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Sleep, Cerebrospinal Fluid, and the Glymphatic System: A Systematic Review

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Summary

Current theories of the glymphatic system (GS) hypothesize that it relies on cerebrospinal fluid (CSF) circulation to disseminate growth factors and remove metabolic waste from the brain with increased CSF production and circulation during sleep; thereby, linking sleep disturbance with elements of CSF circulation and GS exchange. However, our growing knowledge of the relations between sleep, CSF, and the GS are plagued by variability in sleep and CSF measures across a wide array of pathologies. Hence, this review aims to summarize the dynamic relationships between sleep, CSF-, and GS-related features in samples of typically developing individuals and those with autoimmune/inflammatory, neurodegenerative, neurodevelopmental, sleep-related, neurotraumatic, neuropsychiatric, and skull atypicalities. One hundred and ninety articles (total n = 19,129 participants) were identified and reviewed for pathology, CSF circulation and related metrics, GS function, and sleep. Numerous associations were documented between sleep problems and CSF metabolite concentrations (e.g., amyloid-beta, orexin, tau proteins) and increased CSF volumes or pressure. However, these relations were not universal, with marked differences across pathologies. It is clear that elements of CSF circulation/composition and GS exchange represent pathways influenced by sleep; however, carefully designed studies and advances in GS measurement are needed to delineate the nuanced relationships.

Keywords

sleep; glymphatic system; cerebrospinal fluid; neuropathology; typical population

Sleep, Cerebrospinal Fluid, and the Glymphatic System

Coined by Iliff and Nedergaard in 2012, the glymphatic system maintains cerebral homeostasis by circulating cerebrospinal fluid (CSF) through the brain via perivascular

pathways that facilitate solute exchange between CSF and the interstitial fluid, thus clearing neuronal metabolites from the brain parenchyma [1-3]. Current evidence suggests that the glymphatic system is a CSF circulation pathway responsible for immune surveillance and metabolic waste clearance; thereby, implying that CSF circulation is a conduit that links the central nervous and immune systems [4]. Across areas of study, terms for CSF circulation/dynamics and glymphatic system exchange/function are often used interchangeably but reflect inter-related but distinct processes. Furthermore, given that the glymphatic system is a relatively new system of inquiry, its definitions and structures are emerging. Additionally, the modalities to capture these processes in humans are still being developed [5,6]. Hence, within the next sections, we will delineate CSF circulation/dynamics and glymphatic system exchange/function to provide an overarching organization for the forthcoming review.

CSF is continuously produced by the choroid plexus of the ventricles at a rate of 500 cm^3 a day, but the brain can only hold approximately 150 cm^3 at any given time [7]; therefore, efficient CSF absorption and turnover is crucial. CSF moves through the ventricular system into the cisterns and subarachnoid space and, among other pathways, is reabsorbed via the arachnoid villi and meningeal lymphatic vasculature [1,2]. CSF production and circulation are increased dramatically during sleep-wake and circadian cycles.

Glymphatic function refers to the movement of CSF from the subarachnoid compartments into perivascular spaces, with influx along the perivascular spaces surrounding the penetrating arteries throughout the brain parenchyma, which exchange with interstitial fluid [3]. The final efflux pathways are less understood but are believed to involve drainage of solutes along the perivenous spaces and meningeal lymphatic vessels [2]. This process is aquaporin 4 (AQP4) dependent and is modulated by sleep-wake and circadian cycles [8].

While glymphatic function relies on CSF circulation within the brain, other clearance systems for eliminating amyloid-beta across the blood-brain barrier and blood-CSF barrier have been suggested (e.g., blood-brain barrier and blood-CSF barrier) [9,10]. In other words, not all CSF circulation is related to the glymphatic system. For instance, CSF clearance by means of protein or solute transport across the blood-cerebrospinal fluid barrier is also facilitated by CSF. Though these are distinct processes, CSF circulation is inherent to the glymphatic system, and examining elements of CSF can contribute to our understanding of the glymphatic system. For consistency, throughout this review, the terms ‘CSF circulation’ and ‘glymphatic system exchange’ will be used to refer to these related but distinct processes (Figure 1).

CSF circulation in the ventricular system originates in the first few weeks of gestation [11] and circulates essential growth factors needed for progenitor cells to proliferate into immature neurons on the ventricular surface [12-15], thereby playing a driving force in early brain development and potentially having implications for neurodevelopmental disorders like Autism Spectrum Disorder (ASD) or Down Syndrome (DS). Later in life, CSF circulation may slow and/or glymphatic system exchange may slowly degrade; for this reason, adult and aging populations are commonly implicated when assessing CSF circulation or other glymphatic system exchange metrics. Additionally, given the elucidated role of the CSF circulation and glymphatic exchange in removing inflammatory byproducts

in animal models during sleep [11], studies of autoimmune and inflammatory disorders and sleep disorders are also common.

CSF circulation increases during sleep, with several studies documenting increased CSF influx and increased clearance of excess glutamate, lactate, amyloid-beta (Aβ), and other neuropeptides during sleep compared to wakefulness [16,17]. Increases in both CSF volume [18] and CSF circulation [19] have been reported during sleep compared to awake states. Similarly, sleep-wake variability is also observed in the glymphatic system. In a two-photon imaging study where glymphatic system function in mice was observed with fluorescent tracers, Xie and colleagues [20] reported an expansion greater than 60% in the interstitial space and the amount of CSF entering perivascular pathways when mice were sleeping compared to awake states, thus suggesting that a large interstitial space could reflect glymphatic system exchange. Findings have been replicated in humans wherein sleep was associated with greater glymphatic clearance compared to awake states [21] and a night of sleep deprivation [22].

Given that the glymphatic system represents an exchange of fluid and solutes between the CSF and interstitial compartments along the arterial perivascular spaces [2], it is clear that the glymphatic system function is a distinct process that is intricately linked to CSF circulation. Hence, exploring how CSF circulatory pathways are implicated during sleep states can serve as a building block towards understanding the glymphatic system. Therefore, this study aims to review and elucidate the dynamic relationships between sleep and elements of CSF circulation and glymphatic exchange. In light of the varying definitions and modalities to evaluate the glymphatic function, we will examine associations between sleep and metrics (both direct and indirect) of CSF circulation and glymphatic exchange in samples of typically developing individuals and those with autoimmune/inflammatory, neurodegenerative, neurodevelopmental, disordered sleep, neurotraumatic, neuropsychiatric, congenital skull and brain atypicalities, and other pathologies.

Methods

Search strategy

Using PRISMA guidelines [23], we conducted a systematic literature search for articles up to April 3rd, 2020, on the PubMed, Web of Science, and Psychlnfo databases. Keywords used to identify the studies were: *cerebrospinal fluid, CSF, glymphatic system*, and *sleep* (using the algorithms: “glymphatic system AND sleep”, “cerebrospinal fluid AND sleep”, and “CSF AND sleep”). Building on reviewer recommendations, in February of 2021, we expanded our original search to include the keywords *Virchow Robin* and *perivascular space* using the algorithms: “*Virchow Robin AND sleep*” and “*perivascular space AND sleep*”). For this addition, we retained the April 3rd, 2020, study cutoff for consistency. This study is registered in the Open Science Forum (DOI 10.17605/OSF.IO/CTBM6). This registration included a priori description of the systematic review project and all coded data.

Inclusion/Exclusion criteria

Studies were included for the review if they 1) were reported in English, 2) presented original data, 3) were published between 2010 and 2020, 4) used any of the following sleep measurements: physiological measurements, self-report questionnaires, standardized interviews, clinical diagnosis, 5) studied elements of CSF circulation and/or glymphatic exchange. Given the current flex of definitions and measures on the glymphatic system across fields [5], not all included studies are considered *bona fide* (e.g., true measurements of the glymphatic system). However, in the interest of building a comprehensive summary based on current available evidence, we included studies that evaluated key characteristics using both direct and indirect estimates of the glymphatic functions (see Figure 1 for an overview).

Studies were excluded if 1) they were not peer-reviewed (50.9%), 2) data were included in a larger/later published paper (4.0%), 3) they did not analyze sleep parameters with CSF or glymphatic system indices (30.4%). For more details, please refer to Figure 2.

Data Extraction

For each study, details on the number of participants, type of diagnoses, sociodemographic characteristics (i.e., age, gender), CSF metric, glymphatic system measure, and sleep parameters were extracted. Findings specific to the associations of sleep with CSF circulation and/or glymphatic exchange were also reported.

