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"Beyond Sleep: A Glymphatic Perspective on Lifestyle Interventions and Adjuvant Pharmacotherapy to Preserve Brain Health in Night Shift Workers."

by

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Author's Contribution Statement

I certify that I am the author of this thesis and that any assistance I have had in its preparation is fully acknowledged and referenced in the following text. I have also cited any sources from which I have used data, ideas or words, whether they are quoted exactly or paraphrased. I also certify that this thesis was prepared by me personally specifically for the requirements of obtaining a Master's degree in Lifestyle Medicine by the University of Thessaly. I declare that I will respect co-authorship rights in any linked scientific publication and/or presentation stemming from this thesis, in accordance to my signed affirmation, and in respect of the principles of ethics in research. Likewise, I declare I will recognize any funding sources and will acknowledge my affiliation to the University of Thessaly during the preparation of this work in any future presentation.

Jim Verbelen

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A special mention also goes to my supervisor, Professor Sakkas, whose boundless enthusiasm for this field was a constant source of motivation throughout my entire research proces.

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Abstract

Introduction: As an emergency physician working night shifts, I became interested in the possible toll of irregular sleep on brain health, prompting exploration into strategies to mitigate long-term cognitive risks. The Glymphatic System, a brain-wide waste clearance mechanism most active during deep sleep, is disrupted by shift work-induced sleep deprivation, potentially increasing neurodegenerative disease risk. Inspired by studies on meditation's brain-preserving effects in aging monks, this thesis investigates whether lifestyle interventions - beyond sleep - can enhance glymphatic function to support brain health in shift workers.

Aims: This review aims to examine how lifestyle factors, including physical activity, nutrition, environmental adjustments, stress reduction, sleep optimization, and pharmacological interventions, can positively influence glymphatic function in night shift workers. Specific objectives include summarizing current knowledge on glymphatic impairment due to sleep disruption, evaluating interventions that can have a positive impact glymphatic function, assessing their applicability in daily life of shift workers through personal experience, and identifying possible future research.

Methodology: A systematic literature search was conducted on PubMed, covering the last 10 years, using dual-keyword combinations. From 114 identified articles, 54 were included based on relevance to glymphatic function and Alzheimer's disease, focusing on practical interventions. Studies were analyzed for evidence on exercise, nutrition, body position, respiration, stress reduction, and pharmacological options to enhance glymphatic clearance.

Results: Shift work impairs glymphatic function through reduced cerebrospinal fluid (CSF) flow and aquaporin-4 (AQP4) dysfunction, increasing amyloid-β accumulation and cognitive risks. Aerobic exercise and high-intensity interval training enhance CSF dynamics and AQP4 expression, directly improving clearance. Nutrition (e.g., omega-3s, intermittent fasting) and low alcohol intake support AQP4 function, while lateral sleeping and deep respiration boost venous outflow and CSF flow. Meditation and weighted blankets reduce stress and enhance deep sleep, indirectly aiding clearance. Blue light and music show promise but require further study.

Discussion: Lifestyle interventions like exercise, nutritional strategies, lateral sleeping, and stress reduction via meditation offer feasible strategies for shift workers to enhance glymphatic function, potentially mitigating cognitive decline. While pharmacological options (e.g., metformin, melatonin) are speculative, they warrant investigation. Larger human studies are needed to confirm efficacy and tailor interventions for 24/7 societies, informing preventive healthcare guidelines.

Keywords: Glymphatic Function, Shift Work, Lifestyle interventions, Sleep Disruption, Cognitive Decline

Abstract

Inleiding: Als spoedarts met frequente nachtshiften stelde ik me vragen over de impact van onregelmatige slaap op de hersengezondheid, wat me aanzette tot onderzoek naar strategieën om langetermijnrisico ivm cognitief functioneren te beperken. Het glymfatische systeem, een detoxifiëreingsmechanisme in de hersenen, dat het meest actief is tijdens diepe slaap, wordt verstoord door slaaptekort, wat het risico op neurodegeneratieve ziekten kan verhogen. Geïnspireerd door studies over de hersenbeschermende effecten van meditatie bij oudere monniken, onderzoekt deze thesis of leefstijlinterventies, naast slaap, de glymfatische functie kunnen verbeteren bij nachtwerkers.

Doelstellingen: Deze review beoogt te onderzoeken hoe leefstijlfactoren, zoals fysieke activiteit, voeding, omgevingsaanpassingen, stressreductie, slaap- of nap-optimalisatie en farmacologische interventies, de glymfatische functie positief kunnen beïnvloeden bij nachtdienstwerkers. Specifieke doelen zijn het samenvatten van de kennis over glymfatische verstoring door slaaptekort, het evalueren van de impact van deze interventies, het beoordelen van hun toepasbaarheid voor nachtwerkers vanuit de eigen ervaring en het identificeren van mogelijk toekomstig onderzoek.

