6,7,99</sup>. Conversely, Alzheimer's pathology can also drive neuronal degeneration in areas crucial for sleep regulation and spindle activity, such as cholinergic neurons in the basal forebrain or noradrenergic neurons in the locus coeruleus<sup>100</sup>. Up to 66% of persons with AD report or experience poor sleep<sup>6,7,99,101</sup>.

Poor sleep may have a causal role in the pathophysiology of AD  $^{6,9,102}$ . Sleep disorders, including insomnia, restless leg syndrome, and sleep apnoea often appear in the preclinical stage of AD and induce systemic and central nervous system inflammation and neurophysiological changes in the brain that may drive the onset and progression of AD<sup>6,8,103</sup>. Sleep plays vital roles in regulating the clearance of proteins such as  $\beta$ -amyloid (A $\beta$ ) and tau linked to the development and progression of AD<sup>6,24,104</sup>. The cognitive and behavioural symptoms of AD correlate with the accumulation of  $\beta$ -amyloid (A $\beta$ ) and tau<sup>105</sup>.

#### Alzheimer Disease pathophysiology and AD biomarkers

Beta-amyloids are peptides of the 36-42 amino acid sequence and the main component of amyloid plaques that accumulate in the brain in persons with  $AD^{105,106}$ . The amyloid cascade hypothesis proposes that  $A\beta$  is the main cause of the disease, triggering tau pathology and neuronal death that leads to the symptoms of  $AD^{105}$ . Tau is a neuronal microtubule-associated protein mainly found in neuronal axons that plays a leading role in the formation of the neurofibrillary tangles(NFT) that are hallmarks of  $AD^{9,107,108}$ . Tau hyperphosphorylation causes microtubule destabilisation and neurofibrillary tangles, driving downstream neurodegenerative damage and resulting in microglial activation, synaptic loss, and neuronal death.<sup>9,13</sup> Recent findings have called the amyloid cascade hypothesis into question,

suggesting that A $\beta$  and tau may act in parallel in AD, and that tau, rather than A $\beta$ , may be the main determinant of brain atrophy, cognitive changes and clinical decline in AD<sup>109</sup>. Nevertheless, both  $\beta$ -amyloid (A $\beta$ ) and tau play central roles as biomarkers of the development and progression of AD.

However, AD may be a disease of multiple aetiologies as well as overlapping risk factors<sup>110</sup>. Sleep is also linked with other biomarkers of neuroinflammation and neurodegeneration associated with AD, such as neurofilament-light chain (NfL), Chitinase-3-like protein-1 (YKL-40), and neurogranin 36 (Ng36). These fluid biomarkers have emerged as promising diagnostic markers of neuroaxonal damage, disease progression, and cognitive decline in AD<sup>111,112</sup> Identifying and quantifying neuroaxonal damage is a critical for supporting AD diagnosis, disease-staging, and prognosis.

Neurofilament-light chain is a subunit of the neurofilament that plays an important role in axonal and dendritic branching and growth and axonal integrity<sup>113–116</sup>. Neurofilaments provide structural stability for neurons and are essential for impulse conduction along neuronal axons<sup>112,115,116</sup>. Neurofilament-light is strongly expressed in myelinated axons and secreted in the CSF. It is also a biomarker of subcortical, large-calibre axonal degeneration<sup>113–</sup><sup>116</sup>. Neurofilament-light has become one of the most promising CSF markers of neuroaxonal degeneration and disease progression in AD<sup>117,118</sup>. An important feature of NfL is that it can allow detection of AD-related pathophysiological changes in living persons.<sup>119</sup> Increased plasma NfL levels are prognostic for AD/ADRD, and CSF NFL levels predict white matter changes, brain atrophy, and cognitive decline in persons with AD<sup>116,117,120</sup>. The ratio of NfL/Aβ42 also predicts cortical amyloid load and cognition in persons with AD.<sup>117</sup>

Both CSF and plasma neurofilament-light chain (NfL) are also indicators of AD severity and cognitive decline that may be influenced by sleep<sup>117,120–125</sup>. Elevated serum NfL levels have been reported in persons with chronic insomnia disorder.<sup>126</sup> Decreased sleep-depth(more time spend in NREM1, less in NREM3) is also associated with increased CSF NfL levels in persons with mild to moderate AD.<sup>120</sup>

Other biomarkers, including CSF YKL-40 and Ng36 have been linked with both sleep brainhealth in older adults and persons with AD<sup>127</sup>. Chitinase-3-like protein 1 expression is abundant in astrocytes in neuroinflammatory conditions and has been associated with early pathophysiological changes and neuroinflammatory response to amyloid deposition in early AD<sup>128–130</sup>. Increased CSF YKL-40 levels have also been linked with circadian rhythm disfunction, neuroinflammation, and AD progression<sup>127,130</sup>. Concentrations of YKL-40 are higher in AD patients than in cognitively normal individuals and correlated with dementia biomarkers, such as tau proteins and A $\beta$ , supporting its potential role as a complementary biomarker in the diagnosis and prognosis of AD <sup>130130</sup>. Neurogranin-36 (Ng36) is a postsynaptic protein that is enriched in the cortex and hippocampus and is a putative marker of synaptic integrity, synaptic loss, brain atrophy and cognitive decline in AD<sup>127,131–133</sup>. Elevated Ng36 is associated with cognitive decline in persons with AD<sup>127</sup>.

#### Sleep microarchitecture, biomarkers, and AD

Mounting evidence shows that sleep physiology and the sleep-wake cycle directly influences AD biomarkers and subsequent cognitive decline in older adults and persons with  $AD^{134-137}$ . For example, extracellular A $\beta$  and tau in brain interstitial fluid and cerebral spinal fluid (CSF)

fluctuate diurnally, with soluble A $\beta$  levels rising during wakefulness and lowering during sleep<sup>9,136,138,139</sup>. A number of associations between tau and sleep–wake regulation have also been reported, supporting a bidirectional relationship between sleep–wake disruption and tau pathology, similar to the bidirectional relationship between sleep–wake disruption and A $\beta^9$ .

Amyloid-beta levels have also been correlated with sleep disruptions in cognitively normal persons with preclinical AD<sup>6,9,31</sup>. A significant inverse correlation has been found between CSF Aβ42 levels, SWS duration and continuity, and SWA in cognitively normal older adults (controlling for age and APOE4 status), suggesting that sleep disturbances might drive increased soluble brain levels of Aβ prior to amyloid deposition <sup>140</sup> Decreased NREM SWA has been associated with Aβ and tau deposits in cognitively normal older adults and in early stages of AD<sup>35,135</sup>. Decreased NREM SO have also been associated with increased Aβ accumulation in the medial prefrontal cortex<sup>35</sup>. Sleep disruption has also been correlated with higher tau deposition and increased tau pathology in older adults, but the precise mechanisms behind these associations are not known<sup>51,135,141,142</sup>.

Sleep architecture and physiology change with increasing age, but these changes are more pronounced in persons with AD and have been linked to AD progression<sup>29,143,14432,145,146</sup>. Meta-analyses of polysomnography (PSG) measured sleep architecture in persons with AD/ADRD have found increased sleep latency (the time it takes to fall asleep once in bed), decreased total sleep time and sleep efficiency, and increased wake time after sleep onset, and number of awakenings once asleep in persons with AD<sup>78</sup>. Sleep fragmentation and

significant reductions in slow-wave (SWS) and REM sleep have also been found in persons with mild to moderate AD<sup>78,147</sup>.

Decreased SWS and REM sleep and loss of normal slow wave physiology are significantly associated with pathophysiological changes in the brain and the severity of cognitive impairment in persons with AD<sup>29,33–35,78,147</sup>. These changes can also predict or accelerate the progression of cognitive decline and functional impairment in persons with AD<sup>6,7,99</sup>.

Changes in sleep microarchitecture, including SWA, sleep spindles, and SO, have also been linked to the development and progression of AD<sup>29,143,144</sup>. Sleep microarchitecture is altered in persons with AD to a greater degree than what is seen in normal ageing<sup>32,145,146</sup>. Greater reductions in spindle activity, including spindle density and duration, have been found in persons with Mild Cognitive Impairment (a prodromal stage of AD [MCI]) and AD than in healthy older adults<sup>32,78,148–153</sup>. Slow oscillations also decrease in number and amplitude in middle-aged and older adults, but these decreases are also more pronounced in persons with cognitive decline or AD<sup>29,154,155</sup>. The synchronisation (cross-frequency coupling) of slow waves and spindles during NREM that plays an important role in sleep-related memory consolidation in older adults deteriorates to a greater degree with advancing age and AD<sup>50,51,141,156,157</sup>.

#### Alzheimers disease and poor sleep

While poor sleep may play a leading role in AD pathology,  $A\beta$  and tau pathology may also drive changes in sleep in persons with at risk of AD. Their accumulation in cortical regions, the hypothalamus, and nuclei regulating sleep-wake can lead to sleep disturbances and

impaired slow-wave activity (SWA) during non-rapid eye-movement (NREM) sleep, which may also contribute to hippocampus-dependent cognitive decline in older adults<sup>9,35,158</sup>. Cortical atrophy and loss of grey matter volume in the hippocampus, praecuneus, amygdala, and cingulate gyrus may also be associated with declines in spindle and SO activity<sup>31</sup>

During early AD, phosphorylated tau (pTau181) accumulates in areas associated with arousal and sleep regulation and may play a role in sleep-wake disruptions, disrupting spindle activity and impairing memory consolidation<sup>159</sup>. Tau pathology in the medial temporal lobe is associated with reductions in hippocampal ripples and the synchronization of spindle-ripple events, also impairing memory consolidation during sleep<sup>160</sup>. Physiological changes associated with AD progression also reduce synaptic and dendritic integrity and lead to neuronal hyperexcitability and hypersynchronous network activity, further impairing sleep spindle generation and memory consolidation<sup>161</sup>.

These associations between AD pathology and sleep have important implication for persons with AD. They may also accelerate declines in physical and mental health in AD and their severity increases as AD progresses. Sleep difficulties affect up to 25% of persons with mild-to-moderate AD and over 50% of people with moderate-to-severe AD<sup>6,101</sup>. Sleep disturbances and circadian rhythm dysfunction also decrease functional capacity and quality of life for persons with AD and their caregivers<sup>77,162</sup>. In fact, sleep disorders and difficulty sleeping through the night are among the leading causes of caregiver stress and institutionalization for persons with AD<sup>77,162</sup>. They are also associated with increased aggressive behaviour, agitation, and confusion in persons with AD.

#### Evidence gaps and opportunities

Given the growing incidence of AD and its effects on patients and their communities, there is pressing need for greater understanding of factors contributing to cognitive decline and disease progression in persons with AD, and accessible, sustainable methods for early identification and treatment to delay AD onset or slow its progression in persons at risk<sup>4,77,82,83</sup>. The bidirectional relationship between sleep and AD/ADRD pathology offers opportunities for early identification of persons at-risk and the development of sleep-based interventions to reduce AD risk and delay its progression<sup>10,104,145,163–165</sup>.

#### Identification of persons at risk of AD or accelerated AD progression

Levels of AD and neurodegeneration biomarkers, including Aβ (AB40, 42, or AB40/42), totaltau (T-tau), phosphorylated tau (P-tau) and neurofilament light (NfL), measured in plasma, cerebral spinal fluid (CSF) or positron emission tomography (PET) are strongly correlated with their levels in the brain.<sup>119,166,167</sup> However, PET imaging requires expensive, specialized facilities, exposes the participant to radiation, and access to PET scanning can be limited.<sup>119,168</sup> This can also hinder recruitment and retention of participants in studies of AD, particularly participants from minority or under-represented groups.<sup>119</sup>

Recent advances in bioassays have also increased the viability of CSF and plasma tau levels as potential surrogates for the presence neurofibrillary tangles<sup>169</sup>. Lumbar puncture for CSF is more accessible than PET scanning but is invasive and mild adverse reactions may result from lumbar puncture.<sup>84,119</sup> Recent advances in ultra-sensitive blood-based assays also enable accurate measures of AD biomarkers, overcoming some of the high cost, invasiveness, and

potential adverse reactions associated with lumbar-puncture for CSF or PET.<sup>119,120,167</sup> They are not without cost, however, and require blood draws and laboratory analysis with specialised equipment<sup>119,127,167</sup>.

There is growing need for accessible, non-invasive screening for AD risk and progression, Sleep assessments, including sleep alterations correlated with AD biomarkers, offer the potential for accessible, non-invasive screening for AD risk that may increase the possibility sensitive, and non-invasive screening for AD and early identification of persons at risk, before the onset of clinical symptoms, <sup>145,164,165</sup>. Investigating the associations between sleep physiology and these biomarkers may also support the development of interventions targeting sleep to delay AD progression. Changes in sleep quality and efficiency can also precede the onset of cognitive decline and run in parallel with AD pathology and cognitive dysfunction<sup>163</sup>.Changes in sleep architecture can indicate amyloid and tau pathology and predate the onset of cognitive changes by years or decades in persons with AD<sup>8,9,16351,143</sup>.

A growing body of research has explored associations between sleep microarchitecture, biomarkers of neurodegeneration, and cognition in healthy in older adults. However, the majority of research exploring these associations has been undertaken in healthy, cognitively normal, older adults, rather than persons with AD, creating and important gap in our knowledge of the links between sleep physiology and AD progression. For example, Zavecz et al (2023) found that NREM SWA predicted and significantly moderates the effect of Aβ status on memory function in cognitively normal older adults with high AB burden, while those without significant Aβ burden did not benefit similarly from the presence of NREM SWA<sup>170</sup>. Studies by Varga et al. (2016), Mander et al. (2015, 2016), Osorio

et al. (2014) and others have also shown that SWA, specifically SO, is associated with CSF AB levels in cognitively normal, healthy older adults<sup>34,35,67,135,171,172</sup>, and could predict the speed of AB accumulation over time<sup>67</sup>.

Much less is known about predictive associations between SWA, spindles, biomarkers of neurodegeneration, and cognition in persons with AD<sup>9,141</sup>. Whether features of SWA and NREM sleep physiology can be used to predict or alter the progression of amyloid or tau pathology or cognitive decline in persons who already have clinical AD has not been investigated extensively<sup>9,141,151,152,173</sup>. Therefore, these were investigated in the studies in chapters two and three of this thesis.

#### Treatments for AD, cognition, and modifiable risk factors

There are currently few FDA approved, disease-modifying treatment for AD in the US, such as aducanumab, lecanemab-irmb and donanemab-azbt<sup>174</sup>. These target amyloid plaque in persons with early, symptomatic AD, but it can be difficult to identify persons for treatment before Aβ burden is too high<sup>174</sup>. There is growing interest in whether alterations in NREM SWA, including spindles and slow oscillations, could be used to monitor the progression of AD pathology before the onset of clinical symptoms or monitor response to treatment non-invasively<sup>13551,145,175</sup>. These may also offer important and novel treatment targets to delay the onset of AD symptoms or slow their progression. Delaying the onset of AD clinical symptoms by just 5 years may reduce treatment costs for AD by up to 40% and add 2.7 additional life years (about 5 years free of AD) for persons with AD<sup>176</sup>.

#### Treating sleep to preserve brain-health, reduce AD risk, or slow AD progression

Given the limited availability of effective treatment options for AD, identification and prevention of modifiable risk factors for AD, such as physical inactivity or poor sleep, is essential. Treating poor sleep may therefore be an important preventive approach for preserving cognition and brain health and reducing the risk of AD in older adults<sup>72,177</sup>. A number of interventions have been developed to improve sleep health. These include pharmacological treatments, such as sedative antidepressants and benzodiazepine receptor agonists<sup>178,179</sup>, and a range of non-pharmacological interventions<sup>179,180</sup>, including sleep hygiene, mindfulness techniques, cognitive behavioural therapies for insomnia, and physical exercise<sup>180,181</sup>.

**Medications**, including sedative antidepressants, hypnotics, benzodiazepine receptor agonists, can be effective short-term treatments for poor sleep, with dual orexin receptor antagonists (DORA) showing evidence of effectiveness for up to 1 year<sup>182</sup>. However, pharmacological treatment is currently only recommended for acute management of insomnia disorder, and there is little evidence available about their comparative effectiveness against other active treatments, versus placebo, in older adults<sup>183–187</sup>. There is a paucity of long-term data available for their effectiveness or tolerability in older adults.<sup>17</sup> Their adverse effects, such as daytime drowsiness, sedation, and dependence also limit their acceptability for users<sup>188,189</sup>. Other pharmaceutical treatments such as melatonin or melatonin agonists (e.g. ramelteon) have not been shown to be effective (low to very low effects) in metaanalyses of pharmaceutical interventions for acute or long-term treatment of insomnia<sup>183</sup>.

**Non-pharmacological interventions**, such as cognitive-behavioural therapy for insomnia, can therefore play an important role in treating sleep difficulties.<sup>181</sup> **Cognitive-behavioural** 

**therapy (CBTi) for insomnia** is the preferred first-line treatment for sleep problems<sup>190</sup>. It typically takes place over 6-8 weeks, and focuses on restructuring the thoughts, feelings, and behaviours that contribute to the participant's insomnia<sup>191,192</sup>. Therapeutic techniques within a CBTi program include stimulus control, sleep restriction, and relaxation training<sup>191,192</sup>.

Systematic reviews and meta-analyses of CBTi have found large treatment effects (Cohen's criteria) for in person "onsite" CBTi (-1.27;95%CI-1.70,-0.84), group-delivered CBT-I (-1.00;95%CI-1.42.-0.59), and digital CBTi (remotely or by tele-health) (-1.28;95%Cl-2.06,-0.50) on self-reported insomnia severity (e.g. with the Insomnia Severity Index<sup>193</sup>, Athens Insomnia Scale<sup>194</sup>, Insomnia Symptom Questionnaire<sup>195</sup>, or Sleep Condition Indicator<sup>196</sup>) and sleep quality in younger and older adults<sup>197–199</sup>. Generally, CBT-I is associated with robust improvements in self-reported measures of sleep onset latency and (initiation of sleep) and wake after sleep onset (sleep maintenance). However, although CBTi is widely effective for the treatment of insomnia in younger and older adults,<sup>200201</sup> it typically achieves success in only two-thirds of participants<sup>200,202</sup>. It is also particularly effective for improving subjective, rather than objective (e.g., sleep architecture or physiology) sleep outcomes<sup>201</sup>. Meta-analyses consistently find no significant effects of CBTI on objectively assessed (by polysomnography or actigraphy) sleep-related outcomes, including total sleep duration or sleep efficiency<sup>197,203</sup>. This is important, given the strong links between these, sleep microarchitecture, cognition, and the risk of neurodegenerative disorders.

A CBTi treatment program also requires 6-10 treatment sessions, and can be expensive and difficult to access<sup>198,204–207</sup>. Digital cognitive behavioural therapy (eCBTi) are less costly and more accessible have shown promising results<sup>198,208</sup> However, more research is needed to

investigate the high rates of early dropout or disengagement that have been reported in some studies of eCBTi<sup>209</sup>. The feasibility and acceptability of eCBTi with older adults with insomnia has also not been investigated extensively. Additionally, no current treatment for insomnia, including CBTi, has been shown to improve objectively assessed cognition or biomarkers of neurodegeneration in older adults.<sup>210,211</sup> This creates opportunities to complement CBTi with exercise, which does targets sleep physiology including NREM slow-wave activity <sup>212–215</sup>, to boost its effects and achieve wider efficacy.<sup>216–218</sup>.

**Exercise** is now suggested as an adjunct to CBTi in the treatment of insomnia<sup>218,219</sup>. However, exercise has also emerged as an effective and accessible intervention for poor sleep, either independently or in conjunction with other approaches<sup>212,220–223</sup>. Like sleep, exercise is also a highly modifiable lifestyle factor strongly linked to a number of physical and mental health outcomes and quality of life.

Exercise is a promising, widely accessible intervention for sleep difficulties that can be performed in a variety of settings inexpensively or cost-free<sup>224,225</sup>. It may be an ideal complement to other healthy lifestyle approaches to preserving brain health in older adults<sup>218</sup>. Exercise is also associated with a range of benefits for health and quality of life and may protect against functional and cognitive decline in older age<sup>4,224,226,227</sup>. It has been shown to improve learning and memory independently of its effects on sleep in both younger and older adults<sup>228,229</sup>. In fact, exercise of most durations and intensities has been found to improve cognition<sup>230,231</sup>. However, cardiovascular (aerobic) and moderate-intensity exercise have been associated with greater increases in cognition and memory than light or vigorous exercise<sup>231–233</sup>. Recent research has also shown that exercise and sleep can also act

synergistically to benefit cognition, enhance memory consolidation and long-term memory<sup>222,234,235</sup>.

#### Critical review: Evidence for exercise and sleep

There is a robust bidirectional relationship between exercise and sleep<sup>236</sup>. Several metaanalyses have shown that exercise benefits sleep, and these beneficial are seen across adult age groups and sex<sup>212,220,223,224</sup>. Moderate to strong evidence also shows that exercise benefits sleep in persons with insomnia, obstructive sleep apnoea, and other sleep problems<sup>212,223,237</sup>, as well as persons with neurodegenerative disorders<sup>220,238</sup>. Exercise intensity can be categorized as low, moderate, or high-intensity based on the American College of Sports Medicine (ACSM) guidelines (table 1)<sup>239</sup>.

Intensity	HRmax	HRR	VO2max	METs	Borg RPE	
Low	<64%	<40%	≤ 45%	<3	<11 Very light to light	
Moderate	64-76%	40-60%	46-63%	3-5.9	12–13 Fairly light to somewhat	
					hard	
High	≥77%	>60%	64-90	6.0-8.7	14–17 Somewhat hard to very	
(vigorous)					hard	

Table 1:	Exercise	intensity	categories	according to	ACSM guidelines
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A wide-range of exercise modalities, durations, and intensities are reported in the evidencebase. Low-intensity exercises are generally performed at <64% of a person's maximal heart rate (mHR), while moderate intensity exercise are performed at 64-76% of mHR and high intensity exercise is performed at >76% mHR<sup>239</sup>. Examples of exercises interventions targeting poor sleep include stretching, aerobic exercise, aquatic exercise, interval training (e.g. high intensity interval training)<sup>235</sup> resistance training, elastic band exercise, cycling or cycle ergometry, overground walking programs, treadmill training, Pilates exercises, yoga, light Tai Chi, or programs combining different kinds of exercises. However, Kredlow et al (2015) found no differences in sleep outcomes between acute bouts of moderate intensity aerobic or anaerobic exercise, or chronic resistance exercise and mind-body exercise such as Tai chi or yoga), in a meta-analysis of exercise interventions targeting sleep, suggesting that exercise intensity, rather than mode, may have a greater influence on sleep outcomes<sup>224</sup>

#### Mechanisms Underlying the Effect of Exercise on Sleep

The mechanisms underpinning the beneficial effects of exercise on sleep are also less well understood<sup>240</sup>. Several potential mechanisms for these effects have been proposed, including exercise-induced reduction in systemic inflammation, modulation of endocrine or metabolic processes, increased endorphin, melatonin and growth hormone secretion, increasing antiinflammatory cytokines, changes in neurotransmitters regulating sleep, increased brain derived neurotrophic factor (BDNF), changes in heart rate and hear rate variability, body temperature, autonomic function, raising of core body temperature, and entrainment of sleep wake and cycles circadian rhythms, among others<sup>224,241</sup>. Circadian rhythms are, in turn, major determinants of human physiology, endocrinology, and behaviour, including sleep <sup>242</sup>. Other proposed mechanisms include exercise-induced changes in mood, depression, or anxiety influencing sleep <sup>241,243,244</sup>. Features of exercise programs, such as their frequency, duration, or the time of day may also influence these effects.

Exercise may also influence SWS through homeostatic regulation of body temperature, which increases during exercise but decreases during SWS<sup>224,243</sup>. A larger amount of SWS may be needed after exercise to maintain homeostasis<sup>224,243</sup>. Acute and regular moderate

intensity exercise also increases slow-wave activity (SWA) during SWS in younger adults<sup>213,214</sup> and increases electroencephalogram (EEG) power during SWS in older adults.<sup>245</sup>

Exercise has also been shown to decrease levels of biomarkers and cytokines associated with poor sleep, inflammation, and cognitive decline, and increase those linked to sleep, cognition and brain health.<sup>246–248</sup>. Examples include Aβ, Brain-Derived Neurotrophic Factor (BDNF), C-reactive protein (CRP), Glial fibrillary acidic protein (GFAP), and Insulin-like growth factor (IGF-1). Randomised controlled trails of exercise interventions or physical activity levels in healthy older adults and older adults with Mild Cognitive Impairment (MCI) have reported moderate-to-large treatment effects for exercise on Aβ<sup>249–252</sup>. Brain-Derived Neurotrophic Factor is associated with learning and memory, neuronal growth and repair and neuroplasticity, and can protect against neurodegeneration later life.<sup>253–256</sup>. Both acute and regular exercise have been shown to increase BDNF levels, which may mediate memory consolidation after exercise in younger and older adults<sup>246,257</sup>. C-reactive protein (CRP) is an inflammatory protein associated with neuroinflammation, sleep disturbances, cognitive decline, dementia risk, and AD<sup>258,259</sup>. CRP decreases with exercise, regardless of age or sex<sup>260</sup>.

Insulin-like growth factor (IGF-1) is associated with neurogenesis and cognitive function.<sup>261–263</sup>. There is a bidirectional relationship between IGF-1 and sleep regulation, with preferential secretion of IGF-1 during slow-wave sleep<sup>264</sup>. IGF-1 also increases with exercise in younger and older adults<sup>265,266</sup>. Glial fibrillary acidic protein (GFAP) has been linked to neuroinflammation and cognitive decline<sup>267,268</sup> Plasma GFAP concentrations are elevated in chronic insomnia<sup>142</sup> and older adults at risk of AD<sup>269</sup>. Plasma GFAP concentrations decrease

significantly after 30 minutes of aerobic exercise in younger adults<sup>268</sup>, and higher levels of regular physical activity are associated with lower GFAP concentrations in older adults<sup>267</sup>.

#### Exercise and Sleep in Young to Middle-aged Adults

Strong evidence supports the beneficial effects of either acute (single bout) or regular (greater than one week) exercise on sleep in younger and middle-aged adults and persons with insomnia<sup>212,224,237,270</sup>. These benefits include improved subjectively (e.g., the Pittsburgh Sleep Quality Index, Insomnia Severity Index, or sleep diaries) or objectively (actigraphy or polysomnography) assessed sleep quality and quantity (total sleep time), and changes in sleep physiology (sleep microarchitecture, including slow-wave activity, sleep spindles, etc), as well as decreased use of sleep medications<sup>212,224,237,270</sup>. In a 2021 umbrella review of exercise and sleep across the lifespan, Kline et al.<sup>212</sup> found strong evidence for positive effects of acute and regular physical activity on sleep outcomes, including increased total sleep time (TST), sleep efficiency-SE (the amount of time in bed spent asleep), sleep onset latency-SOL (the amount of time it takes to fall asleep once in bed), decreased number of night-time awakenings, and decreased time spent awake after sleep onset-WASO<sup>212</sup>.

#### Exercise and Sleep in Older Adults

Exercise interventions can also benefit sleep in older adults<sup>220,221</sup>. Evidence from controlled interventional trials supports the beneficial effects of acute or chronic exercise on selfreported (subjectively assessed) and objectively measured (e.g. polysomnography or actigraphy) sleep, including improved sleep quality and increased TST, SE, Non-REM stage 3 and SWS, and decreased use of medications for sleep<sup>220,221,225,271–273</sup>. This is an important finding, given the high prevalence of sleep disturbances among older adults ( $\geq$  65 years
old)<sup>274</sup>. Acute and regular exercise also increase the percentage of NREM sleep and SWS<sup>213,214,224,275</sup> in older adults, with important implications for cognition and memory<sup>16</sup>. For example, Vitiello et al (1994) also found that long-term aerobic training increased the total amount of SWS in healthy older adults<sup>276</sup>.

While systematic review of exercise and sleep have found that exercise increased participants' subjective sleep quality and sleep duration, regardless of the exercise mode or the intensity<sup>277</sup>, moderate intensity exercise, performed in a range of frequencies and duration, has most frequently been associated with improvements in sleep outcomes in older adults. <sup>271,278,279</sup>. For example, Vanderlinden et al. reviewed 14 experimental studies of exercise and sleep in healthy older adults. Exercise programs positively influenced sleep in older adults, with moderate-intensity exercise performed thrice weekly for 12-24 weeks associated with the greatest number of improvements in sleep outcomes <sup>271</sup>.

Exercise also improves sleep, cognitive performance, and psychological well-being in older adults<sup>224,227,231,241,243,244</sup> and reduces the detrimental effects of sleep loss on memory in young adults<sup>235</sup>. Exercise of most durations and intensities has been found to improve cognition in older adults.<sup>230,231,280230,231,281</sup> Moderate intensity physical activity and exercise are also associated with beneficial changes in cerebrospinal fluid biomarkers such as A $\beta$  and tau linked to AD and dementia.<sup>249–252</sup> Exercise is a modifiable lifestyle factor that can protect against functional and cognitive decline and mitigate the risk of dementia in older age.<sup>224,282</sup>It may be an ideal complement to other healthy lifestyle approaches for preserving brain health in older adults.<sup>218</sup>

#### Limitations in the body of evidence for exercise and sleep

While the benefits of exercise for sleep are well-evidenced, the optimal exercise mode or dosing of exercise remain unclear<sup>212,224</sup>. Important questions remain about whether there is a minimal dose of exercise (intensity, frequency, duration,) below which sleep is not improved, and whether higher doses of exercise result in greater improvements in sleep<sup>212,224,277</sup>. Exercise of low, moderate, and high intensities have been found to have beneficial effects on subjective or objectively assessed sleep, though the greatest benefits for sleep duration (TST), sleep efficiency, WASO, and increased deep sleep (slow-wave sleep) have been reported with moderate-intensity exercise. The optimal time of day during which exercise should be performed to influence sleep is also uncertain. In older adults, however, greater benefits for sleep have been found with exercise in the evening, compared to exercise in the morning <sup>283</sup>. There is also a lack of agreement about the methodological quality of the body of evidence supporting the effectiveness of exercise interventions targeting sleep in older adults. This is explored extensively in chapters 4 and 5 of this thesis.

#### Evidence gaps: Exercise for sleep in older adults

While evidence suggests that exercise is beneficial for sleep in older adults, the magnitude of these benefits and the effects of exercise on sleep architecture remain unclear<sup>212,224</sup>. Evidence supports the effectiveness of exercise for improving subjectively reported sleep quality in older adults, but few systematic reviews have assessed or meta-analysed objectively-measured (by polysomnography or actigraphy) sleep outcomes in studies of exercise and sleep in older adults, particularly in older adults with Insomnia disorder<sup>212,212,284</sup>.

The effect of moderators such as older adults' age, sex, or degree of sleep difficulty is uncertain, as is the influence of exercise intervention characteristics, such as the time of day during which participants exercise, the duration of exercise sessions, or length of exercise intervention programs, on treatment effect estimates for exercise on sleep in older adults. The optimal exercise mode or dose, and dose-response relationships between exercise and sleep outcomes in older adults also remain unclear<sup>212,224</sup>.

Another important knowledge gap is whether exercise can be an effective treatment for poor sleep in persons with Alzheimer's disease (AD) or related dementias (AD/ADRD). To the best of our knowledge, no prior systematic review has meta-analysed the effectiveness of exercise interventions targeting sleep in persons with AD or critically appraised the quality of evidence for the effectiveness of exercise interventions targeting sleep in this population.

#### Thesis overview

There are strong associations between sleep, cognition, and brain-health. Sleep may also be one of the most important modifiable and treatable risk factors for a range of health conditions, including cognitive decline and AD. Nevertheless, important questions about the interactions between sleep, sleep physiology, cognition, and neurodegeneration remain unanswered.

This thesis explores links between sleep and sleep physiology during non-rapid eyemovement (NREM) sleep stages 2 and 3, brain-health, and cognition in older adults and persons with Alzheimer's Disease and Related Dementias (AD/ADRD). It provides new insights into the associations between sleep, cognition, and biomarkers of neurodegeneration in

older adults (chapter I). It also provides new evidence demonstrating that spindle and slow oscillation activity during NREM sleep constitute predictive and non-invasive biomarkers of neurodegeneration and cognition in Alzheimer's Disease (AD) patients (chapters II-III). Sleep microarchitecture can, therefore, also provide novel therapeutic targets for preserving brainheath and slowing AD progression. It then explores how exercise, a promising and widely accessible intervention targeting sleep physiology, can be an effective intervention for poor sleep in older adults (chapter IV) and persons with Mild Cognitive Impairment (MCI) and AD/ADRD (chapter 5).

#### Evidence gaps, opportunities, and research questions explored in this thesis

Throughout the literature review that informed this chapter (Chapter 1), several knowledge gaps in the evidence for sleep, cognition, Alzheimer's disease and interventions for sleep were identified. Four primary evidence gaps and research questions (RQ) will be addressed in this thesis:

#### 1. Sleep, neurodegeneration, and cognition:

**RQ:** What is known about the links between sleep, Alzheimer's disease , and cognition in older adults? The evidence for associations between sleep, neurodegenerative diseases of ageing, and cognition is reviewed in chapters one through three. The majority of research investigating associations between sleep, cognition, and neurodegeneration has been undertaken in healthy older adults, or those at risk of AD. Less is known about the interrelationships between sleep and the progression of cognitive decline or neurodegeneration in persons already showing clinical AD symptoms. This chapter establishes key evidence gaps to be explored in the thesis.

#### 2. Sleep physiology, neurodegeneration, cognition, and Alzheimer's Disease:

RQ: Does sleep microarchitecture predict cognitive decline and biomarkers of neurodegeneration and in persons with mild-to-moderate Alzheimer's disease? The majority of research has explored links between sleep spindle and slow oscillations, biomarkers of neurodegeneration, and cognition in healthy older adults or older adults at risk of AD, but not those with clinical AD symptoms. It is unknown whether sleep physiology can predict longitudinal cognitive decline in persons already manifesting AD symptoms. This has important implications for clinical care of persons with MCI or AD, and targeting of interventions to slow the progression of AD.

#### 3. Interventions for poor sleep in older adults

**RQ:** Which interventions are effective for poor sleep in older adults? In chapter I, the evidence for pharmacological and non-pharmacological interventions for

poor sleep are reviewed critically, identifying important methodological considerations and evidence gaps that are addressed in chapters four and five of the thesis. Treatment options for AD are limited and depend on early identification of persons with AD before their betaamyloid levels are too high. Given this, early identification of persons at increased risk and prevention of modifiable AD risk factors, like poor sleep, is essential.

#### 4. Exercise, sleep, and older adults.

RQ: Are exercise interventions targeting sleep in older adults effective?

There is strong evidence for the effectiveness of exercise interventions targeting subjectively reported and objectively assessed sleep in young and middle-aged adults, but questions remain about the effectiveness of these interventions in healthy older adults. These are explored in the introduction (chapter I), and in chapter IV, identifying important

characteristics and key modifiers of effective exercise interventions for poor sleep in healthy older adults.

#### 5. Exercise, sleep, and older adults with MCI or AD.

RQ: Is exercise an effective intervention for poor sleep in older adults with MCI or

Alzheimer's' disease ?

No prior systematic review or meta-analysis has investigated the effectiveness of exercise interventions targeting sleep in persons with MCI or AD. A meta-analysis of controlled, interventional trials of exercise targeting sleep in MCI or AD is needed to determine their effectiveness, identify optimal intervention parameters for clinical care of persons with AD, and identify evidence gaps to be explored in future research.

#### Thesis aims and hypotheses:

I. To review state of evidence for sleep, cognition, Alzheimer's disease, and biomarkers for neurodegeneration.

II. To investigate associations between sleep spindles, slow wave activity (SWA), and these biomarkers.

**Hypothesis:** Sleep spindles and slow oscillations predict biomarkers of AD neurodegeneration and neuroinflammation in mild-to-moderate AD.

III. Investigate whether sleep spindles and SWA can predict cognitive decline and neuropsychiatric symptom severity in older adults with mild-to-moderate AD.

**Hypothesis:** Sleep spindles and slow oscillation activity at baseline predict longitudinal cognitive progression and neuropsychiatric symptom severity in older adults with mild-to-moderate AD

IV. Investigate the state of evidence and effectiveness of exercise interventions targeting sleep:

a. in healthy older adults

b. in older adults with Mild Cognitive Impairment (MCI) or AD.

**Hypotheses:** Exercise interventions are effective for improving subjectively reported and objectively assessed (polysomnography and/or actigraphy) sleep outcomes in healthy older adults and older adults with MCI) or AD.

# General methods overview



Figure 1: Thesis flow diagram.

The following subsection lists the primary aims and methods for each chapter.

Chapter I: Introduction:

Main aims: Describe the state or knowledge and evidence gaps for the relationships between

sleep, brain-health, Alzheimer's Disease and Related Dementias, and interventions for poor

sleep in older adults.

Method: Literature review and critical appraisal of evidence.

**Publication:** The contents of this chapter have been adapted and published as "State of the Science: Exercise interventions targeting sleep in older and younger adults," a chapter in "The Cambridge University Handbook of Sleep Models and Theories." Cambridge University Press, UK, 2024 (*in press*).

Chapter II:

**Main aims:** To determine if sleep spindles and slow oscillation activity predicts biomarkers of neurodegeneration at baseline and cognition over three years in persons with mild to moderate Alzheimer's Disease.

**Method:** Analysis of data from a prospective cohort study of the cognitive evolution of persons with mild-to-moderate Alzheimer's Disease.

**Publication:** This chapter has been accepted for publication (in press) as "Sleep spindles and slow oscillations predict cognition and biomarkers of neurodegeneration in mild to moderate Alzheimer's Disease<sup>285</sup>" in Alzheimer's and Dementia, The Journal of the Alzheimer's Association. 11/2024, ADJ-D-24-01771R1.

Chapter III: Sleep microarchitecture predicts neurofilament-light,

biomarkers of neuroinflammation, and cognition in persons with mild-to-moderate Alzheimer's Disease.

**Method:** Analysis of data from a prospective cohort study of the cognitive evolution of persons with mild-to-moderate Alzheimer's Disease.

**Publication**: This chapter was submitted for publication in Brain (Oxford University Press), 11/24.

**Chapter IV**: Exercise interventions benefit sleep in older adults: A systematic review and meta-analysis.

**Main aim:** Systematically review and meta-analyse controlled, intervention trials of exercise interventions targeting sleep in healthy older adults.

**Publication**: This chapter was submitted for publication in BMC Geriatrics (under review), special call for papers: Sleep disorders and older adults, as "Exercise interventions benefit

sleep in older adults: A systematic review and meta-analysis." 09/24 Manuscript ID: 85fd58b4-fbe2-4183-bdb4-d31c9d7355f4 v1.0

**Chapter V**: The effectiveness of exercise interventions targeting sleep in older adults with cognitive impairment or Alzheimer's Disease and Related Dementias (AD/ADRD): A systematic review and meta-analysis.

**Main aim:** Systematically review and meta-analyse controlled, intervention trials of exercise interventions targeting sleep in older adults with MCI or AD.

**Publication**: This chapter was published as "The effectiveness of exercise interventions targeting sleep in older adults with cognitive impairment or Alzheimer's Disease and Related Dementias (AD/ADRD): A systematic review and meta-analysis<sup>220</sup>" in The Journal of Sleep Research, the journal of the European Sleep Research Society, in 03/24.

#### Chapter VI: Thesis conclusions and implications

**Main aim:** Discuss the implications of thesis' findings in the context of clinical care of persons with AD, preserving brain-health and cognition in older adults, and implications of our findings for sleep research.

Chapter II: Sleep spindles and slow oscillations predict cognition and biomarkers of neurodegeneration in mild to moderate Alzheimer's Disease.

# **Chapter Summary**

In this chapter, we investigate how NREM sleep physiology at baseline predicts biomarkers of neurodegeneration and cognition with data from a prospective cohort study of the cognitive evolution of persons with mild-to-moderate Alzheimer's disease(AD). This chapter addresses important knowledge gaps for the role of sleep physiology in AD and AD progression reviewed in the introduction. This chapter has been published as a manuscript in Alzheimer's and Dementia, The Journal of the Alzheimer's Association as:

Páez A, Gillman SO, Dogaheh SB, et al. Sleep spindles and slow oscillations predict cognition and biomarkers of neurodegeneration in mild to moderate Alzheimer's disease. Alzheimer's Dement. 2024;1-17. https://doi.org/10.1002/alz.1442411/2024<sup>285</sup>.



#### Abstract

**INTRODUCTION**: Changes in sleep physiology can predate cognitive symptoms by decades in persons with Alzheimer's disease(AD), but it remains unclear which sleep characteristics predict cognitive and neurodegenerative changes after AD onset.

**METHODS**: Using data from a prospective cohort of mild-to-moderate AD (n=60), we analysed non-rapid eye-movement sleep spindles and slow oscillations (SO) at baseline and their associations with baseline amyloid-beta and tau, and with cognition from baseline to three-years follow-up.

**RESULTS**: Higher spindle and SO activity predicted amyloid-beta and tau at baseline, and statistically significantly lower Alzheimer's Disease Assessment Scale Cognitive Subscale (better cognitive performance), and higher Mini-Mental State Examination scores from baseline to 36-months. Spindles and SO mediated the effect of pTau181/aβ42 on cognition, while pTau181/aβ42 moderated the effect of spindles and SO on cognition.

**DISCUSSION**: Our findings demonstrate that spindle and SO activity during sleep constitute predictive and non-invasive biomarkers of neurodegeneration and cognition in AD patients

#### 1. Background

Poor sleep has been linked to increased risk of Alzheimer's Disease and Related Dementias (AD/ADRD) and can predict or accelerate the progression of cognitive decline in persons with Alzheimer's Disease (AD)<sup>6,7,99</sup>. Up to 66% of persons with AD/ADRD experience poor sleep<sup>6–8,99</sup>. Sleep disorders such as insomnia and sleep apnoea often appear in the preclinical stage of AD<sup>6–8,99</sup>. AD patients also experience greater sleep latency (time to fall asleep once in bed), wake time after sleep onset, and number of nighttime awakenings than healthy older adults, along with significant reductions in total sleep time, sleep efficiency, slow-wave (SWS) and rapid eye-movement (REM) sleep<sup>78</sup>.

There is a bidirectional relationship between sleep and AD/ADRD<sup>9,10</sup>. Sleep plays important roles in the clearance of  $\beta$ -amyloid (A $\beta$ ) and tau linked to AD/ADRD<sup>6,104</sup>. Sleep disturbances have been linked to increased A $\beta$  and tau accumulation in the brain that can precede the first cognitive symptoms of AD by 15-20 years<sup>6,9,31</sup>. Conversely, A $\beta$  and tau pathology in cortical regions, the hypothalamus, and nuclei regulating sleep-wake can lead to sleep disturbances and impaired slow-wave activity (SWA) during non-rapid eye-movement (NREM) sleep, which may also contribute to hippocampus-dependent cognitive decline in older adults<sup>9,35,158</sup>.

Sleep spindles and slow oscillations (SO) during NREM sleep are also altered in AD and have been linked to AD progression<sup>29,143</sup>. Sleep spindles are 9–16 Hz waxing-and-waning oscillations generated within the thalamo-cortical network and consistently associated with sleep-dependent memory consolidation, cognition, and sleep continuity<sup>37</sup>. Spindle density, duration, and amplitude decrease with age, but are further reduced in persons with AD/ADRD<sup>32,78,148</sup>. Large-amplitude, low-frequency slow waves (> 75 microV, 0.5-4Hz) and

slow oscillations (SO)( <1 Hz), largely arising from the prefrontal neocortex, also underlie memory consolidation during sleep<sup>46</sup>. Slow oscillations decrease in number and amplitude in middle-aged and older adults<sup>29,155</sup>. These decreases are more pronounced in persons with cognitive decline or AD/ADRD<sup>29,155</sup>.

#### 1.1 Evidence gaps and opportunities

Changes in sleep physiology can predate the onset of cognitive changes by years or decades in persons with  $AD^{8,9,51,143,163}$ . Sleep assessments including features of NREM sleep correlated with AD pathology or cognitive decline offer the potential for early, non-invasive screening for AD risk before the onset of clinical symptoms and provide novel therapeutic targets to slow AD progression<sup>10,165</sup>. Plasma, cerebrospinal fluid (CSF), and positron emission tomography can provide useful biomarkers of A $\beta$  and tau levels in the brain. However, access to PET can be limited, requiring expensive, specialized facilities<sup>168</sup>. Lumbar puncture for CSF is more accessible but is invasive and carries risk of mild adverse reactions<sup>168</sup>. Ultra-sensitive blood-based assays enable increasingly accurate biomarker measures at lower cost, but require blood draws and specialised laboratory equipment<sup>167</sup>.

Increasingly, research has explored associations between sleep physiology, AD biomarkers, and cognition in healthy older adults<sup>34,35,52,135,143,170–172</sup>. Less is known about predictive associations between spindles, SO, biomarkers, and cognition in persons with  $AD^{9,141}$ . Spindle intensity and density have been correlated with episodic memory and cognition in limited samples of up to 15 persons with  $AD^{151,152}$ . Inverse relationships between 1–2 Hz SWA and CSF tau have also been found in preclinical and early  $AD^{135}$ . However,

associations between spindle and SO characteristics, biomarkers of neurodegeneration, and cognitive performance have not been investigated together in AD patients.

In this study, we investigated associations between baseline NREM spindle and SO activity in a sample of 60 persons with mild-to-moderate AD and:

- 1. AD/ADRD biomarkers at baseline.
- 2. Cognitive performance over three years.

We hypothesised that NREM sleep spindle and SO activity predict Aβ42 and tau levels at baseline. We also hypothesized that higher spindle and SO activity predict higher cognitive performance (direct relationship) in persons with mild to moderate AD. Sleep spindle and SO activity may constitute predictive, non-invasive biomarkers of neurodegeneration and cognition in AD patients and novel therapeutic targets to slow AD progression and preserve brain-heath.

# 2. Methods

### 2.1 Study Design

To test these hypotheses, we performed secondary analyses of data previously collected (from November 2014 to November 2017) in a prospective study of the influence of obstructive sleep apnoea (OSA) on the cognitive evolution of persons with AD (Role of Hypoxia And Sleep Fragmentation in Alzheimer's Disease. ClinicalTrials.gov NCT02814045)<sup>99,286</sup>. Participant eligibility, recruitment, and data collection methods have previously been described extensively<sup>99,286</sup>. Briefly, a cohort of 104 persons with mild-

moderate AD/ADRD were recruited in a prospective, observational study at the Cognitive Disorders Unit of Hospital Universitari Santa Maria (Lleida, Spain). Eligible participants were aged  $\geq$  60 years old with AD diagnosed according to the National Institute on Aging and Alzheimer's Association criteria<sup>287</sup>. Exclusion criteria have previously been described and included use of investigational drugs, beta-blockers, antidepressants, neuroleptics, or hypnotics within 15 days of the overnight polysomnography<sup>99,286</sup>. None of the participants were taking anticonvulsants, antipsychotics, anxiolytics, hypnotics, or medications for poor sleep such as benzodiazepine receptor agonists, that may influence sleep microarchitecture. Five participants had previously taken antidepressants, but not for at least 15 days before their PSG.

The study was approved by the institutional review board of Hospital Arnau de Vilanova de Lleida (CE-1218) and conducted according to the Declaration of Helsinki principles. Data from 60 of the participants (30 females) was available for the analyses described in this paper.

#### 2.2 Data collection

At baseline, participants underwent one-night polysomnography (figure 1). The following morning CSF was collected for biomarkers associated with amyloid deposition, tau pathology, neurodegeneration, axonal damage, synaptic integrity, neuroinflammation, and oxidative damage. At baseline and 12 months follow-up visits, participants underwent a battery of functional and neuropsychological assessments, including the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog)<sup>288</sup>, California verbal learning test (CVLT), Mini-Mental Status Examination (MMSE)<sup>289</sup>, Rey-Osterrieth Complex Figure Test (ROCF) and

others (e.g. Cornell Scale for Depression in Dementia<sup>290</sup>, and Neuropsychiatric Inventory-NPI<sup>291</sup>) capturing mental and physical function<sup>99,286</sup>. At the 24 and 36 month follow-up appointments, only the Mini-Mental Status Examination (MMSE) was administered.

The ADAS-Cog assesses cognitive and behavioural domains most affected by AD and is a gold standard for assessing the efficacy of treatments targeting dementia<sup>288</sup>. The MMSE assesses cognitive function and impairment in older adults<sup>289</sup>. The ROCF<sup>292</sup> and CVLT<sup>293</sup> capture visual and verbal (respectively) learning and memory.



ADAS: Alzheimer's Disease Assessment Scale, cognitive subscale CVLT: California Verbal Learning Test, MMSE: Mini-mental state examination, NPI: Neuropsychiatric Index, ROCF: Rey–Osterrieth Complex Figure Test

Figure 1: Study flow from baseline to 36 months

Polysomnography (PSG) was undertaken in Lleida, Spain, using Philips Respironics Alice 6 LDx (34 channel EEG referenced to the mastoids, 512 Hz sampling rate). Electroencephalography (EEG) records were visually scored by experienced sleep technicians, using Phillips G3 Dreamware software (bandpass filter 0.3Hz – 93.6Hz, sampling frequency 512Hz) in 30-s epochs in one of four stages of sleep (non-rapid eye movement stages 1, 2, or 3 [NREM1,

NREM2, NREM3], and rapid eye movement [REM]) following American Academy of Sleep Medicine (AASM) criteria<sup>294</sup>.

#### 2.2.2 Biomarkers

The collection of CSF samples for biomarker analyses has been described previously<sup>286</sup>. Briefly, CSF samples were collected from participants in the morning, between 8:00 am and 10:00 am, to avoid variations related to circadian rhythms. Samples were collected in polypropylene tubes, centrifuged at 2000 × g for 10 minutes at 4°C, immediately frozen, and stored within 4 hours in an -80°C freezer. The principal AD biomarkers, CSF Aβ42, total tau (t-tau), and phosphorylated tau (pTau181) were measured using commercial kits (Innotest β-Amyloid1-42; Innotest hTAU Ag; and Innotest Phospho-TAU181P, Fujirebio-Europe, Gent, Belgium). All measurements were performed in one round using one batch of reagents by board-certified laboratory technicians blinded to clinical data. Intra-assay coefficients of variation were lower than 10% for internal quality control samples (two per plate).

#### 2.3 Data analyses

# 2.3.1 Cognition

For this present study, the results of the CVLT, ROCF, ADAS-cog, and MMSE were analysed to best capture to cognitive status and progression of cognitive decline in persons with mild to moderate AD. The ADAS-cog ,CVLT and ROCF were available for baseline and the 12-month follow-up. The MMSE was available for the baseline, 12, 24 and 36-month follow-ups.

#### 2.3.2 Polysomnography and EEG analysis

For the present study, participants' sleep EEG records were processed using Wonambi v 7.11, an open-source Python software package developed at the Sleep, Cognition and Neuroimaging Laboratory (SCNLab) at Concordia University, Montreal (<u>https://github.com/wonambi-python/wonambi</u>). Participants' previously scored EEGs were visually checked again by experienced sleep scorers (AP, SG, SB, OW) at the SCNLab, following AASM criteria<sup>294</sup>.

We identified sleep cycles as those periods of sleep containing at least 15 minutes of NREM sleep and 5 minutes of REM sleep, except for the first sleep cycle, which could contain at least 1 minute of REM sleep<sup>295</sup>. We then reviewed the EEG sleep recordings for each participant in 30-s epochs to identify and tag microarousals, artifacts, or instances of poor EEG signal for exclusion from subsequent analyses. Signal aberrations we targeted for removal included poor or dysfunctional signal lasting greater than one 1 second (e.g. signal popping and flat lining)<sup>294</sup>, excessive muscle artifact or movement, micro-arousal activity (sudden transient cortical activations during sleep and abrupt shift in EEG frequency lasting longer than 3 seconds<sup>294</sup>), or periods in an epoch that contained a shift to N1 or wakefulness.

Automatic SO and sleep spindle event detection on EEG were performed using another inhouse software package developed at the SCNLab and run on Spyder (v5.3.3), an opensource environment in Python. The in-house software directly incorporates functions from validated sleep spindle and slow wave detection methods. Based on our review of literature for spindle and slow-wave activity in older adults, we undertook sleep spindle detection over two central channels (C3-A2 and C4-A1)<sup>32,148</sup>, and slow oscillations detection over the two frontal channels (F3-A3, F4-A1)<sup>296</sup>.

An algorithm developed by Staresina et al. 2015 was used to detect SO on channels F3 and F4 during N2 and N3<sup>46</sup>. Artifact-free EEG signals were filtered between 0.16 - 1.25Hz (zero-phase infinite impulse response bandpass filter). The duration threshold for potential SOs was 0.8 - 2.0 sec for two successive positive-to-negative zero crossings, in filtered EEG signals. Following Staresina's criteria, the event amplitude threshold for SOs meeting duration criteria was amplitudes exceeding the 75th percentile of trough-to-peak amplitude between two positive-to-negative zero crossings<sup>46</sup>. We also visually reviewed detected SO events to ensure that they were not false positives.

Sleep spindles were detected during NREM2 and NREM3 (fixed bandwidth 9 - 16Hz) based on Mölle et al.'s (2011) algorithm<sup>40</sup>. We chose a 9-16hz bandwidth based on a review of literature for spindle characteristics in older adults, in MCI, AD, and other neurodegenerative disorders<sup>73,78,173,297–301</sup>. These disorders have been associated with greater declines in spindle characteristics and physiological changes than seen with increasing age<sup>78,151–153,298,299,302,303</sup>. We also wanted to capture slow spindle activity (9-12Hz)<sup>40,297,304</sup> in our sample, given evidence age-related changes in slow spindle activity and their links with cognitive decline<sup>302,303</sup>. On artifact-free, filtered EEG signals in channels C3 and C4, the root mean square (RMS) was computed using a 0.2 sec sliding window, then further smoothed using 0.2 sec moving average. Sleep spindles were identified when standard deviations of RMS values exceeded 1.5 for 0.5 – 3.0 sec. To manually check the accuracy of automatically detected SO and sleep spindle events, we visually inspected the identified sleep spindles with Wonambi, which highlighted the previously detected events on filtered EEG signals. With these methods, we extracted data for sleep spindle count, density (/30 sec), mean duration (sec), peak-to-peak amplitude ( $\mu$ V), power ( $\mu$ V2), and peak power frequency (Hz), and slow oscillation (SO) density (/30 sec), mean duration (sec), peak-to-peak amplitude ( $\mu$ V), power ( $\mu$ V2), and peak power frequency (Hz) in NREM2 and NREM3. In this paper, we report data for spindle duration, density, and power, and SO duration, density, and amplitude in NREM2 and NREM3 combined. Data for NREM2 and NREM3 separately is available in the supplementary materials tables S1-S4.

These characteristics were chosen for their associations with, and ability to predict, cognitive performance<sup>7,32,148,305</sup>. For example, spindle and SO duration and density have been linked to cognitive decline and may be associated with CSF levels of biomarkers for neurodegeneration in healthy older adults<sup>32,51,173,175</sup>. Spindle power has been identified as a predictor of cognitive performance in healthy older adults<sup>306</sup>. Results for the other spindle and SO characteristics, such as spindle or SO count or peak frequency, are available in the supplementary materials tables S1-S4.

#### 2.4 Statistical analyses

Descriptive statistics, including the mean and standard deviation (SD) for parametric data, and median and interquartile range (IQR) for non-parametric data and differences in these between males, females, and persons with high (< 600 ng/l, or AB+<sup>307</sup>) or low (> 600 ng/l, or AB-) b-amyloid burden at baseline were calculated for participant characteristics, sleep, AB42 and tau biomarkers, and cognition-neuropsychological test scores. The normality of distributions were analysed using the Shapiro–Wilk test and visual inspection of histograms and kernel density plots, which approximate the probability density of the variable. We

expected that biomarker and cognition data may be right or left skewed rather than normally distributed, as may be expected in participants with mild to moderate AD<sup>117</sup>.

#### 2.4.1 Sleep microarchitecture and AD biomarkers

We calculated ratios of CSF pTau181/Aβ42 and total tau/Aβ42 to investigate associations between sleep, AD biomarkers, and cognition<sup>308</sup>. These CSF biomarker ratios have been associated with increased brain amyloid and show superior agreement with PET amyloid measures<sup>308</sup>. They have also been shown to be a superior for predicting the risk and rate of clinical decline and progression to dementia in older adults at risk of AD than individual biomarkers<sup>308</sup>.

Associations between slow oscillation (SO) and spindle (SP) metrics (e.g., duration, density, power) and CSF biomarkers (Aβ42, tau (t-tau, pTau181) and their ratios pTau181/Aβ42 and total tau/Aβ42 ) at baseline were investigated with generalized linear models (GLM) with Huber/White/Sandwich robust estimators of variance, reducing the influence of small, non-zero values that may bias the results of linear regression, increasing robustness against non-normally distributed error, and accounting for heteroskedasticity in residual distributions<sup>309</sup>.

The association between SO/SP metrics and biomarkers were modelled with one primary biomarker outcome variable (e.g. pTau181/Aβ42), sleep spindle or slow oscillation characteristics, and covariates for age (continuous), sex (binary), and apnoea-hypopnea index (continuous). Apnoea-hypopnea index (AHI) was included as a covariate in all analyses. The sample was drawn from a population of older adults with a high prevalence of OSA, and hypoxia severity has been associated with amyloid deposition and increased risk of AD in

persons with OSA<sup>104</sup>. For every regression model, there were at least 10 participants per dependent variable or covariate in the model, avoiding over-fitting that may bias regression results.

#### 2.4.2 Sleep microarchitecture and cognition

The associations between SO/SP metrics in NREM2 and NREM3 and cognitive assessments, including the California verbal learning test (CVLT), Rey-Osterrieth Complex Figure Test (ROCF), Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) and MMSE were conducted cross-sectionally (baseline) with GLM and Huber/White/Sandwich robust estimators of variance. Longitudinal analyses from baseline to 12 months for the CVLT, ROCF, ADAS-cog and baseline to 12, 24, 36 months for the MMSE were also conducted with GLM, adjusting for baseline scores. The odds of decline in MMSE scores per unit change in a spindle or SO metric of interest was calculated with the odds ratio of a decline in MMSE from baseline to 36 months.

In all regression models, we checked for multicollinearity among sleep spindle and SO characteristics with the variance inflation factor (VIF), maintaining VIF at <2 for all models (no to low correlation)<sup>310</sup>. The normality of regression residuals was assessed with Shapiro–Wilk tests. Only the residuals for pTau181/Aβ42 were non-parametrically distributed. We visually re-inspected the data for pTau181/Aβ42 and used Tuckey's Ladder of Powers to identify the most appropriate transformation for that outcome variable. We applied a square root transformation to pTau181/Aβ42, and re-ran the regression model with the transformed variable, yielding normally distributed residuals. We corrected for multiple comparisons in all regression analyses with a Benjamini-Hochberg False Discovery Rate<sup>311</sup>.

**2.4.3 Moderation and mediation analyses** were undertaken to explore whether there are mediating or moderating roles for biomarkers in the relationship between spindle and slow oscillation activity and cognitive performance, or a moderating or mediating role for spindle and slow oscillation activity in the relationship between biomarkers and cognitive performance. These exploratory analyses were carried out in STATA using Sobel-Goodman Tests of mediation. following Preacher and Hayes' recommendations<sup>312</sup>. For moderation analyses, we ran GLM regression models with interaction terms. We explored these with the MMSE, ADAS-cog, CVLT and ROCF at baseline and follow-up periods and the pTau181/Aβ42 ratio, given its associations with AD progression and superiority in for predicting clinical decline and progression to dementia than individual biomarkers<sup>308</sup>.

### 3. Results

The 60 participants (30 female) in this study had a mean age of 74.7 at baseline. There were no significant differences between males and females in age, body-mass index (BMI), educational attainment, prevalence of diabetes, depression, or obstructive sleep apnoea (table 1). Participants with A $\beta$ 42<600 pg/ml at baseline had a higher prevalence of OSA than participants with A $\beta$ 42<600 pg/ml (supplementary materials, table S5). Participants had a median A $\beta$ 42 of 516 pg/ml, and no statistically significant differences between males and females in A $\beta$ 42 CSF or tau levels or ratios of A $\beta$ 42 to tau. No statistically significant differences were found between males and females on the Cornell Scale for Depression in Dementia or NPI.