Results

Study Selection

A total of 2914 potential studies were identified. After eliminating 1593 duplications, the titles and abstracts of the remaining 1321 studies were coded (0 = exclude (with a why excluded code), 1 = full-text review recommended). The following were excluded: 136 animal model articles, 25 non-English articles, 576 were not empirical study manuscripts (131 abstracts or poster presentations, 106 opinions/letter to editors, 285 reviews, 41 books or book chapters, 1 correction, 2 protein sequences, and 10 patents), 120 studies did not include sleep measures, 149 studies did not include CSF circulation or glymphatic exchange measures, 4 articles with insufficient information, and 1 was not within the past decade. Inter-rater agreement (Cohen's Kappa) was calculated for full-text review code ($k = 0.89$). Disagreements on study inclusion ($n = 10$), such as studies recommended by only one coder, were reviewed further and discussed to achieve consensus. Lastly, authors were emailed for studies that appear to have overlapping samples. Forty-five studies were removed due to the use of overlapping samples. An additional 75 articles were removed after a full-text review for lack of sleep, CSF circulation, or glymphatic exchange measures. The supplemental search on perivascular space/Virchow Robin resulted in eight additional articles.

Types of Sleep Parameters

There were three main measures of sleep: physiological, self/parent-report questionnaires, and diagnostic history of a sleep disorder. Physiological measures included actigraphy,

videosomnography, electroencephalography, polysomnography, the Multiple Sleep Latency Test (MSLT), and CSF orexin levels (a diagnostic marker for narcolepsy).

There was a range of self/parent/clinician-report questionnaires such as the Pittsburgh Sleep Quality Index, Brief Infant Sleep Questionnaire, Child Sleep Habits Questionnaire, Child Behavior Checklist, Epworth Sleepiness Scale, Nordic Basic Sleep Questionnaire, Stanford Sleep Questionnaire, Insomnia Severity Index, and the use of a nightly sleep diary. There were also multiple diagnostic methods used, including clinical interviews with the use of the International Classification of Sleep Disorders-II and the sleep subscales within the Neuropsychiatric Inventory.

Types of CSF Circulation and Glymphatic Exchange Measures

For CSF circulation, three direct measures were used – (1) phase-contrast MRI to examine the velocity and volume of CSF movement in the 3rd and 4th ventricles, (2) computed tomography (CT) scans to index CSF leaks, and (3) lumbar punctures to index CSF pressure at the opening. For glymphatic exchange, two direct metrics, an indirect metric, as well as a metric that functions as both direct and indirect index, were used. The two direct metrics include dynamic positron emission tomography (PET) scans with radiotracers to capture tracer disbursement and movement and contrast-enhanced MRI to visualize CSF-ISF exchange [2]. The indirect glymphatic system exchange indices include structural/anatomical MRI and CT scans. These scans capture anatomical differences (e.g., enlarged perivascular space) that are hypothesized to reflect atypical glymphatic exchange. The last classification of measures reflects CSF compositions, which are collected via lumbar punctures – these metrics likely reflect a multitude of physiological/pathological processes and may reflect elements of CSF circulation and glymphatic exchange (Figure 1). The presence of or concentrations of the following in CSF are included in this review: hypocretin/orexin, amyloid-beta (Aβ), tau proteins (including p-tau and t-tau), cortisol, melatonin, c-reactive protein, interleukin (IL), antibodies (e.g., IgLON5), and white blood cell (WBC) counts. Blood-based metrics were not included. For consistency, orexin is used throughout this review when referring to hypocretin and orexin.

Pathologies

Studies were categorized according to the target population pathology (Figure 3). A total of 9 categories were identified. Of the 190 studies reviewed, 22 were identified as autoimmune and/or inflammation-related disorders, 48 neurodegenerative disorders, 6 neurodevelopmental disorders, 6 neuropsychiatric disorders, 4 neurotraumatic events/disorders, 5 skull atypicalities, 73 sleep-related disorders, and 4 with other symptoms/diseases. Twenty-two studies included exclusively healthy populations. Given the size of this review, all study details are provided in supplemental Tables S1-S9 and the supplemental reference list.

Autoimmune and Inflammation-related Disorders

Of the 22 studies that were identified as autoimmune and inflammation-related disorders, 12 were descriptive or case studies. In total, $n = 693$ participants were included in these studies (Supplemental Table S1). Autoimmune and inflammatory disorders included

anti-IgLON5 disease, encephalitis, fibromyalgia, rheumatoid arthritis, multiple sclerosis, Lupus, and neuroborreliosis from Lyme's disease. Studies assessed CSF composition for alpha-synuclein (1), amyloid-beta (1), tau proteins (1), angiotensin-converting enzyme (1), IgLON5 antibodies (3), unidentified antibodies (2), interleukin (IL; 3), orexin (3), white blood cells (4), other protein concentration (5), and indirect glymphatic exchange via perivascular space volumes (3).

Antibodies and Proteins.—Three studies [24-26] reported the presence of IgLON5 antibodies with dysfunctional sleep (total $n = 44$). Similarly, a case study by Chung and colleagues reported the presence of IgLON5 antibodies in an individual with poor sleep (e.g., reduced sleep time, sleep fragmentation) and autoimmune encephalitis [27]. However, there were no elevated values of alpha-synuclein, amyloid-beta, or phosphorylated tau (p-tau) proteins in a patient with sleep apnea and anti-IgLON5 disease [28].

There were mixed findings regarding interleukin levels although a pattern emerged; most of the studies reported no differences in IL-6 but increased IL-8 with the presence of sleep disturbance in individuals with autoimmune/inflammatory disorders (total $n = 108$). For example, increased IL-8 levels were associated with greater sleep disturbance in patients with fibromyalgia and rheumatoid arthritis [29]. Another study by Kosek et al. reported higher levels of IL-8 patients with knee osteoarthritis and poor sleep quality [30]. However, Lampa and colleagues [31] reported no significant associations between IL-6 or IL-8 and poor sleep in patients with rheumatoid arthritis ($n = 40$).

Mixed findings on CSF white blood counts and protein concentrations were also reported in four descriptive studies ($n = 48$) on encephalitis and encephalomyelitis. Vliet and colleagues [32] identified normal white blood counts and protein levels in an aging patient with limbic encephalitis and sleep disturbances. This was supported in two studies on individuals with IgLON5 antibodies who also exhibited sleep disturbances (combined $n = 22$) [24,26]. However, Fridingder and Alper reported higher protein and white blood counts in individuals with encephalomyelitis though only 12 of 25 had sleep disturbances [33]. Protein concentrations were also uncorrelated with sleep in adults with Lyme neuroborreliosis disease but were lower in multiple sclerosis patients experiencing fatigue. Increased concentration levels of Tat protein were associated with increased sleep quality in patients with human immunodeficiency viruses.

Other Metabolites.—CFS orexin levels appeared to be correlated with excessive daytime sleepiness in individuals ($n = 4$) with systemic lupus erythematosus [34], reduced sleep efficiency, and sleep fragmentation in an adult with diencephalic encephalitis [35], but not in individuals ($n = 100$) with multiple sclerosis and other inflammatory disorders [36].

Perivascular spaces.—All three studies on perivascular space volumes reported higher volumes with indices of poor sleep (total $n = 110$), of which two were case studies. Specifically, Wang and colleagues [37] reported a positive correlation between the size of perivascular space and sleep fragmentation in patients with cerebral small vessel disease ($n = 108$).

Neurodegenerative Disorders

There were 48 studies that examined neurodegenerative disorders in a total of n = 10,291 individuals with either Alzheimer's disease (AD) and/or mild cognitive impairment (16), Parkinson's disease (PD; 23), dementia with Lewy Body (DLB; 2), amyloid-beta plaque (1), a combination of AD, PD, and DLB (3), Familial Creutzfeldt-Jakob Disease (1), dementia with idiopathic normal pressure hydrocephalus (1), and DNA (cytosine-5)-methyltransferase 1 (DNMT1) syndrome (1) (Supplemental Table S2).

Forty-seven studies examined CSF composition for amyloid-beta (Aβ; 26), tau proteins (23), alpha-synuclein and its oligomers (13), orexin (10), C-reactive protein (1), prion protein (1), neurotransmitters such as serotonin (4) and dopamine (1), iron and transferrin (1), glial fibrillary acidic protein (1). One study examined CSF circulation and volumes.

Amyloid-beta.—Of the 26 studies of patients with neurodegenerative disorders (total n = 8220) that examined Aβ, 12 reported no significant associations between sleep problems and Aβ levels (total n = 3455), 5 studies reported a positive association between sleep problems and Aβ levels (total η = 1972), one study reported mixed findings (total n = 104), and the remaining 8 studies reported a negative association between sleep problems and Aβ (total n = 2689; Figure 4). Each of the studies highlighted above indexed Aβ-42. When considering Aβ-40, three studies of n = 136 reported no differences in Aβ-40 with the presence of sleep problems in individuals with neurodegenerative disorders.