Methodologie: Een systematisch literatuuronderzoek werd uitgevoerd op PubMed, over de afgelopen 10 jaar, met duale zoektermen.Van 114 geïdentificeerde artikelen werden er 54 opgenomen op basis van relevantie voor glymfatische functie en Alzheimer, gericht op praktische interventies. Studies werden geanalyseerd voor beweging, voeding, lichaamshouding, ademhaling, stressreductie en farmacologische opties voor verbetering van de glymfatische klaring.

Resultaten: Nachtwerk verstoort de glymfatische functie door verminderde cerebrospinale vloeistof (CSF)-stroom en aquaporine-4 (AQP4)-dysfunctie, wat beta-amyloidophoping en cognitieve risico's verhoogt. Aerobe oefeningen en hoge-intensiteit intervaltraining verbeteren CSF-dynamiek en AQP4-expressie, wat de klaring direct bevordert. Voeding (bijv. omega-3, vasten) en matig alcoholgebruik ondersteunen AQP4-functie, terwijl zijdelings slapen en diepe ademhaling de veneuze uitstroom en CSF-stroom versterken. Meditatie en verzwaringsdekens verminderen stress en verbeteren diepe slaap, wat indirect klaring ondersteunt. Blauw licht en muziek zijn veelbelovend maar vereisen verder onderzoek.

Discussie: Leefstijlinterventies zoals beweging, zijdelings slapen en stressreductie door meditatie bieden haalbare oplossingen voor nachtwerkers om glymfatische functie te verbeteren, mogelijks de cognitieve achteruitgang verminderend. Farmacologische opties (bijv. metformine, melatonine) zijn speculatief en vragen om verder onderzoek. Grootschalige studies zijn nodig om effectiviteit te bevestigen en interventies voor 24/7-samenlevingen te optimaliseren, ter ondersteuning van preventieve gezondheidsrichtlijnen.

Trefwoorden: Glymfatische functie, ploegendienst, leefstijlinterventies, slaapverstoring, cognitieve achteruitgang.

Περίληψη

Εισαγωγή: Ως ιατρός επειγόντων περιστατικών που εργάζεται σε νυχτερινές βάρδιες, ανέπτυξα ενδιαφέρον για τις πιθανές επιπτώσεις του ακανόνιστου ύπνου στην υγεία του εγκεφάλου, γεγονός που με ώθησε να διερευνήσω στρατηγικές για τη μείωση των μακροπρόθεσμων γνωστικών κινδύνων. Το γλεμφικό σύστημα, ένας μηχανισμός απομάκρυνσης αποβλήτων σε όλο τον εγκέφαλο που είναι πιο ενεργό κατά τον βαθύ ύπνο, διαταράσσεται από τη στέρηση ύπνου που προκαλείται από τη νυχτερινή εργασία, αυξάνοντας δυνητικά τον κίνδυνο νευροεκφυλιστικών νόσων. Εμπνεόμενη από μελέτες για τα εγκεφαλοπροστατευτικά αποτελέσματα του διαλογισμού σε ηλικιωμένους μοναχούς, η παρούσα εργασία διερευνά κατά πόσο παρεμβάσεις στον τρόπο ζωής—πέραν του ύπνου—μπορούν να ενισχύσουν τη λειτουργία του γλεμφικού συστήματος ώστε να υποστηρίξουν την εγκεφαλική υγεία σε εργαζόμενους με βάρδιες.

Σκοπός: Η παρούσα ανασκόπηση αποσκοπεί στην εξέταση του τρόπου με τον οποίο παράγοντες τρόπου ζωής, όπως η σωματική δραστηριότητα, η διατροφή, οι περιβαλλοντικές προσαρμογές, η μείωση του στρες, η βελτιστοποίηση του ύπνου και οι φαρμακολογικές παρεμβάσεις, επηρεάζουν τη λειτουργία του γλεμφικού συστήματος σε νυχτερινούς εργαζόμενους. Ειδικοί στόχοι περιλαμβάνουν τη σύνοψη της υπάρχουσας γνώσης σχετικά με την εξασθένηση του γλεμφικού συστήματος λόγω διαταραχής ύπνου, την αξιολόγηση παρεμβάσεων με πιθανή θετική επίδραση, την εκτίμηση της εφαρμοσιμότητάς τους στην καθημερινή ζωή εργαζομένων με βάρδιες μέσα από προσωπική εμπειρία και τον εντοπισμό πιθανών μελλοντικών ερευνητικών κατευθύνσεων.

