

Sleep abnormalities as potential early
diagnostic biomarkers for Alzheimer's
disease: A scoping review examining the
extent of empirical evidence

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Declaration

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This thesis entitled: **'Sleep abnormalities as potential early diagnostic biomarker for Alzheimer's disease: A scoping review examining the extent of empirical evidence'** is submitted in partial fulfilment for the requirements for the Unitec degree of Master of Osteopathy.

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CANDIDATE'S DECLARATION

I confirm that:

- This Thesis/Research Project represents my own work.
- The contribution of supervisors and others to this work was consistent with the Unitec Regulations and Policies.
- Research for this work has been conducted in accordance with the Unitec Research Ethics Committee Policy and Procedures and has fulfilled any requirements set for this project by the Unitec Research Ethics Committee.

Research Ethics Committee Approval Number: **This study was exempted from ethical approval by the Unitec Research Ethics Committee.**

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A handwritten signature in blue ink, appearing to read 'Lucas Baxter'.

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I dedicate this thesis to my loving grandmother, Lyla, who was diagnosed with Alzheimer's disease in 2019. I would never have been able to finish this thesis without the support of my family, particularly my wife and two kids. They were the motivation I needed.

Abstract

Alzheimer's disease is the most common type of dementia, and its prevalence is increasing world-wide. This disease incurs a wide range of complications for individuals and society. No current therapies exist to cure or stop the progression of the disease once diagnosed within an individual. Many risk factors for Alzheimer's disease are known, although one which has recently emerged within the scientific literature is sleep disturbance. The true implications of the research are at present, incomplete, yet the studies available have shown promise of the potential diagnostic and therapeutic value of sleep. Therefore, this study aimed to examine the extent and nature of research available discussing the role of sleep in Alzheimer's disease development, as well as the potential utility of specific sleep disturbances to be diagnostic biomarkers for Alzheimer's disease. A five-stage scoping review framework developed by Arksey and O'Malley was utilised to ensure an in-depth review of the relevant literature was achieved.

From a total of 2,821 studies, 199 were included into this scoping review and classified into four primary themes: 1) Mechanistic links between sleep disturbance and Alzheimer's disease, 2) Sleep disturbance as a biomarker for Alzheimer's disease, 3) Sleep as a therapeutic target for Alzheimer's disease, and 4) Preclinical Alzheimer's disease definition. This review has covered a range of studies that discussed links between sleep disturbance and Alzheimer's disease pathogenesis. The findings suggests that certain sleep patterns may have diagnostic and therapeutic uses in Alzheimer's disease; however, further experimental research is indicated to substantiate these hypotheses. The term preclinical Alzheimer's disease requires a relevant and concise consensus regarding its definition in order for the aforementioned hypotheses to fully be explored for their respective potential.

Keywords:

Alzheimer's disease, preclinical, sleep disturbances, biomarker, amyloid beta

Table of Contents

CANDIDATE'S DECLARATION.....	ii
Abstract	iv
Keywords:	iv
Introduction to Thesis.....	8
Section 1: Literature Review	11
Overview.....	12
Alzheimer's disease	12
Health and socioeconomic burden of Alzheimer's disease	12
Risk Factors for Alzheimer's Disease	13
Pathological hallmarks	14
Diagnosis of Alzheimer's Disease	14
Preclinical stage of Alzheimer's disease	15
Potential implications for early diagnosis	15
Sleep as a risk factor and potential biomarker for AD development.....	15
Obstructive sleep apnoea	16
The orexin system	17
Summary.....	17
Section 2: Methodology	19
An overview of scoping reviews.....	20
Limitations of scoping review methodology.....	20
Rationale for scoping review	21
Scoping Review Framework.....	21
Stage 1: Identifying the research question	21
Stage 2: Identifying relevant studies	22
Stage 3: Study selection.....	23
Stage 4: Charting the data	25
Stage 5: Collating, summarising and reporting the results.....	25
Stage 6: Consultation.....	26
References.....	27
Section 3: Manuscript.....	39
Abstract	41
Keywords:	41
Introduction	42
Methods.....	42

Stage 1: Identification of the research question.....	43
Stage 2: Identification of the relevant studies.....	43
Stage 3: Study selection.....	44
Stage 4: Charting the data	45
Stage 5: Collating, summarising and reporting the results.....	45
Results	46
Characteristics of included studies.....	47
Observed themes of included studies	48
<i>Theme one: Mechanistic Links between Sleep Disturbance and Alzheimer’s Disease.....</i>	51
Non-Rapid Eye Movement Sleep/Slow-Wave Amplitude Sleep/Amyloid Beta	51
Orexin/Hypocretin system	52
Apolipoprotein Epsilon (APOE).....	52
Obstructive Sleep Apnoea	52
Melatonin	53
Tau Protein	53
K-Complexes.....	54
Gut Microbiome	54
<i>Theme two: Sleep disturbance as a Biomarker of Alzheimer’s Disease</i>	54
Aspects of Sleep with Possible Biomarker Utility	55
<i>Theme Three: Sleep as a Therapeutic Target for Alzheimer’s Disease.....</i>	55
Non-Rapid-Eye-Movement/Slow Wave Amplitude Sleep	56
Continuous Positive Airway Pressure	56
Trans-Cranial Magnetic Stimulation	56
The Orexin/Hypocretin system	56
<i>Theme four: Preclinical Alzheimer’s Disease Definition</i>	57
Definitions of Preclinical Alzheimer’s Disease.....	57
Limitations and Challenges of the Current Definition	57
Discussion	58
<i>Mechanistic Links between Sleep and Alzheimer’s Disease</i>	58
Non-Rapid Eye Movement Sleep/Slow-Wave Amplitude Sleep/Amyloid Beta	58
Orexin/Hypocretin System	59
Apolipoprotein Epsilon	60
Obstructive Sleep Apnoea	60
Melatonin	61
Tau Proteins	61
K-complexes	61
Gut Microbiome	61
<i>Sleep Disturbance as a Biomarker of Alzheimer’s Disease.....</i>	62
<i>Sleep as a Therapeutic Target for Alzheimer’s Disease.....</i>	63
Slow Wave Amplitude Sleep.....	64
Continuous Positive Airway Pressure	64

Trans-Cranial Magnetic Stimulation	65
The Orexin/Hypocretin system	65
<i>Preclinical Alzheimer’s Disease Definition</i>	65
Difference Between Current Definitions and the Necessity of Definition Consensus	66
Ethical Implications of Current Definitions of Preclinical Alzheimer’s Disease	66
The Relationship Between the Observed Themes	67
Limitations	68
<i>Conclusion</i>	69
<i>Recommendations for Future Research</i>	70
<i>References</i>	71
<i>Section 4: Appendices</i>	100
Appendix A: Table of Included Studies.....	101
Appendix B: PRISMA-ScR Checklist	131
Appendix C: Cooper’s Checklist for Scoping Reviews.....	133
Appendix D: Methodological Tracking Document	135
Appendix E: Ethics Exemption Letter	143
Appendix F: Preliminary Search Strategy	144

Introduction to Thesis

Alzheimer's Disease (AD) is one of the most common neurodegenerative diseases associated with direct and indirect socioeconomic and health burdens, primarily affecting people over the age of sixty-five (1,2). In 2018, it was estimated that between 40 and 50 million individuals across the world lived with dementia (3). AD is the most common sub-type of dementia, and is the sixth leading cause of death in the US (4). In New Zealand, approximately 1.3% of the population are currently living with AD, with an expected increase to 3% by 2050 (5), and by then is predicted to cost the national economy approximately five billion dollars (6). This evidence highlights the far-reaching and debilitating socioeconomic effects of this condition on people with AD, their family and carers.

Sleep disturbance is a risk factor for AD that is beginning to be further explored by the scientific community. There are two primary states of sleep, non-rapid eye movement (NREM), and rapid eye movement (REM), both of which involve different neural characteristics and alternate in their cyclical activity across a single period of sleep (7,8). NREM is divided into stages 1-4, each stage being a relative representation of the quality of sleep (7,8). Certain aspects of NREM sleep contribute to memory function and consolidation of memories (9). REM sleep makes up the remainder and is mainly associated with dreaming (7). The functions of sleep regarding restoration and recovery of the central nervous system (CNS) are of emerging interest in the field of AD research.

Sleep disturbance may impair these restorative functions of sleep and play a pivotal role in the development of AD (1,10–13). Sleep disturbance causes dysfunction of normal waste clearance and restorative events (14). Such disruption triggers cerebral inflammation, accumulation of metabolic wastes and an increase of oxidative stress (1,13). A proposed mechanism attributed to this is a reduction of the brain's ability to utilise the glymphatic system (15). The glymphatic system, analogous to the lymphatic system, is a system of waste clearance of the CNS (16). The main function of this system is to break down and eliminate soluble metabolites from the CNS (16). This system is activated during a specific phase of NREM sleep, known as slow wave sleep (SWS) (17). SWS disruption impairs the clearing of metabolites (15), causing accumulation of metabolic waste including the soluble protein

Amyloid beta (A β) (17,18). It has been demonstrated in animals that sustained accumulation of A β changes from soluble protein to insoluble plaque and is less easily cleared by the glymphatic system (15). These plaques then negatively affect SWS patterns, causing the emergence of new and specific sleep patterns (15,19).

The accumulation of A β within the brain is now accepted as a fundamental pathological process of AD development (17,20). Research has shown that levels of A β progressively increase throughout the initial stages of preclinical of AD (21). The preclinical phase does not appear to be well-defined in the literature, although is suspected to begin approximately 20 years prior to cognitive symptoms classically associated with AD (22). The changes in SWS mentioned above may hold utility as an indicator of AD development within the preclinical stage. A preliminary search on the subject yielded numerous animal studies, as well as some studies in humans, though most are related to the mechanisms connecting sleep and AD. Research has implicated a relationship between sleep disruption, A β deposition and AD pathogenesis (23), though conclusive research into the implications of these findings for humans is lacking. Existing studies discuss the role of sleep disturbance in AD development, however, there appears to be a lack of evidence pertaining to the use of specific sleep patterns or quality as early diagnostic markers of AD. For this reason, a systematic review addressing specific key questions is warranted. However, these questions may be best informed by first mapping the existing evidence connecting sleep disturbance to AD development. Therefore, the purpose of this research project was to perform a scoping review examining the empirical evidence available surrounding specific sleep patterns and AD. Furthermore, this project aimed to ascertain whether a consistent definition of preclinical AD exists. Lastly, this scoping review aimed to provide recommendations for future research and the feasibility of undertaking a systematic review.

This thesis has been arranged into four sections. Section 1 consists of a literature review that defines Alzheimer's disease and outlines the health and socioeconomic burden incurred by this disease. The literature review will also discuss risk factors and diagnosis of Alzheimer's disease, with reference to sleep disturbance and its potential implications regarding Alzheimer's disease management. Section 2 contains an outline of the scoping review methodology with contextual reference to the relevant literature. This section will describe

the scoping review process used to conduct this research piece. Section 3 has been arranged in a manuscript format. This section contains the results of the search process of this scoping review and discusses the results in relation to the aims and objectives formulated by the authors. Section 4 contains all relevant appendices including Ethics approval letter, full search strategy results, two scoping review checklists, and table of included studies.

Section 1: Literature Review

Overview

The primary aim of this literature review is to provide background information on the relationship between Alzheimer's Disease (AD) and sleep. In addition, this review describes the socioeconomic burden this disease presents followed by the discussions on risk factors, pathological hallmarks, current methods of AD diagnosis, treatment and potential implications of early diagnosis.

Since the preclinical stage of AD is critical in early diagnosis and delaying the onset of AD, this literature review will also consider whether the existing literature can be used to ascertain the existence of a consistent definition of the preclinical phase of AD. The preliminary literature review initially suggested that there is no clear definition and characterisation of preclinical AD.

Alzheimer's disease

Alzheimer's disease (AD) is an incurable neurological disorder with an expected increase in prevalence from 0.632% to 0.879% of the global population by 2030, burdening individuals, families, societies and health-care systems (4,24,25). It is the most common form of dementia (4) accounting for 60-80% of cases (26). The primary complications involve difficulty with memory, language, and cognitive skills necessary for everyday living (24,26). Although Alzheimer's disease predominantly affects individuals above the age of 65 (27), a variation known as early onset familial Alzheimer's can appear in the 4th or 5th decade of life (25). An exact cause remains elusive (24), yet several lifestyle and genetic risk factors have been identified, which are discussed below. It is particularly noteworthy that despite the well-described risks identified in the research, the prevalence of the disease continues to increase across the globe (26,28).

Health and socioeconomic burden of Alzheimer's disease

As human lifespans increase, so too does the collective encumbrance of age-related disease (29,30). AD places a huge burden on individuals, families, carers, communities and healthcare systems across the globe (2,4,24,25). It is one of the greatest health and economical challenges of this century (1). The average annual care cost estimated for one person living

with AD is between \$41,689 and \$56,290 in U.S. dollars (approximately \$67,958 and \$91,759 NZD, respectively) (31). By 2030, the global financial cost of dementia could swell to approximately two trillion U.S. dollars (32). In 2019, unpaid care-givers and family members spent approximately 18.6 billion hours of their time caring for people with AD and related dementias globally (3). The significant time period from diagnosis to death, lasting approximately 4-8 years, contributes significantly to the burden of AD due to infirmity and dependence of individuals living with AD on carers (3).

In addition to the large-scale economic costs, there exists a wide range of indirect tolls accrued from caring for individuals with AD. Research shows that it is often family members who provide significant amounts of unpaid care for people with AD (33). This unpaid care was valued at approximately \$244 billion in the U.S. in 2019 alone (3). As symptoms progress, additional strain is placed upon the caregiver, resulting in emotional stress and depression, financial difficulty due to interrupted employment schedules, and physical health depletion (3). Caring for a spouse with AD related dementia is also associated with a decline in mental health and reduction of life satisfaction for the carer (34,35). The health and socioeconomic burdens mentioned above appear to be increasing alongside the prevalence of AD despite the current advances in diagnosis, treatment and management. It seems clear that innovative measures are indicated in order to surmount the growing financial, health and societal costs this disease incurs.

[Risk Factors for Alzheimer's Disease](#)

From a lifestyle perspective, certain factors such as smoking, obesity, poor diet, and existing metabolic and cardiovascular conditions have been identified as contributors to AD development (2,36). Genetically, mutations and polymorphisms of certain genes have been implicated in AD pathogenesis and are considered risk factors for AD development (37). Point mutations influencing A β production, such as amyloid precursor protein (APP), presenilin 1 and 2 (PSEN 1&2) have been shown to cause AD and are usually inherited as an autosomal dominant trait (37). Variants of apolipoprotein E (APOE e4) have been shown to increase the chances of AD development (28,37), with differences in susceptibility depending on the number of copies of the allele (37). The effects of these lifestyle and genetic events on the brain include dysfunction of synapses, brain atrophy and hypometabolism, and inflammation,

all of which promote cognitive decline and exhibit clinical signs associated with the presence of AD (26).

Pathological hallmarks

AD is classically characterised by the presence of cerebral intracellular accumulation of two primary biomarkers, phosphorylated Tau proteins, and extracellular A β deposition (38,39). Recent evidence from both animal and human studies suggests that A β accumulation results in disturbed sleep patterns and increased wakefulness (40). It is important to note that these patterns are believed to be different in nature to those leading to the initial plaque accumulation (23). Furthermore, Tau accumulation has been shown to decrease NREM sleep slow wave activity (40).

Diagnosis of Alzheimer's Disease

An accurate diagnosis of AD remains a significant challenge for clinicians (41). It has been said that the 'gold standard' diagnosis for AD can only be achieved by post-mortem brain biopsy which exhibits the biomarkers of phosphorylated Tau and Amyloid Beta mentioned above (38,39,42). AD is generally diagnosed using biomarkers testing in cerebrospinal fluid (CSF), neurological examinations and neuroimaging techniques, as well as consideration of many patient specific lifestyle factors and medical histories (2,41,43). CSF testing is aimed at identifying three core biomarkers strongly associated with AD development (sensitive to >95% and specific to >85%) (44). Biomarkers are anatomical, physiological or biochemical variables measurable *in vivo* that indicate explicit pathological changes in a given disease (45). The three classical biomarkers that have been shown to be positively associated with AD are elevated A β levels, Tau proteins and phosphorylated Tau (44,46,47). As these biomarkers are often present prior to classical AD cognitive symptoms (48–50), and may also present in people who may never progress to AD related dementia in their lifetime (51), controversy exists over their prognostic utility (52). Furthermore, their utility is undermined as, often, by the time they are identified the disease is well-advanced and patients may already be displaying diminished cognitive function (29).

Preclinical stage of Alzheimer's disease

Recent advances in the field of AD research have unveiled pathophysiological changes which begin a number of years prior to the onset of classical AD cognitive symptoms in humans (53). In this preceding phase, pathological change indicative of AD development can be detected in the brain through biomarker analysis, thus cognitive function remains or appears normal (54). This has been labelled preclinical AD, and was first conceptualised almost thirty years ago, however, no consensus has been reached regarding a standard definition (48).

Potential implications for early diagnosis

The ability to diagnose AD earlier than the current standard has the potential to positively affect many aspects of the collective impact of AD. In a recent study it was calculated that a hypothetical intervention which could delay the cognitive symptoms of AD dementia by five years could reduce the number of patients with AD by 57% (22). This would likely result in a significant reduction of the associated socioeconomic burden incurred by AD care. On an individual level, earlier diagnosis may provide the chance to plan for the future regarding management and/or treatment strategies, as well as perhaps the most important, preservation of cognitive function for longer (55).

Sleep as a risk factor and potential biomarker for AD development

It has been well established that sleep disturbances occur as a result of AD (56–59). Emerging evidence now suggests that sleep disturbance may be a risk factor for AD development and have utility in aiding the diagnosis of AD (60–62). Sleep disturbance causes dysfunction of brain homeostatic waste clearance and recovery processes (14). Such disruption triggers cerebral inflammation, oxidative stress, and leads to an accumulation of metabolic wastes in the brain (1,13). Such processes are, under normal circumstances, regulated by the glymphatic system (63). The primary function of this system is to break down and purge metabolic waste from the CNS (16). This system is triggered during slow wave sleep (SWS), a specific phase of NREM sleep (17). Disruption of this stage of sleep impedes the ability of the glymphatic system to clear metabolic waste from the brain (15), causing an accumulation of neuronal debris including the soluble protein Amyloid beta (A β) (17,18). Continued accumulation of A β causes a structural alteration from soluble protein to insoluble plaque

that the glymphatic system is less able to remove (23). These plaques then negatively affect sleep patterns in a bidirectional manner, leading to further sleep disturbances associated with AD development (19,64).