Sample	Male (n=30)	Female (n=30)	Total (n=60)	p value
Age	75.5 ±5.0	74.0 ±5.0	74.7 ±5.0	0.26
body mass index (bmi)	27 (24-29)	28 (24-32)	27 (24-32)	0.71
Depression	6 (20.0%)	12 (40.0%)	18 (30%)	0.09
Diabetes	7 (23.3%)	3 (10%)	10 (16.7%)	0.17
education (≥ high school)	5(16.7%)	5(16.7%)	10 (16.7%)	1.00
0: no formal education	2 (6.7%)	2 (6.7%)	4(6.7%)	
1. Primary school	23 (76.7%)	23 (76.7%)	46(76.7%)	
2. High school	4 (13.3%)	4 (13.3%)	8 (13.3%)	
3. University	1 (3.3%)	1 (3.3%)	2 (3.3%)	
Smoking history	11(36.7%)	2 (6.7%)	41(68.3%)	0.005
0. never	19 (63.3%)	28 (93.3%)	47 (78.3%)	
1. current	2 (6.7%)	0 (0.0%)	2 (3.3%)	
2. former (>6 months ago)	9 (30.0%)	2 (6.7%)	11(18.3%)	
Obstructive sleep apnea (OSA)	24 (96.0%)	23 (88.5%)	47(78.3%)	0.25
Apnea hypoxia index (n/hrTST)	38.14 ±23	29.24 ±22.8	33.7 ±23.14	0.14
0-4.9	1 (3.3%)	2 (6.7%)	3 (5%)	
5-14.9	4 (13.3%)	7 (23.3%)	11 (18.33%)	
15-30	9 (30.0%)	10 (33.3%)	19 (31.67%)	
≥ 30	16 (53.3%)	11 (36.7%)	27 (45%)	
AD Drugs	26 (86.7%)	27(90%)	53 (88.3%)	0.69
None	4 (13.3%)	3 (10%)	7 (11.7%)	
Rivastigmina	9 (30%)	9 (30%)	18 (30%)	
Donepezil	17 (56.7%)	15 (50%)	32 (53.3%)	
Memantine	0	3 (10%)	3 (5.8%)	
CSF values-biomarkers (pg/ml)				
Beta-amyloid (Aβ42)	506 (417-609)	532 (398-627)	516 (411-618)	0.62
Phosphorylated tau (pTau181)	61 (48-98)	90 (54-103)	82 (50-100)	0.90
Total tau	487.4 ±287.7	599.2 ±276.5	543.3 ±285.0	0.16
PTau181/ Aβ42 ratio	0.14 ±0.07	0.17 ±0.08	0.16 ±0.74	0.25
Total-tau/ Aβ42 ratio pg/ml	0.87 (0.52-1.34)	1.10 (0.70-1.63)	0.96 (0.55-1.48)	0.27
Cognition				
ADAS-cog total score	28 (26-32)	29 (25-31)	29 (25-31)	0.89
MMSE	23.4 ±2.3	23.0 ±2.4	23.2 ±2.4	0.55
Neuropsychiatric				
Cornell Scale (CSDD)	7 (2-11)	6 (3-11)	7 (3-11)	0.93
Neuropsychiatric Index (NPI)	4 (0-11)	8 (3-13)	6 (2-12)	0.51

 Table 1: Participants' characteristics at baseline

Participants had a mean total sleep time of 260.4 minutes (±89.9) and a median sleep efficiency of 67% (IQR 48-80) (table 2). There were no significant differences between males and females (table 2) or amyloid positive vs amyloid negative participants in (mean) total sleep time, sleep efficiency, or time spent in NREM2 sleep (supplementary material tables S6). However, females spent more time than males in NREM3. Females had statistically significantly higher spindle density (per 30 second epoch), power (109 µV2) and higher median peak spindle frequency (11.24hz) than males (table 2 and supplementary material table S7). Participants had a mean slow oscillation density of 2.7 (±0.9) per 30 second epoch, median SO duration of 1 second (IQR 1-2), and SO amplitude of 108  $\mu$ V (IQR 81-156). There were no statistically significant differences in SO between males and females (table 2 and supplementary table S7) or in spindle or SO activity between by sex and amyloid status (supplementary table S8).

	Male (n=30)	Female (n=30)	Total (n=60)	р
Sleep architecture				
Total sleep time (min)	247.2 ±93.5	273.6 ±85.6	260.4 ±89.9	0.26
Total time in bed (min)	423 (391-447)	419 (400-443)	421 (392-446)	0.63
Sleep efficiency (%)	60 (44-80)	69 (50-78)	67 (48-80)	0.38
Sleep onset latency (min)	17 (9-33)	27 (14-68)	23 (11-57)	0.35
Wake after seep onset (min)	131 (66-179)	83 (54-136)	101 (58-161)	0.11
NREM 1 duration (min)	70.1 (47-80.5)	44.25 (27.5-57)	51 (35.5 <i>,</i> 78.25)	0.01
NREM2 duration (min)	86 (63-120)	105 (85-154)	92 (69-138)	0.25
NREM3 duration (min)	43 (24-78)	84 (38-106)	60 (28-91)	0.03
N2+N3min/TST (%)	55.6 ±18.2	68.6 ±17.1	62.1 ±18.7	0.006
REM duration (min)	27 (14-42)	26 (15-46)	26 (14-44)	0.83
NREM1 (% of total sleep time)	30 (23-42)	16 (8-22)	22 (10-34)	0.007
NREM2 (% of total sleep time)	37.3 ±14.7	40.8 ±13.3	39.0 ±14.0	0.35
NREM3 (% of total sleep time)	16 (10-26)	30 (15-39)	23 (14-36)	0.008
REM (% of total sleep time)	10 (7-16)	11 (5-16)	10 (6-16)	0.94
Sleep spindle (SP)	Male (30)	Female (30)	Total (60)	р
NREM2+NREM3				
SP density	0.4 ±0.3	0.7 ±0.3	0.5 ±0.3	0.002
SP duration	0.7 ±0.1	0.7 ±0.1	0.7 ±0.1	0.32
SP power	251 (151-300)	280 (211-404)	254 (187-374)	0.54
Slow Oscillations (SO)	Male (30)	Female (30)	Total (60)	р
NREM2+NREM3				
SO density	2.6 ±1.0	2.7 ±0.8	2.7 ±0.9	0.62
SO duration	1 (1-2)	1 (1-2)	1 (1-2)	0.31
SO ptp amplitude	107 (83-144)	116 (80-175)	108 (81-156)	0.66

NREM: Non-rapid eye movement sleep. REM: Rapid eye movement sleep. ptp: peak to peak

 Table 2: Sleep architecture at baseline

At baseline, participants had a mean MMSE score of 22.9  $\pm$ 2.4, median ADAS-cognition subscale total score of 29 (25-31), and no significant differences between males and females in all of the cognitive tests, save for a higher score among males in Rey-Osterrieth long-term visual memory (table 3). At follow-up, both males and females had decreased cognitive performance and MMSE scores at 12, 24, and 36 months compared to baseline, with males showing a greater decline in cognitive performance on the MMSE by 36 months, though the difference between males and females' performance was not statistically significant (table 3). There were no statistically significant differences between males and females in ADAS-Cog total scores and short or long-term verbal memory (CVLT). However, females had statistically significantly poorer performance and greater decline in short and long-term visual memory on the ROCF short and long-term visual memory test at baseline and 12 months than males. Males had higher long-term visual memory scores (ROCF) at 12 months than females. Cognition by amyloid status (positive vs negative) can be seen in supplementary materials table S9.

full sample	Male (n=30)	Female (n=30)	Total (n=60)	p value
Mini mental stage exam (MMSE)				
Baseline	23.4 ±2.3	23.0 ±2.4	23.2 ±2.4	0.55
12 months	23.0 ±2.8	21.5 ±3.9	22.3 ±3.5	0.01
24 months	20.8 ±3.6	20.0 ±3.8	20.4 ±3.7	0.49
36 months	19.1 ±5.4	18.7 ±4.2	18.9 ±4.7	0.84
Change from baseline to 12 months	-0.18 ±2.61	-1.41 ±2.71	-0.81 ±2.71	0.09
Change from baseline to 24 months	-2.17 ±3.27	-2.90 ±3.18	-2.52 ±3.21	0.46
Change from baseline to 36 months	-4.46 ±4.97	-3.84 ±3.88	-4.12 ±4.34	0.74
ADAS-cog				
total score at baseline	28 (26-32)	29 (25-31)	29 (25-31)	0.89
total score 12m	27.7 ±8.4	29.3 ±7.8	28.5 ±8.1	0.44
delayed memory (item 4) baseline	10 (8-10)	10 (8-10)	10 (8-10)	0.38
delayed memory (item 4) at 12 months	9 (8-10)	9 (8-10)	9 (8-10)	0.83
California Verbal Learning Test				
Short-term verbal memory, base	-2 (-2, -1)	-2 (-2, -1)	-2 (-2, -1)	0.83
Short-term verbal memory 12 months	-1.6 ± 0.79	-1.8 ± 1.0	-1.7 ± 0.91	0.44
Long-term verbal memory, base	-1.8 ±.1.0	-1.8 ±1.33	-1.79 ±1.33	0.82
Long term verbal memory 12 months	-1.8 ±0.8	-2.1 ±1.3	-2.0 ±1.1	0.23
Rey–Osterrieth				
Long-term visual memory, base	5.5 (3.5-8.5)	2 (2-5)	5 (2-7)	0.02
long-term visual memory 12 months	6 (2-7.5)	2 (2-6)	4 (2-7)	0.23
Copy-recall, baseline	8 (5-10)	7 (3-9)	7 (3-10)	0.9
Copy-recall 12 months	6 (2-9)	6 (3-8)	6 (2-8)	0.48

ADAS: Alzheimer's Disease Assessment Scale, cognitive subscale CVLT: California Verbal Learning Test, MMSE: Mini-mental state examination, ROCF: Rey–Osterrieth Complex Figure Test

Table 3: Change in cognition from baseline to 12, 24, 36 months

#### 3.1 Biomarkers and cognition

Adjusted for age, sex, and AHI, only the ratio of pTau181/a $\beta$ 42 at baseline predicted cognitive performance (table 4). One unit increase in pTau181/a $\beta$ 42 ratio predicted a statistically significant decrease in MMSE scores at 12 months ( $\beta$ = -13.33, 95%CI: -24.39 -2.26) and 24 months ( $\beta$ = -17.81 95%CI: -30.17 -5.45). No biomarker or biomarker ratio predicted cognitive performance on the ADAS-cog at baseline or 12 months follow-up.

	MMSE b	ase			MMSE 12m							
Biomarker	coef	р	95% low	upper	coef	р	lower	upper				
aβ42	0.00	0.59	-0.003	0.01	0.00	0.92	-0.007	0.01				
pTau181	0.01	0.07	-0.001	0.02	-0.00	0.87	-0.02	0.01				
total-tau	-0.05	0.93	-1.2	1.21	-1.18	0.12	-2.65	0.29				
pTau181/aβ42	-5.79	0.12	-13.11	1.53	-13.33	0.02	-24.39	-2.26				
total-tau/aβ42	0.00	0.86	-0.003	0.00	-0.00	0.05	-0.006	0.000				
	MMSE 2	MMSE 24 months			MMSE 3	6 months						
aβ42	0.00	0.13	-0.001	0.01	-0.00	0.86	-0.01	0.01				
pTau181	0.01	0.59	-0.01	0.02	0.004	0.60	-0.01	0.02				
total-tau	-1.06	0.33	-3.17	1.06	0.44	0.73	-2.04	2.93				
pTau181/aβ42	-17.81	0.01	-30.16	-5.45	-18.23	0.13	-42.07	5.62				
total-tau/aβ42	-0.003	0.21	-0.008	0.002	0.00	0.94	-0.006	0.006				
	ADAS to	tal score l	base		ADAS-to	tal score 1	l2 m					
аβ42	-0.01	0.37	-0.02	0.01	-0.001	0.91	-0.02	0.01				
pTau181	-0.01	0.46	-0.05	0.02	-0.01	0.51	-0.05	0.02				
total-tau	0.01	0.07	-0.001	0.02	0.01	0.10	-0.001	0.02				
pTau181/aβ42	26.79	.79 0.06		54.26	21.03	0.21	-12.06	54.13				
total-tau/aβ42	2.94	0.19	-1.42	7.30	2.31	0.29	-1.96	6.57				

Aβ42: Beta-amyloid, ptau181: phosphorylated tau, ADAS-cog: Alzheimer's Disease Assessment Scale, MMSE: Mini Mental State Ex.

Table 4: AD biomarkers and cognitive performance at baseline, 12, 24 and 36 months

## 3.2 Sleep and cognition

We found that spindle metrics predict cognitive performance on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) total score at baseline and 12 months follow-up (table 5). A unit increase in spindle density predicted a 9 point decrease in ADAS-Cog total score at baseline ( $\beta$ = -9.0, p=0.001) and at 12 months ( $\beta$ = -8.64, p=0.001) (figure 2). One unit increase in spindle power also predicted decreased ADAS-Cog scores at baseline ( $\beta$ = -0.03, p=0.002) and 12 months ( $\beta$ = -0.02, p=0.009). Spindle duration predicted a large decrease of 28 points on the ADAS-cog at baseline ( $\beta$ = -27.6, p=0.03) and a 29 point decrease at 12 months ( $\beta$ = -29.5, p=0.028), but these did not survive FDR correction (table 5, and supplementary materials figure S1). Neither SO density, duration, nor amplitude predicted ADAS-Cog total score at baseline or 12 months.

Spindle duration, density, and power also predicted increased cognitive performance on the Mini Mental State Examination (MMSE) MMSE at baseline, 12, 24 and 36 months (table 5). Spindle density predicted 4-8 point increases in MMSE score at baseline, 12, 24, and 36 months, with the largest increase predicted by spindle density at 36 months ( $\beta$ = 7.85, p=0.003) (figure 2). One unit increase in spindle density at baseline was also associated with a 98.7% lower odds of decreased cognitive performance on the MMSE at 36 months (OR 0.013, 95%CI: 0.001, 0.29), even after adjusting for age, sex, and AHI at baseline. Spindle duration also predicted increased MMSE scores at 12 months ( $\beta$ = 15.2, p=0.01), 24 months ( $\beta$ = 22.92, p=0.02) and 36 months ( $\beta$ = 34.9 p=0.003) (table 5 and supplementary materials figure S1), while spindle power predicted small increases in MMSE scores at baseline, 12, and 36 months (table 5). Slow oscillation duration was associated with decreased MMSE scores at 24 months ( $\beta$ = -25.4, p<0.001) and 36 months ( $\beta$ = -2.91, p= 0.001) (table 5 and supplementary materials figure S2).

Spindle density and power predicted increased performance on the Copy condition of the ROCF copy-figure test at baseline and 12 months that were statistically significant but did not survive FDR correction (table 5). Spindle duration predicted a statistically significant increase in long-term visual memory ( $\beta$ =3.34 p=0.016) on the ROCF. However, analyses of spindle and SO metrics (density, duration, power, amplitude) in NREM2 alone (supplementary materials table S4) found that spindle density also predicted higher Rey copy figure score ( $\beta$ =3.88

p=0.017) ROCF long-term visual memory tests at baseline ( $\beta$ =0.67 p=0.019), and long-term visual memory at 12 months ( $\beta$ =2.13 p=0.02). Slow oscillation amplitude and density in NREM3 also predicted greater performance on the copy-figure test at 12 months, while SO duration predicted increased long-term visual performance at 12 months (supplementary materials table S4).

On the California Verbal Learning Test, spindle duration predicted increased short term verbal memory performance ( $\beta$ =0.65 p=0.01), while spindle power ( $\beta$ =0.001 p=0.006) and SO density ( $\beta$ =0.33 p=0.008), predicted small but statistically significant increases in longterm verbal memory performance at 12 months. Slow oscillation duration predicted decreased long-term verbal memory performance at 12 months ( $\beta$ =-3.44 p=0.028), but it did not survive FDR correction. As with the ROCF, analyses of spindle duration, density and power in NREM2 alone, and SO metrics in NREM3 alone also resulted in statistically significant increases in short and long-term memory performance on the CVLT (supplementary materials table S4).

Cognition	ADAS-co	g base				ADAS-co	og 12 mor	nths			MMSE	base			
Spindles	coef	SE	р	95%Cl low	up	coef	SE	p 9	95%CI low	/ upper	coef	SE	р	95	%CI low upper
SP duration	-27.60	12.84	0.032	-52.76	-2.44	-29.45	13.39	0.03	-55.70	-3.21	8.85	6.56	0.177	-4.00	21.70
SP density	-9.0	2.70	0.001	-14.29	-3.7	-8.64	2.41	0.001	-13.37	-3.91	3.24	0.94	0.001	1.41	5.08
SP energy	-0.03	0.01	0.002	-0.04	-0.01	-0.02	0.01	0.01	-0.03	0.00	0.01	0.00	0.011	0.00	0.01
SO															
SO duration	25.83	11.83	0.029	2.64	49.01	6.78	11.75	0.56	-16.25	29.81	-5.34	4.83	0.268	-14.80	4.12
SO density	-0.08	1.58	0.959	-3.17	3.01	-0.27	1.22	0.83	-2.67	2.13	-0.34	0.34	0.317	-1.02	0.33
SO ptp amplitude	0.007	0.02	0.757	-0.04	0.05	0.04	0.02	0.08	0.00	0.08	0.03	0.01	0.037	0.00	0.06

	MMSE	12 mor	nths			MMSE	24 mon	ths			MMSE 36	months			
Spindles	coef	SE	р	95%CI l	ow up	coef	SE	р	95%CI	low up	coef	SE	р	95%CI lo	w up
SP duration	15.2	5.77	0.011	3.53	26.91	22.92	10.07	0.020	3.19	42.65	34.9	11.74	0.003	11. 87	57.91
SP density	4.2	1.32	0.001	1.61	6.78	5.02	1.74	0.004	1.61	8.42	7.85	2.21	0.000	3.52	12.18
SP energy	0.02	0.00	0.001	0.01	0.02	0.00	0.00	0.681	0.00	0.01	0.03	0.01	0.02	0.004	0.046
so															
SO duration	-5.44	5.91	0.357	-17.03	6.14	-25.38	6.89	0.000	-38.9	-11.87	-1.45	0.48	0.01	-2.59	-0.35
SO density	-0.78	0.75	0.296	-2.25	0.69	0.65	0.78	0.403	-0.88	2.19	0.07	0.58	0.317	-0.07	0.22
SO ptp amplitude	0.05	0.02	0.034	0.00	0.10	-0.02	0.01	0.144	-0.04	0.01	-0.00	0.00	0.105	-0.07	0.006

	ROCF co	py baseli	ne			ROCF co	opy 12 m	onth		ROCF Long term visual memory baseline						
Spindles	coef	SE	р	95%CI lo	w up	coef	SE	р	95%CI I	ow up	coef	SE	р	95%CI	low up	
SP duration	2.24	1.30	0.08	-0.30	4.79	-0.02	1.20	0.99	-2.36	2.33	3.34	1.39	0.01	0.62	6.07	
SP density	3.63	1.73	0.03	0.24	7.02	0.36	0.25	0.16	-0.14	0.85	0.36	0.28	0.19	-0.18	0.91	
SP energy	0.00	0.00	0.72	0.00	0.00	0.001	0.00	0.02	0.00	0.00	0.00	0.00	0.03	0.00	0.00	
so																
SO duration	-11.0	8.57	0.2	-27.8	5.81	-10.37	5.56	0.06	-21.3	0.52	-0.32	0.81	0.69	-1.91	1.26	
SO density	-0.83	0.58	0.15	-1.97	0.31	0.41	0.52	0.43	-0.60	1.42	-0.07	0.11	0.53	-0.28	0.14	
SO ptp amplitude	-0.01	0.01	0.48	-0.03	0.01	0.00	0.01	0.94	-0.02	0.02	0.00	0.00	0.09	-0.01	0.00	

	ROCF Lo	ng term	visual	memory 1	2m	CVLT Lon	g term ver	bal men	n baselin	е	CVLT Long term verbal memory 12m						
Spindles	coef	SE	р	95%CI I	ow up	o coef SE p 95%CI low up		coef	SE	р	95%CI lo	w up					
SP duration	-3.76	7.23	0.6	-17.94	10.41	-0.54	3.11	0.86	-6.63	5.56	2.34	1.88	0.21	-1.34	6.03		
SP density	2.04	1.03	0.04	0.02	4.06	0.29	0.47	0.54	-0.63	1.22	0.68	0.34	0.04	0.02	1.34		
SP energy	0.00	0.00	0.58	0.00	0.01	0.00	0.00	0.56	0.00	0.00	0.001	0.00	0.01	0.00	0.00		
SO																	
SO duration	-7.80	8.23	0.34	-23.94	8.33	1.23	1.85	0.51	-2.40	4.85	-3.44	1.56	0.03	-6.51	-0.38		
SO density	0.00	0.00	0.2	-0.01	0.00	-0.04	0.24	0.87	-0.52	0.44	0.33	0.13	0.01	0.09	0.58		
SO ptp amplitude	-0.01	0.01	0.12	-0.03	0.00	0.00	0.00	0.89	-0.01	0.01	0.00	0.00	0.62	-0.01	0.00		

Biomarkers	аβ42					pTau181	L				tTau				
Spindles	coef	SE	р	95%CI low I	upper	coef	SE	р 9	5%CI low	/ up	coef	SE	р 9	5%CI low u	pper
SP duration	238.99	571.31	0.676	-880.8	1,358.7	8.25	2.15	0.001	4.04	12.45	391.37	738.72	0.596	-1,056.5	1,839.2
SP density	87.64	63.79	0.169	-37.39	212.68	1.44	1.76	0.412	-2.01	4.89	-120.7	158.17	0.445	-430.72	189.31
SP energy	0.250	0.08	0.003	0.09	0.41	-0.01	0.01	0.414	-0.02	0.01	-0.30	0.42	0.472	-1.13	0.52
SO						1									
SO duration	-706.7	326.58	0.030	-1,346.7	-66.58	-5.80	5.24	0.268	-16.1	4.46	-151.9	418.95	0.717	-973.1	669.19
SO density	69.33	20.29	0.001	29.56	109.11	-0.03	0.07	0.659	-0.17	0.11	-0.047	0.09	0.589	-0.22	0.12
SO ptp amplitude	0.006	0.39	0.989	-0.76	0.77	-0.02	0.02	0.410	-0.06	0.02	0.349	1.10	0.751	-1.81	2.51
	tTau/aβ4	2				pTau,	/aβ42								
Spindles	coef	SE	р	95%CI low	upper	coef	SE	p 959	%CI low u	pper					
SP duration	0.507	1.07	0.64	-1.589	2.603	-0.443	0.39	0.261	-1.22	0.33					
SP density	-0.096	0.15	0.53	-0.397	0.204	-0.081	0.03	0.009	-0.14	-0.02					
SP energy	-0.001	0.00	0.05	-0.001	0.000	-0.010	0.00	0.012	-0.01	0.00					
SO															
SO duration	0.251	0.54	0.64	-0.811	1.31	0.170	0.19	0.37	-0.20	0.54					
SO density	-0.005	0.07	0.94	-0.142	0.13	-0.032	0.02	0.07	-0.07	0.00					
SO ptp amplitude	-0.0001	0.00	0.96	-0.002	0.002	0.0002	0.00	0.4	0.00	0.00					

Cognition 

ADAS and 12 months

MAKE base

Results in green are statistically significant. Results in bold remain statistically significant after False Discovery Rate correction for multiple comparisons.

#### Table 5: GLM regression results, sleep spindle (central channels) and slow oscillation (SO) (frontal channels), biomarkers and

SP energy	-0.05	0.01	0.002	-0.04	-0.01	-0.02	0.01	0.01	-0.05	0.00	0.01	0.00	0.011	0.00	0.01		
SO																	
SO duration	25.83	11.83	0.029	2.64	49.01	6.78	11.75	0.56	-16.25	29.81	-5.34	4.83	0.268	-14.80	4.12		-
SO density	-0.08	1.58	0.959	-3.17	3.01	-0.27	1.22	0.83	-2.67	2.13	-0.34	0.34	0.317	-1.02	0.33	3	54
SO ptp amplitude	0.007	0.02	0.757	-0.04	0.05	0.04	0.02	0.08	0.00	0.08	0.03	0.01	0.037	0.00	0.06		



Spindle density and ADAS-cog at baseline and 12 months



Spindle density and MMSE scores at baseline, 12, 24, and 36 months

ADAS: Alzheimer's Disease Assessment Scale, cognitive subscale MMSE: Mini-mental State Examination

# **Figure 2:** Spindle density predicts cognitive performance on the ADAS-Cog and MMSE

# 3.3 Sleep and biomarkers

One unit increase of spindle power statistically significant predicted increased CSF A $\beta$ 42 ( $\beta$ =

0.25 p=0.003) at baseline (table 5). Slow oscillation density also predicted a significant

increase in A $\beta$ 42 ( $\beta$ = 69.33 p=0.001). Spindle duration predicted increased CSF

**Phosphorylated tau** (pTau181) ( $\beta$ = 7.92, p =0.001 (table 5). Spindle density ( $\beta$ = -0.08 p=0.01)

and power ( $\beta$ = -0.01 p=0.01) also predicted decreased **pTau181/Aβ42**. Exploratory analyses of spindle metrics in NREM2 only and SO in NREM3 only (supplementary materials table S1) found several statistically significant associations with Aβ42 (e.g. SO density=  $\beta$  56.34, p=0.001), pTau181/Aβ42 ratio (SO duration, density and amplitude) and **total-tau/Aβ42** (e.g. SO density  $\beta$ = -0.52, p=0.001).

A number of statistically significant associations between spindle and SO metrics and tau biomarkers were also found among persons who were amyloid-positive (CSF A $\beta$ 42 of <600 mg/pl) at baseline (supplementary material table S1). For example, slow oscillation density predicted increased CSF A $\beta$ 42 ( $\beta$ = 29.43, p= 0.01) and density ( $\beta$ = 42.73, p=0.005), while SO duration predicted CSF pTau181 ( $\beta$ = -12.51, p=0.02) and total tau ( $\beta$ = 4.05, p=0.01). Spindle duration, density and energy also predicted biomarker levels in persons who were amyloid positive at baseline.

## 3.4 Mediation and moderating variables

# 3.41 Sleep spindles and slow oscillations mediate the effect of pTau181/a $\beta$ 42 on cognition

Sleep spindle activity had a significant mediating effect on the relationship between pTau181/aβ42 and cognitive performance on the MMSE and ADAS-cog (figure 3). Spindle density mediated 41% of the total effect of pTau181/aβ42 on MMSE scores (indirect effect 69.4% of the direct effect) and spindle density mediated 59% of the total effect of pTau181/aβ42 on ADAS-cog scores. This suggests that a large part of the effect of pTau181/aβ42 on cognition may be due to the mediating role of spindles.



**Figure 3:** Spindle and SO activity mediates the effect of pTau181/aβ42 on cognition (a), while pTau181/aβ42 ratio moderates the effects of spindle and SO characteristics on cognition (b).

Slow oscillation duration had a significant mediating effect on the relationship between pTau181/a $\beta$ 42 and cognitive performance on the MMSE. The pTau181/a $\beta$ 42 ratio had a significant negative effect on MMSE scores which is suppressed by SO duration. The proportion of the total effect that was mediated by SO duration is -0.820, indicating a suppression effect. The ratio of the indirect to direct effect was -0.450, suggesting a significant mediating role and pathway for SO duration in the relationship between pTau181/a $\beta$ 42 ratio and MMSE scores.

# 3.42 PTau181/a $\beta$ 42 moderates the effect of spindles and slow oscillations on cognition

PTau181/a $\beta$ 42 had a moderating, but not mediating, effect on the relationship between sleep spindles and cognition (figure 3). There were statistically significant interactions between pTau181/a $\beta$ 42 and spindle density and power on the ADAS-cog, CVLT long-term verbal memory, MMSE, and ROCF long-term visual memory and copy-figure scores. For example, the effect of increased spindle density on MMSE scores ( $\beta$  35.02 p=0.001), CVLT long-term memory at 12 months ( $\beta$  16.4 p=0.001), ROCF long-term visual memory ( $\beta$  16.4 p=0.001) and Copy-Figure ( $\beta$  62.0 p=0.03) increases as pTau181/a $\beta$ 42 ratio increases. The effect of spindle power on ADAS-cog scores increased as pTau181/a $\beta$ 42 increased ( $\beta$  0.20 p=0.013).

Conversely, pTau181/aβ42 had a statistically significant (p=0.008), negative moderating effect on the relationship between spindle duration and power on CVLT long-term verbal memory (power  $\beta$  -0.15, p=0.001), MMSE (duration  $\beta$  -269.7, p=0.01, power  $\beta$  -0.2, p=0.0001), and ROCF long-term visual memory (duration  $\beta$  -172.6 p=0.006, power  $\beta$  -0.9, p=0.003) and Copy-Figure ( $\beta$  -172.7 p=0.006) scores. The effect of spindle duration or power on MMSE scores decreases as pTau181/a $\beta$ 42 increases. PTau181/a $\beta$ 42 also had a moderating effect on the relationship between spindle duration and power and ADAS-cog scores at 12 months. For example, the effect of increased spindle power on ADAS scores at 12 months increases as pTau181/a $\beta$ 42 ratio increases.

PTau181/a $\beta$ 42 had a statistically significant moderating effect on the effects of SO on cognition scores. For example, pTau181/a $\beta$ 42 had a significant and additive moderating effect on the effects of SO duration on ADAS-cog score ( $\beta$  81.1, p=0.01), SO density on the Rey Copy-figure test ( $\beta$  15.3, p=0.002) and SO amplitude on the MMSE ( $\beta$  2.68, p=0.005). The effects of SO density, and amplitude on cognition increased with higher levels of  $pTau181/a\beta42$ .

#### 4. Discussion

Spindle and SO activity at baseline predicted key biomarkers for AD and cognitive performance from baseline through 36 months. We also found associations between spindle characteristics, biomarkers, and cognition in persons with AD previously unreported, to the best of our knowledge. Our findings have important implications for clinical care in early stages of AD and the development of sleep-based treatment strategies to delay AD progression<sup>9,163</sup>. Delaying the onset of clinical symptoms by just 5 years may reduce treatment costs by 40% and add 2.7 additional life years (5 disease-free years) for persons with AD<sup>176</sup>.

Spindle density had previously been shown to predict better cognitive performance in healthy older adults, but not long-term cognitive performance in persons with  $AD^{7,51,151,152,173}$ . We found that increased spindle density predicted large, clinically significant decreases in ADAS-Cog scores at baseline and 12 months (>10 points), and higher MMSE scores from baseline through 36 months (3-5 points) in persons with mild-to-moderate AD. Lower ADAS-cog scores indicate better cognitive performance, while higher MMSE scores are associated with better cognition. Changes of >4 points on the ADAS-cog and >3 points on the MMSE are clinically important<sup>289</sup>. The ADAS-Cog also assesses cognitive and behavioural domains most affected by AD and is a gold standard for assessing the efficacy of treatments targeting dementia<sup>288</sup>.
Most research has investigated the effects of spindle density, not duration or power, on cognition or disease progression in AD<sup>32</sup>. We found higher spindle duration and power also predicted better cognitive performance over time in persons with AD. Spindle duration predicted increased MMSE scores at 12, 24, and 36 months (15-34 points). Increased spindle density and duration were also associated with significantly lower odds of decreased cognitive performance on the MMSE at 36 months.

Sleep spindles play important roles in cognition, memory consolidation, and synaptic plasticity during sleep<sup>39–41</sup>. Spindles are particularly involved in the transfer of information from short-term memory in the hippocampus to long-term memory in the neocortex that is critical for both declarative and procedural memory<sup>39–41</sup>. Higher spindle activity has been linked with better cognitive performance<sup>7</sup>. The synchronisation (cross-frequency coupling) of NREM SO and spindles also plays an important role in sleep-related memory consolidation in older adults<sup>40,50</sup>.

However, spindle density, duration, frequency, and cross-frequency coupling decrease with normal ageing and are associated with the cognitive decline and impaired memory experienced by older adults<sup>7,39</sup>. Greater reductions in spindle density and duration are found in MCI and AD<sup>78,151–153</sup>. This may be due to several factors<sup>143</sup>. Spindle density is sensitive to prior learning experience, which may be reduced in persons with AD<sup>173</sup>. Additionally, physiological changes associated with AD progression reduce synaptic and dendritic integrity and lead to neuronal hyperexcitability and hypersynchronous network activity, impairing sleep spindle generation and memory consolidation<sup>161</sup>. Alzheimer's pathology can also drive

neuronal degeneration in areas crucial for sleep regulation, spindle activity, or memory consolidation, such as cholinergic neurons in the basal forebrain or noradrenergic neurons in the locus coeruleus<sup>100</sup>. Cortical atrophy and loss of grey matter volume in the hippocampus, praecuneus, amygdala, and cingulate gyrus may also be associated with declines in spindle and SO activity<sup>31</sup>.

The accumulation of pTau and aβ may also influence reductions in spindle activity and cognition in older adults<sup>10,51</sup>. Tau plays a leading role in the formation of neurofibrillary tangles(NFT) that are hallmarks of AD and are strongly correlated with cognitive decline<sup>9</sup>. During early AD, pTau181 accumulates in areas associated with arousal and sleep regulation and may play a role in sleep-wake disruptions, disrupting spindle activity and impairing memory consolidation<sup>159</sup>. Tau pathology in the medial temporal lobe is associated with reductions in hippocampal ripples and the synchronization of spindle-ripple events, also impairing memory consolidation during sleep<sup>160</sup>.

Both spindle density and tau in the brain have been associated with cognition in older adults, but little research had investigated their associations in persons already showing clinical AD symptoms<sup>32</sup>. We found that spindle activity was associated with, and predicts, CSF pTau181, tTau, A $\beta$ 42, and cognitive performance in persons with AD. These is important, given the significant correlations between tau accumulation, neurodegeneration, cognitive impairment, and dementia in AD<sup>9,160</sup>.

Few studies had investigated the association between spindles and A $\beta$ 42 accumulation in AD<sup>34,35,135,136,143,171,172,313</sup>. We found that spindle activity predicted A $\beta$ 42, pTau181/A $\beta$ 42, and

tTau/Aβ42. In fact, we found that spindle activity more frequently predicted Aβ42, tau, and cognitive performance than SO. Nevertheless, SO density predicted a significant increase in Aβ42 at baseline and greater long-term verbal memory performance on the CVLT. Slow oscillation duration also predicted decreased CSF-pTau181 and increased performance on the ROCF.

An unexpected finding was that longer SO duration predicted reduced long-term verbal memory at 12 months (CVLT) and poorer MMSE scores at 24 and 36 months. Previous research correlated reduced SWA with increased cognitive impairment in older adults<sup>314</sup>. Our findings may be driven by AD-related sleep impairments leading to longer depolarisation during SWS and reduced cognitive performance over time. Increased SO duration was also associated with lower CSF Aβ42 (higher amyloid pathology), which could result from disease progression or be accelerated by reduced SWS over time.

Our findings for spindles, SO, and cognition likely reflect complex interactions between sleep, A $\beta$ 42, tau, and cognition in AD<sup>34</sup>. Indeed, we found that pTau181/A $\beta$ 42 moderated the effects of spindle and SO activity on cognition, while spindles and slow oscillations mediated the effects of pTau181/A $\beta$ 42 on cognition (figure 3). Mander et al.(2015) found that sleep mediated the influence of A $\beta$ 42 on reduced memory<sup>35</sup>. Zavecz et al.(2023) also found that NREM SWA significantly suppressed the effect of A $\beta$  status on memory function, particularly in persons with high A $\beta$  burden<sup>170</sup>.

Potential pathways may include orexinergic and glymphatic system activity during NREM sleep, which helps clear AD biomarkers<sup>315</sup>. Orexin levels are higher in moderate-to-advanced

AD, influence A $\beta$ 42 deposition, and can be involved in sleep-wake cycle dysregulation<sup>315</sup>. Impaired NREM sleep also increases A $\beta$ 42 deposition, which can impair NREM sleep in turn, influencing cognition<sup>34</sup>. A $\beta$ 42 may also reduce NREM SO generation, decreasing A $\beta$ 42 clearance, further accelerating AD<sup>135</sup>.

Another intriguing finding was higher spindle activity among females in our sample. Sexbased differences in spindle activity have not been investigated extensively in AD. However, higher spindle density, particularly in fast spindles (>12 Hz), power, and power in the highfrequency portion of the sigma band (13–15 Hz) haven been reported in healthy older females than males<sup>148</sup>. Greater NREM sleep disruption, and up to 50% less SWS, have been found in older males than females<sup>316,317</sup>. These could underlie greater alterations in spindle activity in males than females. We also found no statistically significant sex-based differences in SO activity, though these have been reported for SO and SWA in healthy adults <sup>80,316,317</sup>. This may be related to sex-based differences in the development and progression of AD and its effect on sleep physiology, but these have been under-investigated and need further research, given our findings.<sup>318</sup>.

## 4.1 Implications and future research

Our findings support previous suggestions that spindle and SO activity can act as predictive, non-invasive biomarkers for AD progression and provide therapeutic targets for cognitive decline. This is important, given that there are currently few disease-modifying treatments for AD and it can be difficult to identify persons for treatment before Aβ burden is too high<sup>174</sup>. Accessible, in-home, ambulatory EEG may also improve the feasibility of overnight

PSG for persons with AD. Interventions targeting SWA and memory consolidation in persons with MCI or AD ,such as transcranial direct-current or acoustic stimulation, have also yielded promising results <sup>319,320</sup>.

Lifestyle-based interventions can also enhance sleep in AD. Exercise targets sleep physiology and SWA<sup>214,220</sup>, can protect against functional and cognitive decline<sup>282</sup>, decreases levels of biomarkers associated cognitive decline, and increases those linked to brain-health<sup>247</sup>. Our recent meta-analysis of exercise interventions targeting sleep in older adults with MCI or AD found moderate-to-high-quality evidence for the beneficial effects of exercise on sleep, including SWS<sup>220</sup>.

## 4.2 Strengths and limitations

Our study has several strengths. Our data was collected prospectively in a sex-balanced cohort of persons with high A $\beta$ 42 burden and clinical symptoms consistent with mild-to-moderate AD, using standardised procedures at a centre with expertise in AD/ADRD. We also have comprehensive data for cognition capturing a range of cognitive domains.

We controlled for important confounding factors including age and OSA, while avoiding overfitting our regression models. Alzheimer's disease and OSA share mechanisms and features including altered sleep architecture, AHI, and reduced brain-health<sup>104,321</sup>. Increasing age is also associated with changes in sleep and some AD biomarkers<sup>6</sup>. We adjusted for multiple comparisons, reducing risk of type-1 error

However, observational studies can only imply associations, not causation, between sleep, biomarkers, and cognition, and we had no comparison group of healthy older adults. However, the study sought to follow the cognitive evolution of persons with AD, and associations between sleep physiology, biomarkers, and cognition in healthy older adults have been explored extensively<sup>7,51,151,152,173,314</sup>. Participants also underwent PSG only at baseline, without a preceding accommodation night, so we cannot rule out first-night effects. Overnight PSG with persons with AD carries unique challenges, making this difficult to accomplish. We also cannot rule out the effects of progressive changes in biomarkers or of sleep on cognitive performance as participants' AD progressed. This would be important additional data future studies can collect, along with PET to investigate topographic associations between alterations in spindles and anatomical distribution of NFTs.

Our novel findings demonstrate that reduced NREM spindle and SO activity constitute complimentary, predictive, and non-invasive biomarkers for AD pathology and progression<sup>32,175</sup>. Sleep is an important modifiable risk factor for cognitive decline and the progression of AD/ADRD<sup>6</sup>. Sleep-based biomarkers for AD such as NREM spindle and SO may provide novel therapeutic targets for interventions designed to slow the progression of AD symptoms<sup>9,163</sup>.

### (Supplementary materials can be found in Appendix I)

Chapter III: Sleep microarchitecture predicts neurofilament-light, neuroinflammatory biomarkers, and cognition in Alzheimer's Disease

## Chapter summary:

This chapter further investigates associations between NREM sleep microarchitecture and the progression of AD investigated in Chapter 1. Here, we investigated these associations in complimentary biomarkers of neuroinflammation and neurodegeneration in Alzheimer's Disease (AD). We also investigate associations between these, sleep microarchitecture, cognition, and mental health (neuropsychiatric symptom severity) in AD. This further explores sleep spindles and slow oscillations as novel therapeutic targets for preserving brainheath and slowing AD progression. This chapter has been submitted for publication to the journal Brain as "Sleep predicts neuroinflammatory biomarkers, cognition, and mental health in Alzheimer's Disease. Arsenio, Shahla Bakian Dogaheh, Sam O. Gillman, Anna Carnes, Faride Dakterzada, Ferran Barbé, Thien Thanh Dang-Vu, Gerard Piñol Ripoll. Manuscript ID BRAIN-2024-03009 (11/24).



#### ABSTRACT

**Background and Objectives:** Sleep is essential for brain-health, including clearance of βamyloid, tau, and other biomarkers of neurodegeneration and Alzheimer's Disease (AD): cerebrospinal fluid (CSF) neurofilament-light chain (NfL), neurogranin-36 (NG-36),and Chitinase-3-like protein-1 (YKL-40). However, it remains unclear whether sleep physiology predict these biomarkers or whether these biomarkers predict cognitive or neuropsychiatric decline after AD onset. We aimed to determine if sleep physiology predicts biomarkers and cognition in AD.

**Methods:** Using data from a prospective cohort study of mild-to-moderate AD (n=60, 30female, mean age 74.7), we analysed: a. non-rapid eye-movement sleep spindles and slow oscillations (SO) at baseline and their associations with NfL, YKI-40, NG-36, NfL/Aβ42, YKI-40/Aβ42 and b. whether these biomarkers predict cognition and mental health at baseline and change from baseline to three-years follow-up.

Participants underwent polysomnography, CSF draws and neuropsychological assessment at baseline. Cognitive testing was performed with the Mini-Mental Status Examination(MMSE) at baseline, 12, 24 and 36 months, and the Alzheimer's Disease Assessment Scale-Cognitive Subscale(ADAS-Cog) and Neuropsychiatric Inventory(NPI) at baseline and 12 months. Spindle and SO detection was performed and associations between SO and spindle characteristics(duration, density, power, amplitude), biomarkers, and cognition from baseline to 36 months were investigated with false discovery rate-adjusted Robust Regression controlling for age, sex, apnea-hypopnea index. We performed Sobel-Goodman mediation

analysis and moderation analyses to investigate relationships between NfL, YKL-40, and their ratios with A $\beta$ 42, spindle and SO activity, and cognition.

**Results:** We found previously unreported associations between spindle and SO characteristics, NfL, YKI-40, NG-36, NfL/A $\beta$ 42 ( $\beta$ =-.0029, p=0.001), YKI-40/A $\beta$ 42 ( $\beta$ =0.0004, p=0.003) and cognition in persons with AD. These biomarkers predicted worse cognitive performance (higher ADAS-cog [ $\beta$ =2.28, p=0.004], lower MMSE scores [ $\beta$ = -2.42, p=0.01]) from baseline to 36-months, and a significant increase in neuropsychiatric symptom severity (NPI  $\beta$ =16.93 p<0.001). NfL/A $\beta$ 42 mediated the effects of spindle activity on cognitive performance on the ADAS-cog (p= 0.041) and MMSE (p=0.0019). Biomarkers also moderated the relationships between spindle and SO activity on cognition, and spindles and SO moderated the relationships between these biomarkers and cognition.

**Discussion**: NREM spindle and SO activity, can act as complimentary, non-invasive markers of neurodegeneration and potential therapeutic targets for sleep-related interventions designed to monitor or slow AD symptom progression. They add further evidence for links between NfL, NG-36, YKL-40, sleep, and cognition, and their role as supplemental AD biomarkers and biomarkers of susceptibility to neurodegeneration in cognitively unimpaired persons at higher risk of AD. They also constitute potential targets for sleep-related interventions for cognition in the context of AD and other neurodegenerative disorders.

Keywords: sleep; brain-oscillations; neurodegeneration; Alzheimers; biomarkers; cognition

Running title: Sleep, brain-health, and Alzheimer's

#### INTRODUCTION

Sleep may be one of the most important modifiable risk factors for functional and cognitive decline and dementia in older adults<sup>6,77</sup>. Poor sleep increases the risk of neurodegeneration and neurodegenerative disorders such as Alzheimer's Disease (AD)<sup>6,7</sup>. There is a bidirectional relationship between sleep and AD<sup>9,10</sup>. Poor sleep may have a causal role in the pathophysiology of AD<sup>6,9,102</sup>. Sleep disorders, including insomnia, restless leg syndrome, and sleep apnoea often appear well over a decade before the first clinical symptoms of Alzheimer's Disease (AD)<sup>6,7,67</sup> and induce systemic and central nervous system inflammation and neurophysiological changes in the brain that may drive the onset and progression of AD<sup>6,8,103</sup>. Sleep plays vital roles in regulating the clearance of proteins such as  $\beta$ -amyloid (A $\beta$ ) and tau linked to the development and progression of AD<sup>6,24,104</sup>.

Persons with AD also experience greater reductions in total sleep time and sleep quality than healthy older adults<sup>78</sup>. They can also predict or accelerate the progression of cognitive decline and functional impairment in persons with AD<sup>6,7,99</sup>. Sleep physiology, including sleep spindles and slow oscillations (SO) during NREM sleep, is altered in AD and has been linked to neurodegeneration and the progression of AD symptoms<sup>29,52,143</sup>. We previously showed that both sleep spindles and slow oscillations during non-rapid eye-movement sleep predict CSF amyloid-beta, tau, and cognition over three years in persons with mild-to-moderate-AD<sup>285</sup>.

Sleep spindles are 9–16 Hz waxing-and-waning oscillations generated within the thalamocortical network associated with sleep-dependent memory consolidation, cognition, and sleep continuity<sup>37</sup>. Spindle density, duration, and amplitude decrease with age, but are further reduced in AD<sup>32,78,299</sup>. Large-amplitude, low-frequency slow waves (>75 microV, 0.5-

4Hz) and SO(<1 Hz) and SO, largely arising from the prefrontal neocortex, also underlie memory consolidation during sleep<sup>46</sup>. The number and amplitude SO decrease in in healthy older adults, but these decreases are more pronounced in persons with cognitive decline or AD<sup>29</sup>.

Mounting evidence suggests that AD is a disease of multiple aetiologies and overlapping risk factors<sup>110</sup>. Sleep plays important roles in the clearance of  $\beta$ -amyloid (A $\beta$ ) and tau that are hallmarks of AD, but may also play important roles in the clearance of other biomarkers highly linked to its aetiology and progression, such as cerebrospinal fluid (CSF) neurofilament-light chain (NfL), neurogranin-36 (NG-36), and Chitinase-3-like protein-1 (YKL-40)<sup>6,111</sup>. These have emerged as promising diagnostic markers of neurodegeneration and cognitive decline in AD<sup>111</sup>. An important feature of these biomarkers is that they are highly accurate for discriminating neurodegenerative cognitive decline from non-degenerative forms of cognitive decline, independently of A $\beta$ , and may also help quantify AD-related pathophysiological changes in the brain in living persons<sup>111,117,120</sup>.

Cerebrospinal fluid (CSF) and plasma NfL are biomarkers of neuronal axonal damage and indicators of AD severity that may also be influenced by sleep<sup>117,120</sup>. Increased NfL levels are prognostic of AD and predict white matter changes, brain atrophy, and cognitive decline in persons with MCI and AD<sup>117,120</sup>. Elevated serum NfL levels have been reported in persons with chronic insomnia disorder and persons with AD<sup>117,120</sup>. Increased light sleep (increased NREM1 and decreased NREM3 sleep) has been associated with increased probability of high CSF and plasma NfL levels in AD<sup>286</sup>.

Cerebrospinal fluid NG-36 and YKL-40 have also been linked with both sleep and brain-health in older adults and persons with AD<sup>127</sup>. Neurogranin-36 is a post-synaptic protein enriched in the cortex and hippocampus and a putative marker of synaptic integrity, synaptic loss, brain atrophy and cognitive decline in AD<sup>127</sup>. YKL-40 expression is abundant in astrocytes in neuroinflammatory conditions and has been associated with early pathophysiological changes and neuroinflammatory response to amyloid deposition in early AD<sup>128</sup>. Increased CSF YKL-40 has been linked with circadian rhythm disfunction and AD progression and correlated with both Aβ42 and tau, supporting its potential role as a complementary biomarker in AD diagnosis and prognosis<sup>127</sup>.

#### Evidence gaps and opportunities

Growing evidence supports the diagnostic and prognostic utility of changes in sleep, CSF Aβ, and tau in AD<sup>6,99,110</sup>. However, there continues to be a need for supplemental biomarkers like NfL, NG-36, or YKL-40, representing different aspects of AD pathophysiology, that can improve or support AD diagnosis, disease-staging, and prognosis. While these biomarkers been associated with cognitive decline in healthy older adults, fewer studies have investigated their longitudinal associations with cognition in AD. Additionally, significant associations have been reported between sleep spindle activity, NG-36, and YKL-40 in healthy older adults, but these have not been investigated in persons with AD<sup>29,52,143</sup>. Investigating features of NREM sleep physiology correlated with these biomarkers can support earlier identification of persons at risk during pre-clinical AD and offers opportunities for novel therapeutic targets to slow AD progression.

In this study, we investigated associations between NREM spindle and SO activity and NfL, YKL-40, and Ng-36 at baseline in a sample of 60 persons with mild-to-moderate AD. We also investigated whether these biomarkers predict cognition from baseline to 36 months and neuropsychiatric symptom severity over 12 months in AD. We hypothesised that NREM sleep spindle and SO activity predict levels of these biomarkers, and these biomarkers are associated with reduced cognition and increased neuropsychiatric symptoms at baseline and longitudinally in AD. Sleep spindle and SO activity may therefore constitute predictive, noninvasive biomarkers of neurodegeneration in AD and novel therapeutic targets to slow AD progression and preserve brain-heath.

### METHODS

### Study Design

We analysed data collected between November 2014 to November 2017 in a prospective study of the influence of obstructive sleep apnoea (OSA) on the cognitive evolution of persons with AD (Role of Hypoxia And Sleep Fragmentation in Alzheimer's Disease. ClinicalTrials.gov NCT02814045)<sup>99</sup>. The study was approved by the institutional review board of Hospital Arnau de Vilanova de Lleida (CE-1218) and conducted according to the Declaration of Helsinki principles.

Participant eligibility, recruitment, and data collection methods have been described extensively previously<sup>99</sup>. Briefly, a cohort of 104 persons with mild-moderate AD were recruited in a prospective, observational study at the Cognitive Disorders Unit of Hospital Universitari Santa Maria (Lleida, Spain). Eligible participants were aged  $\geq$  60 years old with AD diagnosed according to the National Institute on Aging and Alzheimer's Association criteria. Exclusion criteria included use of investigational drugs, beta-blockers, antidepressants, neuroleptics, or hypnotics within 15 days of the overnight polysomnography (PSG)<sup>99</sup>.

Data from 60 of the participants (30 females) was available for the analyses described in this paper. None of these participants were taking anticonvulsants, antipsychotics, anxiolytics, hypnotics, or medications for poor sleep such as benzodiazepine receptor agonists, that may influence sleep microarchitecture. Five participants had previously taken antidepressants, but not for at least 15 days before PSG.

# Data collection

At baseline, participants underwent a battery of functional and neuropsychological assessments, including the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog)<sup>288</sup>, Mini-Mental Status Examination (MMSE)<sup>289</sup>, and Neuropsychiatric Inventory (NPI)<sup>322</sup>, followed by one-night of polysomnography (figure 1). The following morning CSF was collected for NfL, NG-36, and YKL-40. The ADAS-cog and NPI was re-administered at 12 months, and the MMSE was re-administered at 12, 24, and 36 months.

### Sleep

Polysomnography was undertaken using Philips Respironics Alice 6 LDx (34 channel EEG referenced to the mastoids, 512 Hz sampling rate). Electroencephalography (EEG) records were visually scored by experienced sleep technicians using Phillips-G3 Dreamware software

(bandpass filter 0.3Hz – 93.6Hz, sampling frequency 512Hz) in 30-s epochs in one of four stages of sleep (non-rapid eye movement stages 1, 2, or 3 [NREM1, NREM2, NREM3], and rapid eye movement [REM]) following American Academy of Sleep Medicine (AASM) criteria<sup>294</sup>.

## Biomarkers

Cerebrospinal fluid samples were collected between 8:00 am and 10:00 am to avoid variations related to circadian rhythms, centrifuged at 2000 × g for 10 minutes at 4°C, immediately frozen, and stored within 4 hours in an -80°C freezer. Concentrations of NG-36 were measured using an in-house enzyme-linked immunosorbent assay (ELISA)<sup>286</sup>, while YKL-40 and NfL were measured with commercial ELISA kits<sup>286</sup>. All measurements were performed in one round using one batch of reagents by board-certified laboratory technicians blinded to clinical data. Intra-assay coefficients of variation were lower than 10% for internal quality control samples (two per plate).

For **apolipoprotein-E (ApoE**) genotyping, DNA was extracted from buffy coat cells with a Maxwell RCS blood DNA kit (Promega, USA) for polymerase chain reaction genotyping.

## Data analyses

Participants' sleep EEG records were processed with Wonambi v 7.11, an open-source Python software package developed at the Sleep, Cognition and Neuroimaging Laboratory (SCNLab) at Concordia University, Montreal (<u>https://github.com/wonambi-python/wonambi</u>) and visually checked again by experienced sleep scorers (AP, SG, SB, OW) at the SCNLab, following

AASM criteria<sup>294</sup>. We also reviewed each EEG recordings in 30-s epochs to identify and tag microarousals, artifacts, or instances of poor EEG signal for exclusion from subsequent analyses. Targeted signal aberrations included poor or dysfunctional signals lasting greater than one 1 second<sup>294</sup>, excessive muscle artifact or movement, micro-arousal activity (sudden transient cortical activations during sleep and abrupt shift in EEG frequency lasting longer than 3 seconds<sup>294</sup>), or periods in an epoch that contained a shift to N1 or wakefulness.

Automatic EEG sleep spindle and SO **event detection** on were performed using another inhouse software package developed at the SCNLab and run on Spyder (v5.3.3), directly incorporating functions from validated sleep spindle and slow-wave detection methods. Based on review of literature for spindle and slow-wave activity in older adults, we undertook sleep spindle detection over two central channels (C3-A2, C4-A1)<sup>32,148</sup>, and slow oscillations detection over the two frontal channels (F3-A3, F4-A1)<sup>296</sup>.

An algorithm developed by Staresina et al. (2015) was used to detect SO on channels F3 and F4 during NREM3<sup>46</sup>. Artifact-free EEG signals were filtered between 0.16 - 1.25Hz (zero-phase infinite impulse response bandpass filter). The duration threshold for potential SOs was 0.8 - 2.0 seconds for two successive positive-to-negative zero crossings, in filtered EEG signals. Following Staresina's criteria, the event amplitude threshold for SOs meeting duration criteria was amplitudes exceeding the 75th percentile of trough-to-peak amplitude between two positive-to-negative zero crossings<sup>46</sup>. We also visually reviewed detected SO events to ensure that they were not false positives.

Sleep spindles were detected during NREM2 (fixed bandwidth 9 - 16Hz) based on Mölle et al.'s (2011) algorithm<sup>40</sup>. We chose a 9-16hz bandwidth based on a review of literature for spindle characteristics in older adults, MCI, AD, and other neurodegenerative disorders<sup>78,173,298,299</sup>. These disorders have been associated with greater declines in spindle characteristics and physiological changes than seen with increasing age<sup>78,173,298,299</sup>. We also wanted to capture slow spindle activity (9-12Hz)<sup>40</sup> in our sample, given evidence age-related changes in slow spindle activity and their links with cognitive decline<sup>7,78,173,298,299</sup>. On artifact-free, filtered EEG signals in channels C3 and C4, the root mean square (RMS) was computed using a 0.2 sec sliding window, then further smoothed using 0.2 sec moving average. Sleep spindles were identified when standard deviations of RMS values exceeded 1.5 for 0.5 – 3.0 sec. To manually check the accuracy of automatically detected SO and sleep spindle events, we visually inspected the identified sleep spindles with Wonambi.

We extracted data for spindle density (/30 sec) mean duration (sec), and power ( $\mu$ V2) in NREM2, and SO density (/30 sec), mean duration (sec), and amplitude ( $\mu$ V) in NREM3. These characteristics were chosen for their associations with brain-health, cognitive decline, and AD progression<sup>7,32,148,305</sup>. For example, spindle and SO duration and density have been linked to cognitive decline and biomarkers of neurodegeneration in healthy older adults<sup>32,51,173</sup>.

### Statistical analyses

We calculated descriptive statistics for participant characteristics, sleep, and biomarkers and differences in these between males and females. We expected that biomarker data may be right or left skewed rather than normally distributed, as may be expected in participants with mild to moderate AD<sup>117</sup>. We also calculated ratios of CSF NfL/Aβ42 and YkL-40/Aβ42<sup>323</sup>.

These biomarker ratios have been associated with increased brain amyloid and shown to be superior for predicting clinical decline and progression to dementia in older adults at risk of AD than individual biomarkers<sup>128,323</sup>.

### Sleep microarchitecture, AD biomarkers, and cognition

We investigated cross-sectional associations between SO and spindle metrics and CSF biomarkers (NfL, ng36, YKL-40, NfL/Aβ42 and YKL-40/Aβ42), and longitudinal associations between these biomarkers at baseline, cognition (MMSE baseline, 12, 24, 36 months, ADAS-cog baseline, 12 months) and neuropsychiatric symptom severity (NPI baseline, 12 months) using Robust Regression with Huber Loss and Tukey's biweight functions. Robust regression models reduce the effects of influential variables or outlying observations which may arise in a sample of persons with mild-moderate AD but are clinically valid and account for potential heteroscedasticity in the data<sup>324</sup>. We checked for multicollinearity among sleep spindle and SO characteristics with the variance inflation factor (VIF), maintaining VIF at <2 (no to low correlation)<sup>310</sup>. All regression results were corrected for multiple comparisons with a Benjamini-Hochberg False Discovery Rate.

We limited covariates in our model to avoiding over-fitting that may bias regression results. We controlled for age (continuous), sex (binary), and apnoea-hypopnea index (AHIcontinuous). The sample was drawn from a population of older adults with a high prevalence of OSA, and hypoxia severity has been associated with amyloid deposition and increased risk of AD in persons with OSA. In secondary analyses, we included baseline CSF Aβ42 levels in our regression model, given associations between the biomarkers we investigated and amyloid deposition, and between amyloid deposition and changes in sleep physiology in AD<sup>117</sup>. In another analysis, we controlled for APOE4 in the regression models for spindles, SO, and biomarkers, given associations between APOE4 and biomarkers of neurodegeneration in older adults<sup>325</sup>. Finally, we investigated whether NfL predicted levels of other primary biomarkers of AD: Aβ42, phosphorylated tau (pTau181), total-tau, ptau181/Aβ42, total-tau/Aβ42, and biomarkers of neuroinflammation and neurodegeneration: CSF NG-36, CSF YKL-40, YKL-40/Aβ42.

We performed mediation analysis with Sobel-Goodman Tests following Preacher and Hayes' recommendation and moderation analyses using regression models with interaction terms. We explored mediating and moderating relationships between NfL, YKL-40, and their rations with Aβ42, spindle and SO activity, and cognition, given our previous findings for the associations between spindle and SO activity and cognition in mild-to-moderate AD<sup>285</sup>.

**DATA AVAILABILITY STATEMENT:** Data not provided in the article because of space limitations may be shared (anonymized) by reasonable request from qualified investigators.

## RESULTS

The 60 participants (30 female) in this study had a mean age of 74.7 and MMSE score of 22.9  $\pm 2.4$  at baseline. There were no significant differences between males and females in age, body-mass index (BMI), educational attainment, prevalence of diabetes, depression, obstructive sleep apnoea, or CSF A $\beta$ 42 (median 516 pg/ml) (table 1). No statistically

significant differences were found between males and females on the MMSE, ADAS-cog, NPI, or Cornell Scale for Depression in Dementia at baseline.

### Sleep

Participants had a mean total sleep time of 260.4 minutes (±89.9) and a median sleep efficiency of 67% (IQR 48-80) (table 2). There were no significant differences between males and females in (mean) total sleep time, sleep efficiency, or time spent in NREM2 sleep. However, females spent more time than males in NREM3 and had and had higher spindle density (per 30 second epoch), power (109  $\mu$ V2) and higher median peak spindle frequency (11.24hz) than males (table 2). Participants had a mean SO density of 2.7 (±0.9) per 30 second epoch, median SO duration of 1 second (IQR 1-2), and SO amplitude of 108  $\mu$ V (IQR 81-156). There were no statistically significant sex-based differences in SO (table 2).

#### Sleep and biomarkers

**Spindles** (table 3 and figure 2): A unit increase in NREM2 spindle power predicted a statistically significant decrease in CSF NfL/A $\beta$ 42 ( $\beta$ =-.0029, p=0.001). Increased spindle density also predicted decreased CSF NfL/A $\beta$ 42 ratio, but it did not survive FDR correction ( $\beta$ =-0.62, p=0.026). A unit increase in spindle power also predicted a statistically significant decrease in the CSF YkL-40/A $\beta$ 42 ratio ( $\beta$ =0.0004, p=0.003).

Among individual biomarkers, one unit increases of spindle power ( $\beta$ =-2.22, p=0.004) and spindle duration ( $\beta$ =-2424.67, p=0.001) each predicted statistically significant decreases in **CSF NfL**. These remained statistically significant when controlling for either A $\beta$ 42 or apoe4

(eTable 1). Spindle power also predicted decreased CSF YKL-40 ( $\beta$ =-0.81, p=0.034) that did not survive FDR correction. However, when adjusted for baseline A $\beta$ 42, the association was stronger ( $\beta$ =-0.98, p=0.013), surviving FDR correction. No statistically significant associations were found between spindle characteristics, plasma NfL or CSF NG-36.

