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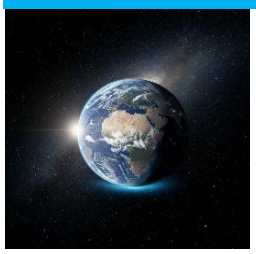

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Physical Activity and the Glymphatic System: Potential Interactions and Implications for Brain Health

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Abstract

Background: The glymphatic system is a perivascular network that promotes the exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF) and assists the elimination of metabolic waste products from the central nervous system.

Aim: The aim of this narrative review was to summarise current evidence regarding possible interactions between physical activity and glymphatic function.

Methods: A literature search was conducted in PubMed to identify studies addressing glymphatic transport, CSF dynamics, and physiological adaptations associated with exercise.

Results: The majority of research on the effect of exercise on the glymphatic system is from experimental studies using animal models, which have found that voluntary exercise is associated with increased influx and clearance of interstitial solutes. These effects have also

been linked to improved vascular health, decreased neuroinflammation, alterations in aquaporin-4 polarisation, and improved sleep health, including increased slow-wave sleep. Recent neuroimaging findings in human research suggest that long-term physical activity is connected with increased MRI measurements of glymphatic and meningeal lymphatic flow.

Conclusions: These findings are all derived from indirect imaging methods, and many studies indicate that physical activity affects multiple physiological pathways involved in glymphatic transport. Further studies combining exercise interventions with advanced neuroimaging approaches are needed to clarify whether and how physical activity influences glymphatic function in the human brain.

Keywords

glymphatic system; cerebrospinal fluid clearance; aquaporin-4; physical activity; slow-wave sleep; brain health

Introduction

Efficient removal of by-products generated by neural activity is vital for maintaining metabolic homeostasis within the central nervous system. Unlike peripheral tissues, which are served by a well-characterised lymphatic system, the brain parenchyma was long considered to lack an equivalent drainage mechanism. For decades, the processes by which the brain cleared interstitial solutes remained incompletely understood, and the accumulation of neurotoxic proteins in conditions such as Alzheimer's disease could not be fully explained by known clearance pathways (Jessen et al., 2015)

This fundamental gap in neurobiological knowledge was substantially addressed in 2012 when Iliff and colleagues used in vivo two-photon microscopy to characterise a paravascular pathway through which cerebrospinal fluid (CSF) enters the brain parenchyma along periarterial spaces, exchanges with interstitial fluid (ISF), and exits along perivenous routes (Iliff et al., 2012). This pathway was subsequently termed the "glymphatic" system by Nedergaard (2013), reflecting both the central role of glial cells - specifically astrocytes - and the functional analogy to the peripheral lymphatic system. The discovery represented a paradigm shift in understanding how the brain maintains its internal environment and disposes of metabolic waste.

The structural basis of glymphatic transport depends critically on aquaporin-4 (AQP4). AQP4 is a water channel protein, which is abundant in the perivascular endfeet of astrocytes

that ensheath cerebral blood vessels. AQP4 allows water to leave blood vessels and flow into cerebrospinal fluid (CSF), thereby facilitating the convective flow of CSF through the parenchyma. In rodent studies, the removal of AQP4 resulted in a reduction of approximately 70% in the amount of lymphatic tracer entering the brain tissue (Iliff et al., 2012). Following parenchymal exchange, interstitial solutes are transported toward perivenous drainage pathways and ultimately cleared from the cranium via meningeal lymphatic vessels and cervical lymph nodes (Tarasoff-Conway et al., 2015). The discovery that this system clears endogenous amyloid-beta during sleep - and that sleep deprivation impairs this process - established a direct mechanistic link between sleep physiology and neurodegenerative disease risk (Xie et al., 2013).

The dependence of glymphatic function on sleep has been thoroughly investigated and described in increasing mechanistic detail. Hablitz and others (2019) demonstrated that glymphatic influx correlates positively with delta wave power in the EEG (electroencephalogram). This constitutes a neurophysiological hallmark of slow-wave NREM sleep, thereby confirming that it is sleep depth - and not simply its duration - that determines the efficiency of waste removal from the brain.