Μεθοδολογία: Διενεργήθηκε συστηματική αναζήτηση βιβλιογραφίας στη βάση δεδομένων PubMed, καλύπτοντας τα τελευταία 10 έτη, με χρήση συνδυασμών διπλών λέξεων-κλειδιών. Από τα 114 εντοπισμένα άρθρα, επιλέχθηκαν 54 με βάση τη συνάφεια με τη λειτουργία του γλεμφικού συστήματος και τη νόσο Alzheimer, δίνοντας έμφαση σε πρακτικές παρεμβάσεις. Οι μελέτες αναλύθηκαν για ενδείξεις σχετικά με την επίδραση της άσκησης, της διατροφής, της στάσης σώματος, της αναπνοής, της μείωσης του στρες και των φαρμακολογικών επιλογών στην ενίσχυση της γλεμφικής κάθαρσης.

Αποτελέσματα: Η εργασία σε βάρδιες επηρεάζει αρνητικά τη λειτουργία του γλεμφικού συστήματος μέσω μειωμένης ροής εγκεφαλονωτιαίου υγρού (ΕΝΥ) και δυσλειτουργίας της ακουαπορίνης-4 (AQP4), αυξάνοντας τη συσσώρευση β-αμυλοειδούς και τους γνωστικούς κινδύνους. Η αερόβια άσκηση και η διαλειμματική προπόνηση υψηλής έντασης ενισχύουν τη ροή του ΕΝΥ και την έκφραση της AQP4, βελτιώνοντας άμεσα την απομάκρυνση αποβλήτων. Η διατροφή (π.χ. ωμέγα-3, διαλείπουσα νηστεία) και η χαμηλή κατανάλωση αλκοόλ υποστηρίζουν τη λειτουργία της AQP4, ενώ η πλάγια στάση ύπνου και η βαθιά αναπνοή ενισχύουν τη φλεβική εκροή και τη ροή ΕΝΥ. Ο διαλογισμός και οι βαριές κουβέρτες μειώνουν το άγχος και ενισχύουν τον βαθύ ύπνο, βοηθώντας έμμεσα στην κάθαρση. Το μπλε φως και η μουσική δείχνουν υποσχόμενα αποτελέσματα αλλά απαιτούν περαιτέρω μελέτη.

Συζήτηση: Παρεμβάσεις στον τρόπο ζωής, όπως η άσκηση, η διατροφική στρατηγική, η πλάγια στάση ύπνου και η μείωση του στρες μέσω διαλογισμού, αποτελούν εφαρμόσιμες προσεγγίσεις για την ενίσχυση της γλεμφικής λειτουργίας στους εργαζόμενους με βάρδιες, με δυνητικά οφέλη στην πρόληψη της γνωστικής έκπτωσης. Αν και οι φαρμακολογικές επιλογές (π.χ. μετφορμίνη, μελατονίνη) παραμένουν υποθετικές, αξίζουν περαιτέρω διερεύνηση. Απαιτούνται μεγαλύτερες μελέτες σε ανθρώπους για να επιβεβαιωθεί η

αποτελεσματικότητα και να προσαρμοστούν οι παρεμβάσεις σε κοινωνίες με 24ωρη λειτουργία, συμβάλλοντας στη διαμόρφωση κατευθυντήριων οδηγιών προληπτικής ιατρικής.

Λέξεις -κλειδιά: Γλεμφική λειτουργία, εργασία σε βάρδιες, παρεμβάσεις στον τρόπο ζωής, διαταραχή ύπνου, γνωστική έκπτωση

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List of abbreviations

LM: Lifestyle Medicine
GS: Glymphatic System
CNS: Central Nervous System
CSF: Cerebrospinal Fluid
ISF: Interstitial Fluid
Aβ: Amyloid Beta
AQP4: Aqueporine-4
SWA: Slow Wave Activity
SWS: Slow Wave Sleep
AD: Alzheimer's Disease
HIIT: High Intensity Interval Training
PUFA: Polyunsaturated Fatty Acids
NBP: L-3-n-butylphtalide
IF: Intermittent Fasting
NREM: Non Rapid eye Movement
PSG: Polysomnography
IJV: Internal Jugular Vein
MRI: Magnetic Resonance Imaging
CUMS-mice: Chronic Unpredictable Mild Stress- mice
MFP: Mifepristone
DEX: Dexamethasone
ELISA: Enzyme-Linked Immunosorbent Assay
GR: Glucocorticoid Receptor
BBB: Blood Brain Barrier
CLAS: Closed Loop Auditory Stimulation
GHB: Gamma Hydroxybutyrate
VCI: Vascular Cognitive Impairment
BCAI: Bilateral Common Carotid Stenosis
mLV: Meningeal Lymphatic Vessels
EMA: European Medicines Agency
EFSA: European Food Safety Authority

1. Introduction

My work as an emergency physician involves regular night shifts. That means long and tiring 12 and 24 hour shifts. Throughout my career it got me thinking about the impact on my body and brain, not just in the short term but also in the long run. The question raised how to maintain good health as I age.