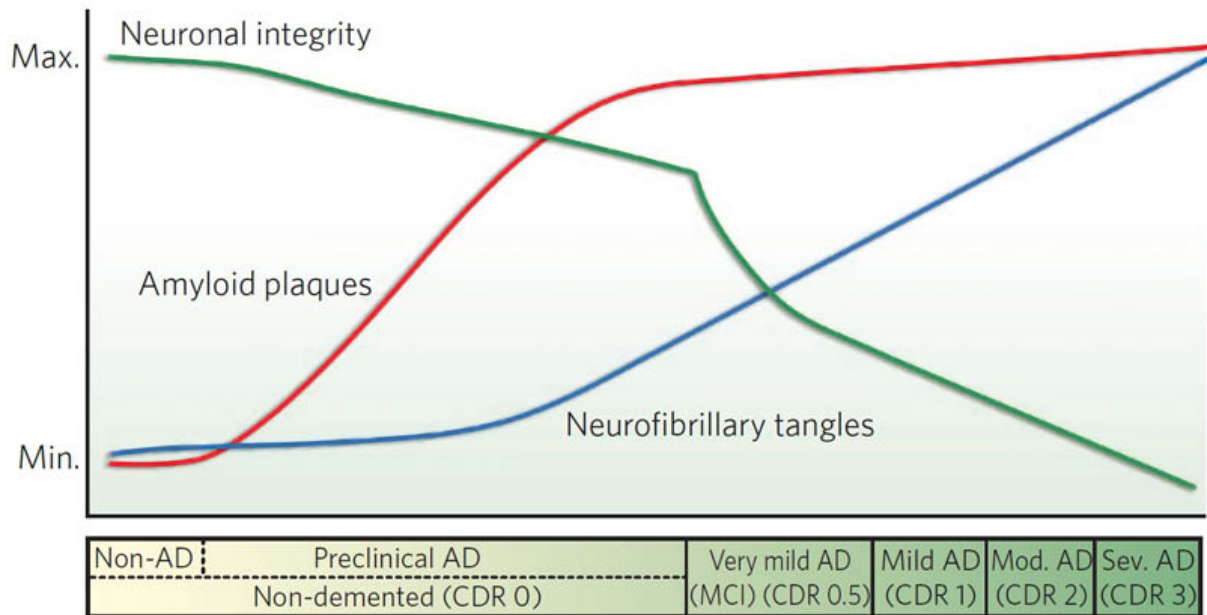


Figure 1. Multimodal techniques for diagnosis and prognosis of Alzheimer’s disease (65).

The accumulation of A β within the CNS is now recognised as a classical event in AD pathogenesis (17,20,66). As depicted by the red line in Figure 1 (67), preclinical AD is associated with a steady increase in A β , suggesting an inverse relationship between AD biomarker levels and neuronal integrity (51,68).

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is a type of sleep disturbance in which normal respiratory function is altered, resulting in partial or complete upper airway closure, leading to blood oxygen desaturation and arousal from sleep (69). OSA has been linked to Alzheimer’s disease progression (70). OSA is often diagnosed using respiratory airflow measurements and pulse oximetry (69), though the gold standard of diagnosis is a combination of electroencephalogram and polysomnography (71).

A proposed mechanistic link between AD and OSA involves similar pathways of neurodegeneration to the sleep disturbances above, namely SWS disturbance, sleep fragmentation, and hypoxia, leading to an increased amyloid burden within the brain (72,73). One study reported patients with OSA exhibit similar biomarkers to AD pathology (74). Further to this, AD and OSA share similar risk factors, such as vascular disease (75). One study found that the sleep fragmentation typical of OSA was associated with an increased risk of AD development after a six-year follow up period (76). Another study found significantly higher levels of AD biomarkers in the plasma of patients with OSA compared to the control group (77). A particularly noteworthy finding from a recent systematic review is that the links between OSA and AD are apparent across all age groups (70). As such, OSA could be categorised as a sleep disturbance with associations to AD pathogenesis through similar hallmark pathways of pathophysiology, and therefore may have utility as a diagnostic biomarker of AD.

The orexin system

The orexin system, or hypocretin/orexin system, is a neuronal network responsible for homeostatic control of certain vital functions, including cognition, mood, energy regulation, and sleep wake states (78). Therefore, dysfunction within this system may be indicative of pathophysiological changes arising as a cause or consequence of sleep disruption. Additionally, one review found that modulation of orexinergic neurons within the CNS had a direct effect on the A β burden in the brain (79). Further to this, excessive activation of the orexinergic system is known to cause insomnia (80). This provides mechanistic explanations of potentially causal pathways relating sleep disturbances to AD pathogenesis, and, as such, should be reviewed to ascertain whether this can inform this scoping review.

Summary

The research surrounding sleep and AD is extensive. However, there are still some key questions which need to be addressed. Much of the research involving the connection between sleep patterns and AD has been undertaken with animal studies, with some human research in progress currently. The research that is available suggests that specific sleep patterns emerge as a result of sustained plaque accumulation in the brain (23,81,82). This has

the potential to be clinically useful as a diagnostic tool for AD in the early preclinical stage. Early diagnosis of AD has the potential to reduce the associated burden for individuals, carers, and society. There is therefore a need to undertake a systematic review in order to identify, evaluate and summarise the evidence surrounding these sleep patterns and AD. However, this should be preceded by mapping the extent of the empirical evidence to assess the scope of the scientific literature and determine whether a systematic review is feasible. The available research also appears to suffer from the lack of a standard definition and characterisation of the preclinical stage of AD.

The purpose of this research project was to perform a scoping review examining the empirical evidence available surrounding specific sleep patterns and AD. Furthermore, this project aimed to ascertain whether a consistent definition of preclinical AD exists. Lastly, the scoping review aimed to provide recommendations for future research and the feasibility of undertaking a systematic review.

Section 2: Methodology

An overview of scoping reviews

Scoping reviews are an increasingly popular methodology of synthesising knowledge from the literature in a particular field (83–85). However, their execution is not yet informed by a definitive or well laid out procedure or definition (83). This has been addressed by many authors and continues to evolve (83,85).

Mays, Roberts & Popay define scoping reviews as studies which aim to quickly represent the key concepts that are supporting a research area (86). Arksey and O'Malley (87) rationalise scoping reviews to be useful for the following reasons: to examine the nature of research on a topic, to determine the utility of undertaking a systematic review, to summarise and disseminate research findings, and/or to identify gaps in the literature. While scoping reviews are similar to meta-analyses and systematic reviews (88), they are, however, inclusive of research not incorporated into the aforementioned methods, such as grey literature (83), qualitative, theoretical and narrative research designs (88). In a scoping review methodology, which scrutinises existing research papers, themes can be identified and evaluated to recognise research trends and gaps, and potentially provide recommendations for future research within the relevant fields (85).

Limitations of scoping review methodology

As with many research methodologies, scoping reviews incur their own inherent limitations. A pertinent limitation is that scoping reviews do not critically appraise the evidence presented in the selected studies or the methodologies of the studies themselves (87). This limitation can affect the ability for the research to effectively translate research findings into applicable concepts and policies for clinical practice (88). Furthermore, as quality appraisal of studies is not a prerequisite for scoping reviews, a wider range of methodologies may be included into the research paper selection, which can create difficulty with cohesive synthesis of results from different types of studies (87). Another potential limitation is the possibility of the search process to miss key studies based on the databases chosen, which may not accumulate all studies relevant to the search (89).

Rationale for scoping review

As the relationship between specific sleep patterns and their potential to be utilised for early diagnosis of Alzheimer's Disease (AD) is a relatively nascent area of research in humans, a design with the aim to map and explore the existing and implicated research was indicated. There are several key questions which need to be addressed by a robust systematic review. However, it is imperative to have a clear understanding to the types of empirical evidence available which may inform as to whether undertaking a systematic review is feasible. Arksey and O'Malley (87) describe such instances as indicative of a scoping review framework in order to examine the nature of evidence available on a topic and provide recommendations for more specific research such as systematic reviews. Additionally, it appears a consistent definition of the preclinical phase of AD has not been widely accepted. Therefore a further reason to employ a scoping review methodology was to clarify key concepts and definitions in the literature, as recommended by the Joanna Briggs Institute (JBI) (90). Furthermore, knowledge gaps were revealed within the current literature, potentially leading to a diversification and consolidation of research in the field of sleep and neurodegeneration. Therefore, undertaking a scoping review seemed to be the most appropriate methodology to answer the research question of this study.

Scoping Review Framework

The scoping review framework for this research was structured in accordance with the six-stage framework devised by Arksey and O'Malley (5), with refinements and recommendations from Levac et al. (85), Peters et al. (88), and Pham et al (91). The stages from one to six consist of identifying the research question, identifying relevant studies, selecting studies, charting the data, the collation, summarisation and reporting of results, and finally, consultation with key stakeholders the research may relate to, which is an optional stage (87).

Stage 1: Identifying the research question

Identification of an applicable research question is the first stage of the scoping review framework, as it informs the subsequent stages (87). Peters et al. (89) state that the research question must be stated concisely, while containing enough breadth to encompass the scope

of the enquiry. Arksey and O'Malley (87) support this, adding that an overly comprehensive question may generate an unmanageable amount of literature to review. Arksey and O'Malley (87) further suggest that a research question should incorporate key aspects of an intended study. As per the aims and objectives of this study, a mapping of the existing empirical evidence within the literature surrounding specific sleep patterns and Alzheimer's disease (AD) was incorporated into the research question. The JBI suggests incorporating the Population, Concept, and Context mnemonic (PCC) (89). Therefore, the research question of this project incorporated people with AD or preclinical AD risk as the intended population, early diagnosis of AD as the context, and a mapping of the empirical evidence for sleep patterns as diagnostic tools for AD, as well as the bi-directional connection between sleep and AD as the concept. This was intended to also inform certain objectives of the research project regarding unveiling of specific research questions which may form the basis of future studies such as systematic reviews. Additionally, the sub question/objective was intended to identify whether a succinct standardised definition of the preclinical stage of AD is in use and/or is indicated to be formulated by future research. This follows the idea put forth by Levac et al. (85) that sub-questions focused on the concept of the research can enhance the quality of the review. With these considerations in mind, the research question decided upon was "What is the extent and nature of the empirical evidence available related to the role of sleep disturbance in AD development and specific sleep patterns as early diagnostic biomarkers for AD?".

Stage 2: Identifying relevant studies

Stage two was aimed toward identifying appropriate studies that are of direct relevance to the research question. To identify the resources relevant to this scoping review, the databases of PubMed, EBSCO Health and ScienceDirect were searched. Arksey and O'Malley (87) recommend a search process that comprehensively spans the literature, although they suggest pragmatic restrictions be implemented at the outset. Arksey and O'Malley (87) also describe the importance of an iterative process with refinements being made as the process advances. Additionally, Levac et al. (85) suggest the research question to be utilised in directing the scope of the research, and that all decisions made on this basis be justifiable and documented should such decisions incur limitations of the project. Levac et al. (85) also describe the importance of the research team possessing the required expertise to conduct a

search. To ensure this recommendation was followed, the help of a librarian specialist was utilised to aid in the development and refinement of search strategies.

Grey literature

Grey literature has been described as uncontrolled information such as unpublished data, dissertations, policy documentation and personal correspondence not controlled by peer-review processes (92). Grey literature is not required to follow similar publishing conventions as empirical literature often is, therefore, it may lead to difficulty in management of data and extracting information from materials that are less structured than other study types (93). Grey literature may be included within scoping reviews (83,85), and may have some benefit in adding breadth to the review (93). However, as the purpose of this scoping review was to examine the extent and nature of the empirical evidence relating to sleep and AD pathology as well as diagnosis, grey literature was not appropriate, and therefore, was not included in the scoping review.

Stage 3: Study selection

Stage three refers to the selection of the appropriate studies for inclusion into the scoping review. The included studies were necessarily required to answer the research question and objectives of this study and therefore needed to meet the inclusion and exclusion criteria of the study. The objectives of this study were to (1) examine the empirical evidence available related to the role of sleep disturbance in AD development and potential use of specific sleep patterns as diagnostic markers of AD development, (2) ascertain whether there is a consistent definition or characterisation of the preclinical phase of AD, and (3) assess the feasibility of undertaking a systematic review and provide recommendations for future research. Following the aforementioned restrictions, languages other than English were excluded, and only articles published within the last twenty years were included. These criteria were devised by the research team a priori, and following Arksey and O'Malley's (87) suggestion, refinements were made as the researcher became more familiar with the literature. An example of this was the refinement of the first objective. The word 'development' was added to reduce the number of studies conducted on known and diagnosed AD, therefore, the search results were limited to studies that incorporated preclinical AD, and AD development and diagnosis, which more closely mirrored the objectives of the study.

The selection process was initially performed by reviewing the titles and abstracts according to the inclusion criteria. The inclusion criteria comprised studies that (1) had been published in the last twenty years, (2) were conducted on AD relating sleep as a major factor, (3) highlighted the potential for sleep patterns or sleep disturbances as biomarkers for preclinical diagnosis of AD, (4) were conducted on humans and animals, and (5) had been published in or translated to English. Search syntaxes were reviewed and refined in an iterative fashion until saturation point was achieved by meeting all inclusion criteria, as per suggestions by Colquhoun et al. (83).

Studies were excluded if they were published prior to 2001, and in languages other than English, due to time constraints. As one of the objectives of this study was to examine the empirical evidence surrounding sleep disturbance and AD, grey literature was excluded. Furthermore, as the study intended to examine the potential links between sleep disturbance and AD development, studies concerning sleep disturbances in already known and diagnosed AD, as well as studies focusing on other health outcomes and/or neuronal disorders than AD were excluded unless they contained information directly relevant to the study. Again Additionally, following Arksey and O'Malley's suggestion of an iterative approach to the criteria formulation (87), refinements were made to certain exclusion criteria. For example, 'studies related to sleep patterns in known and diagnosed AD' was refined from 'studies on known and diagnosed AD'. This was performed to include studies conducted on AD, and exclude studies concerning sleep patterns caused by AD, which were not of relevance to the aims and objectives. A second, more thorough review of the articles was then made by reading the full text of each article. Colquhoun et al. suggest that a portion of selected studies should be reviewed independently by two reviewers to ensure inter-rater reliability, with a third reviewer to mediate any disagreement on selection rationale if necessary (84). Therefore, the selection process for this research project was piloted on 10% of relevant studies between the researcher and one of the supervisors. A 95% inter-rater agreement was reached. A second supervisor acted as moderator where discrepancy arose to ensure all inclusion criteria were met by consensus or percentage agreement. This process led to the inclusion of a total of 199 studies in this scoping review (Appendix A).

Stage 4: Charting the data

This stage refers to the organisation and extraction of data from the results generated by the search process (84). Researchers suggest a form be developed to document information and key aspects of the results relevant to the research question (84,86). For this review, detailed analysis of each selected study was charted within an Excel spreadsheet (Appendix A). Mendeley was used to import studies identified through the search syntax, to assess and delete duplicated studies and to manage data. The filtration factors were determined by the inclusion and exclusion criteria, as well as further rationale agreed upon by the supervisory team. A timeline-oriented column graph was used to demonstrate the temporal focus of research on sleep and AD research.

Stage 5: Collating, summarising and reporting the results

As the material produced by the literature search was unlikely to yield homogenous research types, it became impractical to attempt to predetermine the ideal method of collating, summarising and reporting the results. Arksey and O'Malley (87) recommend a consistent approach to reporting which enables trends, themes, and research gaps to be quickly identified. To address this, once the data was appropriately charted, the relevant numerical and narrative analytical methods and concepts were utilised. For example, reporting frequency of occurrence, categories and concept distribution, study characteristics, definitions and descriptive analysis were performed where indicated. As per the recommendation by Joanna Briggs Institute (JBI) (89), a draft charting table was constructed to provide a framework for thematic analysis once the appropriate studies were selected. The aim of this step was to highlight and summarise key information of relevance to the research question (7). Additionally, the outcomes of this study were reported as per scoping review checklists; the Preferred Reporting Items for Systematic and Meta-Analyses extension for scoping review (PRISMA-ScR) (Appendix B) (94), and Cooper's Checklist for Scoping Reviews (Appendix C) (95). Moreover, following the suggestion by Tricco et al. (94), a flow diagram, which is demonstrating the study selection process, was created (Figure 1; in the 'Manuscript Section').

Stage 6: Consultation (Optional)

As outlined by Arksey & O'Malley (5), a sixth stage is an optional addition to scoping review framework, which aims to consult the relevant professional bodies pertaining to the topic. The JBI recommends implementing this stage into all scoping reviews (89), however, others argue that a specific purpose related to the intended research should be evident prior to its inclusion (85,87,96). Buus et al. (96) also suggest that the consultation phase only is included when the research piece reports on the effect of alternative expressions and invites genuine participation. Following these suggestions, as well as the limitations of time, feasibility and resource constraints of a master's thesis, the decision was made by the research team to not incorporate the optional sixth stage in this scoping review.

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Section 3: Manuscript

Note to the readers: This manuscript has been formatted with the intention to submit to the *Journal of Sleep Research*, available here: https://onlinelibrary.wiley.com/page/journal/13652869/homepage/forauthors.html#After_a_cceptance

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Sleep abnormalities as potential early diagnostic biomarkers for Alzheimer's disease: A scoping review examining the extent of empirical evidence

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Running head: Sleep abnormalities as early diagnostic biomarkers for Alzheimer's disease

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Abstract

Alzheimer's disease is the most common type of dementia, and its prevalence is increasing world-wide. This disease incurs a wide range of complications for individuals and society. No current therapies exist to cure or stop the progression of the disease once diagnosed within an individual. Many risk factors for Alzheimer's disease are known, although one which has recently emerged within the scientific literature is sleep disturbance. The true implications of the research are at present, incomplete, yet the studies available have shown promise of the potential diagnostic and therapeutic value of sleep. Therefore, this study aimed to examine the extent and nature of research available discussing the role of sleep in Alzheimer's disease development, as well as the potential utility of specific sleep disturbances to be diagnostic biomarkers for Alzheimer's disease. A five-stage scoping review framework developed by Arksey and O'Malley was utilised to ensure an in-depth review of the relevant literature was achieved.

From a total of 3,375 studies, 199 were included into this scoping review and classified into four primary themes: 1) Mechanistic links between sleep disturbance and Alzheimer's disease, 2) Sleep disturbance as a biomarker for Alzheimer's disease, 3) Sleep as a therapeutic target for Alzheimer's disease, and 4) Preclinical Alzheimer's disease definition. This review has covered a range of studies that discussed links between sleep disturbance and Alzheimer's disease pathogenesis. The findings suggests that certain sleep patterns may have diagnostic and therapeutic uses in Alzheimer's disease; however, further experimental research is indicated to substantiate these hypotheses. The term preclinical Alzheimer's disease requires a relevant and concise consensus regarding its definition in order for the aforementioned hypotheses to fully be explored for their respective potential.

Keywords:

Alzheimer's disease, preclinical, sleep disturbances, biomarker, amyloid beta

Introduction

Alzheimer's disease (AD) is an increasingly prevalent neurological disorder with no known cure and incurs an extensive range of individual and socioeconomic costs (1–3). Recent research suggests that sleep disturbance may play a role in the development of AD (4–8). Sleep disturbance can cause dysfunction of brain homeostasis processes related to AD (9). Such disruption triggers cerebral inflammation, accumulation of metabolic wastes and an increase of oxidative stress, all of which have been associated with AD (6,8).

Certain biomarkers have been observed in the preclinical stage of AD and are predictive of its onset up to 20 years prior to a classical symptomatic state (10). Researchers within the field believe that this early phase is likely to be more amenable to therapeutic intervention than a later stage of diagnostic pathological state (10–12). This highlights the need for a standardised definition and or characterisation of preclinical AD, accounting for as many variations as possible of the early preclinical stages of the AD continuum. It also warrants thorough research into as many contributing factors that may serve as biomarkers (such as sleep patterns) as possible in order to fully elucidate the potential causative mechanisms and further develop preventative management. Many contributing factors have been proposed by researchers, however, as the intended research pertained to specific sleep patterns and their potential relationship to AD, this is the primary risk factor and potential diagnostic biomarker explored. Therefore, the purpose of this research project was to perform a scoping review examining the empirical evidence available surrounding specific sleep patterns and AD. Additionally, this project aimed to ascertain whether a consistent definition of preclinical AD exists. Finally, the scoping review aimed to provide recommendations for future research and the feasibility of undertaking a systematic review.