Hauglund and colleagues (2025) provided a much more precise description of how the neurovascular dynamics of this relationship work. They demonstrated that synchronised fluctuations in norepinephrine concentration, cerebral blood volume, and CSF flow during NREM sleep are the primary determinants of glymphatic clearance (Hauglund et al., 2025). The lowest levels of norepinephrine activity during deep NREM sleep result in reduced sympathoadrenal state necessary for maximal glymphatic influx, which is essential for maximal glymphatic flow - a finding with direct implications for any physiological intervention, including exercise, that alters noradrenergic tone.

In addition to the glymphatic literature, a large body of evidence has established that regular physical activity confers wide-ranging benefits for brain health. These include improvements in cerebrovascular function and arterial compliance, enhanced cerebral blood flow, reduced inflammation in the body and nervous system, and favourable modifications of sleep architecture, including increases in slow-wave sleep duration and efficiency (Barnes & Corkery, 2018; Kredlow et al., 2015). Epidemiological studies have consistently linked higher levels of habitual physical activity with reduced risk of cognitive decline and dementia, although the underlying biological mechanisms are likely to be multifaceted and only partially understood.

Combining the glymphatic neuroscience and exercise physiology literature yields a scientifically testable hypothesis: exercise may influence brain waste clearance by altering the physiological determinants of glymphatic function. In support of this hypothesis, animal data show that voluntary running enhances glymphatic influx and reduces amyloid-β accumulation in both young and old mice (He et al. 2017; von Holstein-Rathlou et al. 2018). Recent evidence from a study by Yoo et al. (2025) provides the first prospective human neuroimaging evidence that twelve weeks of a structured aerobic exercise program increases potential glymphatic influx and meningeal glymphatic vessels flow, along with a decrease in circulating proinflammatory proteins. This evidence served as the basis of a comprehensive literature review by Ghayourvahdat et al. (2026), which synthesised preclinical animal model and human data and advocated exercise as a non-pharmacological strategy to promote glymphatic clearance and reduce neurodegenerative risk.

Despite these developments in our understanding of how exercise affects glymphatic function in the human brain, the mechanistic relationship still remains incompletely characterised. Direct measurement of glymphatic activity in living humans requires invasive intrathecal contrast procedures unsuitable for exercise research; available non-invasive surrogates provide only indirect estimates of CSF-ISF dynamics. The field is therefore at an early but promising stage, with a mechanistically coherent framework supported by convergent preclinical and preliminary human evidence, but requiring further prospective investigation.

The aim of this narrative review is to synthesise current knowledge across three intersecting topics: (1) the physiological processes involved in regulating glymphatic transport; (2) the link between exercise and glymphatic activity as shown by both experimental and human studies; and (3) the indirect pathways through which physical activity may influence brain waste clearance, including effects on cerebrovascular function, sleep architecture, and neuroinflammatory signalling. By integrating these three domains, the review aims to provide a conceptually coherent account of how physical activity may support brain health through glymphatic mechanisms, and to identify the most important areas for future research.

Methods

A literature search was conducted using the PubMed database. The search was limited to articles published after 2012, coinciding with the initial experimental characterisation of the glymphatic pathway. The following search terms were each used independently and in

various combinations: "glymphatic system," "cerebrospinal fluid clearance," "perivascular pathway," "aquaporin-4," "exercise," "physical activity," "cerebrovascular function," "sleep architecture," "slow-wave sleep," "NREM sleep," and "brain waste clearance." The reference lists of the included studies were analysed manually to identify additional relevant publications.

Studies were eligible for inclusion if they examined glymphatic physiology or CSF-ISF exchange mechanisms, investigated the relationship between physical activity or exercise and brain physiology relevant to glymphatic transport, or were original experimental studies, observational studies, or peer-reviewed narrative or systematic reviews addressing these domains. Animal studies were included if they provided mechanistic evidence not yet available from human research.

Because the studies differed in design and population, the results were combined and analysed narratively rather than quantitatively. There was no appraising instrument utilised for the quality of the studies, as is in accordance with a narrative review. Studies were selected based on having a well-defined experimental protocol and reproducible methodology, and were published in indexed journals.

