The biomechanical Breakdown of the Glymphatic System in Early-Onset Alzheimer's Disease: A Systematic Review

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Abstract

This systematic review focuses on the biomechanical and molecular breakdown of the glymphatic system in Early-Onset Alzheimer's Disease. In contrast to past studies focusing on amyloid-beta overproduction, new perspectives suggest the disorder is caused by the functional failure of the brain's innate clearance system. The transition into the non-rapid eye movement (NREM) phase acts as a mechanical trigger that expands the extracellular space, allowing cerebrospinal fluid to drive out neurotoxic waste through Aquaporin-4 (AQP4). Furthermore, the Intramural Periarterial Drainage (IPAD) pathway harnesses the rhythmic pulsations of arterial blood vessels to pump and clear toxic metabolic waste. A novel "Two-Hit" hypothesis suggests that when inherent genetic vulnerability combines with disrupted sleep architecture, it creates a continuous positive feedback loop of toxic protein accumulation and vascular damage. Findings underscore the need to incorporate polysomnography and neuroimaging biomarkers (like the DTI-ALPS index) into longitudinal research to develop preventative treatments aimed to restore hydrodynamic balance within the brain.

Introduction

The human brain lacks a lymphatic vascular function to filter and clear away the innate constantly generated metabolic wastes from cellular and neural functions. The human central nervos system relies on the complex internal fluid-transport network known as the glymphatic system instead of the lymphatic network. This internal, biological "plumbing system" operates by actively utilizing the brain's cerebrospinal fluid (CSF), driving it to wash deeply through the interstitial spaces of the brain tissue in a convective manner, which effectively and physically flushes out deeply embedded neurotoxic metabolic byproducts, including the highly destructive amyloid-β (Aβ) protein aggregates.The glymphatic system functions by actively driving cerebrospinal fluid (CSF) into the interstitial spaces of the brain tissues, and the efficiency and success of this waste clearance system is inherently dependent on the presence of properly functioning Aquaporin-4 (AQP4) water channels, tiny structural proteins distributed along the astrocytic endfeet (Chen et al., 2024). The activity of AQP4 channels are optimized when these critical AQP4 channels are optimally positioned and structurally polarized exactly at these vital perivascular boundaries, they function as incredibly efficient, high-pressure liquid conduits. They actively facilitate the rapid exchange of fluids between the incoming cerebrospinal fluid (CSF) and the surrounding interstitial fluid (ISF), essentially acting as a microscopic power-washer to sweep away stagnant cellular debris.

Inevitably with aging, the human brain declines in efficiency with this waste clearance function. While the general link between AQP4 dysfunction and late-onset Alzheimer's disease has been

well established, there is still a significant gap of knowledge regarding exactly how early-stage structural detachments and hydrodynamic fluid failures might affect the early-onset Alzheimer's Disease (EOAD). Furthermore, despite the modern incorporation of Intramural Periarterial Drainage (IPAD) pathway in studies suggesting a likely correlation,only a very few studies have investigated and synthesized exactly how that occurs during deep N3 slow-wave sleep affects the pathways to prevent early neurodegeneration (Esmaeli, 2025). To address this gap of knowledge, this systematic review synthesizes the information from current and recent literature on biomechanics of glymphatic and IPAD clearance, analyzing the primary role of sleep architecture and AQP4 polarization amyloid-beta proteostasis.

Methods

To investigate the biomechanical and molecular breakdown of the brain's glymphatic clearance system and its relationship to the EOAD, a comprehensive literature search was conducted. Articles were retrieved primarily through the Google Scholar database with the institutional journal access provided by the Georgia Institute of Technology Library. To allow for more targeted investigation, search parameters were focused on peer-reviewed literature published in recent years to capture the most current scientific consensus on neuro-fluid dynamics, sleep architecture, and proteostasis.

Specifically, the primary search terms included combinations of the following keywords: Glymphatic system, Aquaporin-4 (AQP4) polarization, cerebrospinal fluid (CSF) hydrodynamics, slow-wave sleep (N3), and Amyloid-β kinetics. The paper selection was focused on studies that provided mechanistic or quantitative data for AQP4 localization, glymphatic fluid movement, or amyloid clearance rates to maintain focus of the review.