**Slow Oscillations** (table 4 and figure 3): One unit increase in SO density predicted a statistically significant decrease in plasma NfL ( $\beta$ =-11.22, p=0.0001). SO power was also associated with decreased CSF NG-36 ( $\beta$ =138.77, p=0.006). No other statistically significant associations were found between SO characteristics and other biomarkers. Controlling for APOE4 in associations between spindles, SO, and biomarkers did not change the change the statistical significance of our results (eTable1).

#### Biomarkers, cognition, and neuropsychiatric symptoms

A unit increase in CSF NfL was associated with statistically significant increased **ADAS-cog total score** (poorer cognitive performance) at baseline, even when accounting for A $\beta$ 42 (table 5). Each unit increase in CSF NfL/A $\beta$ 42 predicted a 2.28 point increase in the ADAS-cog (p=0.004). CSF NG-36 also predicted statistically significant increases in ADAS-cog scores at baseline and 12 months ( $\beta$ =0.29, p=0.01), surviving FDR correction when adjusting for A $\beta$ 42, which also resulted in a large increase of 6.45 points on the ADAS-cog at 12months for every unit increase in YKL-40.

Cerebrospinal fluid NfL and NfL/Aβ42 also predicted statistically significant decreases in **MMSE scores (poorer cognition)** at baseline, 12, and 24 months, though only the

association with decreased cognitive performance on the MMSE at 24 months ( $\beta$ =-1.27, p=0.02) survived FDR correction. Plasma NfL predicted poor cognition on the MMSE at 36 months when adjusting for baseline A $\beta$ 42 ( $\beta$ =-0.23, p=0.001). Cerebrospinal fluid YKL-40/A $\beta$ 42 also predicted a statistically significant decrease in the MMSE at 12 months ( $\beta$ = -2.42, p=0.01). Both NfL/A $\beta$ 42 and YKL-40/A $\beta$ 42 at predicted statistically significant increase in the NPI (poorer mental health) at 12 months. The association with YKL-40/A $\beta$ 42 survived FDR correction ( $\beta$ =-16.93, p=0.0001).

#### Secondary analyses

We also found statistically significant associations between **CSF NfL and the other biomarkers** in our study (eTable 2). One unit increase in CSF NfL predicted increased tTau ( $\beta$ =0.58, p=0.009), ptau181/A $\beta$ 42 ( $\beta$ =0.0001, p=0.015), tTau/A $\beta$ 42 ( $\beta$ =0.001, p=0.001) and CSF NG-36 ( $\beta$ =0.091, p=0.006).

Neurofilament-light/Aβ42 **mediated** the effects of spindle activity on cognitive performance on the ADAS-cog (p= 0.041) at baseline and the MMSE at 12 months (Sobel-Goodman p=0.0019), mediating 56% and 27.5% of the effects of spindle activity on cognition, respectively (eTable 3 ). There were statistically significant interactions between NfL, YKI-40, NfL/Aβ42 and YKL-40/Aβ42 and both cognition from baseline to 36 months and sleep, indicating the biomarkers **moderate** the relationships between spindle and SO activity on cognition, and sleep spindles and SO moderate the relationships between these biomarkers and cognition. For example, as levels of these biomarkers increased, ADAS-cog scores at

baseline and 12 months increased (poorer cognitive performance), and MMSE scores from baseline through to 36 months decreased (poorer cognitive performance) (eTable 4).

### DISCUSSION

We found that spindle and SO activity predicts CSF and plasma NfL, and CSF Ng-36, NfL/Aβ42 and YKL-40/Aβ42 in mild-to-moderate AD. To the best of our knowledge, these associations had not been previously reported in persons with AD. These are important findings, given that these biomarkers have previously been linked with longitudinal amyloid accumulation and cognitive decline in older adults<sup>323</sup>. Indeed, we found that these biomarkers predicted poorer cognitive performance and mental health (NPI) over time and play both mediating and moderating roles in the relationships between spindle and SO activity and cognition in mild-to-moderate AD. Our findings have important implications for clinical care in early stages of AD and the development of sleep-based treatment strategies to delay AD progression. Delaying the progression of AD symptoms can have considerable benefits for persons with AD, their caregivers, and communities<sup>176</sup>.

## Neurofilament-light

Most research has explored links between fluid NfL and sleep in healthy older adults or those at risk of AD. For example, Mander et al (2022) found that CSF NfL was associated with spindle density and duration in a sample of 58 cognitively unimpaired, amyloid-negative older adults at risk of AD<sup>52</sup>. However, the associations with spindle density did not remain significant after adjusting for age, sex AHI, and APOE. Our study is the first to report statistically significant associations between spindle and SO characteristics and fluid NfL

measures in AD. The associations we found between spindle activity and NfL may reflect the increased amyloid-positivity, tau phosphorylation, and neuroinflammation of our sample, which could be associated with higher CSF NfL and more robust associations with spindle activity. Indeed, CSF NfL in our sample (median 960.8) was significantly higher than the mean CSF NfL reported by Mander et al  $(92.1 \pm 119.3)^{52}$ .

Our sample also had significantly lower CSF Aβ42 than Mander et al.'s. Amyloid pathology associated with AD progression can drive neuronal degeneration in areas crucial for spindle activity, such as cholinergic neurons in the basal forebrain or noradrenergic neurons in the locus coeruleus.<sup>100</sup> This may reduce synaptic and dendritic integrity, impairing sleep spindle activity but also increasing CSF NfL<sup>161</sup>. Cortical atrophy and loss of grey matter volume in the hippocampus, praecuneus, amygdala, and cingulate gyrus may also be associated with declines in SO activity<sup>31</sup>. Our findings suggest that a decrease in spindle or SO activity may be linked to the clearance of NfL in the brain, similar to the associations found for Aβ42 and pTau181<sup>51</sup>. Decreased clearance of tau may also lead to neurodegeneration and axonal injury, further increasing NfL levels<sup>326</sup>.

Neurofilament-light has also been linked to axonal damage, neurodegeneration, and cognitive decline in a number of proteopathies, including AD<sup>117,325</sup>. Our results support and extend these findings. We found that increased CSF or plasma NfL at baseline predicts poorer cognition cross-sectionally (ADAS-cog) and over three years (MMSE). However, it is intriguing that plasma NfL was not associated with cognitive performance (MMSE) from baseline to 24 months. The reasons underlying this are difficult to explore with our data alone. Previous studies in healthy older adults have also failed find an association between plasma NfL and

measurable decline in global cognition, even when there was a significant association between plasma NfL and neuroimaging measures of neurodegeneration<sup>327</sup>. Our findings may reflect the progressive, cumulative effects of AD pathology and neurodegeneration on global cognition over a longer timespan (36 months). Fluid NfL measures have been associated with magnetic resonance imaging (MRI) assessed brain atrophy and post-mortem neurofibrillary tangle load in persons with clinically apparent AD, further supporting this possibility<sup>117</sup>.

### NG-36 and YkL-40

We found a statistically significant inverse relationship between SO duration and NG-36. This is also an important finding, given that elevated CSF NG-36 has been shown to be a trait specific to AD<sup>328</sup>. It has also been linked to synaptic degeneration that is an early feature of AD and synaptic loss strongly correlated with cognitive decline<sup>328</sup>. Poor sleep may interfere with sleep-dependent synaptic maintenance during NREM sleep, increasing synaptic injury and CSF NG-36<sup>328</sup>. It may also decrease metabolic clearance of amyloid and tau, further interfering with NREM sleep, synaptic maintenance, and SO activity<sup>136</sup>.

Cerebrospinal fluid levels of NfL, NG-36 and YKL-40 can complement other diagnostic fluid biomarkers of early symptomatic AD and help predict future cognitive decline in presymptomatic older adults<sup>328</sup>. Our results support the complementary role of these biomarkers in predicting cognitive decline in AD. We found statistically significant associations between CSF NfL, NG-36, YKL-40 and poorer cognitive performance (ADAS-cog and MMSE). The strong, inverse relationships between NfL/Aβ42, YKL-40/Aβ42 and cognition (ADAS-cog and MMSE) from baseline to 24 months further extends previous evidence that these rations predict clinical decline in older adults at risk of AD<sup>128,323</sup>. It is notable that we also found that YKL-40/A $\beta$ 42 at baseline predicted a large increase in neuropsychiatric symptom severity on the NPI at 12 months (B=16.93, p <0.001). The neuropsychiatric symptoms captures by the NPI include some of the greatest stressors for persons with AD and their caregivers. These including nighttime behavioural disturbances, which are among the leading causes of caregiver stress and institutionalization for persons with AD<sup>162</sup>. There are also strong bidirectional relationships between mood, depression, agitation, sleep and sleep physiology, further underscoring the dynamic relationship between sleep, sleep physiology, mental-health and brain health in older adults<sup>227,230,231,281,329–332</sup>.

## Implications and future research

Our results support previous suggestions that spindle and SO activity can act as predictive, non-invasive biomarkers of brain-health and therapeutic targets for AD progression. They also reflect the complex, bidirectional relationships between sleep and the multiple aetiologies that may underlie the development and progression of AD<sup>34</sup>. The mediating and moderating roles we found for YKI-40, NfL/Aβ42 and YKL-40/Aβ42 in the associations between spindle and SO activity and cognition further underscore the complex relationships between sleep physiology, brain-health, and AD. A number of potential pathways for these relationships have been proposed, including glymphatic system activity during NREM sleep promoting the clearance of AD biomarkers, with impaired NREM sleep disrupting clearance of Aβ42 and tau, influencing disease progression and cognitive decline<sup>34</sup>. Increased Aβ42 deposition may also reduce NREM spindle and SO generation, further decreasing Aβ42

clearance and accelerating the neurodegeneration captured in the biomarkers we invesigated<sup>135</sup>.

There are currently few disease-modifying treatments for AD<sup>174</sup>. It is also difficult to identify persons for treatment before their disease burden is too high, underscoring the important, predictive ability of sleep spindles and SO in AD<sup>174</sup>. Fluid NfL, NG-36, and YKL-40 can play a particularly important role in this, given evidence for their utility as prognostic biomarkers for amyloid deposition, neurodegeneration, and cognitive decline in AD<sup>111,117,120</sup>. They can also play important roles as biomarkers of susceptibility to neurodegeneration in cognitively unimpaired persons at higher risk of AD due to increased amyloid or APOE4<sup>325</sup>.

The increased availability of portable in-home EEG may also improve the feasibility of overnight PSG for persons with AD. Interventions such as transcranial direct current or acoustic stimulation targeting SWA in persons with MCI or AD have also yielded promising results<sup>333</sup>. However, lifestyle-based interventions such as exercise and increased physical activity can also be harnessed to enhance sleep and SWA in persons with AD. Exercise targets sleep physiology, including NREM SWA, decreases levels of biomarkers associated with neurodegeneration, inflammation and cognitive decline, and protects against functional and cognitive decline in older age<sup>220</sup>. Our recent meta-analysis of exercise interventions targeting sleep in persons with MCI or AD found moderate-to-high-quality evidence for the beneficial effects of exercise on sleep, including slow-wave sleep<sup>220</sup>.

### Strengths and limitations

Our study has several strengths. Our data was collected prospectively in a sex-balanced cohort of persons with high Aβ42 burden and clinical symptoms consistent with mild-to-moderate AD, using standardised procedures at a centre with expertise in AD. We also had comprehensive data for cognition capturing a range of cognitive domains over a three-year period. Exclusion criteria also included use of medications associated with altered sleep (beta-blockers, antidepressants, neuroleptics, or hypnotics) within 15 days of the polysomnography. No participants were taking medications for poor sleep that may influence sleep microarchitecture.

We controlled for important confounding factors including age and OSA, which shares mechanisms and features with AD, including altered sleep architecture, AHI, and biomarkers of reduced brain-health<sup>104</sup>. Increasing age is also associated with changes in sleep and some AD biomarkers<sup>6</sup>. We limited our covariates to these variables (age, sex, AHI) to avoid overfitting our regression models, and adjusted for multiple comparisons to reduce the risk of type-1 error.

However, observational study results can only imply associations, not causal relationships, and we did not have a comparison group of healthy older adults. However, the study sought to follow the cognitive evolution of persons with AD. Associations between sleep, biomarkers, and cognition in healthy older adults have been explored extensively<sup>7,51,173</sup>. Participants also underwent PSG only at baseline, and without a preceding accommodation night, so we cannot rule out first-night effects. However, overnight PSG with persons with AD can be difficult to carry-out, making this difficult to accomplish. We also could not

investigate longitudinal associations between changes in sleep and biomarkers as AD progressed in our sample. This would be important data future studies can collect.

# Conclusion

Our novel findings demonstrate that reduced NREM spindle and SO activity can act as complimentary, non-invasive markers of neurodegeneration and therapeutic targets for interventions designed to monitor or slow the progression of AD symptoms<sup>32</sup>. They also add further evidence for links between NfL, NG-36, YKL-40, sleep, and cognition and their potential role as supplemental AD biomarkers. These biomarkers may also constitute potential targets for sleep-related interventions for cognition in the context of AD and other neurodegenerative disorders.



ADAS-C: Alzheimer's Disease Assessment Scale, cognitive subscale, MMSE: Mini-mental State Examination, NPI: Neuropsychiatric Inventory (NPI)

Figure 1: Study flow, "Role of Hypoxia And Sleep Fragmentation in Alzheimer's Disease.

Sample	Male (n=30)	Female (n=30)	Total (n=60)	p value
Age	75.5 ±5.0	74.0 ±5.0	74.7 ±5.0	0.26
Body mass index (BMI)	27 (24-29)	28 (24-32)	27 (24-32)	0.71
Depression	6 (20.0%)	12 (40.0%)	18 (30%)	0.09
Diabetes	7 (23.3%)	3 (10%)	10 (16.7%)	0.17
Education (≥ high school)	5(16.7%)	5(16.7%)	10 (16.7%)	1.00
0: No formal education	2 (6.7%)	2 (6.7%)	4(6.7%)	
I. Primary school	23 (76.7%)	23 (76.7%)	46(76.7%)	
2. High school	4 (13.3%)	4 (13.3%)	8 (13.3%)	
3. University	I (3.3%)	I (3.3%)	2 (3.3%)	
Smoking history	(36.7%)	2 (6.7%)	41(68.3%)	0.005
0. Never	19 (63.3%)	28 (93.3%)	47 (78.3%)	
I. Current	2 (6.7%)	0 (0.0%)	2 (3.3%)	
2. Former (>6 months ago)	9 (30.0%)	2 (6.7%)	11(18.3%)	
Obstructive sleep apnoea (OSA)	24 (96.0%)	23 (88.5%)	47(78.3%)	0.25
Apnoea hypoxia index (n/hrTST)	38.14 ±23	29.24 ±22.8	33.7 ±23.14	0.14
0-4.9	I (3.3%)	2 (6.7%)	3 (5%)	
5-14.9	4 (13.3%)	7 (23.3%)	(18.33%)	
15-30	9 (30.0%)	10 (33.3%)	19 (31.67%)	
≥ 30	16 (53.3%)	(36.7%)	27 (45%)	
AD Drugs	26 (86.7%)	27(90%)	53 (88.3%)	0.69
None	4 (13.3%)	3 (10%)	7 (11.7%)	
Rivastigmina	9 (30%)	9 (30%)	18 (30%)	
Donepezil	17 (56.7%)	15 (50%)	32 (53.3%)	
Memantine	0	3 (10%)	3 (5.8%)	
CSF values-biomarkers (pg/ml)				
Beta-amyloid (Aβ42)	506 (417-609)	532 (398-627)	516 (411-618)	0.62
Neurofilament-lite (NfL)	986.8 (724.1-1212.8)	958.5 (557.3-1330.7)	960.8 (672.3-1212.8)	0.46
Neurogranin-36 (NG-36)	277.7 ±136.7	299.7 ±95.6	288.96 ±116.7	0.53
Chitinase-3-like protein (YKL-40) (ng/m)	288.7 (225.7-412.5)	289.8 (194.9-378.9)	281.6 (224.5-389.2)	0.65
Plasma biomarkers (pg/ml)	33.4 (23.8-44.1)	25.1 (19.5-31.5)	26.1 (20-37.2)	0.20
NfL				
Cognition				
ADAS	23.4 ±2.3	23.0 ±2.4	23.2 ±2.4	0.55
MMSE				
Neuropsychiatric				
Cornell Scale (CSDD)	7 (2-11)	6 (3-11)	7 (3-11)	0.93
Neuropsychiatric Index (NPI)	4 (0-11)	8 (3-13)	6 (2-12)	0.51

 Table 1: Participants' characteristics at baseline

	Male (n=30)	Female (n=30)	Total (n=60)	р
Sleep architecture				
Total sleep time (min)	247.2 ±93.5	273.6 ±85.6	260.4 ±89.9	0.26
Total time in bed (min)	423 (391-447)	419 (400-443)	421 (392-446)	0.63
Sleep efficiency (%)	60 (44-80)	69 (50-78)	67 (48-80)	0.38
Sleep onset latency (min)	17 (9-33)	27 (14-68)	23 (11-57)	0.35
Wake after seep onset (min)	131 (66-179)	83 (54-136)	101 (58-161)	0.11
NREM I duration (min)	70.1 (47-80.5)	44.25 (27.5-57)	51 (35.5, 78.25)	0.01
NREM2 duration (min)	86 (63-120)	105 (85-154)	92 (69-138)	0.25
NREM3 duration (min)	43 (24-78)	84 (38-106)	60 (28-91)	0.03
N2+N3min/TST (%)	55.6 ±18.2	68.6 ±17.1	62.1 ±18.7	0.006
REM duration (min)	27 (14-42)	26 (15-46)	26 (14-44)	0.83
NREMI (% of total sleep time)	30 (23-42)	16 (8-22)	22 (10-34)	0.007
NREM2 (% of total sleep time)	37.3 ±14.7	40.8 ±13.3	39.0 ±14.0	0.35
NREM3 (% of total sleep time)	16 (10-26)	30 (15-39)	23 (14-36)	0.008
REM (% of total sleep time)	10 (7-16)	(5- 6)	10 (6-16)	0.94
Sleep spindle (SP)	Male (30)	Female (30)	Total (60)	р
NREM2+NREM3				-
SP density	0.4 ±0.3	0.7 ±0.3	0.5 ±0.3	0.002
SP duration	0.7 ±0.1	0.7 ±0.1	0.7 ±0.1	0.32
SP power	251 (151-300)	280 (211-404)	254 (187-374)	0.54
Slow Oscillations (SO)	Male (30)	Female (30)	Total (60)	р
NREM2+NREM3				-
SO density	2.6 ±1.0	2.7 ±0.8	2.7 ±0.9	0.62
SO duration	l (l-2)	l (l-2)	l (l-2)	0.31
SO ptp amplitude	107 (83-144)	116 (80-175)	108 (81-156)	0.66

NREM: Non-rapid eye movement sleep. REM: Rapid eye movement sleep. ptp: peak to peak

 Table 2: Sleep architecture at baseline by sex.

Spindles (SP)	NREM2				
CSF-NfL	coef	SE	P value	95%Cl lower	upper
SP duration	-2424.674	693.4369	0.001*	-3829.711	-1019.638
SP density	352.8109	221.4231	0.119	-95.43682	801.0585
SP power	-2.215239	0.7121991	0.004*	-3.657011	-0.7734675
plus A642					
SP duration	-2341.786	718.5329	0.002*	-3799.038	-884.5334
SP density	352.0558	242.7829	0.156	-140.3307	844.4424
SP power	-1.381578	.3490971	0.000*	-2.089579	6735757
Plasma NfL					
SP duration	30.47967	28.65704	0.294	-27.35257	88.31191
SP density	-1.159311	6.171612	0.852	-13.61413	11.29551
SP power	0097233	.0198087	0.626	0496988	.0302523
plus Aβ42					
SP duration	31.49667	30.55308	0.310	-30.52939	93.52273
SP density	-1.567106	6.721672	0.817	-15.21283	12.07861
SP power	0059887	.0216489	0.784	0499383	.0379609
NG-36	(0) 0005	200.2014			100 1711
SP duration	-406.3935	399.3046	0.315	-1215.462	402.6746
SF density SP power	-41.72272	/3.0/342	0.575	-170.007	107.4211
	0736801	.0884974	0.410	252993	.1056327
plus Aβ42					
SP duration	-417.6573	418.6901	0.325	-1266.8	431.4856
SP density	86.57386	91./5631	0.352	-77.51657	272.6643
Sr power	0786192	.1032266	0.451	2879725	.1307341
CSF YKL-40	140 0000	277 2002	0 5 4 2	201 2421	721 2594
SP density	-20.86094	81 18594	0.343	-185 2133	143 4914
SP power	-20.00074	0.2474225	0.777	-105.2155	0429519
	-0.000	0.3070223	0.034	-1.551125	0057517
SD duration	214 1142	202 22/2	0.470	200 2212	909 4497
SP density	214.1142	273.3263	0.470	-360.2213	110 9294
SP power	-0.9834	3784485	0.13*	-244.1044	- 21728
CSF NfL/AB42	-0.7634	.5767705	0.015	-1.745	21720
SP duration	2 670308	2 350408	0.263	-2 092071	7 432687
SP density	- 617374	2644092	0.205	-1.155958	- 0787901
SP power	-0.0029	000839	0.020	- 0046214	- 0012183
CSE XKL-40/AR42	-0.0027		0.001	0010217	0012103
SP duration	0.3956	.7924905	0.621	-1.210219	2.001258
SP density	-0.1804	.1792477	0.321	5435996	.1827812
SP power	-0.0049	0.0013	0.000*	-0.0074	-0.0023

\*significant after Benjamini-Hochberg FDR Aβ42: Beta-amyloid, NfL: neurofilament light-chain, NG-36: neurogranin 36, YKL-40: Chitinase-3-like protein

Table 3: Sleep spindles and biomarkers

Slow oscillations (SO)	NREM3				
CSF-NfL	coef	SE	P value	95%Cl lower	upper
SO duration	131.8638	217.8706	0.549	-309.1922	572.9198
SO density	17.43615	82.85814	0.834	-150.3014	185.1737
SO ptp amplitude	-1.722552	1.439158	0.239	-4.635974	1.190871
plus Aβ42	107.007.0		<i></i>	210 2005	572 0022
SO duration	127.38/4	219.9277	0.566	-318.2285	573.0033
SO density	25.30379	90.06282	0.780	-157.1808	207.7884
SO ptp amplitude	-1.770908	1.463652	0.234	-4.736548	1.194732
Plasma NfL	7 1 1 5 2 2 2	4 272102	0.111	1710124	15 04070
SO duration	7.115322	4.373192	0.111	-1./10136	15.940/8
SO density	-11.2236	1.734601	0.000*	-14.72437	-7.722024
SO ptp amplitude	.0649213	.0293448	0.032	.0057011	.1241416
plus Aβ42					
SO duration	8.227774	5.165947	0.120	-2.259657	18.7152
SO density	-10.66489	1.983012	0.000*	-14.69062	-6.639162
SO ptp amplitude	.0769256	.0314427	0.020	.0130935	.1407577
NG-36	120 7/52	47.0004	0.00(*	225 7701	41 75140
SO duration	-138./653	47.9224	0.006*	-235.//91	-41./5149
SO density	30.24508	21.49155	0.167	-13.26229	73.75245
SO ptp amplitude plus Aβ42	5393477	.5415793	0.326	-1.635718	.5570222
SO duration	-130.9712	52.83777	0.018*	-238.0307	-23.91168
SO density	32.22441	23.60494	0.180	-15.60375	80.05257
SO ptp amplitude	1194187	.3836146	0.757	8966958	.6578583
CSF YKL-40					
SO duration	-55.29139	70.90252	0.440	-198.826	88.24327
SO density	-1.696327	24.97845	0.946	-52.26256	48.8699
SO ptp amplitude	1971385	.4338491	0.652	-1.07542	.681143
plus Aβ42					
SO duration	-58.53722	66.54012	0.385	-193.3603	76.28588
SO density	-8.047407	27.24891	0.769	-63.25894	47.16413
SO ptp amplitude	1739342	.4428344	0.697	-1.071202	.7233335
CSF NfL/AB42					
SO duration	.3506004	.5105225	0.497	6838164	1.385017
SO density	1159567	.1932569	0.552	5075324	.2756189
SO ptp amplitude	0069261	.0058203	0.242	0187191	.0048669
CSF YKL-40/AB42					
SO duration	1387297	.1448362	0.344	4321958	.1547365
SO density	0617642	.0575688	0.290	1784096	.0548813
SO ptp amplitude	0016059	.0017549	0.366	0051618	.0019499

\*significant after Benjamini-Hochberg FDR Aβ42: Beta-amyloid, NfL: neurofilament light-chain, NG-36: neurogranin 36, YKL-40: Chitinase-3-like protein

 Table 4: Slow oscillations and biomarkers

Biomarker	coef	Р	95% low	upper	coef	Р	lower	upper
	ADAS-C	base			ADAS-C	I2m		
CSF NfL	0.01	0.01*	0.001	0.01	0.004	0.08	-0.001	0.001
CSF Nfl and base aβ42	0.01	0.004*	0.002	0.001	0.01	0.07	-0.004	0.01
CSF NfL/aβ42	2.28	0.01*	0.48	4.07	1.64	0.14	-0.58	3.87
Plasma NfL	-0.03	0.65	-0.14	0.04	-0.40	0.55	-0.17	0.094
Plasma NfL and base aβ42	-0.02	0.73	-0.14	0.98	-0.04	0.54	-0.18	0.98
CSF NG-36	0.02	0.06	-0.001	0.041	0.27	0.028	0.01	0.054
CSF Ng-36 and base aβ42	0.02	0.02*	0.004	0.041	0.29	0.01*	0.01	-0.049
CSF YKL-40	1.98	0.49	-3.82	7.79	3.07	0.28	-2.57	8.7
CSF YKL-40 and base aβ42	0.	0.72	-0.01	0.02	6.45	0.03	0.56	12.34
CSF YKL-40/aβ42	2.68	0.1	-5.43	10.78	7.71	0.08	-1.23	16.65
	MMSE	base			MMSE	l 2m		
CSF NfL	-0.001	0.11	-0.003	0.003	-0.002	0.047	-0.003	-0.0002
CSF Nfl and base aβ42	0.001	0.09	-0.003	0.000	-0.002	0.51	-0.003	7.34
CSF NfL/aβ42	-0.68	0.03	-1.29	-0.06	-0.74	0.028	-1.39	-0.82
Plasma NfL	0.012	0.58	-0.029	0.54	0.012	0.54	-0.28	0.052
Plasma NfL and base aβ42	0.012	0.57	-0.029	0.54	0.032	0.08	-0.004	0.067
CSF NG-36	0.002	0.59	-0.01	0.01	-0.01	0.12	-0.015	0.002
CSF Ng-36 and base aβ42	0.002	0.62	-0.01	0.01	-0.01	0.04	-0.015	-0.004
CSF YKL-40	0.002	0.49	-0.004	0.01	-0.002	0.56	-0.01	0.01
CSF YKL-40 and base aβ42	0.41	0.67	-1.55	2.38	-1.71	0.08	-3.68	0.26
CSF YKL-40/aβ42	0.3	0.83	-2.43	3.02	-2.42	0.01*	-4.27	-0.58
	MMSE	24			MMSE	36		
CSF NfL	-0.03	0.016*	-0.01	-0.001	0.002	0.68	-0.01	0.01
CSF Nfl and base aβ42	-0.04	0.12	-0.01	-0.001	0.002	0.69	-0.001	0.01
CSF NfL/aβ42	-1.27	0.02*	-2.33	-0.21	-0.85	0.98	-2.89	2.71
Plasma NfL	-0.06	0.20	-0.15	0.03	-0.10	0.2	-0.27	0.06
Plasma NfL and base aβ42	-0.02	0.71	-0.12	0.08	-0.23	0.001*	-0.35	-0.11
CSF NG-36	-0.001	0.84	-0.02	0.01	0.002	0.93	-0.04	0.054
CSF Ng-36 and base aβ42	-0.002	0.77	-0.02	0.01	0.002	0.92	-0.04	0.05
CSF YKL-40	-1.40	0.44	-5.04	2.23	-2.18	0.18	-5.46	1.09
CSF YKL-40 and base aβ42	-0.01	0.27	-0.02	0.01	0.01	0.50	-0.04	0.02
CSF YKL-40/aβ42	-2.71	0.07	-5.71	0.29	-4.04	0.45	-15.3	7.25
	NPI	base			NPI	l 2m		
CSF NfL/aβ42	0.36	0.73	-1.72	2.45	2.1	0.04	0.07	4.13
CSF YKL-40/aβ42	0.3	0.94	-7.83	8.44	16.93	0.000*	10.1	23.76

ADAS-C: Alzheimer's Disease Assessment Scale, cognitive subscale, MMSE: Mini-mental State Examination, NPI: Neuropsychiatric Inventory (NPI), Aβ42: Beta-amyloid, NfL: neurofilament light-chain, NG-36: neurogranin 36, YKL-40: Chitinase-3-like protein

Table 5: biomarkers and cognition



Aβ42: Beta-amyloid, NfL: neurofilament light-chain, NG-36: neurogranin 36, YKL-40: Chitinase-3-like protein

**Figure 2:** Spindle activity predicts CSF NfL, NfL/AB42 and YKL-40/AB42, while SO activity predicts plasma NfL and CSF NG-36.
Chapter IV: Exercise interventions benefit sleep in older adults: A systematic review and meta-analysis.

# Chapter summary:

In the introduction, we presented and overview of evidence for the treatment of poor sleep and its importance for maintaining brain-health and preserving cognition in older adults. This chapter expands on that overview of evidence by investigating the evidence for the effectiveness of exercise interventions targeting sleep in older adults. It builds on the findings from chapters II and III that sleep physiology plays important roles in the progression of AD and cognitive decline for persons with AD, and evidence (chapter I)that exercise interventions target sleep physiology, with potential help preserve brain-health in older adults. The effectiveness of exercise interventions targeting sleep in older adults is systematically reviewed and meta-analysed here, also providing a foundation for the meta-analysis of exercise interventions targeting sleep in persons with MCI or AD in chapter V. This chapter is currently under review in BMC Geriatrics, as part of a special call for papers on sleep disorders and older adults, as "Exercise interventions benefit sleep in older adults: A systematic review and meta-analysis." \*Arsenio Páez, Emmanuel Frimpong , Thien Thanh Dang-Vu MD PhD<sup>1</sup> Manuscript ID: 85fd58b4-fbe2-4183-bdb4-d31c9d7355f4 v1.0



#### ABSTRACT

**Background:** Sleep plays a vital role in maintaining brain health, including regulating the clearance of proteins such as  $\beta$ -amyloid (A $\beta$ ) and tau linked to neurodegenerative diseases. Sleep loss in older adults is associated with multiple morbidities, poor brain-health, and increased mortality. Exercise is a promising, acceptable, and sustainable intervention for poor sleep but the optimal mode, dose and intensity, and moderators of its effectiveness in older adults remain unclear.

**Study Objectives:** To systematically review and meta-analyse data for the effects of exercise (both acute and regular) on subjectively and objectively-assessed sleep in older adults, including those with or without pre-existing sleep disturbances, and moderators of those effects, such as age, sex, exercise intensity, and duration.

**Methods:** A systematic review and meta-analysis of controlled, interventional studies of structured physical activity and exercise targeting subjectively or objectively (polysomnography, actigraphy) assessed sleep in adults over 60 years of age, following the guidance of the Cochrane Handbook. Searches were conducted without date or language restrictions in PubMed, Embase, Scopus, the Cochrane Library.

**Results:** In a sample of studies representing the experiences of 8506 older adults across 82 interventional studies, we found strong evidence for the beneficial effects of exercise on self-reported and objectively measured sleep in older adults. There is a dose-response relationship between exercise and self-reported sleep in older adults, with moderate intensity exercise associated with the largest, clinically important benefits for sleep.

**Conclusions:** The results of our meta-analysis have important implications for clinical care, health promotion and gerontology, supporting the development and dissemination of

effective exercise interventions for sleep difficulties that may also aid secondary prevention of sleep-related health problems in older persons.

**Keywords:** sleep, insomnia, brain-health, exercise, physical activity, older adults, treatment effects, meta-analysis

#### 1. BACKGROUND

Sleep plays a vital role in maintaining brain health, including regulating the clearance of proteins such as β-amyloid (Aβ) and tau linked to neurodegenerative diseases.<sup>6,24</sup> Sleep is also critical for learning and memory.<sup>14</sup> Nearly half of persons over the age of 65 experience difficulty initiating or maintaining sleep, and up to 65% report disrupted or nonrestorative sleep, raising their risk of cognitive decline and neurodegenerative disorders such as dementia and Alzheimer's disease (AD).<sup>53,58,62,70–72,334</sup> Sleep loss is also associated with increased risk of mortality<sup>335</sup> and a range of morbidities ranging from depression,<sup>2</sup> to cardiovascular disease,<sup>3</sup> falls,<sup>336,337</sup> social disengagement,<sup>338</sup>and reduced quality of life.<sup>339,340</sup> Sleep problems also increase the probability of long-term care placement in older adults.<sup>341,342</sup> Sedentariness, comorbidities, and polypharmacy can increase with age and are also associated with poor sleep, further reducing sleep quality in later life.<sup>62–64</sup>

## 1.1 Interventions for poor sleep

Given the strong associations between sleep and neurodegeneration, treating poor sleep may be a preventive approach for preserving cognition and brain health in older adults<sup>6,7,72,99,177</sup> Non-pharmacological interventions can play an important role in treating sleep difficulties. Medications such as sedative antidepressants and benzodiazepine receptor agonists can be effective short-term treatments, but do not treat the root causes of sleep loss.<sup>188</sup> Their adverse effects, such as daytime drowsiness, sedation, and dependence, also limit their acceptability for users.<sup>189,204,343</sup> Cognitive-behavioural therapy for insomnia (CBTi) is the preferred first-line treatment for insomnia disorder.<sup>181</sup> However, it usually requires 6-10 treatment sessions, can be expensive, and difficult to access.<sup>198,205–207</sup> CBTi also typically achieves success in only two-thirds of patients.<sup>200,202,344</sup> It is particularly effective for

improving subjective (self-reported), rather than objective (sleep architecture) sleep outcomes.<sup>201</sup> Additionally, no current treatment for insomnia, including CBTi, has been shown to improve cognition or biomarkers of neurodegeneration in older adults.<sup>210,211</sup> This creates opportunities to complement CBTi with exercise, which does targets sleep physiology including Non-Rapid Eye Movement (NREM) slow-wave activity <sup>212–215</sup>, to boost its effects and achieve wider efficacy.<sup>216–218</sup>

#### 1.11 Exercise, sleep, and brain-health

Exercise is an accessible and sustainable intervention that improves sleep quality and has a range of benefits for health and quality of life.<sup>4,224</sup> Exercise also improves sleep, cognitive performance, and psychological well-being in older adults<sup>224,227,231,241,243,244</sup>. Moderate intensity physical activity and exercise are also associated with beneficial changes in cerebrospinal fluid biomarkers of neurodegeneration such as A $\beta$  and tau linked to AD and dementia.<sup>249–252</sup> Exercise is a modifiable lifestyle factor that can protect against functional and cognitive decline and mitigate the risk of dementia in older age.<sup>224,282</sup>It may be an ideal complement to other healthy lifestyle approaches for preserving brain health in older adults.<sup>218</sup>

There is a strong bidirectional relationship between exercise and sleep, but the mechanisms underpinning the beneficial effects of exercise on sleep are less well understood.<sup>236</sup> Several have been proposed, including exercise-induced reduction in systemic inflammation, changes in neurotransmitters regulating sleep, increased growth hormone and brain derived neurotrophic factor, changes in heart rate variability, body temperature, autonomic function, and entrainment of circadian rhythms and sleep wake cycles.<sup>224,241,243,244</sup>

Strong evidence supports beneficial effects of both acute and regular exercise on sleep quality and decreased use of sleep medications in younger and middle-aged adults.<sup>212,224</sup> However, there is mixed-evidence for the effectiveness of exercise interventions for sleep problems in older adults, or their effects on sleep architecture.<sup>212</sup> The effect of moderators such as participant or intervention characteristics, the optimal exercise mode or dose, and dose-response relationships between exercise and sleep outcomes in older adults remain unclear and have not been systematically reviewed extensively.<sup>212,224</sup> Previous systematic reviews have also limited their also limited searches to publications in English<sup>212,271</sup> or failed to include data from grey literature (non-commercially published literature, such as conference proceedings, government and non-governmental agency reports, etc)<sup>345</sup> introducing publication bias.<sup>345,346</sup>

#### 1.2 Purpose and objectives of this systematic review

A systematic review of current evidence for the effects of exercise on sleep in older adults, including older adults with sleep problems, is needed to support appropriate targeting of exercise interventions for sleep and guide future research. Our objectives were to:

1. Systematically review and meta-analyse data for the effects of exercise (both acute, or single bouts, and regular, or repeated bouts) on subjectively (self-reported) and objectively assessed sleep quantity, quality, or sleep architecture in older adults with and without sleep problems.

2. Explore potential effect moderators, including associations between age, sex, exercise intensity and duration on the efficacy of exercise interventions for sleep in older adults.

3. Determine the dose-response relationship between acute or regular exercise and sleep quality or quantity in older adults.

# 2. METHODS

Our systematic review and meta-analysis were conducted following recommendations of the Cochrane Handbook for Systematic Reviews of Interventions<sup>346</sup> and reported along Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>347</sup>. The protocol (CRD42021289528) was registered on PROSPERO<sup>348</sup>.

# 2.1 Search Strategy and selection criteria

We conducted systematic searches with keywords and Medical Subject Heading (MeSH) terms related to physical activity, exercise, strengthening (programs, activities, training), sleep, and sleep-related keywords, from inception and without language or date restrictions on PubMed, Embase, the Cochrane Library, Scopus, and PROSPERO. To ensure literature saturation, we undertook citation searching and re-ran keyword searches on PubMed limited to the most recent 12-months to capture papers not yet indexed under MESH (supplementary materials figure 1)

Two reviewers screened search results against our eligibility criteria. Disagreements about eligibility were resolved through consensus. When necessary, study authors were contacted for additional information to resolve questions about papers' eligibility or acquire additional data.

## 2.2 Eligibility criteria

Eligible studies met the following criteria:

P: Included participants 60 years old or older, or extractable data for that age group.I: Interventional studies of structured physical activity or exercise (any mode, frequency, duration).

C: Control interventions: no treatment, wait-list control, educational or non-exercise interventions.

O: Sleep quantity, quality, or architecture, measured objectively (actigraphy,

polysomnography) or subjectively (self-report with validated scales or questionnaires such as the Pittsburgh Sleep Quality Index [PSQI]<sup>349</sup> sleep diaries or logs), reported as a categorical or continuous outcomes.

Study design: controlled, interventional studies.

Single-subject, uncontrolled, or observational studies, case series, or studies reporting sleep as a dichotomous outcome were excluded. Studies of participants with disorders highly associated with poor sleep and difficulty exercising such as stroke, cerebral vascular accident, dementia and major psychiatric disorders were excluded<sup>350</sup>.

# 2.3 Data Extraction

We extracted data for characteristics of individual papers (authors, year, design, population) and their samples (age, sex, and sleep difficulties). Exercise interventions and their characteristics (mode, intensity, duration, frequency) were extracted. Exercise intensity was categorized as low, moderate, or high-intensity based on the American College of Sports

Medicine (ACSM) guidelines (supplementary materials, table 2).<sup>351</sup> We extracted data for sleep **outcomes** (treatment effect estimates) as mean differences and measures of variance.

**2.4 Risk of Bias** in included papers was assessed with the Cochrane Revised Tool to Assess Risk of Bias in Randomized Trials(RoB-2)<sup>352</sup> and the Cochrane Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)<sup>353</sup> tool for non-randomised controlled studies.

## 2.5 Meta- analysis

We expected clinical and statistical heterogeneity between studies resulting from variable samples, interventions, and effect sizes. We conducted inverse-variance weighted random-effects (Der Simonian and Laird) meta-analyses with Review Manager 5.41<sup>346</sup>. We derived mean differences in sleep outcomes between experimental and control groups to calculate pooled intervention effect estimates<sup>346</sup>. We assessed statistical heterogeneity using t<sup>2</sup>, Chi2 (significance level: 0.1) and l<sup>2</sup> statistics<sup>346</sup>. Statistical heterogeneity was also evaluated graphically in Forest plots. **Publication and reporting bias** were explored with funnel plots.

## 2.5.1 Sensitivity and subgroup analyses

We conducted sensitivity analyses by risk of bias, and undertook subgroup analyses to explore sources of heterogeneity and differences in treatment effects between groups<sup>354–356</sup> These were based on age, sex<sup>357</sup>, sleep quality or sleep difficulties at baseline<sup>224</sup>, exercise characteristics including intensity (low, moderate, high-intensity), dosage, time of day<sup>212</sup>, and subjective versus objective sleep measures (disparities between subjective and objective sleep measures in older adults are frequently reported)<sup>358</sup>. We also performed random

effects (Der Simonian and Laird) **meta-regression** with STATA 16.1 to further investigate heterogeneity and associations between age (continuous and categorically), exercise dosage, or frequency (sessions or exposures to exercise per week) and total hours of exercise dose over the course of the study (times per week multiplied by hours per week and number of weeks) as both continuous and categorical variables, and risk of bias on sleep outcomes.<sup>54,212,359</sup>

## 2.5.2 Other analyses

We calculated 95% **prediction intervals (PI)** for pooled effect sizes to examine whether treatment effect estimates would vary across projected future studies of exercise for sleep.<sup>360</sup> Prediction intervals estimate the expected range of true intervention effects in similar studies that might be conducted in the future or in different settings, also showing the range of possible intervention effects in relation to harm or clinical benefit, and giving a better sense of the uncertainty around effect estimates than confidence intervals when heterogeneity is high.<sup>360,361</sup>

**Publication and reporting bias** for the primary meta-analyses were explored with funnel plots.

## 3. RESULTS

Our searches yielded 5783 publications (figure 1). After removing 1671 duplicates, 256 papers were assessed by full text. Eighty-two interventional trial papers were included in the systematic review (75 in the meta-analysis). Included studies and their characteristics are

found in the supplementary materials (supplementary material, table 1). Thirty of the 82 papers were assessed at low risk of bias, 40 at some concerns, and 12 at high risk of bias (figure 2). Studies with high risk of bias were excluded from meta-analyses.



Figure 1: PRISMA flow diagram, search results and included papers.



Figure 2: Risk of bias in a. randomised controlled trials, b. non-randomised controlled trials.

# 3.1 Sample characteristics

The 82 included interventional studies represent the experience of 8506 persons(5122 females), with a mean age of 68 years (range of 55 years<sup>362</sup>-83 years<sup>363</sup>) recruited from community, clinical, and research settings. Included papers were published between 1990<sup>364</sup> and 2022<sup>363</sup>, with a mean sample size of 98 (median 118.5), ranging from 10<sup>283</sup> to 1635<sup>365</sup> participants. Seven studies investigated the effects of exercise on sleep in participants with no diagnosed or subjectively assessed sleep disorders<sup>366–372</sup>, while 75 studies included participants with sleep disorders or poor sleep quality (PSQI >5) at baseline (supplementary materials table 1).

## 3.2 Interventions

A wide range of exercise frequencies and duration were reported. Only three studies<sup>244,373,374</sup> investigated the effects of acute bouts of 42<sup>244</sup>, 50<sup>374</sup>, or 60<sup>373</sup> minutes of low<sup>374</sup>, moderate<sup>373</sup>, or high-intensity<sup>244</sup> exercise on sleep. Seventy-nine studies investigated regular exercise programs, with dosages ranged from once weekly<sup>375,376</sup> to daily bouts <sup>272,368,377,378</sup> (mean 3.3) over one<sup>244,373,374</sup> to 104<sup>365</sup> weeks (mean 17.3 weeks, SD 15.7). Exercise duration ranged from 22 minutes<sup>379</sup> to 150 minutes<sup>362</sup> (mean 53.2 minutes, SD 19.1). The total exercise dose, calculated as the product of the frequency (days per week), duration (minutes or hours), and program length (days or weeks), ranged from 10.7<sup>380</sup> to 433<sup>365</sup> hours (mean 51 hours, SD 63 hours).

**3.2.1 Exercise intensity:** Twenty-nine papers investigated low-intensity exercises, or those performed at <65% maximal Heart rate according to ACSM guidelines<sup>239</sup> or <40% heart rate reserve (HRR)<sup>364</sup>. These included stretching, low-intensity aerobic exercise<sup>283,381,382</sup>, light

physical activity or exercises<sup>272,383</sup>, elastic band exercise<sup>384,385</sup>, resistive training, cycling or cycle ergometry<sup>364,386</sup>, Pilates exercises<sup>387,388</sup>, overground walking programs<sup>365,368,380,389,390</sup>, treadmill walking at <50% age-predicted maximal heart rate<sup>374,391</sup>, light or silver yoga<sup>392–395</sup>, aquatic exercise<sup>396</sup>, light Tai Chi.<sup>376,397,398</sup>

Moderate-intensity exercises were most frequently investigated (57 trials), including aerobic exercise<sup>381,399,408,400–407</sup>, Baduanjin (a mind-body exercise program)<sup>409–411</sup>, cycling or bicycle ergometry<sup>244,386</sup>, walking<sup>412–414</sup>, Tai Chi<sup>371,379,385,398,415–418</sup>, treadmill<sup>279,419</sup>, resistance or strengthening exercise<sup>372,377,398,407,420–425</sup>, yoga<sup>375,426</sup> or combinations of moderate-intensity exercises<sup>278,363,432–438,365,383,385,427–431</sup>. Thirteen studies investigated the effects of high-intensity exercises, including cycling<sup>366</sup>, treadmill<sup>273,279</sup>, aerobics<sup>439</sup>, resistance or strength training<sup>362,373,423</sup>, or combinations of high-intensity exercises<sup>279,435,440</sup>.

# 3.3 Outcomes

A variety of assessment tools were used to collect sleep outcomes, including sleep diaries, questionnaires, actigraphy, and polysomnography (PSG). Nine studies assessed sleep objectively with the gold-standard- PSG <sup>244,272,273,373,376,378,403,424,441</sup>, collecting data for total sleep time (TST), sleep onset latency (SOL), wake time after sleep onset (WASO), sleep efficiency (SE), stages 1, 2, slow wave sleep, rapid eye movement (REM) sleep, and REM sleep latency (table 2). Nine collected sleep data using actigraphy (table 3).<sup>362,366,374,396,419,442</sup> The three eligible studies of acute exercise interventions<sup>244,373,374</sup> used objective sleep measures, while regular exercise programs predominantly used subjective sleep assessments such as the PSQI.<sup>349</sup>

The majority of included studies (52) assessed the effects of exercise on subjectively assessed sleep with the PSQI<sup>349</sup> and/or sleep diaries. Ten out of 52 studies investigated the effects of exercise on sleep in persons with baseline PSQI scores or <5, or no report of greater than mild sleep difficulties or diagnosed sleep disorders.<sup>273,366–368,370–372,397,400,435</sup> Four studies<sup>365,383,398,414</sup> assessed subjective sleep outcomes with the Insomnia Severity Index (ISI)<sup>193</sup>, five<sup>365,368,376,406,443</sup> with the Epworth sleepiness scale.<sup>444</sup> Other sleep outcome measures used include the Athens Insomnia Scale<sup>194,376,398</sup>, Sleep Disorders Questionnaire,<sup>445,446</sup> Mini-Sleep Questionnaire (MSQ),<sup>447</sup> Sleep Problems Index from the 6-item Medical Outcomes Study Sleep Scale,<sup>278,448</sup>, and customized sleep quality tools.<sup>364,428,449</sup>

# 3.4 Meta-analyses

Seventy-five studies, representing the experiences of 7287 participants across 79 comparisons between exercise and non-exercise interventions were eligible for meta-analysis.

# 3.4.1 Subjective sleep assessments: PSQI

Pooled results for 6119 participants in studies of any exercise intervention (all intensities and duration) showed improved subjective sleep the PSQI, with a pooled effect size of -2.51 (95%CI:-3.03,-1.99), or decrease of 2.51 points on the PSQI compared to control groups (figure 3).

				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Std. Mean Difference	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 Low-Mod ROB all	groups				
Badelmi 2009	-9.01	0.5368	2.4%	-9.01 [-10.06, -7.96]	
Khajavi 2015	-6.01	0.2226	2.6%	-6.01 [-6.45, -5.57]	<del>-</del>
Tseng 2020	-5.2	0.9657	1.9%	-5.20 [-7.09, -3.31]	
Reid 2010	-4.92	1.2553	1.6%	-4.92 [-7.38, -2.46]	<u> </u>
Brandao 2018	-4.6	0.4919	2.4%	-4.60 [-5.56, -3.64]	(
Nauven 2012	-4.38	0.6947	2.2%	-4.38 [-5.74, -3.02]	
Liu 2010	-4.37	0.7245	2.2%	-4.37 [-5.79, -2.95]	
Chen 2012	-4.28	0.7414	2.2%	-4.28 [-5.73, -2.83]	
M.C.Chen 2012	-4.28	0.7414	2.2%	-4.28 [-5.73, -2.83]	
Zhou 2022	-4 2342	0.8969	2.0%	-4 23 [-5 99 -2 48]	
King 1997 fm	-3.8	0.0505	1.9%	-3 80 [-5 70 -1 90]	
Raker 2021	_3.8	0.8134	2.1%	-3 80 [-5 39 -2 21]	
Sekerci and Ricer 2019	-3.43	0.8649	2.1%	-3 43 [-5 13 -1 73]	
Karimi 2016	-3.34	0.0049	1 0%	-3.34 [-5.26 -1.42]	
Sharif 2015	-5.54	0.5010	2 20/	2 22 [ 1 16 2 20]	
Sharma 2012	-3.33	1 6612	2.3/0	2 25 [ 6 51 0 01]	
Chan 2000	-3.23	0.6214	2.3/0		
Tabaannang 2008	-3.04	0.0214	2.3/0	-3.04 [-4.20, -1.02]	
Fam 2020	-2.8	0.9002	1.9%	-2.60 [-4.06, -0.92]	
Aiban Almanín 2010	-2.7	1 2041	2.270	-2.70 [-4.15, -1.27]	
Albar - Almazan 2019	-2.68	1.2041	1.7%		
Zheng 2019	-2.65	0.0506	2.6%	-2.65 [-2.75, -2.55]	<u> </u>
Wang 2020	-2.45	0.5403	2.5%	-2.45 [-3.51, -1.39]	
King 1997 m	-2.4	1.4306	1.5%	-2.40 [-5.20, 0.40]	· · · · · · · · · · · · · · · · · · ·
Irwin 2008 PSQI >5	-2.18	0.9569	1.9%	-2.18 [-4.06, -0.30]	
Siu 2021	-2.1	0.4286	2.4%	-2.10 [-2.94, -1.26]	
Kamrani 2014	-2.075	0.2906	2.5%	-2.08 [-2.64, -1.51]	
Curi 2018	-1.99	1.1776	1.7%	-1.99 [-4.30, 0.32]	
Haripasad 2013	-1.91	0.6325	2.3%	-1.91 [-3.15, -0.67]	
ChanYu 2016	-1.8	0.7961	2.1%	-1.80 [-3.36, -0.24]	
Irwin 2014	-1.6	0.8062	2.1%	-1.60 [-3.18, -0.02]	
Jimenez-Garcia 2021	-1.5724	1.0692	1.8%	-1.57 [-3.67, 0.52]	
Chan 2016	-1.5	1.011	1.9%	-1.50 [-3.48, 0.48]	
Maccaulay 2021	-1.5	0.7766	2.1%	-1.50 [-3.02, 0.02]	
Berger 2018	-1.4	0.5571	2.3%	-1.40 [-2.49, -0.31]	
Song Yu 2019	-1.257	0.1796	2.6%	-1.26 [-1.61, -0.90]	-
King 2008	-1.11	1.0428	1.9%	-1.11 [-3.15, 0.93]	
Hosseini 2011	-1.109	0.6069	2.3%	-1.11 [-2.30, 0.08]	
Cheung 2014	-1.1	0.7354	2.2%	-1.10 [-2.54, 0.34]	
Jurado-Fasoli 2020	-1.06	0.7754	2.1%	-1.06 [-2.58, 0.46]	
Lü 2017	-1.01	1.255	1.6%	-1.01 [-3.47, 1.45]	
Choi 2018	-1	0.6332	2.3%	-1.00 [-2.24, 0.24]	
Hsiao 2018	-0.81	3.5208	0.5%	-0.81 [-7.71, 6.09]	
Aoki 2017	-0.69	0.4003	2.5%	-0.69 [-1.47, 0.09]	
Mizayaki 2021	-0.4513	0.3136	2.5%	-0.45 [-1.07, 0.16]	
Cai 2014	-0.38	0.8045	2.1%	-0.38 [-1.96, 1.20]	
Fragoso 2015	-0.26	0.1225	2.6%	-0.26 [-0.50, -0.02]	-
Bullock 2020	0.55	1.2253	1.7%	0.55 [-1.85, 2.95]	<del>_</del>
Irwin 2008 PSQI <5	0.82	0.5649	2.3%	0.82 [-0.29, 1.93]	+
Subtotal (95% CI)	5102		100.0%	-2.51 [-3.03, -1.99]	◆
Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z	72; Chi <sup>2</sup> = 990.90, df = = 9.46 (P < 0.00001)	47 (P <	0.00001);	; $I^2 = 95\%$	
Total (95% CI)			100.0%	-2.51 [-3.031.99]	•
Heterogeneity: $Tau^2 = 2$	72. $Chi^2 = 990.90 df =$	47 (P -	0.00001)	$1^2 = 95\%$	
Test for overall effect: 7	= 9.46 (P < 0.0001)		5.555001)	, 5570	-10 -5 0 5 10
Test for subgroup differe	ences: Not applicable				exercise control

ROB: risk of bias. PSQI: Pittsburgh Sleep Quality Index

Figure 3: Forest plot, exercise versus non exercise and PSQI assessed sleep

Subgroup analyses by PSQI score at baseline found that persons without sleep problems at

baseline (PSQI <5) <sup>367,368,370–372</sup> had small but not clinically significant improvements in

subjective sleep quality (-1.09 (95%CI:-2.16,-0.02), while a larger improvement (-2.66

(95%CI:-3.17,-2.16) was found in participants with PSQI >5 at baseline (supplementary

materials, figures 2-3).

### 3.4.2 Moderators of the effects of exercise on sleep- PSQI:

#### Age

Participants' mean age was analysed categorically, in 5–6-year groups. Pooled PSQI scores increased with each age category between 55 years to 74.9 years old, with the highest treatment effect found among 70-74.9-year-old persons (-2.81, 95%CI:-4.73,-0.90) (supplementary materials, figure 4).

### Sex

A total of 63.6% (5413) of participants across all included studies were female, yet only two studies including both sexes reported sleep outcomes separately for males and females.<sup>382,434</sup> Fourteen studies examined exercise for sleep in all-female samples<sup>278,374,433,439,450,451,375,387,388,391,401,406,417,430</sup>, while 6 examined these in all-male samples <sup>244,273,373,389,403,452</sup>. Larger beneficial effects on PSQI assessed sleep were found for females (MD -3.11, 95%CI:-4.91,-1.30) than males (MD -2.89, 95%CI:-4.05,-1.73) supplementary materials, figure 5).

## Exercise intensity

There was a statistically significant difference and a dose-response<sup>453</sup> relationship between exercise intensity and sleep outcomes on the PSQI (figure 4). Pooled treatment effect estimates of -2.08 (95%CI:-3.11,-1.06) were calculate for low-intensity exercise,-3.12 (95%CI:-3.62,-2.61) for moderate-intensity exercise, and -1.02 (95%CI:-2.03, 0.00) for high-intensity exercise interventions. Only moderate-intensity exercise interventions achieved a minimum clinically important difference (MCID) of 3 points on the PSQI.<sup>454</sup> Statistically significant improvements in PSQI scores were seen with all doses (number of times exercised per week x

hours x weeks duration) of moderate-intensity exercise when meta-analysed categorically by

dose.

	<u> Mean Difference</u>	SE	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
11.1.1 Low intensity exercise	2				
Sharif 2015	-6.2	0.4564	2.2%	-6.20 [-7.09, -5.31]	
Sekerci and Bicer 2019	-3.43	0.8649	1.8%	-3.43 [-5.13, -1.73]	
Karimi 2016	-3 34	0.9818	1 7%	-3 34 [-5 26 -1 42]	
Aibar Almazán 2010	2.54	1 2041	1.770	3.54 [ 5.20, 1.42]	
Albar-Almazan 2019	-2.68	1.2041	1.5%	-2.68 [-5.04, -0.32]	
Haripasad 2013	-1.91	0.6325	2.1%	-1.91 [-3.15, -0.67]	
ChanYu 2016	-1.8	0.7961	1.9%	-1.80 [-3.36, -0.24]	
Frye 2007	-1.6	1.3325	1.4%	-1.60 [-4.21, 1.01]	
rwin 2014	-1.6	0.8062	1.9%	-1.60 [-3.18, -0.02]	
Chan 2016	-1.5	1.011	1.7%	-1.50 [-3.48, 0.48]	
Camrani 2014 LowInt	-1.43	0.3142	2.4%	-1.43 [-2.05, -0.81]	-
Then (Li) 2016	_1.29	0 5 8 6 7	2 1%	_1 29 [-2 44 _0 14]	
Mizeveki 2021	-1.29	0.3007	2.1/0	-1.29 [-2.44, -0.14]	-
	-0.4515	0.5150	2.4%	-0.45 [-1.07, 0.16]	
ragoso 2015	-0.26	0.1225	2.4%	-0.26 [-0.50, -0.02]	• <sup>1</sup>
Subtotal (95% CI)			25.5%	-2.08 [-3.11, -1.06]	<b>•</b>
Heterogeneity: Tau <sup>2</sup> = 2.95; C Test for overall effect: Z = 4.0	hi <sup>2</sup> = 189.57, df 0 (P < 0.0001)	= 12 (P <	: 0.00001	); $I^2 = 94\%$	
1.1.2 Moderate intensity ex	ercise				
3adelmi 2009	_9.01	0.5368	2 2%	-9.01 [-10.06 -7.96]	
Econd 2020	-5.01	0 8007	1 00/		
7 hou 2022 HALPT	-0	0.0097	1.9%		
LINU ZUZZ-HALKI	-5.24	0.961	1./%	-5.24 [-7.12, -3.36]	
keia 2010	-4.92	1.2553	1.4%	-4.92 [-7.38, -2.46]	
Brandao 2018	-4.6	0.4919	2.2%	-4.60 [-5.56, -3.64]	
Nguyen 2012	-4.38	0.6947	2.0%	-4.38 [-5.74, -3.02]	— <b>·</b>
_iu 2010	-4.37	0.7245	2.0%	-4.37 [-5.79, -2.95]	
Chen 2012	-4.28	0.7414	2.0%	-4.28 [-5.732.83]	<u> </u>
Zhou 2022-AT	-4.09	1 0252	1 7%	-4.09[-6.10, -2.08]	
	-4.06	1 0212	1 7%	-4.06 [-6.06, -2.06]	
	-4.00	0.0124	1.770	-4.00 [-0.00, -2.00]	
Saker 2021	-3.8	0.8134	1.9%	-3.80 [-5.39, -2.21]	•
Lhen 2010	-3.64	1.0135	1.7%	-3.64 [-5.63, -1.65]	
Zhou 2022-RT	-3.53	0.9687	1.7%	-3.53 [-5.43, -1.63]	
King 1997 fm	-3.4	0.9701	1.7%	-3.40 [-5.30, -1.50]	
Sharma 2013	-3.3	1.0439	1.7%	-3.30 [-5.35, -1.25]	
(ing 1997 m	-3.1	1.542	1.2%	-3.10 [-6.12, -0.08]	
Then 2009	-3.04	0.6214	2.1%	-3 04 [-4 26 -1 82]	
Sin 2021 tch	_3	0.4763	2.1%	-3 00 [-3 93 -2 07]	
Sambassi 2016	20	1 0 4 4	1 70/	3.00[3.55, 2.07]	
	-2.9	1.044	1.7%	-2.90 [-4.95, -0.85]	
aboonpong 2008	-2.8	0.9602	1.7%	-2.80 [-4.68, -0.92]	
Kamrani 2014 ModInt	-2.72	0.2801	2.4%	-2.72 [-3.27, -2.17]	-
Fan 2020	-2.7	0.7306	2.0%	-2.70 [-4.13, -1.27]	
Zheng 2019	-2.65	0.0506	2.5%	-2.65 [-2.75, -2.55]	•
Wang 2020	-2.45	0.5403	2.2%	-2.45 [-3.51, -1.39]	_ <b>_</b>
rwin 2008 PSOL $>5$	-2.18	0 9569	1 7%	-2 18 [-4 06 -0 30]	
Enve 2007	_2.10	1 2311	1.5%	-2 10 [-4 51 0 31]	
Tye 2007	-2.1	1 1 7 7 6	1.5%	1 00 [ 4 30 0 32]	
2011 2010	-1.99	1.1//0	1.5%	-1.99 [-4.50, 0.52]	· _
song Yu 2019	-1.257	0.1796	2.4%	-1.26 [-1.61, -0.90]	<b>T</b>
siu 2021 ex	-1.2	0.4989	2.2%	-1.20 [-2.18, -0.22]	
King 2008	-1.11	1.0428	1.7%	-1.11 [-3.15, 0.93]	
Hosseini 2011	-1.109	0.6069	2.1%	-1.11 [-2.30, 0.08]	
Cheung 2014	-1.1	0.7354	2.0%	-1.10 [-2.54, 0.34]	— <del>—</del> —
urado-Fasoli 2020	-1.06	0.7754	1.9%	-1.06 [-2.58. 0.46]	<del></del>
ü 2017	_1 01	1 255	1 4%	-1 01 [-3 47 1 45]	
-4 2017	-1.01	1.233	1.7/0 2 10/		
imenez-Garcia 2021 MIIT	-0.6	1.2533	1.4%	-0.60 [-3.06, 1.86]	
Heterogeneity: Tau <sup>2</sup> = 1.69; C	hi <sup>2</sup> = 334.67, df	= 35 (P <	0.00001	); $l^2 = 90\%$	▼
Subtotal (95% Cl) Heterogeneity: $Tau^2 = 1.69$ ; C	$hi^2 = 334.67, df = 14 (B < 0.0001)$	= 35 (P <	67.4%	-3.12 [-3.62, -2.61] ); $I^2 = 90\%$	•
Lü 2017 Choi 2018 Jimenez-Garcia 2021 MIIT Subtotal (95% CI)	-1.00 -1.01 -1 -0.6	1.255 0.6332 1.2533	1.9% 1.4% 2.1% 1.4% <b>67.4%</b>	-1.06 [-2.38, 0.46] -1.01 [-3.47, 1.45] -1.00 [-2.24, 0.24] -0.60 [-3.06, 1.86] -3.12 [-3.62, -2.61]	 
Subtotal (95% CI)	-U.U	- 25 /0	67.4%	-3.12 [-3.62, -2.61]	◆ <sup>1</sup>

Figure 4: Forest plot, PSQI scores by exercise intensity (low, moderate, high)

### 3.4.3 Other subjective sleep outcomes

Twelve studies reported data from sleep logs separately from PSQI data. Among these, exercise interventions were associated with large clinical and statistically significant improvements in total sleep time and sleep efficiency and significantly decreased sleep onset latency, wake after sleep onset compared to control groups (table 1). Four studies assessed sleep outcomes for 2,101 participants with the Insomnia Severity Index (ISI)<sup>193</sup> Exercise interventions had a small, beneficial, but not minimally clinically or statistically significant<sup>455</sup> effect on ISI assessed insomnia (-2.05, 95%CI:-4.38, 0.28).<sup>365,383,398,414</sup> Five studies assessed daytime sleepiness in 2096 participants with the Epworth sleepiness scale (ESS)<sup>444</sup> scale.<sup>365,368,376,406,443</sup> Exercise had a small but not statistically significant beneficial effect (1.44 95%CI:-2.96, 0.07) approaches a MCID of 2 points on the ESS.<sup>456</sup> Forest plots can be found in the supplementary materials (supplementary figures 6-7).