Results

Physiological Mechanisms of Glymphatic Transport

The glymphatic system operates as a fluid clearance network that encompasses the entire brain, organised around perivascular channels that run along the external surfaces of cerebral arteries, capillaries, and veins. CSF, produced primarily by the choroid plexus, circulates through the subarachnoid space and enters the brain parenchyma through periarterial spaces. Within the parenchyma, CSF mixes with ISF through a process of convective bulk flow, driven in part by arterial wall pulsations generated during the cardiac cycle (Iliff et al., 2013). The exchanged fluid carries interstitial solutes, including metabolic by-products (such as amyloid-beta, tau, alpha-synuclein, and lactate), toward perivenous drainage pathways and subsequently into meningeal lymphatic vessels and the systemic circulation (Tarasoff-Conway et al., 2015).

The central molecular basis of this system is AQP4, which demonstrates unusually high levels of expression in astrocytic endfeet, forming a continuous sheath around cerebral blood vessels. Polarisation of perivascular AQP4 provides a low-resistance pathway for water movement between the CSF compartment and the parenchymal ISF, enabling convective flow that sustains glymphatic clearance. The functional significance of this

localisation is underscored by experiments in AQP4 knockout mice, in which interstitial tracer clearance is reduced by approximately 70% compared with wild-type animals (Iliff et al., 2012). Conditions that disrupt AQP4 polarisation - including traumatic brain injury, neuroinflammation, and normal ageing - negatively affect glymphatic transport consistently, demonstrating that AQP4 localisation is a major modifiable influence on clearance efficiency (Jessen et al., 2015).

Glymphatic circulation also relies on other physiological forces, aside from water movement associated with aquaporin-4 (AQP4). Arterial pulsatility, generated by cardiac contraction and transmitted along vessel walls, has been proposed as a primary driver of perivascular CSF influx (Iliff et al., 2013). Another contributor to the movement of CSF within the cranial cavity is the oscillatory changes in intracranial pressure that occur with respiration. Recent evidence suggests that slow vasomotion - rhythmic oscillations in cerebral arterial tone - is an important regulator of pulsatile CSF flow during sleep. Additionally, the glymphatic system is functionally connected to the meningeal lymphatic system, which provides an exit route for interstitial solutes drained from the perivenous compartment (Tarasoff-Conway et al., 2015). Impairment of meningeal lymphatics in aged mice reduces glymphatic clearance and promotes amyloid-beta accumulation, highlighting the interdependence of these two clearance systems.

There are many different types of evidence that all point towards the sleep-dependence of glymphatic activity. Xie et al. (2013) found that during sleep, the volume of the cortical interstitial space increases by 60%, thereby increasing the volume of fluid exchange (CSF-ISF) compared with being awake. This expansion was shown to facilitate more rapid clearance of fluorescent tracers and, crucially, of endogenously produced amyloid-beta. The mechanism appears to involve the suppression of norepinephrine during NREM sleep. While awake, norepinephrine provides support for cellular volume regulation and decreases the amount of interstitial fluid present in the brain, restricting glymphatic drainage. Hablitz et al. (2019) expanded on these previous findings by demonstrating that there is a positive correlation between glymphatic influx under anaesthesia and EEG delta power, and an inverse correlation with heart rate, linking the neurophysiological characteristics of deep NREM sleep specifically to glymphatic efficiency.

Hauglund et al. (2025) have provided the most mechanistically detailed description of how glymphatic function is regulated during sleep through the use of fiber photometry and widefield imaging in mice, characterising the neurovascular dynamics driving clearance during NREM sleep. In their analysis, they found that the strongest predictors of

parenchymal clearance were coordinated oscillations at around 0.1 Hz, including slow fluctuations in locus coeruleus norepinephrine release, cerebral blood volume changes (vasomotion), and phasic CSF influx events. These data support the idea that the glymphatic system functions as an oscillatory phasic-driven clearance mechanism rather than a continuous state of clearance. This mechanistic insight has direct implications for understanding how any intervention that modifies noradrenergic tone, sympathetic activation, or sleep architecture (including exercise) may alter glymphatic functioning.

To accurately and directly measure glymphatic transport in humans, intrathecal injection of gadolinium-based contrast agents is required, followed by a series of MRI scans. However, this process is invasive and impractical for most research contexts. To address this limitation, several non-invasive methods have been developed to estimate glymphatic transport. These include the DTI-ALPS index (diffusion tensor imaging analysis along the perivascular space), which estimates water diffusivity in the perivascular compartment; perivascular space (PVS) volume on T2-weighted MRI, where enlarged PVSs may indicate impaired drainage; and plasma or CSF concentrations of amyloid-beta and tau as indirect markers of clearance efficiency. Each of these non-invasive measures captures different aspects of glymphatic physiology, but each has significant technical limitations. None of these measures has been fully validated against direct clearance measurements, and their interpretation requires caution (van Hattem et al., 2025). Hablitz and Nedergaard (2021) provided a comprehensive review of glymphatic biology and its measurement challenges, noting that the development of reliable non-invasive human biomarkers remains one of the most important methodological needs in the field.