Tau.—Of the 23 studies (total n = 7550) that examined tau proteins, 13 reported no significant associations between CSF tau protein levels and sleep problems (n = 4529), 6 reported increased tau proteins associated with increased sleep problems (n = 1071), and two reported decreased tau proteins associated with increased sleep problems (n = 1950) in those with neurodegenerative disorders. Specifically, a longitudinal study (n = 1639) by Bubu and colleagues [38] reported patients with mild cognitive impairment and OSA had accelerated tau accumulation but decreases in Aβ compared to those without OSA. There were also two studies that examined Aβ/tau ratios one (n = 20) reported increased ratios with sleep problems [39], and the other (n = 421) reported decreases in ratios [40].

Alpha-synuclein.—Of the 12 studies (total n = 3453) that examined alpha-synuclein, 6 reported no associations between alpha-synuclein levels and sleep problems (n = 2084), 3 reported increased alpha-synuclein associated with increased sleep problems (e.g., Rapid eye movement (REM) sleep behavior disorder; n = 505) whereas 2 other studies reported decreased alpha-synuclein associated with increased sleep problems in those with neurodegenerative disorders (n = 864). Notably, the relations between sleep and alpha-synuclein are not always unidimensional. For example, Compta and colleagues [41] reported no differences in total alpha-synuclein but decreases in alpha-synuclein oligomer; whereas, Hu and colleagues reported increased alpha-synuclein oligomer with sleep disturbance [42].

Orexin.—There were 10 studies (total n = 239) that examined orexin levels in neurodegenerative disorders. Three studies (n = 41) did not report significant associations between sleep behaviors and/or durations and orexin levels [43-45]. Five studies (n

= 75) reported decreased orexin associated with excessive daytime sleepiness (related to narcolepsy symptoms), whereas two reported increased orexin associated with sleep dysregulation (e.g., clinical levels of reduced sleep duration or sleep fragmentation) in 123 patients with neurodegenerative disorders.

Neurotransmitters.—Two studies (total $n = 369$) reported serotonin levels were reduced with sleep problems, whereas one study and a case study ($n = 74$) reported no associations [46,47]. Additionally, Piao and colleagues also reported reduced dopamine levels with increased sleep problems in a sample of 218 patients [48].

Other Metabolites/Components.—Across 8 studies (total $n = 703$), sleep problems were associated with elevated iron, transferrin, prion proteins, GFAP, YKL-40 glycoprotein, and melanin-concentrating hormone in CSF samples of individuals with neurodegenerative disorders.

CSF circulation.—Ringstad and colleagues [49] reported that CSF circulation peaked during the night in patients with idiopathic normal pressure hydrocephalus dementia ($n = 23$).

Neurodevelopmental Disorders

There were six studies (total $n = 273$) that examined neurodevelopmental disorders (NDD) (Supplemental Table S3). Specifically, studies of children with ASD (1), Down syndrome (2), muscular dystrophy in NDD (1), juvenile myoclonic epilepsy (1), and Smith-Magenis syndrome (1). A range of CSF metabolites and components were measured, of which four were associated with sleep problems. Specifically, elevated Aβ, elevated tau, lower orexin, the presence of glutamate receptor autoantibodies, and lower L-dopa levels were reported in four case studies of individuals with NDD with sleep problems. One case study [50] reported normal white cell counts, protein concentrations, antibodies, and the absence of oligoclonal bands in an individual with juvenile myoclonic epilepsy and disordered sleep.

Glymphatic system exchange.—Only one study ($n = 236$) examined an indirect metric of glymphatic system exchange - CSF volumes in the subarachnoid space. Specifically, Shen and colleagues [51] reported a positive association between excessive CSF volume in the subarachnoid space, known as extra-axial CSF (EA-CSF), and sleep disturbances in children with autism. Specifically, children with ASD who had abnormally elevated EA-CSF volume (1.5 standard deviations above the typical development group) had greater sleep problems than both children with ASD and typically developing children with normal levels of extra-axial CSF.

Sleep-related Disorders

There were 73 studies ($n = 5148$) on a range of sleep disorders. Thirty-five studies examined narcolepsy, 4 narcolepsy with cataplexy, 6 narcolepsy with hypersomnia, 1 narcolepsy with insomnia, 12 obstructive sleep apnea (OSA), 5 hypersomnia only, 1 cataplexy only, 2 insomnia only, 2 sleep-disordered breathing (SDB), 2 restless leg syndrome, 1 Kleine-Levin Syndrome, and 2 on human African trypanosomiasis. Given this study composition,

studies will be summarized based on narcolepsy (all types), SDB and OSA, and other sleep pathologies across measurements of Aβ, tau, orexin, other metabolites, and CSF circulation (i.e., CSF pressure and leaks) and indirect glymphatic exchange (i.e., CSF volume and perivascular spaces).

Of the 73 studies, 64 examined metabolites in CSF. Of which, 47 (73.4%) reported significant associations between sleep and CSF metabolite composition or levels. Nine measured Aβ, 9 measured tau protein, and 47 measured orexin. There were also single measures of several additional elements (e.g., c-reactive protein, histamine, cytokines, t-cells, IgLON antibodies, interleukin).

Amyloid-beta.—For individuals with narcolepsy, two studies (total $n = 96$) reported lower Aβ, and two studies (total $n = 86$) reported normative Aβ levels (Figure 4). For SDB and OSA, one study ($n = 50$) reported lower Aβ levels, one study ($n = 208$) reported normative levels, and two studies ($n = 113$) reported elevated Aβ with more disordered sleep. Aβ was not assessed in any of the other sleep concerns studies.

Tau.—All three narcolepsy studies reported no significant association between tau and sleep disturbance (total $n = 129$). Three studies (total $n = 163$) on OSA/SDB reported increased tau with greater sleep disturbance, whereas one ($n = 208$) reported no association (Figure 5). There were no significant associations between tau and sleep disturbance in the other sleep concerns category (which in this case included two studies of insomnia; total $n = 59$).

Orexin.—All of the studies that assessed Type 1 narcolepsy endorsed low orexin levels (.$n = 2846$; Figure 6). This is not surprising given orexin's diagnostic role in narcolepsy, but individuals with other forms of narcolepsy presented with a more mixed picture (Supplemental Table S4). Orexin was only assessed in one SDB study ($n = 5$) and reported normative CSF concentrations. For other sleep disorders, hypersomnia was not associated with atypical orexin patterns (5 studies, total $n = 316$); however, elevated daytime sleepiness was associated with low to intermediate orexin concentrations [52,53].

Other Metabolites.—Studies of other metabolites documented each of the following in CSF with disordered sleep: higher CD4 T-cells, chemokine ligand 4 (CCL-4), GFAP, histamine, and white blood cell counts but did not endorse relations between sleep and melanin (Supplemental Table S4).

CSF leaks.—Two out of three studies (66.7%; $n = 187$) reported OSA diagnoses were associated with increased CSF leaks [54,55], whereas Huyett and colleagues [56] did not report any relationship between the presence of OSA and CSF leaks ($n = 44$).

CSF pressure.—In Xin et al. [57] and Rabbani et al. [58], individuals with OSA had increased risk of developing higher CSF pressure (combined $n = 128$).

CSF volume.—Kumar and colleagues reported no differences in CSF volumes with OSA ($n = 104$) [59].

Perivascular space volumes.—Huang et al., [60] and Song et al., [61] reported enlarged perivascular spaces with the diagnosis of OSA and higher apnea-hypopnea counts (combined $n = 295$). Compared to patients without periodic limb movements, Kang and colleagues [62] reported increased perivascular space volumes in patients with periodic limb movement ($n = 50$).

Neuropsychiatric Disorders

The studies (total $n = 269$) on neuropsychiatric disorders (Supplemental Table S5) included depression, psychosis, schizophrenia, and post-traumatic stress disorder. A range of components in CSF was measured: melatonin (1), norepinephrine (1), orexin (3), and lymphocytic pleocytosis protein (1).

In patients with depression, there were no significant associations between orexin [63] or melatonin [64] with sleep disturbances ($n = 135$). In patients with schizophrenia (combined $n = 64$), Sansa et al. [65] found no associations between orexin and sleep disturbances in three adults, whereas Tsutsui et al. ($n = 63$) reported low levels of orexin only in three adults with schizophrenia or psychotic symptoms [66]. There were mixed findings on orexin levels in patients with schizophrenia. Positive associations between norepinephrine and sleep disturbances were reported in individuals ($n = 69$) with PTSD and a long history of trauma [67]. High protein levels were associated with decreased sleep in a case study of psychosis [68].

Skull/brain Atypicalities

There were five studies on skull or brain atypicalities – craniosynostosis (2), Chiari malformation (2), achondroplasia (1) (Supplemental Table S6). None of the studies examined metabolites or components in the CSF. Three studies reported significant CSF disturbances, such as increased intracranial pressure, syringomyelia hydrocephalus, and herniation which could be interpreted as indirect evidence that poor glymphatic system exchange is associated with sleep problems.