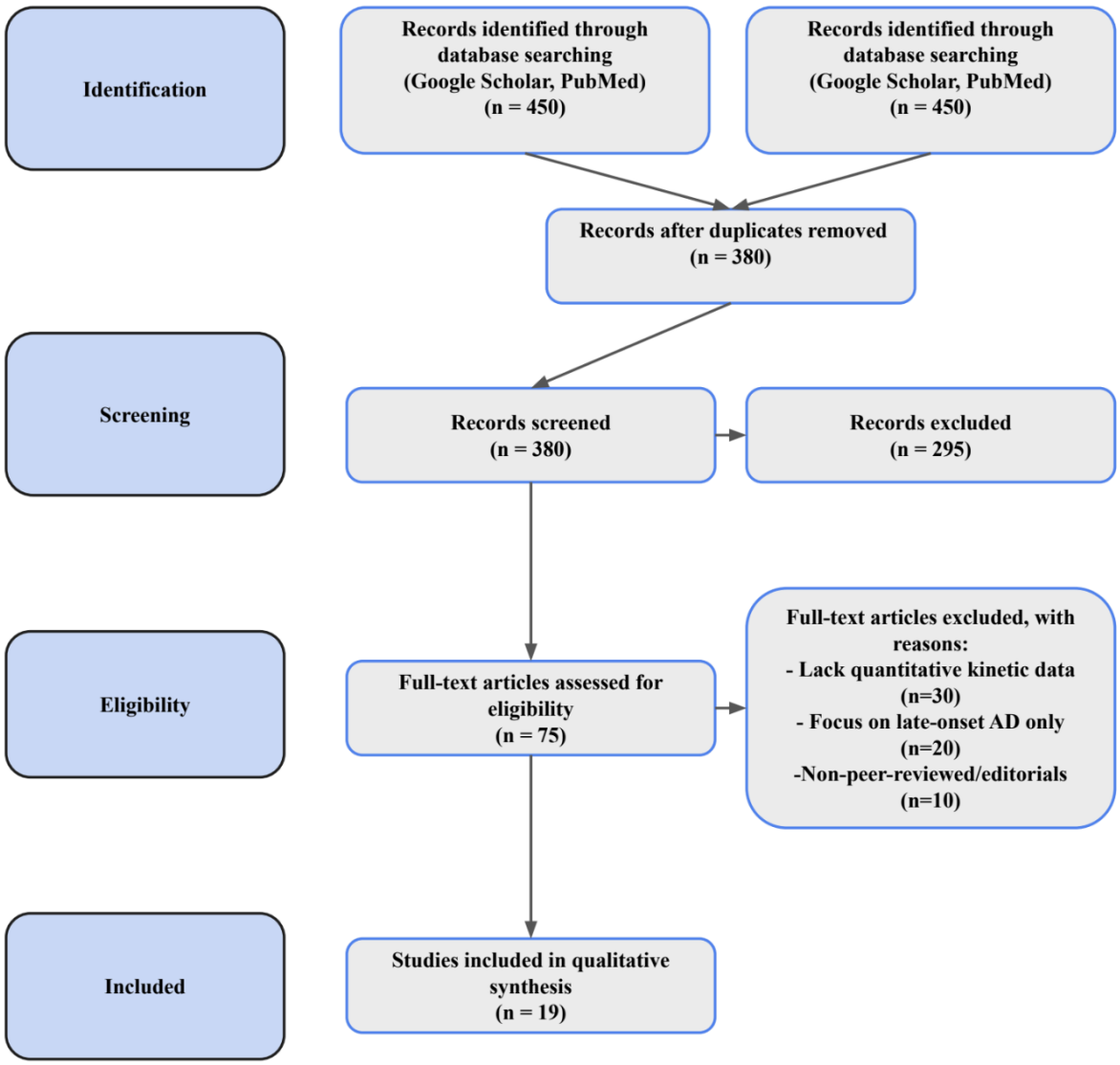

Figure 1.1 PRISMA flow diagram illustrating the screening process of the review.

Results and Discussion

The Molecular Machinery: AQP4 and the Perivascular Space

Before addressing the pathological accumulation of neurotoxic proteins, it is necessary to establish the model of healthy, operational infrastructure of the brain's waste disposal system. In healthy models, the glymphatic system actively facilitates the penetration of cerebrospinal fluid (CSF) into the brain tissues, allowing for chemical exchange with the existing interstitial fluid (ISF) to successfully export toxic metabolic byproducts from the brain (Bohr et al., 2022). The overall efficiency fluid exchange process heavily relies on the presence and functionality of Aquaporin-4 (AQP4) water-conducting channels. Under this state, these AQP4 channels are highly polarized, meaning that they are positioned exactly at the astrocytic endfeet, directly contacting the perivascular space surrounding the blood vessels (Bohr et al., 2022). With this

optimal structure, the orthogonal arrays of particles (OAP) are formed to strengthen cellular hydropermeability and support homeostasis of potassium ions inside and outside the cell (Ma & Zhang, 2025). Cerebrospinal fluids are then strongly propelled through the brain tissue scaffolds, removing neurotoxic debris including amyloid-beta (Bohr et al., 2022), tightly packed brain tissue, effectively power-washing the brain and successfully sweeping away dangerous neurotoxic debris, which notably includes the highly dangerous, soluble oligomeric forms of amyloid-beta (Aβ).