Direct Experimental Evidence Linking Exercise to Glymphatic Activity

The experiment conducted by He et al. (2017) provided the first systematic evidence for the hypothesis that exercise improves glymphatic function. Using in vivo two-photon imaging to examine the dynamics of fluorescent tracers, they found that the glymphatic clearance in exercising mice was significantly greater than that in age-matched sedentary controls. The effect of exercise on glymphatic clearance was also associated with the restoration of perivascular polarisation of AQP4, which declines with normal ageing; a marked reduction in reactive astrogliosis and microglial activation; decreased parenchymal amyloid-beta accumulation; and preservation of dendritic spine density in the hippocampus. Because of the concurrent improvements observed in glymphatic clearance, neuroinflammation, and AQP4 localisation, it is possible that exercise may act through a unified mechanism in

which reduced neuroinflammatory signalling restores astrocytic AQP4 polarisation, thereby reinstating the structural basis for efficient glymphatic transport.

Von Holstein-Rathlou et al. (2018) extended these findings to young, healthy mice, demonstrating that several weeks of voluntary wheel running increased CSF tracer influx across multiple brain regions compared with sedentary controls, establishing that the glymphatic-enhancing effects of exercise are not restricted to the ageing brain. An important negative finding in this study was that no increase in glymphatic influx was detectable during acute exercise itself - indeed, glymphatic function appeared transiently suppressed during active running relative to the resting state. This dissociation between acute exercise and subsequent sleep-period clearance is mechanistically consistent with the Hauglund et al. (2025) framework: during exercise, elevated sympathoadrenal activity and high locus coeruleus norepinephrine release reduce interstitial space volume and suppress CSF influx, while the subsequent low-norepinephrine state of post-exercise NREM sleep creates the conditions for enhanced clearance. This finding underscores that the glymphatic benefits of exercise are likely realised primarily during the recovery sleep period, not during the exercise bout itself.

Liang et al. (2025) investigated the exercise-glymphatic relationship in a transgenic APP/PS1 mouse model of Alzheimer's disease, examining the effects of four weeks of aerobic swimming training. Exercised mice demonstrated enhanced CSF-ISF exchange as measured by parenchymal tracer distribution, restored hippocampal AQP4 polarisation that had been disrupted by amyloid pathology, and significant reductions in amyloid-beta plaque burden. Importantly, the study employed adeno-associated viral vector-mediated knockdown of AQP4 expression to establish causality: animals in whom AQP4 was suppressed failed to show the cognitive improvements observed in normally exercising transgenic mice, even when exercise was performed, establishing AQP4-dependent glymphatic transport as a necessary mechanistic intermediary - not merely a correlate - of exercise-related neuroprotection in this model.

Human evidence for exercise-related enhancement of glymphatic function remained largely absent until the prospective neuroimaging study by Yoo et al. (2025), published in Nature Communications. In this study, healthy adult volunteers were randomised to a twelve-week structured aerobic exercise programme using a cycle ergometer, with imaging conducted before and after the intervention. Post-exercise MRI using intravenous contrast-enhanced dynamic T1 mapping demonstrated a significant increase in putative glymphatic influx specifically within the putamen - a region implicated in motor learning and reward

processing. Black-blood MRI of meningeal lymphatic vessels demonstrated significant increases in vessel calibre and estimated flow following the exercise intervention. Plasma proteomics identified significant decreases in circulating pro-inflammatory proteins - including S100A8, S100A9, PSMA3, and DEFA1A3 - and increases in immunoglobulin J chain, with changes in these inflammatory markers correlating significantly with the imaging-derived measures of glymphatic influx. These findings collectively constitute the most direct human evidence currently available that sustained aerobic exercise enhances brain clearance pathway function, and implicate neuroinflammation reduction as a key mechanistic bridge.