## 3.5 Objective sleep measures:

Nine studies assessed sleep objectively with polysomnography (PSG), <sup>244,272,273,373,376,378,403,424,441</sup> investigating the effects of acute moderate-intensity,<sup>244,457</sup> or regular low<sup>272,283,376</sup>, moderate<sup>424</sup> or high-intensity<sup>273,403</sup> exercise . Seven studies<sup>244,272,273,373,403,424,441</sup> scored PSGs using Rechstaffen and Kale's criteira<sup>458</sup>, and two<sup>376,378</sup> followed the American Academy of Sleep Medicine (AASM) Manual (2007 or subsequent updates).<sup>294</sup> Among statistically significant meta-analysed findings, TST and SE increased by 12 minutes and 4.6%, respectively, while WASO decreased by 10 minutes among participants in exercise interventions compared to non-exercise controls (table 2). There was a non-statistically significant increases in SOL (1 min) among exercise group participants, who also had more frequent (5) awakenings after sleep onset than control group participants. Exercise interventions produced non-statistically significant decreases in stage 1 sleep (-7 min), and NREM2 sleep (-5 minutes) compared to control groups. Exercise also produced statistically significant increases in NREM3 sleep of 7 and REM sleep of 6 minutes, while REM sleep latency decreased by 25 minutes in exercise groups.

Nine studies collected and reported actigraphy assessed sleep outcomes (table

2)<sup>362,366,374,396,399,419,437,442,459</sup>, with exercise interventions resulting in beneficial changes in all

				•		(, , , , , , , , , , , , , , , , , , ,
actigraphy re	ecorded sleep	measures	compared to	o non-exercise	control gr	ouns (fable 1)
acciorapity is	ecoraca sicep	measures	comparea e		COLLED BI	

Objective sleep measures	Pooled treatment effect (MD)	95% CI	<sup>2</sup> (Hetero- -geneity)	N studies	n sample	mean age (range)
Polysomnography (PSG)						
Total sleep time (min)	11.89	2.30, 21.48	0%	9	463	68.6 (60-90)
Sleep efficiency (%)	4.64	3.85, 5.43	94%	9	463	68.6 (60-90)
Sleep onset latency (min)	0.98*	-0.01, 1.95	56%	8	361	67.2 (60-75)
Wake after sleep onset (min)	-9.64	-10.77, -8.50	36%	8	361	67.2 (60-75)
Number of awakenings	4.90*	4.14, 5.66	60%	2	92	62.7 (57-70)
NREM1 (min)	-6.88	14.75, 1.0	0%	5	204	68.8 (61-75)
NREM2 (min)	-5.02	-11.81, 1.76	31%	5	204	68.8 (61-75)
NREM3 (min)	7.32	5.94, 8.69	96%	5	204	68.8 (61-75)
REM (min)	6.40	1.16, 11.65	0%	5	260	70.3 (64-75)
REM sleep latency (min)	-35.4	-41.39,-29.69	96%	2		
Actigraphy sleep outcomes	MD	95% CI		Ν	n sample	mean age
				studies		
Total sleep time (min)	25.57	17.53, 33.62	18%	7	593	64.0 (60-75)
Sleep efficiency (SE) (%)	4.44	2.36, 6.51	93%	7	706	64.55 (60-75)
Sleep onset latency (SOL) (min)	-4.44	-7.27, -1.62	96%	5	593	65.65 (60-75)
Wake after sleep onset WASO (min)	-11.12	-16.74, -5.50	91%	5	641	67.2 (60-75)
Number of awakenings	-2.25	-3.45, -1.06	69%	2	61	64.7 (57-70)
Subjective sleep outcomes (diaries)	MD	95% CI		N studies	n sample	mean age
Total sleep time (min)	31.56	18.47, 44.65	97%	8	845	67.9 (55-81)
Sleep efficiency (SE) (%)	5.55	2.89, 8.21	41%	4	638	65.5 (62-81)
Sleep onset latency (SOL) (min)	-12.45	-16.13, -8.76	53%	7	789	67.9 (55-81)
Wake after sleep onset WASO (min)	-24.30	-37.30, -	98%	3	614	65.1 (55-81)
		11.31				
Number of awakenings	-0.17	-0.44, 0.10	0%	4	624	65.5 (62-81)

\* favours control group, **bold** data favours exercise

Table 1: Meta-analysis of pooled, PSG, Actigraphy, and sleep diary/log derived sleep measures

# 3.51: Subgroup analyses, objectively assessed sleep outcomes

The mean ages and ranges of participants in studies reporting objectively assessed sleep outcomes did not allow for subgroup analyses by age. Additionally, an insufficient number of studies reporting objectively-assessed sleep outcomes also reported data for male and female participants separately or examined recruited all male or all female participants to allow for subgroup analysis of objectively measured sleep by sex. However, it was possible to conduct subgroup analysis for objectively measured sleep outcomes by exercise intensity (low, moderate, or high, as reported previously in this review). Moderate-intensity exercise was associated with greater, statistically significant improvements in total sleep time and wake after sleep onset than low or high-intensity exercise (table 2). Low-intensity exercise was associated with greater, statistically significant improvement in sleep efficiency and sleep onset latency than moderate or high-intensity exercise.

Objective measures (PSG, Actigraphy)	Low intensity Pooled effect and 95% Cl	l <sup>2</sup> (Hetero- geneity)	Mod. intensity Pooled effect and 95% Cl	l <sup>2</sup> (Hetero- geneity)	High intensity Pooled effect and 95% Cl	l <sup>2</sup> (Hetero- geneity)
Total sleep time (min)	3.11 (-4.94, 11.7)	0%	25.01 (20.0, 30.0)	0%	15.53 (3.17, 27.89)	0%
Sleep efficiency (%)	5.41 (3.22, 7.59)	0%	4.78 (2.29, 7.27)	68%	4.4 (-0.38, 9.18)	43%
Sleep onset latency (min)	-5.10 (-10.22, 0.01)	65%	-0.31 (-2.30, 1.68)	82%	1.59 (0.06, 3.13)*	30%
Wake after sleep onset (min)	-16.67 (-27.38, -5.96)	7%	-19.56 (-27.63, -11.5)	54%	-14.78 (-20.27, -9.29)	0%

\* favours control intervention. PSG: Polysomnography

 Table 2: Subgroup analysis- objectively measured sleep outcomes by exercise intensity.

## 3.6 Heterogeneity in the meta-analyses

Substantial heterogeneity was found in pooled meta-analyses of PSQI-assessed sleep. This may be influenced by clinical variability and lack of uniformity among exercise interventions and doses. **Meta-regression** found that only exercise intervention duration (in weeks), had a statistically significant (p=0.014) effect on heterogeneity, with PSQI scores increasing by 0.68

(95%CI:0.14,1.22) with every 11-week increase in intervention duration (supplementary materials, table 3). The effect remained statistically significant when adjusted for age, total hours (dose) of intervention and risk of bias. Generally, lower heterogeneity was found for polysomnography-assessed sleep outcomes, except for sleep efficiency. The highest overall heterogeneity was found in actigraphy-assessed sleep outcomes. There were not enough studies reporting either to allow for meta-regression to explore sources of heterogeneity.

# 3.7 Prediction intervals

The 95% PIs (table 3) were wider (less precise) than confidence intervals but did not change the statistical significance in most of the treatment effect estimates, suggesting the stability of the meta-analyses results and predicted benefit of exercise for sleep in future studies.

Outcome (Low-mod risk of bias only)	mean and 95% Cl	95% PI
All exercise-Pittsburgh Sleep Quality Index (PSQI)	-2.51 (-3.03, -1.99)	-4.79, -0.23
PSQI <5 at baseline	-1.09 (-2.16,-0.02)	-4.49, 2.31
PSQI >5 at baseline	-2.66 (-3.17, -2.16)	-5.28, -0.42
PSQl> 5, Low intensity	-2.08 (-3.11,-1.06)	-4.88, 0.70
PSQI> 5, Moderate intensity	-3.12 (-3.62, -2.61)	-5.76, -0.47
PSQI> 5, High intensity	-1.02 (-2.03, 0.00)	-4.33. 2.29

Table 3: 95% prediction intervals (PI)

# 3.8 Publication bias

No obvious asymmetries were found on visual inspection of funnel plots for the main

outcomes in the meta-analysis, indicating publication bias is unlikely (figure 8, supplementary

materials).

#### 4. DISCUSSION

We systematically reviewed and meta-analysed evidence for the effectiveness of exercise interventions targeting sleep in older adults. To the best of our knowledge, this is the largest sample of interventional studies of exercise and physical activity targeting sleep to be metaanalysed, representing the experiences of 8506 older adults across 82 studies. We found strong evidence for the beneficial effects of exercise on subjectively and objectively assessed sleep and a dose-response relationship between exercise and sleep in older adults. The results of our meta-analysis have important implications for clinical care, gerontology and health promotion.

#### 4.1 Subjectively-assessed sleep

Exercise and physical activity interventions benefit subjectively-assessed sleep. While all exercise participant subgroups reported improved subjectively assessed sleep, significantly larger reductions in PSQI scores were found in participants with sleep difficulties at baseline (PSQI >5) -2.66 (-3.17,-2.16) than in good sleepers (-1.09 95%CI:-2.16,-0.02). The prediction intervals for our main analyses also suggest that future studies of exercise for sleep in older adults would find exercise benefits sleep in older adults, with PSQI scores decreasing by -5.28 to -0.42 in persons with poor sleep. These findings are noteworthy, given that decreased perceived sleep quality has been associated with decreased quality of life and mental health among older adults.<sup>460</sup>

Our results extend those of Vanderlinden <sup>271</sup>, Kredlow<sup>224</sup>, Yang<sup>461</sup>, and Dolezal<sup>277</sup>, who found that regular exercise interventions were associated with significant improvements in PSQI total scores in older adults. In contrast to Yang's findings, however, we found participants in

exercise interventions self-reported (sleep diaries) statistically significant improvements in total sleep time, SOL, SE, and WASO compared to those in control conditions (table 2). These differences may arise from the larger number of studies meta-analysed in our review and reporting these sleep measures.

#### 4.1.1 Moderators of the effect of exercise on subjectively-assessed (self-report) sleep

Important participant characteristics such as age and sex are not well addressed in the current evidence-base. A large proportion of the studies we reviewed had samples made up of 50% or greater females, and females made up 63.6% of the 8506 persons whose data was pooled in our review. Despite this, very few adjusted analyses for sex or present data for males and females separately. The lack of exploration of sex differences in the evidence-base is important, given the higher risk and prevalence of poor sleep, insomnia, physical inactivity, and disorders influenced by them, such as dementia and Alzheimer's disease, among females than males.<sup>77,357,462</sup> Larger beneficial effects on PSQI assessed sleep were found for females (MD -3.11, 95%CI:-4.91,-1.30) than males (MD -2.89, 95%CI:-4.05,-1.73) in our meta-analysis, further highlighting the importance of investigating sex-based differences in the effects of non-pharmacological interventions for poor sleep in older adults.

We also found a linear relationship between age and the effects of exercise on PSQI scores, with the greatest benefits seem among 70–75-year-olds (-2.81, 95%CI:-4.73,-0.90). The effects of exercise decreased among adults over 75 years of age (-1.95, 95%CI:-2.63,-1.27). The reasons for this decrease cannot be determined in our meta-analysis. They may reflect underlying, age-related neurobiological changes including neural atrophy, decreased neuroplasticity, or changes in neuroendocrine and neuromodulatory functions, or decreased

ability to participate in physical activity, frailty, comorbidities, or polypharmacy influencing exercise capacity and sleep.<sup>463,464</sup>

### 4.1.2 Exercise intensity, dosage, and mode

While all three exercise intensities (low, moderate, or high) were associated with improved self-reported sleep quality, we found the largest effect and minimal clinically important different change on the PSQI with moderate-intensity exercise interventions.<sup>454</sup> Moderate-intensity exercises, at a range of frequencies and durations, were most frequently associated with improvements in sleep in our review, supporting a growing body of evidence finding that they are most likely to result in significant improvements in sleep outcomes in older adults.<sup>271,278,279</sup>

Important questions remain about whether there is a minimal dose of exercise (intensity, frequency, duration,) below which sleep is not improved, and whether higher doses of exercise result in greater improvements in sleep.<sup>212,224,277</sup> Few studies compared the effectiveness of different exercise intensities or dosages within the same study.<sup>279,362,423</sup> However, our finding that high-intensity exercise had the lowest effect on sleep suggest that there may be an intensity upper threshold for the beneficial effects of exercise in sleep in older adults.<sup>279</sup> Similar thresholds have been proposed for the effects of exercise on cognition in older adults, with one meta-analysis of 44 RCTs finding no minimal threshold for the beneficial effects of exercise on loep remains uncertain. It has previously been suggested that high-intensity exercise may lead to muscle soreness, increased oxygen deficit, or increased physiological arousal, dampening the beneficial effects.

of exercise on sleep in older adults.<sup>423</sup> However, our previous meta-analysis found that acute, high-intensity exercises performed 2-4 hours before bedtime does not disrupt night-time sleep in healthy, young and middle-aged adults.

The dose-response effect may be moderated by other factors, including how various modes of exercise influence the mechanisms by which exercise influences sleep<sup>240</sup> Several potential mechanisms have been proposed, but uncertainty remains about how exercise influences sleep. Features of exercise programs, such as their frequency, duration, or the time of day may also influence these effects. Our meta-regression analyses found longer intervention durations (number of weeks) yielded smaller improvement in self-reported sleep quality on the PSQI. A meta-analysis of 22 RCTs of exercise for insomnia by Xie also found short-term interventions (up to 3 months) resulted in significantly greater reductions in sleep disturbance than long-term interventions (>3 months).<sup>465</sup> This may reflect decreasing participant adherence to interventions spanning several weeks due to a complex array of inter-personal and contextual factors.<sup>466</sup>

These findings may also reflect changes in participants' other risk factors for poor sleep or changes in their health over time. In studies with education-based control conditions or waitlist controls, participants may also have engaged with other interventions or activities facilitating lifestyle changes influencing sleep, such as relaxation, lifestyle changes or drug treatments.

The mechanistic pathways may also differ between acute and regular exercise,<sup>241</sup> but the effects of acute exercise on sleep in older adults and older adult have been under

investigated.<sup>244,373,374,467</sup> It is not well understood whether a single exercise bout impacts the corresponding night's sleep in older adults with poor sleep, presenting an important opportunity to investigate whether acute exercise can benefit sleep in situations where sleep is restricted by necessity or demands arising from daily life.

Our results support the benefits of exercise for sleep quality in older adults, but we cannot determine whether improvements are also due to exercise mode (ex. aerobic, resistance, mind-body, etc), frequency, or duration. At least 16 distinct modes, from yoga to aerobics, were identified in various frequencies and durations. Few studies directly compared the impact of different exercise modes on sleep. Previous meta-analyses found no differences in sleep outcomes between acute or regular bouts of moderate-intensity aerobic or anaerobic, resistance or mind-body exercise, suggesting that exercise intensity, rather than mode, may have a greater influence on sleep outcomes.<sup>224,362,465,468</sup>

## 4.1.3. Moderating factors

Given the available evidence, key questions about other potential moderators of the doseresponse relationship between exercise and sleep, such as exercise timing, cannot currently be answered. The optimal time of day to perform exercise to influence sleep remains uncertain. Few studies examined the relationship between exercise timing and sleep in older adults. No controlled studies in our meta-analysis directly compared exercise at multiple times of day in older adults, and few studies reported the time of day exercise took place.<sup>283</sup> Evening exercise has been associated with significantly improved subjectively and objectively measured sleep latency and satisfaction and larger effects on sleep compared to morning exercise,<sup>283</sup> but these results have not been replicated in other studies.<sup>469</sup> Given the potential influence of circadian rhythms and other factors on both sleep and exercise, further research examining the timing of exercise interventions is needed.

Key participant characteristics, such as baseline fitness levels and use of sleep-influencing medications were also poorly reported among included studies. For example, Insufficient data was available to investigate the effect of **baseline fitness** on treatment outcome. For example, 17 studies reported investigated the effects exercise on sleep in sedentary older adults, but few studies reported objective baseline fitness measures. Their influence on the results of studies we reviewed cannot be quantified.

## 4.2 Objectively assessed sleep

We also found statistically significant improvements in actigraphy and polysomnography measured TST, sleep efficiency (SE), sleep onset latency (SOL) and WASO for participants in exercise interventions compared to control groups, supporting previous findings that both acute and regular exercise can increase TST and sleep efficiency, and reduce WASO in adults.<sup>224</sup> These findings can have important implications for older adults, as decreased SE and increased SOL or WASO have been associated with increased morbidity and mortality in older adults and are targets of interventions for poor sleep,<sup>470</sup>

A dose-response effect was also observed, in which low-intensity exercise produced greater improvements in SE and SOL, while moderate-intensity exercise produced greater benefits for TST and WASO compared to high-intensity exercise (table 2). There is a lack of consensus on the mechanisms underlying the effects of exercise on sleep, making it difficult to determine why lower and moderate intensity exercise produced greater benefits in

objectively measured sleep.<sup>236</sup> It may be possible that lower and moderate intensity exercises are more acceptable to a broader population of older adults and are associated with a lower risk of injuries than higher intensity exercise, improving their exercise adherence and producing more robust results among participants in low and moderate-intensity exercise programs compared to high intensity exercise-programs.<sup>471</sup> Exercise adherence was very infrequently reported among the studies included in our systematic review, making it impossible to determine this empirically with the current-evidence base.

Few controlled trials investigated the effects of exercise on sleep microarchitecture in older adults, and only a handful of studies reported statistically significant changes in time participants spent in individual sleep stages.<sup>272,273,373,403,424,441</sup> We found statistically significant increased NREM3 sleep and rapid eye movement (REM) sleep, along with reduced REM sleep latency, supporting previous findings about the effects of exercise on sleep architecture.<sup>240</sup> Regular exercise has previously been shown to increase the duration of NREM 3 sleep or slow wave sleep (SWS) in younger and middle-aged adults<sup>224,240</sup>, and SWS in healthy older adults.<sup>276</sup>

This has important implications for brain-health in older adults. A significant inverse correlation has been found between cerebrospinal Aβ levels, SWS duration and continuity, and slow wave activity (SWA) in cognitively normal older adults, suggesting that sleep disturbances might drive increased soluble brain levels of Aβ prior to amyloid deposition.<sup>140</sup> Loss of normal slow wave physiology has been linked to cognitive impairment and pathophysiological changes in older adults at risk of, and already diagnosed with, AD.<sup>33–35</sup> Decreased NREM SWA has also been associated with Aβ and tau deposits and

neurodegeneration in cognitively normal older adults and in those in the early stages of AD<sup>35,135</sup> Decreased SWS and REM sleep are also significantly associated with the severity of cognitive impairment in persons with AD<sup>29,78</sup>.

Contrary to previous studies, however, we did not find statistically significant changes in objectively measured NREM1 or NREM2 sleep among exercise groups compared to control groups.<sup>277</sup> These divergent findings may result from the wide range of experimental conditions and procedures investigated in eligible studies, modifying factors such as age, sex, or setting, and confounding of effects by comorbidities (for example, sleep apnoea) and other factors not controlled for (ex. daytime naps). Characteristics of the interventions themselves, including the time of day they were performed and dosage may also moderate the effects of exercise on sleep architecture.<sup>472</sup>

The smaller number of eligible studies assessing sleep with polysomnography or actigraphy also reported key moderating factors such as age, sex, baseline physical fitness or exercise characteristics less frequently than papers assessing sleep through subjective assessments, making it impossible to investigate the influence of those factors on the results of objective sleep outcomes in our meta-analyses.

#### 4.3 Strengths and Limitations

Our review has several strengths. We followed a carefully developed protocol with comprehensive search strategies, finding studies in several languages and settings which had not been previously meta-analysed, to the best of our knowledge. Publication bias was not

found in funnel plot analyses and is unlikely in our review. Subgroup analyses and metaregression were also kept to a minimum, reducing the risk of spurious associations. We also used prediction intervals, in addition to confidence intervals, exploring the potential for harm or clinical benefit in future studies of exercise interventions targeting sleep in older adults.<sup>473</sup>

There are also limitations in this review. Few studies examined aspects of the relationship between exercise and sleep, such as the time-of-day participants exercised, or key participant characteristics, such as baseline fitness levels, the presence or severity of sleep apnoea, lack of reporting of apnoea-hypopnea index (AHI) or use of medications influencing sleep, as well as the influence of lifestyle or environmental factors on participants' sleep. The evidencebase for exercise and sleep in older adults also has limitations, including differences in studies' designs, heterogeneic samples, and unanticipated confounding factors and inherent biases which may distort the magnitude of their effects and the results of meta-analyses<sup>. 474</sup> We limited meta-analysis to controlled studies with low to moderate risk of bias to minimize these effects, and our eligibility criteria were designed to reduce potential confounding in our analyses. Our subgroup, sensitivity, and meta-regression analyses found no change in the direction or magnitude of pooled treatment effects for exercise on sleep.

# 4.6 Recommendations for future research

Our systematic review highlights important areas in need of further investigation. The optimal time of day to preform exercise to influence sleep remains uncertain. Controlled trials investigating the effect of the timing (time of day) of exercise interventions targeting sleep in older adults are needed. Similarly, very few studies have investigated the effects of

different doses and exercise intensities on either subjectively or objectively measured sleep in older adults, and the most influential moderators of these relationships remains unclear. As a result, the optimal amount of exercise needed to improve sleep in older adults cannot be determined with certainty with currently available evidence. The effects of acute exercise or sleep restriction on sleep or the effectiveness of physical activity interventions targeting sleep in older adults have also not been investigated extensively but may yield important insights into the mechanisms and moderators of the bidirectional relationships between sleep, physical activity, and cognition. Given the many physical and mental health benefits associated with both improved physical activity and improve sleep, these areas for future research are critical for clinicians, policymakers, and the public to make informed choices about exercise interventions targeting improved sleep, activity, and quality of life in older adults.

The effects of exercise on sleep architecture and microarchitecture in older adults has generally been under investigated. These are important evidence gaps, given that better understanding of the mechanisms underpinning physical exercise and sleep and their effects on brain processes during sleep could provide important information leading to more effective exercise interventions aimed at maintaining or improving the memory functions of sleep.<sup>240</sup> This may also be of particular importance for persons at risk of, or in the early stages, of cognitive decline and their caregivers.

#### 5. Conclusion

Poor sleep is one of the most frequently reported health problems among older adults and is strongly associated with poor brain-health and reduced quality of life.<sup>475</sup> Sleep may also be one of the most important modifiable risk factors for a range of health conditions, including functional and cognitive decline and dementia in older adults.<sup>6,77</sup> We found strong evidence for the beneficial effects of exercise on self-reported and objectively measured sleep in older adults, including those with poor sleep.

Our findings have important implications for public health. Exercise is a widely accessible and sustainable intervention for sleep difficulties that can be performed by persons of almost any physical ability in most settings, inexpensively or cost-free. Our results show that even low intensity exercise can improve older adults' sleep. Exercise is also associated with a range of benefits for health and quality of life and may protect against functional and cognitive decline in older age. With ageing and increasingly sedentary populations, there is growing and pressing need for sustainable and effective interventions, like exercise, for poor sleep. The results of our systematic review support the development and dissemination of effective exercise interventions for sleep difficulties that may also aid secondary prevention of sleep-related health problems in older adults.

# AUTHOR CONTRIBUTIONS

**AP:** Development of the protocol, systematic review and meta-analysis, literature searches, data collection, risk of bias assessments, data analyses, data interpretation, write-up of review.

**EF:** Literature searches, data collection, risk of bias assessments, interpretation, paper review, and reviewing before submission.

**TDV:** Development of the systematic review, data interpretation, paper review, and reviewing before submission.

**CONFLICTS OF INTEREST DISCLOSURE:** The authors assert that they have no competing interests of conflicts of interests to declare.

**SUPPLEMENTARY INFORMATION:** Supplementary Information is available for this paper.

# (See appendix 3 of this thesis for supplementary material)

Chapter V: The effectiveness of exercise interventions targeting sleep in older adults with cognitive impairment or Alzheimer's Disease and Related Dementias (AD/ADRD): A systematic review and meta-analysis.

# Chapter summary:

In this chapter, we build on the findings of previous chapters by systematically reviewing and meta-analysing evidence for the effectiveness of exercise interventions targeting sleep in older adults with MCI or AD. This is the first such systematic review or meta-analysis, finding moderate to high quality evidence for the beneficial effects of exercise on sleep in older adults with cognitive impairment and AD/ADRD. The results of our systematic review support the development and dissemination of effective exercise interventions for sleep difficulties in persons with AD This chapter was published as "The effectiveness of exercise interventions targeting sleep in older adults with cognitive impairment or Alzheimer's Disease and Related Dementias (AD/ADRD): A systematic review and meta-analysis<sup>220</sup>" in The Journal of Sleep Research, the journal of the European Sleep Research Society, in 03/24.



#### ABSTRACT

Sleep loss is associated with reduced health and quality of life and increased risk of Alzheimer's Disease and Related Dementias (AD/ADRD). Up to 66% of persons with AD/ADRD experience poor sleep, which can predict or accelerate the progression of cognitive decline. Exercise is a widely accessible intervention for poor sleep that can protect against functional and cognitive decline. No previous systematic reviews have investigated the effectiveness of exercise for sleep in older adults with mild cognitive impairment(MCI) or AD/ADRD.

We systematically reviewed controlled interventional studies of exercise targeting subjectively or objectively (polysomnography/actigraphy) assessed sleep in persons with MCI or AD/ADRD. We conducted searches in PubMed, Embase, Scopus, and Cochrane-Library(n=6745). Nineteen randomised and one non-randomised controlled interventional trials were included, representing the experiences of 3278 persons with MCI or AD/ADRD. Ten had low-risk, nine moderate-risk, and one high-risk of bias. Six studies with subjective and 8 with objective sleep outcomes were meta-analysed (random-effects model). We found moderate to high quality evidence for the beneficial effects of exercise on self-reported and objectively-measured sleep outcomes in persons MCI or AD/ADRD. However, no studies examined key potential moderators of these effects, such as sex, napping, or medication use.

Our results have important implications for clinical practice. Sleep may be one of the most important modifiable risk factors for a range of health conditions, including cognitive decline and the progression of AD/ADRD. Given our findings, clinicians may consider adding exercise as an effective intervention or adjuvant strategy for improving sleep in older persons with MCI or AD/ADRD.

Keywords: exercise, sleep, mild cognitive impairment, dementia, Alzheimer's disease
#### INTRODUCTION

Sleep plays vital roles in brain health, including regulating clearance of proteins (e.g. βamyloid) linked to neurodegenerative disorders.<sup>6,24</sup> Nearly half of persons over the age of 65 experience difficulty initiating or maintaining sleep<sup>53,334,476,477</sup>, and up to 65% report disrupted or non-restorative sleep<sup>58</sup>. Sleep loss is associated with increased risk of falls, social disengagement, and reduced quality of life in older adults<sup>102</sup>. Poor sleep also increases the risk of mortality<sup>478</sup> and a range of morbidities ranging from cardiovascular disease and dementia to Alzheimer's Disease and Related Dementias (AD/ADRD)<sup>102</sup>.

Up to 66% of persons with AD/ADRD report or experience poor sleep, and it can predict or accelerate the progression of cognitive decline<sup>6,7,99</sup>. Sleep disorders, including insomnia, restless leg syndrome, and sleep apnoea can often appear in the preclinical stage of AD/ADRD and changes in sleep patterns in older adults can increase the risk of AD/ADRD<sup>6,8</sup>. Sleep disturbances induce systemic and central nervous system inflammation, neurophysiological changes, and increased tau and  $\beta$ -amyloid burden in the brain that may drive the onset and progression of AD/ADRD disease<sup>6</sup>. Poor sleep has also been linked to declines in functional connectivity between brain regions and networks linked to cognitive decline in AD/ADRD disease and other neurodegenerative disorders <sup>145</sup>.

Sleep disorders are also one of the leading causes of caregiver stress and institutionalization for persons with AD/ADRD<sup>77,162</sup>. In older adults and persons with AD/ADRD, the combination of sleep problems and medications used to treat poor sleep may also increase the risk of falls<sup>479</sup>, while a history of falls also considerably increases the risk of institutionalization, morbidity and mortality in persons with AD/ADRD<sup>479–482</sup>. Caregivers of persons with AD also

experience increased risk of insomnia, mental and physical health difficulties, and increased mortality, with considerable costs to healthcare systems and communities<sup>483,484</sup>. Insomnia is also associated with considerably higher healthcare costs and healthcare resource utilisation in persons with ADRD compared to those without insomnia<sup>485</sup>.

# Interventions for sleep

Non-pharmacological strategies play an important role in treating poor sleep<sup>486,487</sup>. Cognitivebehavioural therapy for insomnia (CBTi) is the preferred first-line treatment for insomnia disorder<sup>190</sup>. However, it often requires 6-10 treatment sessions, may be expensive and difficult to access<sup>198,205–207</sup>. Deficits in cognition, executive function, arousal and awareness associated with AD/ADRD progression may also make CBTi unfeasible in later stages of dementia or AD/ADRD<sup>488–490</sup>. Additionally, CBTi typically achieves success in only two-thirds of participants<sup>200,202,344</sup> and is particularly effective for improving subjective, rather than objective (sleep architecture) sleep outcomes.<sup>201</sup> This may be an important consideration, given that loss of normal Non-Rapid Eye Movement (NREM) sleep slow wave activity has been linked to cognitive impairment in older adults and pathophysiological changes in Alzheimer's disease<sup>33–35,48–50</sup>.

Medications such as benzodiazepine receptor agonists and sedative antidepressants can be effective short-term (1-12 weeks) treatments but do not treat the root causes of sleep loss<sup>188</sup>. Sleep loss in persons with AD or dementia may be caused by a variety of factors ranging from, age-related changes the brain, age-related changes in sleep and circadian rhythms, sleep apnoea, parasomnias such as REM behaviour disorder (RBD), chronic illnesses, medication effects, impaired mobility, environmental influences (e.g. institutionalisation),

reduced brain performance, or AD/ADRD disease progression<sup>6,9,491–495</sup>. The adverse effects of medications used to treat poor sleep, including daytime drowsiness, sedation, and dependence, may also limit their acceptability for patients and their caregivers<sup>189</sup>. There is also limited evidence for the effectiveness of pharmacological treatment of insomnia in persons with dementia<sup>496</sup>.

Exercise is a promising, widely accessible, highly customisable intervention for sleep difficulties that can be performed in most settings, by persons of almost any ability, inexpensively or cost-free<sup>224,497</sup>. Exercise refers to intentional, structured physical activity, or physical activity that is planned and repetitive with a goal of improving or maintaining health or physical fitness<sup>498,499</sup>. Physical activity includes any bodily movement produced by skeletal muscles that results in energy expenditure and can include occupational, household, sports, exercise, conditioning, or other activities<sup>498,499</sup>.

Exercise is associated with a range of benefits for health and quality of life in older adults<sup>4,224</sup>. It may also protect against functional and cognitive decline in older age, and benefits cognition and several neuropsychiatric symptoms, such as depression, mood, and agitation in persons with AD/ADRD<sup>332,500,501</sup>. Exercise also targets sleep physiology including NREM slowwave activity <sup>212–215</sup>, which has been linked to memory consolidation in older adults<sup>7,48–50</sup>.

There is a robust bidirectional relationship between exercise and sleep<sup>212</sup>. Strong evidence supports the beneficial effects of exercise on sleep quality and decreased use of sleep medications in older adults<sup>212,224,271</sup>. However, less is known about the effectiveness of exercise for sleep problems in older adults with cognitive decline, dementia, or AD/ADRD<sup>212</sup>.

To the best of our knowledge, no previous systematic reviews have investigated the effectiveness of exercise or structured physical activity interventions targeting sleep in older adults with cognitive impairment or AD/ADRD. A systematic review of current evidence is needed to support clinical care for older adults affected by cognitive decline and guide future research. This systematic review critically appraises and meta-analyses available evidence to determine the effectiveness of exercise interventions targeting subjective or objective sleep outcomes in older adults with Mild Cognitive Impairment (MCI) or AD/ADRD.

#### METHODS

Our systematic review and meta-analysis were conducted following the Cochrane Handbook for Systematic Reviews of Interventions<sup>346</sup> recommendations and reported along Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>347</sup> (PRISMA checklist is included in the supplementary materials). The protocol (CRD42021289528) was registered on PROSPERO<sup>348</sup>.

**Eligibility criteria** for the systematic review: Eligible studies met the following criteria: **P:** Included participants  $\geq$  60 years old with cognitive impairment, MCI, or AD/ADRD, or extractable data for that age group.

Participants must have a clinical diagnosis of MCI or AD/ADRD at baseline. Diagnosis of MCI must be made according to recognized criteria, such as the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease<sup>287,502</sup>, Petersen's criteria (P-MCI)<sup>503</sup>, or the Diagnostic and Statistical Manual of Mental Disorders (DSM)<sup>504</sup>, or using validated

cognitive screening tools (e.g. Montreal Cognitive Assessment [MoCA]<sup>505</sup>, Mini Mental State Examination [MMSE]<sup>505</sup>) and qualitative clinical information.

Diagnosis of Alzheimer's disease must be made according to recognized criteria, including the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria<sup>506</sup>, the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease<sup>287</sup>, the Diagnostic and Statistical Manual of Mental Disorders criteria<sup>504</sup>, or ; other method of formal medical diagnosis reported in the paper.

I: Interventional studies of exercise (any mode, frequency, duration).

**C**: Control interventions: no treatment, wait-list control, educational or non-exercise interventions.

**O:** Sleep quantity, quality, or architecture, measured objectively (actigraphy, polysomnography) or by self-report (ex: the Pittsburgh Sleep Quality Index [PSQI]<sup>507</sup>, sleep diaries...), reported as a categorical or continuous outcome.

Study design: controlled, interventional studies.

**Exclusion criteria:** Single-subject, uncontrolled, or observational studies, case series, or studies reporting sleep as a dichotomous outcome were excluded. Studies of participants with disorders highly associated with poor sleep and difficulty exercising such as stroke,

cerebral vascular accident, or major psychiatric disorders (other than MCI or AD/ADRD) were excluded<sup>350</sup>. We did not restrict eligibility by the study location or study sample size.

**Eligibility for meta-analysis:** To be eligible for meta-analysis, papers included in the systematic review had to report sleep quantity, quality, or architecture, measured objectively (actigraphy, polysomnography) or by self-report (ex: the Pittsburgh Sleep Quality Index [PSQI]<sup>507</sup>, sleep diaries...) as a continuous outcome. To minimise the potential for biased pooled treatment effects arising from poor study quality, we limited our meta-analyses to studies with low or moderate risk of bias on the Cochrane ROB, excluding those at high risk of bias.

# Information sources and search strategy

We conducted systematic searches with keywords and Medical Subject Heading (MeSH) terms related to physical activity, exercise, sleep, cognitive impairment, MCI, dementia, or AD/ADRD, from inception and without language restrictions on PubMed, Embase, the Cochrane Library, Scopus, and PROSPERO (supplemental material). To ensure literature saturation, we undertook citation searching and re-ran keyword searches on PubMed limited to the most recent 12-months to capture papers not yet indexed under MESH.

Records identified through the literature and citation-list searches were imported to the Mendeley reference management program and duplicates were removed. We also created a Microsoft Excel spreadsheet with the records identified through our literature and citation searches and visually scanned for duplicates to confirm no duplicates were missed. In our

selection process, two reviewers (AP and EF) independently screened a selection of 100 records from our search results against our eligibility criteria to pre-test and refine our eligibility criteria and establish inter-rater reliability. Subsequently, these two reviewers independently screened all search results against our eligibility criteria, first by title and abstract and then by full text (see figure 1). Full-texts for all potentially eligible studies were retrieved. When necessary, study authors were contacted for additional information to resolve questions about papers' eligibility or acquire additional data for data extraction or synthesis and registered or published study protocols were consulted when available. Disagreements about eligibility were resolved through consensus. Records not meeting our inclusion criteria were excluded and the reason for exclusion was recorded at the full-text screening.

#### Data extraction and data items

A data extraction sheet was developed with Microsoft Excel and pilot tested with 10 randomly selected eligible papers. One reviewer (AP) performed the initial data extraction for all included papers and a second reviewer (EF) checked the data extraction. We extracted data for study characteristics (authors, year, design, population), sample characteristics (age, gender, diagnoses) at baseline, exercise interventions (mode, intensity, duration, frequency), and effect measures.

## Effect measures

We extracted data for self-reported or objectively measured sleep outcomes (sleep duration, sleep architecture and microarchitecture, and sleep quality) measured through actigraphy,

polysomnography (PSG), sleep diaries, and subjective assessments including the Pittsburgh Sleep Quality Index (PSQI)<sup>349</sup>, Insomnia Severity Index (ISI)<sup>193</sup>, Mini-Sleep Questionnaire (MSQ)<sup>447</sup>, Neuropsychiatric Inventory (NPI)<sup>508</sup>, Sleep Disorders Inventory (SDI)<sup>509</sup>, and customized sleep quality tools as continuous treatment effect estimates (mean differences and measures of variance). We extracted measures of treatment effect from included studies that were adjusted for potential confounding variables over reported estimates that were not adjusted for potential confounding. Where studies used multiple follow-up periods, we used data from the first follow-up period after the end of the intervention period (most recent).

Risk of Bias was assessed with the Cochrane Collaboration's Revised Tool to Assess Risk of Bias in Randomized Trials(RoB-2)<sup>352</sup> for randomised trials, and Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tools<sup>510</sup> for non-randomized trials. Two reviewers (AP and EF) independently assessed studies for risk of bias . Any disagreements were resolved through discussion and consensus.

# Data synthesis

Papers were categorised by study population, as either a study of persons with MCI or of persons with AD/ADRD, as described in our eligibility criteria. Exercise intensity was categorized as low, moderate, or high-intensity according to how they were reported by the study authors, or based on the American College of Sports Medicine (ACSM) guidelines<sup>351</sup>. Sleep outcome measures were categorised as either subjective (PSQI or self-reported sleep measures), or objective (actigraphy or polysomnography). All sleep outcome measures in this

systematic review were synthesised as mean-differences between the exercise and nonexercise groups and measures of variance (e.g. standard deviation or standard error) with the Cochrane Collaboration's Review Manager 5.41 (RevMan 5.41) systematic review and metaanalysis software<sup>346</sup>. The results of these syntheses are described narratively in the systematic review, as summary of findings in tables 1 and 2, and graphically (for metaanalyses) in figures 3 and 4.

#### Meta- analysis

We expected clinical diversity and heterogeneity between studies resulting from variable samples (e.g. mean ages, proportion of males and females, and clinical presentation of MCI or AD/ADRD), study locations and settings, differences in interventions and their doses, and effect sizes. Following the guidance of the Cochrane Handbook for Systematic Reviews of Interventions<sup>346</sup>, we conducted inverse-variance weighted random-effects (Der Simonian and Laird) meta-analyses with RevMan 5.41<sup>346</sup>. With RevMan, we derived mean differences in sleep outcomes between experimental and control groups to calculate pooled intervention effect estimates<sup>346</sup>. These were displayed graphically with Forest plots<sup>354,355,511</sup>.

We assessed statistical heterogeneity using t<sup>2</sup>, Chi2 (significance level: 0.1) and l<sup>2</sup> statistics<sup>346</sup>. Statistical heterogeneity was also evaluated graphically in Forest plots<sup>354–356</sup>. We conducted sensitivity analyses to determine if any one study contributed significantly to heterogeneity in meta-analysis<sup>346</sup>. Subgroup analyses were not conducted, given the small number (13) of studies meta-analysed, low power, and increased risk of a high false-positive rate<sup>512</sup>. Meta-regression was not conducted, as a there were insufficient studies eligible for meta-analysis

reporting characteristics to be modelled in meta-regression. It is recommended that at least ten studies in a meta-analysis should be available for each characteristic modelled in a metaregression<sup>346</sup>. In order to minimise the risk of bias due to missing results (arising from reporting biases), we also checked the reporting of outcomes in each study as part of our risk of bias assessments and compared these to study protocols or registrations when they were available.

#### Additional sensitivity analyses:

We also conducted sensitivity analyses by risk of bias (keeping only papers with low risk of bias) to assess the robustness of our meta-analysed results<sup>354–356</sup>

# **Publication bias**

There was an insufficient number of studies for any one meta-analysed outcome for funnel plots or Egger's tests for publication bias (minimum of 10 recommended by the Cochrane Collaboration and Cochrane Handbook of Systematic Reviews) <sup>346</sup>. In meta-analyses with a small sample of studies per outcome, the power of these tests is too low to distinguish real asymmetry from chance<sup>346</sup>. As a result, funnel plots or Egger's tests for publication bias were not undertaken.

# RESULTS

Our searches yielded 6745 publications (figure 1). After duplicates were removed, 4593 papers were screened against our eligibility criteria by title and abstract. Two hundred fifty six papers were deemed eligible or likely eligible. Full-text manuscripts were sought for these 256 papers. We were unable to access full-text manuscripts for 3 papers after extensive searches in online databases (see methods), internet searches, and interlibrary loan requests<sup>513–515</sup>. After full-text screening, twenty interventional trial papers were eligible for inclusion in the systematic review and 12 in the meta-analysis (table 1).



Figure 1: PRISMA flow chart

Ten papers were assessed at low-risk of bias, nine as some-concerns or moderate, and one as high-risk (figure 2a, 2b).

		Risk of bias domains						
		D1	D2	D3	D4	D5	Overall	
	Alessi et al, 1999	-	-	-	+	-	-	
	Badelmi et al, 2018	-	-	+	-	+	-	
	Chan et al, 2016	+	+	+	-	+	-	
	Choi et al, 2018	+	+	+	+	+	+	
	Eggermont et al, 2010	-	+	+	+	+	-	
	Fragoso et al, 2015	+	+	+	+	+	+	
	Hoffman et al, 2016	+	+	+	+	+	+	
	Karydaki et al, 2017	-	-	-	-	-	-	
	Kumar et al, 2014	+	-	-	-	-	-	
Study	Landri et al, 2004	X	X	X	X	X	X	
	Li et al, 2021	+	+	+	+	+	+	
	McCurry et al, 2011	+	+	+	+	+	+	
	Nascimento et al, 2014	+	+	+	+	+	+	
	Öhman et al, 2017	+	+	+	+	+	+	
	Ricjards et al, 2011	+	+	+	+	+	+	
	Song and Yu, 2019	+	+	+	+	+	+	
	Song and Yu 2023	+	+	+	+	+	+	
	Stella et al, 2011	+	+	-	+	+	-	
	Wang et al, 2020	+	-	+	+	+	-	
		Domains:	sing from the	randomization	process	Judge	ement	
		D2: Bias due to deviations from intended intervention.						
		D3: Blas due to missing outcome data. D4: Blas in measurement of the outcome.						
		D5: Bias in selection of the reported result.						





Figure 2: Risk of bias assessments: a. ROB-2 b. ROBINS-I

а

b.

#### Sample characteristics

The 20 included studies represent the experience of 3278 persons, 2066 of which were female (63%), with a mean age of 68 years (range 55 to 95 years), recruited from community, clinical, and research settings. Included papers were published from 1995-2022, with a mean sample size of 158 participants.

# Interventions (table 1)

A wide range of exercise interventions and dosages were reported, ranging from onceweekly<sup>516</sup> to daily bouts<sup>377,459</sup> over four<sup>449</sup> to 104 weeks<sup>365</sup>, for 30-minutes<sup>421</sup> to 80minutes<sup>377</sup>. Four papers investigated low-intensity exercises, including low-intensity aerobic exercise, physical activity, elastic band or resistive exercise, overground walking programs, and light Tai Chi<sup>397,459,517,518</sup>.

Moderate-intensity exercises were most frequently investigated (12 trials), including aerobic exercise, cycling or bicycle ergometry, resistance or strength training, walking programs, Tai Chi, yoga, or combinations of moderate-intensity exercises<sup>365,377,522,523,408,421,425,449,516,519–521</sup>. Two studies investigated the effects of moderate to vigorous intensity (MTVA)<sup>524</sup> exercise, including aerobic dance<sup>525</sup> and combined aerobic and strength training exercises<sup>526</sup>. Two studies investigated the effects of high-intensity exercises<sup>441,526</sup>, including cycling or treadmill exercise, resistance training, or combinations of high-intensity exercises at greater than 80% maximal heart rate.

### **Sleep Outcomes**

A variety of assessment tools were used to collect sleep outcomes, including actigraphy, polysomnography (PSG), sleep diaries, and subjective assessments including the Pittsburgh Sleep Quality Index (PSQI)<sup>349</sup>, Insomnia Severity Index (ISI)<sup>193</sup>, Mini-Sleep Questionnaire (MSQ)<sup>447</sup>, Neuropsychiatric Inventory (NPI)<sup>508</sup>, Sleep Disorders Inventory (SDI)<sup>509</sup>, and customized sleep quality tools.

Sleep outcomes in persons with cognitive impairment or Mild Cognitive impairment (MCI) Nine studies investigated the effects of exercise on sleep in persons with MCI (excluding diagnosed AD/ADRD or dementia) or MMSE scores between 19-24 (mean 22.3) or Montreal Cognitive Assessment scores between 18-25 (mean 22.05) ( details in table 1). Exercise interventions improved self-reported sleep outcomes in persons with MCI. Only one study assessed the effects of exercise on objective sleep outcomes in persons with MCI. Only one study (2021) reported that a 12-week, moderate-intensity resistance training program improved both actigraphy and subjectively measured sleep, with statistically significantly increased sleep efficiency and decreased wake after sleep onset and sleep fragmentation in 62 assisted living facility older adults (mean age 72.2) with MCI<sup>519</sup>.

Among the remaining 8 studies, a range of exercise modalities, intensities, frequencies and durations were reported. Two studies investigated the effects of low-intensity exercise on sleep in older adults with MCI. Alessi et al (1999) and investigated the effects of 14-weeks of daily low-intensity physical activity on sleep and agitation in 29 nursing home-dwelling older adults (mean age 88.3) with MCI<sup>517</sup>. Participants in the exercise intervention showed increased total sleep time, longer sleep episodes, and less daytime sleepiness and agitation compared to the non-exercise group. Chan et al (2016) found that a low-intensity Tai chi

(TCG) exercise program increased sleep duration (+48 minutes), sleep efficiency, and improved sleep quality on the PSQI in 52 community-dwelling, sedentary older adults with cognitive impairment and poor sleep (PSQI score >5 at baseline)<sup>397</sup>.

The majority of studies with persons with MCI investigated the effects of moderate intensity exercise on sleep. Bademli et al (2018) found that a 20-week, moderate-intensity, exercise and walking program improved sleep quality on the PSQI (MD -9.0) and cognition in 77 sedentary, nursing home-dwelling persons over 65 years of age with MCI<sup>377</sup>. Choi et al (2018) investigated the effects of a 12-week, 4 times per week seated yoga exercise program on sleep, physical fitness, and depression in community-dwelling, sedentary older adults with MMSE scores  $\geq 19^{421}$ . Participants in the exercise group reported a small, but not statistically significant improvement in sleep quality on the PSQI. The authors noted, however, that sleep quality was measured during the hottest summer recorded in Korea, with 22 nights of extreme heat during the reference-month, possibly countering the effects of the intervention on participants' sleep quality.

Fragoso et al (2015) found that a 24-30 month, moderate-intensity, exercise program reduced the likelihood of participants developing poor sleep quality (PSQI >5) over the intervention period and produced a small improvement in sleep quality in a sample of 1635 community-dwelling, sedentary older adults (aged 70-89) with cognitive impairment (figure 2)<sup>365</sup>. Karydaki et al (2017) investigated the effects of a 12-week resistance training program on subjective sleep quality in females with MCI, finding that resistance training improved subjective sleep quality (decreased global PSQI score) <sup>527</sup>.

Song et al (2019) investigated the effects of a 16-week moderate-intensity aerobic exercise program on health related quality of life, including sleep quality, and cognitive function in 120 sedentary, community-dwelling older adults with MCl<sup>408</sup>. Compared to participants in the health-education control group, participants in the aerobic exercise group exercise group reported significantly greater improvement in sleep quality on the PSQI. In a separate study of a 16 week, moderate-intensity aerobic dance exercise program, Song et al (2023) also found that aerobic dancing (moderate-to vigorous intensity) significantly improved overall sleep quality (PSQI), sleep duration, sleep efficiency, and sleep onset-latency in older adults with MCl and poor sleep<sup>525</sup>.

Finally, Wang et al (2020), found that a 24-week, thrice weekly moderate-intensity exercise program significantly improved sleep quality (lower PSQI scores ) in a sample of 116 sedentary, community-dwelling older adults (mean age 68 years) with MCl<sup>425</sup>. Sleep quality also had a strong mediating effect on the effects of the exercise program on participants' cognitive function.

Sleep outcomes in persons with Alzheimer disease and related dementias (AD/ADRD) Ten studies examined the effects of exercise or physical activity interventions on sleep outcomes in persons with AD/ADRD (7) or dementia (3), finding exercise had beneficial effects on their sleep quality (table 2). Eggermont (2010) investigated the effects of a 30minute walking program on sleep and sleep disturbances in 79 older adults aged  $\geq$  70 with AD/ADRD<sup>518</sup>. Participants in the walking program did not show improved night-time restlessness or actigraphy-measured sleep compared to the control group. However, it was possible that participants may not have had sufficient sleep disturbances at baseline to show

a treatment-effect. The timing of the physical activity interventions also varied frequently and may have influenced the study results<sup>212</sup>.

Hoffman et al (2016) found that a 16- week, moderate-to-high-intensity aerobic exercise program decreased sleep disturbances in a sample of 200 persons aged 50-90 with mild AD<sup>526</sup>. Kumar et al (2014) investigated the effects of a 5-week, Occupational Therapist-delivered exercise and structured physical activity program (OTP), finding that OTP improved sleep quality and decreased daytime sleepiness in a sample of 77 persons with dementia.<sup>520</sup>

Landi et al (2004) investigated the effects of a 4-week, moderate-intensity exercise program on behavioural problems, including sleep disturbances, in a pilot study with 30 nursing-home -dwelling persons with dementia<sup>521</sup>. Compared to the control group, the exercise group showed a statistically significant reduction in sleep disturbances at the 4-week follow-up. The study has several important limitations, however, including poor or absent reporting of participants age, who delivered the intervention or how often, who collected outcome data or when, and no reporting of the units of measurement used for outcome assessments.

McCurry et al (2011) investigated 30 daily minutes of continuous walking in a study of 132 persons with AD/ADRD, finding that participants in the exercise group had significantly greater improvements in sleep duration and quality than the control groups, even after adjustment for participant age, sex, depression, comorbidity, cognitive impairment, and sleep apnoea<sup>459</sup>. Nascimento et al (2014) found once-weekly, moderate-intensity multimodal exercise was associated with statistically significant improved sleep and reduced sleep

disturbances in an RCT of 35 persons with AD/ADRD<sup>516</sup>.

Namazi et al (1995) found a multimodal, moderate-intensity exercise program increased sleep quality and duration in a sample of 22 institutional-dwelling persons with AD/ADRD, but a small sample size and large range of MMSE scores at baseline may have influenced the results<sup>449</sup>. Öhman's secondary analysis of the Finnish Alzheimer Disease Exercise Trial (FINALEX) trial<sup>528</sup> found that exercise did not lead to statistically significant changes in sleep problems in community-dwelling persons with AD/ADRD<sup>522</sup>. However, they used only the Neuropsychiatric Inventory (NPI) to assess sleep outcomes. The NPI has only one item (11) assessing sleep by caregiver reports of sleep behaviours but not changes in frequency or sleep quantity<sup>508</sup>. A high proportion of participants also took medications which may have influenced their sleep or response to the interventions.

Richards et al (2012) found high-intensity exercise improved sleep quantity and efficiency, and increased minutes of REM sleep in institutional-dwelling persons with dementia and AD/ADRD<sup>441</sup>. A high proportion (43%) of participants had sleep apnoea, and whether their apnoea was treated during the study was not reported. However, when apnoea was included as a covariate in the authors' statistical models, it did not have a statistically significant effect on the relationship between exercise and total sleep time. Finally, Stella et al (2011) investigated the effects of a six month, thrice-weekly aerobic and balance exercise program on neuropsychiatric symptoms, including sleep disturbances, in 32 community-dwelling persons with mild to moderate AD/ADRD<sup>523</sup>. Compared to the control group, the exercise group attained statistically significantly greater reduction in sleep disturbances on the NPI.