CSF pressure.—The two studies on craniosynostosis (total $n = 65$) reported no significant correlations between intracranial pressures and sleep problems such as obstructive sleep apnea symptoms [69,70]. However, one MRI study [70] ($n = 31$) reported narrow external CSF spaces were associated with elevated intracranial pressure during sleep.

CSF flow.—Zaffanello et al. [71] reported positive associations between poor sleep quality and cerebellar herniation in a preschool child with Chiari malformation. However, associations between cerebellar herniation and sleep quality were not supported by Losurdo and colleagues ($n = 53$), though they reported increased syringomyelia with sleep disturbance in school-aged children with Chiari malformation and obstructive SDB [72].

CSF volumes.—Shimony and colleagues also reported that seven of eight infants with achondroplasia and sleep disturbances had decreased CSF volume around the foramen magnum and some degree of increased extra-axial CSF [73].

Neurotraumatic disorders

There were four studies that examined neurotraumatic disorders ranging from traumatic brain injury (2), stroke (1), and penetrating brain injury (1) (Supplemental Table S7). Only two studies examined CSF components, mainly arginine-vasopressin and oxytocin, and white blood cells, glucose, and protein. In the case study of an adult with penetrating brain injury, the patient had periodic sleep apnea episodes and mildly elevated white blood cells but normal glucose and protein levels. Separately, there were no diurnal fluctuations of oxytocin and arginine-vasopressin concentrations reported in individuals with intracranial hemorrhage or tumor when compared to controls ($n = 20$) [74].

Perivascular spaces and volumes.—The two remaining studies examined the volume of perivascular spaces as a measure of glymphatic pathways. One MRI study in adults with traumatic brain injury reported enlarged perivascular space (i.e., perturbed glymphatic pathways) associated with poor sleep (e.g., short sleep duration and lower sleep efficiency; $n = 38$). Similarly, Berezuk et al. [75] also reported increased perivascular space volumes with reduced sleep efficiency in patients with ischemic brain disease or stroke ($n = 26$).

Other diseases or disorders

There were four studies that examined behaviors, syndromes, or disorders that did not fall under the eight other categories. Specifically, these studies examined sleep and CSF composition in individuals who were smokers or had cluster headaches, obesity, and postlaminectomy syndrome (Supplemental Table S8). Xu and colleagues reported that heavy smokers had poorer sleep quality and lower CSF glutamate concentrations compared to non-smokers ($n = 147$) [76]. In a case study on a school-age child with obesity, there was an absence of CSF orexin and the presence of sleep problems (e.g., short sleep latency, sleep fragmentation) [77]. A study on adults ($n = 38$) with post-laminectomy syndrome reported associations between poor sleep quality and higher IL-8 levels but not IL-6 [78].

Typical Population

Twenty-two studies ($n = 2004$) recruited school-aged children to aging populations with no known pathologies (i.e., typical populations) (Supplemental Table S9). Eighteen of the studies examined metabolites in CSF, of which 17 (94.4% of studies) indicated a significant relationship between sleep and CSF metabolites. Of the 18 articles on metabolites, 14 examined Aβ, 8 examined t-tau and/or p-tau, 2 examined orexin, and 1 study examined alpha-synuclein.

Amyloid-beta.—Eight (combined $n = 844$) of 14 studies (total $n = 1101$) that examined Aβ reported increased sleep problems (or reduced sleep duration) were associated with increased Aβ production or deposits (Figure 4). Three studies (combined $n = 80$) reported no significant differences in Aβ in relation to sleep and three (combined $n = 177$) reported decreased Aβ with poor sleep.

Tau.—For the studies with typical populations (total $n = 602$), 76.9% of study samples (combined n = 463) reported increased sleep problems were associated with increased tau proteins (Figure 5). Two reported (combined $n = 89$) no differences in tau protein in relation

to sleep, whereas one study (n = 50) reported a decrease in tau proteins with elevated sleep problems.

Orexin.—Both studies that examined orexin reported positive associations between orexin and sleep problems in aging populations (combined n = 13; Figure 6).

Other Metabolites.—Five studies examined cortisol, melatonin, and IL levels in typical populations. They reported increased CSF melatonin and alpha-synuclein levels after sleep deprivation (combined n = 27) [79,80] and increased YKL-40 glycoprotein associated with sleep problems [81]. Circadian rhythmicity of cortisol (n = 8) [82] and IL-6 levels in the CSF (n = 10) were also reported [83].

CSF volumes.—Demiral and colleagues (n = 50) reported larger CSF volumes during sleep after a night of sleep deprivation compared to awake state following a night of rested sleep [18].

CSF circulation.—Fultz et al. [19] reported greater CSF dynamics at the fourth ventricle during sleep (when compared to awake state) in 13 research participants.

Perivascular spaces.—One study (n = 457) reported increased basal ganglia perivascular space visibility, or enlargement (an indirect metric of glymphatic system exchange), associated with interrupted sleep, whereas another study with a sample of 338 adults reported no associations between sleep quality and basal ganglia perivascular spaces but significant associations between poor sleep efficiency and enlarged basal ganglia perivascular spaces [84].

Discussion

Overall, the studies reviewed demonstrate a robust relationship between sleep and several CSF indices that represent CSF circulation and approximate glymphatic system exchange. Interestingly, although studies used vastly different metrics to index sleep, CSF, and glymphatic system exchange, consistent findings still emerged. Specifically, when sleep is reduced or disordered, CSF circulation is reduced, and CSF concentrations of Aβ, tau proteins, and IL-8 may be elevated. This summative statement reflects a majority of the studies reviewed - these patterns were not universally endorsed across studies. Not surprisingly, CSF orexin concentrations were implicated in narcolepsy, and other orexin findings were more mixed. Emerging evidence demonstrates that CSF circulation follows a circadian pattern and waste drainage peaks during sleep [85], however, how/where pathology alters this system is still emerging.

A recent study by Fultz et al. [19] demonstrates a potential link between slow-wave sleep and CSF flow dynamics in the fourth ventricle. Using a combination of electroencephalogram (EEG) and blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI), Fultz and colleagues reported a coupling between slow-wave activity and low-frequency vasomotor oscillations. The model presented by Fultz et al. highlights that slow neural rhythms in sleep may be associated with increased CSF

movement, with hemodynamic oscillations acting as the mechanistic mediator linking the two processes.

Components of CSF

It is important to note that many of the findings reviewed in the above studies followed a complex pattern, which reflects our nascent knowledge of this relatively newly discovered system. For example, when considering the relationship between CSF orexin concentrations and sleep in neurodegenerative disorders, the findings appear rather mixed (Figure 6). However, detailed examination reveals that studies of sleep behaviors (high to low sleep durations) do not report altered orexin concentrations, but studies of neurodegeneration and narcolepsy report lower orexin concentrations (as do most studies of narcolepsy). Additionally, studies of neurodegeneration and other sleep pathologies (i.e., insomnia) reported elevated orexin concentrations. Considered as a whole, the findings may appear unclear but when broken down, they generate a compelling story of the intersections between sleep behavior/pathology and CSF orexin concentrations. Notably, differences in orexin concentrations in narcolepsy reflect known physiological/pathological processes. Within this review, we are not implying that orexin concentrations reflect elements of the glymphatic system; rather, we aim to provide an overview of the complex processes that implicate sleep, CSF, and the GS.

The relations between Aβ and sleep are similarly nuanced (Figure 4). In AD, Aβ-42 was associated with sleep deficiency/problems in 58.0% of the assessed individuals, whereas Aβ-40 was not implicated. In typical populations, a similar 76.7% had elevated Aβ when disordered sleep was present. Conversely, none of the studies of PD observed an increase in Aβ accumulation with the presence of sleep problems. Taken together, these studies highlight that sleep disruption may increase Aβ deposits in normative aging and AD but not in PD. However, as indicated in Figure 4, there appears to be an age effect with older samples having a greater likelihood of a coupling between sleep problems and Aβ accumulation. This may reflect a shared risk pathway with sleep problems and Aβ accumulation both increasing with age or could reflect the incremental age-related changes in glymphatic system exchange (i.e., the longer glymphatic system exchange is inefficient, the more likely it will contribute to Aβ accumulation). Christensen et al. provides a summary of the glymphatic function on Aβ clearance during sleep-wake states [86].

As illustrated in Figure 5, evidence for elevated tau protein accumulation in sleep problems is not as robust (when compared to Aβ). The strongest support for a tau-sleep connection is present in typically developing samples, followed by those with OSA/SDB. The differences between AD and PD may reflect either different mechanistic pathways to tau accumulation that are unrelated to sleep or differences in the pathogenesis of the disease that may have greater effects than sleep problems such as the death of dopaminergic receptors in PD.