Synthesising the preclinical and human evidence, Ghayourvahdat et al. (2026) conducted a comprehensive review that identified exercise as a potent non-pharmacological strategy to enhance glymphatic clearance, preserve neural homeostasis, and potentially reduce neurodegenerative risk. The review confirmed that the benefits of exercise on glymphatic function appear to be highly dependent on AQP4 expression and on the timing of the exercise intervention relative to established pathological processes. The authors drew particular attention to the methodological challenges facing the field - including the limitations of non-invasive imaging surrogates, the difficulty of establishing causality in human studies, and the current reliance on relatively short-term interventions - calling for longitudinal, multimodal studies that integrate neuroimaging, cardiovascular, sleep architecture, and cognitive outcome measures.

Exercise, Cerebrovascular Function, and Glymphatic Physiology

Arterial pulsatility is a primary mechanical driver of CSF movement along perivascular pathways, and conditions that reduce vascular compliance - including hypertension, arterial stiffness, and normal ageing - are associated with diminished glymphatic influx (Iliff et al., 2013). Regular aerobic exercise exerts well-documented beneficial effects on the vascular system, including improvements in endothelial function, increases in arterial compliance, reductions in pulse wave velocity, and augmentation of resting and exercise-induced cerebral blood flow (Barnes & Corkery, 2018). These adaptations are plausibly relevant to glymphatic function because greater arterial elasticity and more effective pulsatile energy transmission along vessel walls may augment the driving force for perivascular CSF influx. In support of this vascular mechanism, studies in aged mice have demonstrated that exercise-related restoration of cerebrovascular pulsatility accompanies improvements in glymphatic clearance (He et al., 2017). The human study by Yoo et al. (2025) similarly reported exercise-associated improvements in vascular imaging markers alongside

glymphatic outcomes, although disentangling vascular from anti-inflammatory contributions to the observed glymphatic changes was not possible within the study design. Ghayourvahdat et al. (2026) identified enhanced vascular dynamics as one of the four principal mechanistic pathways through which exercise supports glymphatic clearance, noting that the combination of improved arterial pulsatility, reduced peripheral and cerebral vascular resistance, and enhanced endothelial nitric oxide bioavailability may act in concert to augment perivascular CSF influx. Prospective studies specifically designed to quantify exercise-induced changes in cerebrovascular pulsatility alongside glymphatic surrogates are needed to establish the magnitude of this contribution.

Exercise, Sleep Architecture, and Glymphatic Clearance

The relationship between sleep and glymphatic function is one of the most robustly established findings in the field. Deep NREM slow-wave sleep, characterised by high-amplitude EEG delta oscillations and the lowest levels of locus coeruleus norepinephrine activity, represents the physiological state most favourable for glymphatic clearance (Xie et al., 2013; Hablitz et al., 2019; Hauglund et al., 2025). Conversely, sleep deprivation, sleep fragmentation, and conditions that suppress slow-wave sleep have been associated with elevated CSF amyloid-beta concentrations and enlarged perivascular spaces in human studies, consistent with impaired clearance (van Hattem et al., 2025).

Physical activity has been consistently associated with improvements in sleep architecture. A meta-analysis by Kredlow et al. (2015) concluded that exercise is associated with significant improvements in total sleep time, sleep efficiency, sleep onset latency, and - most relevantly - slow-wave sleep duration, with effects most pronounced in middle-aged and older adults and in individuals with pre-existing sleep difficulties. The mechanisms through which exercise promotes slow-wave sleep likely include temperature-mediated effects (post-exercise core body temperature decline promotes sleep initiation and slow-wave sleep), adenosine accumulation during prolonged physical effort, and circadian rhythm stabilisation through regular daytime activity patterns.

Van Hattem et al. (2025), in a comprehensive review of strategies to modulate glymphatic clearance through sleep physiology, explicitly identified regular physical activity as a behavioural approach to enhancing glymphatic function via its effects on sleep architecture. The review noted that the magnitude of slow-wave sleep augmentation achievable through exercise is likely sufficient to produce meaningful changes in glymphatic clearance based on the dose-response relationship between delta power and glymphatic influx established by Hablitz et al. (2019). Ghayourvahdat et al. (2026) similarly identified sleep quality

improvement as one of the central mediating pathways through which exercise enhances glymphatic function, emphasising that the post-exercise sleep period is the primary window during which exercise-induced glymphatic enhancement occurs.