Methods

This scoping review followed a five-stage framework devised by Arksey and O'Malley (13) in conjunction with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist by Tricco et al. (Appendix B) (14), and Cooper's Checklist for Scoping Reviews (Appendix C). The scoping review framework employs

a five-stage framework, with an optional sixth stage. The stages are 1) identification of the research question, 2) identification of the relevant studies, 3) study selection, 4) charting the data, and 5) collating, summarising and reporting the results.

Stage 1: Identification of the research question

The research question that guided the scoping review was “What is the extent and nature of the empirical evidence available related to the role of sleep disturbance in Alzheimer’s Disease (AD) development and specific sleep patterns as early diagnostic biomarker for AD?”. This question was specifically formulated to focus on research discussing sleep disturbances and their potential contribution to AD development, as opposed to already known and diagnosed AD, in which different sleep disturbances arise as a result of existing AD pathophysiology.

Stage 2: Identification of the relevant studies

The search strategy was developed by the researcher with the help of the supervisory team and a specialist librarian. Initially, key terms relating to the research question were entered into PubMed, EBSCO Health, and ScienceDirect databases. The results of this preliminary search were used to identify further topic specific keywords in order to generate the appropriate search syntaxes to be used to identify the existing literature relevant to the research question. The eight syntaxes generated from this were as follows; ((sleep disturbance) AND (amyloid beta)) AND (Alzheimer’s disease), ((Preclinical Alzheimer’s disease) AND (definition)), ((sleep disturbance) AND (Alzheimer’s disease)) AND (Biomarker), ((sleep disruption) AND (Alzheimer’s disease)) AND (biomarker), (sleep disturbance) AND (preclinical Alzheimer’s disease), (sleep disruption) AND (preclinical Alzheimer’s disease), “sleep disruption” AND “Alzheimer’s disease”, and (sleep patterns) AND (preclinical Alzheimer’s disease) (Appendix D). These syntax combinations were also entered into PubMed, EBSCO Health, and ScienceDirect databases.

Due to the unmanageable number of studies not relevant to the research generated by ScienceDirect, changes were made to the parentheses structured to surround the key terms and Boolean operators. While parentheses were used in PubMed and EBSCO search syntaxes,

inverted commas were used when searching ScienceDirect to reduce the number of results. The search identified 2821 articles, which were then imported into the referencing software Mendeley. After removing duplicates, 1612 articles remained.

A second and final search was performed using the same syntax combinations and databases as the original search. This was decided by the research team to be the cut-off for including new articles into the scoping review based on feasibility and time constraints. This search performed in December 2021 identified a further 33 articles within the literature which had been made available following the original search.

Stage 3: Study selection

Eligibility criteria were established prior to execution of the search, and as per suggestions by Arksey & O'Malley (13) was an iterative process that was adjusted as the researcher became familiar with the existing literature. The first filter to determine suitability of studies was an "eyeball screen" of the title and abstract of each article. An article passed through this stage when it contained a combination of major keywords pertaining to the research topic - sleep/sleep disturbance AND Alzheimer's disease, or other similar and related phrasing referring to links between sleep and AD or the preclinical phase of AD. If this was not found in the title, the abstract was required to contain reference to parts of the article which were related specifically to the research question, aims and objectives and/or inclusion criteria of the research project.

This screen identified 356 articles for further scrutiny through application of the inclusion and exclusion criteria (Table 1). The inclusion criteria were formulated to be specific to the aims and objectives of the research and was an iterative process.

A second search was performed with all eight syntaxes in order to ascertain whether any new research had been published in the time succeeding the first search. Of the 33 articles identified during the second search, 28 were excluded through "eyeball screen", 2 were removed by application of the inclusion/exclusion criteria (Table 1), leaving 3 to be included within the review. This indicated saturation point had been achieved, and no further articles were considered for inclusion. This brought the total to 359 after removing duplicates.

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
1. Studies published in the last twenty years	1. Non peer-reviewed research (websites, blogs, letters, guidelines, grey literature)
2. Research conducted on AD relating sleep as a major factor	2. Studies involving sleep and health outcomes and/or neuronal disorders other than AD
3. Studies highlighting the potential for sleep patterns or sleep disturbances as biomarkers for preclinical diagnosis of AD	3. Studies relating to sleep patterns in known and diagnosed AD
4. Human and animal studies	
5. Studies published in English	

Screening of the articles using the inclusion/exclusion criteria removed studies unrelated to the aims and objectives of the research, bringing the total of studies to be included into the review to 199.

Stage 4: Charting the data

After inclusion and exclusion criteria were applied, all remaining articles were transferred into a separate Excel spreadsheet containing only the studies to be included in the project. Data extraction fields for this process included author/s, year of publication, study aim, DOI, study type, outcome, and a short summary of the paper by the primary researcher.

Stage 5: Collating, summarising and reporting the results

Following the charting process, all 199 articles were read, compared and contrasted, and categorised according to the aims and objectives of the review, and by apparent themes arising from the literature. This process was iterative with themes being refined as the researcher became more familiar with the included studies. Each study was classified into one of the following themes. 1) Mechanistic links between sleep disturbance and AD 2), sleep disturbance as a biomarker of AD, 3) sleep as a therapeutic target for AD, and 4) preclinical AD definition. Each of these themes included one or more sub-themes. This study was exempt from the requirement of ethical approval following a review by Unitec Research Ethics Committee (Appendix E).

Results

Overall, the search syntax combinations yielded 3,375 studies, which after the removal of 515 sets of duplicates, was reduced to 1645. After the initial screening phase, 1286 of these were deemed unsuitable as they did not relate to the research topic, leaving 359 studies remaining. A further 166 studies were then omitted after reading the full text due to not meeting the inclusion criteria, and as a result a total of 199 remained and were included in the scoping review (Figure 1).

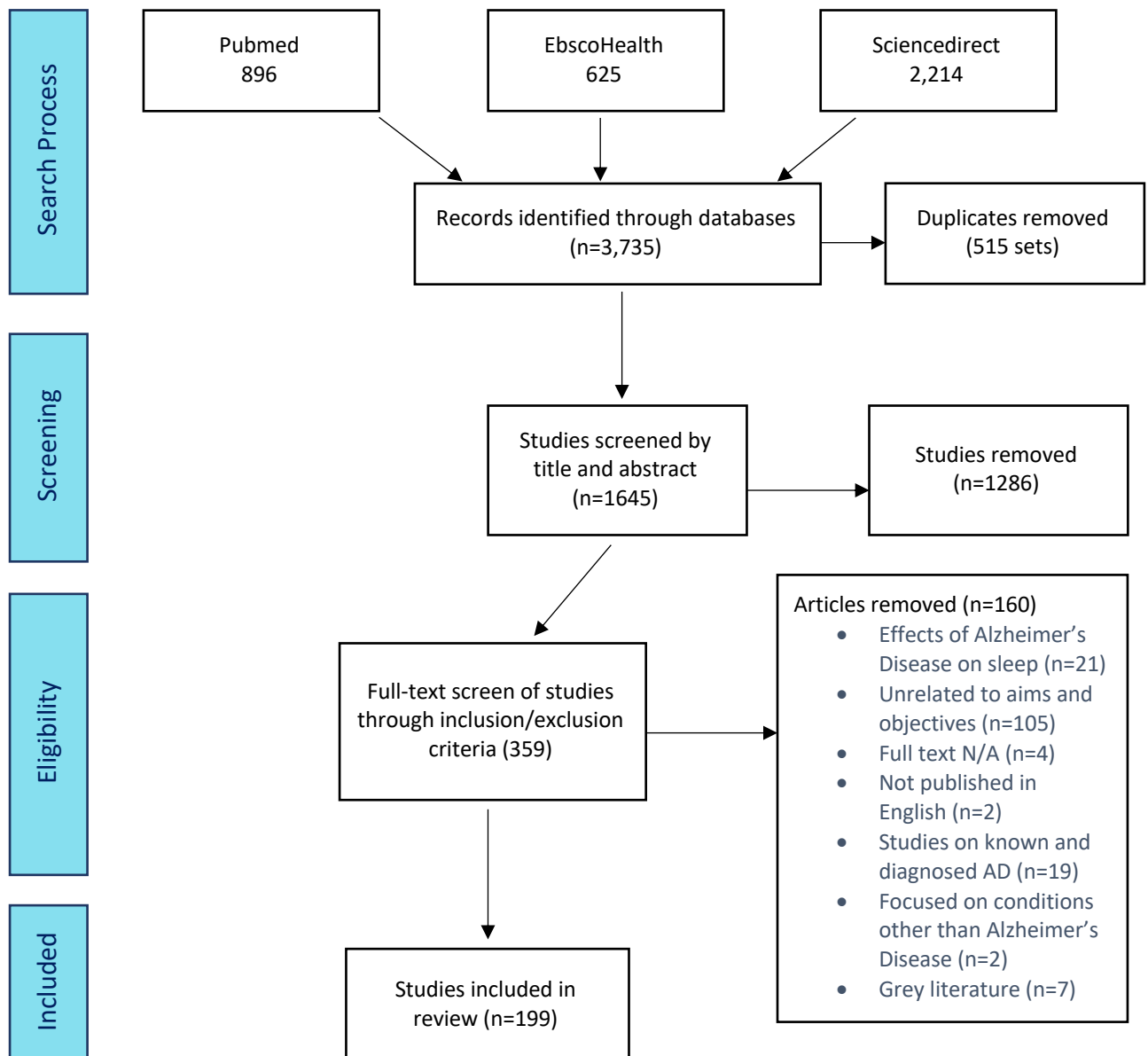


Figure 1: PRISMA-ScR flow diagram of search strategy and study selection process (14).

Characteristics of included studies

This scoping review included 199 studies published between 2001 and 2021. The majority of included studies were published in 2020, with an increase in the frequency of publication from 2010 onwards. Eighty-four percent of these were published from 2014 onwards. None were published in 2002 or 2007, and less than four percent of the total included studies were published between 2001 and 2009 (Figure 2).

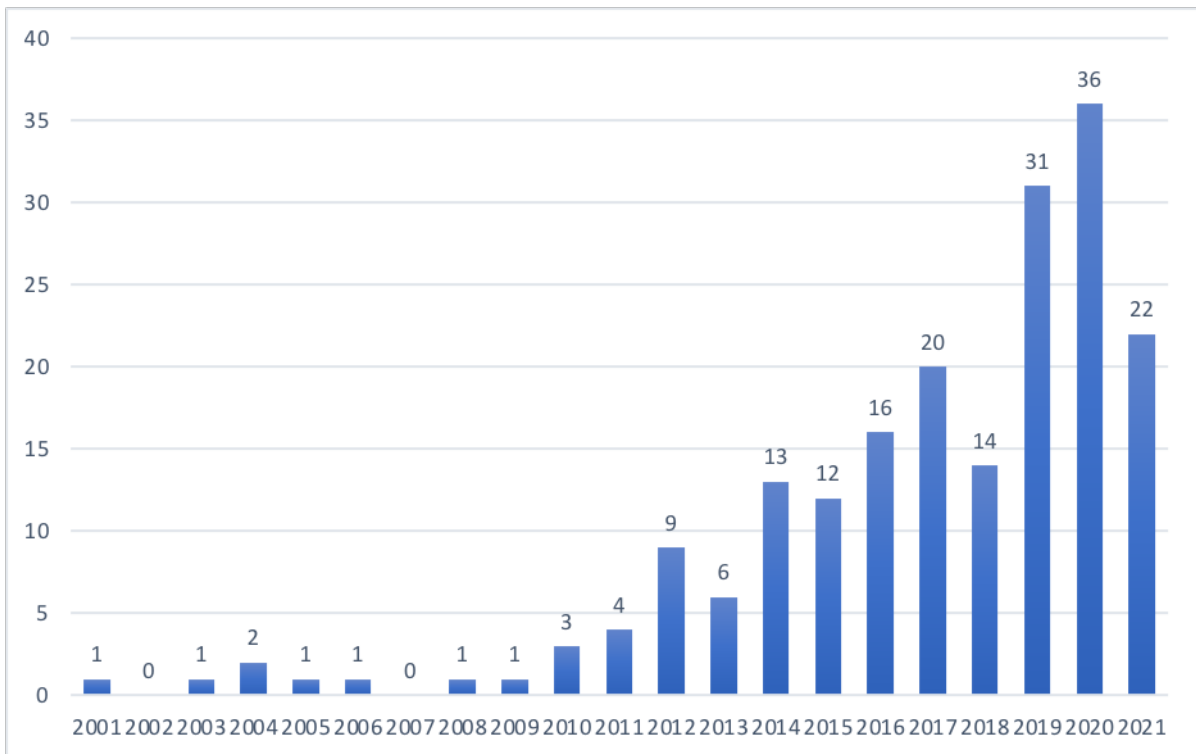


Figure 2. Number of included studies by year of publication

The included studies were comprised of 16 different study types; however, literature reviews were the predominant design, accounting for 52.2% (n=103) of all included studies. Unspecified experimental designs made up 28% of the included studies. Nine clinical trials were included, accounting for five percent of the total included studies.

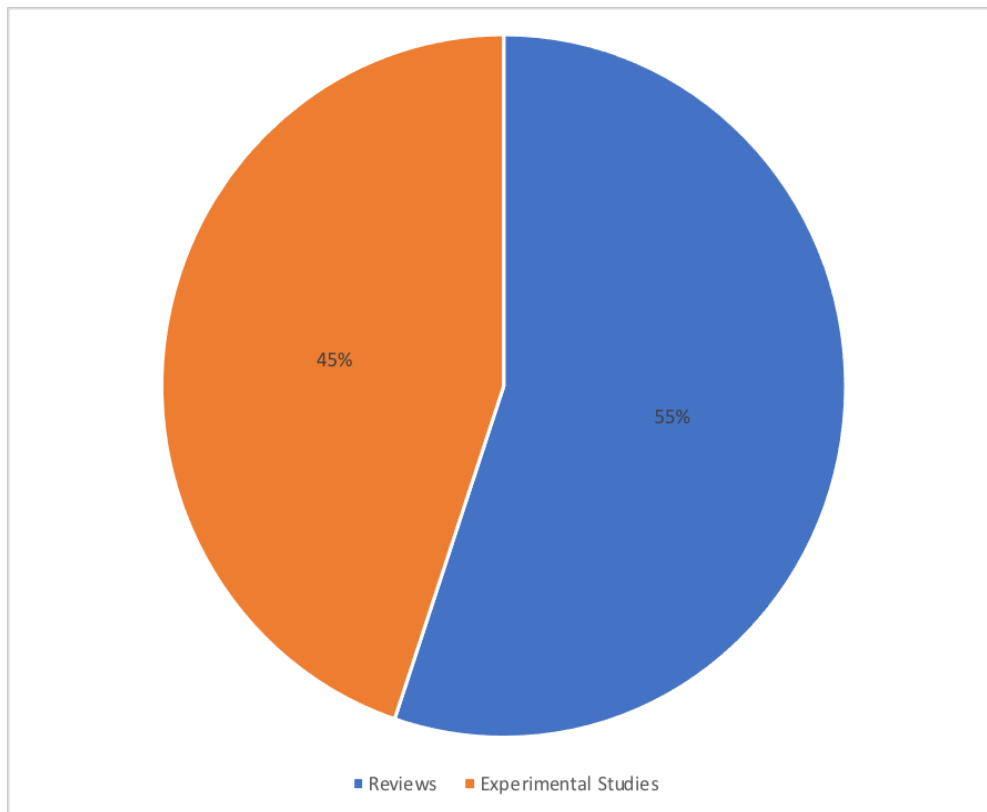


Figure 3: Number of studies in review form versus experimental studies

Observed themes of included studies

The included studies often contained information of relevance to more than one theme and thus were overlapping in their numerical representation of the observed themes (Figure 4). A majority of studies contained content relevant to theme one; 'mechanistic links between sleep disturbance and AD' (81.9%, n=163), followed by theme two; 'sleep disturbance as a biomarker for AD' (43.8%, n=89), and theme three; 'sleep as therapeutic target' (42.8%, n=87). Theme four; 'Preclinical Alzheimer's Disease definition' contained the smallest number of studies (9.4%, n=19) (Table 2).