Proteostasis and the Kinetics of Amyloid Clearance

In contrast to historical perspectives that focused on the biological overproduction of amyloid beta protein as the primary cause of the disease, modern analysis of data suggests the failure of the brain's fluid clearance system as the stronger cause of neurodegenerative diseases. For instance, studies quantified that amyloid beta protein variants' half-life within the brain is significantly increased—by approximately 60%—over 50 years of aging, indicating failure in the functional efficiency of the brain's clearance system in clearing out the amyloid beta proteins (Bohr et al., 2022). This evidence establishes that the brain's innate plumbing system declines in functionality. This profound kinetic failure in clearance speed is deeply, inextricably intertwined with a massive microscopic structural breakdown occurring at the cellular level. This kind of decline in functional capacity is mainly due to intrinsic and extrinsic factors that leads to instability at the endfeets of AQP4, causing it to undergo depolarization that ultimately leads to dysfunction in glymphatic clearance and the build-up of neurotoxic proteins (Ma & Zhang, 2025). This loss of AQP4 is therefore the primary cause that is directly correlated to the brain's accumulation of neurotoxins, which explains the aggressive onset of EOAD in patients with premature clearance rate decline (Ma & Zhang, 2025).

Sleep Architecture and the Biomechanics of Fluid Hydrodynamics

While the precise microscopic polarization and structural anchoring of Aquaporin-4 (AQP4) channels successfully provides the necessary anatomical "hardware" and physical infrastructure required for massive fluid exchange, it is absolutely critical to understand that this entire plumbing system remains largely dormant, sluggish, and highly inactive during standard periods of daytime wakefulness (Boespflug & Iliff, 2018). Although polarization of AQP4 provides the infrastructure required for fluid exchange, it is important to acknowledge that the fluid exchange system is mostly inactive when the brain is awake (Bohr et al., 2022). The transition from the state of wakefulness to non-rapid eye movement (NREM) slow-wave sleep, on the other hand, triggers the waste clearance (Lyckenvik et al., 2025). A recent study refers to mice models that were used in previous studies to record the difference in glymphatic clearance activity during sleep, in which they found the mice's extracellular space doubling from 14% during the awake state to 24% during NREM (Bohr et al., 2022). This expansion in space between brain cells allows for more cerebrospinal fluid flow, therefore it facilitates the clearance of neurotoxic waste

accumulation such as amyloid beta protein from the brain, preventing the plaques from forming (Chen et al., 2024; Mullins et al., 2025).

The IPAD Pathway and Arterial Pulsatility

The glymphatic system's convective flow of cerebrospinal fluid is further enhanced by a secondary waste removal system referred to as Intramural Periarterial Drainage (IPAD) pathway (Esmaeli, 2025). In contrast to the glymphatic system, which washes the fluid through the spaces outside the blood vessels, the IPAD pathway squeezes the fluid as well as toxic wastes directly through the dense walls of arteries. This process is primarily driven by the rhythmic physical contraction/expansion of the smooth muscle cells in the arteries, squeezing ISF along the directional path of the contractional wave (Esmaeli, 2025). Therefore, the physical pulsing throughout the blood vessels contributes to the clearance of neurotoxins by acting as the pump (Esmaeli, 2025; Vikner et al., 2024). Additionally, the blood pressure and arterial pulse change that occur during the N3 slow-wave sleep drives the pumps for IPAD.

The Pathological Feed-Forward Cycle of Sleep Deprivation

Both glymphatic expansion and IPAD pumping mechanisms rely heavily on NREM; therefore, there is a clear relationship between the sleep deprivation and amyloid beta accumulation that can be described as a “positive feedback loop” (Ahern et al., 2025). Aging itself already disrupts the brain’s capability to enter deep slow-wave sleep, which consequently, limits the brain’s waste clearance process, thus increasing amyloid beta accumulation. In return, the accumulated neurotoxin eventually damages the areas of the neural network required to enter deep sleep (Gao et al., 2025; Mullins et al., 2025). This accumulation further impairs the efficiency of the clearance process and potentially promotes disease processes, creating a loophole of consequences (Ahern et al., 2025; Can et al., 2025). To expand even more, sleep deprivation not only contributes to the loss of clearance time, but it also is a direct contributing factor to the structural failure by increasing stress that “drives AQP4 mis-localization,” leading to AQP4 depolarization (Ma & Zhang, 2025). Some studies have also suggested non-genetic factors such as respiration pattern and sleep posture as a potential contributor to glymphatic clearance efficiency during sleep (Hu et al., 2024).