The timing of exercise relative to sleep onset is an important practical consideration. High-intensity exercise performed within two to three hours of habitual sleep time can delay sleep onset, reduce sleep efficiency, and suppress slow-wave sleep - effects attributable to persistent sympathoadrenal activation and sustained core body temperature elevation (Dolezal et al., 2017). These acute sleep-disruptive effects of late-evening intense exercise may transiently counteract the longer-term sleep architecture benefits of habitual exercise. For the purpose of maximising post-exercise glymphatic clearance, moderate-intensity exercise completed at least three hours before sleep onset is likely to be more beneficial than high-intensity late-evening exercise, though direct evidence specifically examining this relationship in the context of glymphatic outcomes is not yet available.

Neuroinflammation, AQP4 Polarisation, and the Exercise Effect

Neuroinflammation and reactive astrogliosis represent a convergent pathway through which ageing, neurodegenerative pathology, and poor lifestyle factors impair glymphatic function. Activated astrocytes undergo morphological changes - including retraction of perivascular endfeet and redistribution of AQP4 away from the perivascular membrane - that reduce the efficiency of CSF-ISF exchange. Activated microglia contribute to a pro-inflammatory parenchymal environment that perpetuates astrocytic dysfunction and vascular inflammation (Jessen et al., 2015). These neuroinflammatory processes are particularly prominent in the ageing brain and in the early stages of amyloid-beta accumulation, creating a pathological cycle in which impaired glymphatic clearance promotes further protein aggregation and neuroinflammation.

Exercise is among the most potent lifestyle interventions for reducing neuroinflammatory signalling. In the study by He et al. (2017), aged mice performing voluntary wheel running demonstrated significant reductions in GFAP-positive reactive astrocytes and Iba1-positive activated microglia, accompanied by restoration of AQP4 perivascular polarisation and enhanced glymphatic clearance. The causal importance of this anti-inflammatory-AQP4 axis was further supported by Liang et al. (2025), who showed that AQP4 knockdown abolished the cognitive and clearance benefits of exercise in Alzheimer model mice despite unchanged levels of exercise-induced anti-inflammatory signalling. Olegário et al. (2024) proposed that exercise-induced reduction of neuroinflammation may represent the primary upstream mechanism through which exercise restores glymphatic function, with improved

AQP4 polarisation as the direct structural consequence, and enhanced clearance as the functional outcome.

In humans, Yoo et al. (2025) provided translational evidence consistent with this pathway, demonstrating that exercise-associated reductions in circulating S100A8 and S100A9 - calcium-binding proteins involved in innate immune activation and neuroinflammatory signalling - correlated significantly with improvements in MRI-derived glymphatic influx markers. Wang and Li (2025) synthesised these findings in a broader review, identifying AQP4 polarisation restoration, vascular enhancement, neuroinflammation reduction, and sleep improvement as the four interdependent mechanisms through which exercise supports glymphatic clearance, and noting that targeting these pathways simultaneously through regular physical activity may yield benefits greater than those achievable by addressing any single pathway in isolation.

Discussion

This review has synthesised evidence from glymphatic neuroscience, exercise physiology, sleep research, and neuroinflammation biology to characterise the potential interactions between physical activity and brain waste clearance. The central finding is that a mechanistically coherent and empirically supported framework exists linking regular physical activity to enhanced glymphatic function - a framework resting on four converging pathways: improvements in cerebrovascular pulsatility, augmentation of slow-wave sleep, reduction of neuroinflammation and restoration of AQP4 polarisation, and direct enhancement of CSF-ISF exchange dynamics. Each of these pathways has independent experimental support, and their convergence suggests that the relationship between exercise and glymphatic function may be substantial in magnitude and robust across different physiological contexts.

The animal model evidence is the most mechanistically detailed and internally consistent. Studies spanning aged mice, young mice, and transgenic Alzheimer models demonstrate that voluntary exercise enhances glymphatic clearance through AQP4-dependent mechanisms, reduces neuroinflammatory activation, and prevents or partially reverses the age-related decline in glymphatic efficiency (He et al., 2017; von Holstein-Rathlou et al., 2018; Liang et al., 2025). The causal relationship between exercise, AQP4 polarisation, and glymphatic clearance has been established through genetic intervention studies, providing a level of mechanistic rigour not yet achievable in human research. Nevertheless, important caveats apply to the translation of these findings. Rodents sleep in polyphasic patterns, have

substantially higher metabolic rates, and differ from humans in brain anatomy, AQP4 distribution, and amyloid-beta metabolism. The exercise modalities employed - principally voluntary wheel running and forced swimming - do not directly correspond to human aerobic exercise patterns, and the duration and intensity of exercise relative to total rest time differs substantially between species.