Table 2: Themes and Sub-themes of Included Studies

Primary Themes	Sub-themes	Number of studies per sub-theme	Number of studies/ (% of total)
1.Mechanistic links between sleep disturbance and Alzheimer’s disease	<ol style="list-style-type: none"> 1. Amyloid Beta/Slow wave Amplitude sleep 2. Orexin/hypocretin SYSTEM 3. Apolipoprotein E (APOE) 4. Obstructive Sleep Apnoea (OSA) 5. Melatonin 6. Tau 7. K-complexes 8. Gut Microbiome 	<p>133</p> <p>14</p> <p>16</p> <p>35</p> <p>6</p> <p>26</p> <p>3</p> <p>1</p>	163/ (81.9%)
2.Sleep as a biomarker of Alzheimer’s disease	<ol style="list-style-type: none"> 1. Slow Wave Amplitude Sleep 2. REM Sleep 3. Sleep Spindle Activity 4. Melatonin Levels 	<p>11</p> <p>8</p> <p>1</p> <p>2</p>	76/ (37.4%)
3.Sleep as a therapeutic target	<ol style="list-style-type: none"> 1. Slow Wave Amplitude Sleep 2. Continuous Positive Airway Pressure 3. Trans-cranial Magnetic Stimulation 4. Orexin/Hypocretin system 	<p>15</p> <p>13</p> <p>1</p> <p>2</p>	86/ (43.7%)
4.Preclinical Alzheimer’s disease definition	<ol style="list-style-type: none"> 1. Definition of Preclinical Alzheimer’s Disease 2. Limitations and Challenges of the Current Definition 	<p>19</p> <p>11</p>	19/ (9.5%)

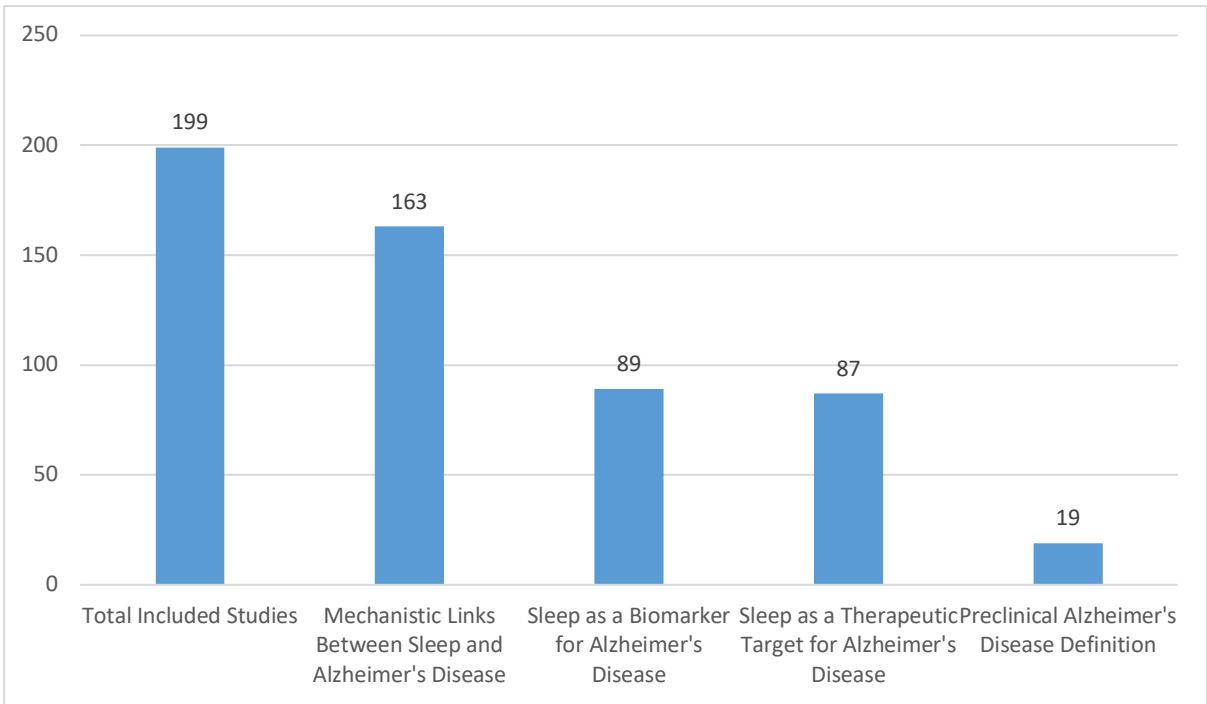


Figure 3: Numerical representation of included studies by thematic classification

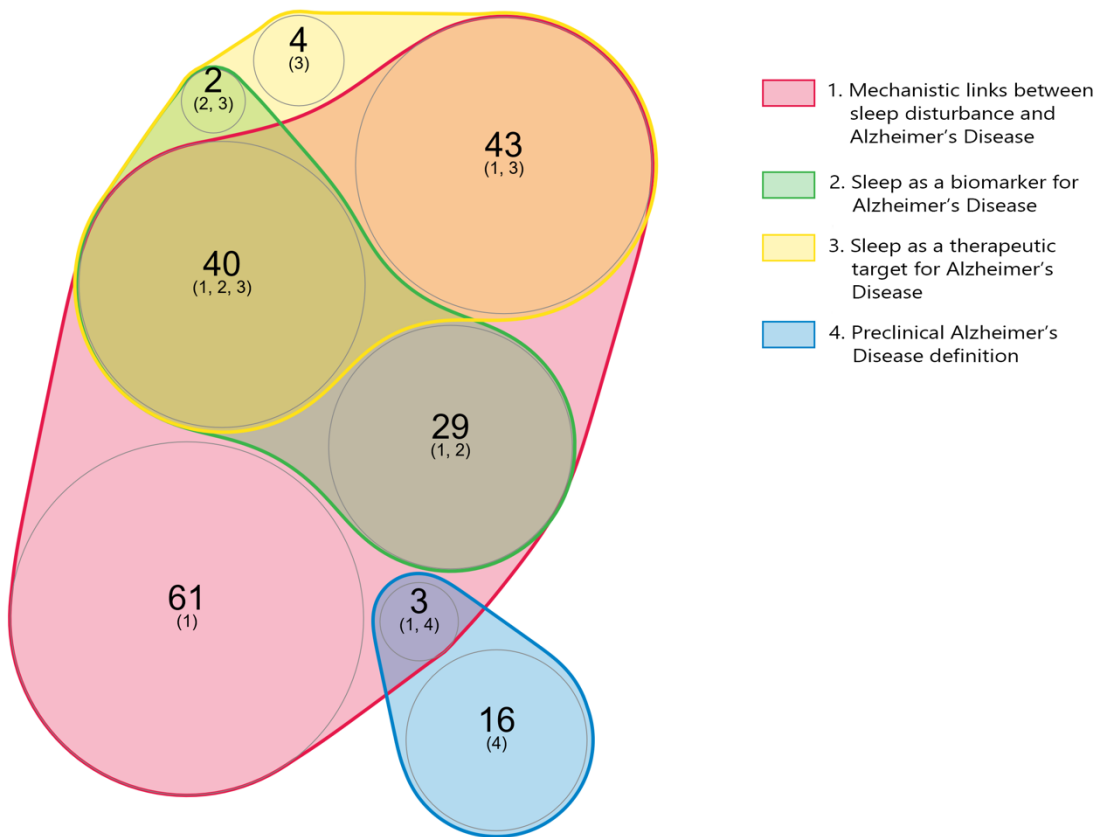


Figure 4: Euler diagram showing overlap of studies between the four primary themes

Theme one: Mechanistic Links between Sleep Disturbance and Alzheimer's Disease

This theme included articles that contained information regarding hypothesised and/or observed pathophysiological mechanisms linking the effect of sleep disturbance to AD pathogenesis and/or progression. This theme contained the largest number of studies (n=163), discussing multiple pathways in which sleep disturbance may result in pathophysiological changes associated with AD. The predominant study type in this theme were reviews (n=87), including three systematic reviews. (15–17). The remaining studies were comprised of nine clinical trials (18–25), two secondary data analyses (26,27), two longitudinal studies (28,29), and one each of the following; mendelian randomisation (30), randomised crossover study (31), nested case-control (32), nested survey (33), one clinical trial protocol (34). The remaining fifty-five were unspecified quantitative studies.

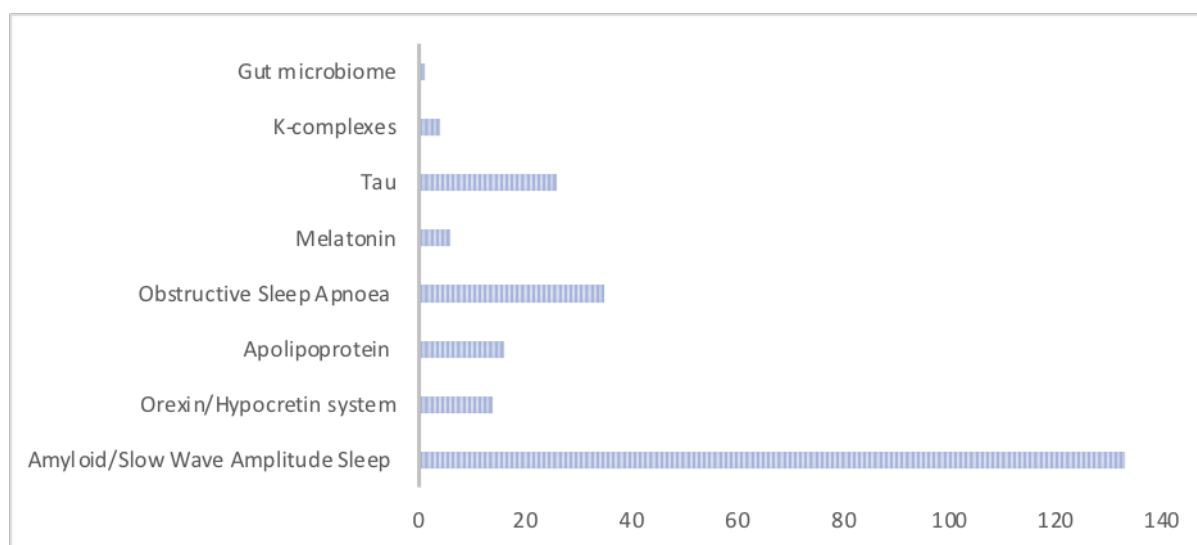


Figure 4. Physiological mechanisms linking sleep disturbance and Alzheimer's Disease reported by studies from theme one.

Non-Rapid Eye Movement Sleep/Slow-Wave Amplitude Sleep/Amyloid Beta

81.6% of the studies (n= 133) in theme one focused on Slow Wave Amplitude (SWA) or Non-Rapid Eye Movement (NREM) sleep, and its relationship with the molecule Amyloid Beta (A β). Reviews were the most common study type in theme one, accounting for 65% (n=87) of the 133 studies. Of the 87 reviews included in theme one, 74 described the A β hypothesis as a potential mechanistic pathway in which sleep disturbance may contribute to

pathophysiological changes associated with AD (5,6,8,15,17,35–108). In discussing the amyloid hypothesis, these 74 studies referenced a wide range of research including other reviews and many original research experiments. There appear to be no major discrepancies regarding the role of A β in AD development between the 74 reviews and the experimental studies within this theme. The majority of these studies further discussed a reduced capacity of the glymphatic system resulting from SWA sleep loss to be a potential mechanistic pathway of A β accumulation and a precipitating factor in AD pathogenesis (8,28,36,37,49,58,60,61,68,70,77,82,83,97,100,106,108–113). The studies in this sub-theme appear to be consistent in reporting disruption of SWA results in A β aggregation within the brain and is a contributing factor of AD pathogenesis.

Orexin/Hypocretin system

Fourteen of the articles in theme one discussed the role of the hypocretin/orexin system in sleep and AD development (8,19,23,38,95,108,111,114–120). Studies in this sub-theme spanned a publication date range from 2012 to 2021. Eight of these studies were in review form (8,38,95,111,116,119–121). Seven were experimental designs, including two clinical trials (19,23), one mendelian randomised analysis, and four which did not specify the type of experiment (113–115,118). Nine of these studies discussed the role of orexin in regulation of A β levels (23,95,108,111,114–116,118,120). These studies show broad agreement that disruption of the orexin/hypocretin system due to sleep disturbance is implicated in the pathogenesis of AD.

Apolipoprotein Epsilon (APOE)

The genetic influence of APOE was reported as a contributing factor to AD development by seventeen included studies (5,6,18,26,42,55,73,74,81,90,94,100,122–126). These studies were published over seventeen years, from 2004-2021. All of these studies considered the influence of APOE on sleep, AD biomarkers and the presence of APOE as a risk factor for AD (5,6,18,26,42,55,73,74,81,90,94,100,122–126).

Obstructive Sleep Apnoea

Obstructive Sleep Apnoea (OSA) was identified by 35 articles as being a risk factor for developing AD (5,6,15–17,21,28,29,35,41,42,45,53,66,72,73,76,81,88,94,95,99,106,107,109,

113,123,125,127–132). The articles discussing OSA spanned the full range of the twenty-year inclusion period, demonstrating a wider range of publication dates than other sub-themes. These included 21 literature reviews (5,6,35,41,42,45,53,66,72,73,76,81,88,94,95,99,106,107,128,131,132), and three systematic reviews (15–17). The remaining 12 were of experimental designs, including one clinical trial (21), two longitudinal studies (28,29), and nine which did not specify the type of experiment (109,113,123,125,129,130,133–135). The studies within this sub-theme show a consistent theme regarding the interaction between OSA and AD biomarker progression and/or pathophysiological changes associated with AD.

Melatonin

Six studies mentioned the involvement of the hormone melatonin in the AD pathogenesis process (39,63,103,119,120,136). These studies were published between 2003 and 2021. One was a non-randomised controlled trial (136), and the remaining five were literature reviews (39,63,103,119,120). Five studies discussed the role of melatonin in regulating A β levels (39,63,103,120,136). Two studies reported a higher level of melatonin having a neuroprotective effect on A β burden (63,103). Additionally, two studies argued that a lower level was a clinically observable sign in preclinical AD (39,63). One study found that decreased melatonin promotes the dysfunction of neural networks related to cognition, thereby contributing to AD pathogenesis (119). The studies within this sub-theme appear to report similar findings regarding the potential role of melatonin in AD pathogenesis.

Tau Protein

Tau proteins were discussed by 31 of the studies in theme one regarding their bidirectional relationship with sleep disturbance (8,17–19,28,41,44,45,48,49,53,55,57,63,66,72,75,84,87,98,111,125,133,137–144). These studies were published between 2014 and 2021, with greater frequency from 2018 onwards. Reviews were the most common study type in this sub-theme, accounting for 17 of the 31 studies (54.8%) (8,41,44,45,48,49,53,55,57,63,66,72,75,84,98,111,145). Unspecified experimental study designs accounted for seven of the 31 studies (22.6%) (125,133,138–141,143). The remainder was made up of two clinical trials (18,19), two controlled trials (137,142), one longitudinal study (28), one two-condition crossover study (144), and one systematic review (17).

K-Complexes

K-complexes were described by three articles as having a mechanistic relationship to AD pathogenesis (25,37,45). These were made up of two literature reviews (37,45) and one prospective cohort study (25). These studies were published within a shorter date range than other sub-themes, from 2020-2021. Two of these studies defined K-complexes as a hallmark of stage two NREM sleep, characterised by a negative slow sharp brain wavelength, succeeded by a positive slow brain wavelength (25,45). All three studies exhibit agreement in reporting a decrease of K-complexes in those with aMCI, a precursive state of AD (25,37,45). One study further discussed K-complexes as having a role in sleep preservation (25).

Gut Microbiome

One study discussed the relationship between the gut microbiome, sleep and circadian rhythms (146). The study was a literature review conducted in 2021 that compiled research regarding the mechanistic links between gut and brain health in relation to AD.

Theme two: Sleep disturbance as a Biomarker of Alzheimer's Disease

The articles in this theme described ways in which sleep disturbances may precede, initiate or cause AD pathogenesis. Furthermore, the authors of these articles suggested the potential for sleep disturbances to be considered for their utility as biomarkers of AD. A total of 76 articles described the feasibility of specific sleep disturbances as potential biomarkers for AD or preclinical AD (6,7,18,25,29,32,34–37,44,47,49,50,52,53,55–57,59,60,62,63,69,74,75,78, 82–84,86,87,90,93,95–97,99,115,124,125,136,137,139,142–144,147–174). 40.8% (n=32) of these studies were published in the latter two years of the twenty-year inclusion period, between 2020 and 2021. Only four studies in theme two were published prior to 2010, with a steady increase in publication frequency after 2014. Six studies concluded that sleep disturbances could be useful as biomarkers of neurodegeneration, but not AD specifically (35,111,137,158,164,165). Ten studies discussed the role of sleep disturbance as a risk factor to be screened for to aid AD diagnosis or identify risk of development (34,63,144,147,149, 150,161,168,169,174). 45.6% of the studies in theme two (n=36) explicitly described the potential for sleep disturbances to have utility as biomarkers for AD or preclinical AD

(7,18,39,44,49,50,55,57,59,60,62,69,74,75,78,82,83,87,90,93,95,97,99,139,142,153,156,157,159,160,162,163,170,171,175).

Aspects of Sleep with Possible Biomarker Utility

Altered SWA sleep was the predominant sleep pattern reported to have value as a biomarker, mentioned in 11 articles (6,36,37,47,52,53,84,124,148,166,173). Decreased REM sleep was the next most considered sleep stage, mentioned in eight articles for its potential diagnostic use (37,115,143,154,167,172,173,176). Altered sleep spindle activity, occurring in NREM stage 2, was recommended to have diagnostic value by two studies (53,152). One study found K-complexes of a spontaneous nature to have high specificity and sensitivity as biomarkers for aMCI, the precursive state of neurodegeneration to AD (155). Two studies discussed altered melatonin levels to be a potential biomarker of AD development (136,171).

Theme Three: Sleep as a Therapeutic Target for Alzheimer's Disease

The studies included in this theme contained suggestions of the possible amelioration or prevention of AD related pathophysiological changes by the treatment of sleep disturbances. 42.4% (n=86) of the total included studies for this scoping review described sleep as a potential therapeutic target for AD prevention, symptom amelioration, and/or slowing disease progression (5,6,8,16,18,21,25,27–29,34–37,39,42–52,55–57,59,61–66,68,69,71,76–80,84–86,88,90,91,93–95,98–100,106–108,116,124,125,131,132,136–138,152–154,159, 161–166,174,177–185). Studies in this theme spanned the full twenty-year inclusion period. 2020 saw the highest publication frequency of articles suggesting sleep as a therapeutic target for AD (n=19). Reviews were the predominant study type in this theme, accounting for 70.1% (n=61) of the included articles. Two clinical trials were included (18,21), one of which suggested the use of a CPAP machine to normalise AD biomarkers and stabilise AD pathophysiology (21), and the other targeting SWA sleep improvement to alleviate cognitive symptoms in early or preclinical AD (18). Five studies in theme three mentioned pharmacological approaches as a way to improve sleep in order to prevent AD (94,164,177, 182,186). Ten studies described non-pharmacological means as potential therapeutic targets to improve sleep and prevent or slow AD (8,27,37,64,65,98,136,186).

Non-Rapid-Eye-Movement/Slow Wave Amplitude Sleep

SWA sleep as a possible target for either AD prevention or amelioration and/or cognitive stabilisation was discussed by 15 of the studies included in theme three (6,18,35,39,43,47,52,55,76,79,83,84,86,124,152). One study recommended auditory treatment to improve memory retention and augment SWA sleep quality (43). Another discussed improvement of SWA sleep as a means to reduce symptoms associated with cerebral small vessel disease, a known contributor to AD (52). The results of this sub-theme show agreement regarding the potential for SWA sleep to have utility as a therapeutic target for AD prevention and/or amelioration. No discrepancies appear to be evident between the studies of this sub-theme regarding the potential role of SWA sleep enhancement for AD prevention/symptom reduction.

Continuous Positive Airway Pressure

Continuous Positive Airway Pressure (CPAP) treatment was mentioned in 13 of the studies included in theme three as a potential therapeutic target to prevent or treat preclinical AD and/or already diagnosed AD (16,21,28,29,45,66,100,107,125,131,132,162,180). 54% (n=7) of these studies were reviews, being made up of five literature reviews, (45,66,100,107,131), one systematic review (16), and one narrative review (132). The remaining studies were of varying experimental designs, including two longitudinal studies (28,29), and one clinical trial (21). The majority of these studies show broad agreement regarding the effects of CPAP treatment on AD biomarkers, and phases of sleep associated with AD. However, one study found no improvements in AD biomarker levels in individuals treated with CPAP (107). This study used retrospective data from 19 participants who were part of a routine diagnostic patient population.

Trans-Cranial Magnetic Stimulation

One study described the use of Trans-Cranial Magnetic Stimulation (TMS) as technology to enhance sleep in order to treat and/or prevent AD (50).

The Orexin/Hypocretin system

Five studies discussed a potential role for orexin in a therapeutic context to improve sleep quality and reduce AD risk (8,108,111,115,116). Two studies addressed the orexin/hypocretin

system as a potential therapeutic target to improve sleep/wake activity in preclinical AD (108,116). Another suggested orexin receptor antagonists may improve sleep quality in diagnosed AD patients (8).

Theme four: Preclinical Alzheimer's Disease Definition

This theme contained the least number of articles (n=19) and included studies mentioning or discussing the term 'preclinical AD'. This theme was only noted in studies published in the second half of the twenty-year inclusion criteria (2010 to 2021). The predominant study types included were quantitative experimental designs, accounting for 42% of studies included in theme four (187–194), and literature reviews, accounting for 37% (195–201). The remaining 21% was made up of two perspective reviews (10,202), one longitudinal study (203), and one systematic review and meta-analysis (204).