Volumes of CSF and perivascular space

When considering neurodevelopmental disorders, the largest study (n = 236) assessed how the glymphatic exchange (via an indirect metric) could inform the early development of autism. Within this study, sleep problems and excess EA-CSF were implicated in the

development of autism. This greater CSF volume could be a potential indicator of altered CSF circulation and glymphatic exchange, which has been previously associated with impaired Aβ clearance and disturbances in sleep. This is further supported by evidence from Shen et al. [87,88] that indicates that infants who are later diagnosed with ASD have increased EA-CSF but do not have significantly increased lateral ventricle volume or a significant association between lateral ventricle volume and EA-CSF volume, which suggests a problem with absorption and circulation and not CSF overproduction. There is a 60% increase in the influx of CSF during sleep [20]; therefore, it is hypothesized that sleep disturbances might interrupt CSF circulation and result in an accumulation of Aβ observed in histological examinations of individuals with ASD [89-92].

Furthermore, there is mounting evidence that enlarged perivascular spaces (a proposed indirect metric of glymphatic exchange) are associated with increased sleep problems in healthy populations, sleep-related disorders, and neuroinflammatory disorders. In elderly healthy adults, enlarged basal ganglia PVS was associated with sleep disruptions and lower sleep efficiency [84]. PVS enlargement in the basal ganglia and centrum semiovale has been associated with higher apnea-hypopnea severity in adults with obstructive sleep apnea [60,61]. Patients with neuroinflammatory disorders have also exhibited correlations between PVS enlargement and sleep disturbances and sleep apnea.

Taken together, results on PVS suggest that there might be inefficient perivascular drainage in people who experience sleep problems, thereby possibly resulting in PVS enlargement. It is important to note that the directionality of the relationship between sleep and enlarged PVS is currently unknown; sleep problems might contribute to fluid stagnation in PVS or enlarged PVS might have adverse impacts on the brain structures involved in sleep regulation (e.g., hypothalamus), thus leading to sleep problems. Secondly, the studies reviewed were nearly all dependent on qualitative, visual inspection of PVS enlargement, with the exception of Berezuk and colleagues' [75] examination of volumetric PVS. Advancements in methodology will hopefully lead to increased use of automated, quantifiable estimations of PVS volume, width, and diameter (for example, Piantino et al., [93]), which will allow for greater sensitivity and specificity in relationships between PVS and sleep, while also reducing rater subjectivity. Future studies will need to examine this relationship quantitatively and longitudinally in order to gain further insight. One potential method would be to couple non-invasive neuroimaging and sleep assessments in a large sample of children at high risk for developing sleep problems (e.g., in autism) at multiple time intervals throughout development to determine whether PVS enlargement precedes or follows the onset of sleep disturbances.

The associations between sleep and CSF composition are involved in a range of processes, including CNS circulation, exchange processes between the brain interstitium and CSF, and rates of CSF secretion and reabsorption. Additionally, IL is a group of cytokines produced during immune activation (i.e., response to inflammation), tau proteins and GFAP are related in cellular injury during neurodegeneration, whereas orexin is part of the hypothalamic neurotransmission. Similarly, Aβ40 and Aβ42 behave differently in the aggregation of amyloid plaques in aging and neurodegenerative disorders. In sum, the elements of CSF

composition noted in this review reflect more than just sleep, CSF circulation, or glymphatic system exchange.

Despite several reviews summarizing neuroimaging techniques and CSF mechanics associated with glymphatic system solute transport [9,94,95], there remains confusion surrounding the terms and measures used to index CSF circulation and glymphatic system exchange. As alluded to in Figure 1, CSF dynamics and circulation is key to glymphatic system exchange, so too is the flow of the interstitial fluid and CSF-ISF exchange. CSF and ISF flow are integral to other clearance systems though each of these processes alone does not constitute the entirety of the glymphatic system. Furthermore, the influence of sleep and circadian cyclicity on glymphatic system exchange has only recently been established [8]. Hence, clarity in terms and metric usage are necessary when describing CSF movement and glymphatic exchange in future sleep studies. For example, CSF composition and several MRI techniques (see Taoka & Naganawa, 2020 [94]) reflect both direct and indirect indices of CSF circulation and glymphatic system exchange. Even though our findings highlight that indirect assessments remain useful and relevant, careful interpretation should be considered, and terms should be clearly defined as not to confound different brain fluid processes (i.e., CSF, ISF, and blood).

Improving Glymphatic System Assessment

Since the discovery of the glymphatic system in 2013, there has been a rapid increase of methods developed for measuring fluid movement and neurobiological processes within the system. Xie and colleagues [20] documented the relationship between sleep and the glymphatic system through the use of fluorescent tracers and two-photon microscopy in mice. Recent work has highlighted the function of the choroid plexus as more than just the primary source of CSF production, but also as a barrier between blood and brain [96,97]. Through novel, awake two-photon imaging methods in mice, Lehtinen and colleagues [12] have observed that choroid plexus immune cells respond to immune challenges and elicit subsequent neuroinflammation. By surgically implanting a cannula and a glass window in the lateral ventricle, this method can be used to observe cellular level activity within the choroid plexus in real time and can possibly lead to further exploration of how proinflammatory proteins are cleared during the sleep cycle. In order to extend the current understanding of the glymphatic system in humans, there will need to be a continued move towards non-invasive imaging methods. The next step in methods advancements will be to develop imaging techniques to observe specific components of the glymphatic system *in vivo* across a range of ages and populations. Currently, the primary techniques used to evaluate the glymphatic system in humans with MRI have included: tracer studies [2,22], phase-contrast MRI (PC-MRI), inversion pulse sequences, diffusion-weighted imaging (DWI) [94], and more recently, magnetic resonance encephalography that also monitors spatiotemporal effects of CSF pulsations [98]. Phase-contrast imaging remains a popular and powerful technique to non-invasively image and quantify the movement of CSF within the cerebral aqueduct, and the advancement of inversion pulse sequences [99] offers the ability to observe CSF circulation across the central nervous system, particularly the subarachnoid space and parenchyma, which are areas of the glymphatic system that are linked with pathology.

Limitations

Measures of the Glymphatic System.—To fully capture the glymphatic function, researchers employ dynamic imaging of contrast movement after intrathecal injection of tracers. However, this process is invasive and typically unsuitable for a majority of human populations. To expand our scope beyond the small number of studies that use these methods, this review included studies that were conducted with different modalities/methodologies and readouts such as CSF flow from phase-contrast MRI of CSF dynamics in non-contrasted scans or diffusion-tensor imaging (DTI) MRI that measures general water fluxes in the brain. Therefore, not all peer-reviewed articles can be considered *bona fide* glymphatic studies that truly examine the exchange of fluid and solute between the CSF and interstitial compartments along perivascular spaces. However, a broader inclusion criteria allowed us to build a comprehensive summary that (1) explored consistency across key characteristics related to the glymphatic system despite the lack of clarity in definitions and current limitations and differences in available methodologies, as well as (2) increased generalizability of the associations between sleep, CSF circulation, and glymphatic system exchange across human populations.

Pathology specificity.—Admittedly, this review is broad and covers several CSF factors with distinct mechanistic pathways and developmental patterns. For example, it is well-established that different processes contribute to the accumulation of Aβ40, Aβ42, and tau proteins, but our efforts in this review are not to detail the role(s) of sleep in each of these mechanistic pathways but to identify larger (potentially global) patterns of less optimal sleep with less optimal CSF circulation and glymphatic system exchange metrics. We did not find a universal impact across pathologies but rather, we identified that the relations between sleep and indices of the CSF are nuanced and likely pathology (or pathology class) specific; functionally, our review is limited with only modest pathology specificity.

Case studies/Descriptive studies/Brief communications.—Fifty-five of the 191 total papers reviewed were case studies or descriptive studies. These studies did not conduct any analysis and the findings may not be generalizable beyond the study sample. However, these studies as a cumulative mass provide detailed information on comorbidities and how treatment of sleep problems could improve CSF indices [35,50,100]. Additionally, certain sleep parameters may implicate features of the glymphatic system, particularly in specific conditions such as illnesses with sleep comorbidity (e.g., [77]). Therefore, these case studies were included in this review.

Publication Bias.—Several studies in this review reported no significant associations between sleep and CSF metrics (across a cumulative *n* of 12,718). Most of these studies were published because of significant effects on other variables of interest. However, our systematic sampling likely includes publication bias; wherein, studies that do not report a significant association were less likely to be published. Therefore, the reported patterns warrant further investigation with well-powered samples before conclusive connections between sleep, CSF circulation, and glymphatic system exchange can be established.