The human evidence, while limited in quantity, is nonetheless encouraging. The prospective study by Yoo et al. (2025) is methodologically significant: it employed a controlled exercise intervention with pre-post neuroimaging, demonstrated changes in both putative glymphatic influx and meningeal lymphatic function, and linked these imaging changes to correlated shifts in inflammatory biomarkers - providing a chain of evidence from the intervention through a plausible mechanism to a measurable brain health outcome. This study is, however, a single investigation with a relatively small sample of healthy adults, and the imaging markers employed (intravenous contrast-enhanced T1 mapping, black-blood meningeal vessel imaging) represent indirect and not fully validated proxies for glymphatic transport. Replication in larger samples, older populations, and individuals with neurological risk factors is needed before firm conclusions can be drawn about the clinical significance of exercise-induced changes in these markers.

A critical mechanistic nuance emerging from this synthesis concerns the temporal dissociation between exercise and glymphatic enhancement. Von Holstein-Rathlou et al. (2018) demonstrated that acute exercise suppresses rather than enhances glymphatic influx, and the mechanistic work of Hauglund et al. (2025) provides a clear explanation: the high norepinephrine environment during exercise reduces interstitial space volume and inhibits the slow vasomotion-CSF coupling that drives glymphatic clearance. The benefit of exercise on glymphatic function is therefore not a direct, immediate effect of the exercise session itself, but rather an indirect, delayed effect mediated by the subsequent sleep period - specifically by the promotion of deeper and more efficient slow-wave sleep in which low norepinephrine, high delta power, and synchronised vasomotion create optimal conditions for clearance. This temporal dissociation has important practical implications: exercise programmes that impair sleep quality - whether through excessive intensity, poor timing relative to sleep, or cumulative fatigue - may not confer the expected glymphatic benefits and could theoretically impair clearance if they reduce slow-wave sleep. These considerations are particularly relevant in athletic populations, in whom high training loads have been documented to reduce slow-wave sleep and overall sleep quality.

The role of exercise timing relative to sleep deserves particular attention given its practical relevance. Dolezal et al. (2017) identified late-evening high-intensity exercise as a risk factor for sleep disruption through thermogenic and sympathetic mechanisms, while moderate-intensity exercise earlier in the day was consistently associated with improved sleep architecture. For the specific purpose of optimising post-exercise glymphatic clearance, the available evidence would support exercise at times that maximise the subsequent slow-wave sleep opportunity - favouring morning or early afternoon sessions for most individuals, and avoiding high-intensity exercise within approximately three hours of sleep onset. However, it must be acknowledged that no study has directly examined this timing question in the context of measured glymphatic outcomes, and this represents one of the most practically important gaps in the current evidence base.

The neuroinflammatory pathway is notable for the degree of mechanistic convergence it offers. Neuroinflammation reduces AQP4 polarisation, impairs glymphatic clearance, promotes amyloid-beta accumulation, and perpetuates further inflammation - a self-amplifying cycle that exercise may interrupt at multiple points. The correlation between exercise-induced reductions in inflammatory proteins and imaging markers of glymphatic improvement in the Yoo et al. (2025) human study is particularly encouraging, as it suggests that the anti-inflammatory effects of exercise observable in the peripheral circulation reflect changes that are meaningfully linked to central clearance mechanisms. Whether reducing neuroinflammation through exercise can halt or reverse established glymphatic dysfunction in neurodegenerative disease - rather than merely preserving function in healthy individuals - remains an open question of substantial clinical relevance.

The practical implications of this synthesis extend beyond the question of how much exercise to prescribe. If the glymphatic benefits of exercise are mediated substantially through sleep architecture, then optimising sleep quality in exercising individuals becomes as important as the exercise itself. This is relevant not only for the general population but particularly for athletes and individuals in demanding occupational roles in whom sleep restriction is common. Conversely, in populations with obstructive sleep apnoea or other sleep disorders - conditions characterised by chronic slow-wave sleep suppression and associated with accelerated amyloid-beta accumulation - exercise may provide partial benefit through non-sleep-dependent pathways (vascular and anti-inflammatory), while sleep disorder treatment may be necessary to fully restore glymphatic function. The interdependence of exercise and sleep as modulators of glymphatic physiology suggests that

integrative interventions targeting both simultaneously may be more effective than either alone.