Study	Mild cognitive impairment and diagnosed MCI Sample and age	Exercise Intensity 1: low 2: mod. 3. high	Exercise and/or control intervention	Sleep measures	Main findings (sleep)	Risk of Bias
Alessi et al, 1999 <sup>517</sup>	N=29 (26 female) mean age 88.3 nursing home dwelling older adults with dementia (mean MMSE 13.3) and urinary incontinence.	1	Exercise: 5 days per week over 14 weeks physical activity program: structured arm and leg exercises, sit-to-stands, and walking or wheelchair propulsion. Control: Night-time environmental program meant to reduce intrusive nursing care at night (light, noise, procedures, etc).	Observational Sleep Assessment Index (OSAI) and 5 nights of actigraphy. Observations to assess sleep versus wakefulness, time spent in bed, and agitation.	Participants in the exercise intervention group showed increased total sleep time, longer sleep episodes, and less daytime sleepiness and agitation compared to the non-exercise group. Baseline sleep percentage (ex- group) 51.7 (95%CI:42.8. 60.6) Follow-up: 62.5 (95%CI:50.6, 74.4)	Mod
Bademli et al, 2019 <sup>377</sup>	N= 60 (25 female) ≥ 65 years old Mean age 71.5 years Diagnosed mild cognitive impairment, living in nursing homes, and baseline PSQI 5-21.	2	Exercise: 20-week , 4 times/week Physical Activity Program: 10- min warm-up, 20-min rhythmic exercises, 10- min cool down exercises, and 40-min of free walking. Control: non-exercise control.	PSQI Baseline scores exercise group: 13.04 ± 2.06 control 12.14 ± 2.46	PSQI measured sleep quality of improved considerably (md -9.01 [- 10.06, -7.96] after a 20-week Physical Activity Program compared to the control group.	Mod
Chan et al, 2016 <sup>397</sup>	N= 52 (44 female) ≥ 60 years old With cognitive impairment: mini- mental state examination (MMSE) score of 13–26, PSQI >5.	1	Exercise: Twice weekly, 60-minute Tai Chi (TCQ) sessions for 2 months. Control: Non-exercise, observation only group.	PSQI (Chinese) at baseline, 2 months, and 6 months Baseline scores: exercise group 10.2 Control 9.8	Participants in the TCQ group reported better sleep quality (PSQI mean difference of -1.80 global score), sleep duration (P=0.003), habitual sleep efficiency (P=0.002) than the control group. The TCQ group's sleep duration increased +48 minutes, sleep efficiency increased 9.1%.	Mod
Choi et al, 2018 <sup>421</sup>	N= 77 (59 female) ≥ 65 years old (mean age 78.2) Community -dwelling, MMSE 19-26.	2	Exercise: 30-40 min sessions of floor seated exercise , 4 times per week for 12 weeks following ACSM guidelines. Control: Non-exercise, "usual care" control group.	PSQI Baseline scores Exercise group 6.12 ± 2.72 control group 5.83 ± 2.64	The exercise program had no significant effect on sleep quality: mean difference 1.00 ( 2.15 to 0.15), p 0.087. However, the authors note: "considering that the previous month, which served as a reference for the measurement of sleep quality, was part of the hottest summer ever with 22 tropical nights, it might have been difficult for the FSEP to fully affect the participants' sleep quality scores."	Low
Fragoso et al, 2015 <sup>365</sup>	N= 1635 (1098 female) 70-89 years old mean age 79 Community -dwelling adults with mobility and cognitive impairments, MMSE	2	Exercise: Walking 5 times per week (moderate intensity) with a goal of 150 minutes per week, as well as 5 times per week strength, flexibility, and balance training exercises at moderate-intensity over 24 months. Control: health education only.	Insomnia Severity Index (ISI), Epworth Sleepiness Scale (ESS) and PSQI at baseline 6, 18, and 30 months. Baseline PSQI: 5.9 for both groups	Compared with health education, structured physical activity reduced the likelihood of developing poor sleep quality (PSQI >5) over the intervention period, but no statistically significant effect on existing poor sleep quality (PSQI) or the ISI or ESS.	Low

Karydaki et al, 2017 <sup>527</sup>	N=49 (all female) Mean age 72.6 Adults with MCI (Petersen criteria) confirmed by MMSE scores.	n/a	Exercise group a: Twice weekly, 45-minute resistance training exercises (no intensity described) over 12 weeks. Non -exercise control group.	PSQI at baseline and at 12 weeks. Baseline PSQI: exercise group 6.1 control group 7.4	Compared to the control group, the exercise group reported significantly improved subjective sleep quality- global PSQI score (t=2.335, df15, p=0.03) at the 12- week assessment.	Mod
Li et al, 2021 <sup>519</sup>	N=41 (36 female) ≥ 60 years old (mean age 72.2) Assisted living facility - dwelling, sedentary adults with mild cognitive impairment Montreal Cognitive Assessment (MoCA) ≥ 18.	2	Three 60 minute, moderate-intensity resistance training (elastic band) exercise sessions per week for 12 weeks with at least 48 h between sessions. Control group: No exercise control group.	Actigraphy: non- dominant wrist for 3-4 consecutive days at baseline and post- intervention. Sleep diaries.	Compared to the control group, resistance training decreased sleep fragmentation and improved sleep quality in older adults with MCI, with statistically significant increase in sleep efficiency (9.9%, 95%Ci: 5.1,14.7) and decreased wake after sleep onset (WASO) - 52.3 minutes (95%CI: 76.9, 27.6). Total sleep time increased in the exercise group, but not statistically significantly: 23.6 minutes (95%CI:- 18.4, 65.6).	Low
Song et al, 2019 <sup>408</sup>	N= 120 (90 female) ≥ 60 years old community -dwelling, sedentary adults with mild cognitive impairment (MCI) MoCA 18-26.	2	3 time per week, 60- minute exercise sessions of a moderate-intensity aerobic exercise programme over 16 weeks. Control: 16-week health education program	PSQI Self-reported sleep quality Baseline PSQI Exercise: 9.47 ±3.66 Control: 8.98 ±3.94	A statistically significant change (improvement) in PSQI was found in the exercise compared to control group: -1.257 (-1.609, - 0.825) p <0.001 d=0.89	Low
Song et al, 2023 <sup>525</sup>	N=89 (68 female) ≥ 60 years old (mean age 76), community dwelling older adults with MCI Montreal Cognitive Assessment (MoCA) 19-26	2,3	3 times per week, 60- minute group moderate intensity aerobic dancing program over 16 weeks. Intensity monitored with Borg scale (12-14). Control: Health education with no exercise.	PSQI Baseline PSQI Exercise: 11.07 ±2.65 Control: 10.66 ±3.14	Participants in the exercise group had significantly greater reduction in PSQI total scores (b: 1.74; 95% Cl, 3.41, 0.08; p=.04), and statistically significantly improved sleep duration, sleep latency, and sleep efficiency compared to the control group.	Low
Wang et al, 2020 <sup>425</sup>	N=116 (68 female) ≥60 years old (Mean age 63.3) Community -dwelling older adults with diagnosed MCI (Portet et al 2006 criteria), MoCA <26.	2	3 time per week, 60 min supervised limbs- exercise sessions over 12 weeks: 10-min limbering-up exercise, 40-min of upper and lower limbs exercise, followed by a 10-min relaxation exercise Wait list control	PSQI Baseline PSQI Exercise: 9.25 ±3.85 Control 8.63 ±3.56	Compared to the control group, the exercise group reported improved sleep quality (PSQI), with a mean Difference (95% CI) of -2.5 (95%CI: -351, .39), Cohen's d of 0.87.	Mod

Table 1: Exercise interventions for sleep in persons with mild cognitive impairment

	Dementia or AD/ADRD	Exercise Intensity 1: low 2: mod.	Exercise and/or control intervention	Sleep measure	Main findings (sleep)	ROB
Egger- mont et al, 2010 <sup>518</sup>	N=79 (63 female) ≥ 70 years old (mean age 84.3) participants with diagnosed AD/ADRD (in medical record), mild-to-moderate cognitive impairment (MMSE >10).	1	Exercise: Indoor walking program, 30 minutes per day, five times per week for 6 weeks. Control: indoor social visit (no exercise) for 30 minutes, five times per week over the 6 weeks.	Actigraphy: Actiwatch worn on the dominant wrist. Baseline sleep efficiency: Exercise: 74.01 (SD 9.37) Control: 70.0 (SD 10.11).	Participants in the walking program did not show a beneficial effect on night-time restlessness or other actigraphy-measures sleep parameters compared to the control group.	Mod
Hoffman et al, 2016 <sup>526</sup>	N=200 (87 female) 50-90 years old community-dwelling persons with mild- moderate Alzheimer's disease according to NINDS-ADRDA criteria and MMSE >19.	2,3	3 weekly group exercise sessions supervised by a Physiotherapist over 16 weeks. The first 4 weeks leg strengthening exercises. The remaining 12 weeks: moderate to high-intensity aerobic exercise (70–80% of maximal HR) on an ergometer bicycle, cross trainer, and treadmill. Control: Usual care (no exercise).	The 12-item Neuropsychiatric Inventory (NPI- 12).	Compared to the control group, the exercise group showed improved (decreased) scores on the NPI's Sleep and Night-time behavioural change components at the end of the intervention period.	Low
Kumar et al, 2014 <sup>520</sup>	N=77 (15 female) ≥ 60 years old (mean age 69) with mild /moderate dementia based on DSM-IV criteria and neurological evaluation: MMSE ≤23, confirmation by neurological exam, Clinical Dementia Rating Scale and Blessed Dementia Rating Scale.	2	Ten sessions of 20-30 minutes of exercise and structured physical activity over 5 weeks delivered by occupational therapists. Control: standard activities without exercise or structured physical activity.	WHOQOL-BREF, which includes sleep and rest under the physical health and level of independence domain.	Participants in the exercise group reported improved sleep quality and decreased daytime sleepiness, compared to the control group.	Mod
Landi et al, 2004 <sup>521</sup>	N=30 (15 female) nursing home-dwelling older adults with Alzheimer's' disease and/or dementia according to DSM-IIIR criteria. The mean age or age range were not reported in the paper.	2	Exercise: moderate- intensity exercise program (combination of aerobic or endurance activities, strength training, balance, and flexibility training). Control: usual care, with no added exercise or physical activity.	Sleep data for participants collected with The Minimum Data Set Instrument for Nursing Homes (MDS-NH) for the baseline and 4 week follow up.	Participants in the exercise group had a statistically significant reduction in sleep disorders at the 4-week follow up. *Note: the units of measurement for outcome variables are not included in the paper, making it impossible to identify what units were measured (e.g. %, frequency, number of occurrences, etc).	High
McCurry et al, 2011 <sup>459</sup>	N=132 (73 female) (mean age 81.7) persons with Alzheimer's Disease (medical records) and two or more sleep problems occurring several times a week, measured with the 7-item Sleep Disorders Inventory (SDI) <sup>509</sup> .	1	Exercise: 30 minutes of continuous walking daily over 2 months. Control: contact control (no exercise), light exposure group, walking and light group (not included in this meta- analysis).	Wrist actigraphy and caregiver ratings of participant sleep quality on the Sleep Disorders Inventory (SDI). <sup>509</sup> Baseline SDI: Exercise group: 1.0 (SD 0.3). Control 0.8 (SD 0.2). >69% all participants had	Participants in the walking group had moderate effect size improvements in total sleep time (30.80 min, 95%Cl -23.94, 85.54), higher sleep efficiency (1.00 95%Cl:-6.01, 8.01), and fewer (but not statistically significant) night- time awakenings (-0.80, 95%Cl: - 5.67, 4.07) compared to control group. Significant differences remained after adjustment for participant age, sex, depression, comorbidity, cognitive impairment, and sleep apnoea. No significant improvements seen on the SDI.	Low

				sleep problems at baseline.		
Nascime nto et al, 2014 <sup>516</sup>	N=35 (19 female) Mean age 76.8 ± 6.8 persons with Alzheimer's Disease diagnosed according to DSM-IV TR and ADRDA criteria and mild- moderate dementia ion the Clinical Dementia Rating (CDR).	2	Exercise: 60 minutes of moderate-intensity (60- 80% HRmax) resistance, and aerobic exercise one day per week for 6 months. Control: no exercise, usual care.	Mini-Sleep Questionnaire (MSQ) scores. Baseline MSQ: Exercise: 26.7 (SD 4.1) Control: 20.2 (SD 4.6)	Compared to control group, participants in the exercise group had statistically significant improvement in sleep scores (reduced sleep disturbances) on the MSQ, (mean difference of -1.10, p=0.01.	Low
Namazi et al, 1995 <sup>449</sup>	N=22 (14 females) Mean age 80.73 (SD 5.83) institutional - dwelling persons with AD/ADRD according to NINDS-ADRDA criteria.	2	Exercise: 40 minutes of moderate intensity, multimodal aerobic exercise daily for 4 weeks. Control: social activity (no exercise)	Customized sleep log: sleeping soundly; resting (awake, but in bed), awakened: (just awakened by staff, noises, or other patients but still in bed), awake and out of bed doing normal things (walking, talking, sitting in room), awake and in the bathroom, or restless, for 12 hours per night over 4 weeks.	Compared to the control group, the exercise group showed a greater increase in "sleeping soundly" (25% increase, mean difference of 530.00 episodes 95%CI:278.7, 781.3) after the intervention.	Mod
Öhman et al, 2017 <sup>522</sup> 522	n=210 (81 females) 65 years old or older, mean age 77.8 (5.2) Community dwelling persons with AD/ADRD according to NINDS- ADRDA criteria and evaluated by a geriatrician or neurologist.	2	Exercise: 60 mins, 2 days per week over 12 months. Two exercise groups: a. Group-based: aerobic and strength exercise, balance training. B. Individual/home- exercise group: aerobic exercises (Nordic walking. exercise bike), strength and balance training. Control: usual care and health education.	The Neuropsychiatric Inventory (NPI): sleeping problems item. Baseline: Exercise group 0.96 (2SD .38) Control: 0.97 (SD 2.50)	Compared to the control group, participants in the exercise intervention did not show statistically significant improvements in sleep on the NPI.	Low
Richards et al, 2011 <sup>441</sup>	N=193 (116 female) Mean age 81.8 ± 8.1 Nursing home and assisted living-dwelling persons with dementia and/or AD and MMSE 4 or greater (mean MMSE 19.8, range 4-28).	3	Exercise group: 3 days per week of high- intensity resistance strength training and 2 days of walking for 45 minutes over 7 weeks. Control: usual care or social activity with no exercise .	Portable (in home) polysomnograph y (PSG) for 2 nights at baseline and 2 nights at 7 weeks (post intervention). Baseline AHI: Exercise group 16.2, (SD 14.6) Control 18.8 (SD 18.3)	Compared to the control group, the exercise group : Increased total sleep time of 23.7 min (MD 25.10 min, 95%CI: 21.99, 28.21), improved sleep efficiency (MD 6.80, 95%CI 6.18, 7.42), increased NREM sleep (9.30 min, 95% CI: 6.08,12.52) and REM sleep (15.80 min, 95% CI:14.37, 17.23) Sleep onset latency increased in the exercise group compared to the control (MD 8.80 min 95% CI: 6.67, 10.93).	Low
Stella et al, 2011 <sup>523</sup>	N=32 (20 female) Mean age 77.8 (5.8) Sedentary community- dwelling persons with mild to moderate AD/ADRD according to NINDS-ADRDA criteria, evaluated by a	2	Exercise: moderate- intensity aerobic exercise for 60 minutes, three times per week on non-consecutive days over 6 months .	NPI Sleep disturbance mean at baseline: Ex group 2.8 (SD 4.2)	Compared to the control group, the exercise group had statistically significantly greater reduction in sleep disturbances on the NPI, mean difference -2.4, 95%CI: - 5.20, -0.4).	Mod

clinician and diagnosis also reported by their caregivers.	Control: Usual care, non-exercise group.	Control 4.4 (5.6)	

**Table 2:** Exercise interventions for sleep in persons with dementia, AD/ADRD

### Meta-analyses

In total, 13 papers reported continuous data for sleep outcomes and were eligible for metaanalysis<sup>377,397,525,527,408,421,425,441,459,517–519</sup>. Of the remaining 7 papers, one was at high risk of bias and was excluded from meta-analysis<sup>521</sup>. One did not report data with sufficient detail to allow meta-analysis, only displaying sleep outcome results visually on a graph (we were unable to determine the actual values from the graph)<sup>526</sup>. The remaining 5 papers reported custom sleep metrics that could not be pooled with data from other papers for metaanalysis<sup>449</sup>, or used sleep outcome measures for which less than 2 papers reported outcomes<sup>516,520,522,523</sup>.

Seven studies, representing the experiences of 1986 participants with mild cognitive impairments or MCI in exercise and non-exercise interventions were eligible for metaanalysis (figure 3). Exercise interventions had a statistically significant beneficial effect on PSQI assessed sleep quality in persons with mild cognitive impairments and MCI (-1.54, 95%CI:-2.23,-.86).

				Mean Difference	Mean Differe	nce
Study or Subgroup	Mean Difference	SE	Weight	IV, Random, 95% CI	IV, Random, 95	»% CI
Badelmi 2009	-9.91	2.5891	1.7%	-9.91 [-14.98, -4.84]		
Wang 2020	-2.45	0.5403	14.9%	-2.45 [-3.51, -1.39]		
Karydaki 2017	-1.9	1.0761	7.2%	-1.90 [-4.01, 0.21]		
ChanYu 2016	-1.8	0.7961	10.5%	-1.80 [-3.36, -0.24]		
Song 2023	-1.74	0.8521	9.7%	-1.74 [-3.41, -0.07]		
Song 2019	-1.257	0.1796	21.8%	-1.26 [-1.61, -0.90]	-	
Choi 2018	-1	0.6332	13.1%	-1.00 [-2.24, 0.24]		
Fragoso 2015	-0.53	0.2306	21.1%	-0.53 [-0.98, -0.08]	•	
Total (95% CI)			100.0%	-1.54 [-2.23, -0.86]	•	
Heterogeneity: Tau <sup>2</sup> =	= 0.52; Chi <sup>2</sup> = 26.50		- <u>+</u>			
Test for overall effect: $Z = 4.43$ (P < 0.00001)					Favours [exercise] Favo	ours [control]

Figure 3: Forest plot, PSQI in adults with MCI.

# Objectively measured sleep

Five studies, representing the experiences of 446 persons with MCI or AD/ADRD, assessed sleep with actigraphy (4 studies)<sup>517,518,529,530</sup> or PSG (1 study)<sup>441</sup>, and were eligible for metaanalysis (figure 4). Only total sleep time and sleep efficiency were reported by more than two studies. Exercise interventions had a statistically significant beneficial effect on participants' total sleep time (increased by 34 minutes), and sleep efficiency (improved by 6%).

				Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
15.5.1 Total Sleep Ti	ime (min)				
Li 2021	23.6	21.429	4.9%	23.60 [-18.40, 65.60]	
McCurry 2011	35	5.1391	85.7%	35.00 [24.93, 45.07]	
Richards 2011	25.1	15.5068	9.4%	25.10 [-5.29, 55.49]	
Subtotal (95% CI)			100.0%	33.51 [24.18, 42.83]	•
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>2</sup> = 0.59,	df = 2 (P	= 0.74); I	$^{2} = 0\%$	
Test for overall effect	:: Z = 7.04 (P < 0.00	0001)			
15.5.2 Sleep efficien	су (%)				
Alessi 1999	10.7	1.7569	22.5%	10.70 [7.26, 14.14]	+
Eggermont 2010	-1.78	3.7753	12.2%	-1.78 [-9.18, 5.62]	<b>_</b>
Li 2021	9.9	2.449	18.4%	9.90 [5.10, 14.70]	
McCurry 2011	4.9	0.4761	28.8%	4.90 [3.97, 5.83]	
Richards 2011	5.4	2.509	18.1%	5.40 [0.48, 10.32]	
Subtotal (95% CI)			100.0%	6.40 [3.03, 9.78]	●
Heterogeneity: Tau <sup>2</sup> =	= 10.09; Chi <sup>2</sup> = 17.1	19, df = 4	(P = 0.00)	2); $I^2 = 77\%$	
Test for overall effect	Z = 3.72 (P = 0.00)	02)			
				-	
					Favours [control] Favours [exercise]

Figure 4: Forest plot, objective sleep measures.

Heterogeneity

Substantial heterogeneity was found in pooled meta-analyses of PSQI-assessed sleep and pooled sleep efficiency, while no heterogeneity for total sleep time. The heterogeneity found for PSQI assessed sleep and sleep efficiency may be influenced by clinical variability and lack of uniformity among exercise interventions and samples. Sensitivity analyses did not reveal any one study contributing significant heterogeneity in either case.

No one study, when removed during sensitivity analysis, significantly modified the pooled treatment effect estimates for the effect of exercise interventions and PSQI-assessed sleep quality in figure 3. Only the study by Eggermont (2010)<sup>518</sup>, when removed, modified the effect of exercise on sleep efficiency, which increased to 7.52%, 95% CI:4.08, 10.95. Heterogeneity was unchanged, however. Eggermont did not find a beneficial effect on night-time restlessness or other actigraphy-measures sleep parameters after a 6 week, low-intensity exercise intervention. However, it was possible that participants may not have had sufficient sleep disturbances at baseline to show a treatment-effect, and the timing of the physical activity interventions also varied frequently, both of which may have influenced the study results<sup>212</sup>.

#### DISCUSSION

This systematic review investigated the effectiveness of exercise interventions targeting sleep in older adults with MCI or AD/ADRD. To the best of our knowledge, this is the first systematic review and meta-analysis of exercise interventions targeting sleep in this population. It represents the experiences of 3278 persons with MCI or AD/ADRD across 20 interventional studies. We found moderate to high quality evidence for the beneficial effects of exercise on self-reported and objectively measured sleep in older adults with cognitive impairment and persons with AD/ADRD.

Exercise interventions resulted in statistically significant improvements in subjective sleep quality in persons with mild to moderate cognitive impairment (PSQI -1.54, 95% CI:-2.23,-..86)., as well as improved sleep efficiency and total sleep time (figures 1-2), emphasising the beneficial effects of exercise for sleep in this population. Exercise of any intensity, from low to high, improved sleep quality in older adults with cognitive impairment. This is significant, given that persons with cognitive impairment of AD/ADRD may also experience physical deconditioning or motor difficulties, and low and moderate intensity exercise may be more feasible<sup>531</sup>.

A variety of potential mechanisms underlying the effects of exercise on sleep have been proposed, ranging from exercise-induced reduction in systemic inflammation, changes in neurotransmitters regulating sleep, increased growth hormone and brain-derived neurotrophic factor, changes in heart rate variability, body temperature, autonomic function, and entrainment of circadian rhythms and sleep-wake cycles<sup>224,241,243</sup>. Exercise interventions in a generally sedentary population of persons with cognitive impairment may also increase

exposure to other factors associated with improved sleep, such as daylight, social activity, and decreased daytime napping<sup>4,332,500,501</sup>. These factors could not be accounted for in this systematic review but offer important targets for future research.

#### Alzheimer's Disease and Related Dementias (AD/ADRD)

Fewer controlled studies investigated the effects of exercise on sleep in persons diagnosed with AD/ADRD. However, the available studies did find improved sleep quality and quantity as a result of exercise in persons with AD/ADRD. Mounting evidence suggests that poor sleep influences disease progression and cognitive decline in persons with AD/ADRD<sup>6,7,9,99</sup>. Exercise can improve sleep and may have potential to attenuate cognitive decline and neurodegeneration in AD/ADRD. A larger body of RCTs has investigated exercise interventions targeting cognition in persons with AD/ADRD, finding that increased physical activity and exercise improve cognitive function and may delay cognitive decline<sup>532</sup>. The mediating role of sleep in these effects has been underexplored, however.

Much else remains unknown about the effects of exercise on sleep in persons with AD/ADRD. For example, only one RCT investigated the effects exercise on PSG measured sleep outcomes<sup>441</sup>. No RCTs investigated the effects of exercise on sleep microarchitecture such as NREM slow-wave activity or sleep spindles. These have also been under-investigated in studies of exercise targeting sleep in healthy older adults. This creates important evidence gaps, given that multiple facets of sleep neurophysiology are strongly associated with cognitive performance in older adults<sup>7</sup>. Better understanding of the mechanisms underpinning the effects of exercise on brain processes during sleep could lead to more

effective exercise interventions aimed at maintaining or improving the memory functions of sleep<sup>240</sup>. This may be of particular importance for older adults, persons at early stages of cognitive decline, and those at risk of AD/ADRD and their caregivers.

#### Recommendations for future research

Our systematic review highlights important areas in need of further investigation. Given the many physical and mental health benefits associated with both improved physical activity and improved sleep, these areas for future research are critical for clinicians, policymakers, and the public to make informed choices about exercise interventions targeting improved sleep, activity, and quality of life in older adults with cognitive impairment.

For example, the optimal time of day to perform exercise or minimum exercise dosage required to influence sleep in older adults remains uncertain. As a result, the optimal amount of exercise needed to improve sleep in older adults with cognitive impairments, or older adults generally, cannot be determined with certainty with currently available evidence. Previous systematic reviews and meta-analysis of exercise interventions targeting cognition in persons with MCI or dementia have found that multicomponent exercise combining aerobic and resistance training tends to be the most effective in protecting global cognition and executive function in persons with MCI, while resistance training is associated with slowing the progression of cognitive decline<sup>533</sup>. Meta-analyses of exercise interventions targeting sleep in older adults report larger treatment effects for moderate intensity exercise (exercise at 60% of maximal oxygen uptake, VO2max, or maximal heart rate for age) on insomnia (d=0.87, 95%CI:1.68,0.06)<sup>284</sup>, and moderate-intensity aerobic exercise has been associated with greater increases in cognition and memory than light or vigorous exercise<sup>231–</sup>

<sup>233</sup>. The greatest benefits for sleep quality in older adults have been reported with exercise programs combining moderate intensity aerobic and resistive exercise training<sup>534</sup>. However, the optimal exercise modality for influencing sleep in persons with MCI or AD/ADRD cannot be determined from the evidence we reviewed.

The most influential moderators of the relationships between exercise and sleep in older adults, such as age, sex, gender, or disease progression also remain unclear. For example, none of the studies we reviewed reported sleep outcomes for males and females separately, however, despite 63% of the participants in the studies included in our systematic review being female. Biological sex has been shown to contribute to variations in sleep<sup>71,535</sup>, risk of dementia<sup>536</sup> and Alzheimer's disease<sup>537,538</sup>, physiological responses to exercise<sup>357</sup>, and effects of exercise on cognitive outcomes in older adults.<sup>539</sup> Meta-analyses have found higher rates of insomnia  $^{71,462}$ , poor memory performance,  $^{71,72}$  and prevalence of dementia  $^{540}$  and AD  $^{537}$ among females than males. Sex differences have also been found in various risk factors for AD and dementia<sup>536,541</sup>, and gender has been shown to influence the risk of cognitive decline or dementia<sup>538</sup>. Larger treatment effect sizes have also been reported for females than males in studies of exercise targeting cognition,<sup>539</sup> though less is known about sex differences in studies of exercise and sleep. Few studies have examined sex differences in the effectiveness of exercise interventions targeting sleep in older adults, though some evidence suggests exercise leads to greater self-reported measures of sleep quality in females than males.<sup>390</sup>

Sleep disturbances increase functional impairment and disease progression and negatively affect cognitive function in persons with AD/ADRD.<sup>99</sup> Exercise may improve sleep

disturbances and has potential to attenuate neurodegeneration in AD/ADRD. However, much is unknown about the effects of exercise on sleep in this population. For example, few RCTs have investigated the effects of exercise on PSG-measured sleep or sleep microarchitecture (e.g. slow wave activity<sup>7,212–215</sup>) in persons with AD/ADRD, to the best of our knowledge. Only one paper in this review included PSG-assessed sleep architecture, but it did not report sleep microarchitecture metrics<sup>441</sup>. This is represents an important knowledge-gap, given that Non-Rapid Eye Movement (NREM) slow-wave activity has been linked to memory consolidation in older adults <sup>7,48–50,212–215</sup>, and loss of normal non- rapid eye midmovement (Non-REM) sleep slow wave activity has been linked to cognitive impairment in older adults and pathophysiological changes in Alzheimer's disease<sup>33–35,48–50</sup>.

The effects of exercise on sleep architecture and microarchitecture in older adults has generally been under investigated. A larger body of RCTs has investigated exercise interventions targeting cognition in persons with AD/ADRD, finding that exercise improves cognitive function and may delay cognitive decline in persons with AD/ADRD.<sup>532</sup> The mediating role of sleep in these effects has been underexplored, however. Better understanding of the mechanisms underpinning exercise and sleep and their effects on brain processes during sleep could provide important information leading to more effective exercise interventions aimed at maintaining or improving the memory functions of sleep.<sup>240</sup> This may also be of particular importance for persons with cognitive decline or those at risk of AD/ADRD and their caregivers.

Additional research is also needed to understand the pathogenesis of sleep dysfunction in AD/ADRD to facilitate more effective treatments targeting sleep, including exercise. These

may include primary mechanisms, such as AD/ADRD related loss of neurons in the basal forebrain, hypothalamus, thalamus, midbrain, or circadian regulating areas, synucleinopathies, and orexinergic system dysfunction.<sup>6</sup> Secondary (indirect) mechanisms, may include poor sleep hygiene, co-morbidities, medication side effects, nocturia, and a variety of environmental factors.<sup>6</sup> Greater understanding of the interactions and effects of these mechanisms will facilitate identification of the most effective exercise therapies for sleep in persons with AD/ADRD.<sup>332</sup>

# Strengths and Limitations

Our review has several strengths. We followed a carefully developed protocol with comprehensive search strategies, including grey literature, and found studies in several languages and settings which had not previously been meta-analysed, to the best of our knowledge. However, publication bias could not be investigated in our review. Another strength is that we included only studies with low or moderate risk of bias in our metaanalyses, and 19 of the 20 studies we systematically reviewed were appraises as having either low (9 studies) or moderate (10 studies) risk of bias.

There are also limitations in this review. No studies examined key potential moderators of the relationship between exercise and sleep, such as sex, daytime napping, medication use, or the time-of-day participants exercised. It was also not possible to meta-analyse data for the effectiveness of exercise interventions on sleep in persons with AD/ADRD. The variability amongst available studies may reflect the complexities of administering exercise interventions with reduced cognitive capacity or frailty. The evidence-base for

exercise and sleep in older adults with cognitive impairment shares these limitations, including heterogeneic study designs, samples, and unanticipated confounding factors and inherent biases which may distort the magnitude of treatment effects and the results of meta-analyses<sup>346</sup>. We limited meta-analysis to controlled studies with low to moderate risk of bias to minimize these effects, and our eligibility criteria were designed to reduce potential confounding in our analyses.

Additionally, the majority of studies included in this systematic review utilised self-reported or caregiver-reported sleep outcome measures such as the PSQI, ISI, or the Sleep Disorders Inventory (SDI)<sup>509</sup>, rather than objective sleep measures such as PSG or actigraphy. Previous research with older adults with cognitive decline , reduced functional capacity, or insomnia has found that they are more likely to show greater discordance between self-reported (e.g. the PSQI or sleep diaries) and objective sleep measures<sup>542–544</sup>. Vulnerable older adults also either underestimate or overestimate their sleep efficiency when it is compared with objective wrist actigraphy or PSG<sup>542–544</sup>. Sleep diaries and subjective assessments may be also be challenging for older adults with cognitive impairments to complete, requiring caregiver assistance<sup>543</sup>.

Objective sleep measures such as actigraphy or the gold-standard PSG can offer more accurate and less biased measures of sleep and responses to exercise in older adults with MCI or AD/ADRD. Polysomnography also allows for assessment of the effects of exercise on sleep microarchitecture in persons with MCI or AD/ADRD. More research assessing the effects of exercise on sleep and sleep microarchitecture is needed and could help facilitate the development of effective interventions for sleep and cognitive decline in older adults and

person with MCI or AD/ADRD. However, in-lab PSG is expensive, can be burdensome and difficult to complete for persons in advance stages of AD/ADRD.<sup>545</sup> It can also be difficult to access<sup>546,547</sup>. Nevertheless, the continued development and feasibility of wearable, EEG headbands for in-home monitoring sleep and sleep neurophysiology offers important opportunities to overcome the difficulties of performing in-lab PSG with persons with AD/ADRD<sup>157</sup>.

Both subjective and objective sleep outcomes are important in understanding the effects of exercise on sleep in older adults with cognitive decline. Subjective measures provide valuable information about persons' perceived and experienced sleep outcomes<sup>544,548,549</sup>. Future research can supplement subjective sleep assessments with actigraphy to provide a more complete picture of sleep patterns and responses to exercise in older adults with MCI or AD/ADRD. The proliferation and continued development of wearable sleep devices also offers important opportunities to supplement self-reported sleep measures with objective data that can be obtained unobtrusively in older adults with MCI or AD/ADRD<sup>157,546,550</sup>.

# Implications for practice or policy

The results of our systematic review have important implications for clinical care, gerontology, public health and health promotion, given the many physical and mental health benefits associated with both improved exercise and improved sleep<sup>332,500,501</sup>. Sleep may be one of the most important modifiable risk factors for a range of health conditions, including cognitive decline and the progression of AD/ADRD<sup>6,77</sup>. The number of people with AD/ADRD

is expected to triple to more than 132 million by 2050, with the greatest increase expected in low and middle-income countries<sup>82,83</sup>. This will present profound challenges for families, communities, and societies in resource-constrained settings<sup>82,83</sup>. With ageing, increasingly sedentary populations and growing incidence of AD/ADRD, the need for sustainable, accessible, and effective interventions, like exercise, for both poor sleep and AD/ADRD is pressing.

Exercise is a widely accessible, cost-effective intervention for sleep difficulties. It is also associated with a range of benefits for cognitive performance, health and well-being, and quality of life in older adults<sup>227</sup>. Exercise interventions may also be used to target lifestyle factors and health conditions associated with increased risk of poor sleep or cognitive decline and dementia. For example, poor cardiometabolic health, including hypertension and diabetes, obstructive sleep apnoea, and depression each increase the risk of poor sleep or cognitive decline and dementia in older adults<sup>551,552</sup>. Exercise has been shown to be an effective adjuvant treatment for these conditions and other health and lifestyle factors influencing health outcomes in older adults<sup>553,554</sup>. Regular exercise can contribute to the management of cardiovascular and lifestyle risk factors and help reduce the risk of cognitive decline and dementia in older adults<sup>552,555</sup>.

Exercise may also be an important complement to other therapeutic interventions for poor sleep in persons with, or at increased risk of, AD/ADRD<sup>555,556</sup>. For example, it is now recommended as an adjunct to cognitive behavioural treatment for insomnia (CBTi), the first-line treatment for insomnia.<sup>218,219</sup> Available evidence also suggests that multimodal

interventions that include the exercise are effective from both poor sleep and functional and cognitive decline in older adults<sup>557–560</sup>. Promoting increased exercise, improved sleep, and other lifestyle changes in older adults in the presymptomatic and prodromal stages of dementia has the potential to delay the progression of dementia in up to one third of cases worldwide<sup>555</sup>.

# Conclusion

This systematic review include 20 studies examining the effectiveness of exercise interventions targeting sleep in older adults with MCI or AD/ADRD. We found moderate to high quality evidence for the beneficial effects of exercise on sleep in older adults with cognitive impairment and AD/ADRD. The results of our systematic review support the development and dissemination of effective exercise interventions for sleep difficulties in older adults. We found that exercise of any intensity (low, moderate, or high) and a range of frequencies and duration can improve subjectively and objectively measured sleep in this population. This has important implications for clinical care and public health. Improving sleep through exercise may support cognition and memory functions in older persons with MCI or AD/ADRD and also support secondary prevention of sleep-related health problems. Given our findings and previous research showing that exercise is also associated with a range of benefits for physical and mental health, clinicians may consider adding exercise as an effective intervention or adjuvant strategy for improving sleep in older persons with cognitive impairment or AD/ADR.

# SUPPLEMENTARY INFORMATION

Supplementary Information is available for this paper.

# AUTHOR CONTRIBUTIONS

AP: Development of the protocol, systematic review and meta-analysis, literature searches, data collection, risk of bias assessments, data analyses, data interpretation, write-up of review.

EF: Development of the systematic review, literature searches, risk of bias assessments,

interpretation, paper review, and reviewing before submission.

MM: Development of the systematic review, data interpretation, paper review, and reviewing before submission.

TDV: Development of the systematic review, data interpretation, paper review, and reviewing before submission.

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### (Supplementary materials can be found in appendix IV of this thesis)
# Chapter VI: Discussion and conclusions

# **Chapter Summary**

In this chapter, the aims and objectives achieved, insights gained, and strengths and limitations of this thesis are discussed. Future research directions and opportunities arising from this thesis are also presented.



This thesis investigated the links between sleep, cognitive decline, and exercise interventions in older adults and persons with AD. It addressed several important knowledge gaps for the associations between sleep microarchitecture, biomarkers of neurodegeneration and neuroinflammation, and cognition in Alzheimer's disease (chapters II-III). It also critically appraised and meta-analysed the evidence for exercise interventions targeting sleep in older adults, including those with MCI and AD. It yielded important new insights about their effectiveness and optimal parameters to influence sleep. The findings of this thesis are important in the context of clinical care of persons with AD and for preserving brain-health and cognition in older adults. They also raise new questions about the relationships between sleep, exercise, and cognition with implications for sleep research and gerontology.

#### Aims achieved and their implications: Aims I-III

There has been growing interest in the roles of sleep in cognition, brain-health, and neurodegeneration in older adults<sup>6</sup>. Nevertheless, important evidence gaps in our understanding of the role of sleep physiology in cognition and brain-health remain. For example, associations between NREM sleep microarchitecture, cognitive performance, and biomarkers of neurodegeneration had been explpred extensively in healthy older adults <sup>7,32,40,50,51,151,152,173,314</sup> However, these had not been investigated extensively in persons with AD, creating important knowlege gaps for the neural mechanisms linking sleep to brain-health in this population.

This thesis helps to address these gaps. It includes one of the few studies to have investigated NREM sleep spindle and slow oscillation activity, cognitive performance, and biomarkers of neurodegeneration in older adults with mild-to-moderate Alzheimer's disease<sup>285</sup>. In it, we hypothesised that spindle and SO activity at baseline would predict baseline AD fluid biomarker levels and cognitive performance over time in AD. Our findings confirmed this hypothesis. Sleep spindle and SO activity at baseline predicted key biomarkers for neurodegeneration and neuroinflammation in AD. Spindle and SO activity also predicted cognitive performance over three years and mental health from baseline to 12 months, even after adjusting for variables such as age, sex, and AHI.

This thesis also expands our knowledge of the roles spindles may play in cognition, mental health, and brain-health in Alzheimer's disease. Few previous studies had investigated the association between spindles, Aβ42, or tau accumulation in this population<sup>34,35,135,136,143,171,172,313</sup>. A larger body of evidence examined associations between SO activity and AD<sup>33,561</sup>. We found a number of significant associations between spindle activity, Aβ42, tau, and the other biomarkers we investigated. In fact, we found that spindle activity predicted these and cognitive performance more consistently than SO activity. We also found important associations between spindle power and spindle duration, biomarkers, and cognition in AD. The majority of research had investigated the effects of spindle density, but not duration or power, on cognition or disease progression in AD<sup>32</sup>.

This thesis yielded a number of novel findings about the relationships between sleep physiology and AD progression. Many of the associations we found between spindle characteristics, CSF Aβ42 and tau, and cognition in persons with AD were previously unreported, to the best of our knowledge. We also found previously unreported associations between spindle and SO characteristics and other biomarkers of neuroinflammation and neurodegeneration highly linked to AD (NfL, YKI-40, NG-36, NfL/Aβ42, YKI-40/Aβ42). These are important findings, given that these biomarkers have been linked with longitudinal amyloid accumulation and cognitive decline in older adults<sup>323</sup>. Indeed, we found that these biomarkers not only predicted poorer cognitive performance (higher ADAS-cog and lower MMSE scores). We also found that they predicted poorer mental health and significantly increased neuropsychiatric symptom severity (NPI scores from baseline to 12 months) in our sample of persons with mild-to-moderate AD. This is an important finding, as the rates of

long-term care placements rise as neuropsychiatric symptom (e.g. agitation, aggression, nighttime behavioral disturbances) severity increases among persons with AD<sup>562,563</sup>.

We also found previously unreported moderating and mediating roles between spindle and SO activity, these biomarkers, and cognition in AD. These findings generate new insights into the complex interplay between sleep physiology, brain-health, and cognition in the context of AD and raise important questions about whether similar interplays exist in other neurodegenerative disorders such as Parkinson's Disease<sup>564,565</sup>. They also support a promising role for NREM spindle and SO activity, and NfL, NG-36, and YKL-40 as complimentary, non-invasive markers of neurodegeneration, in addition to A $\beta$ 42 and tau, and potential therapeutic targets for sleep-related interventions designed to monitor or slow AD symptom progression.

The findings in chapters II-III are also important in light of the increasing development of interventions such as transcranial direct current, transcranial magnetic stimulation (rTMS) or acoustic stimulation targeting SWA in older adults<sup>566</sup>. These interventions have also begun to yield promising results on cognition in persons with MCI or AD<sup>333,566,566–568</sup>. Lifestyle-based interventions such as exercise and increased physical activity can also be harnessed to enhance sleep and SWA in older adults and persons with AD, as was investigated in chapters IV and V (AIM IV).

### Aims achieved and their implications: AIM IV

This thesis also helps to address knowledge gaps about the effectiveness of exercise interventions for improving sleep in older adults and persons with MCI or AD. It includes what are, to the best of our knowledge, both the largest meta-analysis of interventional studies of exercise and sleep in healthy older adults (chapter IV), and the first systematic review and meta-analysis of exercise interventions targeting sleep in person with MCI or AD (chapter V)<sup>220</sup>.

The results of both meta-analyses show that exercise can be an effective intervention for improving sleep in older adults, including older adults with sleep difficulties and persons with AD and MCI. They also addressed knowledge gaps about the dose-response relationship between exercise intensity and improvements in sleep in older adults. This is an important finding, given that there was previously a lack of consensus for the most effective exercise intensity for improving seep in older adults<sup>212</sup>.

It is notable that our meta-analyses found that even low intensity exercise can improve older adults' sleep. In fact, low and moderate intensity exercises of any modality were the most effective at improving sleep in older adults as well as in those with MCI or AD. This is a particularly important finding in the context of ageing, increasingly sedentary populations with a higher prevalence of chronic diseases such as osteoarthritis, obesity, or cardiovascular disease, for whom higher intensity exercises may be more difficult and less acceptable. It also has important implications for persons with MCI or AD, for whom lower-intensity exercises of a variety of modes may be more feasible than higher intensity exercise<sup>531</sup>.

Our meta-analyses also found moderate-to-high-quality evidence for the beneficial effects of exercise on objectively assessed (actigraphy or polysomnography) sleep outcomes. These included and sleep efficiency and wake after sleep onset, which are strongly linked to increase risk of dementia<sup>569</sup>. We also found that exercise interventions yield statistically significant improvement in slow-wave sleep<sup>220</sup>. Exercise may influence SWS through homeostatic regulation of body temperature, which increases during exercise but decreases during SWS<sup>224,243</sup>. A larger amount of SWS may be needed after exercise to maintain homeostasis<sup>224,243</sup>. Previous studies have reported increased EEG power during SWS in older adults after exercise<sup>245</sup>. This is an important finding, given the associations we also found between NREM sleep spindles, SO, AD biomarkers, and cognition in chapters II-III.

Our meta-analyses also spotlight a lack of research examining the effects of exercise interventions on sleep microarchitecture during NREM, particularly in persons with AD or other neurodegenerative disorders. Few studies have investigated the effects of exercise on NREM spindle or SO activity<sup>213</sup>. This is an important evidence gap that can be explored in future research. This, and other limitations and opportunities for future research on exercise and sleep are discussed extensively in chapters IV-V.

What is clear, however, is that exercise can play an important role in improving sleep in older adults. Exercise is also a widely accessible, highly adaptable, and sustainable intervention that can be performed by persons of almost any physical ability in most settings, inexpensively or cost-free. As populations age and the prevalence of lifestyle diseases grows, there will be increasing strain on healthcare resources and a growing need for sustainable and effective

interventions, like exercise, that can benefit sleep and aid secondary prevention of chronic diseases influenced by both physical inactivity and poor sleep<sup>477,570</sup>

## Strengths and limitations

The strengths and limitations of individual components of this thesis have been discussed in their respective chapters. Wider issues are briefly described here. The thesis has several strengths. It addresses important knowlege gaps in our understaing of the relationships between sleep, sleep physiology, brain-health, and cognition in AD and the effectiveness of exercises in interventions targetting sleep in older adults.

It also includes robust methodological, statistical, and analytical methods. The studies in chapters two and three of this thesis anaylsed data that was collected prospectively, in a single centre with expertise in AD/ADRD, using standardised procedures and polysomnography in a sex-balanced cohort of persons with high A $\beta$ 42 burden and clinical symptoms consistent with mild-to-moderate AD. This helped to overcome limitations typically reported in studies of sleep and AD, including lack of objectively measured sleep outcomes and imbalances in participant characteristics<sup>571–573</sup>. We also had comprehensive data for cognition capturing a range of cognitive domains over a three year period. These novel features of this thesis add to the robustness of its findings.

Nevertheless, data from observational studies cannot imply causal relationships, and we did not have a comparison group of healthy older adults in the study in chapters II and III. However, the cohort study sought to follow the cognitive evolution of persons with AD, and

associations between sleep, biomarkers, and cognition in healthy older adults have been explored extensively<sup>7,51,173</sup>. Longitudinal studies with persons with AD also carry unique challenges and expenses and can be difficult to conduct, potentially limiting their size and scope. Future prospective cohort studies with persons with AD could address this through multicentre collaborations and sharing of resources. They may also be able to harness innovative clinical trials methods such as use of historical (existing) data previously collected in cohorts of healthy older adults to serve as a data-based control group. These have been explored extensively in pharmaceutical trials, observational studies in medicine, and in realworld evidence studies in healthcare<sup>574–577</sup>. The benefits and limitations of these methods are beyond the scope of this thesis, but they offer intriguing possibilities to expand on the data and knowledge gained in studies such as ours<sup>574–577</sup>.

Another strength is that we followed gold-standard recommendations for the conduct of systematic reviews and meta-analyses from the Cochrane Collaboration in chapters IV-V. We also avoided commonly reported limitations in these reviews, including publication bias, by not limiting our literature searches by date of publication or language. Indeed, we found and reviewed a large number of studies in several languages and settings which had not been previously meta-analysed, to the best of our knowledge. We also used advanced statistical methods such as meta-regression to further investigate associations between age, exercise intervention characteristics, and risk of bias on sleep outcomes<sup>54,212,359</sup>.Our meta-analyses are also among the first to report prediction intervals, in addition to confidence intervals, in studies of intervention for sleep in older adults, allowing us to explore the potential for harm or clinical benefit in future studies of exercise interventions targeting sleep in older adults.<sup>473</sup>

The greater body of evidence for exercise interventions in older adults has limitations that our analyses could not overcome, however. The reporting of intervention details in clinical trials of complex interventions like exercise, is often poor, despite the availability of a number of checklists and reporting guidelines such as the Template for Intervention Description and Replication (TIDieR<sup>578</sup>), or Consensus on Exercise Reporting Template (CERT<sup>579</sup>) that were developed to improve the reporting and reproducibility of exercise interventions in clinical trial publications<sup>580–583</sup>. This makes it difficult to assess the effects of potential moderators of sleep outcomes after exercise interventions, such as the time of day participants exercise, use of equipment or instructor guidance, cointerventions, characteristics of control interventions, or the influence of other exercise program characteristics<sup>580</sup>. These are limitations shared by all meta-analyses of exercise interventions, however, as they rely on the description of the interventions in trial publications and reported data for meta-analysis.

The other benefits associated with exercise, including improved depression, mood, agitation, and cognition, might also influence the effects of exercise on sleep we found in our metaanalyses<sup>227,230,231,281,329–332</sup>. There are bidirectional relationships between mood, depression, agitation, cognition, and sleep<sup>584–587</sup>. The effects of exercise on these have also been investigated extensively previously in older adults and persons with AD, with moderate-to-high quality evidence supporting the effectiveness of exercise for improving them in older adults and persons with AD<sup>588–591</sup>. These relationships cannot be explored through meta-analysis alone, but provide important avenues for future research into the interactions between exercise, mental health, and sleep in older adults and AD.

#### Opportunities for future research arising from this thesis

A number of opportunities for future research arise from this thesis. For example, future research can build on the results of chapters II and III and investigate the predictive associations of spindles and SO with AD biomarkers or risk of accelerated disease progression in persons in the **prodromal stages of AD**. This research could also further establish whether spindle and SO activity or the biomarkers of neuroinflammation and neurodegeneration (NfL, YKL-40, NG-36) we investigated can act as biomarkers of susceptibility to neurodegeneration in cognitively unimpaired persons at higher risk of AD due to increased amyloid or APOE4 or those in prodromal AD<sup>111,117,120,325</sup>. As that there are currently few disease-modifying treatments for AD, it is increasingly important to identify persons for treatment before their disease burden is too high<sup>174</sup>.

The associations between sleep microarchitecture and other biomarkers associated with sleep and brain-health can also yield important insights and therapeutic targets for poor sleep and cognitive decline in AD or other neurodegenerative disorders. For example, **Orexin-A** is a key sleep-wake cycle regulator. Cerebrospinal fluid orexin levels are higher in MCI and AD and associated with sleep deterioration, increasing risk of cognitive decline AD progression<sup>315,592–594</sup>. Dual orexin receptor antagonists (DORA) improve sleep in insomnia and AD may reduce tau and Aβ deposition in older adults<sup>182,592–595</sup>.

However, little research has investigated associations between DORA, sleep microarchitecture, cognition, or mental health in AD<sup>596</sup>. Investigating these might also yield insights into sleep microarchitecture features that predict response to treatment or vulnerabilities associated with poor response to treatment of insomnia with DORA in AD. Dang-Vu et al. (2017) previously showed that lower spindle density at pre-treatment

predicted lower response to treatment with CBTi at 12 months in persons with insomnia<sup>597</sup>. The associations between sleep spindles, SO, orexin, cognition and mental health are currently being investigated by this author in the next stage of the program of research in chapters II and III of this thesis.

Sex-based differences in sleep microarchitecture in AD are also an area in need of further research. An intriguing finding in chapters II and III was the sex-based differences in spindle and SO characteristics in our sample of persons with AD. Females had statistically significantly higher spindle density, particularly in fast spindles (>12 Hz), higher spindle power, and higher median peak spindle frequency (11.24hz) than males. Previous research in healthy middle aged and older adults has found higher fast-spindle density and greater power in the high-frequency portion of the sigma band (13–15 Hz) in healthy older females than males<sup>148</sup>. Sexbased differences in spindle and SO activity have not been investigated extensively in AD, however.

Previous research has also found that males experience greater disruption in NREM sleep than females, with males over 70 years of age experiencing up to 50% greater reduction in slow wave sleep<sup>316,317</sup>. Females also report better sleep duration, efficiency, and quality than males<sup>304</sup>. This could lead to greater alterations in spindle activity in males than females. Indeed, we found that males in our sample had statistically longer NREM1 sleep duration and shorter NREM3 sleep duration than females.

It is also interesting that there were no statistically significant differences between males and females in other variables that could affect spindle activity, such as NREM2 sleep duration,

total sleep time, AHI, amyloid positivity, CSF Aβ42 or tau, or baseline cognition. The reasons for the differences in spindle activity we found between males and females are likely complex and cannot easily be addressed within our data. They may be related to sex-based differences in the development and progression of AD and its effect on sleep physiology, but these have been under-investigated in AD<sup>318</sup>. Similarly, sex-based differences were underexplored and underreported in the studies of exercise interventions and sleep in chapters IV and V, creating a gap in our understanding of the influence of biological sex on the effects of exercise on sleep in older adults.

Additionally, the effects of exercise on either sleep or exercise on cognition have been studied extensively. However, the **effects of exercise on both sleep** *and* **cognition** in older adults with or without insomnia has not been investigated. Exercise and sleep can influence cognition through independent mechanisms,<sup>598</sup> but recent research has shown that exercise and sleep may also act synergistically to benefit cognition and memory.<sup>222,234,235</sup> Evidence for such an interplay is lacking in older adults however, especially in those with insomnia.

Future research may investigate the combined effects of exercise and sleep on cognition in older adults with insomnia and the neurophysiological (sleep architecture) and biological (biomarker) mechanisms through which exercise affects sleep and cognition in older adults. Understanding these mechanisms is vital for designing effective treatments to reduce the risk of cognitive decline in older adults.<sup>240</sup> It will also provide new insights into the mechanisms by which healthy lifestyle factors such as exercise and sleep influence cognition, aiding the development of accessible approaches to promote cognition and brain health in older adults.

Finally, future research may also investigate the effectiveness of **exercise as an adjunct intervention to complement CBTi** in the treatment of insomnia in older adults. Treating insomnia may constitute a preventive approach for preserving brain health in older adults.<sup>177,599</sup> Cognitive behavioural therapy for insomnia is the first-line treatment for insomnia, but typically achieves success in only two-thirds of participants<sup>200,202,344</sup>. It is particularly effective for improving subjective, rather than objective (sleep architecture) sleep outcomes<sup>201</sup>. This has important implications, given the findings of our thesis (chapters II and III).

However, our meta-analyses show that exercise targets sleep physiology including slow-wave activity, creating opportunities to complement CBTi with exercise to boost its effects and achieve wider efficacy<sup>212–218</sup>. Exercise has also improves cognition in older adults, including those with  $AD^{588,589,591}$ . It has also been shown to decrease levels of biomarkers and cytokines associated with poor sleep, inflammation, and cognitive decline, including  $A\beta$ , and increase those linked to sleep, cognition and brain health<sup>246–252</sup>. This creates intriguing opportunities to investigate the combined effects of exercise and CBTi, or indeed exercise and other treatments for poor sleep, in the context of preserving or improving cognition and brain-health in older adults.

## Conclusions

In summary, the body of work contained in this thesis met its goals of adding new knowledge and addressing evidence gaps for the relationships between sleep microarchitecture, cognition, and brain health in older adults. It found important and previously unreported

associations, and both mediating and moderating relationships, between sleep spindles, slow oscillations, and biomarkers of neurodegeneration and neuroinflammation in mild-tomoderate AD. It also showed that sleep spindles and slow oscillations can predict cognition and mental health longitudinally in AD, highlighting the importance of sleep for both cognition and brain health and raising new questions about the role of sleep physiology in the progression of neurodegenerative disorders of ageing. It extends previous evidence showing that sleep may be one of the most important modifiable risk factors for functional and cognitive decline and dementia in older adults<sup>6,77</sup>.

This thesis sheds light on sleep microarchitecture as potential and novel therapeutic targets for delaying or slowing AD progression. It also showed that exercise can be an effective intervention to improve sleep in older adults, including those with MCI or AD, targeting aspects of sleep associated with cognitive decline, dementia, and AD. These findings can serve as a springboard for future research on sleep-based strategies to preserve brain health in older adults and delay the progression of AD symptoms, with considerable potential benefits for persons with AD, their caregivers, and communities<sup>9,163,176</sup>.

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### Appendices

#### Appendix I: Supplementary materials for chapter II

"Sleep spindles and slow oscillations predict cognition and biomarkers of neurodegeneration in mild to moderate Alzheimer's Disease."



ADAS: Alzheimer's Disease Assessment Scale, cognitive subscale MMSE: Mini-mental State Examination

**Supplementary material Figure S1:** Spindle duration at baseline predicts cognitive performance on the ADAS-cog and MMSE (margins plot)



MMSE: Mini-mental State Examination

**Supplementary material Figure S2:** Slow oscillation duration predicts MMSE at 24 and 36 months (margins plot)

Following page:

Supplemental table S1: Spindles, SO, biomarkers

| Image: constraint of the                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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<td>International<br/>matrix         International<br/>matrix         Internati</td> <td>Interface         Interface         <t< td=""><td>Image: constrained by the co</td><td>multiple         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010         0.010     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 0.437         0.111         0.035         0.437         0.011         0.447         0.011         0.447         0.011         0.035         0.417         0.013         0.417         0.013         0.417         0.013         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.114         0.015         0.015         0.015         0.015         0.015         0.015         0.015         0.015         0.015         0.015         0.015         0.015         0.015         0.015         0.015         0.015         0.015         0.015    
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                          | 1         0.00         0.03         0.03         0.00         0.047         0.011         0.031         6.4373         0.011         6.4573         0.011         6.4573         0.011         6.4573         0.011         6.4573         0.013         6.4573         0.013         6.4573         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013   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| 0         77136         53.20         0.03         51.41         61.42         0.101         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601         0.601     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0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011     
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        61.80116         61.80116         61.80116         61.80116         0.031         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.0311         0.03111         0.0311         0.0311 <td>1         77,13         5,5,2         0.03         414         432,7         0.03         414,7         5,5,13         0.031         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         1,173         1,173         1,173&lt;</td> <td>(i) (i) (i) (i) (i) (i) (i) (i) (i) (i)</td> <td>010         7.135         52.32         003         61.34         1.11         3.74         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115         63.115     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   43630         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391         0391        
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                              | 1         77,13         5,5,2         0.03         414         432,7         0.03         414,7         5,5,13         0.031         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173         6,173     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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Wetwerker<br>(sectore)         Cold         Cold </td <td>Interview         56.30         16.33         0.001         0.131         63.33         0.003         0.131         63.33         0.003         0.131         63.33         0.003         0.131         63.33         0.003         0.131         63.33         0.003         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013</td> <td>The function of the fun</td> <td>International consistent of the state in the st</td> <td>International constraints         55.42         13.33         0.001         14.33         85.43         13.35         0.001   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<td>The fields         56.34         13.33         0.00         10.01         3.311         8.816         0.000         0.011         3.016         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011        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                                                                                                                                                                                                                                                                                                                                                                                                           | (Functional state)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)         (1)33(1)        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0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014</td> <td>(Function)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)         (1000)     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        0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014</td>                                                                                                                                                                                                                                                                                                                                                                                                                         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0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014                              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                                                                                                              | (memory line)         3131         0.003         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              
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| 1000         0001         0011         0.001         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010         0010      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      7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.966371         7.967311         7.</td><td>1000         0011         0012         0011         0012         0011         001241         0011         001241         0011         001241         0011         001241         0011         001241         0011         001241         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0344         0300         0344         0300         0344         0300         0344         0300         0344         0300         0344         0344         0300         0344         0300         0344         0300         0344         0300         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         0344         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01344         01344                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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| Interview         94.05379         44.1058         0.033         7.61.613         18.04599         34.51         1.330         0.005         1.00         5.861         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         0.633         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| Interprete         1.13539         1.27343         0.53456         0.7301         0.27344         0.2741         0.53466         0.001         0.012         0.001         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         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| Multi-         0.775656         0.0001         0.323442         1.118339         0.0001         0.323442         1.118339         0.001         0.036         0.003         0.037         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         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| 1-135108         2.0615         -666378         3833164         -9.028         5.113         0.077         -19.049         0.933         -0.388         1.78         0.345           2.0517         1.0         0.665         -666378         3833164         2.063         1.216         0.077         -19.049         0.933         0.318         1.78         0.345           2.0517         1.0         1.0         1.0         1.216         0.013         -0.477         0.017         0.406         0.371         0.273           1.0157         1.0139         1.012         1.216         0.013         0.214         0.277         0.206         0.201         0.277         0.201         0.277         0.201         0.277         0.202         0.201         0.201         0.201         0.201         0.201         0.201         0.201         0.201         0.201         0.201         0.201         0.201         0.201         0.201         0.201         0.201         0.201         0.201         0.201         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Net (Marching)         1.35.3713         0.065         6.66.378         38.33.314         0.028         0.111         0.107         1.309         0.039         0.338         1.378         0.341         0.313         0.345         0.345         0.345         0.345         0.341         0.313         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         0.345         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| R55112         6.454955         0.466         5.47475         171.127         2.693         1.206         0.063         -0.270         4.457         0.466         0.371         0.273           mod         18.3846         0.311         0.311         2.336519         0.663         0.054         0.014         1.148         0.077         0.014         1.048         0.072         0.020         0.003         0.001         0.017         0.014         0.017         0.014         0.017         0.014         0.017         0.014         0.017         0.014         0.021         0.020         0.020         0.020         0.020         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.031         0.031         0.031         0.031         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     18.3.8642         18.15.277         0.311         -1.12923         5.3.96619         0.631         0.206         0.011         1.14         1.48         0.077         0.001         0.017         0.012         0.003         0.002         0.003         0.003         0.001         0.017         0.013         0.011         0.012         0.001         0.001         0.017         0.013         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001 
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     4.457         0.466         0.371         0.273           Rev         18.366.21         3115.277         0.311         -7.112325         5.386519         0.631         0.264         0.017         0.114         1.467         0.077         0.002         0.003         0.001         0.0172         0.010         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.012         0.003         0.003         0.001         0.013         0.016         0.011         0.012         0.012         0.013         0.012         0.012         0.013         0.012         0.012         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.013         0.014         0.014         0.014         0.046         0.446         0.446         0.445         0.445         0.445         0.445         0.013         0.013         0.013         0.013         0.013         0.013         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                          | Ref         2.85.11         6.03955         0.066         5.4.2.12         0.11         0.11213         0.13         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.213         0.021         0.021         0.023         0.021         0.021         0.023         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         0.021         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                                                                                                                                                                                                                                                            | Mode         2.83.84/2         0.610353         0.016         5.4.1112         0.610353         0.111         0.111         0.111         0.111         0.111         0.111         0.111         0.111         0.111         0.111         0.111         0.111         0.111         0.111         0.111         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011         0.011     
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| Operation         Operation <t< td=""><td>Output         Output         Output&lt;</td><td>Operation         Description         <thdescription< th=""> <thdescription< th="">         &lt;</thdescription<></thdescription<></td><td>Month         Description         <thdescripion< th=""> <thdescription< th=""> <thdes< td=""><td>Month         Description         <thdescripion< th=""> <thdescription< th=""> <thdes< td=""><td><math display="block"> \begin{array}{ c c c c c c c c c c c c c c c c c c c</math></td><td>Month         Description         Control of the contro of the control of the contro</td><td><math display="block"> \begin{array}{ c c c c c c c c c c c c c c c c c c c</math></td><td>Model         Occurrence         Occurrence<!--</td--><td>Interpretation         Interpretation         Interpreadow         Interpretation         Interpret</td></td></thdes<></thdescription<></thdescripion<></td></thdes<></thdescription<></thdescripion<></td></t<>                                  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th=""> <thd033< th=""></thd033<></thd033<></thd033<></td> <td>Under         1         0.033946         0.040450         0.01440         0.001         0.014         0.002         0.002         0.002         0.002         0.002         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001 
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C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C         C <thc< td=""><td>Unde         D         C0.239645         C0.216313         C0.240445         C0.202         C0.20</td></thc<>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Unde         D         C0.239645         C0.216313         C0.240445         C0.202         C0.20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Allow (from)         SO         NERN2-3 cont<br>(073448)         NERN2-3 cont<br>(073448) </td <td>Investigation         Outcome         Outcome</td> <td>Name         28,4316         11,744.14         0.012         6,413-68         2,5445         0,547         0,477         0,190         -1-54         0,217         0,173         0,293         0,201         0,173         0,293         0,201         0,126         0,126         0,127         0,017         0,173         0,203         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,003         0,003         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004</td> <td>Turney         -365-18.18         362.477         0.453         369.477         4.72.045         3.08.67         1.47.346         5.550         -1.12.07         5.587         0.065           Indee         0.0337214         0.0377244         0.12.467.2         0.000         0.012         0.473         0.000         0.000         0.046           Indee         0.0437214         0.12.467.2         0.000         0.012         0.835         0.000         0.000         0.066         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046      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          MRM3         0.247753         0.387718         0.387         -0.3074439         0.7324959         0.001         0.666         0.001         0.666         0.667         0.687         0.687         0.687         0.687         0.687         0.687         0.687         0.687         0.687         0.687         0.687         0.686         0.001         0.666         0.686         0.003         0.686         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.</td> <td>pilude         0.227553         0.2307218         0.337         0.3074493         0.7325595         0.001         0.624         -0.016         0.001         0.004         0.637           MEMSA         0.137568         0.0474176         0.004         0.44433         0.7325595         0.001         0.002         0.616         0.004         0.004         0.0371           MEMSA         0.137568         0.044176         0.004         0.04429         0.330026         0.001         0.002         0.656         0.004         0.038         0.2311           0         0.127609         56.5312         0.446         0.24817         0.0331         1.445         3.72         0.653         9.000         0.024         0.3311           0         0.01         0.022         0.653         9.003         0.244         0.734         0.734           0         0.01         0.023         0.4457         0.0331         0.4467         0.0331         0.446         0.744         0.734           0         0.01         0.023         0.453         0.6630         0.004         0.034         0.734         0.734           0         0.01         0.023         0.656         0.004         0.036</td> <td>MRM3         0.1373638         0.047176         0.0044         0.044429         0.330026         0.001         0.002         0.656         0.004         0.0038         0.234         0.731           2.12.00         36.8313         0.48         9.48737         5.08319         1.845         3.72         0.653         9.004         0.036         0.264         0.734         0.731          </td> <td>Minimum         Mathematical         Mathematical</td> <td>CECU DOLI PLUE CONTRACTOR CO</td> <td></td>                                                                                                                                                                                                                                                                                                                                                                                                                                                             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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Name         28,4316         11,744.14         0.012         6,413-68         2,5445         0,547         0,477         0,190         -1-54         0,217         0,173         0,293         0,201         0,173         0,293         0,201         0,126         0,126         0,127         0,017         0,173         0,203         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,013         0,003         0,003         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004         0,004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Turney         -365-18.18         362.477         0.453         369.477         4.72.045         3.08.67         1.47.346         5.550         -1.12.07         5.587         0.065           Indee         0.0337214         0.0377244         0.12.467.2         0.000         0.012         0.473         0.000         0.000         0.046           Indee         0.0437214         0.12.467.2         0.000         0.012         0.835         0.000         0.000         0.066         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046         0.046             
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Methode         0.00383919         0.00373018         0.0071704         0.1240542         0.000         0.002         0.885         -0.003         0.000         0.000         0.666           0.014         0.247753         0.387718         0.387         -0.3074439         0.7324959         0.002         0.685         -0.016         0.000         0.666         0.666           MRM3         0.247753         0.387718         0.387         -0.3074439         0.7324959         0.001         0.666         0.001         0.666         0.667         0.687         0.687         0.687         0.687         0.687         0.687         0.687         0.687         0.687         0.687         0.687         0.686         0.001         0.666         0.686         0.003         0.686         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         0.734         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0.227553         0.2307218         0.337         0.3074493         0.7325595         0.001         0.624         -0.016         0.001         0.004         0.637           MEMSA         0.137568         0.0474176         0.004         0.44433         0.7325595         0.001         0.002         0.616         0.004         0.004         0.0371           MEMSA         0.137568         0.044176         0.004         0.04429         0.330026         0.001         0.002         0.656         0.004         0.038         0.2311           0         0.127609         56.5312         0.446         0.24817         0.0331         1.445         3.72         0.653         9.000         0.024         0.3311           0         0.01         0.022         0.653         9.003         0.244         0.734         0.734           0         0.01         0.023         0.4457         0.0331         0.4467         0.0331         0.446         0.744         0.734           0         0.01         0.023         0.453         0.6630         0.004         0.034         0.734         0.734           0         0.01         0.023         0.656         0.004         0.036                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | MRM3         0.1373638         0.047176         0.0044         0.044429         0.330026         0.001         0.002         0.656         0.004         0.0038         0.234         0.731           2.12.00         36.8313         0.48         9.48737         5.08319         1.845         3.72         0.653         9.004         0.036         0.264         0.734         0.731                                                                                                                                                                                                                                                                                                                                                                                 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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | CECU DOLI PLUE CONTRACTOR CO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Intervision         NetWork 20 error                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   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0.001         0.665         0.001         0.665         0.001         0.665         0.001         0.665         0.001         0.665         0.665         0.001         0.665         0.665         0.001         0.665         0.550         0.123         0.655         0.001         0.665         0.001         0.665         0.665         0.001         0.665         0.655         0.266         0.246         0.756         0.557         0.655         0.601         0.665         0.665         0.665         0.665         0.665         0.665         0.665         0.665         0.665         0.665         0.665         0.665         0.665                                                                                                                                                                                                                                                                                                                                                                              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    0.124.452         0.000         0.001         0.003         0.060         0.066         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         0.646         <                                                                                                                                                                                                  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   0.221753         0.337714         0.317         0.01240547         0.1240547         0.001         0.666         0.002         0.666           Micha         0.221753         0.337714         0.3174059         0.3793599         0.005         0.611         0.624         0.011         0.614         0.001         0.666           Micha         0.1371658         0.3377146         0.004         0.00429         0.3793599         0.001         0.002         0.656         0.004         0.004         0.671         0.671         0.671         0.671         0.671         0.671         0.671         0.671         0.671         0.671         0.671         0.671         0.671         0.671         0.671         0.671         0.671         0.731         0.731         0.731         0.731         0.731         0.731         0.731         0.731         0.731         0.731         0.731         0.731         0.734         0.734         0.734         0.734         0.734         0.734         0.734        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0.857           MRMS         0.137563         0.28771         0.3877         0.30743305         0.301         0.624         0.016         0.027         0.016         0.024         0.657         0.031         0.557         0.031         0.551         0.031         0.551         0.031         0.551         0.031         0.551         0.031         0.551         0.034         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551         0.551    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                                                                         | WEMS         01373658         00444176         0.004429         0.2303026         0.0001         0.002         0.653         0.004         0.002         0.634         0.731           1         22.14.09         36.85031         0.546         0.44429         2.3303026         0.001         0.002         0.653         0.004         0.002         0.644         0.731           1         2.2.14.09         36.85031         0.546         9.43.571         5.008319         1.845         3.722         0.623         5.509         9.200         0.741         1.166         0.535           1         1.133471         0.5471         0.5501         1.2127         0.5501         0.523         1.126         0.536         0.766         0.786         0.786         0.786         0.786         0.786         0.786         0.786         0.786         0.786         0.786         0.786         0.786         0.786         0.786         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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | ULUTION         ULUTION <t< td=""><td>34316         11.7414         0.012         6.41348         5.2469         0.5417         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131</td><td>Image: contract of the second of th</td><td>Indef         0.058/3910         0.0335(18)         0.031         0.001         0.002         0.835         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.004         0.031         0.011         0.012         0.012         0.013         0.001         0.003         0.013         0.013         0.013         0.013         0.014         0.023         0.013         0.001         0.004         0.031         0.013         0.013         0.014         0.013         0.014         0.013         0.014         0.013         0.014         0.013         0.014         0.014         0.014         0.013         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014</td><td>Inde         0.247755         0.2877         0.2077         0.2877         0.2077         0.2017         0.001         0.6877         0.001         0.6977         0.001         0.6977         0.001         0.6971         0.001         0.6971         0.001         0.6971         0.001         0.6971         0.001         0.6971         0.001         0.6971         0.001         0.6971         0.001         0.6971         0.6911         0.6971         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911     
   0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911</td><td>NUERAS         01373558         0044175         0.004         0.04439         0.2303026         0.001         0.002         0.656         -0.004         0.002         0.734           1         22.14209         5656331         0.344         9.436737         50.0839         1.44573         50.0839         0.435         -3752         0.623         -5.909         0.074         1.166         0.355           1         2.2.14209         5656331         0.544         -9.45773         50.0839         1.4457         0.023         -5.909         0.200         0.714         1.166         0.355           1         2.2.14209         5656331         0.5549         9.122         0.553         -5.509         9.200         0.714         1.166         0.355           1         2.7.25075         9.4043         0.656         7.5599         -9.122         0.559         -7.202         0.369         0.357         0.369         0.365         0.3657         0.3657         0.3656         0.718         0.355           0.007         1.7.2075         9.4467         9.55391         7.202         1.1691         0.558         0.496         0.365         0.367         0.365           0.0165         0.017</td><td>UL373059         UUM         UL4984U         <thul4984u< th=""> <thul4984u< th=""> <thul49< td=""><td>Alternation         Constraint         Constr</td><td>Network         Network         <t< td=""></t<></td></thul49<></thul4984u<></thul4984u<></td></t<>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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  0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         0.131         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                                                                                                                                                                                                                                                                                                         | Indef         0.058/3910         0.0335(18)         0.031         0.001         0.002         0.835         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.003         0.001         0.004         0.031         0.011         0.012         0.012         0.013         0.001         0.003         0.013         0.013         0.013         0.013         0.014         0.023         0.013         0.001         0.004         0.031         0.013         0.013         0.014         0.013         0.014         0.013         0.014         0.013         0.014         0.013         0.014         0.014         0.014         0.013         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014         0.014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Inde         0.247755         0.2877         0.2077         0.2877         0.2077         0.2017         0.001         0.6877         0.001         0.6977         0.001         0.6977         0.001         0.6971         0.001         0.6971         0.001         0.6971         0.001         0.6971         0.001         0.6971         0.001         0.6971         0.001         0.6971         0.001         0.6971         0.6911         0.6971         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911         0.6911                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | NUERAS         01373558         0044175         0.004         0.04439         0.2303026         0.001         0.002         0.656         -0.004         0.002         0.734           1         22.14209         5656331         0.344         9.436737         50.0839         1.44573         50.0839         0.435         -3752         0.623         -5.909         0.074         1.166         0.355           1         2.2.14209         5656331         0.544         -9.45773         50.0839         1.4457         0.023         -5.909         0.200         0.714         1.166         0.355           1         2.2.14209         5656331         0.5549         9.122         0.553         -5.509         9.200         0.714         1.166         0.355           1         2.7.25075         9.4043         0.656         7.5599         -9.122         0.559         -7.202         0.369         0.357         0.369         0.365         0.3657         0.3657         0.3656         0.718         0.355           0.007         1.7.2075         9.4467         9.55391         7.202         1.1691         0.558         0.496         0.365         0.367         0.365           0.0165         0.017                                                                                                                                                                                                                                                                                    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td=""></t<></td></thul49<></thul4984u<></thul4984u<>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Alternation         Constraint         Constr                                                                                                                                                                                                                                                              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Supplemental Table S2	coef	SE	р	95% CI: lower	upper	coef	SE	р	95% CI: lower	upper
SpinIdes, SO, ADAS-Cognition										
	ADAS-cognitio	on total score	baseline			ADAS-cogniti	on total 12 mo	onths		
Spindles (central channels)	NREM2+NREM	413				NREM2+NREM	/13			
SP count	-0.0124922	0.0043038	0.004	-0.0209275	-0.0040569	-0.0128247	0.0044418	0.004	-0.0215305	-0.0041189
SP duration	-27.59773	12.83681	0.032	-52.75742	-2.438043	-29.45345	13.3921	0.028	-55.70148	-3.205427
SP density	-8.995733	2.700106	0.001	-14.28784	-3.703622	-8.635537	2.41355	0.0001	-13.36601	-3.905067
SP peak frequency	0.7122608	1.048431	0.497	-1.342626	2.767147	-0.7353991	1.131832	0.516	-2.953749	1.482951
SP energy	-0.0275724	0.0087315	0.002	-0.0446858	-0.010459	-0.0190872	0.0073345	0.009	-0.0334624	-0.0047119
SP ptp amplitude	-0.0149351	0.035937	0.678	-0.0853703	0.0555001	-0.0443294	0.0340072	0.192	-0.1109823	0.0223234
	NREM2									
SP count	-0.0207376	0.0065235	0.001	-0.0335234	-0.0079518	-0.0179695	0.0055986	0.001	-0.0289425	-0.0069964
SP duration	-15.71328	15.66998	0.316	-46.42588	14.99933	-12.72816	16.55401	0.442	-45.17342	19.71709
SP density	-10.80323	2.914141	0.0001	-16.51484	-5.091618	-9.077017	2.153744	0.001	-13.29828	-4.855756
SP peak frequency	0.3625849	1.164196	0.755	-1.919197	2.644367	-0.6712701	1.071623	0.531	-2.771612	1.429072
SP energy	-0.0265293	0.0085093	0.002	-0.0432073	-0.0098514	-0.0184918	0.0074793	0.013	-0.0331511	-0.0038326
SP ptp amplitude	-0.001674	0.0014713	0.255	-0.0045576	0.0012097	-0.0173659	0.0360919	0.63	-0.0881047	0.0533729
Slow Oscillations (frontal)	NREM2+NREM	VI 3				NREM2+NREM	/13			
SO count	0.0011102	0.0032828	0.735	-0.0053241	0.0075445	-0.0000312	0.0021287	0.988	-0.0042035	0.004141
SO duration	25.82524	11.83087	0.029	2.637155	49.01332	6.781139	11.75169	0.564	-16.25174	29.81402
SO density	-0.0816215	1.577041	0.959	-3.172564	3.009321	-0.2672274	1.224172	0.827	-2.66656	2.132105
SO peak frequency	-58.21416	34.84573	0.095	-126.5105	10.08222	-19.34175	28.14689	0.492	-74.50863	35.82513
SO energy	0.0014765	0.0030888	0.633	-0.0045774	0.0075303	0.0089291	0.003548	0.012	0.0019752	0.015883
SO ptp amplitude	0.0065562	0.0212317	0.757	-0.0350571	0.0481696	0.0385478	0.0217044	0.076	-0.003992	0.0810876
	NREM3									
SO count	0.0123377	0.0068923	0.073	-0.001171	0.0258464	0.0036449	0.0046602	0.434	-0.0054889	0.0127786
SO duration	-1.604588	2.329533	0.491	-6.170388	2.961212	-1.449177	2.696474	0.591	-6.734169	3.835815
SO density	0.0584803	2.013963	0.977	-3.888815	4.005775	-1.699991	1.808157	0.347	-5.243913	1.843932
SO peak frequency	-5.124683	12.35529	0.678	-29.3406	19.09124	6.869429	11.77921	0.56	-16.2174	29.95625
SO energy	-0.0010838	0.0027726	0.696	-0.006518	0.0043504	0.005493	0.0029702	0.064	-0.0003284	0.0113144
SO ptp amplitude	-0.0158002	0.0183425	0.389	-0.0517508	0.0201504	0.0265652	0.018374	0.148	-0.0094472	0.0625776
*p < 0.02is significant after False										
Discovery Rate correction										