Orexin.—Several studies that recruited individuals with narcolepsy used CSF orexin levels to determine diagnosis (i.e., individuals with narcolepsy would naturally have reduced or negligible levels of orexin in their CSF). For those studies, CSF compounds were used to examine both sleep and as an indirect metric of CSF circulation and glymphatic system exchange. For instance, orexin was used as a sleep parameter (i.e., narcolepsy diagnosis) and Aβ as an indirect measure (i.e., metabolites in the CSF). Furthermore, since orexin is a sleep-regulating neurohormone, sleep-related variability likely reflects changes in orexin and not glymphatic function and CSF circulation. These studies demonstrate there is not always independence between the sleep and the assessed CSF measures in this systematic review.

Use of Medications and Assessment Time.—Medication use was not controlled for in the studies that recruited individuals with pathologies (e.g., levodopa in Parkinson's disease or selective serotonin reuptake inhibitor in depression). Additionally, not all studies included the type or dosage of medications or indicated if they controlled for the use of medications. Therefore, we were unable to prove if or how medication may moderate the reported associations. Similarly, time of assessment was not considered for most studies. Given the established and emerging evidence that CSF concentrations and flow follow a circadian pattern, this confounding variable could be especially informative. Future studies should consider the time of assessment when comparing across participants or studies.

Conclusion

Overall, pathways to pathology can include alterations in CSF production, accumulation/distribution, flow/circulation, ISF exchange, and composition. Within this review, disordered sleep was associated with altered CSF amount/distribution and composition, which potentially implicates both CSF circulation and glymphatic system exchange. Current glymphatic system assessment methods in humans limit our ability to clearly link sleep processes with CSF production and circulation, but promising non-invasive tools are being developed. Specific sleep problem patterns included alterations in CSF pressure and amount with OSA/SDB, decreased orexin with narcolepsy, and increased tau protein concentrations with OSA/SDB. Similarly, elevated Aβ deposits were documented most consistently with sleep problems in typically developing samples, and IL-8 was elevated with sleep problems in most studies that assessed IL. Future studies should leverage emerging CSF and glymphatic system exchange methods to investigate sleep-inform mechanistic pathways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary of terms

ACE	Angiotensin-converting enzyme
AD	Alzheimer's disease
AHI	Apnea hypopnea index
AQP-4	Aquaporin-4
ASD	Autism spectrum disorder
Aβ	Amyloid-beta
BOLD fMRI	Blood-oxygen-level-dependent functional magnetic resonance imaging
CCL-4	Chemokine ligand 4
CM	Chiari malformation
CSF	Cerebrospinal fluid
CT	Computed tomography
DLB	Dementia with Lewy body
DNMT1	DNA (cytosine-5)-methyltransferase 1
DS	Down syndrome
DWI	Diffusion-weighted imaging
EA-CSF	Extra-axial cerebrospinal fluid
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
EMG	Electromyography
ESS	Epworth sleepiness scale
FR	Frandsen method
FSS	Fatigue severity scale

GFAP	Glial fibrillary acidic protein
GS	Glymphatic system
HIV	Human immunodeficiency virus
HS	Hypersomnolence
ICP	Intracranial pressure
ICSD-II	International Classification of Sleep Disorders, 2nd edition
IL	Interleukin
iNHP	Idiopathic normal pressure hydrocephalus
iRBD	Idiopathic REM sleep behavior disorder
ISF	Interstitial fluid
LDOPA	Levodopa
MAI	Muscle activity index
MCH	Melanin-concentrating hormone
MCI	Mild cognitive impairment
MCP1	Monocyte chemoattractant protein 1
MMSE	Mini-mental state examination
MOS	Medical outcomes study sleep scale
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSLT	Multiple sleep latency test
N3	Non-REM sleep stage 3
NC	Narcolepsy with cataplexy
NDD	Neurodevelopmental disorders
NPI	Neuropsychiatric inventory questionnaire
NPS	Neuropsychiatric inventory
NT1/NT2	Narcolepsy type 1/ type 2
OSA	Obstructive sleep apnea
p-tau	phosphorylated tau
PC-MRI	Phase-contrast MRI

PD	Parkinson's disease
PEM	Phasic electromyographic metric
PET	Positron emission tomography
PSG	Polysomnography
PSQI	Pittsburgh sleep quality index
PTSD	Post-traumatic stress disorder
RBD	REM sleep behavior disorder
RBDSQ	REM sleep behavior disorder screening questionnaire
REM	Rapid eye movement
REM-L	Latency to the first episode of rapid eye movement sleep
RLS	Restless leg syndrome
SDB	Sleep-disordered breathing
SOREMPs	Sleep onset REM periods
SSS	Stanford sleepiness scale
t-tau	Total tau
TBI	Traumatic brain injury
TNF	Tumor necrosis factor
WBC	White blood cell

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Practice Points

Associations between sleep, CSF circulation, and glymphatic system exchange are abundant and follow a few notable patterns.

1. Emerging studies in neurodevelopmental disorders highlight differences in CSF disbursement with the presence of sleep problems.
2. Elevated amyloid-beta concentrations were most consistently linked with sleep problems in typical populations. Associations between amyloid-beta and sleep were more mixed in neurodegenerative disorders.
3. Sleep-disordered breathing/Obstructive Sleep Apnea (SDB/OSA) was associated with increased CSF pressure and leaks. Tau protein concentrations were also elevated in SDB/OSA in a majority of the assessed studies.
4. In autoimmune and inflammation-related disorders, elevated interleukin (IL)-8 levels (but not IL-6) were associated with several sleep problem indices.
5. Orexin levels were the most commonly implicated CSF element in narcolepsy.

Research Agenda

1. Current assessment methods limit the ability to clearly understand the links between sleep processes, CSF circulation, and glymphatic system exchange. Future studies should employ new methods to expand our mechanistic understanding.
2. Future studies should assess categories of sleep problems, including decreased sleep durations, OSA/SDB, and narcolepsy, as each of these sleep pathologies demonstrate potentially distinct CSF and glymphatic system profiles.

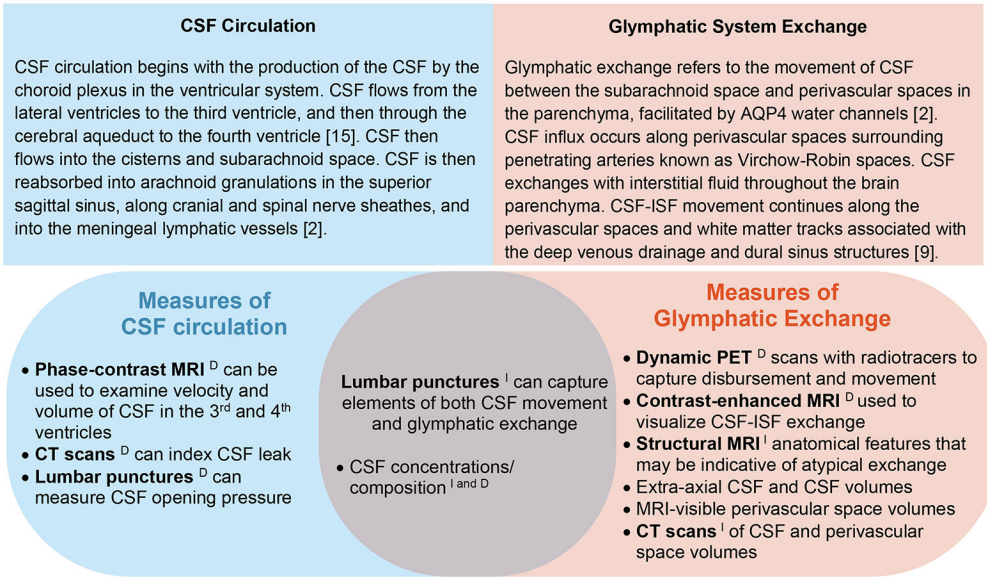

Fig 1. Current conceptual models and measures of CSF circulation and glymphatic system exchange– related but distinct processes.

Notes.

D A direct measure of CSF movement or GS function

I An indirect measure of CSF movement or GS function.

CSF = cerebrospinal fluid. CT = computed tomography. MRI = magnetic resonance imaging. PET = positron emission tomography.

For more details on clearance systems in the brain, please refer Table 1 of Tarasoff-Conway et al., 2015 [9].