Definitions of Preclinical Alzheimer's Disease

89.5% (n=17) of studies in theme four cited a definition of preclinical AD (10,188–203). One study (10) cited an article in which the definition is believed to have been first coined (205). This article defined preclinical AD as “the presence of Alzheimer's biomarkers on post-mortem examination of cognitively unimpaired individuals” (205). A refinement by the International Working Group (IWG) and the American Alzheimer's Association (AAS) changed this to include living individuals with signs of Alzheimer pathology who are asymptomatic (10). Eight of the nineteen studies in theme four used this definition (10,189,191–193,197,202,203). Seven cited a further refined definition formulated by the National Institute on Aging and Alzheimer's Association (NIA-AA), which describes AD in the context of a continuum (187,190,194,198–201,204). Two studies referred to preclinical AD but did not explicitly define the term using either of the above definitions (195,196).

Limitations and Challenges of the Current Definition

Eleven studies in theme four highlighted limitations and challenges surrounding the definition of preclinical AD (10,187,192,193,195–198,200,201,204). Of these eleven studies, three discussed ethical considerations surrounding the diagnosis of preclinical AD (10,196,200). All three of these studies questioned the implications of diagnosing preclinical AD in individuals

which, though meeting the preclinical criteria, may not transition to AD in their lifetime (10,196,200). Two studies questioned the rationale of delivering a preclinical AD diagnosis in a time where there is no available treatment (197,200). Two studies raised the issue of specificity regarding the NIA-AA staging of preclinical AD and described the potential for biomarkers such as A β or neuronal injury evidence to arise from other pathologies than preclinical AD (193,201). One study suggested that stage three of the NIA-AA preclinical framework be termed “clinical” rather than preclinical, as the positive biomarkers in conjunction with altered cognition is likely indicative of true AD, rather than a precursor phase (204). One study questioned the diagnostic advantage of biomarkers associated with preclinical AD, with the authors asserting that biomarker presence in cognitively normal subjects may be the result of a normal brain ageing process, rather than pathology (201). Additionally, the authors described the concept of preclinical AD as ‘doubtful’, due to the inability for the cognitive dysfunction associated with stage 3 of preclinical AD to be objectively measured (201).

Discussion

The overall aim of this scoping review was to examine the extent and nature of the literature available relating sleep disturbance to AD development. This was performed in order to 1) ascertain the role of sleep in the development of AD, and 2) to assess whether specific sleep disturbances could be employed as biomarkers of preclinical AD. Four primary themes were observed within the included literature. These were 1) mechanistic links between sleep and AD, 2) sleep disturbance as a biomarker for AD, 3) sleep as a therapeutic target for AD, 4) preclinical AD definition.

Mechanistic Links between Sleep and Alzheimer’s Disease

Non-Rapid Eye Movement Sleep/Slow-Wave Amplitude Sleep/Amyloid Beta

The most predominant phase of sleep reported to have a causative role in AD/preclinical AD development was NREM sleep disturbance and the associated A β build-up thought to result from such disturbance (5,6,8,15,17,18,20,22,24,28–30,32,33,35–108,113,114,118,124,126,133,135,137–140,142–144,147,148,151,156,157,159,160,162,163,166,170,174,177,179,182,183,186,206–212). An important finding of the results was the number of studies that were

in review form (n=74) (5,6,8,15,17,35–108). This could potentially weaken the evidence implicating the A β hypothesis as a causative factor in AD. If a greater percentage of experimental studies was observed within the literature, it is possible that the A β hypothesis could more accurately be represented. However, a number of quantitative experimental studies addressed the A β hypothesis with relatively consistent results. Several of these studies reported that disturbance of SWA sleep was associated with increased levels of circulating A β within the brain (20,22,148,166,170,206,207), including two clinical trials (20,22). Interestingly, one study which restricted participants' sleep, while preserving SWA sleep found no increase in circulating A β levels (31). This is a noteworthy study, as although sleep disturbance was induced and resulted in no increased A β levels, the phase of sleep many researchers deem integral to maintain in order to avoid AD pathogenesis was not disturbed. Therefore, this study appears to demonstrate the conclusions reached by other studies discussing SWA sleep as a regulator of pathological processes associated with AD pathogenesis. A study performed on participants with amnesic Mild Cognitive Impairment (aMCI) reported a decrease in SWA sleep compared to control participants without aMCI (213). The authors concluded that sleep disturbance was likely indicative of neurological decline (213).

Orexin/Hypocretin System

The orexin/hypocretin system was discussed by fifteen of the included studies in relation to its association with sleep and AD (8,19,23,38,95,108,111,113–120). The majority of these studies agreed that the orexin/hypocretin system regulated the sleep/wake cycle in a bidirectional manner (8,19,23,38,95,108,111,113–120). However, one study reported a lack of substantial evidence implicating sleep disturbances as having causal effects on AD risk (117). This study was a mendelian randomisation using Genome Wide Association Studies (GWAS) in conjunction with self-reported sleep measures (117). A different approach taken by this study was the inclusion of subjective sleep reports from participants into the results. This is interesting, as such reports have been shown to correlate poorly with objective sleep quality (124). However, the included studies appear to indicate a mechanism whereby sleep disturbance interferes with the orexin/hypocretin system and contributes to AD pathogenesis.

Apolipoprotein Epsilon

The genetic variation of Apolipoprotein Epsilon e4 (APOEe4) was implicated by the results of this scoping review to contribute to AD pathogenesis through disruption of processes associated with sleep homeostasis (5,6,18,26,42,55,73,74,81,90,94,100,122–126). The studies discussing APOE spanned a 17-year publication period. Among the sub-themes of theme one, this topic is one of those with a wider timespan of publication dates of individual studies. This may indicate the research on the link between this genetic variation and AD to be reasonably robust. Four of the 17 studies discussing APOEe4 agreed that improved sleep quality reduced the risk of AD development conferred from the APOEe4 genetic variation (6,90,94,100). This may have interesting implications for future research on the role of sleep in attenuating the genetic influence of APOE on AD pathogenesis and/or progression. One study found mice with the APOE4 gene experienced excessive sleep problems (123). Two studies reported a correlation between improved sleep quality and attenuation of the effect of APOE4 on AD risk (94,100). One study found that those with the APOE3 genotype and sleep-disordered breathing showed higher levels of circulating AD biomarkers than those with only sleep-disordered breathing (125). Two studies described the presence of APOE as a risk factor for AD, and both added that it was typically associated with sleep disturbances, such as SWA and REM sleep reduction (6,94).

Obstructive Sleep Apnoea

The nocturnal breathing disorder Obstructive Sleep Apnoea (OSA) was discussed by 34 of the included studies (6,15–17,21,28,29,35,41,42,45,53,66,72,73,76,81,88,94,95,99,106,107,109,113,123,125,127–132). These articles spanned the full 20-year inclusion period of this scoping review. This sub-theme also included a higher percentage of experimental studies compared to others within theme one. These included two longitudinal studies (28,29), a secondary data analysis (26), one non-randomised controlled trial (113), one clinical trial (21) and a mixture of human and animal experimental studies (109,113,123,125,127,129,130,133,135). Three systematic reviews (15–17) also discussed OSA as a contributing factor of AD. The results show broad agreement on the influence of OSA on AD pathogenesis. This may present an opportunity for further research into treatment of OSA as a means to reduce its own complications, as well as a possible preventative measure against AD onset.

Melatonin

Melatonin was discussed by six of the included studies with regard to its role in the pathogenesis of AD (39,63,103,119,120,136). All six studies reported similar results regarding melatonin's associations with AD pathogenesis. Five studies discussed the role of melatonin in regulating A β levels (39,63,103,120,136), with a higher level having a neuroprotective effect on A β burden (63,103) and a lower level being a clinically observable sign in preclinical AD (39,63). One study further found that decreased melatonin promotes the dysfunction of neural networks related to cognition, thereby contributing to AD pathogenesis (119).

Tau Proteins

Four studies agreed that Tau protein abnormalities occurred typically as a downstream effect following A β accumulation and aggregation (19,87,98,133). However, some studies indicated a causal link between sleep disturbances and abnormal Tau metabolism (8,66,72,125,138). One study describes abnormal Tau activity as the earliest observable sign of AD, accumulating in sleep-regulating areas of the brain even prior to observable A β changes (87). One experiment investigated links between sleep quality and AD biomarkers, finding self-reported sleep disturbances were associated with increased levels of Tau in the cerebro-spinal fluid (CSF) (138).

K-complexes

All three studies in this sub-theme discuss K-complexes as having a mechanistic link to AD pathogenesis (25,37,45). The prospective cohort study reported significant differences regarding K-complex density between participants with aMCI and those with AD, and further suggested such differences to have robust diagnostic utility with high specificity and sensitivity (25). Furthermore, the authors described K-complexes as having protective effects on NREM sleep (25). This is interesting, given the suggested relationship between NREM sleep and AD pathogenesis discussed by many of the studies included in this scoping review.

Gut Microbiome

This sub-theme contained one study in which the authors discussed a mechanistic link between sleep disturbance, gut microbiota and AD (146). The authors proposed that chronic

sleep disturbance altered behavioural and lifestyle changes causing dysbiosis of the gut microbiota (146). The authors further suggest this in turn had a synergistic pathological effect with sleep disturbance, contributing to AD pathogenesis (146). It is difficult to know the strength of this review within a scoping review context. However, this sub-theme may have interesting implications for AD and sleep disturbance. Recent research suggests gut microbiota dysbiosis contributes to systemic inflammation and vascular dysfunction (214), both of which have been associated with increased AD biomarkers and pathogenesis (61,215). Therefore, this may represent a potential research avenue for AD prevention.

The results show broad agreement within the included literature that sleep disturbances can contribute to the pathogenesis of AD. Multiple physiological pathways and/or aspects of sleep were identified by the included literature as having bi-directional relationships with AD/preclinical AD. Identification of these links between sleep and AD may warrant further research into each mechanism to ascertain whether they may serve as therapeutic targets to prevent, slow and/or ameliorate AD.

Sleep Disturbance as a Biomarker of Alzheimer's Disease

The results of this scoping review indicate that most of the included studies agree that certain sleep disturbances have diagnostic validity in AD and/or preclinical AD. 45.6% of the studies discussing the diagnostic value of sleep disturbances in AD/preclinical AD recommend their use as biomarkers in explicit terms (7,18,39,44,49,50,55,57,59,60,62,69,74,75,78,82,83,87, 90,93,95,97,99,139,142,153,156,157,159,160,162,163,170,171,175). The phase of sleep most frequently reported to have as a biomarker for AD/preclinical AD was the third phase of NREM sleep, SWA (6,36,37,47,52,53,84,124,148,166,173). Two longitudinal studies examined the utility of sleep disturbances as biomarkers for AD (148,157). One of these studies reported that the rate of A β build-up was able to be predicted based on the severity with which SWA was diminished (148). Both studies highlighted that this finding had the potential to forecast future brain atrophy and the initial development of cognitive impairments as far as the actual onset of clinical AD (148,157). Carnicelli et al. (157) added that A β burden resulting from sleep disturbance may in turn negatively affect NREM sleep and further contribute to cognitive decline. These longitudinal studies may be of importance to the hypothesis of sleep

disturbances having utility as AD biomarkers, as this methodology is well-suited to evaluating risk factors and disease development (216). However, few studies of this nature were identified by the chosen search parameters. This may be due to the fact that the majority of the studies recommending sleep as a biomarker for AD were published in the latter half of the 20-year inclusion period. Therefore, it is possible that clinical studies may be underway pursuing this hypothesis yet are incomplete as the hypothesis of sleep as a biomarker for AD is relatively nascent. However, there is widespread agreement between the included studies of the promise of sleep disturbances as biomarkers of AD. Research suggests that diagnostic information resulting from sleep disturbances may be able to predict AD up to 20 years prior to the onset of classical symptoms such as cognitive decline (10). There is evidence to suggest that such early detection coincides with a phase within the AD spectrum that is amenable to intervention, or even prevention of the onset of true AD (11,12,62). Sperling et al. (217) estimated that interventions delaying the onset of cognitive decline even by five years may reduce overall AD patient numbers by up to 57%. Therefore, the potential ability for sleep disturbances to predict AD decades in advance of the current diagnosis may have an exponential impact on the global burden of AD and further highlights the importance early identification of AD risk.

Sleep as a Therapeutic Target for Alzheimer's Disease

42.4% (n=87) of the studies included within this scoping review suggested sleep to be addressed as a potential therapeutic target in order to reduce risk of and/or ameliorate preclinical AD symptoms (5,6,8,16,18,21,25,27–29,34–37,39,42–52,55–57,59,61–66,68,69, 71,76–80,84–86,88,90,91,93–95,98–100,106–108,116,124,125,131,132,136–138,152–154, 159,161–166,174,177–185). However, this hypothesis appeared to be experimentally tested by only 10 studies (18,21,28,29,125,163,174,177,178,180), and analysed by one systematic review (16). The remaining studies in theme three appear to have suggested sleep as a potential therapeutic target based on their respective results. All 10 of the studies that tested sleep's validity as a therapeutic target in AD/preclinical AD prevention or amelioration agreed that it was a promising target for future interventional research (18,21,28,29,125,163,174, 177,178,180). Given the amount of research suggesting this in combination with the results of the aforementioned 10 studies who tested the hypothesis, this may be an indication for

further research. More studies of experimental designs testing this hypothesis are necessary to ascertain the total potential sleep may have as a therapeutic target to prevent and/or ameliorate AD progression.

Slow Wave Amplitude Sleep

The studies of this sub-theme all share similar suggestions regarding the potential impact SWA sleep interventions may have on either prevention of AD pathogenesis, or reduction of symptoms in preclinical or fully diagnosed AD. The findings from these studies are interesting, as disturbance of SWA sleep was the mechanism implicated by many of the studies from theme one by which AD pathogenesis is initiated. It therefore appears logical that enhancement of SWA sleep prior to AD related changes in the brain may have a limiting effect on AD pathogenesis. If such an approach was successful, it could be inferred that it would have the potential to reduce the global burden of AD significantly. However, Mander et al. (6) caution against enhancement of SWA sleep to the point where it may interfere with normal sleep spindle activity, as these processes are involved in memory processing and consolidation. Regardless, some researchers argue there is a need for more experimental testing of this hypothesis to fully ascertain the potential benefit of SWA improvement (6,18,39,55,84,86). This may be potential avenue for future research in order to address the global burden of AD.

Continuous Positive Airway Pressure

The studies included within this sub-theme appear to agree on the potential for CPAP treatment to either ameliorate, prevent, and/or reduce symptoms associated with AD. Four studies in this sub-theme reported results indicating CPAP treatment had the potential to stabilise altered AD associated biomarker levels (21,28,66,131). A further four studies discussed how CPAP treatment of OSA may slow cognitive decline and reduce AD risk (29,125,132,180). This seems to align with suggestions that the best window for AD intervention is prior to the onset of clinical symptoms. Further to this, one study suggested CPAP treatment of OSA had the potential to improve known and diagnosed AD symptoms (100). One study reported improved SWA sleep in subjects with MCI (162), and another reported improvement in both SWA and REM sleep (45). These are interesting findings, as disruption of SWA sleep was the phase of sleep predominantly associated with AD

pathogenesis by the included studies of this scoping review. This may strengthen the results of the aforementioned study. One study found no changes in A β levels following treatment of OSA from CPAP (107). However, the authors did not specify the duration of CPAP treatment the participants received, which some argue to be a salient factor in the efficacy of CPAP treatment of OSA (16). The authors did, however, suggest severe OSA may predispose younger people to A β burden, in the absence of metabolic or structural brain alterations (107). This is an interesting finding, as it may indicate earlier than usual signs of AD pathogenesis prior to potentially irreversible structural changes.

Trans-Cranial Magnetic Stimulation

The authors of this study proposed that TMS had the potential to stimulate and enhance quality of sleep as well as improve clearance of proteins in AD patients and healthy elderly individuals (50). Considering this is only represented by one study within this scoping review, it would be useful to investigate this approach more within the scientific literature to ascertain the scope of evidence surrounding TMS and AD. It is possible that such an approach may hold utility as a preventative treatment of sleep disturbances and/or AD.

The Orexin/Hypocretin system

Two studies suggested that by improving the sleep/wake cycle via targeting the orexin/hypocretin system, there would likely be an ameliorating effect on A β and Tau levels, thereby potentially slowing AD pathogenesis (108,116). One review cited research stating orexin receptor antagonist drugs have been shown to lower levels of A β in mice. All studies in this sub-theme discussed the orexin/hypocretin system a possible means to improve sleep quality, in order to prevent or ameliorate AD progression.

Preclinical Alzheimer's Disease Definition

Although two main definitions have been identified within the existing literature, challenges appear to remain surrounding their successful implementation into the scientific consensus. The IWG definition of preclinical described only individuals without cognitive symptoms who harbour AD positive biomarkers (10). In the NIA-AA format, preclinical AD was divided into

three stages of 1) asymptomatic with A β pathology, 2) asymptomatic with A β and Tau pathology, and 3) subtle cognitive changes with biomarker pathology (190,194,198–201,204).

Difference Between Current Definitions and the Necessity of Definition Consensus

The initial IWG definition described preclinical AD as the phase which precedes observable clinical signs of AD (10), while the NIA-AA definition included a clinically observable state of cognitive decline within its preclinical continuum (190,194,198–201,204). This appears to be the most prominent distinction between the two definitions. One study argued that a clinically observable state of cognitive decline is incongruent with the term 'preclinical' and crosses into 'clinical' territory (204). Furthermore, Sperling et al. (218) proposed that individuals within stage 2 of the NIA-AA preclinical continuum may already be resistant to current anti-amyloid therapies, and suggested the most ideal window for intervention may be prior to this stage. Therefore, it may be that if preclinical AD is not defined within a time frame that is amenable to treatment or intervention, the advantage of early diagnostic information could be undermined. Current pharmacotherapies for diagnosed AD, as opposed to preclinical, offer limited symptomatic relief, without curing or halting the disease (219). This highlights the need for as early identification as possible in order to maximise the potential of reversing or slowing AD pathophysiology. To ascertain whether sleep can be used as a biomarker and/or treatment for preclinical AD, a standardised definition seems necessary as a target on which to base future research outcome measures exploring preventative measures of AD.