ADAS: Alzheimer's Disease Assessment Scale, cognitive subscale MMSE: Mini-mental State Examination, NREM: Non-rapid eye movement sleep, SP: spindles, SO: slow oscillations, ptp: peak to peak

Supplementary table 2: Spindles, SO, ADAS-cog

Supplementary Table S3																				
Spindles, SO, MMSE-cognition	coef	SE	96 d	5% CI: lower	upper	coef	SE	6 d	5% CI: lower	upper	coef	SE	p 959	S CI: lower L	Ipper	coef	SE	p 959	CI: lower	Ipper
Spindles (central channels)	MIMSE Dase				2 2	IREM2-3 coef				M	ASE 24 months EM2-3 coef				MM	SE 36 MONTRS				
SP count	0.004	0.002	0.147	-0.001	0.008	0.0048224	0.0028437	60:0	-0.0007511	0.010396	0.0040573	0.0035938	0.259	0.0029864	0.0111011	0.0045428	0.0124	0.715	0.0288518	0.0197661
SP duration	8.848	6.556	0.177	-4.001	21.697	15.21759	5.96399	0.011	3.528379	26.90679	22.92186	10.06765	0.02	3.189631	42.65409	34.89067	11.74411	0.003	11.87263	57.90871
SP density	3.243	0.935	0.001	1.410	5.077	4.2	1.317163	0.001	1.614361	6.777543	5.015518	1.735068	0.004	1.614846	8.41619	7.848695	2.208161	0	3.520778	12.17661
SP peak frequency	-0.201	0.267	0.451	-0.724	0.322	-0.0397858	0.3682582	0.914	-0.7615587	0.6819871	-0.1350597	0.667535	0.84	-1.443404	1.173285	0.0192789	0.0697546	0.782	0.1174376	0.1559955
SP energy	0.006	0.003	0.011	0.001	0.011	0.0171998	0.003081	0.001	0.0111612	0.0232384	0.0013281	0.0032271	0.681	0.0049968	0.007653	0.0246987	0.0108086	0.022	0.0035141	0.0458832
SP ptp amplitude	-0.001	0.005	806.0	-0.010	600:0	0.006/445	0.00/3502	0.359	-0.0076618	0.0211507	-0.0234276	0.0114882	0.041	-0.045944	0.0009113 .	0.0022665	0.0335024	0.946	-0.06/93	0.063397
SP count	0.006	0.002	0.002	0.002	0.010	0.0095661	0.0050445	0.058	-0.0003209	0.0194532	0.0095661	0.0050445	0.058	0.0003209	0.0194532	0.0045441	0.0142759	0.75	0.0234361	0.0325243
SP duration	4.051	5.807	0.485	-7.331	15.433	-5.279213	7.437662	0.478	-19.85676	9.298336	-5.279213	7.437662	0.478	-19.85676	9.298336	39.29273	12.70619	0.002	14.38905	64.19641
SP density	3.219	0.948	0.001	1.360	5.078	4.650135	1.210224	0.001	2.278139	7.02213	5.436773	1.695267	0.001	2.114112	8.759435	0.4336138	0.1423463	0.002	0.1546202	0.7126073
SP peak frequency	-0.201	0.267	0.451	-0.724	0.322	-0.0403452	0.3391152	0.905	-0.7049989	0.6243085	-0.1743159	0.6402327	0.785	-1.429149	1.080517	0.0180942	0.0659046	0.784 -	0.1110765	0.1472648
SP energy	0.002	0.001	0:050	0.000	0.005	0.0170275	0.0030781	0.001	0.0109946	0.0230604	0.0010552	0.003147	0.737	0.0051129	0.0072232	0.0020192	0.0003288 (	0.00001	0.0013747	0.0026638
SP ptp amplitude	-0.001	0.005	0.858	-0.011	600.0	0.0069963	0.0066086	0.29	-0.0059563	0.0199489	0.0069963	0.0066086	0.29	0.0059563	0.0199489	0.0379766	0.0215788	0.078	0.0802703	0.0043171
Slow Oscillations (frontal)	NREM2 and 3				Z	IREM2-3 coef				NR	EM2-3 coef				WN	coef				-
SO count	0.0001493	0.0007436	0.841	-0.0013081	0.0016067	-0.0019681	0.0011054	0.075	-0.0041347	0.0001984	0.000361	0.0012668	0.776	0.0021218	0.0028438	0.0063286	0.0038733	0.102	0.0139201	0.0012629
SO duration	-5.340839	4.825629	0.268	-14.7989	4.11722	-5.444539	5.909157	0.357	-17.02627	6.137197	-25.37818	6.890206	0.0001	-38.88274	-11.87362	-1.45463	0.5812781	0.01	-2.593914	0.3153455
SO density	-0.3445214	0.3445632	0.317	-1.019853	0.3308101	-0.782311	0.7489983	0.296	-2.250321	0.6856987	0.654255	0.7819447	0.403	0.8783285	2.186838	0.0747322	0.0746865	0.317	0.0716507	0.2211152
SO peak frequency	18.82623	8.822152	0.033	1.535131	36.11733	18.34656	9.615656	0.056	-0.4997819	37.1929	35.39015	11.8336	0.003	12.19673	58.58357	22.09452	19.10475	0.247	-15.3501	59.53915
SO energy	0.0021273	0.0016206	0.189	-0.001049	0.0053035	0.0054956	0.0038911	0.158	-0.0021308	0.013122	-0.0021239	0.0021742	0.329	0.0063853	0.0021374	0.0050953	0.0058746	0.386	0.0064188	0.0166093
so ptp amplitude	0.0305224	0.0146355	0.037	0.00183/3	02620.0</th <th>1606640.0</th> <th>0.02341/4</th> <th>0.034</th> <th>0.0036118</th> <th>2009260.0</th> <th>-0.016/463</th> <th>0.0114652</th> <th>0.144</th> <th>//1765010</th> <th>- 197/9000</th> <th>1//60000</th> <th>0.0016133</th> <th>- GOT-O</th> <th>700/0/070</th> <th>0.006/039</th>	1606640.0	0.02341/4	0.034	0.0036118	2009260.0	-0.016/463	0.0114652	0.144	//1765010	- 197/9000	1//60000	0.0016133	- GOT-O	700/0/070	0.006/039
	NKEM 3	1000000	0100		N	REM3	000000000000000000000000000000000000000	0000	101000000	NR	EM3	0.000000			NRE	M3	0.0000	1000	0.910100.0	000000000
so count so duration	-0.0014/90	10000CL2 U	0/7/0	100168 C	TEGTIONO	00T/CDU/-	1 103234	0.067	00T6600'0-	10VC1510	C2C3200.0-	20060000		CEUGEUU.U		CC000000	0.1470225		CT/CC000	ST#07700
	02302100	0 E1600E1	100.0	TOOTTO'L	C0120000	100001.2	31V2V00 U	0000	2 GAEODA		1 5/2/27	10320100	10		70010C C	100000	2020000	10166		100100000
SO generative	0/0001 c	TEOODTEIN	6/6/0	4C40701-	COT/SEE'O	17COTT6'0-	0.004/410	202.0	4000407-	0.0220233	2010001	1200216.0	T'D	0.2030333	160167.0	0.5124057	0.0402020	- LUO 0	564//ZOO	T0C+T0T-0
SU peak trequency	715896.2-	2.94498	0.383	-8.34U3bb	3.203/42	4.3103/1	c/q0#c.c	0.43/	-0.00000	48691.CI	-9.20703	4./52005	0.044	- 18.80446	0.2369447	79047150	0.30884 / /	/60'0	14767600	1.11//3b
SO energy SO ete amelituda	0.0024637	0.0011/98	0.037	0.0001513	0.0047762	0.0058391	0.0034301	0.089	0.0008837	0.012562	-0.0002553	0.0014058	0.856	0.0030106	3622001	0.0050438	0.0033595	0.133	0.0015407	0.0116283
eo pup ampinuue *n < 0.02is significant after False	000012000	CTOCCOVO	con:0	ENERGYCNYN	+0+0000	1011700	T /T /0T0'0	10.0	CC+/00000	740 10400	0,00406.0	0007070	CTOYO	CCTC7T0'0	070/07770	C / DODDOD'D	C / 0TT 0000	+C'D	0000000	1077000
Discovery Rate correction																				
Supplementary Lable 55 Spindles: SO. MMSE-cognition	coef	SF	u u	5% CI: Inwer	upper	coef	SF	6	5% CI: lower	unner	cnef	SF	96 U	% CI: lower	unner					
	MMSE change f	rom base to 12 m	onths			AMSE change ba	se to 24 mont	5		Σ	MSE change bas	e to 36 month	5		B	ds (OR) of ded	ine in MMSE ove	er 36 months		
Spindles (central channels)	NN				>	Vhole Night														
SP count	-9.63E-06	0.0001229	0.938	-0.0002506	0.0002313	0.0016235	0.0021009	0.44	-0.0024941	0.0057412	0.0000934	0.000327	0.775	-0.0005475	0.0007343	0.9963094	0.0029874	0.218	0.9904714	1.002182
SP duration	-0.2508316	0.2542757	0.324	-0.7492028	0.2475396	11.9216	7.944354	0.133	-3.649048	27.49225	1.54559	0.7557413	0.041	0.0643646	3.026816	0.0000246	0.0002381	0.273	1.44E-13	4218.019
SP density	-0.0173702	0.0471804	0.713	-0.1098421	0.0751017	2.327483	1.18103	0.049	0.0127071	4.642259	0.353676	0.166826	0.034	0.0267032	0.6806489	0.0131715	0.0206886	0.006	0.0006062	0.2861745
SP peak frequency	-0.0013319	0.0145193	0.927	-0.0297892	0.0271254	0.2416082	0.4424787	0.585	-0.6256341	1.10885	0.0059346	0.0499399	0.905	-0.0919458	0.1038151	0.879748	0.4867668	0.817	0.2974311	2.602137
SP energy	0.0002/3/	0.0001222	0.025	0.0000341	0.0005132	0.00660/2	0.003028	0.029	0.0006/25	0.012542	0.0015444	0.0005325	0.004	0.0005007	0.002588	0.9887021	0.00/6613	0.143	0.9/3/998	1.003833
sk ptp amplitude	0.00032	7810000	6/0.0	-0.000036/	0.0006/66	-0.0118038	0.00/544	0.118	-0.0265838	7786700.0	0.0018822	0.001/669	0.28/	-0.0015808	0.0053451	0.9910888	0.0159408	8/5.0	0.9603327	1.02283
SP count	-1.39E-07	0.000191	0.999	-0.0003746	0.0003743	0.0047233	0.0027783	0.089	-0.000722	0.0101686	0.0001085	0.0003727	0.771	-0.0006219	0.0008389	0.9949719	0.0043328	0.247	0.9865159	1.0035
SP duration	-0.321557	0.1813559	0.076	-0.6770079	0.033894	-5.644784	5.042303	0.263	-15.52752	4.237948	1.5273	0.7279279	0.036	0.100587	2.954012	0.0000512	0.0003607	0.161	5.10E-11	51.31585
SP density	-0.0006609	0.0468106	0.989	-0.0924079	0.0910862	2.913939	1.151584	0.011	0.6568751	5.171003	0.3551506	0.1672507	0.034	0.0273452	0.6829559	0.0093589	0.0154748	0.005	0.0003662	0.2391552
SP peak frequency	-0.0003525	0.0142239	0.98	-0.0282309	0.0275259	0.2305693	0.4444044	0.604	-0.6404474	1.101586	0.0033569	0.0474605	0.944	-0.0896641	0.0963778	8060.761	95822.2	0.449	6.13E-07	1.06E+14
SP energy	0.0002357	0.0001117	0.035	0.0000167	0.0004547	0.0065506	0.0030329	0.031	0.0006061	0.012495	0.0016409	0.0005059	0.001	0.0006493	0.0026325	0.9857612	0.0079876	0.077	0.9702294	1.001542
SP ptp amplitude	0.0003219	0.0001518	0.034	0.0000244	0.0006195	-0.0099754	0.0040082	0.013	-0.0178312	-0.0021195	-0.0026035	0.0011943	0.029	-0.0049444	-0.0002627	0.9937872	0.0163786	0.705	0.9621986	1.026413
SIOW USCIIIATIONS (Trontal)	WN coet	1000000	0.100	20075000		VN coet	2.300000	0.240	0.0010106	W	N coet	00000000	767.0	0.00000	1000011		0.0013007	0.45	0 00674.4	1 001665
SO duration	3 766314	10000000	061.0	25 63956	13 17719	-15 16571	6 158505	0.014	3198C LC-	-3 095259	2015100/0-	8 053619	360.0	70,750,77	2 319338	795/02 48	515621 6	0.087	7397867	2 64F+10
SO density	-0.0214027	0.5502759	696.0	-1.099924	1.057118	1.115782	0.5066033	0.028	0.1228579	2.108706	1.170961	1.317477	0.374	-1.411246	3.753168	0.2944132	0.2112785	0.088	0.0721296	1.201714
SO peak frequency	-5.727607	8.939799	0.522	-23.24929	11.79408	25.73136	11.2214	0.022	3.737821	47.7249	15.54488	10.27721	0.13	-4.598085	35.68785	0.0004395	0.0047599	0.475	2.66E-13	727410
SO energy	0.000149	0.0013817	0.914	-0.002559	0.0028571	-0.000871	0.0017129	0.611	-0.0042281	0.0024862	0.0046847	0.0034947	0.18	-0.0021647	0.0115341	0.9998377	0.0021574	0.94	0.9956183	1.004075
SO ptp amplitude	0.0093023	0.0110375	0.399	-0.0123308	0.0309353	-0.0034065	0.00941	0.717	-0.0218497	0.0150367	-0.0087737	0.0234482	0.708	-0.0547313	0.0371838	1.004817	0.0139626	0.729	0.9778201	1.032559
	NREM3				z	IREM3														
SO count	-0.0042073	0.001/2/8	0.015	-0.00/5938	-0.0008208	0.0000579	0.0026466	686.0	-0.0051293	0.0052452	0.0112424	0.005/185	0.049	0.0000343	0.0224505	11086886.0	0.0042054	0.016	0.9815929	6//0866:0
SO duration	2.74492	0.8027736	0.001	1.171512	4.318327	-0.0284674	0.8294794	0.973	-1.654217	1.597282	1.535838	1.283717 A 7700570	0.232	-0.9802021	4.051878	0.0043216	0.0331758	0.478	1.26E-09	14794.66
SU density	-0.410/252	234/882 Actor c	0.074	1628241-	12 65647	71460690	1.972737	90.0	-0.02966/4	CCL14.1	T. DADAGE	3/508///0	0.000	4280222.0-	CP34840.2	0.0010755	0.0078061	5010	T/ADDCT/D	r ocoop
SU peak irequericy	100000	HCTCHC'C	4-CU.U	10701000 v	191000101 v	#11/CET	1.0/020/01	0 507	CCV2100 0	CLCSEUU U	COPCPULD NACASON A	5202500 V	0.005	CCCCCTTC-	TCOULCT	0123000 V	1000/00100 U	121.0	D.222-U/	360505.C
so energy SO ata amalitude	0.008918	0.0111047	0.427	16002000-	0.0306828	0.0096133	0.0095314	0.313	8290600-0-	2/20000	0.0079493	0.0163441	0.057	-0.0290846	0.0349832	0.9986658	1.0104661	668.0	0.9783618	1.019391
*p < 0.02is significant after False	81			-				1										-		
<b>Discovery Rate correction</b>																				

ADAS: Alzheimer's Disease Assessment Scale, cognitive subscale MMSE: Mini-mental State Examination, SP: spindles, SO: slow oscillations, NREM: non-rapid eye movement sleep

Supplementary table S3: Spindles, SO, MMSE

Supplemental Table S4	coef	SE	d	95% CI: lower	upper	coef	SE	đ	95% CI: lower	upper	coef	SE	26 d	% CI: lower	upper	coef	SE	p 95	6 CI: lower	upper
SpinIdes, SO, CVLT-ROCF-Cognit	uo	3				1	,				:	-								
Spindles (central channels)	NREM2 and 3					NREM2-3 coef				ž	REM2-3 coef				N N	EM2-3 coef	77 Å IGUIAITI IPRO	_		
SP count	-0.0005684	0.0006943	0.413	-0.0019291	0.0007924	-0.000044	0.0006914	0.949	-0.0013991	0.0013111	0.5690067	0.2788734	0.041	0.0224248	1.115589	0.0043186	0.0018064	0.017	0.0007781	0.007859
SP duration	2.242887	1.298668	0.084	-0.3024551	4.788229	-0.0158696	1.19673	0.989	-2.361416	2.329677	3.342544	1.389417	0.016	0.6193373	6.065751	-3.764164	7.230664	0.603	-17.93601	10.40768
SP density	3.631841	1.729875	0.032	0.2413492	7.022333	0.3578048	0.2531419	0.158	-0.1383443	0.8539539	0.3644725	0.2792716	0.192	-0.1828898	0.9118348	2.042909	1.031573	0.048	0.0210627	4.064756
SP peak frequency	0.0677042	0.0720522	0.347	-0.0735155	0.2089238	0.0391361	0.0683761	0.567	-0.0948786	0.1731508	0.028978	0.0826411	0.726	-0.1329956	0.1909516	-0.2847571	0.4134419	0.491	-1.095088	0.5255741
SP energy	-0.000096	0.0002679	0.72	-0.0006209	0.000429	0.0012265	0.0005398	0.023	0.0001686	0.0022844	-0.0018596	0.0008608	0.031	-0.0035467	-0.0001726	0.001196	0.0021596	0.58	0.0030367	0.0054287
SP ptp amplitude	-0.0019434	0.0015403	0.207	-0.0049624	0.0010756	0.0006417	0.0013113	0.625	-0.0019284	0.0032118	-0.0022081	0.0019307	0.253	-0.0059923	0.0015761	0.0062754	0.0065926	0.341	0.0066459	0.0191967
	NREM2					NREM2				ž	REM2				ž	EM2				
SP count	-0.0000279	0.0010728	0.979	-0.0021306	0.0020747	0.0005677	0.0009841	0.564	-0.0013612	0.0024965	-0.0010391	0.0010475	0.321	-0.003092	0.0010139	0.0061537	0.0020958	0.003	0.0020459	0.0102615
SP duration	1.377547	1.208361	0.254	-0.9907968	3.74589	-1.018558	1.206436	0.399	-3.383128	1.346012	2.480591	1.686903	0.141	-0.8256777	5.786859	-5.156632	5.701963	0.366	-16.33228	6.01901
SP density	3.879306	1.629215	0.017	0.686104	7.072509	0.3704235	0.263698	0.16	-0.1464151	0.887262	0.6709013	0.2851138	0.019	0.1120885	1.229714	2.129349	0.9142911	0.02	0.3373714	3.921327
SP peak frequency	0.0411869	0.0745325	0.581	-0.1048941	0.1872679	0.0439922	0.0652646	0.5	-0.083924	0.1719084	0.0262267	0.0770643	0.734	-0.1248165	0.1772699	0.2227204	0.3276083	0.497	0.4193801	0.8648209
SP energy	-0.0000368	0.0002625	0.889	-0.0005513	0.0004778	0.0009718	0.0004382	0.027	0.0001129	0.0018307	-0.0020275	0.0008733	0.02	-0.0037392	-0.0003159	-0.0036929	0.0037095	0.319	0.0109633	0.0035775
SP ptp amplitude	-0.001674	0.0014713	0.255	-0.0045576	0.0012097	0.0009761	0.0013511	0.47	-0.001672	0.0036241	-0.0023621	0.0020783	0.256	-0.0064356	0.0017113	0.0146716	0.012973	0.258	0.0107551	0.0400983
Slow Oscillations (frontal)	NREM2 and 3					NREM2-3 coef				N	KEM2-3 coef				NR	EM2-3 coef				
SO count	-0.002292	0.0009614	0.017	-0.0041763	-0.0004076	-0.001337	0.0007655	0.081	-0.0028373	0.0001632	-0.0001361	0.0001743	0.435	-0.0004777	0.0002054	0.3357081	0.5292927	0.526	0.7016866	1.373103
SO duration	-10.99049	8.569832	0.2	-27.78706	5.806069	-10.36867	5.555647	0.062	-21.25754	0.5202028	-0.3240559	0.8086501	0.689	-1.908981	1.260869	-7.802918	8.232154	0.343	-23.93764	8.331808
SO density	-0.828528	0.5809641	0.154	-1.967197	0.3101407	0.4087529	0.5155179	0.428	-0.6016437	1.41915	-0.0663576	0.1067048	0.534	-0.2754952	0.14278	-0.0026148	0.0020324	0.198	0.0065982	0.0013687
SO peak frequency	33.90085	18.0695	0.061	-1.51472	69.31642	10.35058	9.662944	0.284	-8.588439	29.28961	1.649718	1.981629	0.405	-2.234205	5.53364	-1.691042	10.68819	0.874	-22.63952	19.25743
SO energy	-0.000834	0.0016616	0.616	-0.0040907	0.0024227	0.0012248	0.0020999	0.56	-0.002891	0.0053407	-0.0001436	0.0002854	0.615	-0.0007029	0.0004158	-0.0009484	0.0012814	0.459	0.0034599	0.0015631
SO ptp amplitude	-0.0080992	0.0115251	0.482	-0.030688	0.0144897	0.000713	0.008835	0.936	-0.0166033	0.0180292	-0.0028434	0.0016948	0.093	-0.0061652	0.0004784	-0.0116251	0.0074908	0.121	0.0263068	0.0030567
	NREM3					NREM3				ž	tem3				NR	EM3				
SO count	-0.0065806	0.0021181		-0.0107319	-0.0024293	-0.0039474	0.001549	0.011	-0.0069833	-0.0009115	-0.0002141	0.000384	0.577	-0.0009668	0.0005387	-0.0018345	0.001489	0.218	0.0047529	0.0010839
SO duration	0.6636282	1.088301	0.542	-1.469403	2.79666	0.8041884	1.088402	0.46	-1.32904	2.937417	0.2568404	0.2049624	0.21	-0.1448785	0.6585593	2.050021	0.9001956	0.023	0.2856702	3.814372
SO density	-0.5863802	0.512868	0.253	-1.591583	0.4188226	1.251324	0.5579316	0.025	0.1577978	2.34485	-0.0482662	0.142662	0.735	-0.3278787	0.2313462	-0.4715301	0.5246376	0.369	-1.499801	0.5567406
SO peak frequency	15.51538	12.15369	0.202	-8.305418	39.33619	-3.863601	3.712431	0.298	-11.13983	3.412631	0.500099	0.885327	0.572	-1.23511	2.235308	6.136053	3.414004	0.072	0.5552729	12.82738
for a second contract of the second contract	Pageoro o	0.0020010	0.00	90,000,0-	0 00EEEE	PUCOUUU U	0.0016202	0.573	acrccon n-	0.0001127	CE30000 0-	0.0001001	0 727	0.0004319	0.000305.0	VV000 0-	0.00015.0	0 500	000000	0.0011507
SO nto amolitude	0.0011895	0.0186884	730.0	-0.015439	0.057818	7190000	0.013031	200	0.0004874	U DEGEGE	10 0005794	0.003722	208.0	01052289	CUTUADO 0	0.0078135	500000	BUC U	7000000	70CTT0000
*p < 0.02is significant after			1000	0000		11044000	100000	40:0	-				5		40.00.000	200	204400000	24.0		
False Discovery Rate correction		L					L					L					L			
Supplemental Table 54 Sninldes SO_CVLT.ROCF.Cosnit	coel	K	<b>D</b> .	1: Iower	upper	COEL	ž	а.	2% CI: Iower	upper	coel	ž	с. Г	% CI: Iower	upper	coel	K	d K	6 CI: Iower	upper
0	CVLT (California	Verbal) Long to	erm verbal me	mory baseline		CVLT Long term	verbal memor	y 12m		U	/LT short ter	n verbal mem	ory base		2	LT short tern	n verbal memo	ry 12m		
Spindles (central channels)	NREM2-3 coef					NREM2-3 coef				ž	EM2-3 coef				NR	EM2-3 coef				
SP count	0.0002954	0.0011412	0.796	-0.0019413	0.0025322	0.0007908	0.0010075	0.433	-0.0011839	0.0027655	0.0020644	0.0006468	0.001	0.0007966	0.0033322	0.0019831	0.0006377	0.002	0.0007333	0.0032329
SP duration	-0.5361997	3.111046	0.863	-6.633739	5.561339	2.344338	1.878663	0.212	-1.337774	6.02645	0.252748	1.754245	0.885	-3.185509	3.691005	-1.159463	1.946631	0.551	-4.974791	2.655864
SP density	0.2936058	0.4729647	0.535	-0.633388	1.2206	0.6834568	0.3371792	0.043	0.0225978	1.344316	0.6506957	0.264454	0.014	0.1323753	1.169016	0.5536925	0.303516	0.068	0.0411878	1.148573
SP peak frequency	-0.0916993	0.1412643	0.516	-0.3685722	0.1851736	-0.0450128	0.1278659	0.725	-0.2956254	0.2055998	-0.1395182	0.0937577	0.137	-0.32328	0.0442435	0.0059336	0.1130974	0.958	0.2157332	0.2276004
SP energy	0.0004277	0.0007339	0.56	-0.0010107	0.001866	0.0013373	0.0004899	0.006	0.0003772	0.0022975	0.0002182	0.0004072	0.592	-0.00058	0.0010163	0.0009322	0.0004773	0.051	-3.23E-06	0.0018676
SP ptp amplitude	0.0009081	0.0021296	0.67	-0.0032658	0.0050819	0.0016537	0.0014384	0.25	-0.0011656	0.0044729	0.001418	0.0014736	0.336	-0.0014701	0.0043061	0.0064264	0.0042528	0.131	0.0019089	0.0147618
CD count		0.0015260	0.076	3710000	0000000		0.0007015	0.155	C1CV000 0-	CCN3COO O		D 0011335	0.010				Vacanno o	0.001	0.0010457	CCCCVUU U
SP duration	PUNCAEN 0-	0.112879	0.986	-4 179367	4 102965	3 140624	1 934753	0.105	-0.6514226	6 93767	-0.2417071	1 39487	0.834	-3 075602	2 442188	-1 797248	1 451077	0 217	-4 636306	1 051809
SP density	0.3745232	0.4504126	0.406	-0.5082694	1.257316	0.7792745	0.3283429	0.018	0.1357343	1.422815	0.5603517	0.2612541	0.032	0.048303	1.0724	0.6969187	0.2931006	0.017	0.1224522	1.271385
SP peak frequency	-0.0938452	0.1411263	0.506	-0.3704476	0.1827572	-0.0829931	0.1154441	0.472	-0.3092594	0.1432732	-0.0633313	0.0945498	0.503	-0.2486455	0.1219828	0.0278037	0.108123	0.797	0.1841134	0.2397208
SP energy	0.0004051	0.0006604	0.54	-0.0008893	0.0016994	0.0012522	0.000463	0.007	0.0003447	0.0021597	0.0002316	0.0003903	0.553	-0.0005335	0.0009666	0.0008374	0.0004423	0.058	0.0000295	0.0017044
SP ptp amplitude	0.0005589	0.00177	0.752	-0.0029102	0.0040279	0.0058235	0.0051668	0.26	-0.0043033	0.0159503	0.0013329	0.0013314	0.317	-0.0012765	0.0039423	0.0055396	0.0037539	0.14	0.0018179	0.0128972
Slow Oscillations (frontal)	NREM2-3 coef					NREM2-3 coef				N	EM2-3 coef				NR	EM2-3 coef				
SO count	-0.000056	0.0004079	0.891	-0.0008554	0.0007434	0.0003602	0.0002582	0.163	-0.0001459	0.0008663	0.0001394	0.0002426	0.565	-0.000336	0.0006149	0.0002014	0.0002831	0.477	0.0003535	0.0007562
SO duration	1.225539	1.847337	0.507	-2.395174	4.846253	-3.443185	1.564055	0.028	-6.508676	-0.3776944	0.4531379	1.670265	0.786	-2.820521	3.726796	-0.1699516	1.334016	0.899	-2.784574	2.444671
SO density	-0.039458	0.2428259	0.871	-0.5153881	0.4364721	0.3319977	0.1256314	0.008	0.0857648	0.5782307	0.0173398	0.1879323	0.926	-0.3510008	0.3856803	0.031521	0.1656475	0.849	0.2931422	0.3561842
SO peak frequency	-0.3324572	5.167837	0.949	-10.46123	9.796318	5.185738	3.597321	0.149	-1.864882	12.23636	-2.814202	3.935565	0.475	-10.52777	4.899364	1.294599	3.541206	0.715	-5.646036	8.235235
SO energy	-0.0004591	0.0005912	0.437	-0.0016177	0.0006996	-0.0002506	0.0004791	0.601	-0.0011896	0.0006883	-0.0003865	0.0004006	0.335	-0.0011716	0.0003987	-0.0005929	0.0003762	0.115	0.0013303	0.0001445
50 ptp amplitude	-0.000597	0.0044656	0.894	-0.0093494	0.0081553	-0.001271	0.0025495	0.618	-0.0062679	0.003726	-0.0042483	0.0024777	0.086	-0.0091045	0.0006079	-0.0033868	0.0020834	0.104	0.0074701	0.0006965
	NREM3					NREM3				Ż	EM3		;		ž	EM3				
SO count	-0.0004451	0.000/7/6	0.567	-0.0019692	0.0010/89	0.0007/45	0.0005249	0.14	-0.0002542	0.0018032	0.0000968	0.0004247	0.82	-0.000/35/	2626000.0	80600000	0.0006468	0.888	0.0011/69	0.0013584
50 duration	0.7094011	0.2722722	600.0	0.1757575	1.243045	0.5111969	0.2374689	0.031	0.0457664	0.9766274	0.5025632	0.1669544	0.003	0.1753387	0.8297878	0.4450997	0.251134	0.076	0.0471139	0.9373134
SO density	-0.0853451	0.2907584	0.769	-0.6552211	0.484531	0.2786561	0.0863298	0.001	0.1094528	0.4478595	-0.0445984	0.1340766	0.739	-0.3073837	0.2181869	-0.0215986	0.1750813	0.902	0.3647516	0.3215545
50 peak frequency	1.309582	1.541182	0.395	-1.71108	4.330244	1.914764	0.5111777	0	0.9128745	2.916654	0.9445372	0.4598335	0.04	0.0432802	1.845794	1.305928	1.031161	0.205	-0.715111	3.326967
50 energy	-0.000143	0.000262	0.585	-0.0006565	0.0003704	0.0000731	0.0003414	0.83	-0.000596	0.0007423	0.0003388	0.0004506	0.452	-0.0005443	0.0012219	0.0003835	0.0002841	0.177	0.0009402	0.0001733
50 ptp amplitude	-0.0031488	0.0025846	0.223	-0.0082145	0.0019168	0.0068975	0.003603	0.056	-0.0001644	0.0139593	-0.0017755	0.0039355	0.652	-0.009489	0.0059381	-0.0026126	0.0020636	0.206	0.0066572	0.0014321
False Discovery Rate correction																				

ADAS: Alzheimer's Disease Assessment Scale, cognitive subscale CVLT: California Verbal Learning Test, MMSE: Mini-mental State Examination, NREM: Non-rapid eye movement sleep, SP: spindles, SO: slow oscillations, ptp: peak to peak **Supplementary table S4:** Spindles, SO, CVLT-ROCF Cognition

Amyloid + (<600 pg/ml) only	n=19 (51.3%)	n=18(48.7%)	n=37	0.84
age	75.6 ±5.74	73.3 ±5.4	74.5±5.6	0.22
bmi	27.4 ±3.9	28.2 ±4.8	27.8 ±4.3	0.58
depression	5 (26.3%)	9 (50%)	14 (37%)	0.14
diabetes	4 (21%)	2 (11%)	6 (16 %)	0.42
education (≥ high school)	4 (21.1%)	3 (16.7%)	7 (19%)	0.73
0: no formal education	2 (10.5%)	2 (11.1%)	4 (10.8%)	
1. Primary school	13 (68.4%)	13 (72.2%)	26 (70.3%)	
2. High school	3 (15.79%)	2 (11.1%)	5 (13.5%)	
3. University	1 (5.3%)	1 (5.6%)	2 (5.4%)	
Apnoea hypoxia index (n/hrTST)	39.58 ±20.24	33.07 ±24.39	36.42 ±24.4	0.38
AD Drugs	18 (95%)	16 (89%)	34 (92%)	0.51
none	1 (5.3%)	2 (11.1%)	3(8.1%)	
Rivastigmina	5 (26.3%)	5 (27.8)	10 (27%)	
Donepezil	13 (68.4%)	8 (44.4%)	21 (56.8%)	
Memantine	0	3 (6.7%)	3 (8.1%)	
Lab values-biomarkers (pg/ml)				
Aβ42, pg/ml	450.53 ±88.0	460.22 ±84.07	455.24 ±85.05	0.73
CSF p-tau pg/ml	71.53 ±35.24	4.21 ±27.98	77.87 ±32.0	0.24
plasma tau, pgml	2.21 ±1.0	2.89 ±,93	2.55 ±1.01	0.05
CSF total tau, pg/ml	483.0 ±332.12	594.67 ±249.71	537.33 ±296.31	0.26
CSF p-tau/ AB42 ratio pg/ml	0.16 ±0.075	0.189 ±0.072	$0.1/4 \pm 0.74$	0.25
CSF total-tau/ Aβ42 ratio pg/ml	$1.09 \pm 0.75$	$1.34 \pm 0.63$	$1.21 \pm 0.70$	0.29
Cognition, mental health				0.40
ADAS-cog total score	30 (25-33)	29.5 (25-35)	30 (25-34)	0.49
ADAS-cog delayed memory	30 (25-33)	29.5 (25-35)	30 (25-34)	0.42
	/.4 ±0.3	7.6 ±5.4	7.46 ±5.8	0.88
1,1,1,1,2,1	Z3.Z ∸Z.J	ZZ.0 - Z.4	ZZ.J ∸Z.4	0.43
By amyloid status at baseline	<600 pg/ml (p 23)	>600 ng/ml (n 37)	n value	
By amyloid status at baseline	<600 pg/ml (n 23) 75 09 (4 04)	>600 pg/ml (n 37) 74 51 (5 63)	<b>p value</b>	
By amyloid status at baseline Age Female	<600 pg/ml (n 23) 75.09 (4.04) 12 (52 2%)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48 6%)	<b>p value</b> 0.67	
By amyloid status at baseline Age Female BMI	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32)	<b>p value</b> 0.67 0.79 0.70	
By amyloid status at baseline Age Female BMI Smoking history	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32)	<b>p value</b> 0.67 0.79 0.70	
By amyloid status at baseline Age Female BMI Smoking history 0. never	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%)	<b>p value</b> 0.67 0.79 0.70 0.94	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%)	<b>p value</b> 0.67 0.79 0.70 0.94	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago)	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%)	<b>p value</b> 0.67 0.79 0.70 0.94	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%)	<b>p value</b> 0.67 0.79 0.70 0.94 0.009	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST)	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3)	p value 0.67 0.79 0.70 0.94 0.009 0.17	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%)	<b>p value</b> 0.67 0.79 0.70 0.94 0.009 0.17	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%)	<b>p value</b> 0.67 0.79 0.70 0.94 0.009 0.17	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%) 11 (29.7%)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%)	<b>p value</b> 0.67 0.79 0.70 0.94 0.009 0.17	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99 ≥ 30	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%) 11 (29.7%) 19 (51.4%)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%) 8 (34.8%)	p value 0.67 0.79 0.70 0.94 0.009 0.17	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99 ≥ 30 Cognition, mental health	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%) 11 (29.7%) 19 (51.4%)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%) 8 (34.8%)	p value 0.67 0.79 0.70 0.94 0.009 0.17	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99 ≥ 30 Cognition, mental health ADAS-cog total score	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%) 11 (29.7%) 19 (51.4%) 27.43 (5.64)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%) 8 (34.8%) 30.36 (8.25)	p value 0.67 0.79 0.70 0.94 0.009 0.17 0.16	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99 ≥ 30 Cognition, mental health ADAS-cog total score ADAS-cog delayed memory	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%) 11 (29.7%) 19 (51.4%) 27.43 (5.64) 7 (6-8)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 30.36 (8.25) 7(6-7)	p value 0.67 0.79 0.70 0.94 0.009 0.17 0.16 0.15	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99 ≥ 30 Cognition, mental health ADAS-cog total score ADAS-cog delayed memory Cornell Scale (CSDD)	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%) 11 (29.7%) 19 (51.4%) 27.43 (5.64) 7 (6-8) 7 (2-11)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 30.36 (8.25) 7(6-7) 7 (3-14)	p value 0.67 0.79 0.70 0.94 0.09 0.17 0.15 0.96	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99 ≥ 30 Cognition, mental health ADAS-cog total score ADAS-cog delayed memory Cornell Scale (CSDD) MMSE baseline	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%) 11 (29.7%) 19 (51.4%) 27.43 (5.64) 7 (6-8) 7 (2-11) 23.65 (2.29)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 7 (6-7) 7 (3-14) 22.49 (3.77)	p value 0.67 0.79 0.70 0.94 0.94 0.009 0.17 0.16 0.15 0.96 0.19	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99 ≥ 30 Cognition, mental health ADAS-cog total score ADAS-cog delayed memory Cornell Scale (CSDD) MMSE baseline NPI	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%) 11 (29.7%) 19 (51.4%) 27.43 (5.64) 7 (6-8) 7 (2-11) 23.65 (2.29) 9.10 (16.14)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 7 (6-7) 7 (3-14) 22.49 (3.77) 10.75 (13.12)	p value 0.67 0.79 0.70 0.94 0.94 0.009 0.17 0.16 0.15 0.96 0.19 0.68	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99 ≥ 30 Cognition, mental health ADAS-cog total score ADAS-cog delayed memory Cornell Scale (CSDD) MMSE baseline NPI Lab values-biomarkers (pg/ml)	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%) 11 (29.7%) 19 (51.4%) 27.43 (5.64) 7 (6-8) 7 (2-11) 23.65 (2.29) 9.10 (16.14)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 30.36 (8.25) 7(6-7) 7 (3-14) 22.49 (3.77) 10.75 (13.12)	p value 0.67 0.79 0.70 0.94 0.009 0.17 0.16 0.15 0.96 0.19 0.68	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99 ≥ 30 Cognition, mental health ADAS-cog total score ADAS-cog delayed memory Cornell Scale (CSDD) MMSE baseline NPI Lab values-biomarkers (pg/ml) Aβ42, pg/ml	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%) 11 (29.7%) 19 (51.4%) 27.43 (5.64) 7 (6-8) 7 (2-11) 23.65 (2.29) 9.10 (16.14)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 7 (6-7) 7 (3-14) 22.49 (3.77) 10.75 (13.12)	p value 0.67 0.79 0.70 0.94 0.009 0.17 0.16 0.15 0.96 0.19 0.68 <0.001	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99 ≥ 30 Cognition, mental health ADAS-cog total score ADAS-cog delayed memory Cornell Scale (CSDD) MMSE baseline NPI Lab values-biomarkers (pg/ml) Aβ42, pg/ml CSF p-tau pg/ml	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%) 11 (29.7%) 19 (51.4%) 27.43 (5.64) 7 (6-8) 7 (2-11) 23.65 (2.29) 9.10 (16.14) 737.27 (145.44) 76.23 (30.90)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 7 (6-7) 7 (3-14) 22.49 (3.77) 10.75 (13.12)	p value 0.67 0.79 0.70 0.94 0.009 0.17 0.16 0.15 0.96 0.19 0.68 <0.001 0.53	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99 ≥ 30 Cognition, mental health ADAS-cog total score ADAS-cog delayed memory Cornell Scale (CSDD) MMSE baseline NPI Lab values-biomarkers (pg/ml) Aβ42, pg/ml CSF p-tau pg/ml plasma tau, pgml	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%) 11 (29.7%) 19 (51.4%) 27.43 (5.64) 7 (6-8) 7 (2-11) 23.65 (2.29) 9.10 (16.14) 737.27 (145.44) 76.23 (30.90) 2.52 (1.29)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 7 (6-7) 7 (3-14) 22.49 (3.77) 10.75 (13.12) 455.24 (85.05) 88.82 (73.70) 2.55 (1.01)	p value 0.67 0.79 0.70 0.94 0.009 0.17 0.16 0.15 0.96 0.19 0.68 <0.001 0.53 0.92	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99 ≥ 30 Cognition, mental health ADAS-cog total score ADAS-cog delayed memory Cornell Scale (CSDD) MMSE baseline NPI Lab values-biomarkers (pg/ml) Aβ42, pg/ml CSF p-tau pg/ml Plasma tau, pgml CSF total tau, pg/ml	<600 pg/ml (n 23) 75.09 (4.04) 12 (52.2%) 28.32 (5.98) 18 (78.3%) 1 (4.3%) 4 (17.4%) 15 (78.9%) 32.6 (16.4-56.3) 0 7 (18.9%) 11 (29.7%) 19 (51.4%) 27.43 (5.64) 7 (6-8) 7 (2-11) 23.65 (2.29) 9.10 (16.14) 737.27 (145.44) 76.23 (30.90) 2.52 (1.29) 558.07 (264.23)	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 30.36 (8.25) 7(6-7) 7 (3-14) 22.49 (3.77) 10.75 (13.12) 455.24 (85.05) 88.82 (73.70) 2.55 (1.01) 537.33 (296.31)	p value 0.67 0.79 0.70 0.94 0.94 0.009 0.17 0.16 0.15 0.96 0.19 0.68 <0.001 0.53 0.92 0.82	
By amyloid status at baseline Age Female BMI Smoking history 0. never 1. current 2. former (>6 mths ago) OSA diagnosis Apnoea hypoxia index (n/hrTST) 0-4.9 5-14.99 15-29.99 ≥ 30 Cognition, mental health ADAS-cog total score ADAS-cog delayed memory Cornell Scale (CSDD) MMSE baseline NPI Lab values-biomarkers (pg/ml) Aβ42, pg/ml CSF p-tau pg/ml CSF p-tau pg/ml CSF p-tau, Aβ42 ratio pg/ml	$ \begin{array}{c} < 600 \ pg/ml (n 23) \\ 75.09 (4.04) \\ 12 (52.2\%) \\ 28.32 (5.98) \\ \hline \\ 18 (78.3\%) \\ 1 (4.3\%) \\ 4 (17.4\%) \\ 15 (78.9\%) \\ 32.6 (16.4-56.3) \\ 0 \\ 7 (18.9\%) \\ 32.6 (16.4-56.3) \\ 0 \\ 7 (18.9\%) \\ 11 (29.7\%) \\ 19 (51.4\%) \\ 19 (51.4\%) \\ 27.43 (5.64) \\ 7 (6-8) \\ 7 (2-11) \\ 23.65 (2.29) \\ 9.10 (16.14) \\ \hline \\ 737.27 (145.44) \\ 76.23 (30.90) \\ 2.52 (1.29) \\ 558.07 (264.23) \\ 0.17 \pm 0.74 \\ \end{array} $	>600 pg/ml (n 37) 74.51 (5.63) 18 (48.6%) 27.81 (4.32) 29 (78.4%) 1 (2.7%) 7 (18.9%) 32 (100.0%) 23.4 (11.2-47.3) 3 (13%) 4 (17.4%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 8 (34.8%) 30.36 (8.25) 7(6-7) 7 (3-14) 22.49 (3.77) 10.75 (13.12) 455.24 (85.05) 88.82 (73.70) 2.55 (1.01) 537.33 (296.31) 0.11 ± 0.52	p value 0.67 0.79 0.70 0.94 0.94 0.009 0.17 0.16 0.15 0.96 0.19 0.68 <0.001 0.53 0.92 0.82 0.72	

**Supplementary Table S5** : Characteristics of participants with Aβ42<600 pg/ml at baseline

		Amyloid at baseline	
	<600 (SD)	>600 (SD)	Test (p)
	N=23	N=37	
TST (min)	244.80 (78.78)	270.11 (95.88)	0.293
SE (%)	58.22 (18.91)	65.08 (22.85)	0.240
WASO (min)	129.18 (59.79)	108.59 (77.73)	0.299
SOL (min)	44.09 (44.48)	36.66 (52.12)	0.573
NREM 1 (min)	65.91 (33.89)	51.45 (31.33)	0.097
NREM2 (min)	97.38 (39.04)	110.40 (68.80)	0.412
NREM3 (min)	52.04 (40.48)	73.04 (50.09)	0.096
N2+N3 dur (min)	149.43 (61.58)	183.44 (97.06)	0.139
N2N3/TST (%)	60 % (16)	64 % (20)	0.423
REM (min)	29.47 (24.15)	34.53 (31.73)	0.515
REM_latency	151.04 (94.44)	182.10 (93.12)	0.255
N1 %	29.67 (18.62)	24.00 (20.04)	0.279
N2 %	39.65 (11.78)	38.66 (15.35)	0.793
N3 %	19.97 (13.20)	25.09 (15.06)	0.185
REM %	10.73 (7.22)	12.24 (10.41)	0.545
N1 latency (min)	44.09 (44.48)	37.71 (51.57)	0.626
N2 latency (min)	49.48 (43.68)	47.55 (60.71)	0.895
N3 latency (min)	83.91 (65.36)	77.33 (72.37)	0.724
REM latency (min)	142.07 (97.58)	166.93 (102.63)	0.381
AHI (#/hr TST)	29.94 (24.67)	36.42 (22.29)	0.304

TST: total sleep time, SE: sleep efficiency, WASO: wake after sleep onset, SOL: sleep onset latency, NREM: non-rapid eye movement sleep REM: rapid-eye movement sleep, AHI: apnoea-hypopnea index

Supplementary Table S6: Sleep architecture by amyloid status

There were no statistically significant differences in total sleep time, sleep efficiency, or sleep

macro-architecture between persons with amyloid < than 600 pg/ml (AB+) or > 600 pg/ml

(AB-) (table 3) .

Sleep Spindles	Males (30)	Females (30)	All	р
NREM2				
SP density	0.4 ±0.3	0.7 ±0.3	0.6 ±0.3	0.002
SP duration	1 (1-1)	1 (1-1)	1 (1-1)	0.62
SP power	257 (151-312)	272 (221-408)	265 (188-381)	0.63
NREM3				
SP density	0 (0-1)	1 (0-1)	0 (0-1)	0.006
SP duration	1 0.7 ±0.1	1 0.7 ±0.1	1 0.7 ±0.1	0.29
SP power	223 (143-328)	315 (199-386)	243 (179-349)	0.26
Slow Oscillations				
NREM2				
SO density	2.6 ±1.0	2.6 ±0.8	2.6 ±0.9	0.87
SO duration	1 (1-2)	1 (1-1)	1 (1-2)	0.16
SO ptp amplitude	104 (79-137)	114 (76-164)	107 (77-145)	0.77
NREM3				
SO density	3 (2-3)	3 (2-4)	3 (2-4)	0.36
SO duration	2 (1-2)	2 (1-2)	2 (1-2)	0.62
SO ptp amplitude	114.6 ±65.7	125.9 ±66.2	120.2 ±65.6	0.51

NREM: non-rapid eye movement sleep REM: rapid-eye movement sleep. SP: spindles, SO: slow oscillations, ptp: peak to peak

Supplementary Material Table S7: NREM2 and NREM2 microarchitecture, whole sample

There were no statistically significant differences in SO between males and females, save for

higher SO count in NREM among females than males.

amyloid + (<600pg/ml)	Male (n=19)	Female (n=18)	Total (n=37)	р
Total sleep time- TST (min)	261.6 (172-328)	302.8 (258.5-359)	274.1 (218-343.5)	0.10
Total time in bed (min)	405.2 ±35.9	424.2 ±26.6	414.41 ±32.7	0.08
Sleep efficiency (%)	61.8 (50.6-80.3)	70.95 (59.4-82.6)	70.7 (53.9-80.8)	0.24
Sleep onset latency (min)	17.6 (6-27.9)	23.7 (11.3-67.9)	20.3 (10.8-33)	0.57
Wake after seep onset (min)	146 (56.5- 193.3)	71.55 (39.8-100.7)	79.4 (52.1-161.5)	0.08
NREM 1 (min)	31.1 (13.4-46.7)	12.45 (8.4-20.5)	17.6 (9.3-32)	0.06
NREM2 (min)	97.7 ±74	123.8 ±62.1	110.40 ±68.80	0.14
NREM3 (min)	53.82 ±49.8	93.3 ±42.9	73.04 ±50.09	0.003
N2+N3min/TST (%)	55.5 ±21.6	72.2 ±14.8	63.1 % (20.23)	0.01
REM (min)	30 (9-44)	25 (16.5-45.5)	28.5 (14.5-44)	0.95
NREM1 (% of TST)	31.1 (13.4-46.7)	12.45 (8.4-20.5)	17.6 (9.3-32)	0.008
NREM2 (% of TST)	37.06 ±17.04	40.34 ±17.04	38.66 ±15.35	0.52
NREM3 (% of TST)	25.09 ±14.92	32.17 ±11.88	25.09 ±15.06	0.004
REM (% of TST)	9 (3.3-17.3)	11.55 (5.4-14.1)	11.3 (5.4-16.2)	0.72
Sleep spindle (SP)				
NREM2+NREM3				
SP density	0.442 ±0.28	0.595 ±0.252	0.517 ±0.274	0.09
SP duration	0.697 ±0.758	0.7 ±0.048	0.699 ±0.063	0.88
SP power	234.06 ±181.69	300.16 ±112.66	266.22 ±153.69	0.20
NREM2				
SP density	0.454 ±0.288	0.626 ±0.233	0.538 ±0.276	0.06
SP duration	0.7 (0.66-0.73)	0.71 (0.67-0.72)	0.071(0.66-0.72)	0.89
SP power	196.39 (125.56-	279.64 (210.9-374)	241.91 ((161.68-	0.20
	269.88)		304.23)	
Slow Oscillations (SO) NREM2+NREM3				
SO density	2.63 ±0.99	2.75 ±0.77	2.48 ±0.94	0.47
SO duration	1.49 (1.46-1.55)	1.51 (1.47-1.53)	1.5 (1.46-1.54)	0.84
SO ptp amplitude	117.473 ±46.7	111.79 ±47.99	114.68 ±46.74	0.72
NREM3				
SO density	2.29 ±1.25	2.63 ±1.11	2.46 ±1.81	0.39
SO duration	1.49 (1.46-1.55)	1.51 (1.5-1.53)	1.50 (1.46-1.54)	0.63
SO ptp <b>amplitude</b>	106.44 ±66.87	116.11 ±62.88	111.14 ±64.24	0.65

NREM: non-rapid eye movement sleep REM: rapid-eye movement sleep. SP: spindles, SO: slow oscillations, ptp: peak to peak

**Supplementary material Table S8.** Sleep microarchitecture among persons with amyloid beta <600 pg/ml at baseline

Amyloid-positive females spent more time in NREM3, both in minutes and as the percentage of their total sleep time (p= 0.003) and NREM2 and NREM3 as a percentage of total sleep time (p=0.006) than A $\beta$ + males, who spent less time in NREM3 and had statistically greater percentage of NREM1 sleep out of their total sleep time than females.

amyloid + (<600 pg/ml)	n=19	n=18	total	p value
Mini mental stage exam (MMSE)				
baseline	23.2 ±2.5	22.6 ±2.4	22.9 ±2.4	0.49
12 months	22.9 ±2.7	21.2 ±3.4	22.1 ±3.1	0.01
24 months	21.5 ±3.9	18.6±3.5	20.2 ±3.9	0.04
36 months	20.6 ±4.3	17.7 ±4.4	19.3 ±4.5	0.22
Change from base to 36 months	-2.89 ± 3.26	-4.57 ±4.99	-3.63 ±4.1	0.43
ADAS-cog				
total score	30 (25-33)	29.5 (25-35)	30 (25-34)	0.49
total score 12m	30 (25-33)	29.5 (25-35)	30 (25-34)	0.42
California Verbal Learning Test				
Short-term verbal memory, base	-1.7 ± 0.82	-1.4 ± 1.7	-1.6 ± 1.3	0.59
Short-term verbal memory 12m	-1.7 ± 0.75	-1.9 ± 1.2	-1.8 ± 1	0.51
Long term verbal memory base	-1.7 ±.0.89	-1.8 ±1.3	-1.8 ±1.1	0.68
Long term verbal memory 12m	-1.9 ±0.87	-2.4 ±1.5	-2.2 ±1.2	0.29
Rey–Osterrieth				
Long-term visual memory, base	6 (4-9)	2 (2-6)	5 (2-7)	0.31
long-term visual memory 12m	2 (5.5-8)	2 (2-6)	3 (2-7)	0.74
Copy-recall, baseline	7.1 ±3.5	7 ±4.4	7 ±3.9	0.97
Copy-recall 12m	6.6 ±2.8	5 ±2.4	5.8 ±2.7	0.08

ADAS: Alzheimer's Disease Assessment Scale, cognitive subscale,

**Supplementary material Table S9:** Cognition among person with amyloid beta <600pg/ml at baseline

Among amyloid-positive participants, females had a greater decline in cognitive performance

on the MMSE at 36 months than males, though the difference was not statically significant.