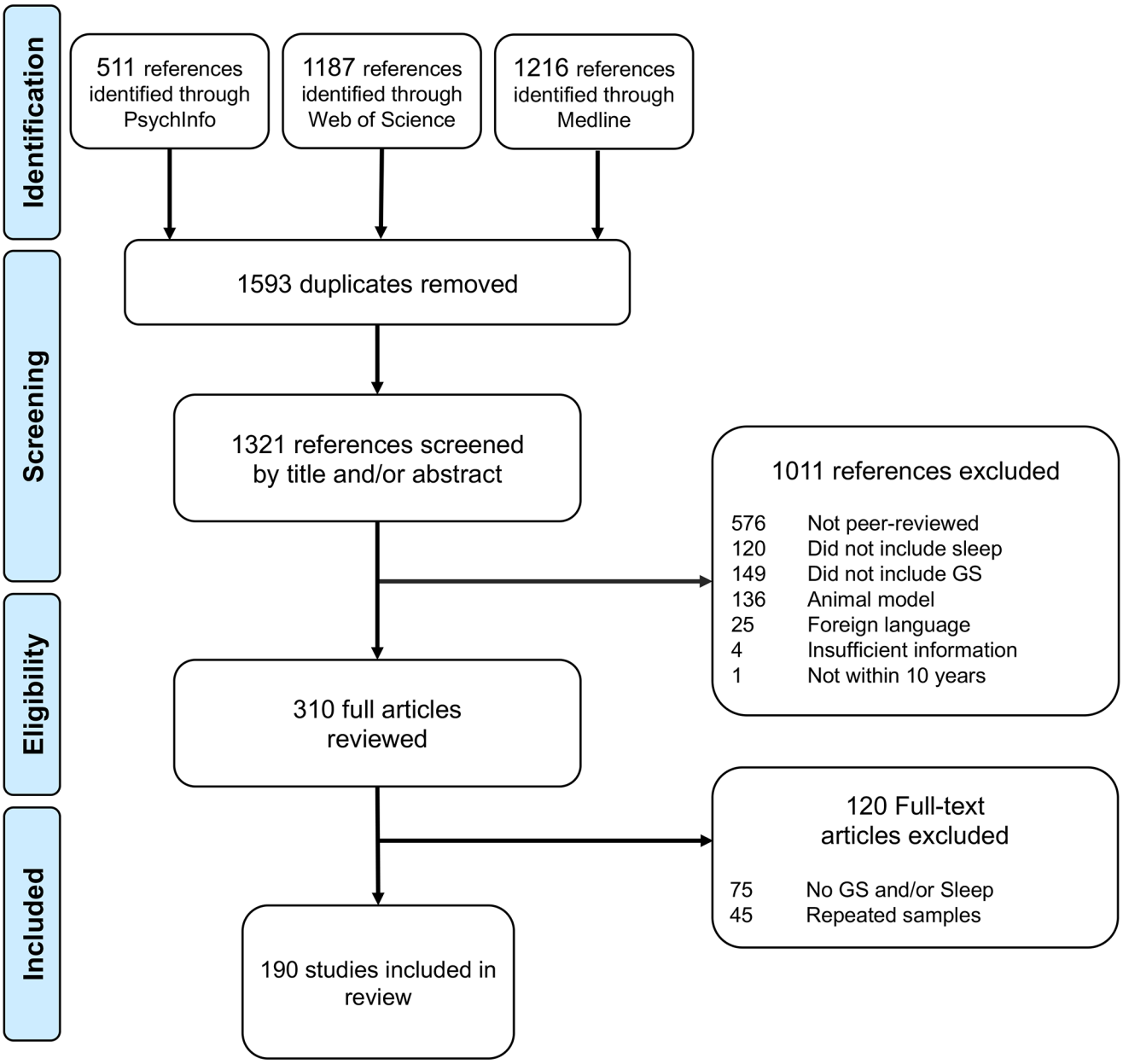

Fig 2. PRISMA flowchart of study inclusion

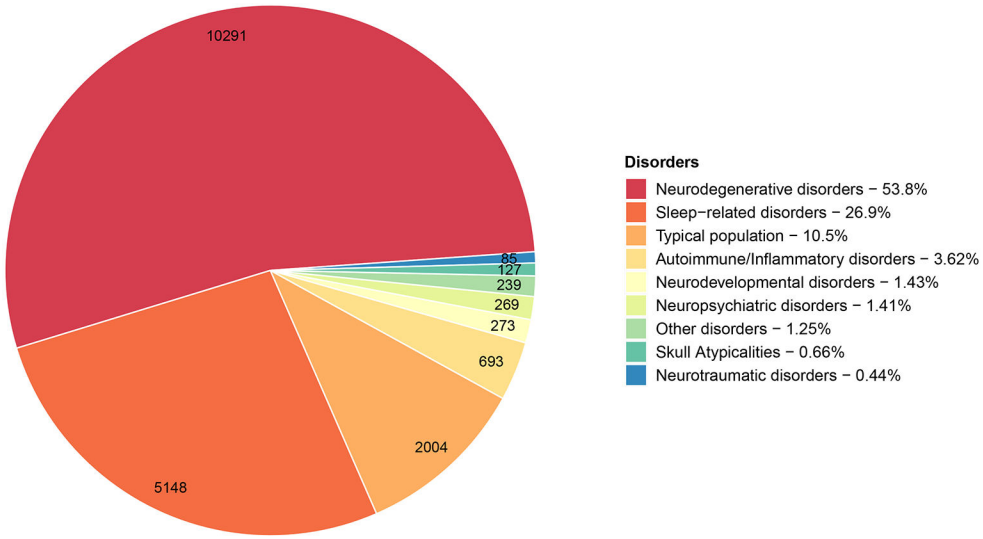

Fig 3. Cumulative study sample sizes stratified by review categories

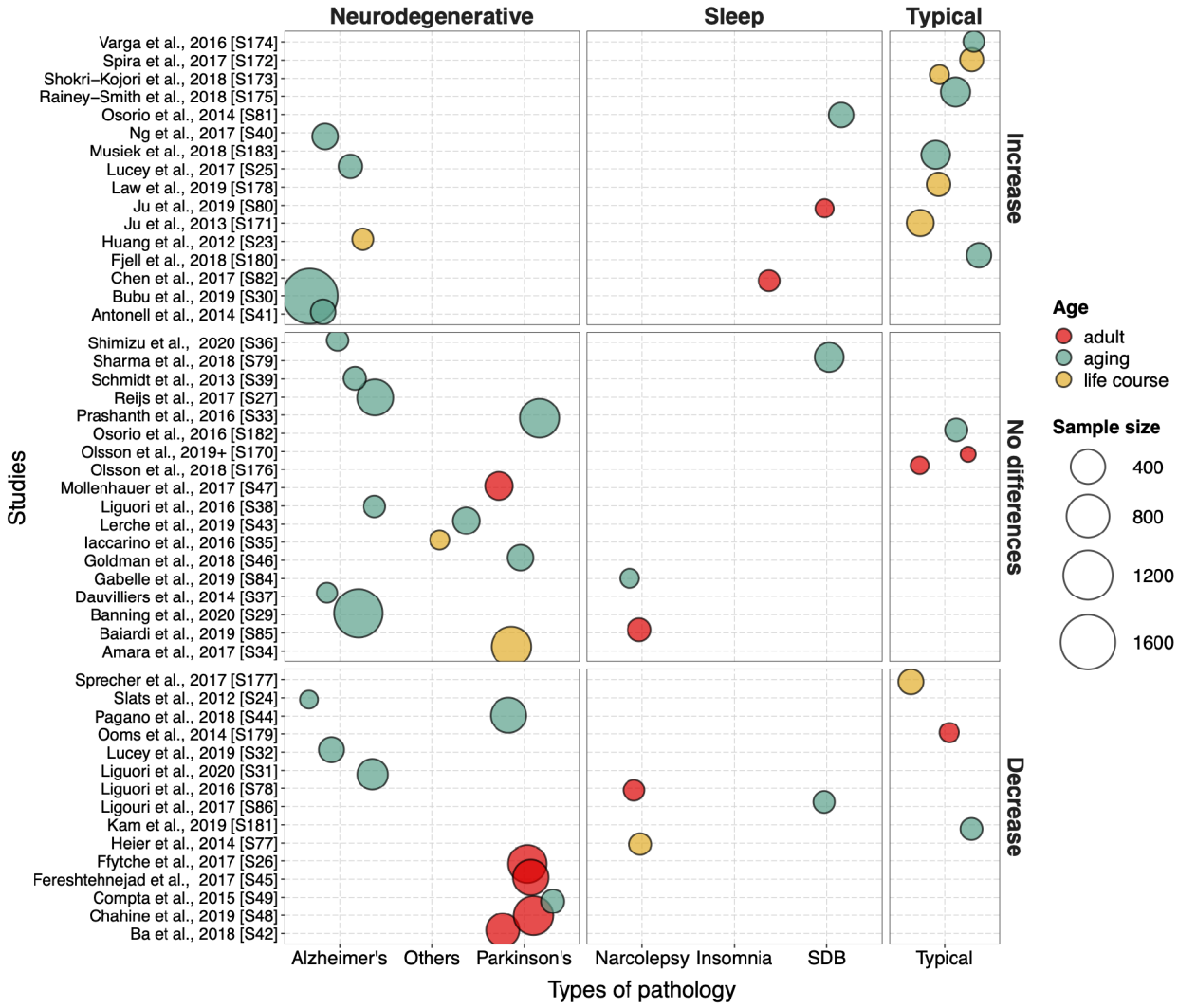

Fig 4. Correlations, age, and sample sizes drawn from studies that assess sleep and amyloid-beta

Note. Distribution of studies that indicated positive, null, or negative associations between sleep problems and amyloid-beta levels. Each circle represents one study. Other neurodegenerative disorders include dementia with Lewy bodies.