Ethical Implications of Current Definitions of Preclinical Alzheimer's Disease

Three studies discussed the ethical implications of diagnosing people with preclinical AD (10,196,200). These studies questioned the ethical implications of diagnosing individuals with preclinical AD based on biomarker status, when they may not clinically develop the disease in their lifetime (10,196,200). Chételat et al. (200) argued that instead of a diagnosis, such information would be better labelled as 'risk information'. Berti et al. (196) agreed that biomarker abnormalities associated with AD place cognitively normal people at increased risk of developing AD. However, they cite a lack of accurate prognostic tools available to determine the likelihood of such individuals actually developing AD (196). Moreover, the

likelihood of an individual developing AD is influenced by individual factors such as cognitive reserve (196). Such variation in how an individual responds in pathophysiological terms may dilute the diagnostic value of current definitions of preclinical AD in diagnostic terms. Dubois et al. (10) further mention a lack of consensus as to whether AD should be defined by the classical symptoms of cognitive decline, or the appearance of AD related biomarkers despite a lack of clinical symptoms. This raises an important question regarding how strong the predictive ability of AD biomarkers is in identifying those who will develop the disease. Of note, is that one study found that individuals with preclinical AD did not necessarily follow a temporal pattern the same as that proposed by the A β cascade hypothesis (192). Another study questioned whether the presence of biomarkers such as A β was due to normal ageing, or actually indicative of AD pathology (201). The authors based this on another study they cited, which stated abnormal AD biomarkers were present in approximately 50% of individuals over 65 year of age (220). Chételat et al. (200) further questioned the ethics of delivering an AD related diagnosis to people who may not develop AD. The authors suggested such information may be better labelled 'risk information' (200). This may potentially raise issues for the IWG definition, and possibly the first two phases of the NIA-AA definition preclinical criteria. Furthermore, a longitudinal study by Vos et al. (193) described heterogenous causes of neuronal injury biomarkers such as Tau proteins. This may potentially affect the sensitivity and specificity of preclinical AD as a diagnosis. A separate study discussed the concept of risk factors v biomarkers (196). The authors suggested risk factors for AD may be useful in determining the likelihood of an individual developing AD, while biomarkers could highlight where an individual sits on the AD spectrum (196). This is interesting within the context of preclinical AD, as the authors further suggest biomarkers to be fluid in nature (196). Given the inherent variability within individuals within the preclinical phase, there may be utility in labelling biomarker presence within the stage researchers believe to be 'reversible' as risk information, and possibly employing a formal diagnosis approach to individuals situated further along the AD spectrum.

The Relationship Between the Observed Themes

Between the four primary themes from the results, overlap occurred. Theme one "mechanistic links between sleep and Alzheimer's Disease" shared the most overlap with the remaining three primary themes. This may be a result of mechanistic information being an

underpinning theme of studies from themes two and three. The association particularly between themes two and three may indicate the suggestion of sleep as a therapeutic target to have arisen organically from results generated by some studies focusing on sleep as a biomarker, rather than a therapeutic target specifically. It appears that the majority of studies exhibiting overlap between themes two and three suggested, but did not test, sleep as a therapeutic target of AD. Four studies from theme three did not show overlap between themes (180,181,184,185). This may be a further indicator of the low number of the included studies that set out to test the hypothesis of sleep as a therapeutic target of AD/preclinical AD. This may indicate research studying sleep improvement as therapy for AD prevention/amelioration to be in its infancy and be indicative of a potential future target for researchers. Theme four “preclinical AD definition” exhibited the least overlap between themes. This may be due to the specificity of keywords used in the literature search of this scoping review. As the aim of the search pertaining to preclinical AD was to ascertain whether a specific definition or characterisation for preclinical AD existed, it was not imperative that the included papers contained reference to sleep. Therefore, the parameters for inclusion of studies potentially addressing this aim required only that they contained or made reference to a definition of preclinical AD.

Limitations

Scoping reviews incur inherent limitations. One of note is that scoping reviews do not critically appraise the evidence presented in the selected studies or the methodologies of the studies themselves (13). This can affect the ability for the research to effectively translate research findings into applicable concepts and policies for clinical practice (221). Therefore, it was difficult to ascertain the quality of key studies included in this review. Furthermore, as quality appraisal of studies is not a prerequisite for scoping reviews, a wider range of methodologies may be included into the research paper selection, which can create difficulty with cohesive synthesis of results from different types of studies (13). The inclusion period of articles between 2001 and 2021 may have limited the available research on sleep disturbances as biomarkers of AD, however prior to 2001 there appeared to be a paucity of research in this area. Another potential limitation was the exclusion of articles published in languages other than English. This may have caused articles with important information on the topic to be excluded from this scoping review.

A significant limitation of this scoping review was the high proportion of reviews within the included literature. Over half of the studies included were in the form of reviews. Lunny et al. (222) note that overlap may occur when reviews on a given topic include one or more of the same primary articles. If the included reviews comprised different primary articles without significant overlap, the number of reviews might not have significantly affected the results of this scoping review. However, many of the primary experimental studies included were represented within multiple review articles in this scoping review, resulting in excessive representation. Lunny et al. (222) further suggest that such overlap within the results may disproportionately strengthen the findings of individual studies, potentially impacting the narrative of the scoping review. To mitigate this, choosing one high-quality review for inclusion and synthesising it to inform the scoping review results could have been a potential strategy (222). Furthermore, given the high number of review articles identified by the search strategy, an alternative methodology might have been considered to address the research question.

Conclusion

Multiple physiological mechanisms connecting sleep disturbances and AD were discussed within the included studies, without significant disagreement as to how each pathway may affect brain homeostasis and contribute to pathological decline associated with AD. The potential role of sleep as a potential biomarker for AD/preclinical AD was also widely considered by the included studies. This may present an opportunity for future research in order to identify the pathogenesis of AD within a potentially reversible phase of its progression. It is possible that such an advancement in the diagnosis and treatment of AD could significantly reduce the global burden of the disease. The results of this scoping review further indicate certain sleep phases may be able to serve as therapeutic targets for sleep therapies in order to reduce AD risk or ameliorate disease progression. However, there appears to be a lack of experimental research substantiating these claims, and further research testing these hypotheses is required. Two definitions of preclinical AD were identified within the results of this scoping review, yet a consensus appears to be lacking regarding their utility within a clinical setting. If the research pertaining to sleep in both a diagnostic and therapeutic context is to be further explored in order to potentially reduce the

global burden of AD, a clinically relevant and consistent characterisation of the preclinical phase seems essential. The ethical implications of such a definition becoming a diagnosis for individuals is also an important consideration.

Recommendations for Future Research

This scoping review identified certain gaps within the included literature. The foremost perhaps was a lack of longitudinal experimental study designs, testing the hypotheses of the utility of sleep as either a biomarker or therapeutic target for AD/preclinical AD. As these hypotheses are relatively nascent, studies of these designs are likely underway. It is likely that further experimental testing of such hypotheses may consolidate the available evidence and contribute to an improved understanding of the relationship between sleep and AD. Therefore, future researchers may consider conducting more experimental studies addressing these hypotheses prior to undertaking a systematic review.

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Section 4: Appendices

Appendix A: Table of Included Studies

Title	Year of Publication	Author/s	DOI	Study Type
Sleep disturbances in patients with alzheimer's disease: Epidemiology, pathophysiology, and treatment	2001	Vitiello, M. V. Borson, S.	10.2165/00023210-200115100-00004	Review
Molecular Changes Underlying Reduced Pineal Melatonin Levels in Alzheimer Disease: Alterations in Preclinical and Clinical Stages	2003	Wu et al.	10.1210/JC.2003-030833	Non-Randomised controlled trial
Sleep/Wake Disruption in Alzheimer's Disease: APOE Status and Longitudinal Course	2004	Yesavage et al.	10.1177/0891988703261994	Cohort Study
Sleep and quantitative EEG in neurodegenerative disorders	2004	Petit et al.	10.1016/J.JPSYCHORES.2004.02.001	Unspecified experiment
Pineal clock gene oscillation is disturbed in Alzheimer's disease, due to functional disconnection from the "master clock"	2006	Wu et al.	10.1096/FJ.05-4446FJE	Post-mortem research
Biomarkers for the early detection of Parkinson's and Alzheimer's disease	2008	Berg, Daniela	10.1159/000113682	Mini Review
Amyloid-β dynamics are regulated by	2009	Kang, et al.	10.1126/SCIENCE.1180962	Unspecified Experiment

orexin and the sleep-wake cycle

EEG, activity, and sleep architecture in a transgenic AβPP swe/PSEN1A246E Alzheimer's disease mouse	2010	Jyoti et al.	10.3233/JAD-2010-100879	Animal Study
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Diagnóstico pré-clínico da doença de Alzheimer: Prevenção ou vaticínio?	2010	Nitrini, Ricardo	10.1590/S1980-57642010DN40400002	Review
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Alzheimer's Disease: Aging, Insomnia and Epigenetics	2010	Wu et al.	10.1016/S1028-4559(10)60099-X	Mini Review
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Neurocognitive dysfunction associated with sleep quality and sleep apnea in patients with mild cognitive impairment	2011	Kim et al.	10.1097/JGP.0B013E3181E9B976	Unspecified Experiment
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Evolution of the diagnostic criteria for degenerative and cognitive disorders	2011	Lopez et al.	10.1097/WCO.0B013E32834CD45B	Review
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Cognition and beta-amyloid in preclinical Alzheimer's disease: Data from the AIBL study	2011	Pike et al.	10.1016/J.NEUROPSYCHOLOGIA.2011.04.012	Unspecified Experiment
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Pre- and post-synaptic cortical cholinergic deficits are proportional to amyloid plaque	2011	Potter et al.	10.1007/S00401-011-0831-1	Unspecified Experiment
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presence and density at preclinical stages of Alzheimer's disease

Pro: Alzheimer's disease and circadian dysfunction: Chicken or egg?	2012	Bedrosian, Tracy A. Nelson, Randy J.	10.1186/ALZRT128	Mini Review
Sleep disturbances in Alzheimer's and Parkinson's diseases	2012	Rothman, Sarah M. Mattson, Mark P.	10.1007/S12017-012-8181-2	Review
Disturbed Sleep Patterns in Elders with Mild Cognitive Impairment: The Role of Memory Decline and ApoE ε4 Genotype	2012	Hita-Yanez et al.	10.2174/156720512800107609	Unspecified Experiment
Identifying earlier Alzheimer's disease: Insights from the preclinical and prodromal phases	2012	Molinuevo et al.	10.1159/000332806	Review
Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease	2012	Knopman et al.	10.1212/WNL.0B013E3182563BBE	Unspecified Experiment
Human apolipoprotein E4 targeted replacement in mice reveals increased susceptibility to sleep disruption and intermittent hypoxia	2012	Kaushal, Navita Ramesh, Vijay Gozal, David	10.1152/AJPREGU.00025.2012	Quantitative Animal Study

Disruption of the sleep-wake cycle and diurnal fluctuation of amyloid-β in mice with Alzheimer's disease pathology	2012	Roh et al.	10.1126/SCITRANSLME D.3004291	Unspecified Experiment
Discrepancy between subjective and objective sleep disturbances in early-and moderate-stage alzheimer disease	2012	Most, Els I.S. Aboudan, Samir Scheltens, Philip Van Someren, Eus J.W.	10.1097/JGP.0B013E31 8252E3FF	Unspecified Experiment
Does abnormal non-rapid eye movement sleep impair declarative memory consolidation? Disturbed thalamic functions in sleep and memory processing.	2012	Lu, William Göder, Robert	10.1016/J.SMRV.2011.0 8.001	Review
Reciprocal interactions between sleep, circadian rhythms and Alzheimer's disease: Focus on the role of hypocretin and melatonin	2013	Slats et al.	10.1016/J.ARR.2012.04. 003	Review
Biomarkers of alzheimer disease: Current and future applications to diagnostic criteria	2013	Sperling, Reisa Johnson, Keith	10.1212/01.CON.00004 29181.60095.99	Review
Amyloid imaging in cognitively normal individuals, at-risk populations and	2013	La Joie et al.	10.1016/J.NICL.2013.02 .006	Review

**preclinical
Alzheimer's disease**

Sleep Disturbance is Associated with Incident Dementia and Mortality	2013	Sterniczuk et al.	10.2174/15672050113109990134	Unspecified Experiment
Polysomnographic and subjective sleep markers of mild cognitive impairment	2013	Hita-Yañez, Eva Atienza, Mercedes Cantero, Jose L.	10.5665/SLEEP.2956	Unspecified Experiment
Sleep loss as risk factor for neurologic disorders: A review	2013	Palma, Jose Alberto Urrestarazu, Elena Iriarte, Jorge	10.1016/j.sleep.2012.11.019	Review
Definitions of dementia and predementia states in Alzheimer's disease and vascular cognitive impairment: consensus from the Canadian conference on diagnosis of dementia	2013	Chertkow, Howard Feldman, Howard H Jacova, Claudia Massoud, Fadi	10.1186/ALZRT198	Review
A hypnic hypothesis of alzheimer's disease	2013	Clark, Camilla N. Warren, Jason D.	10.1159/000350060	Review
Objectively measured sleep and β-amyloid burden in older adults: A pilot study	2014	Gagnon et al.	10.1016/J.PATBIO.2014.05.015	Review
Perspective on future role of biological markers in clinical therapy	2014	Antonell et al.	10.3233/JAD-140624	Randomised Controlled Trial

trials of Alzheimer's disease: A long-range point of view beyond 2020

Circadian misalignment and sleep disruption in mild cognitive impairment 2014 Naismith et al. 10.3233/JAD-131217 Randomised Controlled Trial

Can sleep apnea cause Alzheimer's disease? 2014 Pan, Weihong
Kastin, Abba J. 10.1016/J.NEUBIOREV.2014.10.019 SYSTEMATIC REVIEW

Sleep deprivation impairs memory, tau metabolism, and synaptic integrity of a mouse model of Alzheimer's disease with plaques and tangles 2014 Di Meco, Antonio
Joshi, Yash B.
Praticò, Domenico 10.1016/J.NEUROBIOLAGING.2014.02.011 Controlled Experiment

Correction to Potential role of orexin and sleep modulation in the pathogenesis of Alzheimer's disease [The Journal of Experimental Medicine, 211, 13, (2014), 2487-2496] 2014 Roh et al. 10.1084/JEM.20141788 Unspecified Experiment

The sleep-wake cycle and Alzheimer's disease: what do we know? 2014 Lim, Miranda M.
Gerstner, Jason R.
Holtzman, David M. 10.2217/NMT.14.33 Review

A change in sleep pattern may predict alzheimer disease 2014 Hahn et al. 10.1016/J.JAGP.2013.04.015 Longitudinal study

The interaction between sleep- 2014 Osorio et al. 10.1016/J.NEUROBIOLAGING.2013.12.030 Unspecified Experiment

disordered breathing and apolipoprotein E genotype on cerebrospinal fluid biomarkers for Alzheimer's disease in cognitively normal elderly individuals

Sleep and Alzheimer disease pathology-a bidirectional relationship	2014	Ju, Yo El S. Lucey, Brendan P. Holtzman, David M.	10.1038/NRNEUROL.2013.269	Review
Amyloid-β diurnal pattern: Possible role of sleep in Alzheimer's disease pathogenesis	2014	Lucey, Brendan P. Bateman, Randall J.	10.1016/J.NEUROBIOLA GING.2014.03.035	Review
Sleep-dependent memory consolidation in healthy aging and mild cognitive impairment	2015	Pace-Schott, Edward F. Spencer, Rebecca M.C.	10.1007/7854_2014_300	Review
The New Conceptualization of Alzheimer's Disease under the Microscope of Influential Definitions of Disease	2015	Alexopoulos, Panagiotis Kurz, Alexander	10.1159/000441327	Review
Diagnostic value of cerebrospinal fluid Aβ ratios in preclinical Alzheimer's disease	2015	Adamczuk et al.	10.1186/S13195-015-0159-5	Unspecified Experiment
Consequences of circadian disruption	2015	Videnovic, Aleksandar Zee, Phyllis C.	10.1016/J.JSMC.2015.08.004	Review

on neurologic
health

Amyloid burden is associated with self-reported sleep in nondemented late middle-aged adults	2015	Sprecher et al.	10.1016/J.NEUROBIOLAGING.2015.05.004	Unspecified Experiment
Non-rapid eye movement sleep instability in mild cognitive impairment: A pilot study	2015	Maestri et al.	10.1016/J.SLEEP.2015.04.027	Unspecified Experiment
The synergistic relationship between Alzheimer's disease and sleep disorders: An update	2015	Villa, Chiara Ferini-Strambi, Luigi Combi, Romina	10.3233/JAD-150138	Review
Self-reported sleep disturbance is associated with Alzheimer's disease risk in men	2015	Benedict et al.	10.1016/J.JALZ.2014.08.104	secondary data analysis
Sleep and Alzheimer's disease	2015	Peter-Derex et al.	10.1016/J.SMRV.2014.03.007	Review
Sleep, Cognition and Dementia	2015	Porter, Verna R. Buxton, William G. Avidan, Alon Y.	10.1007/S11920-015-0631-8	Review
Subtle Cognitive Decline and Biomarker Staging in Preclinical Alzheimer's Disease	2015	Edmonds et al.	10.3233/JAD-150128	Secondary data analysis
Sleep, circadian rhythms, and the pathogenesis of Alzheimer disease	2015	Musiek, Erik S. Xiong, David D. Holtzman, David M.	10.1038/EMM.2014.121	Review

Sleep: A Novel Mechanistic Pathway, Biomarker, and Treatment Target in the Pathology of Alzheimer's Disease?	2016	Mander et al.	10.1016/J.TINS.2016.05.002	Review
Self-Reported Sleep Apnea and Dementia Risk: Findings from the Prevention of Alzheimer's Disease with Vitamin E and Selenium Trial	2016	Ding et al.	10.1111/jgs.14393	Secondary data analysis
Neurocognitive impairment is correlated with oxidative stress in patients with moderate-to-severe obstructive sleep apnea hypopnea syndrome	2016	He et al.	10.1016/J.RMED.2016.09.009	Unspecified Experiment
Associations between sleep, cortisol regulation, and diet: Possible implications for the risk of Alzheimer disease	2016	Pistollato et al.	10.3945/an.115.011775	Review
Mechanisms linking circadian clocks, sleep, and neurodegeneration	2016	Musiek, Erik S. Holtzman, David M.	10.1126/SCIENCE.AAH4968	Review
Subjective sleep quality and daytime sleepiness in late midlife and their association with	2016	Waller et al.	10.1016/J.SLEEP.2015.01.004	Unspecified Experiment

**age-related changes
in cognition**

Circadian Rhythms, Sleep, and Disorders of Aging	2016	Branger et al.	10.1016/J.NEUROBIOLA GING.2016.02.009	Unspecified Experiment
Obstructive sleep apnea decreases central nervous system–derived proteins in the cerebrospinal fluid	2016	Ju et al.	10.1002/ANA.24672	Unspecified Experiment
Rapid eye movement sleep disruption and sleep fragmentation are associated with increased orexin-A cerebrospinal-fluid levels in mild cognitive impairment due to Alzheimer's disease	2016	Ligouri et al.	10.1016/J.NEUROBIOLA GING.2016.01.007	Unspecified Experiment
Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria	2016	Dubois et al.	10.1016/J.JALZ.2016.02 .002	Review
Orexin-A is associated with increases in cerebrospinal fluid phosphorylated-tau in cognitively normal elderly subjects	2016	Osorio et al.	10.5665/SLEEP.5846	Unspecified Experiment
Biomarkers of Alzheimer disease in children with obstructive sleep apnea: Effect of adenotonsillectomy	2016	Kheirandish-Gozal et al.	10.5665/SLEEP.5838	Unspecified Experiment

NIA-AA staging of preclinical Alzheimer disease: Discordance and concordance of CSF and imaging biomarkers	2016	Vos et al.	10.1016/J.NEUROBIOLA GING.2016.03.025	Unspecified Experiment
Exploring the bi-directional relationship between sleep and beta-amyloid	2016	Brown et al.	10.1097/YCO.00000000 00000285	Review
Chronic sleep disturbance and neural injury: Links to neurodegenerative disease	2016	Abbott, Sabra M. Videnovic, Aleksandar	10.2147/NSS.S78947	Review
Orexin and Alzheimer's disease	2017	Liguori, Claudio	10.1007/7854_2016_5 0	Review
Sleep in Alzheimer's Disease - Beyond Amyloid	2017	Holth, Jerrah Patel, Tirth Holtzman, David M	10.1016/j.nbscr.2016.0 8.002	Review
Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels	2017	Ju et al.	10.9758/cpn.2017.15.2. 89	Clinical Trial
Role of sleep disturbance in the trajectory of Alzheimer's disease	2017	Kang, Dong Woo Lee, Chang Uk Lim, Hyun Kook	10.9758/cpn.2017.15.2. 89	Review
Obstructive sleep apnea is associated with early but possibly modifiable Alzheimer's disease biomarkers changes	2017	Ligouri et al.	10.1093/SLEEP/ZSX011	Clinical Trial