# Appendix II: Supplementary material for chapter III

"Sleep microarchitecture predicts neurofilament-light, neuroinflammatory biomarkers, and cognition in Alzheimer's Disease."

Following pages:

**eTable 1:** Sleep spindle and SO characteristics predict NfL, Ng-36, YKL-40 and ratios, adjusted for APOE4.

Spindles	NREM2				
CSF-NfL	coef	SE	P value	95%Cl lower	upper
SP duration	-2751.72	677.2248	0.000*	-4126.56	-1376.881
SP density	325.1979	229.6481	0.165	-140.55	790.9459
SP power	-1.366974	.3132021	0.000*	-2.002808	7311394
Plasma NfL					
SP duration	37.88897	19.28434	0.057	-1.117282	76.89522
SP density	1.481757	5.895541	0.803	-10.4431	13.40661
SP power	0131499	.0085059	0.130	0303547	.0040548
NG-36					
SP duration	-406.3935	399.3046	0.315	-1215.462	402.6746
SP density	-41.72292	73.67342	0.575	-190.867	107.4211
SP power	0736801	.0884974	0.410	252993	.1056327
CSF YKL-40					
SP duration	360.7332	366.0517	0.331	-381.654	1103.12
SP density	-27.3937	80.13521	0.734	-189.9154	135.128
SP power	3113961	.2574765	0.234	8335827	.2107905
CSF NfL/AB42					
SP duration	3185097	3.206329	0.921	-6.834553	6.197534
SP density	.6406506	.6774285	0.351	7360498	2.017351
SP power	002985	.0008428	0.001*	0046978	0012721
CSF YKL-40/AB42					
SP duration	.5964513	.6620412	0.374	7475638	1.940466
SP density	1349536	.1956853	0.495	5322158	.2623086
SP power	0004418	.0001846	0.022	0008165	000067
Slow oscillations	NREM3				
CSF-NfL	coef	SE	P value	95%Cl lower	upper
SO duration	197.1932	250.0177	0.435	-309.8661	704.2526
SO density	20.69929	94.50891	0.828	-170.9737	212.3722
SO ptp amplitude	-3.676372	2.783613	0.195	-9.321801	1.969057
Plasma NfL					
SO duration	9.465808	4.654712	0.05	.0582845	18.87333
SO density	-11.5991	1.84226	0.000*	-15.32244	-7.875752
SO ptp amplitude	.2187332	.0556139	0.000*	.1063334	.3311331
NG-36					
SO duration	-96.31514	64.25545	0.143	-226.6312	34.00095
SO density	45.25346	24.28913	0.071	-4.007177	94.5141
SO ptp amplitude	6563659	.7153986	0.365	-2.107261	.7945296
CSF YKL-40					
SO duration	-67.81596	70.0662	0.340	-209.9168	74.28487
SO density	1.700496	26.74715	0.950	-52.54523	55.94622
SO ptp amplitude	1701593	.4548606	0.711	-1.092659	.7523408

CSF NfL/AB42					
SO duration	.2879918	.5106699	0.576	7487231	1.324707
SO density	1334058	.1954132	0.499	5301156	.263304
SO ptp amplitude	0034196	.0033172	0.310	0101539	.0033146
CSF YKL-40/AB42					
SO duration	1420198	.1566861	0.371	4601094	.1760698
SO density	0591345	.0622957	0.349	1856016	.0673325
SO ptp amplitude	0001144	.0010297	0.912	0022048	.001976

Aβ42: Beta-amyloid, NfL: neurofilament light-chain, NG-36: neurogranin 36, YKL-40: Chitinase-3-like protein, SP: spindles, SO: slow oscillations, ptp: peak to peak, NREM: non-rapid eye movement sleep

**eTable 1:** Sleep spindle and SO characteristics predict NfL, Ng-36, YKL-40 and ratios, adjusted for APOE4.

	coef	SE	P value	95%CI lower	upper
CSF-NfL					
Αβ42	1572719	.5098966	0.759	-1.188635	.8740914
ptau181	.5941694	.9583706	0.539	-1.34277	2.531109
total tau (tTau)	.5789582	.2092487	0.009*	.1560508	1.001866
ptau181/Aβ42	.0001	.0000179	0.015*	9.25e-06	.0000817
total tau/Aβ42	.0005189	.0001501	0.001*	.0002152	.0008226
CSF NG-36	.0909046	.0309828	0.006*	.0282359	.1535732
CSF YKL-40	.0133266	.0187613	0.482	0245914	.0512446
YKL-40/Aβ42	.0000916	.0000914	0.322	0000933	.0002765
plasma NfL					
Αβ42	-3.240285	1.590059	0.049	-6.462051	0185184
ptau181	1350565	.2495413	0.592	6402264	.3701134
total tau (tTau)	-1.459514	2.289422	0.528	-6.094206	3.175178
ptau181/Aβ42	.0018402	.0007566	0.020*	.0003057	.0033747
total tau/Aβ42	0030058	.0052577	0.571	0136496	.0076379

Aβ42: Beta-amyloid, NfL: neurofilament light-chain, NG-36: neurogranin 36, YKL-40: Chitinase-3-like protein, ptau181: phosphorylated tau 181

eTable 2: Associations between CSF and NfL and AD biomarkers

NfL/Aβ42 and ADAS-cog at	Est	Se	р
baseline			
Sobel	-0.015	-2.01	0.04
Aroian	-0.015	-1.98	0.04
Goodman	-0.015	-2.04	0.04
Proportion of total effect that is mediated	0.57		
NfL/Aβ42 and MMSE at 12 months	Est	Se	р
Sobel	0.005	0.002	0.02
Aroian	0.005	0.002	0.02
Goodman	0.005	0.002	0.02
Proportion of total effect that is mediated	0.28		

Aβ42: Beta-amyloid, NfL: neurofilament light-chain, ADAS-cog: Alzheimer's Disease Assessment Scale, cognition subscale, MMSE: Mini Mental State Examination

**eTable 3:** Mediating roles for NfL/A $\beta$ 42 and YKL-40/ A $\beta$ 42 in the relationship between sleep spindles and SO and cognition in mild-to-moderate AD.

NfL moderates relationship	coef	se	р	95% CI lower	upper
between sleep and:					
ADAS-cog at baseline					
SO density	.0071457	.0022909	0.004	.0024995	.0117919
SO peak to peak (ptp)	.0001827	.0000772	0.023	.0000262	.0003392
SO duration	.0190373	.0061722	0.004	.0065194	.0315551
ADAS-cog at 12 months					
Spindle power	.00012	.00005	0.029	.00001	.000215
SO peak-to-peak	.00022	.00009	0.019	.00004	.000394
So density	.0073946	.0031731	0.026	.0009462	.0138431
MMSE at 12 months					
Spindle density	0040758	.0018569	0.035	0078455	000306
Spindle power	-5.58e-06	2.48e-06	0.031	0000106	-5.56e-07
MMSE at 24 months					
Spindle power	0000267	.000012	0.035	0000513	-2.01e-06
MMSE at 36 months	1299747	.0279786	0.001	1932666	066683
Spindle power	.0002095	.0000896	0.048	2.79e-06	.0004162
SO duration	1299747	.0279786	0.001	1932666	066683
SO ptp	0002683	.0000724	0.005	000432	0001046
Sleep moderates: NfL and:					
ADAS-cog baseline					
SO density	.0071457	.0022909	0.004	.0024995	.0117919
SO peak-to-peak	.0001827	.0000772	0.023	.0000262	.0003392
SO duration	.0190373	.0061722	0.004	.0065194	.0315551
ADAS-cog 12					
SO energy	.0001136	.0000499	0.029	.0000123	.0002149
SO density	.0073946	.0031731	0.026	.0009462	.0138431
MMSE 36 months					
SO ptp	0002683	.0000724	0.005	000432	0001046
NfL/Aβ42 moderates the					
relationship between:					
Sleep and ADAS-cog at baseline					
SO density	7.313159	1.914998	0.001	3.429363	11.19695
SO duration	18.39841	5.403878	0.002	7.438841	29.35798
Sleep and ADAS-cog at 12					
months					
SO density	8.961244	2.450947	0.001	3.985556	13.93693
Sleep and MMSE 12					
Spindle power	006312	.0023952	0.012	0111745	0014494
Spindle duration	-2.832905	11.78446	0.012	-26.78181	-0.811
SO density	-1.773641	.8623727	0.047	-3.524351	0229312
SO ptp	0430679	.0197839	0.036	0832314	0029044
Sleep and MMSE 24					
Spindle power	0094019	.0032132	0.007	0159837	00282
Spindle duration	-37.63196	14.59755	0.016	-67.58366	-7.68025
Sleep moderates between					
NfL/Aβ42 and:					
ADAS-cog baseline					
SO density	7.313159	1.914998	0.001	3.429363	11.19695
SO duration	18.39841	5.403878	0.002	7.438841	29.35798
ADAS-cog 12m					
SO density	8.961244	2.450947	0.001	3.985556	13.93693
Sleep moderates <b>NfL/Aβ42 and</b>					
MMSE 12m					
Spindle power	006312	.0023952	0.012	0111745	001449

SO density	-1.773641	.8623727	0.047	-3.524351	0229312
SO ptp	0430679	.0197839	0.036	0832314	0029044
Sleep moderates NfL/Aβ42 and MMSE 24 months					
Spindle energy	0093395	.0032909	0.009	0160918	002587
Spindle duration	-37.63196	14.59755	0.016	-67.58366	-7.68025
YKL-40 moderates relationships	coef	se	р	95% CI lower	upper
between sleep and:			-		
ADAS cog baseline	.0001114	.0000506	0.034	8.88e-06	.0002139
Spindle power					
MMSE baseline					
SO ptp	0001588	.0000767	0.045	0003142	-3.54
MMSE 12 months					
Spindle power	0000576	.0000175	0.002	0000932	000022
Spindle duration	0957076	.0433282	0.034	1835813	007834
MMSE 24 months					
Spindle power	000103	.000027	0.001	0001584	0000476
SO density	0084627	.0038446	0.036	0163513	0005742
SO duration	.1750756	.0810666	0.040	.0084408	.3417104
MMSE 36 months					
SO ptp	.0006728	.0002323	0.016	.0001552	.0011903
Sleep moderates between YKL-					
40 and:					
ADAS-cog at baseline					
Spindle power	.0001114	.0000506	0.034	8.88e-06	.0002139
MMSE baseline					
SO ptp	0001588	.0000767	0.045	0003142	-3.54
MMSE 12 months					
Spindle power	0000576	.0000175	0.002	0000932	0000221
Spindle duration	0957076	.0433282	0.034	1835813	0078339
MMSE 24 months					
Spindle power	0001028	.000028	0.001	0001604	0000453
SO density	0084627	.0038446	0.036	0163513	0005742
SO duration	.1750756	.0810666	0.040	.0084408	.3417104
MMSE 36 months					
SO ptp	.0006728	.0002323	0.016	.0001552	.0011903
YKL40/Aβ42 moderates					
relationships between sleep and:					
ADAS-cog at baseline	0115070	101710	0.040	0001000	4000007
Spindle power	.2145372	.101749	0.042	.0081806	.4208937
	6.999151	3.2174	0.036	.4800799	13.51822
MMSE baseline	0011000	0010700	0.010	1 4 4 5 0 7 7	0170000
	0811992	.0312728	0.013	1445077	0178906
MMSE 12 months	0100740	0070000	0.000	0004000	001400
Spindle duration	0169746	.0076388	0.033	0324668	001483
Spindle duration	-57.90105	25.75665	0.031	-110.1898	-5.61227
Prindle neuror	0450000	017100	0.014	000750	010040
Spinule power	0403988	1 600051	0.014	000/52	010046
	-5.104402	1.022051	0.004	-0.432377	-1.//023
Prindle duration	60,00005	20 70 45 0	0.040	6150054	107 4400
So ntn	09.02925	0021700	0.048	1029510.	137.4432
Sleen moderatos hotwaan VVI	.2403102	.0331708	0.024	.0309127	.4041070
A0/ AB/2 and					
ADAS-cog baseling					
ADAD-COR DASELILLE			1		

Spindle power	.2145372	.101749	0.042	.0081806	.4208937
SO density	6.999151	3.2174	0.036	.4800799	13.51822
MMSE baseline					
SO ptp	0811992	.0312728	0.013	1445077	017891
MMSE 12 months					
Spindle power	0169746	.0076388	0.033	0324668	0014825
Spindle duration	-57.90105	25.75665	0.031	-110.1898	-5.612269
MMSE 24 months					
Spindle power	0605478	.0135127	0.000	0883235	0327721
MMSE 36 months					
Spindle duration	69.02925	30.70453	0.048	.6152951	137.4432

Aβ42: Beta-amyloid, NfL: neurofilament light-chain, NG-36: neurogranin 36, YKL-40: Chitinase-3-like protein, SP: spindles, SO: slow oscillations, ptp: peak to peak ADAS: Alzheimer's Disease Assessment Scale, cognitive subscale CVLT: California Verbal Learning Test, MMSE: Mini-mental State Examination

eTable 4: Moderating relationships: biomarkers, sleep, cognition

### STROBE Statement—Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the	1
The and abstract	1	abstract	
		(b) Provide in the abstract an informative and balanced summary of what was	2-3
		done and what was found	
In two des ett on			
Background/rationale	2	Explain the scientific background and rationals for the investigation being	4-6
Background/fationale	2	explain the scientific background and rationale for the investigation being	
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Mathada	5	State opeome objectives, menading any prospective hypotheses	
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting locations and relevant dates including periods of	7-8
Setting	5	recruitment exposure follow-up and data collection	
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of	7-8
1 un no spunio	Ū	participants. Describe methods of follow-up	
		(b) For matched studies, give matching criteria and number of exposed and	n/a
		unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and	7-11
		effect modifiers. Give diagnostic criteria, if applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of	7-11
measurement		assessment (measurement). Describe comparability of assessment methods if	
		there is more than one group	
7Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,	9-13
		describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for	9-13
		confounding	1.0
		(b) Describe any methods used to examine subgroups and interactions	13
		(c) Explain how missing data were addressed	n/a
		(d) If applicable, explain how loss to follow-up was addressed	n/a
		(e) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study-eg numbers potentially	7-8
		eligible, examined for eligibility, confirmed eligible, included in the study,	
		completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	32
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social)	13-
		and information on exposures and potential confounders	33-
			34
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	

Main results	16	( <i>a</i> ) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14- 16,35- 40
		(b) Report category boundaries when continuous variables were categorized	n/a
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	12-13, 16
Discussion			
Key results	18	Summarise key results with reference to study objectives	17-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or	21-22
		imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20-21, 23
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other informati	on		·
Funding	22	Give the source of funding and the role of the funders for the present study and, if	31
		applicable, for the original study on which the present article is based	

\*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

eFigure 1: STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement checklist

#### Appendix III: Supplementary material for chapter IV

"Exercise interventions benefit sleep in older adults: A systematic review and meta-analysis."

#### Figure 1: Search strategies

#### PubMed

(((((((("acute exercise"[Title/Abstract]) OR ("acute physical activity"[Title/Abstract])) OR (("physical activity"[Title/Abstract]) OR ("exercise"[Title/Abstract]))) OR ("strengthening"[Title/Abstract])) OR ("strength training"[Title/Abstract] OR "strength program"[Title/Abstract] OR "interval training"[Title/Abstract]) OR "conditioning"[Title/Abstract] OR "aerobic"[Title/Abstract]) AND ("sleep"[Title/Abstract]) OR (sleep quality[Title/Abstract])) AND (("clinical trial"[Publication Type] OR ((clinicalstudy[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR meta-analysis[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] AND ("middle aged"[MeSH Terms] OR "aged"[MeSH Terms] OR "middle aged"[MeSH Terms] OR "aged"[MeSH Terms] OR "aged, 80 and over"[MeSH Terms])) NOT ("parkinson s"[Title/Abstract] AND ((clinicaltrial[Filter]) AND (aged[Filter] OR 80andover[Filter]))) NOT ("diet"[All Fields] AND ((clinicaltrial[Filter] OR meta-analysis[Filter] OR randomized controlled trial [Filter] OR systematic review [Filter]) AND (middleagedaged[Filter] OR middleaged[Filter] OR aged[Filter] OR 80andover[Filter]))) AND ((clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (middleagedaged[Filter] OR middleaged[Filter] OR aged[Filter] OR 80andover[Filter]))) NOT ("parkinsons"[All Fields] AND ((clinicaltrial[Filter] OR metaanalysis[Filter] OR randomized controlled trial[Filter] OR systematic review[Filter]) AND (middleagedaged[Filter] OR middleaged[Filter] OR aged[Filter] OR 80andover[Filter]))) AND ((clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (middleagedaged[Filter] OR middleaged[Filter] OR aged[Filter] OR 80andover[Filter]))) NOT ((("parkinson s"[Title/Abstract]) OR ("parkinsons disease"[Title/Abstract])) OR ("parkinson s disease"[Title/Abstract]) AND ((clinicaltrial[Filter]

OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (middleagedaged[Filter]

## Pubmed: Search for un-indexed

Search: (((((("exercise"[Title/Abstract]) OR ("physical activity"[Title/Abstract])) OR ("interval training"[Title/Abstract])) OR ("strengthening"[Title/Abstract])) OR
("conditioning"[Title/Abstract])) OR ("aerobic"[Title/Abstract])) AND ("sleep"[Title/Abstract])
Filters: Clinical Study, Clinical Trial, Clinical Trial, Phase II, Clinical Trial, Phase II, Clinical Trial, Phase IV, Controlled Clinical Trial, Meta-Analysis, Pragmatic Clinical Trial, Preprint,
Randomized Controlled Trial, Systematic Review, in the last 1 year

### Embase

((sleep:ab,ti OR insomnia:ab,ti) AND exercise:ab,ti OR physical activity':ab,ti OR 'resistance training':ab,ti OR 'aerobic exercise':ab,ti OR exercise:ab,ti NOT 'obese patient':ti,ab,kw NOT 'parkinson disease':ti,ab,kw NOT fibromyalgia:ti,ab,kw NOT cancer:ti,ab,kw NOT obese:ti,ab,kw NOT 'chronic obstructive lung disease':ti,ab,kw NOT 'heart disease':ti,ab,kw NOT 'stroke' ti,ab,kw NOT 'rheumatoid arthritis':ti,ab,kw NOT 'lupus erythematosus':ti,ab,kw) AND ([aged]/lim OR [middle aged]/lim OR [very elderly]/lim) AND ('clinical trial'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'human'/de OR 'intervention study'/de OR 'meta analysis'/de OR 'pilot study'/de OR 'randomized controlled trial'/de OR 'systematic review'/de)

## Scopus

((TITLE-ABS-KEY ( sleep ) OR TITLE-ABS-KEY ( insomnia ) AND TITLE-ABS-KEY ( exercise ) OR TITLE-ABS-KEY ( "physical activity" ) AND NOT TITLE-ABS-KEY ( parkinson's ) AND NOT TITLE-ABS-KEY ( diabetes ) AND NOT TITLE-ABS-KEY ( fibromyalgia ) ) ) AND ( older AND adults ) OR ( elderly ) OR ( senior ) AND ( LIMIT-TO ( EXACTKEYWORD , "Controlled Study" ) )

## Cochrane Library

(sleep):ti,ab,kw OR (insomnia):ti,ab,kw AND (exercise):ti,ab,kw OR (physical activity):ti,ab,kw AND (older adults):ti,ab,kw OR ("pensioner"):ti,ab,kw OR ("old age"):ti,ab,kw OR ("elderly"):ti,ab,kw NOT (apnea) NOT ("fibromyalgia syndrome"):ti,ab,kw NOT ("Cancer"):ti,ab,kw NOT ("Parkinsons disease"):ti,ab,kw NOT (stroke):ti,ab,kw

# Exercise Intensity categories

Intensity	HRmax	HRR	VO2max	METs	Borg RPE
Low	<64%	<40%	≤ 45%	<3	<11 Very light to light
Moderate	64-76%	40-60%	46-63%	3-5.9	12–13 Fairly light to somewhat hard
High (vigorous)	≥77%	>60%	64-90	6.0-8.7	14–17 Somewhat hard to very hard

Table: 2 Exercise intensity categories according to ACSM guidelines

Main findings	A single session of light-intensity walking led to a modest reduction in sleep latency and improvement of sleep efficiency in older women with mild sleep impairment. exercise group had significantly reduced sleep latency (SMD 0.58, 95% cl 0.08 to 1.08], and medication use (SMD 0.44, 95% cl 0.14 to 0.74]. Groups did not differ significantly in sleep duration, sleep efficiency, sleep disturbance, or daytime functioning.	No main effects were found for the acute exercise challenge, post hoc analyses showed that high levels of body heating during exercise predicted increased sleep fragmentation for both fit and sedentary subjects.	Resistance group: lower rate of awakening during the night and a lower percentage of time spent in stage-1 sleep compared to the control group. A session of resistance training at 60% of one repetition maximum was able to modify sleep patterns in men aged 65–80 years.	Main findings	A 12-month walking exercise intervention improved sleep quality in older adults. The high step count-
Sleep measures	Actigraph, worn on the nondominant wrist for 4 nights: sleep latency, total counts, sleep efficiency, total sleep efficiency, total sleep time [TST], wake after sleep onset (WASO), number of awakenings, length of awakenings, time in bed. Sleep log/diary	PSG One control PSG and one PSG night after exercise. At least a 7-day interval between PSGs.	PSG: TST, SE, SI, WASO,SWS, REM, non REM sleep	Sleep measures	PSQI and daytime sleepiness with the
Exercise and/or control intervention	Light intensity treadmill for 50 minutes (10 minutes of warm-up, 30 minutes of walking at 45% to 55% of age- predicted maximal heart rate (MaxHR), and 10 minutes of cool- down) in the afternoon Quite rest control	HIIT (Borg hard/very hard) exercise on bicycle ergometer 40-42 minutes to exhaustion. 1 bout.	50-60 min resistance exercise at 60% of the 1RM	Exercise and/or control intervention	Daily walking program, step count measured by
Exercise intensity: 1: low 2: mod. 3. high		m	7 7	Exercise intensity: 1: low 2: mod. 3. high	1 and 2
Sample age and eligibility criteria	55+ Mean 60.4 (+/-4.7) Community dwelling, sedentary women: no cognitive Impairment, reporting poor sleep quality but not taking sleep/psychotropic medications; no clinical diagnosis of sleep apnea or other sleep disorder	60+ mean age 65.41 12 aerobically fit and 12 sedentary older men. Excluded if smokers, history of major medical or psychiatric illness or or psychiatric illness or or psychiatric illness or antidepressive or antidepressive or antidepressive or anxiolytic meds. No sleep disorders.	65-80 Mean age ex group 67.77 ± 2.16 Sedentary and healthy men. Exclusion: known cardiovascular, pulmonary, and pulmonary, and musculoskeletal system diabetes, use of sleep medication	Sample age and eligibility criteria	60+ Mean age 72.3
z	40	24	40	z	190
Title	Effects of an Acute Bout of Light- Intensity Walking on Sleep in Older Women with Sleep Impairment: A Randomized Controlled Trial	Aerobic Fitness, Acute Exercise and Sleep in Older Men	The effects of a session of resistance training on sleep patterns in the elderly.	Tite	Effects of the 12 months walking
Clinical Trials: Acute exercise	Chen et al, 2019 <sup>1</sup>	Edinger et al, 1993²	Viana et al, 2012³	Chronic Exercise Programs, PSQI < 5 at baseline or no sleep disorders	Aoki et al, 2017 <sup>4</sup>

 Table 1: Included interventional studies and their characteristics (pages 357-377)
h				
walking exercise group showed significant improvements in ESS (p <0.01), PSQI global score (p <0.01), subjective sleep quality (p <0.05), sleep disturbance (p <0.05) compared to baseline scores.	Reduction in sleep fragmentation index of 18.9 for AG and 13 for ARG ( $p < 0.01$ ). Sleep efficacy improved in the exercise groups, with Sleep for ARG ( $p = 0.02$ ) and a 6.1% increase for ARG ( $p = 0.01$ ). Sleep quality: Percentage of minutes motionless increased by 8.2% for AG and 6.9% for ARG ( $p < 0.01$ )	At 3 and 6 months, participants in exercise group had improved overall sleep quality, sleep latency and sleep duration compared with control group. Significant changes continued throughout the six- month study. 1-26 points lower (PSQIO exercise than control group	Improved sleep quality in yoga group compared to controls. sleep latency, daytime dysfunction decreased, subjective sleep quality improved.	Significant groupxtime interaction effects were found in sleep onset latency, F(1,58)=6.921, p=.011, partial eta squared=.011, and in sleep efficiency, F(1,
Epworth Sleepiness Scale: ESS Baseline PSQL 4.5±2.61	Actigraphy On non-dominant wrist, Continuously and continuously and recorded at one-minute intervals during wake fulness and sleep. Sleep diary	PSQI Baseline scores: 4.06 control 5.02 experimental	PSQI Baseline group score: 4.65 (3.16)	Actigraphy measured sleep parameters and sleep diaries
accelerometer/pedometer, over a 12-month period. Participants encouraged to increased step-count monthly until they reached average of 10,000 average of 10,000 steps/day. Non-exercise control group instructed to maintain their typical daily routines.	Exercise 3x/week, 25-30 minutes, over 10 weeks for 30 sessions. 3 groups: aerobic group (AG), combined aerobic and resistance group (ARG), and control untrained group (CG) Heart rate monitoring with Polar monitor, Borg perceived exertion scale	Elastic band (SEB) exercise programme and aerobic exercises, 3x/week for 40 minutes for 6 months. control group: usual routines	3x/week, 70-min silver yoga exercise program for 6 months. Wait list control	2x/week, 60 minute aquatic exercise program over 8- weeks
	0	2	1	1
Healthy, community dwelling older adults with no contraindications for exercise. Participants already walking 10,000/steps per day at baseline were excluded.	60-70 (68.5 ± 5.1) taking antihypertensive Exclusion: factors that might interfere with exercise or assessment of the effect of exercise: previous diagnosis of cerebrovascular, cardiac, pulmonary, or musculoskeletal diseases, diabetes melitus, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyperthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism, hyberthyroidism,	65+ Community dwelling adults, no dementia or cognitive issues, no mobility issues, sedentary	60+ community-dwelling older adults, independent mobility, no cognitive disorders	55-70 mean age 65.7
	4	199	128	67
exercise intervention on sleep quality in older adults	Effect of different types of exercise on sleep quality of elderly subjects	Self-perceived health status and sleep quality of older adults living in community after eastic band exercises	Sleep quality, depression state, and health status of older adults after silver yoga exercises: cluster randomized trial	Effects of Aquatic Exercise on Sleep in Older Adults with
	Bonardi et al, 2016 <sup>5</sup>	Chan and Chen, 2017 <sup>6</sup>	Chen et al, 2009 <sup>7</sup>	Chen et al, 2016 <sup>8</sup>

61)=16.909, p<0.001, partial eta squared=.217. The exercise group report- ed significantly less time on sleep onset latency (mean difference=7.9 min) and greater sleep efficiency (mean difference= 5.9 %) than the control group at post-test. There was no significant difference between groups in change of total sleep time, wake after sleep onset, activity total sleep time, wake after sleep onset, activity counts, or number and length of awakenings.	Practicing Tai Chi for 24 weeks positively affected sleep quality among older adult women. PSQJ scores in the Tai Chi group decreased at week 24 by 18.8%, 24.7%, 5.7% and 24.6. At week 28, PSQJ scores in the Tai Chi group decreased by 20.4%. Improving sleep quality was sustained 4 weeks after Tai Chi was stopped.	In exercise group, significantly reduced frequency of feeling fatigued, and improvement in quality of sleep at follow-up (p < 0.05). no such changes observed in the control group.	higher subjective sleep quality, and less daytime dysfunction in exercise than control group.
	PSQI *No baseline or follow-up PSQI scores are reported- only percentage decrease. Emailed authors for access to PSQI scores	Custom Quality of sleep scores, points assigned to each item based on yes or no answers. light sleep, lying awake in bed, sleeping but still waking several times during the night (0–3). Lower score represents better quality of sleep.	PSQI and SF-12 baseline mean global PSQI 3.14 (SD: 3.01)
	Tai Chi group practised 24- form simplified Tai Chi exercises for 24 weeks (3X/ week, 60 minutes/session, including 5-minute warm- up and relaxation) control group was required to maintain their usual home lifestyle for the 28- weeks study period, without additional regular physical exercise. Participants tracked and followed by telephone or face-to-face to assess living conditions and ensure they were not performing other forms of physical exercise or taking medication affecting mental status or sleep. Participants that did not meet these not meet these analyses.	Ex group: regular moderate-intensity (3METs; metabolic equivalents) exercise, 3 x/ week for 12 weeks. Control: no ex Adherence monitored.	3 x/week with instructor for 6 months, 40 min exercise followed by
	7	2	1
Community dwelling, no cognitive or psychiatric impairments, no diagnosed sleep disorders or apnea, cardiovascular disease or conditions disease or conditions limiting participation in moderate intensity exercise.	60-70 mean 65.1 (+-2.2) healthy, sedentary older women who passed health questionnaires and physical examinations; were in the postmenopausal stage; and were not taking any medication affecting mental status and sleep. Exclusion: Women with movement disorders, obvious joint injuries, and cardiovascula diseases and those who practised regular Tai chi or other physical exercise in the last 1 year.	65+ (mean 73.7) Healthy, sedentary, community dwelling caregivers of persons with AD. Exclusion: history of stroke, MI, or any serious medical condition precluding ex	65+ mean 74.25 (SD 5.73) Recruited from community care centres:
	6 E	31	232
Mild Sleep Impairment: a Randomized Controlled Trial	Effect of Tai Chi on symptoms and sleep quality among older adult women after exercise cessation	Influence of regular exercise on subjective sense of burden and physical symptoms in community- dwelling caregivers of dementia patients: A randomized controlled trial	Self-Perceived Health and Sleep Quality of Community Older
	cheng et al, 2021 <sup>9</sup>	Hirano et al, 2011 <sup>10</sup>	Hsiao et al, 2018 <sup>11</sup>

	<ul> <li>Iity Participants in Tai Chi ex greater improvement in PSQI/sleep quality than HE control. Persons with poor sleep quality also showed significant improvements in PSQI global score (P &lt; 0.001) as well as in the sleep parameters of rated sleep quality (P &lt; 0.05), habitual sleep parameters of rated sleep quality (P &lt; 0.05), habitual sleep efficiency (P &lt; 0.01).</li> </ul>	quality Statistically significant improved sleep quality in exercise group.	he Significant difference on the sleep subscale of the TAAQOL between the intervention and control groups at 6 months ( (F = 3.07; P < 0.05). AQOL) <sup>15</sup>	Exercise group showed significant improvements in sleep quality on PSQI sleep quality (p<.05) tible 3), fall age factual
	PSQI for sleep qual two groups: PSQI < PSQI < 5 group (n= baseline: 2.96 (0.85) ex 2.52 (1.18)control	Customized sleep of measure	Sleep subscale of ti TNO-AZL adult quality of life questionnaire (TAA	PSQI Only items subjecti sleep quality (possi subscale score, 0 sleep latency (i.e., average time in minutes needed to asleep) and sleep duration (i.e., avera duration (i.e., avera) duration (i.e., avera) du
relaxation. 6 months DVD instruction after.	40 minutes Tai Chi 3 x/ week for a total 120 minutes/week for 16 weeks. Control: matched quantity health education	50 minute,3 x week/12 weeks lower-extremity exercise intervention	15 60-min exercise sessions following Groningen active lliving model (GALM): moderate intensity recreational sports activities and consists of fife of min sessions at a frequency of once a week Wait-list control	12 months of home-based, telephone-supervised, moderate-intensity exercise: 4 x 30- to 40- minute endurance exercise sessions (brisk walking) per week at 60% to 75% of heart rate reserve on peak treadmill exercise heart treadmill exercise heart
	2	2	2	2
independent mobility, no neuropsychiatric dx	59-86 healthy older adults with moderate sleep complaints-PSQI global score of =/-5. Excluded: major psychiatric disorders including syndromal insomnia; alcohol greater than 3 alcohol greater than 3 alcohol greater than 3 alcohol greater than 3 to study protocol to study protocol	55+ Community dwelling adults. Excluded persons with neurological disorders (PD, etc), communication dificulties, CVD or musculoskeletal disorders influencing exercise ability.	55-65 Community dwelling, sedentary adults	49-82 M age 62.2 ex group 63.3 control Women, sedentary, no CVD or medical conditions limiting ability to engage in mod intensity exercise
	112	100	181	100
Adults after Acupunch Exercises	Improving Sleep Quality in Older Adults with Moderate Sleep Complaints: A Randomized Controlled Trial of Tai Chi Chih	Lower Extremity Exercise Improves Functional Fitness, Physiological Indexes, Exercise Self-Efficacy, Sleep Quality, and Mental Health in Middle- Aged and Older Individuals* poper in Chinese	Six-month effects of the Groningen active living model(GALM) on physical activity, health and fitness outcomes in sedentary and underactive older adults aged 55–65	Effects of moderate-intensity exercise on physiological, behavioral, and emotional responses to family caregiving: A randomized controlled trial
	lrwin et al, 2008 <sup>12</sup>	Jhang et al, 2020 <sup>13</sup>	de Jong et al, 2006 <sup>14</sup>	King et al, 2002 <sup>16</sup>

ose response ffects of exercise aining on the	437	45-75 Women, postmenopausal,	2	Participants randomised to one of four treatments: 6	Sleep Problems Index from the 6-item Medical Outcomes Study Sleep	Exercise training induced significant improvement in subjective sleep quality in postmenopausal women, with even a low dose of exercise resulting in greatly
		sedentary, no hypertension,		months duration: a non- exercise control treatment	Scale	reduced odds of having significant sleep disturbance.
		cardiovascular disease, recent hospitalisation for		(n1/492) or one of three dosages of moderate-		
		mental illness or significant symptoms of depression or health		UO2peak), designed to		
		conditions baring		(n1/499) or 150% (n1/495)		
		exercise.		Health Consensus		
				Development Panel physical activity recommendations		
		60-80 years of age; living indemendantly 'NO' to all	2	12 week, 3 x week, 1 hour	PSQI hacalina nra-	Decreased PSQI scores pre to post exercise intervention d= 1.0 301.
		questions on the Physical		total-body strength	intervention, and post-	PSQI 5.0 (+/-3.0) to 3.5 (+/- 1.75)
		Activity Readiness		program using machine-	intervention	
		receive medical clearance		Throughout the program.	Baseline PSOI 4.0	
		from a physician; 24 or		volume linearly decreased,		
		higher score on the Mini		and intensity linearly		
		Examination: no known		Increased. Control: officits of		
		history of neurological		intervention were		
		disease, cerebral infarct,		compared to that of an 12		
		or traumatic brain injury;		week control period. Thus,		
		Type 1 Diabetes: and do		participants served as their		
		not self-report engaging		asked to not change their		
		in heavy RT in the last 6		eating or exercise habits		
		months		outside of the study and		
				were encouraged to continue their normal activities		
	13	57-70	3	Aerobic exercise 3x weekly	PSQI and PSG	Acute exercise following training resulted in a 71%
		m 64 (+/- 3)		(non-consecutive days) for		increase in SWS during subsequent sleep in
		Community-dwelling,		16 wks. with no	Only selected	comparison with the non-exercise condition before
		Excluded orthopaedic		exercise-brisk, inclined	reported.	Following training, acute exercise reduced total wake
_		limitations, medication		treadmill walking (60 min,		time by 30% and REM onset latency by 14% (P b
		acting on sleep or		68–69%V O2 peak).		0.05). Acute exercise improved sleep continuity by
		serotonergic tone, e.g.				decreasing total wake time. No difference seen in
		tricyclic antide pressants,				total PSQI score
		artupsycriotics, or monoamine oxidase				
		inhibitors during the year				
		prior to the study,				

	The physical activity group increased amounts of slow-wave sleep. Low intensity activity in an elderly population can increase deep sleep.	A significant correlation was found between energy expenditure and sleep efficiency (r = 0.627, p = 0.029) in young adults, but not in older participants (r = -0.158, p = 0.49). Physical fitness did not correlate with sleep efficiency in either group. Exercise training significantly improved physical fitness (15.0%, p < 0.001), but failed to alter sleep characteristics such as sleep efficiency, sleep onset latency and awakenings.
	PSG: 30 s epochs	Accelerometery: sleep efficiency
	14 days of 10 min of stretching, 20-minute light physical activity (walking stationary upper and lower body exercises), 25 min cool down exercise	3x week/12 months 40 min cycling exercise training (n = 11) or control period (n = 10)
	1	m
diabetes, obesity or smoking. on PSG data , no leg movement index > 15 h - 1 causing arousals or wake [13]; more than 10 h - 1 episodes of sleep apnea and/or hypopnea (respectively > 80% and > 50% reduction of airflow mean amplitude) causing arousals or wake; professional evening or night activities; regular nap habits (> 30 min); or PSQI > 5.	65-92 mean age 75.2 ±2.6 no unstable or acute medical conditions, normal to mildly depressed mood, none to mild dementia, no major prychiatrici illness/DSM- IIP.R, were not taking hypnotic or psychoactive medications and all were independent in activities of daily living	65+ mean 69 (SD 3) in one group (21 persons) of healthy, sedentary older individuals at least 65 verso f age, screened extensively through medical history, physical examination and blood testing, free of self- reported sleep and mood disturbances and did not use sleep medication, anti-depresants or cardiovascular medication. Exclusion: cardiovascular medication. Exclusion: cardiovascular medication. Exclusion: diseases that may interfree with sleep quality such as obesity (BMI 1 30 kg/m 2 ),
	14	21
	Daily Social and Physical Activity Increases Slow- Wave Sleep and Daytime Neuropsychological Performance in the Elderly	Impact of physical fitness and daily energy expenditure on sleep efficiency in young and older humans
	Naylor et al, 2000 <sup>20</sup>	Oudegeest Sander et al, 2013 <sup>21</sup>

diabetes mellitus and         diabetes mellitus and           hypertension.         hypertension.           Effect of Exercise         72         65+ (mean 73.3)           and Cognitive         26 community-residing         HR. Exercise	diabetes mellitus and     diabetes mellitus and       hypertension.     2       72     65+ (mean 73.3)       26 community-residing     1R. Exc	diabetes mellitus and hypertension. 65+ (mean 73.3) 2 Mod in 26 community-residing HR. Exe	2 Mod in HR. Exe	Mod in HR. Exe	tensity: 65-75% max ercise: YMCA for 60	Change in sleep quality using seven questions	significant difference between the study arms in change in sleep quality over time (p<.005). Mean
Activity on Self- Activity on Self- Reported Sleep Quality in Community- Dwelling Older Adults with Adults with Cognitive Rendomized Complaints: A Complaints: A Complaints: A Complaints: A Complaints: A Complaints and Self-reported Sleep problems at baseline, which was defined as rating at least one of seven sleep questions as countrolled Trial Controlled Trial	adults with low activity levels and mild and cognitive complaints and self-reported sleep problems at baseline, which was defined as rating at least one of seven sleep questions as occurring often (5–15 times/month) or almost	adults with low activity levels and mid and cognitive complaints and self-reported sleep problems at baseline, which was defined as rating at least one of seven sleep questions as occurring often (5–15 times/month) or almost			minutes per day, 3 days per week for 12 weeks. 10 minutes of aerobic exercise (dance-based aerobics), 5 minutes of strength training, and 5 minutes of stretching and relaxation 4 arms: aerobic+cognitive	from the Sleep Dusorders Questionnaire <sup>23</sup> on the 2005–06 National Health and Nutrition Examination Survey (range 0–28, with higher scores reflecting worse sleep quality).	change in succeptions of the significantly more in sleep quarky scores improved significantly more in the stretching+educational DVD significantly more in than in the stretching+cognitive training (1.2 points), aerobic+tognitive training (0.25 points) arm (all p<.05, corrected for multiple comparisons). Differences between arms were strongest for waking at night (p=.02) and taking sleep medications (p=.004)
atways (21b times/month)       at baseline (n=72)       at baseline (n=72)       Effects of a       50-75* (mean 60.7)	a the serie (n=72) at baseline (n=72) 50-75* (mean 60.7) 2	atways (zub times/month) at baseline (n=72) 50-75* (mean 60.7) 2	2		training, aerobic+educational DVD, stretching+cognitive stretching+educational DVD EX group: moderate	Subjective sleep quality	Both stretching and exercise interventions may
Yearlong Moderate- Includes sedentary, mildly Intensity Exercise overweight and obese and a Stretching women: May not be Intervention on Intervention on Non-obese women only. Postmenopausal Non-obese women only. Non-obese women only. Non-obes	Includes sedentary, mildly overweight and obese women: May not be possible to take data for non-obese women only. No information about pre-existing sleep or psychiatric disorders. Exclusion: hormone replacement therapy, smoking, and medical contraindicating moderate-intensity exercise	Includes sedentary, mildly overweight and obese women: May not be possible to take data for non-obese women only. No information about pre-existing sleep or psychiatric disorders. Exclusion: hormone replacement therapy, smoking, and medical contraindicating moderate-intensity exercise			intensity aerobic exercise, 45 minutes, 5 days per week over 12 months. Control group: 60-minute low-intensity stretching and relaxation session each week, conducted by a trained exercise physiologist	with the Women's Health Initiative Insomnia Rating Scale: sleep quality (very rest-less/restless, average, sound/very average, sound/very average, sound/very average, sound/very average, sound/very average, sound/very medications or alcohol to help sleep (ves, no), sleep duration (≤ 6 hours, > 6 hours), trouble falling average (no, <1 time/wk., ≥ 1 time/wk.) and napping during the day (no, <1 time/wk., ≥ 1 time/wk.)	improve sleep quality in sedentary, overweight, postmenopausal women. Increased fitness was associated with improvements in sleep. However, the effect of moderate-intensity exercise may depend on the amount of exercise and time of day it is performed.
Title N Sample age and Exercise intensity: eligibility criteria intensity: 1: low 1: low 2: mod. 3: high	N Sample age and Exercise eligibility criteria intensity: 1: low 2: mod. 3. high	Sample age and Exercise eligblifty criteria intensity: 1: low 2: mod. 3. high	Exercise intensity: 1: low 2: mod. 3. high		Exercise and/or control intervention	Sleep measures	Main findings
Effects of Pilates         110         Women 60+         1           training on sleep         69.15 ± 8.94 years         1           quality, anxiety,         Post menopausal.         1           depression and         Exclusion: Exclusion         1           fatigue in         criteria were conditions         1	110     Women 60+     1       69.15 ± 8.94 years     Post menopausal.       Post menopausal.     Exclusion       Exclusion: Exclusion     criteria were conditions	Women 60+ 1 69.15 ± 8.94 years Post menopausal. Exclusion: Exclusion criteria were conditions	1		of 2x 60 minutes for 12 weeks.	PSQI sleep quality Baseline scores: control 7.10 ± 4.42 ex 8.56 ± 4.98	Significant improvements were observed after Pilates training in all PSQI domains as well as in the PSQI total score, with small to medium-size effects, while significant between-group differences in post-

enopausal n: A mized biled trial biled trial Resistance Resistance	46	that contraindicated the performance of the exercise program such as psychiatric psychiatric or neurological disorders, systemic diseases (i.e. diabetes mellitus, cancer or heart disease, or skeletal conditions), or being already enrolled in another training program. 60-86 Community dwelling, sedentarv. no illness	7	Pilates exercise. either a control (n = 55) or a Pilates (n = 55) group 8 weeks strength and aerobic training, 2x/week for 60 minutes. Walk group	PSQI, sleep quality Baseline PSQI 5.0 control, 5.8 and 5.9 ex erous	intervention measures were observed only for sleep duration (d=0.69) and sleep disturbances (d=0.78). PSCI was significantly improved in SSSH (-19.8%) over both WALK (6.3%) and CON (3.1.1%) (post hoc t tests n < .016)
	60	sedentary, no litness preventing physical activity, dementia, Alzheimer's, cognitive issues. 65+ Mean 71.5 y/o Mild cognitive impairment and living in nursing homes	0	for 60 minutes. Walk group 2x/week walking Rx. Control group: no exercise. 20-week Physical Activity Program: 10-min warm-up, 20-min rhythmic exercises, 10-min cool down exercises, and 40-min of free walking.	5.8 and 5.9 ex groups PSQI Baseline scores experimental: 13.04 ± 2.06 control 12.14 ± 2.46	tests p < .016) PSQI measured sleep quality of elderly individuals improved considerably (md -9.01 [-10.06, -7.96] after a 20-week Physical Activity Program.
e p		40-80, mean age 63±7 years, Healthy adufts with <b>OSA</b> Exclusion: current treatment for DSA; cardiovascular or respiratory conrbidities and/or Eworth Sleepiness Scale (ESS) score >10 justifying immediate initiation of CPAP; respiratory or heart disease contraindicating exercise discovered during stress testing; and Parkinson's disease.	m	3x week,60 min exercise sessions over 9 months: 10 min warm-up, 40 min of combined resistance and aerobic resistance and aerobic threshold, 10 min of cool- down, Control: two group educational sessions about healthy diet and physical activity recommendations	PSG (no data provided) at baseline and 9 months PSQI Baseline PSQI 7.0 and 7.4 control and ex groups	Exercise group showed a significant drop in ESS and PSQI scores compared to the control, group in which sleep quality worsened. Iong-term physical activity programmes in real-life community settings may help improve moderate OSA.
	131	60+ mean age 68 ± 7 (88% female)	2	Home exercise (aerobic and muscle strengthening) program performed 3 x/week over 12 weeks.	PSQI, Epworth sleepiness scale (ESS) and clinical questionnaire of Berlin	Semi-supervised home exercise is effective in improving sleep quality and daytime sleepiness in sedentary older adults with sleep problems. The exercise group showed significant improvement in

	sleep and daytime sleepiness of elderlies: a		Community dwelling, sedentary (IPAQ), with no cognitive impairment (mini mental state		Ex: home exercise program and a lifestyle/ sleep hvidere hooklet (n = 65)		sleep quality with a mean reduction of 4.9 ± 2.7 (p < 0.01) points on the PSQI total score and in all its 7 components. Improved daytime sleepiness with a docine of 2.8 + 2.7 onints in the ESC (n < 0.01)
	controlled trial		examination). Excluded				decime of 2.0 ± 2.1 points in the 533 (p < 0.01) compared to control group.
			persons undergoing sleep treatments (meds. CBTI)		control group sleep hvgiene and lifestvle		
			and those with disorders contraindicating exercise.		booklet (n = 66)		
Bullock et	Optimizing Sleep in		60+	2	3x/week for 12 weeks. 43	PSQI	Exercise improved sleep quality for poor sleepers,
al,	Older Adults:		Mean age 71.93	<del>ი</del>	min high-intensity interval	Mean baseline scores	but the intensity mattered. MICT and STRETCH
2020 <sup>29</sup>	Where Does High-				training group (n = 20), 52	ranged 6.8-7.8 by group	improved sleep efficiency for poor sleepers, whereas
	Intensity Interval Training Fit?		sedentary		continuous training (n = 19)	(nign intensity, moderate intensity, stretching), 70%	HILI did not (p < 0.05). MICLI and STRETCH may be more effective than HILT for optimizing sleep in poor
	0				group, and 30 min	of sample >5 PSQI/poor	sleepers.
					stretching control (Borg <8	sleepers.	-
					) (STRETCH; $n = 22$ )		
Buman et	Moderators and	99	55-79	2	classes 2 days per week for	In-home PSG	Initially less active individuals with higher initial
al, 2011 <sup>30</sup>	mediators of		mean age 61.42 (+/-6.72)		60 minutes moderate-		physical function and poorer sleep quality improved
	exercise-induced		underactive midlife and		intensity endurance		the most. Affective, functional, and metabolic
	objective sleep		older adults reporting		exercise, including brisk		mediators specific to different parameters of sleep
	improvements in		mild/ moderate sleep		walking and aerobic		architecture were suggested.
	midlife and older		complaints		movement and home-		
	daals min sieep				based exercise an		
	complaints				additional 3 days per week for 30 minutes over 12-		
					months		-
Buman et	Exercise Effects on	99	55-79 more and 61 47 (4 / 6 77)	2	classes 2 days per week for	PSQI, sleep logs, in home	Twelve months of moderate-intensity exercise
al, 2011 <sup>51</sup>	Night-to-Night		mean age b1.42 (+/-b.72)		bu minutes moderate-	Por 2/27 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	reduced night-to-night fluctuations in self-rated time دو قرال مدامون
	Fluctuations in Self-		community devolution		Intensity endurance	Baseline score 8.12 (3.28)	to fall asleep.
	Older Adults with				exercise, including prisk		
	Sleep Complaints		persons with mild- moderate sleep		warking and aeropic movement and home-		
			complaints hut otherwise		haced exercice an		
			healthy (?)		additional 3 days per week		
			-		for 30 minutes over 12-		
		;		,	months		
Cai et al,	Effects of a group-	19	postmenopausal	m	40–45 minutes of step	PSQI Baseline 0.4 ev group	A 10-week high-intensity step aerobics training
1107	training on sleep		to 65 years PSOI = />5		per week for 10 weeks at	7.56 control group	the melatonin levels in sleep-impaired PMW.
	quality and		Exclusion: PSQI≤5, or		an intensity of 75–85% of		Exercise group's PSQI score significantly decreased
	melatonin levels in		they had taken sleeping		the heart rate reserve,		(from 9.40 SD 0.81 to 7.40 SD 0.43; CG from 7.56 SD
	sleep-impaired		pills, caffeinated		whereas the participants in		0.34 to 7.78 SD 0.68;between-group difference =
	postmenopausal		beverages, or antioxidant		the CG maintained their		2.22, p < 0.05) and melatonin levels significantly
	women		supplements for at least 2 months before the study.		regular lifestyle.		increased ex group.
Chan et al,	Tai chi qigong as a	52	+09	1	2x 60-minute TCQ	PSQI (Chinese) at	TCQ participants reported better sleep quality, sleep
201633	means to improve		With cognitive		sessions/week tor 2	baseline, 2 months, and 6	duration (P=0.003), habitual sleep efficiency
	night-time sleep		impairment: mini-mentai		months. Non-	months	(P=0.002than the control group.
	Hudiny annuls war		Sidle evaluitianori				

	The exercise group had improved sleep quality on PSQI groups compared to the control group, mean difference -1.28 (95%CI: -2.12, -0.14).	Sleep disturbance was improved at 4 and 8 week follow up (post intervention) but the PSQI total score declined significantly at 20 weeks after intervention.
*PSQI at baseline 9.8 control, 10.2 ex	22	PSQI at baseline and 8 weeks (baseline 5.4 control, 6.5 for yoga group).
exercise/observation control group	3x/week, 40 minutes per session over 12 months (144 sessions). Phase 1 (6 months): Volunteer guided warm up, range of motion, aerobic, stretching. Phase 2 (6 months): DVD guided warm-up, range of motion, aerobic (shadow boxing), stretching. Usual activity control, wait list for ex intervention.	1 60-minute Hatha yoga class/week x 8 weeks. Sessions included asanas (poses) in the seated, supine, and standing positions; pranas positions; pranas positions; pranas deficions; pranas positions; pranas with static stretching, balance, and strength exercises. Control: wait list control.
		2
(MMSE) score of 13–26, PSQI >5. Excluded impaired mobility/MSK disorders, pharma treatment for sleep disorders.	65+ (mean 79.46, +/- 7.06) Inclusion: 65+ years old, using wheelchairs for mobility, (3) living in the facility for at least three months, (4) cognitively intact (Short Portable Mental Status Questionnaire, SPMSQ, score 8) heavy or moderate dependency in ADL. Exclusion criteria: (1) having severe or acute cardiovascular, musculoskeletal, or pulmonary illnesses, or clos suffering from a spinal cord injury with no rehabilitation potential.	65-90 Mean age 72 y/o Community dwelling women with knee osteoarthritis. Short portable Mental Status Questionnaire (SPMSQ) <8 Exclusion: significant medical comorbidities that might preclude exercise participation: uncontrolled high blood pressure or existing heart condition; and b) other comorbid condition with overlapping symptoms (i.e. fibronnyalga, rheumatoid arthritis.
	127	36
adults with cognitive impairment: a pilot randomized controlled trial	Feasible modalities and long-term effects of elastic band exercises in nursing home older adults in wheelchairs: A cluster randomized controlled trial	Yoga for managing knee osteoarthritis in older women: a pilot randomized controlled trial
	Chen (LI) et al, 2016 <sup>34</sup>	cheung et al, 2014 <sup>35</sup>