Neuroimaging and Diagnostic Biomarkers in Living Humans

While the foundational, underlying biological principles governing glymphatic fluid clearance and the microscopic structural polarization of astrocytic Aquaporin-4 (AQP4) channels were historically and heavily established through the extensive use of murine (mouse) biological models, successfully transitioning this highly theoretical research over to actual, practical human clinical application absolutely requires the implementation of incredibly advanced, highly sophisticated, and strictly non-invasive neuroimaging technologies. Historically, studies of AQP4 polarization were established with mice models; however, to translate these findings to practical applications, highly sophisticated non-invasive neuroimaging technologies are needed. One

current application of this approach is the utilization of Diffusion Tensor Imaging Analysis Along the Perivascular Space (DTI-ALPS), where it provides quantitative tracking method to the microscopic movement of the fluids moving deep within the live human brain (Shang et al., 2024; Xie et al., 2024). This procedure provides an index which acts as a biological marker that considers the overall clearance efficiency (Xie et al., 2024). Importantly, a pivotal study in 2024 successfully connected the gap between the cardiovascular biomechanics with the microscopic fluid flow (Xie et al., 2024). The study found that abnormal arterial pulsation decreased ALPS scores, relating a failure in the cardiovascular pump to impaired glymphatic clearance in the brain affected by neurodegenerative disease (Touroutoglou et al., 2023).

The EOAD Phenotype and the Two-Hit Hypothesis

Achieving a deep, nuanced understanding of this absolutely catastrophic plumbing and fluid failure is entirely essential and undeniably necessary for adequately explaining the extraordinarily aggressive, fast-moving nature of Early-Onset Alzheimer's Disease (EOAD).Understanding this clearance failure and cascading consequences is important for explaining the aggressive nature of EOAD. EOAD is not just an accelerated version of Late-Onset Alzheimer (LOAD), but it is a distinct and much more aggressive condition characterized by rapid disease progression (Sirkis et al., 2022). Massive statistical meta-analyses already proved that patients with EOAD are much more likely to experience cognitive destruction and brain decline compared to older patients with LOAD (Seath et al., 2023). This kind of extraordinary acceleration can be explained through a “Two-Hit” hypothesis: a genetic vulnerability meets a biomechanical sleep deprivation to simultaneously combine to a “tipping point” (Ahern et al., 2025). Upon reaching this tipping point, the patient's body enters a positive feedback loop, where continuous neurotoxin build-up has a cascading effect on other brain functionalities including the glymphatic clearance mechanism, which contributes back to even more build-up of neurotoxins, contributing to the permanent damage (Seath et al., 2023). From the clinical scope, the reality of this mechanical failure is also supported by modern atrophy signatures. Advanced neuroimaging taken directly from the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) data cohort confirms the damage in specific parts of the brain progresses the fastest in EOAD patients, exactly matching with the highly specific anatomical areas where glymphatic fluid is known to stagnate the most (Touroutoglou et al., 2023).

Conclusion

Previously, the vast majority of therapeutic interventions designed to treat Alzheimer’s disease have focused heavily on attempts to chemically cease the brain's innate overproduction of the amyloid-beta protein. However, rigorous biomechanical neuroimaging data synthesized and evaluated within this systematic review strongly suggest that for patients suffering specifically from Early-Onset Alzheimer's Disease, the underlying pathology is actually fundamentally rooted in a failure of the biological clearance mechanism itself rather than the production of toxic

proteins. From the micro-level depolarization of AQP4 channels to the massive macro-level mechanical failure of deep N3 slow-wave sleep and necessary arterial pulsatility, the failure of the glymphatic system acts as the ultimate biological obstacle in maintaining healthy neuro-proteostasis. Extensive understanding and acceptance of this vision will provide the medical/clinical community with a new clinical framework and perspective for actively preventing and successfully treating the next incoming generation of neurodegenerative patients. To effectively leverage the findings of modern glymphatic research, it is important that future LEADS clinical trials and any similar longitudinal, long-term studies incorporate advanced polysomnography (highly detailed sleep studies) directly alongside their standard DTI-ALPS neuroimaging scans (Hammers et al., 2023; Touroutoglou et al., 2023; Xie et al., 2024). By actively tracking exactly how a patient's glymphatic fluid failure and their nightly sleep disruption correlate with their cognitive decline over a long period of time, the broader medical community can pivot away from chemical trials and move toward highly targeted, revolutionary preventative treatments, such as deploying specific pharmacological drugs for AQP4 upregulation or utilizing highly advanced N3 sleep enhancement technologies, to restore the human brain's hydrodynamic equilibrium to prevent the onset of neurodegenerative diseases (Chen et al., 2024; Mullins et al., 2025).

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