Sleep, Cognitive impairment, and Alzheimer's disease: A Systematic Review and Meta-Analysis	2017	Bubu et al.	doi:10.1093/sleep/zsw032	Systematic Review and Meta-Analysis
Candidate mechanisms underlying the association between sleep-wake disruptions and Alzheimer's disease	2017	Cedernaes et al	10.1016/J.SMRV.2016.02.002	Review
Brain rhythm attractor breakdown in Alzheimer's disease: Functional and pathologic implications	2017	Karageorgiou, Elissaios Vossel, Keith A.	10.1016/J.JALZ.2017.02.003	Review
Does selection for short sleep duration explain human vulnerability to Alzheimer's disease?	2017	Nesse, Randolph M. Finch, Caleb E. Nunn, Charles L.	10.1093/EMPH/EOW035	Review
Chronic sleep restriction promotes brain inflammation and synapse loss, and potentiates memory impairment induced by amyloid-β oligomers in mice	2017	Kincheski et al.	10.1016/J.BBI.2017.04.007	Clinical Trial
Orexin Impairs the Phagocytosis and Degradation of Amyloid-β Fibrils by Microglial Cells	2017	An et al.	10.3233/JAD-170108	Clinical Trial

Sleep Deprivation Induced Plasma Amyloid-β Transport Disturbance in Healthy Young Adults	2017	Wei et al.	10.3233/JAD-161213	Clinical Trial
Sleep and hippocampal neurogenesis: Implications for Alzheimer's disease	2017	Kent, Brianne A. Mistlberger, Ralph E.	10.1016/J.YFRNE.2017.02.004	Review
Chronic Sleep Restriction Induces Cognitive Deficits and Cortical Beta-Amyloid Deposition in Mice via BACE1-Antisense Activation	2017	Zhao et al.	10.1111/CNS.12667	Review
Neurologic Diseases and Sleep	2017	Barone et al.	10.1016/J.JSMC.2016.10.007	Review
Is Sleep Disruption a Risk Factor for Alzheimer's Disease?	2017	MacEdo, Arthur Cassa Balouch, Sara Tabet, Naji	10.3233/JAD-161287	Narrative Review
Sleep deprivation accelerates the progression of alzheimer's disease by influencing Aβ-related metabolism	2017	Chen et al.	10.1016/J.NEULET.2017.04.047	Unspecified Experiment
Poor sleep is associated with CSF biomarkers of amyloid pathology in cognitively normal adults	2017	Sprecher et al.	10.1212/WNL.00000000000004171	Unspecified Experiment
Does sleep disturbance affect	2017	Yulug, Burak Hanoglu, Lutfu	10.1111/PCN.12539	Mini Review

the amyloid clearance mechanisms in Alzheimer's disease?

Kilic, Ertugrul

Circadian Disruption Associated with Alzheimer's Disease	2017	Saeed, Yumna Abbott, Sabra M.	10.1007/S11910-017-0745-Y	Review
Sleep deprivation and cerebrospinal fluid biomarkers for Alzheimer's disease	2018	Olsson et al.	10.1093/SLEEP/ZSY025	Randomised Crossover Study
The Emerging Relationship Between Interstitial Fluid–Cerebrospinal Fluid Exchange, Amyloid-β and Sleep	2018	Boespflug, Erin L. Iliff, Jeffrey J.	10.1016/J.BIOPSYCH.2017.11.031	Review
Integrating Sleep and Alzheimer's Disease Pathophysiology: Hints for Sleep Disorders Management	2018	Proserpio et al.	10.3233/JAD-180041	Review
New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation	2018	Zisapel, Nava	10.1111/BPH.14116	Unspecified Experiment
Obstructive sleep apnoea and Alzheimer's disease: In search of shared pathomechanisms	2018	Polsek et al.	10.1016/J.NEUBIOREV.2017.12.004	Review
Alzheimer's disease and sleep–wake disturbances:	2018	Vanderhyden et al.	10.1523/JNEUROSCI.1135-17.2017	Review

Amyloid, astrocytes, and animal models

β-Amyloid accumulation in the human brain after one night of sleep deprivation	2018	Shokri-Kojori et al.	10.1073/PNAS.1721694115	Unspecified Experiment
Effect of sleep on overnight cerebrospinal fluid amyloid β kinetics	2018	Lucey et al.	10.1002/ANA.25117	Unspecified Experiment
Risk of Alzheimer's disease in obstructive sleep apnea syndrome: Amyloid-β and tau imaging	2018	Elias et al.	10.3233/JAD-180640	Unspecified Experiment
Disturbed sleep and diabetes: A potential nexus of dementia risk	2018	Hollingue et al.	10.1016/J.METABOL.2018.01.021	Review
Biomarkers of dementia in obstructive sleep apnea	2018	Baril et al.	10.1016/J.SMRV.2018.08.001	Review
Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis	2018	Shi et al.	10.1016/J.SMRV.2017.06.010	Systematic Review and Meta-Analysis
Low-grade inflammation in the relationship between sleep disruption, dysfunctional adiposity, and cognitive decline in aging	2018	Atienza, Mercedes Ziontz, Jacob Cantero, Jose L.	10.1016/J.SMRV.2018.08.002	Review

Genetic variation in Aquaporin-4 moderates the relationship between sleep and brain Aβ-Amyloid burden	2018	Rainey-Smith et al.	10.1038/S41398-018-0094-X	Cross-sectional Observation Study
Sleep and β-Amyloid Deposition in Alzheimer Disease: Insights on Mechanisms and Possible Innovative Treatments	2019	Susanna Annarumma, Ludovica Rossini, Paolo Maria De Gennaro, Luigi	10.3389/FPHAR.2019.00695	Review
Prevalence and risk of progression of preclinical Alzheimer's disease stages: A systematic review and meta-analysis	2019	Parnetti et al.	10.1186/S13195-018-0459-7	Systematic Review with Meta-Analysis
Beyond the sleep-amyloid interactions in alzheimer's disease pathogenesis	2019	Ning, Shen Jorfi, Mehdi	10.1152/JN.00118.2019	Review
A longitudinal study of polysomnographic variables in patients with mild cognitive impairment converting to Alzheimer's disease	2019	Carnicelli et al.	10.1111/JSR.12821	Unspecified Experiment
Delayed daily activity and reduced NREM slow-wave power in the APP^{swe}/PS1^{dE9} mouse model of Alzheimer's disease	2019	Kent et al.	10.1016/J.NEUROBIOLA GING.2019.01.010	Unspecified Experiment

Naturalistic Measurement of Sleep in Older Adults with Amnestic Mild Cognitive Impairment: Anxiety Symptoms Do Not Explain Sleep Disturbance	2019	Cavuoto et al.	10.2174/1567205016666190301104645	Unspecified Experiment
Obstructive sleep apnea may induce orexinergic system and cerebral β-amyloid metabolism dysregulation: is it a further proof for Alzheimer's disease risk?	2019	Ligouri et al.	10.1016/J.SLEEP.2019.01.003	Randomised Controlled Trial
Association between circadian rhythms and neurodegenerative diseases	2019	Leng et al.	10.1016/S1474-4422(18)30461-7	Review
Sleep disorders and cognitive alterations in women	2019	Guarnieri, B.	10.1016/J.MATURITAS.2019.04.214	Mini review
Cardiorespiratory fitness modifies influence of sleep problems on cerebrospinal fluid biomarkers in an at-risk cohort	2019	Law et al.	10.3233/JAD-180291	Unspecified et al.
Sleep-wake regulation and the hallmarks of the pathogenesis of Alzheimer's disease	2019	Van Egroo et al.	10.1093/SLEEP/ZSZ017	Review
CPAP Adherence May Slow 1-Year	2019	Richards et al.	10.1111/JGS.15758	Unspecified Experiment

Cognitive Decline in Older Adults with Mild Cognitive Impairment and Apnea

The role of sleep deprivation and circadian rhythm disruption as risk factors of Alzheimer's disease 2019 Wu et al. 10.1016/J.YFRNE.2019.100764 Review

Alzheimer's disease: Neurotransmitters of the sleep-wake cycle 2019 Van Erum, Jan
Van Dam, D.
De Deyn, Peter Paul 10.1016/J.NEUBIOREV.2019.07.019 Review

The Interaction Between Sleep and Metabolism in Alzheimer's Disease: Cause or Consequence of Disease? 2019 Carroll, Caitlin M.
Macauley, Shannon L. 10.3389/FNAGI.2019.00258 Review

Relationships between objectives sleep parameters and brain amyloid load in subjects at risk for Alzheimer's disease: The INSIGHT-preAD Study 2019 Ettore et al. 10.1093/SLEEP/ZSZ137 Unspecified Experiment

Obstructive sleep apnea treatment, slow wave activity, and amyloid- β 2019 Ju et al. 10.1002/ANA.25408 Longitudinal Study

Alteration in sleep architecture and electroencephalogram as an early sign of Alzheimer's disease preceding the 2019 Zhang et al. 10.1016/J.JALZ.2018.12.004 Unspecified Experiment

**disease pathology
and cognitive
decline**

Obstructive sleep apnea and longitudinal Alzheimer's disease biomarker changes 2019 Bubu et al. 10.1093/SLEEP/ZSZ048 Longitudinal Study

Sleep as a Therapeutic Target in the Aging Brain 2019 Bah, Thierno M. Goodman, James Iliff, Jeffrey J. 10.1007/S13311-019-00769-6 Review

Sleep as a potential biomarker of tau and -amyloid burden in the human brain 2019 Winer et al. 10.1523/JNEUROSCI.0503-19.2019 Unspecified Experiment

Sleep disturbance as a potential modifiable risk factor for alzheimer's disease 2019 Minakawa et al. 10.3390/IJMS20040803 Review

Associations between quantitative sleep EEG and subsequent cognitive decline in older women 2019 Djonlagic et al. 10.1111/JSR.12666 Nested Case Control

Alzheimer's disease pathogenesis: The role of disturbed sleep in attenuated brain plasticity and neurodegenerative processes 2019 Havekes et al. 10.1016/J.CELLSIG.2019.109420 Review

Corticothalamic network dysfunction and Alzheimer's disease 2019 Jagirdar, Rohan Chin, Jeannie 10.1016/J.BRAINRES.2017.09.014 Review

Sleep experiences during different lifetime periods and in vivo Alzheimer pathologies	2019	Choe et al.	10.1186/S13195-019-0536-6	Unspecif Experiment
Implications of sleep disturbance and inflammation for Alzheimer's disease dementia	2019	Irwin, Michael R. Vitiello, Michael V.	10.1016/S1474-4422(18)30450-2	Review
Alzheimer's disease and sleep disturbances: a review	2019	Borges et al.	10.1590/0004-282X20190149	Review
Bidirectional relationships between sleep and amyloid-beta in the hippocampus	2019	Dufort-Gervais, Julien Mongrain, Valérie Brouillette, Jonathan	10.1016/J.NLM.2018.06.009	Review
Association of β-Amyloid Burden with Sleep Dysfunction and Cognitive Impairment in Elderly Individuals with Cognitive Disorders	2019	You et al.	10.1001/JAMANETWORKOPEN.2019.13383	Nested Survey
Sleep Deprivation and Neurological Disorders	2020	Bishir et al.	10.1155/2020/5764017	Review
The effect of insomnia on development of Alzheimer's disease	2020	Sadeghmousavi et al.	10.1186/S12974-020-01960-9	Review
Sleep Deprivation Affects Tau Phosphorylation in Human Cerebrospinal Fluid	2020	Barthélemy et al.	10.1002/ANA.25702	Unspecified Experiment

Sleep is bi-directionally modified by amyloid beta oligomers	2020	Özcan et al.	10.7554/ELIFE.53995	Unspecified Experiment
Chronic sleep fragmentation shares similar pathogenesis with neurodegenerative diseases: Endosome-autophagosome-lysosome pathway dysfunction and microglia-mediated neuroinflammation	2020	Xie et al.	10.1111/CNS.13218	Unspecified Experiment
Therapeutic effects of CPAP on cognitive impairments associated with OSA	2020	Wae et al.	10.1007/S00415-019-09381-2	Systematic Review
Local Sleep and Alzheimer's Disease Pathophysiology.	2020	Mander, Bryce A	10.3389/fnins.2020.525970	Review
Spontaneous K-Complexes may be biomarkers of the progression of amnesic mild cognitive impairment	2020	Liu et al.	10.1016/J.SLEEP.2019.10.015	Clinical trial
Sleep and diurnal rest-activity rhythm disturbances in a mouse model of Alzheimer's disease	2020	Filon et al.	10.1093/SLEEP/ZSAA087	Unspecified Experiment
Rapid Eye Movement Sleep Behavior Disorder and	2020	Zhang et al.	10.14336/AD.2019.0324	Review

Neurodegenerative Diseases: An Update

Cognitive behavioral therapy for insomnia to enhance cognitive function and reduce the rate of Aβ deposition in older adults with symptoms of insomnia: A single-site randomized pilot clinical trial protocol	2020	Siengsukon et al.	10.1016/J.CCT.2020.106190	Clinical trial protocol
Sleep dysregulation, memory impairment, and CSF biomarkers during different levels of neurocognitive functioning in Alzheimer's disease course	2020	Ligouri et al.	10.1186/S13195-019-0571-3	Non-Randomised Controlled Trial
Progressive changes in sleep and its relations to amyloid-β distribution and learning in single app knock-in mice	2020	Maezono et al.	10.1523/ENEURO.0093-20.2020	Unspecified Experiment
Mathematical Model Shows How Sleep May Affect Amyloid-β Fibrillization	2020	Hoore et al.	10.1016/J.BPJ.2020.07.011	Unspecified Experiment
Bidirectional relationship between sleep and Alzheimer's disease:	2020	Wang, Chanung Holtzman, David M.	10.1038/S41386-019-0478-5	Review

**role of amyloid, tau,
and other factors**

The sleeping brain: Harnessing the power of the glymphatic system through lifestyle choices	2020	Reddy, Oliver Cameron van der Werf, Ysbrand D.	10.3390/BRAINSCI10110868	Review
Is sleep disruption a cause or consequence of alzheimer's disease? Reviewing its possible role as a biomarker	2020	Lloret et al.	10.3390/IJMS21031168	Review
Sleep spindle abnormalities related to Alzheimer's disease: a systematic mini-review	2020	Weng, Yuan Yuan Lei, Xu Yu, Jing	10.1016/J.SLEEP.2020.07.044	Review
Sleep as a novel biomarker and a promising therapeutic target for cerebral small vessel disease: A review focusing on alzheimer's disease and the blood-brain barrier	2020	Semyachkina-Glushkovskaya et al.	10.3390/IJMS21176293	Review
Impaired Hippocampal-Cortical Interactions during Sleep in a Mouse Model of Alzheimer's Disease	2020	Benthem et al.	10.1016/J.CUB.2020.04.087	Unspecified Experiment
The wrinkling of time: Aging, inflammation, oxidative stress, and	2020	Lananna, Brian V. Musiek, Erik S.	10.1016/J.NBD.2020.10.4832	Review

**the circadian clock
in
neurodegeneration**

Sleep, Noninvasive Brain Stimulation, and the Aging Brain: Challenges and Opportunities	2020	Romanella et al.	10.1016/J.ARR.2020.101067	Review
Circadian and sleep dysfunction in Alzheimer's disease	2020	Uddin et al.	10.1016/J.ARR.2020.101046	Review
Candidate mechanisms linking insomnia disorder to Alzheimer's disease risk	2020	Chappel-Farley et al.	10.1016/J.COBEHA.2020.01.010	Review
Slow Wave Sleep Is a Promising Intervention Target for Alzheimer's Disease.	2020	Lee et al.	10.3389/fnins.2020.00705	Review
Effects of acute sleep loss on diurnal plasma dynamics of CNS health biomarkers in young men	2020	Benedict et al.	10.1212/WNL.00000000000088662	Condition crossover study
Interacting influences of aging and Alzheimer's disease on circadian rhythms	2020	Duncan, Marilyn J.	10.1111/EJN.14358	Review
Obstructive Sleep Apnea and Its Treatment in Aging: Effects on Alzheimer's disease Biomarkers, Cognition, Brain	2020	Mullins et al.	10.1016/J.NBD.2020.105054	Review

Structure and Neurophysiology

Feasibility of Using a Wearable Biosensor Device in Patients at Risk for Alzheimer's Disease Dementia 2020 Saif et al. 10.14283/JPAD.2019.39 Unspecified Experiment

Obstructive sleep apnea, cognition and Alzheimer's disease: A systematic review integrating three decades of multidisciplinary research 2020 Bubu et al. 10.1016/J.SMRV.2019.101250 Systematic Review

Sleep spindles, K-complexes, limb movements and sleep stage proportions may be biomarkers for amnesic mild cognitive impairment and Alzheimer's disease 2020 Liu et al. 10.1007/S11325-019-01970-9 Clinical trial

It's complicated: The relationship between sleep and Alzheimer's disease in humans 2020 Lucey, Brendan P. 10.1016/J.NBD.2020.105031 Review

CCCDT5 recommendations on early non cognitive markers of dementia: A Canadian consensus Manuel 2020 Montero-Odasso et al. 10.1002/TRC2.12068 Review

Self-reported Sleep Problems Related to Amyloid Deposition 2020 Fjeil et al. 10.1093/CERCOR/BHZ228 Unspecified Experiment

in Cortical Regions with High HOMER1 Gene Expression

Association of Sleep-Disordered Breathing with Alzheimer Disease Biomarkers in Community-Dwelling Older Adults: A Secondary Analysis of a Randomized Clinical Trial 2020 André et al. 10.1001/JAMANEUROL.2020.0311 Cross-sectional study

Sleep Disturbance Forecasts β -Amyloid Accumulation across Subsequent Years 2020 Winer et al. 10.1016/J.CUB.2020.08.017 Unspecified Experiment

The role of slow wave sleep in the development of dementia and its potential for preventative interventions 2020 Wunderlin et al. 10.1016/J.PSCYCHRESN.S.2020.111178 Review

Modifiable Risk Factors Associated with Alzheimer’s Disease with Special Reference to Sleep Disturbance 2021 Chauhan et al. 10.2174/187152732066210319111852 Review

Biomarkers of Alzheimer’s disease in severe obstructive sleep apnea–hypopnea syndrome in the Chinese population 2021 Kong et al. 10.1007/S00405-020-05948-2 Review