Chen et al, 2012 <sup>36</sup>	The effect of a simple traditional		60+ Community dwelling, healthy adults:	2	Baduanjin exercise, 3x/week/30 min/12 weeks. Adherence monitored	PSQI Baseline scores 11.11 /SD 3 37/ control	Exercise group significantly improved overall sleep quality, subjective sleep quality, sleep latency, sleep duration clean efficiency, and
	programme		independent mobility,			11.93 (3.50) exercise	daytime dysfunction after 12 weeks of intervention (n < 0.001) No cimilitant difference in clean such th
	exercise) on sleep quality of older adults: a randomized		depression.				rp < 0.001, No sgimtant unter ence in steep quanty in control group.
	controlled trial						
Choi et al, 2018 <sup>37</sup>	The Effects of Floor- seated Exercise	77	65+ Community dwelling. no	2	30-40 min sessions of floor seated exercise . 4 x/week	PSQI Baseline 6.12 ± 2.72 ex	Exercise program had no significant effect on sleep quality: mean difference 1.00 (2.15 to 0.15). p
	Program on	_	unstable physical		for 12 weeks following	group	0.087.
	Physical Fitness,		conditions, evidence of		ACSM guidelines	control group 5.83 ± 2.64	Authors' note: "considering that the previous month,
	Depression, and	_	terminal illness, or history				which served as a reference for the measurement of sleep quality was part of the hottest summer ever
	Adults: A Cluster						with 22 tropical nights, it might have been difficult
	Randomized Controlled Trial						for the FSEP to fully affect the participants' sleep quality scores."
Curi et al,	Effects of 16-weeks		+09	1	2 x 60 minutes/week	PSQI	Stat. significant time x group effects in exercise
2018 <sup>38</sup>	of Pilates on health		sedentary, community		intermediate level Pilates	Baseline 7.07 ± 5.38	group: PSQI-BR total score (p = 0.017, $\eta$ 2 = 0.09),
	perception and		dwelling women.		exercise classes over 16	control group, 6.32 ± 3.16	and the sleep latency (p = 0.023, n2 = 0.09) and use
	sleep quality among elderly women		old. SD 0.14) exercise		Control: no exercise, usual	exercise group	01 Steeping medication subscales (p = 0.015, r)2 = 0.09). indicating better improvements (reductions) in
			group, 63.75 years old		activities.		these outcome variables for the Pilates EG when
			control group.				compared to the CG
El-Kader	Aerobic exercise	40	61-74	2	supervised aerobic exercise	PSG: sleep architecture	Significant increase in total sleep duration, sleep
and Al-	modulates cytokine		mean age group a: 64.98		intervention group (group	sleep quality	efficiency and sleep onset latency in group(A) after 6
Jiffri,	profile and sleep		± 4.15y		A, n=25) or control group		months of aerobic exercise training, while, wake
2019 <sup>2</sup>	quality in elderly	_	group b: 65.7 ± 3.86 Sedentary, healthy		(group B, n=25) 3 times per week for 6 months at 60-		time atter sleep onset and rapid eye movement (REM) latencv significantly reduced after 6 months of
			community dwelling men		80% HRmax.		aerobic training compared with values obtained
			with difficulty falling				prior to aerobic exercise training
			and/or staying asleep, tor				
			without significant				
			cognitive deficits/				
			major psychiatric				
			disorder, alcohol				
			or substance abuse,				
			neurological disorders,				
			jserious medical				
			cardionulmonanu disease				
			contraindicating exercise.				
			shift work.				
Evangelista	Effects of Xbox	29	+09	2	Exercise program-	PSQI	The 6-week intervention with Xbox Kinect exercise
de Lima,	Kinect exercise		no movement limitations;		strengthening, balance,	over a 1-month time	significantly improved sleep quality. Compared with
2021 <sup>40</sup>	training on sleep		no smoking; not		stretching using X-box	interval	the CONTROL group, the XBOX group had significant

reductions (23.4%) in the PSQi global score (t26 = - 2.1; p = 0.04).	Intervention group reported significant improvements in overall sleep quality after 24 weeks compared with those randomized to control (PSQI endpoint-to-baseline change = $2.6 \pm 4.0$ vs $0.5 \pm 4.2$ , time × group interaction p = 0.007). Baduanjin exercise is an effective and feasible approach to improve self-reported sleep quality.	Structured physical activity reduced the likelihood of developing poor sleep quality (PSQI >5) over the intervention period, when compared with health education, but had no effect on prevalent cases of poor sleep quality, or on sleep-wake behaviours evaluated by the ISI or ESS. These results suggest that the benefit of physical activity in this sample was preventive and limited to sleep-wake behaviours evaluated by the PSQI.	Significant differences in PSQI between the exercise groups and the control group ( $p < .05$ ). The control group's mean score increased (more problems sleeping) over time by more than 11% (pre: 6.2 ± 5.04; post: 7.0 ± 5.07), whereas the scores for both exercise groups decreased.
Baseline controls: 6.9 ± 4.0 ex group: 8.0 ± 3.9	PSQI Baseline control 9.8 ±3.6 ex 9.2 ± 3.4	Insomnia Severity Index (ISI) (28 defined insomnia), Epworth Sleepiness Scale (ESS) (210 defined daytime drowsiness), and Pittsburgh Sleep Quality) Index (PSQI) (> 5 defined poor sleep quality) — administered at baseline and subsequently at 6, 18, and 30 months. Baseline PSQI: 5.9 both groups	PSQJ Sleep disturbances subscale of the PSQJ at baseline and 12-14 weeks
Kinect 3 x/week for 60 min over 6 weeks. Control- no exercise.	Baduanjin exercise intervention group 5xweek, 45-min exercise sessions for 24 weeks. Control: instructed to maintain their usual lifestyle behaviours.	Walking with a goal of 150 minutes/week, as well as strength, flexibility, and balance training. 2 centre- based sesions/week and home-based activity 3–4 x/week for the duration of the study: walking 5-days a week at moderate intensity, 10 minutes of lower extremity strength training, 10 minutes of balance training, and large muscle group flexibility exercises.	3 x60-minute exercise (either Tai Chi or physical fitness training) classes per week for 12-weeks.
	2	2	2
performing regular exercise; no cognitive impairment. Exclusion criteria: inability to perform exercises with the Xbox Kinect and/or the physical/functional tests; difficulty answering the questionnaires; intake of psychotropic of psychotropic uncontrolled clinical disease.	60+ Community dwelling, PSQI score ≥ 5, (not currently employed () not being athletes, physical education teachers or coaches, and practicing martial arts. Exclusion criteria: severe physical or mental illness, regular physical exercise based on the screening questionnaire (e.g., Tai Qin Xi.)	70-89 mean age 79 Community dwelling adults with mobility impairments impairments	52-82 mean age 69.2 ± 9.26 (M ± SD) years, Participants must not have not regularly exercised for at least 3
	139	1635	84
quality, anxiety and functional capacity in older adults	The efficacy of mind-body (Baduanjin) exercise on self- reported sleep quality and quality of life in elderly subjects with sleep disturbances: a randomized controlled trial	Effect of Structured Physical Activity on Sleep-Wake Behaviors in Sedentary Elderly Adults with Mobility Limitations	Tai Chi and Low Impact Exercise: Effects on the Physical Functioning and Psychological Well-
	Fan et al, 2020 <sup>41</sup>	Fragoso et al, 2015 <sup>42</sup>	Frye et al, 2007 <sup>43</sup>

	rted, Note: no PSQI scores reported, only number of participants with  PSQI 5 at baseline and after intervention. Findings: More women in the exercise group reported better sleep quality compared to women in the control group.	No statistically significant effect on sleep: Pre-post change in PSQI: effect size (d) –0.13 (95%CI: –0.73 to 0.48) • Actual post Rx scores not reported	Subjects in the yoga group had significant improvement in all the domains of QOL and total sleep quality after controlling for the effect of baseline difference in education between the two groups.	At 6 months post-baseline, the physical activity group showed significantly reduced insomnia symptom severity (F8,26 = 5.16, P = 0.03), with an average reduction of four points on the ISI.
	PSQI: no scores repor only number of participants with > baseline and after intervention	PSQI Means at baseline: 8.2 (4.1) yoga group 8.9 (3.9) control	PSQI Baseline scores 7.65 (3.36) 8.19 (3.46)	ISI, actigraphy
PF: cardiovascular exercise, strength, flexibility, endurance, and balance TC: 10-posture choreography made up of basic and classic postures from the Yang family style. Control: no exercise	resistance training at least 12 wks. with an intensity of 80% of 1RM, 2 times wk-1 with 3 sets of 8 repetitions maximum Non-exercise control	60 min, 2x week/10 weeks yoga or a parallel health education comparison group. Silver Age Yoga program	yoga 60 min daily for 1 month, weekly until 3 months and encouraged to practice yoga without supervision until for 6 months. Wait-list control.	5 x/week, 150 minutes moderate intensity exercise (walking) for 6 months. Non-exercise control group.
	2	F	F	7
months (less than 1 hour of purposeful exercise per week), and to provide a note from their MD stating that they were physically fit to participate in a low to moderate intensity exercise program	65 ± 3 women, sedentary with and without skeletal muscle problems, and with and without chronic degenerative diseases	60–89 years Mean 71.6 (8.3) in exercise group self-reported sedentary lifestyle, provided a physician-signed health clearance form. Exclusion criteria: a) practiced yoga >2x in the last year; b) life expectancy <12 months.	60+ Excluded dementia , neurodegenerative disorder, stroke, major depressive disorder, psychosis, anxiety disorder, severe hearing disorder, severe hearing and those unable to perform Yoga	Mean age 59.8 years Persons meeting Research Diagnostic Criteria for insomnia (Edinger et al. 2004 <sup>48</sup> ); ambulant,independent in activities of daily living: moderate to vigorous intensity physical activity participation less than 30 minutes per day, on 5, ormore days or or
	16	22	118	41
Being of Older People	Resistance Training Contributes to Variability in Heart Rate and Quality of the Sleep in Elderly Women Without Comorbidities	Yoga to prevent mobility limitations in older adults: feasibility of a randomized controlled trial	Effects of yoga intervention on sleep and quality- of-life in elderly: A randomized controlled trial	Increased physical activity improves sleep and mood outcomes in inactive people with insomnia: a randomized controlled trial
	Gambassi et al, 2016 <sup>44</sup>	Groessl et al, 2018 <sup>45</sup>	Hariprasad et al, 2013 <sup>46</sup>	Hartescu et al, 2015 <sup>47</sup>

			week in the previous 6				
			months; and stable on				
			any non-excluded medication taken over the previous 3 months				
Hosseini et al.	The effect of Tai Chi exercise on the	62	60+ Mean 69.08	2	10-stage Tai Chi exercise program. 3x/week for 25	PSQI Baseline >5	Sleep quality (PSQI) improved significantly in Tai Chi proup. There was no significant improvement in
2011 <sup>49</sup>	sleep quality of the		Residents in an elderly		minutes over 12 weeks.		sleep quality (PSQI) in the control group.
	elderly residents in Isfahan.		care home with no record of exercising or		Minimum adherence of 90%		
	Sadeghieh elderly		continuous				
	home		and regular physical				
			but not major depression				
			(Beck). Medical clearance				
			for exercise, no CVD prohibiting exercise.				
Irwin et al,	Improving Sleep	112	59-86	2	40 minutes Tai Chi 3 x week	PSQI for sleep quality	Participants in Tai Chi ex greater improvement in
200812	Quality in Older		healthy older adults with		for a total 120	two groups: PSQI  5	PSQl/sleep quality than HE control. Persons with
	Adults with		moderate sleep		minutes/week for 16	PSQI > 5 group (n=55)	poor sleep quality also showed significant
	Moderate Sleep		complaints-PSQI global		weeks.	baseline:	improvements in PSQI global score (P < 0.001) as
	Complaints: A		score or =/>5. Excluded:		Control: matched quantity	0.01 (1.24) eX	well as in the sleep parameters of rated sleep quality
	Kandomized		disorders including		nealth education	10TU00 (C2.5) 81.8	(P < 0.05), habitual sleep efficiency (P < 0.05), sleep duration (P < 0.01) and clean disturbance (P < 0.01)
	Tai Chi Chih		aisoraers incraanig				ממופנומנו (ב > מימד), פוום אבבף מוצומו מפווכב (ב > מימד).
			synuronnar msomma, alcohol greater than 3				
			drinks per day: and/or				
			unwillingness to adhere				
			to study protocol				
Irwin et al,	Cognitive	112	55+	1	2-hour group sessions /	PSQI	TCC was associated with improvements in sleep
201450	behavioral therapy		mean age 66.35		week for 4 months.	Athens Insomnia Scale,	quality, fatigue, and depressive symptoms as
	vs. Tai chi for late		Community-dwelling			(AIS)	compared to SS (all P's < 0.05), but not insomnia
	life insomnia and		adults satisfying DSM-IV		Ex: Tai Chi emphasized	Daily sleep diaries for 2	remission. PSG measures did not change.
	inflammatory risk: a		criteria for primary		control over physical	weeks (i.e., Pittsburgh	
	randomized		Evolucion: modical and		runction and arousal-	sieep Ulary). DCG for D nights officer	<ul> <li>Table ST In paper has PSUJ and sleep diary results for troatmost completion up to 16 months follows</li> </ul>
	comparative		exclusion: meancar and psychiatric disorders		repetitions ponsiveness.	adantation	
	efficacy trial.		presence of another sleep		slow-paced movement.		
			disorder, shift work or			Multidimensional Fatigue	
			irregular sleep pattern;		Controls:	Symptom Inventory	
			use of hypnotic		1. CBT control	[MDFSI] and Epworth	
			medications or alcohol for		2. Sleep School (Sleep	Scales	
			sleep major depression,		hygiene education- SSH)		
			cognitive impairment,		control	baseline PSQI:	
			tobacco smoking: (8)			10.4 (2.9) CBT control	
			body mass index > 35 kg/m2:			10.7 (3.1) SSH CONTROI 11.1 (2.9) TCC eX	
Jimenez-	Effects of HIIT and	82	60+	2	Twelve weeks of 2x/week,	PSQI	Post-intervention sleep quality measurements
Garcia et	MIIT Suspension		Community dwelling,	ŝ	45 minute	Mean baseline score for	revealed a statistically significant interaction group $\times$
al, 2021 <sup>51</sup>	Training Programs		healthy adults, no			total sample 7.74 (4.31)	

	on Sleep Quality and Fatigue in Older Adults: Randomized Controlled Clinical Trial		systemic diseases, mobility impairments or mental health diagnoses or medication that may alter the balance, systematic diseases (i.e., cancer, diabetes mellitus, musculoskeletal conditions or heart disease), psychiatric or neurological pathologies, conditions or already enrolled in an exercise		high intensity or moderate intensity suspension exercise interval training. Non-exercise control group		time (p < 0.005). Greater improvements in sleep quality with the HIIT
Jurado- Fasoli et al, 2020 <sup>52</sup>	Exercise training improves sleep quality: A randomized controlled trial	69	45-65 (median 55) Sedentary, healthy adults.	m	2-3x/week 65 min, physical activity program (WHO recs) or high-intensity interval training (HIIT) or high- intensity interval training and electro-stm, or no ex. control grout	PSQI and accelerometers Baseline PSQI: control 6.5 ± 4.0 hit ex 5.5 ± 3.7	All intervention groups showed a lower PSQI global score (all P < .022). HIT-EMS group improved all accelerometer parameters, with higher total sleep time and sleep efficiency, and lower wake after sleep onset (all P < .016). No differences were found between groups in any sleep quality parameter
karimi et al, 2016 <sup>53</sup>	Surveying the effects of an exercise program on the sleep quality of elderly males	46	60+ Primary insomnia and PSQI score <5. Exclusion: persons with secondary insomnia.	f	3x/week, 30 min walk exercise program for 8 weeks: 5 minute warm up, walking as fast as possible (10 minutes), slow walking to cool down (5 minutes), and resting and relaxation (10 minutes). Non exercise control	PSQI, weekly over 2 months Baseline scores: ex 7.59 (0.68) control 5.5 (0.51)	Improved sleep quality/sleep onset latency in exercise group compared to control (p <0.05) on PSQI.
Kamrani et al, 2014 <sup>54</sup>	The effect of low and moderate intensity aerobic exercises on sleep quality in men older adults		60-70 No sleep apnea, (c) not smoking, (d) not engaged particularly in moderate and vigorous physical activity, (e) no taking hypnotic drugs, (f) without any musculoskeletal problems that would prevent participation in aerobic exercises.	7 7	8 weeks aerobic exercises, 2x week, based on Rockport one-mile walking/running test. (40-50% MaxHR) and moderate intensity (60- 70% MaxHR) exercise and a control group (regular daily activities) Ex groups: 10 min warm-up at 20-30% MaxHR, 35 minutes low or moderate aerobic exercises, 10 min cool-down	(PSQI) in pre-test and post-test stages Control: 5.12 (0.95) Low int: 5.60 (1.07) HIT: 5.20 (1.06)	Aerobic exercises with moderate intensity (60-70% MaxHR) have a positive and significant effect on sleep quality and its components. Significant differences were found between control and experimental groups in PSQI (P<0.05). Tukey Post Hoc showed moderate intensity group had better scores in total sleep quality and its components than other groups (P<0.05). The low intensity group scores in total sleep quality and its components were better than control group (P<0.05).
Khajavi and Khanmoha madi, 2015 <sup>55</sup>	The Effect of "Green Exercise" on Improving the Sleep Quality of Female	45	60+ (mean 60±4.08) sedentary women (and no regular exercise within 2 weeks of study) with	2	<ol> <li>60 minute sessions/week over 10 weeks of stretching, strengthening, strength and endurance,</li> </ol>	PSQI Mean at baseline: exercise group: 14.86±0.84	Exercise group had a significant improvement in sleep quality (total), subjective quality of sleep, usual sleep efficiency, total sleep duration, daily

	Elderly without Regular Physical Activity in Arak City		with poor sleep quality (minimum PSQI 6), no sleep medications, no cardiovascular disease or musculoskeletal conditions restricting exercise.		including brisk walking climbing and descending stairs, resistance exercises. Non-exercise control group (no intervention)	control group: 12.97±0.56	dysfunction, duration of time needed to fall asleep than control group.
King et al, 1997 <sup>56</sup>	Moderate-intensity exercise and self- rated quality of sleep in adults.	4 3	60+ mean age 61.18, with <b>primary insomnia</b> , screened for dementia and depression. Living in the community (mean age of 62), no CVD. No clinical depression.	7	Ex group" 16 weeks of mod. Intensity community- based exercise training (4 x 30–40 min) Wait-list control group	PSQI, Sleep diaries, including data on onset, latency, efficiency, duration. baseline and 16 weeks baseline PSQI scores (men wormen, ex, control groups) >7.8 (SD 4.2)	Compared with controls (C), subjects in the exercise training condition (E) showed significant improvement in the PSQI global sleep score, sleep parameters of rated sleep quality, sleep-onset latency, sleep duration at 16 weeks.
King et al, 2008 <sup>57</sup>	Effects of moderate-intensity exercise on polysomnographic and subjective sleep quality in older adults with mild to moderate sleep complaints	9	55+ nonclinical sample of underactive adults with mild-mod sleep complaints complaints	7	3 days per week, 60 min exercise classes and 3 x/week, 30 min home exercises over 12-months. Moderate-intensity endurance exercise (n=36) Control: health education control program (n=30)	PSG and PSQI Baseline PSQI: 8.467 ex 7.57 control	A moderate-intensity exercise program improved some objective and subjective dimensions of sleep to a modest degree: Exerciser group had significantly less time in PSG measured Stage 1 sleep (between-arm difference=2.3, 95% confidence interval [CI], 0.7-4.0; p=003), more time in Stage 2 sleep (between-arm difference=3.2, 95% CJ, 0.6-5.7; p=.04), and had fewer awakenings during the first third of the sleep period (between-arm difference=1.0, 95% CJ, 0.39-1.55; p=.03). Exercisers reported greater 1.2-month improvements relative to controls in Pittsburgh Sleep Quality Index (PSQI) sleep diary-based minutes to fall asleep (p=.01), and feeling more rested in the morning (p=.02).
Liu et al, 2010 <sup>58</sup>	Influence of 8-week shadow boxing exercise on the indexes for evaluating sleep behaviour in older adults.	82	60+ Mean ages: exercise group 65.94 ±10.33 , control group 66.13 ± 12.74 12.74 community dwelling, older adults.	2	30 min/session, 5 times per week, for 8 consecutive weeks shadow boxing exercise. Control group: No additional physical activity (usual routines).	PSQI Baseline scores >11 exercise, >15 control groups	Exercise group had improved sleep quality/PSQI compared to control. Mean diff: -4.37 (-5.79, -2.95).
Lü et al, 2017 <sup>59</sup>	Effect of Tai Ji Quan training on self- reported sleep quality in elderly Chinese women with knee osteoarthrittis: a randomized controlled trail	46	60-70 clinical diagnosis knee OA, stable medication use. Exclusion: a neurological disease (e.g., Parkinson's, dementia, vertigo, or cerebral program of regular exercise.	7	3x /week, 60 min Tai Ji Quan group exercise sessions over 24 weeks control group: bi-weekly educational classes.	PSQI Baseline scores ex 6.00 (3.02) control 8.47 (4.78)	Compared with the control group, participants in the Tai Ji Quan group had significantly improved primary outcome (global PSQ) score, p = 0.005 and secondary outcomes, including three PSQI sub- scores (sleep latency, p = 0.031; sleep duration, p = 0.043; daytime dysfunction, p = 0.007), total sleep time (p = 0.033), and SF-36 PCS (p = 0.006). The Tai Ji Quan group also had significant improvements compared with baseline in three PSQI sub-scores (sleep latency, p = 0.031; habitual sleep efficiency, p

							= 0.049; sleep disturbance, $p = 0.016$ ), sleep latency ( $p = 0.003$ )
21 <sup>60</sup>	Effects of light-to- moderate intensity aerobic exercise on objectively measured sleep parameters among community- dwelling older people	64	65.7 ± 5.7 years Community dwelling older adults. 13 males 45 females, BMI 25.1 ± 4.3 kg/m2) No exclusion criteria included in paper	1, 2	1x/week, 60 minutes group-based exercise training consisting for 3 months at moderate intensity (aerobic exercise) plus bench step exercises at home ≥3 days per week (≥20 min per session), with a goal of performing ≥140 min of exercise in their home per week for the 3-month period Control: regular routine, no additional physical activity.	PSQI baseline 6.2 (SD 3.2) actigraphy (hip) 4 consecutive days and 3 nights	The three-month aerobic exercise improved objectively measured sleep quality in the exercise group. Total sleep time, hours in waking after sleep onset, sleep efficiency and consecutive wake episodes 210 min (WSO210 min) significantly improved (p<0.05). The exercise group showed a significantly greater reduction in WASO210 min than the control group (p<0.05).
<b>u</b> #	A randomized controlled trial of Tai chi for balance, sleep quality and cognitive performance in elderty Vietnamese	102	60-79 Community dwelling adults. Exclusion: serious diseases, such as symptomatic coronary insufficiency, angina, insuffinia, orthostatic hypotension, and dementia.	0	2x/week, 60 minutes over 6 months Tai Chi Program. Control: no intervention control group	PSQI baseline scores: ex 9.38 ± 4.99 control 8.06 ± 4.09	Improved sleep quality and PSQI scores with tai-chi compared to control group. F (1, 71) = 43.69, P , 0.001.
i et al, <sup>62</sup>	Mindfulness-based therapy for insommia for older adults with sleep difficulties: a randomized clinical trial	127	50-80, (mean 61.2) PSQI >5.5, no cognitive impairments. Exclusion: Major neurological or psychiatric conditions, piong term use of sleep long term use of sleep neds, contraindications for MRI or if could not consent.	1	<ol> <li>60 min group sessions over 8 weeks: SHEEP group includes low intensity exercise, stretching and breathing exercise. Control: Mindfulness based therapy (MBTI)</li> </ol>	PSQI baseline ISI Actigraphy, home-based PSG	Intention-to-treat analysis showed reductions in insomnia severity in both groups [MBTI: Cohen's effect size $d = -1.27$ , 95% confidence interval (Cl) $-1.61$ to $-0.89$ , SHEEP $d = -0.69$ , 95% Cl $-0.96$ to $-0.43$ ], with significantly greater improvement in MBTI. Sleep quality improve equivalently in both groups (MBTI: $d = -1.12$ ; SHEEP: d = -1.02). No significant interaction effects were observed in objective sleep measures
sa al,	Aerobic exercise improves self- reported sleep and quality of life in older adults with insomnia	23	55+ Community dwelling, healthy adults with primary insomnia for at leap duration <6.5h and a Pittsburgh Sleep Quality Index (PSQI) score >5.Excluded: All participants screened for other sleep disorders (sleep apnea, PLMS) with overnight PSG, depression (CES-D), cognitive	0	4x/week, average of 30 minutes, for 16 weeks of aerobic physical activity plus sleep hygiene at 55% Max HR first 4-6 weeks, 75% MaxHR 6-16 weeks. Control: sleep hygiene only	PSQI, sleep quality, Epworth Sleepiness Scale [ESS] Baseline PSQI 9.9 ex 9.8 control Wrist actigraphy, PSG	The exercise group improved in sleep quality on the global PSQI (p<.0001), sleep latency (p=.049), sleep duration (p=.04), daytime dysfunction (p=.027), and sleep efficiency (p=.036) PSQI sub-scores compared to the control group. Reduced daytime sleepiness (p=.02) exercise group compared to control.

			function (MMSE), sleep quality (PSQI) and 7 days of activity monitoring using wrist actigraphy and a sleep log.				
Seol et al, 2021 <sup>64</sup>	Effects of Morning Versus Evening Home- Based Exercise on Subjective and Objective Sleep Parameters in Older Adults: A Raudomized Controlled Trial	60	65-79 Mean age 72.3 ± 2.3 Community dwelling, no diagnosis of insomnia, no restrictions on exercise	Ħ	30 minutes low intensity aerobic exercise daily/9 weeks, am or pm Adherence monitored by accelerometery, logs, supervision	PSQI, sleep diary, actigraph baseline PSQI 7.2 ± 3.0	Evening exercise group: subjectively and objectively measured sleep latency significantly improved. postintervention subjective sleep satisfaction was significantly higher in the evening group (5.2 + 1.4 points, P J/4.006), sleep variables related to evening exercise had larger effect sizes (Cohen d) than morning's.
Sharma et al, 2013 <sup>65</sup>	Effect of Resistance Training Over Aerobic Exercise in Improving Quality of Sleep in Older Adults	4 S	60+ Community dwelling, active, independently mobile, poor sleepers, mini mental state examination >24. Exclusion: sedative medication, exercising >1 hour/week, impaired vision or hearing, unstable cardiac unstable cardiac condition, hypertensive, musculoskele tal, psychiatric, or neurological problems that would prevent participations in moderate levels of physical activity	0	30 min, 5x week/6 weeks Resistance training group: upper and lower extremity resistance training protocol Aerobic group: mod intensity (60-70%MHR) 5 days per week for 6 weeks Control group: No exercise control group.	PSQI baseline > 5 in inclusion criteria baseline PSQI 12-13 all groups groups	Sleep in subjects in both the resistance and aerobic groups improved over 6 weeks training as compared to control group. A statistical significant difference was observed between the Resistance and Aerobic groups in Pittsburgh Sleep Quality Index. In subjects with poor sleep, addition of resistance training proved to be effective than Aerobic exercises in improving quality of sleep in older adults
Sekerci and Bicer, 2019 <sup>66</sup>	The effect of walking exercise on quality of life and sleep in elderly individuals: A randomized controlled study	60	65+ Nursing home dwelling adults without major medical, psychiatric or mental health issues (long list of exclusion criteria in paper)	1	40-minute walking program twice/week for 8 weeks. No-exercise control group	PSQI baseline 6.56 ex group, 7.73 control	Significant improved sleep quality (mean =4.33 SD 2.39) in exercise group compared to control group (p<0.001).
Sharif et al, 2015 <sup>67</sup>	The Effect of Aerobic Exercise on Quantity and Quality of Sleep Among Elderly People Refering to Health Centers of Lar City, Southern	60	60-75 Community dwelling older adults, no psychiatric diagnoses, cognitive or cardiovascular diseases, use of hypnotics physical	1	3x/week, 60min aerobic sessions for 12 weeks. Control: non-exercise control	PSQI, sleep quantity Baseline scores 5.99 (SD 1.14) ex group, 6.23 (1.22) control	PSQI scores improved by 44.46% in ex group (p<0.0001). Sleep duration improved by 98/16% (p=0.038) and sleep latency by 76/6% in the ex group. Changes in sleep latency between groups not statistically significant (p=0.089).

Conventional exercise and tai chi improved sleep and the beneficial effects sustained for 24 months, although the absolute improvements in sleep parameters were modest. Improvements in objective sleep parameters were not different between the tai chi and exercise groups, suggesting that tai chi can be an alternative approach for managing insomnia.	Stat. significant change in PSQI in exercise compared to control group1.257 (-1.609, -0.825) p <0.001 d=0.89 The exercise-cognition relationship was significantly mediated by reduced depressive symptoms and improved sleep quality (indirect effect: β=-0.205; 95% CI: -0.122, 0.831).	A low intensity Tai Chi exercise for 12 weeks improves sleep quality in the experimental group with significantly greater change in PSQI (p<. 01).
PSQI, actigraphy, Insomnia severity index (ISI). baseline, end of the intervention (postintervention), and 24 months after the months after the intervention (follow-up) baseline PSQI: 11.4 (3.2) 11.4 (2.9) 11.3 (2.9) control, ex, TCQ	PSQI Self-reported sleep quality Baseline PSQI 9.47 (3.66) ex, 8.98 (3.94) group	PSQI at the first and fourteenth weeks of the study. Baseline scores: ex 9.84 (SD 4.39) control 9.68 (3.35)
3x/week, 60 minutes for 12-week tai chi training, or groups. Control: no intervention (3-arm, parallel group, assessor-masked clinical trial).	3 time per week, 60- minute exercise sessions over 16 weeks: moderate- intensity aerolic exercise programme. Control: 16-week health education program	22 minutes Tai Chi 3 times per week for 12 weeks. control group: usual activities, without Tai Chi.
7	2	7
conditions limiting exercise 60+ Me an age 67.3 (SD 6.8) Chinese adults with chronic insomnia (DSM-V criteria). Exclusion: (1) regular moderate- intensity exercise or tai intensity exercise or tai intensity exercise or tai intensity exercise or tai intensity exercise or tai condicion: (2) physical disability precluding participation in the interventions, (3) major confounding conditions known to induce sleep perturbations, such as severe chronic diseases and related treatments	(ex. cancer). 60+ mild cognitive impairment. participants with conditions: participants with conditions with conditions with conditions for exercise training, prescription of antidepressant agents, prescription of antidepressant agents, prescription of arkinson's disease), regular moderate or vigorous-intensity aerobic exercises > 150 min/week	60+ Living in two residential care centres in Thailand. Criteria: participants have normal orientation to place, time and person, no illnesses limiting movements, uncontrolled epilepsy and have not
320	۵	20
of Iran; A Randomized Controlled Clinical Trial Effects of Tai Chi or Effects on Sleep in Older Adults With Insomnia: A Randomized Clinical Trial	Effects of a moderate-intensity aerobic exercise programme on the cognitive function and quality of life of community- dwelling elderly dwelling elderly people with mild cognitive impairment: A randomised controlled trial	The Effects of Tai Chi on Sleep Quality, Well-Being and Physical Performances among Older Adults
Siu et al, 2021 <sup>68</sup>	Yu, 2019 <sup>69</sup>	g et al, 2008 <sup>70</sup>

			engaged in Tai Chi or other exercises except stretching exercise. Must have experienced sleep problems in previous chankes in meds.				
Tseng et al, 2020 <sup>71</sup>	Effects of exercise training on sleep quality and heart rate variability in middle-aged and older adults with poor sleep quality: a randomized controlled trial	40	middle-aged and older community-dwelling adults mean age = 62 years; 82.5% female). PSQJ>5 Exclusion: uncontrolled uncontrolled cardiovascular diseases /systemic diseases /systemic diseases contraindicate exercise , clinically diagnosed primary sleep disorder/ percesion, any ongoing medication documented medication documented medication documented medication documented physical exercise.	7	3 mod intensity, 50 min exercise training x week/ 12 weeks: 40 minutes of supervised aerobic exercise (graded treadmil walking) 50–60% of VO2peak and 10 min stretching exercises. Control: No exercise, asked not to change their physical activity habits during the study	PSQI Chinese version (CPSQI) and an actigraph Baseline PSQI control 11.5 (3.1) ex 13.3 (3.9) ex 13.3 (3.9)	Exercise group showed significant improvements in total scores and all subscales of PSQI questionnaire ( $P < .001$ ). Self- reported sleep duration significantly increased by 1.5 hours, and self-reported sleep-onset latency was significantly reduced by nearly 18 minutes after 12 weeks of training in the exercise group. No significant improvement was found in any scale in the control group. Actgraphy: sleep onset latency decreased significantly from 24.6 \pm 16.2 to 16.3 \pm 8.2 minutes after exercise training in the exercise group. Exercise group also showed significant post-test differences in sleep efficiency ( $P = .035$ ), but no such differences control group.
Wang et al, 2020 <sup>72</sup>	Effects and mediating mechanisms of a structured limbs- exercise program on general cognitive function in older adults with mild cognitive impairment: A randomized controlled trial	116	community dwelling older adults, age 60 years and over. age 260 years and (mild cognitive impairment; (3) absence of self-reported visual or auditory impairment; (4) no regular physical exercise excluded if history of neurological, psychiatric and other severe medical issues that may affect brain function; unstable cardiac disease, significant cere brovascular disease, significant musculoskeletal impairment and other severe medical conditions	0	3 /week, 60 min session for 12 weeks supervised limbs- exercise sessions: 10-min limbering-up exercise, 40-min of upper exercise, 40-min of upper exercise, 40-min exercise, 40-min relaxation exercise Wait list control	PSQI Baseline PSQI ex group 9.25 ±3.85 Control 8.63 ±3.56	Intervention Group (n = 57) Wait List Control Group (n = 54) Mean Difference (95% Cl) Cohen's d PSQI T1 9.25 ±3.85 8.63 ±3.56 0.62 ( -0.782, 2.014) 0.384 0.167
Zheng et al, 2019 <sup>73</sup>	Baduanjin exercise intervention for community adults at risk of ischamic stroke: A	170	50-75 Community dwelling, sedentary older adults at risk of stroke due to age, sedentariness. Excluded:	2	5x/week, 60 minutes per session for 12 weeks supervised Baduanjin exercises,	PSQI Baseline scores control group 7.68 ± 0.37 Exercise group 7.81 ± 0.38	Improved sleep quality on PSQI with exercise group over control group. Mean difference 2.65 (1.74, 3.57), p < 0.001 PSQI .

	Sleep quality (PSQJ) improved significantly in the four exercise groups (all p < 0.05).The largest improvements were in the HALRT and HRLAT groups. No statistically significant difference observed in the control group.
	PSQI baseline scores: control group 12.11 ±3.35 exercise groups from 11.66±2.22 to 13.76± 3.46
Non-exercise, monitoring control group	3x/ week for 60 min over 12 weeks: warm-up and stretching (10 min) and 50 min moderate intensity exercise minutes at a Fitness Centre. 4 Exercise groups: aerobic training (AT), high aerobic training (RT), high aerobic with low resistance with low aerobic training (HRLAT), Control: no exercise, normal routines
	2
severe cerebrovascular diseases, musculoskeletal system diseases or other sport contraindications or if they had a history of stroke or a communication disorder	60+ Older adults with metabolic syndrome. Excluded: cardiac function grade ≥2 that might preclude moderate-intensity exercise, acute infectious disease, vision loss, diabetic foot, and inability to complete the aerobic and resistance exercise
	91
randomized controlled trial	Benefits of different combinations of aerobic and resistance exercise for improving plasma glucose and lipid metabolism and sleep quality among elderly patients with metabolic syndrome: a randomized controlled trial
	Zhou et al, 2022 <sup>74</sup>

Table 1: Included interventional studies and their characteristics.

				Mean Difference	Mean Difference
Study or Subgroup	Mean Difference         SE         Weight         Mean Difference           0009 $-3.04$ $0.6214$ $18.7\%$ $-3.04$ $(-4.26, -1.82]$ alay 2021 $-1.5$ $0.7766$ $16.4\%$ $-1.50$ $-3.02$ $(-4.26, -1.82]$ and Chen 2017 $-1.26$ $0.43$ $21.4\%$ $-1.26$ $(-2.10, -0.42]$ 2018 $-0.81$ $3.5208$ $2.2\%$ $-0.81$ $-7.71, 6.09$ $-0.069$ 017 $-0.69$ $0.4003$ $21.8\%$ $-0.69$ $-1.47, 0.09$ $-0.82$ $-0.82$ $-0.92$ $-0.82$ $-0.92$ $-0.82$ $-0.92$ $-0.92$ $-0.92$ $-10$ $-10$ geneity: Tau <sup>2</sup> = 1.21; Chi <sup>2</sup> = 22.54, df = 5 (P = 0.0004); l <sup>2</sup> = 78\% $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$ $-10$			IV, Random, 95% CI	
Chen 2009	-3.04 0	0.6214	18.7%	-3.04 [-4.26, -1.82]	
Maccaulay 2021	-1.5 0	0.7766	16.4%	-1.50 [-3.02, 0.02]	
Chan and Chen 2017	ccaulay 2021 $-1.5$ $0.7766$ $16.4\%$ $-1.50$ [an and Chen 2017 $-1.26$ $0.43$ $21.4\%$ $-1.26$ [-iao 2018 $-0.81$ $3.5208$ $2.2\%$ $-0.81$ [ki 2017 $-0.69$ $0.4003$ $21.8\%$ $-0.69$ [rin 2008 PSQI <5		-1.26 [-2.10, -0.42]		
Hsiao 2018	-0.81 3	3.5208	2.2%	-0.81 [-7.71, 6.09]	
Aoki 2017	-0.69 0	0.4003	21.8%	-0.69 [-1.47, 0.09]	
Irwin 2008 PSQI <5	0.82 0	0.5649	19.5%	0.82 [-0.29, 1.93]	<b>+-</b> -
Total (95% CI)			100.0%	-1.09 [-2.16, -0.02]	•
Heterogeneity: Tau <sup>2</sup> =	1.21; Chi <sup>2</sup> = 22.54, di	lf = 5 (P	= 0.000	4); $I^2 = 78\%$	
Test for overall effect: 2	Z = 2.00 (P = 0.05)				Favours exercise Favours control

Figure	2:Effect of	exercise on a	subjective s	leep, k	baseline F	°SQI ·	< 5
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Study or Subaroup	Mean Difference	SE	Weight	IV Pandom 95% CL	IV Bandom 95% Cl
adalmi 2000		0 5268	2 2%		17, Kandolii, 55% Ci
France 2020	-9.01	0.3300	2.5%	-9.01 [-10.06, -7.96]	
(haiavi 2015	-0	0.8097	2.0%	-8.00 [-9.59, -6.41]	· _
Chajavi 2015	-6.01	1 2552	2.5%	-0.01 [-0.45, -5.57]	
Reid 2010	-4.92	1.2555	1.0%	-4.92 [-7.38, -2.46]	
Stanuao 2018	-4.0	0.4919	2.3%	-4.00 [-5.50, -5.04]	·
vguyen 2012	-4.38	0.6947	2.1%	-4.38 [-5.74, -3.02]	
_iu 2010	-4.37	0.7245	2.1%	-4.37 [-5.79, -2.95]	
Chen 2012	-4.20	0.7414	2.1%	-4.20 [-5.75, -2.05]	
W.C.Chen 2012	-4.28	0.7414	2.1%	-4.28 [-5.73, -2.83]	
2022	-4.2342	0.8969	1.9%	-4.23 [-5.99, -2.48]	
Saker 2021	-3.8	0.8134	2.0%	-3.80 [-5.39, -2.21]	
King 1997 fm	-3.8	0.9701	1.9%	-3.80 [-5.70, -1.90]	
_nen 2010	-3.64	1.0135	1.8%	-3.64 [-5.63, -1.65]	
sekerci and Bicer 2019	-3.43	0.8649	2.0%	-3.43 [-5.13, -1.73]	
Karimi 2016	-3.34	0.9818	1.8%	-3.34 [-5.26, -1.42]	
sharir 2015	-3.33	0.5782	2.2%	-3.33 [-4.46, -2.20]	
snarma 2013	-3.25	1.6613	1.2%	-3.25 [-6.51, 0.01]	
Jampassi 2016	-2.9	1.044	1.8%	-2.90 [-4.95, -0.85]	
aboonpong 2008	-2.8	0.9602	1.9%	-2.80 [-4.68, -0.92]	
Kamrani 2014 Modint	-2.72	0.2801	2.4%	-2./2 [-3.2/, -2.1/]	
-an 2020	-2.7	0.7306	2.1%	-2./0 [-4.13, -1.2/]	
Albar-Almazan 2019	-2.68	1.2041	1.6%	-2.68 [-5.04, -0.32]	
Zheng 2019	-2.65	0.0506	2.5%	-2.65 [-2.75, -2.55]	•
imenez-Garcia 2021 HIII	-2.47	1.1268	1.7%	-2.47 [-4.68, -0.26]	
Wang 2020	-2.45	0.5403	2.3%	-2.45 [-3.51, -1.39]	
King 1997 m	-2.4	1.4306	1.4%	-2.40 [-5.20, 0.40]	
rwin 2008 PSQI > 5	-2.18	0.9569	1.9%	-2.18 [-4.06, -0.30]	
Siu 2021	-2.1	0.4286	2.4%	-2.10 [-2.94, -1.26]	
Kamrani 2014	-2.075	0.2906	2.4%	-2.08 [-2.64, -1.51]	
Luri 2018	-1.99	1.1776	1.7%	-1.99 [-4.30, 0.32]	
Haripasad 2013	-1.91	0.6325	2.2%	-1.91 [-3.15, -0.67]	
rye 2007	-1.8745	1.1956	1.6%	-1.87 [-4.22, 0.47]	
ChanYu 2016	-1.8	0.7961	2.0%	-1.80 [-3.36, -0.24]	
rwin 2014	-1.6	0.8062	2.0%	-1.60 [-3.18, -0.02]	
Chan 2016	-1.5	1.011	1.8%	-1.50 [-3.48, 0.48]	
Berger 2018	-1.4	0.5571	2.3%	-1.40 [-2.49, -0.31]	
Chen (Li) 2016	-1.28	0.5824	2.2%	-1.28 [-2.42, -0.14]	
song Yu 2019	-1.257	0.1796	2.5%	-1.26 [-1.61, -0.90]	-
King 2008	-1.11	1.0428	1.8%	-1.11 [-3.15, 0.93]	
Hosseini 2011	-1.109	0.6069	2.2%	-1.11 [-2.30, 0.08]	
Cheung 2014	-1.1	0.7354	2.1%	-1.10 [-2.54, 0.34]	
urado-Fasoli 2020	-1.06	0.7754	2.1%	-1.06 [-2.58, 0.46]	
_ü 2017	-1.01	1.255	1.6%	-1.01 [-3.47, 1.45]	
Choi 2018	-1	0.6332	2.2%	-1.00 [-2.24, 0.24]	
Evangelista DeLima 2021	-0.7	1.528	1.3%	-0.70 [-3.69, 2.29]	
imenez-Garcia 2021 MIIT	-0.6	1.2533	1.6%	-0.60 [-3.06, 1.86]	
Mizayaki 2021	-0.4513	0.3136	2.4%	-0.45 [-1.07, 0.16]	
Cai 2014	-0.38	0.8045	2.0%	-0.38 [-1.96, 1.20]	
Fragoso 2015	-0.26	0.1225	2.5%	-0.26 [-0.50, -0.02]	-
Bullock 2020	0.55	1.2253	1.6%	0.55 [-1.85, 2.95]	
					•

-4 -2 0 2 4 Favours [experimental] Favours [control]

Figure 3: PSQI scores >5 at baseline

Study	Effect Size with 95% CI	Weigh (%)
Age group: 55-60 y/o		. ,
Cai2014	-0.38 [ -1.96, 1.20]	1.72
Hartescu	1.60 [ -1.01, 4.21]	1.27
Jurado-Fasoli 2020	-1.06 [ -2.58, 0.46]	1.74
Khajavi 2015	-6.01 [ -6.45, -5.57]	2.11
Sharma 2013 aerobic	-2.80 [ -6.75, 1.15]	0.83
Sharma 2013 rt	-4.30 [ -8.30, -0.30]	0.81
Zheng 2019	-2.65 [ -2.75, -2.55]	2.15
Heterogeneity: r <sup>2</sup> = 5.09, l <sup>2</sup> = 97.51%, H <sup>2</sup> = 40.23	-2.25 [ -4.11, -0.38]	
Test of $\theta_i = \theta_j$ : Q(6) = 241.39, p = 0.00		
61-65.9 y/o		
Berger 2018	-1.40 [ -2.49, -0.31]	1.92
Buman 2010	-0.21 [ -1.71, 1.29]	1.75
Chen 2016 (Aqt)	-1.50 [ -3.48, 0.48]	1.54
Curi 2018	-1.99 [ -4.30, 0.32]	1.39
Gambassi	-2.90 [ -4.95, -0.85]	1.51
Irwin 2014 sh vs ex 4m	-1.60 [ -3.18, -0.02]	1.72
Kamrani 2014 LowInt	-1.43 [ -2.05, -0.81]	2.07
Kamrani 2014 ModInt	-2.72 [ -3.27, -2.17]	2.09
King 1997 fm	-3.80 [ -5.70, -1.90]	1.57
King 1997 m	-2.40 [ -5.20, 0.40]	1.19
King 2008	-1.11 [ -3.15, 0.93]	1.51
Reid 2010 -	-4.92 [ -7.38, -2.46]	1.33
Sharif 2015	-3.33 [ -4.46, -2.20]	1.90
Tseng 2020 -	-5.20 [ -7.093.31]	1.58
Heterogeneity: τ <sup>2</sup> = 0.91, I <sup>2</sup> = 68.86%, H <sup>2</sup> = 3.21	-2.35 [ -3.01, -1.69]	
lest of $\theta_i = \theta_j$ : Q(13) = 41.75, p = 0.00		
66-69.9 y/o Aibar-Almazán 2019	-2 68 [ -5 04 -0 32]	1.37
Baker 2021		1 74
Brandao		1.07
Brandao	-4.60 [ -5.56, -3.64]	1.97
Chen2009 cluster		1.87
- Evangelista DeLima 2021	-0.70[-3.69, 2.29]	1.12
Frye	-1.87 [ -4.21, 0.47]	1.38
Irwin 2008 PSQI	- 0.82 [ -0.29, 1.93]	1.91
Jimenez-Garcia 2021 HIIT	-2.47 [ -4.68, -0.26]	1.44
Jimenez-Garcia 2021 MIIT	-0.60 [ -3.06, 1.86]	1.33
Karimi 2016	-3.34 [ -5.26, -1.42]	1.56
Liu 2010	-4.37 [ -5.79, -2.95]	1.78
Lū 2017	-1.01 [ -3.47, 1.45]	1.33
Maccaulay 2021	-1.50 [ -3.02, 0.02]	1.74
Nguyen 2012	-4.38 [ -5.74, -3.02]	1.81
Siu 2021 ex	-1.20 [ -2.18, -0.22]	1.96
Siu 2021 tch		1.98
Wang 2020	-2.45 [ -3.51, -1.39]	1.93
Heterogeneity: $\tau^2 = 2.25$ , $l^2 = 81.31\%$ , $H^2 = 5.35$ Test of $\theta_i = \theta_i$ : Q(16) = 85.62, p = 0.00	-2.45 [ -3.28, -1.63]	
70-74 9 v/o		
Aoki	-0.69 [ -1.47, 0.09]	2.03
Badelmi 2009 -	-9.01 [ -10.06, -7.96]	1.93
ChanChen2016	-1.26 [ -2.10, -0.42]	2.01
Chen 2012	-4.28 [ -5.73, -2.83]	1.77
Cheung 2014	-1.10 [ -2.54, 0.34]	1.78
Fan 2020	-2.70 [ -4.13, -1.27]	1.78
Hsiao 2018 cluster -	-0.81 [ -7.71, 6.09]	0.37
Irwin 2008 PSQI >5	-2.18 [ -4.06, -0.30]	1.58
Manjunath	-1.50 [ -3.02, 0.02]	1.74
Sekerci and Bicer 2019	-3.43 [ -5.13, -1.73]	1.66
Heterogeneity: τ <sup>2</sup> = 8.52, I <sup>2</sup> = 95.20%, H <sup>2</sup> = 20.83	-2.81 [ -4.73, -0.90]	
Test of $\theta_i = \theta_j$ : Q(9) = 187.46, p = 0.00		
75-82.8		
Chan TCQ 2016	-1.80 [ -3.36, -0.24]	1.72
Chen (Li) 2016 cluster	-1.28 [ -2.42, -0.14]	1.90
Choi 2018 cluster	-1.00 [ -2.24, 0.24]	1.86
Fragoso 2015	-0.26 [ -0.50, -0.02]	2.14
Haripasad 2013	-1.91 [ -3.15, -0.67]	1.86
Miyazaki 2021	-0.45 [ -1.06, 0.16]	2.07
Song Yu 2019	-1.26 [ -1.61, -0.90]	2.13
Taboonpong 2008	-2.80 [ -4.68, -0.92]	1.58
Zhou 2022- RT	-3.53 [ -5.43, -1.63]	1.57
Zhou 2022-AT	-4.09 [ -6.11, -2.07]	1.52
Zhou 2022-HALRT -	-5.24 [ -7.12, -3.36]	1.58
Zhou 2022-HRLAT	-4.06 [ -6.062.06]	1.53
Heterogeneity: $\tau^{2}$ = 0.98, $I^{2}$ = 87.31%, $H^{2}$ = 7.88	-1.95 [ -2.63, -1.27]	
Test of $\theta_i = \theta_j$ : Q(11) = 86.66, p = 0.00	Ŧ	
Overall	-2.43 [ -2.88, -1.97]	
Heterogeneity: $\tau^{2}$ = 2.54, $l^{2}$ = 94.30%, $H^{2}$ = 17.54	,	
Test of $\theta_i = \theta_j$ : Q(59) = 1034.59, p = 0.00		
Test of group differences: Q <sub>b</sub> (4) = 1.40, p = 0.84		
-10	-5 0 5	
landom-effects DerSimonian-Laird model		

Figure 4: PSQI, subgroup analysis by age (categorical)

				Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
7.1.1 Men PSQI					
Sharif 2015	-4.23	0.4177	6.7%	-4.23 [-5.05, -3.41]	(
Karimi 2016	-3.34	0.9818	6.1%	-3.34 [-5.26, -1.42]	
King 1997 m	-3.1	1.542	5.3%	-3.10 [-6.12, -0.08]	
Kamrani 2014 ModInt	-2.72	0.2801	6.8%	-2.72 [-3.27, -2.17]	
Kamrani 2014 LowInt	-1.43	0.3142	6.8%	-1.43 [-2.05, -0.81]	
Subtotal (95% CI)			31.7%	-2.89 [-4.05, -1.73]	◆
Heterogeneity: Tau <sup>2</sup> = 2	L.29; Chi <sup>2</sup> = 29.95,	df = 4 (P	< 0.0000	01); I <sup>2</sup> = 87%	
Test for overall effect: 2	Z = 4.88 (P < 0.000)	01)			
7.1.2 Women PSQI					
Sharif 2015	-8.16	0.2008	6.8%	-8.16 [-8.55, -7.77]	-
Khajavi 2015	-6.01	0.2226	6.8%	-6.01 [-6.45, -5.57]	-
Reid 2010	-4.92	1.2553	5.8%	-4.92 [-7.38, -2.46]	
King 1997 fm	-3.4	0.9701	6.1%	-3.40 [-5.30, -1.50]	
Gambassi 2016	-2.9	1.044	6.1%	-2.90 [-4.95, -0.85]	
Aibar–Almazán 2019	-2.68	1.2041	5.8%	-2.68 [-5.04, -0.32]	
Curi 2018	-1.99	1.1776	5.9%	-1.99 [-4.30, 0.32]	
Cheung 2014	-1.1	0.7354	6.4%	-1.10 [-2.54, 0.34]	
Lü 2017	-1.01	1.255	5.8%	-1.01 [-3.47, 1.45]	
Choi 2018	-1	0.6332	6.5%	-1.00 [-2.24, 0.24]	
Cai 2014	-0.38	0.8045	6.3%	-0.38 [-1.96, 1.20]	
Subtotal (95% CI)			68.3%	-3.11 [-4.91, -1.30]	$\bullet$
Heterogeneity: Tau <sup>2</sup> = 8	3.46; Chi <sup>2</sup> = 321.58	, df = 10	(P < 0.00)	0001); I <sup>2</sup> = 97%	
Test for overall effect: 2	Z = 3.38 (P = 0.000)	7)			
					-
Total (95% CI)			100.0%	-3.06 [-4.54, -1.58]	$\bullet$
Heterogeneity: Tau <sup>2</sup> = 8	3.34; Chi <sup>2</sup> = 598.81	, df = 15	(P < 0.00)	$(0001); I^2 = 97\%$	
Test for overall effect: 2	Z = 4.05 (P < 0.000)	1)			Favours [experimental] Favours [control]
Test for subgroup diffe	rences: Chi <sup>2</sup> = 0.04	, df = 1 (	P = 0.84)	$  ^2 = 0\%$	rateaus (experimental) rateaus (control)

#### Figure 5: Subgroup analysis, changes in PSQI by sex

			Mean Difference	Mean Difference
Study or Subgroup	Mean Difference SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Fragoso 2015	0.19 0.1621	28.5%	0.19 [-0.13, 0.51]	•
Hartescu 2015	-2.64 1.4423	20.2%	-2.64 [-5.47, 0.19]	
Siu 2021 ex	-2.3 0.7781	25.5%	-2.30 [-3.83, -0.77]	
Siu 2021 tch	-3.8 0.7299	25.9%	-3.80 [-5.23, -2.37]	
Total (95% CI)		100.0%	-2.05 [-4.38, 0.28]	
Heterogeneity: Tau <sup>2</sup> = Test for overall effect	= 4.94; Chi <sup>2</sup> = 39.98, df = 3 :: Z = 1.72 (P = 0.09)	(P < 0.00	0001); I <sup>2</sup> = 92%	-10 -5 0 5 10 Favours exercise Favours control

Figure 6 : Insomnia Severity Index

Study or Subgroup	Mean Difference S	E Weight	Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
Aoki 2017	-0.92 0.540	3 23.1%	-0.92 [-1.98, 0.14]	
Brandao 2018	-2.46 0.404	3 24.3%	-2.46 [-3.25, -1.67]	+
Fragoso 2015	0.19 0.126	1 25.8%	0.19 [-0.06, 0.44]	•
Irwin 2014	-1.4 0.974	8 18.4%	-1.40 [-3.31, 0.51]	
Reid 2010	-5.1 2.207	2 8.4%	-5.10 [-9.43, -0.77]	
Total (95% CI)		100.0%	-1.44 [-2.96, 0.07]	•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect	= 2.30; Chi <sup>2</sup> = 48.55, df = :: Z = 1.87 (P = 0.06)	4 (P < 0.00	0001); I <sup>2</sup> = 92%	-20 -10 0 10 20 Favours exercise Favours control

Figure 7: Epworth Sleepiness Scale

Meta regression variable	Coef.	Std. Err.	z	p>[z]	95% Cl
age (categorical: 5-year	0.015	0.128	0.08	0.934	-0.342, 0.372
increments)					
exercise intensity (categorical:	-0.471	0.420	-1.12	0.262	-1.295, 0.004
low, moderate, high)					
exercise frequency	-0.101	0.190	-0.53	0.597	-0.473, 0.272
dose (hours)	0.003	0.002	1.24	0.216	-0.002, 0.008
dose hours (categorical)	0.172	0.151	1.14	0.254	-0.124, 0.449
duration- weeks (categorical)	0.913	0.269	22.36	0.018	0.155, 1.67 *
risk of bias (low, mod, high)	-0.425	0.351	-1.21	0/225	-1.112, 0.468
age and dose hours					
age (categorical)	-0.004	0.190	-0.02	0.981	-0.377, 0.368
dose hours (categorical)	0.173	0.153	1.13	0.257	-0.126, 0.472
age, dose hours, risk of bias					
age	-0.495	0.195	-0.25	0.799	-0.421, 0.332
dose hours (categorical)	0.17	0.153	1.11	0.267	-0.130, 0.471
risk of bias (categorical)	-0.431	0.358	-1.20	0.228	-1.131, 0.270
duration, dose, age					
duration (categorical)	0.926	0.423	2.19	0.029	0.097, 1.755*
dose (categorical)	-0.157	0.205	-0.77	0.444	-0.559, 0.245
age (categorical)	-0.064	0.180	-0.36	0.721	-0.417, 0.288
duration, dose, age, risk bias					
duration (categorical)	1.052	0.418	2.52	0.012	0.233, 1.870 *
dose (categorical)	-0.208	0.201	-1.03	0.302	-0.603. 0.187
age (categorical)	-0.130	0.179	-0.73	0.468	-0.482, 0.222
risk of bias (categorical)	-0.576	0.327	-1.76	0.078.	-1.216, 0.638

\* Statistically significant

**Table 2:** Meta-regression, PSQI scores (continuous) by age (categorical), dose hours (total hours, categorical), duration (weeks, categorical), age (categorical, 5-year increments) and risk of bias (categorical: low, moderate, high)

### Funnel plots: publication bias







c.



d.

Figure 8: Funnel plots a. PSQI all ROB all ex groups b.PSQI low-mod ROB all ex groups c. Actigraphy, all exercise groups, d. PSG, all exercise groups



PRISMA 2020 Checklist

Section and Topic	ltem #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1, 2,6, 7
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-7
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6-7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7-9
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	8, 9 supplementary materials
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	supplementary materials
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7-10
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	8-10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7-10
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7-10
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	10, figure 2
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	9-11
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7-9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	9-11
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9-11
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	9-11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	9-11
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	10-11
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	11

Section and Topic	item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9-11
RESULTS		·	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	11, figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	appendix
Study characteristics	17	Cite each included study and present its characteristics.	table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	11, figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	16-23, supplementary materials
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	11
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	16-23 tables 2 and 3, and supplementary materials
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	19-20, 22
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	19-22, supplementary materials
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	17, supplementary materials
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	not in scope of this review
DISCUSSION	•		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	23-32
	23b	Discuss any limitations of the evidence included in the review.	33-34
	23c	Discuss any limitations of the review processes used.	33-34
	23d	Discuss implications of the results for practice, policy, and future research.	34-36
OTHER INFORMA	TION		
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	7
protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n/a
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	36

Section and Topic	ltem #	Checklist item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	36
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be <u>found</u> ; template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	will be available at publication

From: Page MJ, McKenzie JE, Bossuyt PM, Boutton I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmi.n71 For more information, visit: http://www.prisma-statement.org/

**PRISMA Checklist:** Exercise interventions benefit sleep in older adults: A systematic review and meta-analysis.

### Appendix IV: Supplementary materials for chapter V

"The effectiveness of exercise interventions targeting sleep in older adults with cognitive impairment or Alzheimer's Disease and Related Dementias (AD/ADRD): A systematic review and meta-analysis."

# Figure I. Search strategies

# Pubmed 1

(((("dementia"[Title/Abstract] OR "cognitive impairment"[Title/Abstract] OR "mild cognitive impairment"[Title/Abstract] OR "alzheimer"[Title/Abstract]) OR "older adult" [Title/Abstract]) OR "elderly"[Title/Abstract]) OR "aged"[Title/Abstract]) OR "middle-aged"[Title/Abstract]) OR "senior"[Title/Abstract]) AND ("exercise"[Title/Abstract] OR "physical activity"[Title/Abstract] OR "interval training"[Title/Abstract] OR "aerobic"[Title/Abstract])) OR ("mind body"[Title/Abstract] OR "yoga"[Title/Abstract] OR "tai chi"[Title/Abstract] OR "baduanjin"[Title/Abstract])) OR ("strengthening"[Title/Abstract])) OR ("strength training"[Title/Abstract]) OR "strength program"[Title/Abstract] OR "interval training"[Title/Abstract]) OR "conditioning"[Title/Abstract] AND ("sleep"[Title/Abstract] OR "sleep quality"[Title/Abstract]) OR ("sleep quantity "[Title/Abstract]) OR (insomnia[Title/Abstract]) OR ("sleep problems"[Title/Abstract]) OR ("sleep difficulties" [Title/Abstract]) OR ("sleep problems"[Title/Abstract]) OR ("sleep difficulties"

# Pubmed 2

(((((((((((("acute exercise"[Title/Abstract]) OR ("acute physical activity"[Title/Abstract])) OR (("physical activity"[Title/Abstract]) OR ("exercise"[Title/Abstract]))) OR ("strengthening"[Title/Abstract])) OR ("strength training"[Title/Abstract] OR "strength program"[Title/Abstract] OR "interval training"[Title/Abstract]) OR "conditioning"[Title/Abstract]

OR "aerobic"[Title/Abstract]) AND ("sleep"[Title/Abstract] OR "sleep quality"[Title/Abstract])) OR ("sleep quantity "[Title/Abstract]) OR (insomnia[Title/Abstract]) OR ("sleep problems"[Title/Abstract]) OR ("sleep difficulties" [Title/Abstract]) AND (("clinical trial"[Publication Type] OR ((clinicalstudy[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR meta-analysis[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] AND ("middle aged"[MeSH Terms] OR "aged"[MeSH Terms] OR "middle aged"[MeSH Terms] OR "aged"[MeSH Terms] OR "aged, 80 and over"[MeSH Terms]) AND ((clinicaltrial[Filter] OR meta-(linicaltrial[Filter] OR solution])) NOT ("diet"[All Fields] AND((clinicaltrial[Filter] OR metaanalysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (middleagedaged[Filter] OR middleaged[Filter] OR aged[Filter] OR 80andover[Filter]))) AND ((clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (middleagedaged[Filter] OR middleaged[Filter] OR aged[Filter] OR 80andover[Filter]))) NOT ("parkinsons"[All Fields] AND ((clinicaltrial[Filter] OR metaanalysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (middleagedaged[Filter] OR middleaged[Filter] OR aged[Filter] OR 80andover[Filter]))) AND ((clinicaltrial[Filter] OR meta-analysis[Filter] OR aged[Filter] OR 80andover[Filter]))) AND ((clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (middleagedaged[Filter] OR middleaged[Filter] OR aged[Filter] OR 80andover[Filter])) NOT ((("parkinson s"[Title/Abstract]) OR ("parkinsons disease"[Title/Abstract])) OR ("parkinson s disease"[Title/Abstract]) AND ((clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (middleagedaged[Filter]

# Pubmed 3: Search for un-indexed

Search: (((((("exercise"[Title/Abstract]) OR ("physical activity"[Title/Abstract])) OR ("interval training"[Title/Abstract])) OR ("strengthening"[Title/Abstract])) OR ("conditioning"[Title/Abstract])) OR ("aerobic"[Title/Abstract])) AND (((("dementia"[Title/Abstract] OR "cognitive impairment"[Title/Abstract] OR "mild cognitive impairment"[Title/Abstract] OR "mild cognitive impairment"[Title/Abstract] OR "alzheimer"[Title/Abstract]) OR "older adult" [Title/Abstract]) OR "elderly"[Title/Abstract]) OR "aged"[Title/Abstract]) OR "middle-aged"[Title/Abstract]) OR "senior"[Title/Abstract]) AND ("sleep"[Title/Abstract]) OR "sleep quality"[Title/Abstract]) OR (insomnia[Title/Abstract]) OR ("sleep problems"[Title/Abstract]) OR ("sleep difficulties" [Title/Abstract]) OR ("sleep difficulties" [Title/Abstract]) OR ("sleep problems"[Title/Abstract]) OR ("sleep difficulties" [Title/Abstract]) OR ("sle

# Embase

((sleep:ab,ti OR insomnia:ab,ti) AND exercise:ab,ti OR physical activity':ab,ti OR 'resistance training':ab,ti OR 'aerobic exercise':ab,ti OR exercise:ab,ti NOT 'obese patient':ti,ab,kw NOT 'parkinson disease':ti,ab,kw NOT fibromyalgia:ti,ab,kw NOT cancer:ti,ab,kw NOT obese:ti,ab,kw

NOT 'chronic obstructive lung disease':ti,ab,kw NOT 'heart disease':ti,ab,kw NOT 'stroke' ti,ab,kw

NOT 'rheumatoid arthritis':ti,ab,kw NOT 'lupus erythematosus':ti,ab,kw) AND ([aged]/lim OR [middle aged]/lim OR [very elderly]/lim) AND ('clinical trial'/de OR 'controlled clinical trial'/de OR

'controlled study'/de OR 'human'/de OR 'intervention study'/de OR 'meta analysis'/de OR 'pilot

study'/de OR 'randomized controlled trial'/de OR 'systematic review'/de)

#### Scopus

((TITLE-ABS-KEY (sleep) OR TITLE-ABS-KEY (insomnia) AND TITLE-ABS-KEY (exercise) OR TITLE-ABS-KEY ("physical activity") AND NOT TITLE-ABS-KEY (parkinson's) AND NOT TITLE-ABSKEY(diabetes) AND NOT TITLE-ABS-KEY (fibromyalgia))) AND (older AND adults) OR ( elderly) OR (senior) AND (LIMIT-TO (EXACTKEYWORD, "Controlled Study"))

### Cochrane Library

(sleep):ti,ab,kw OR (insomnia):ti,ab,kw AND (exercise):ti,ab,kw OR (physical activity):ti,ab,kw AND (older adults):ti,ab,kw OR ("pensioner"):ti,ab,kw OR ("old age"):ti,ab,kw OR ("elderly"):ti,ab,kw NOT (apnea) NOT ("fibromyalgia syndrome"):ti,ab,kw NOT ("Cancer"):ti,ab,kw NOT ("Parkinsons disease"):ti,ab,kw NOT (stroke):ti,ab,kw



PRISMA 2020 Checklist

Section and Topic	ltem #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1,7
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	7
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	7
METHODS	_		
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7-9
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	9 supplementary materials
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	supplementary materials
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	9-11
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	9-10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	8, 11-12
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	10-12
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	11, 14, 16, 17, figure 2a and b
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	10-12
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	10-12
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	11-12
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	12
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	12, 13
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	12,13
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	13
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	12

Section and Topic	ltem #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	2
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	13-14, figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Available on request
Study characteristics	17	Cite each included study and present its characteristics.	18-28, tables 1, 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	16,17, figure 2a and b, tables 1 and 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	18-20
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8, 10-19
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	28-30
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	30
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	30
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	n/a
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	not in scope of this review
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	31-28
	23b	Discuss any limitations of the evidence included in the review.	32-38
	23c	Discuss any limitations of the review processes used.	36-38
	23d	Discuss implications of the results for practice, policy, and future research.	33-36, 39-40
OTHER INFORMA	TION		
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	7
protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n/a
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	n/a no funding
Competing interests	26	Declare any competing interests of review authors.	42
Availability of	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included	available on

Section and Topic	ltem #	Checklist item	Location where item is reported
data, code and other materials		studies; data used for all analyses; analytic code; any other materials used in the review.	request after publication

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. dgi: 10.1136/bmi.n71 For more information, visit: http://www.prisma-statement.org/

**PRISMA Checklist:** The effectiveness of exercise interventions targeting sleep in older adults with cognitive impairment or Alzheimer's Disease and Related Dementias (AD/ADRD): A systematic review and meta-analysis.