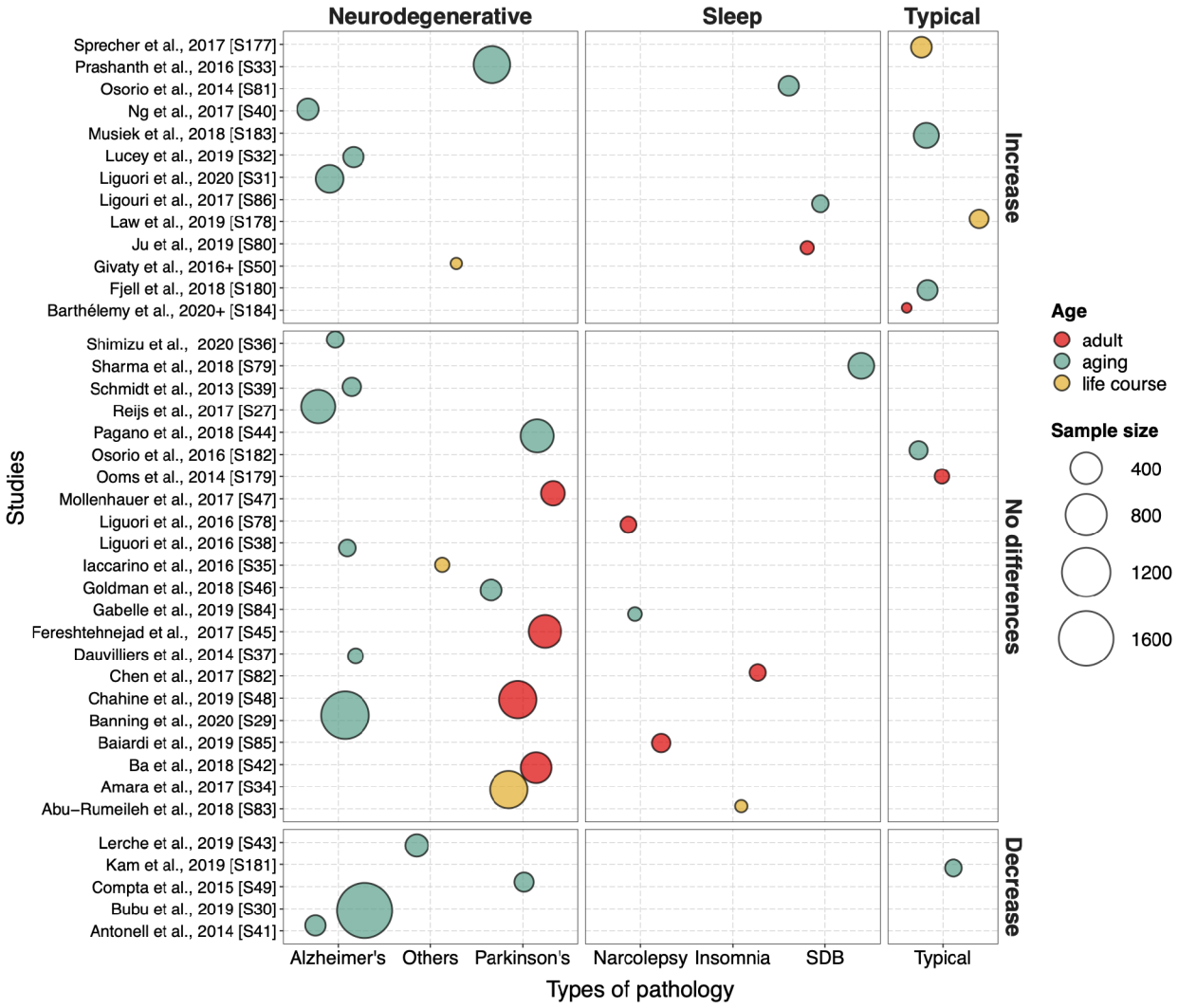

Fig 5. Correlations, age, and sample sizes drawn from studies that assess sleep and tau protein

Note. Distribution of studies that indicated positive, null, or negative associations between sleep problems and tau levels. Each circle represents one study. Other neurodegenerative disorders include dementia with Lewy bodies and Familial Creutzfeldt-Jakob Disease.

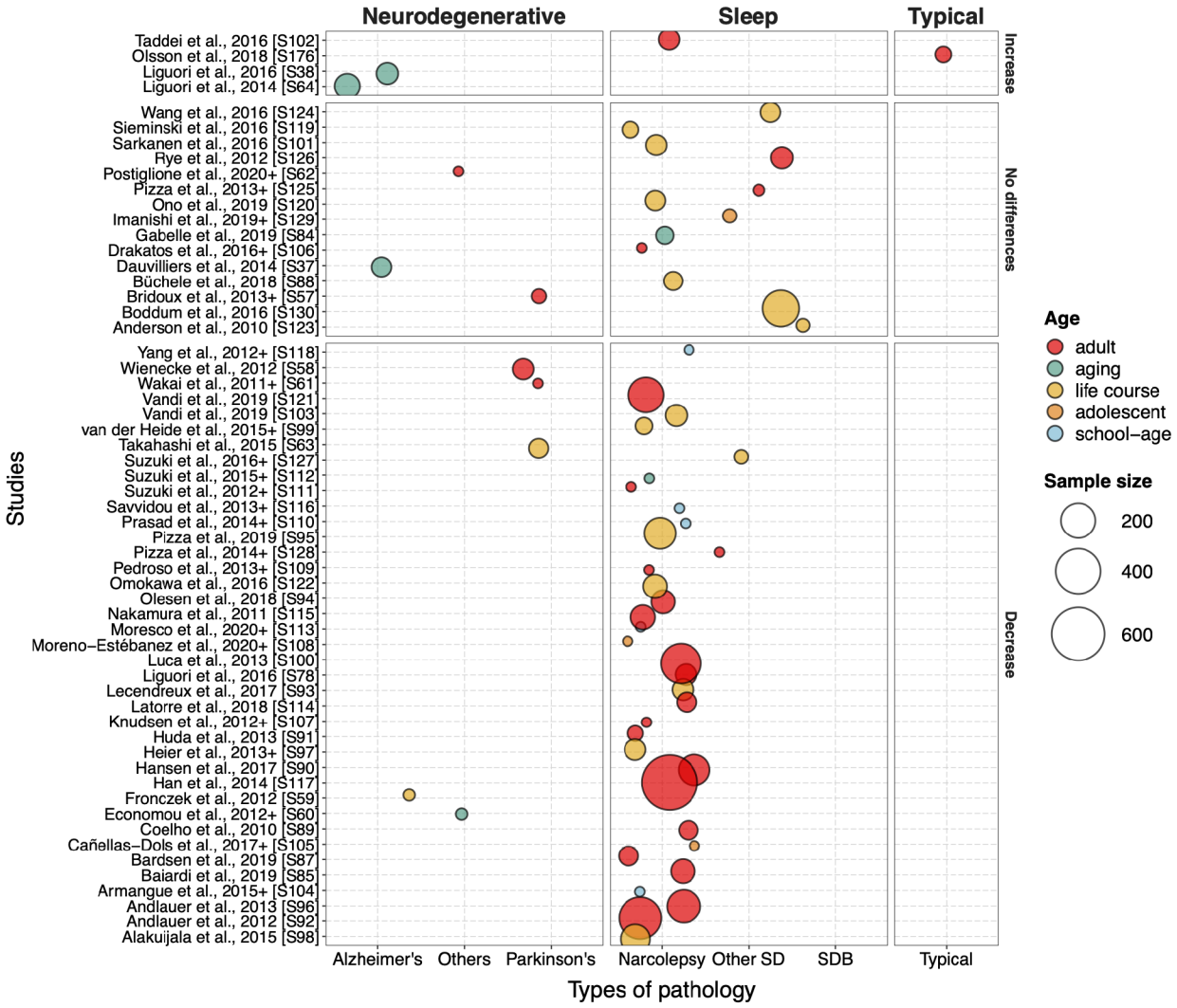

Fig 6. Correlations, age, and sample sizes drawn from studies that assess sleep and orexin

Note. Distribution of studies that indicated positive, null, or negative associations between sleep problems and orexin levels. Each circle represents one study. Other neurodegenerative disorders include DNA-methyltransferase 1 disorder.