Brain changes associated with 2021 André, Claire Laniepce, Alice 10.1016/J.ARR.2020.10.1252 Review

sleep disruption in cognitively unimpaired older adults: A short review of neuroimaging studies			Chételat, Gaël Rauchs, Géraldine		
Obstructive sleep apnea and Alzheimer's disease-related cerebrospinal fluid biomarkers in mild cognitive impairment	2021		Díaz-Román	10.1093/SLEEP/ZSAA13 3	Unspecified Experiment
Sleep and its regulation: An emerging pathogenic and treatment frontier in Alzheimer's disease	2021		Kent, Brianne A. Feldman, Howard H. Nygaard, Haakon B.	10.1016/J.PNEUROBIO. 2020.101902	Review
Dysregulation of the orexin/hypocretin system is not limited to narcolepsy but has far-reaching implications for neurological disorders	2021		Berteotti, Chiara Liguori, Claudio Pace, Marta	10.1111/EJN.15077	Review
The Sleep Side of Aging and Alzheimer's Disease	2021		Romanella et al.	10.1016/J.SLEEP.2020.0 5.029	Review
Insomnia Moderates the Relationship between Amyloid-β and Cognitive Decline in Late-Life	2021		Xu, Wei Tan, Chen Chen Zou, Juan Juan Cao, Xi Peng Tan, Lan	10.3233/JAD-201582	Unspecified Experiment

Adults without Dementia

Is the glymphatic system the missing link between sleep impairments and neurological disorders? Examining the implications and uncertainties	2021	Christensen et al.	10.1016/J.PNEUROBIO.2020.101917	Review
Sleep-disordered breathing and the risk of Alzheimer's disease	2021	Ligouri et al.	10.1016/J.SMRV.2020.101375	Review
Empirically defining the preclinical stages of the Alzheimer's continuum in the Alzheimer's Disease Neuroimaging Initiative	2021	Kiselica, Andrew M.	10.1111/PSYG.12697	Unspecified Experiment
Sleep, circadian rhythm and gut microbiota: alterations in Alzheimer's disease and their potential links in the pathogenesis	2021	Li et al.	10.1080/19490976.2021.1957407	Review
Sleep-based interventions in Alzheimer's disease: Promising approaches from prevention to treatment along the disease trajectory	2021	Cordone et al.	10.3390/PH14040383	Review
The role of orexin in Alzheimer disease:	2021	Gao, Fan Liu, Tao	10.1016/J.NEULET.2021.136247	Review

From sleep-wake disturbance to therapeutic target

Tuo, Miao
Chi, Song

Is disrupted sleep a risk factor for Alzheimer's disease? Evidence from a two-sample Mendelian randomization analysis	2021	Anderson et al.	10.1093/IJE/DYAA183	Mendelian randomisation
Sleep/wake cycle alterations as a cause of neurodegenerative diseases: A Mendelian randomization study	2021	Cullel et al.	10.1016/J.NEUROBIOLA GING.2021.05.008	Mendelian randomisation
Decoding Causal Links Between Sleep Apnea and Alzheimer's Disease	2021	Ferini-Strambi, Luigi Hensley, Michael Salsone, Maria	10.3233/JAD-201066	Narrative review
Severe Obstructive Sleep Apnea and Increased Cortical Amyloid-β Deposition	2021	Ylä-Herttuala et al.	10.3233/JAD-200736	Review
Alzheimer's disease genetic risk and sleep phenotypes in healthy young men: Association with more slow waves and daytime sleepiness	2021	Muto et al.	10.1093/SLEEP/ZSAA137	Unspecified Experiment
Sleep, neuronal hyperexcitability, inflammation and neurodegeneration:	2021	Ahnaou, A. Drinkenburg, W. H.I.M.	10.1016/J.NEUBIOREV. 2021.06.039	Review

Does early chronic short sleep trigger and is it the key to overcoming Alzheimer's disease?

Sleep and longitudinal cognitive performance in preclinical and early symptomatic Alzheimer's disease	2021	Lucey et al.	10.1093/brain/awab272	Clinical trial
Association between Sleep, Alzheimer's, and Parkinson's Disease.	2021	Matsumoto, Sumire Tsunematsu, Tomomi	10.3390/biology10111127	Review
Altered Biological Rhythm and Alzheimer's Disease: A Bidirectional Relationship.	2021	Wang et al.	10.2174/1567205018666211124104710	Review
Sleep deficits in mild cognitive impairment are related to increased levels of plasma amyloid-β and cortical thinning	2021	Sanchez-Espinosa, Mayely P. Atienza, Mercedes Cantero, Jose L.	10.1016/J.NEUROIMAG E.2014.05.027	Unspecified Experiment

Appendix B: PRISMA-ScR Checklist (94).

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	49
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	50
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	50
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualise the review questions and/or objectives.	50
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	51-54
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	53
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	51
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	117
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	21
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	51
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	117
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A

Synthesis of results	13	Describe the methods of handling and summarising the data that were charted.	53-54
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	55
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Appendix A
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Appendix A
Synthesis of results	18	Summarise and/or present the charting results as they relate to the review questions and objectives.	55-69
DISCUSSION			
Summary of evidence	19	Summarise the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	69-78
Limitations	20	Discuss the limitations of the scoping review process.	77
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	77-78
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	49

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley^[23] and Levac et al.^[28] and the JBI guidance^[246] refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

Appendix C: Cooper's Checklist for Scoping Reviews (95).

Key Criteria	Checklist Items	Score one point for each item
1. Study aim, purpose, and research question	1. The rationale/purpose for the scoping review was stated.	1
	2. Appropriate scoping review methodology was used.	1
	3. At least two reviewers conducted the review.	1
	4. The research question/s was/were used to guide the scope of inquiry (Participants, concept, and context included ^a).	1
2. Relevant studies	5. An in-depth literature search was conducted to identify all relevant literature. ^b	1
	6. A comprehensive list of relevant studies that balances breadth with feasibility was identified.	1
3. Study selection	7. The inclusion and exclusion criteria were clearly described and were used to determine eligibility of studies.	1
	8. The study selection involved an iterative process, including searching the literature, refining the search strategy, and reviewing articles for inclusion.	1
	9. At least two reviewers independently reviewed the title and abstracts and reached consensus on studies for inclusion.	1
	10. The study selection process was summarised in a flow chart.	1
4. Charting the data	11. The research team collectively developed a data charting format and determined which variables to extract to answer the research question.	1
	12. The data were charted through sifting and sorting; tables include study details based on full-texts.	1
	13. A numerical analysis of the extent and nature of included studies was reported.	1
	14. The quality of papers was assessed. ^c	-
5. Collating, summarising, and reporting the results	15. Results were presented in a logical descriptive or diagrammatic or tabular format.	1
	16. A narrative account of results was presented.	1
	17. The results were aligned with the review aim, purpose/research question/s.	1
	18. Issues associated with bias were discussed.	1
	19. Implications for future research, education, practice, and/or policy were discussed.	1
	20. The conclusion described the current state of the overall literature in relation to the topic.	1
	Total	19/20
6. Optional stage: consultation	Stakeholder/participant voices were included in the review when appropriate.	
	If included:	
	21. The process of stakeholder consultation was clearly described.	-
	22. Findings were re-examined in the light of stakeholder input, to justify final conclusions.	-
	Total	19/22
Additional Guidance	Additional guidance: a. Item 4: Scoping reviews have a broad scope with even broader inclusion criteria, so participants may be selected from a wide group. The concept (area of interest/condition being explored, etc.) will also have a wide remit and the context may be	

	<p>left open, for example, any health care setting in any region.</p> <p>b. Item 5: This should include searches of an adequate number of different sources (databases/electronic sources, research registers; reference lists/hand searches, etc.).</p> <p>c. Item 14: Paper quality should also include a check to ensure that reports have not been retracted.</p>	
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Appendix D: Methodological Tracking Document

Syntax 1: ((sleep disturbance) AND (amyloid beta) AND (Alzheimer's disease))
30/09/2021:

Ebsco: 112

PubMed: 185

ScienceDirect

Refinement:

Syntax changed to "sleep disturbance" AND "amyloid beta" AND "Alzheimer's disease"
Research articles, review articles, mini reviews, short communications, and 'other' included into uploaded results

Purpose:

To reduce the number of non-specific results in ScienceDirect

Outcome:

Number of non-specific results satisfactorily reduced

Results: 411

(Year range of 2001-2021 applied to all databases)

All uploaded to New ALL FILES ALL SYNTAXES FOLDER

Syntax 2: ((Preclinical Alzheimer's disease) AND (definition))
30/09/2021:

Ebsco: 35

PubMed: 150

ScienceDirect

Refinement:

Syntax changed to "preclinical Alzheimer's disease" AND "definition"
Research articles, review articles, mini reviews, short communications, and 'other' included into uploaded results

Purpose:

To reduce the number of non-specific results in ScienceDirect

Outcome:

Number of non-specific results satisfactorily reduced

Results: 174

(Year range of 2001-2021 applied to all databases)

All uploaded to New ALL FILES ALL SYNTAXES FOLDER

Syntax 3: ((sleep disturbance) AND (Alzheimer's disease)) AND (Biomarker)
30/09/2021:

Ebsco: 84

PubMed: 102

ScienceDirect

Refinement:

Syntax changed to "Sleep disturbance" AND "Alzheimer's disease" AND "biomarker"
Research articles, review articles, mini reviews, short communications, and 'other' included into uploaded results

Purpose:

To reduce the number of non-specific results in ScienceDirect

Outcome:

Number of non-specific results satisfactorily reduced

Results: 779

(Year range of 2001-2021 applied to all databases)

All uploaded to New ALL FILES ALL SYNTAXES FOLDER

Syntax 3 VERSION 2: ((sleep disruption) AND (Alzheimer's disease)) AND (biomarker)
(1/10/2021)

PubMed: 33

Ebsco: 42

ScienceDirect

Refinement:

Syntax changed to "Sleep disruption" AND "Alzheimer's disease" AND "biomarker"
Research articles, review articles, mini reviews, short communications, and 'other' included into uploaded results

Purpose:

To reduce the number of non-specific results in ScienceDirect

Outcome:

Number of non-specific results satisfactorily reduced

Results: 181

(Year range of 2001-2021 applied to all databases)

All uploaded to New ALL FILES ALL SYNTAXES FOLDER

Syntax 4: (sleep disturbance) AND (preclinical Alzheimer's disease)
(30/09/2021)

PubMed: 45

Ebsco: 21

ScienceDirect

Refinement:

Syntax changed to "sleep disturbance" AND "preclinical Alzheimer's disease"
Research articles, review articles, mini reviews, short communications, and 'other' included into uploaded results

Purpose:

To reduce the number of non-specific results in ScienceDirect

Outcome:

Number of non-specific results satisfactorily reduced

Results: 32
(Year range of 2001-2021 applied to all databases)
All uploaded to New ALL FILES ALL SYNTAXES FOLDER

Syntax 4: (VERSION 2) (sleep disruption) AND (preclinical Alzheimer's disease)
(30/10/2021)

PubMed: 22
Ebsco: 2

ScienceDirect

Refinement:

Syntax changed to "sleep disruption" AND "preclinical Alzheimer's disease"
Research articles, review articles, mini reviews, short communications, and 'other' included into uploaded results

Purpose:

To reduce the number of non-specific results in ScienceDirect

Outcome:

Number of non-specific results satisfactorily reduced

Results: 14

(Year range of 2001-2021 applied to all databases)

All uploaded to New ALL FILES ALL SYNTAXES FOLDER

Syntax 5: "sleep disruption" AND "Alzheimer's disease"
(30/09/2021)

Ebsco: 325

PubMed: 311

ScienceDirect

Refinement:

Syntax changed to "sleep disruption" AND "Alzheimer's disease"
Research articles, review articles, mini reviews, short communications, and 'other' included into uploaded results

Purpose:

To reduce the number of non-specific results in ScienceDirect

Outcome:

Number of non-specific results satisfactorily reduced

Results: 614

(Year range of 2001-2021 applied to all databases)

Syntax 6: "Sleep patterns" AND "preclinical Alzheimer's disease" / (sleep patterns) AND (preclinical Alzheimer's disease)
(01/10/2021)

Ebsco: 4

PubMed: 48

ScienceDirect

Refinement:

Syntax changed to “sleep patterns” AND “preclinical Alzheimer’s disease”

Research articles, review articles, mini reviews, short communications, and ‘other’ included into uploaded results

Purpose:

To reduce the number of non-specific results in ScienceDirect

Outcome:

Number of non-specific results satisfactorily reduced

Results: 9

(Year range of 2001-2021 applied to all databases)

Total of ALL SYNTAX results prior to duplicate removal:

(1/10/2021): 2821 (515 sets of duplicates found)

Total of ALL SYNTAX results after duplicate removal:

(1/10/2021): 1612

“Eyeball” screen criteria: 25/08/2021

Title must contain a combination of major keywords pertaining to the topic of research (sleep/sleep disturbance AND Alzheimer’s disease, or other similar and related phrasing referring to links between sleep and Alzheimer’s disease or the preclinical phase of Alzheimer’s disease).

If this is not found in the title, the abstract should contain reference to parts of the article which relate specifically to the research question and/or inclusion criteria of the research project.

Purpose: To create an objective method of quickly screening out irrelevant studies generated by the search syntaxes in a manner that can explain their omission from the research as well as document the percentage removed by eyeball screen in order to test specificity of syntaxes used.

Outcome: As above

Start number of studies prior to eyeball screen: 1612

Remaining after screen: 356

2/11/2021:

Action: Added word 'development' to end of objective 1 in proposal

Purpose: To clarify intention of research to review studies describing potential utility of sleep to be used as a diagnostic biomarker of Alzheimer's disease, rather than reviewing the sleep disturbances arising as a RESULT OF Alzheimer's.

Outcome: Intention of research clarified and aims, and objectives met by highlighting difference between the two types of sleep disturbances

2/11/2021:

Action: Added 5th exclusion criteria to research

Purpose: To solidify the above point and justify exclusion of articles relating to AD's effect on sleep which does not meet the aims & objectives of this research.

Outcome: Justification of exclusion of articles on known and diagnosed AD and AD's effect on sleep which do not meet aims & objectives of intended research.

14 & 16/11/2021: Piloting of studies

Piloting of selected studies performed by primary and associate supervisors SS and SA.

A total of 35 studies were selected, out of which 7 required discussion, upon which consensus was achieved with %100 of the piloted studies.

4/12/2021:

Action: New sheet in study selection folder (a copy of which is uploaded in methods section of google drive) titled **INC STUDIES** was formed.

Purpose: To document only studies that will be included in scoping review, not those that may be used in the initial literature review, those will be found in **Studies passed eyeball** sheet in same excel folder.

Also, to delineate between studies removed due to lack of suitability to research aims, objectives and inclusion criteria

Also, to identify number of studies ruled out by exclusion.

Outcome: Successful delineation between studies to be included in scoping review and those unsuitable for inclusion into scoping review.

Saturation points re-search of all syntaxes all databases

7/12/2021

Action: A search with all original syntaxes and databases was performed

Purpose: To ascertain if any new and relevant research was published between 30/10/2021 and 7/12/2021. If such is the case, the relevant research identified by the syntax searches will be screened in the same manner as prior studies identified by those same syntaxes

Outcome: *All refinements for ScienceDirect database were maintained as in original searches.

33 Studies identified and imported to Mendeley to assess for further inclusion/exclusion factors.

Syntax 1: ((sleep disturbance) AND (amyloid beta)) AND (Alzheimer's disease)

PubMed: 4

Ebsco: 3

ScienceDirect: 3

Syntax 2: ((Preclinical Alzheimer's disease) AND (definition))

PubMed: 3

Ebsco: 0

ScienceDirect: 0

Syntax 3: ((sleep disturbance) AND (Alzheimer's disease)) AND (Biomarker)

PubMed: 3

Ebsco: 4

ScienceDirect: 6

Syntax 3 VERSION 2: ((sleep disruption) AND (Alzheimer's disease)) AND (biomarker)

PubMed: 0

Ebsco: 0

ScienceDirect:

Syntax 4: (sleep disturbance) AND (preclinical Alzheimer's disease)

PubMed: 0

Ebsco: 0

ScienceDirect: 0

Syntax 4: (VERSION 2) (sleep disruption) AND (preclinical Alzheimer's disease)

PubMed: 0

Ebsco: 0

ScienceDirect: 0

Syntax 5: "sleep disruption" AND "Alzheimer's disease"

PubMed: 4

Ebsco: 3

ScienceDirect: 3

Syntax 6: (sleep patterns) AND (preclinical Alzheimer's disease)

PubMed: 0

Ebsco: 0

ScienceDirect: 0

Saturation point article inclusion/exclusion

28/2/22

Action: 33 articles found using original search syntaxes performed on 7th December 2021, screened as follows:

28 removed by eyeball screen

2 were removed after further reading, as they did not meet research aims & objectives.

3 out of the saturation point search were included into the scoping review.

Final number of articles:

After all syntaxes were searched, including the saturation search performed on 7th Dec 2021, and all articles were eyeball screened and sieved through inclusion/exclusion criteria, the final number of articles to be included within this scoping review is 199.

14/2/22: Inclusion criteria adjustment.

Action:

Discussion with supervisors resulted in decision to limit research to 10 years only, due to feasibility constraints of a 90-credit thesis.

Purpose: Reduce number of articles included in research

Outcome: 11 articles removed from publication dates from 2001-2010. 2011 & onwards included.

22/2/22: Inclusion criteria adjustment reversal.

Action: Reverse above decision to remove 10 years of research

Purpose: To reinstate articles removed back into research piece to broaden research time frame, as 11 articles will not significantly impact feasibility of 90 credit thesis.

Outcome: articles removed 14/2/22 have been re-included in research and will form part of scoping review

18/03/2022: Emailed Dipti Vora to request access to articles where full text was not available.

Action: Request article access

Purpose: to gain full access to articles identified by search

Outcome: Articles successfully accessed and screened through inclusion/exclusion criteria

Appendix E: Ethics Exemption Letter



Tuesday 18th May 2021

To whom it may concern,

Re: *Lucas Baxter*

This is a letter to advise that Lucas Baxter's thesis does not require approval from the Unitec Research Ethics Committee.

Should you have any questions regarding this matter, please email ethics@unitec.ac.nz

Nga mihi,

A handwritten signature in blue ink, appearing to be 'Asher Lewis', positioned above a dotted line.

Asher Lewis
UREC Secretary, Tuapapa Rangahau; Partnering Research and
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New Zealand

Northern campus
10 Rothwell Ave
North Harbour
Auckland 0632
New Zealand

Waitakere campus
5-7 Ratanui St
Henderson
Auckland 0612
New Zealand

Appendix F: Preliminary Search Strategy

Date	Search engine	Syntax	Number of results
14/06/2021	PubMed Ebsco Scopus	"Alzheimer's disease" AND "sleep disturbance"	1202 1164 7788
14/06/2021	PubMed Ebsco Scopus	"Alzheimer's disease" AND "sleep disruption"	322 310 1750
14/06/2021	PubMed Ebsco Scopus	"Alzheimer's disease" OR "preclinical Alzheimer's disease" AND "sleep disturbance" OR define	218277 838417 25620
15/06/2021	PubMed Ebsco Scopus	"Sleep disturbance" AND "preclinical Alzheimer's disease"	6 9 2323
16/06/2021	PubMed Ebsco Scopus	"Sleep disturbance" AND "Amyloid beta pathology" OR "Tau pathology"	2885 7478 385
16/06/2021	PubMed Ebsco Scopus	"Preclinical Alzheimer's disease" AND "Define"	15 74 607
16/06/2021	Pubed Ebsco Scopus	"Sleep as a biomarker for AD"	248 54 0