Several important methodological limitations affect the conclusions of this review. The narrative design does not permit formal quantitative synthesis and is susceptible to selection bias in the choice of included studies. The majority of available mechanistic evidence derives from rodent models that may not translate directly to human physiology. Human studies are small, typically short-term, and reliant on indirect glymphatic surrogates whose validity as proxies for actual CSF-ISF exchange remains incompletely established. No study has yet prospectively examined glymphatic function across a full exercise training programme in humans while simultaneously monitoring sleep architecture with polysomnography - the combination that would most directly address the central hypothesis of this review. Finally, the optimal exercise dose, modality, intensity, and timing for glymphatic benefit in humans remains entirely uncharacterised.

Conclusions

The glymphatic system has emerged as a fundamental mechanism of brain homeostasis, responsible for the sleep-dependent clearance of metabolic waste products from the central nervous system through coordinated CSF-ISF exchange driven by arterial pulsatility, astrocytic AQP4-mediated water transport, and the neuromodulatory environment of NREM slow-wave sleep. Dysfunction of this system - whether through sleep disruption, ageing, neuroinflammation, or loss of AQP4 perivascular polarisation - impairs the clearance of amyloid-beta and tau, contributing to the pathophysiological processes underlying neurodegenerative disease.

The evidence reviewed here supports the proposition that regular physical activity may enhance glymphatic function through multiple converging and mutually reinforcing mechanisms. In animal models, voluntary exercise has consistently been shown to increase glymphatic influx, restore AQP4 polarisation, reduce neuroinflammatory activation, and decrease amyloid-beta accumulation - with the AQP4-dependence of these effects established through genetic intervention. In humans, the first prospective neuroimaging evidence demonstrates that twelve weeks of structured aerobic exercise increases putative glymphatic influx and meningeal lymphatic flow, with correlated reductions in circulating inflammatory proteins. Exercise also promotes slow-wave sleep - the physiological state of maximal glymphatic activity - through thermogenic, adenosinergic, and circadian mechanisms, providing an important indirect pathway to enhanced clearance.

Cerebrovascular improvements associated with exercise training may additionally augment the arterial pulsatility that drives perivascular CSF influx.

A critical mechanistic insight emerging from this synthesis is that the glymphatic benefits of exercise are not realised during the exercise session itself - during which sympathoadrenal activation suppresses glymphatic function - but rather during the subsequent sleep period, in which the low noradrenergic state of deep NREM sleep creates optimal conditions for CSF-ISF exchange. This temporal dissociation implies that the sleep opportunity following exercise is an essential component of the clearance benefit, and that interventions or lifestyle factors that impair post-exercise sleep quality may attenuate or negate the expected glymphatic effects of physical activity. Exercise prescription for brain health should therefore attend not only to the characteristics of the exercise itself but to the sleep conditions it engenders.

The current evidence base has important limitations: most mechanistic data originate from animal models, human studies are small and rely on indirect glymphatic surrogates, and no study has yet prospectively characterised glymphatic outcomes across a structured exercise programme with concurrent polysomnographic sleep monitoring. These gaps represent the most important priorities for future research. Longitudinal studies combining controlled exercise interventions with validated neuroimaging assessment of glymphatic function, polysomnographic sleep characterisation, and measurement of neuroinflammatory biomarkers are needed to establish the clinical magnitude of exercise-related glymphatic enhancement in humans, to identify the exercise characteristics that optimise this effect, and to determine whether such enhancement is achievable in populations with established neurodegenerative risk.

Despite these limitations, the convergence of animal, human, and mechanistic evidence provides a scientifically credible and practically accessible framework for recommending regular physical activity as a strategy to support glymphatic function and long-term brain health. Sleep quality and exercise interact as interdependent determinants of glymphatic clearance, and integrative lifestyle approaches targeting both simultaneously may offer greater neurological benefit than either intervention alone. Understanding how physical activity influences the glymphatic system may ultimately contribute to evidence-based strategies for the prevention of neurodegenerative disease.

Disclosure

Author's contribution

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