In 2019 I came across a science book discussing meditation and its impact on brain health in Tibetan monks as older individuals who meditate regularly. The studied monks displayed remarkably youthful and well-preserved brain structures.

This made me reflect on the effects of chronic night shifts on the brain. Do they lead to structural or functional alterations and can practices such as meditation potentially mitigate or reverse these changes?

Back in 2019 I asked this questions to a neurologist who focuses on consciousness and brain aging. His honest advise was : "Try to get enough sleep. I'm afraid meditation can't compensate for sleep loss."

Well, that can be quite challenging to attain when working night shifts.

This led me to explore methods to enhance brain function. Not by substituting sleep but as a supplement. Methods that came across my mind were physical activity, balanced diet, surroundings, meditation, and in some cases even supplements or medication on indication.

In fact it was one important of the many reasons why I joined this masters program.

Throughout our Lifestyle Medicine Masters, we encountered the Glymphatic System. A brain cleansing mechanism that has been identified more recently. It's especially active during deep sleep, playing a vital role in eliminating toxins and preserving cognitive well being.

With individuals experiencing ongoing disruptions in their sleep patterns, decreased glymphatic clearance could potentially play a part in neurodegenerative developments.

While obviously getting sleep is crucialy important, the question arises wether there are alternative ways to support the Glymphatic System.

Could engaging in activities or making dietary changes affect its function positively? Or can creating a conducive living environment or practicing meditation techniques help enhance its efficiency too?

Or is it possible to enhance the quality of our sleep that remains or make short naps more effective in terms of clearance?

Finally: Are there specific supplements or medications that could be beneficial to aid glymphatic function?

This review delves into these inquiries to explore strategies beyond sleep for safeguarding brain health among individuals engaged in night or shift work schedules. It originates from a personal need but seeks to enrich the ongoing dialogue in the fields of medicine and public health regarding the preservation of brain function, in a 24/7 society.

2. Aims – Significance

General objective

Science has documented multiple severe sleep deprivation effects which include cognitive impairment and elevated chronic illness risks.
Sleep deprivation creates negative effects on both the brain and all major physiological systems in the body. Health problems caused by sleep deprivation are not only brain related but also extend to cardiovascular health, metabolism, immune function and reproductive systems.
This review examines how lifestyle elements such as physical activity, nutrition and supplements, environmental factors, stress reduction and sleep or napping optimization can positively affect glymphatic function in people who work irregular night shifts.

Specific objectives

1. To provide an overview of current knowledge regarding the Glymphatic System and the impact of disrupted sleep on its brain-cleansing function.
2. To summarize the potential influence of physical activity, nutrition, environmental factors (e.g. light, sound, temperature), stress reduction techniques (such as meditation), strategies to optimize sleep or naps and supplements/medication on the functioning of the Glymphatic System.
3. To assess, from a personal view, to which these lifestyle interventions, including sleep or nap optimization, are applicable to the daily lives of shift workers.
4. To formulate potential options for future research.

Relevance of the research

The nature of shift work disrupts sleep patterns which leads to negative impacts on brain health throughout the long term. The discovery of the Glymphatic System provides new insights about how sleep functions to clean the brain while preventing neurodegeneration. People who cannot achieve sufficient sleep can consider alternative lifestyle elements that enhance sleep quality, nap effectiveness and certain pharmacological interventions to support the Glymphatic System.

This review aims to advance knowledge about practical interventions that promote brain health for night workers while motivating additional research and public awareness among medical professionals and society members. The acquired knowledge shows potential to help create guidelines in the future which address the needs of 24/7 societies.

3. Literature Review

Multiple studies have proven that night shift work leads to obesity, arterial hypertension and cardiovascular issues which together can lead to the metabolic syndrome. Also cancer is a known risk of night shift work.
While it's worth mentioning, this work doesn't expand on this, since there's already extensive scientific literature on these themes.
This thesis specifically examines the Glymphatic System which functions as a brain clearance mechanism disrupted by sleep deprivation.
Since it's only discovered recently, the Glymphatic System remains understudied regarding its role in this context, which makes it essential to investigate its broader health effects on night shift workers.
The process of brain clearance involves the elimination of soluble proteins and waste metabolites from neural tissues. The removal of waste occurs through multiple physiological pathways (Fig.1) which include extracellular enzymatic degradation and cellular uptake by neurons and nonneuronal cells and transport across the blood-brain barrier to blood circulation, microglia phagocytosis and Glymphatic System clearance[1].

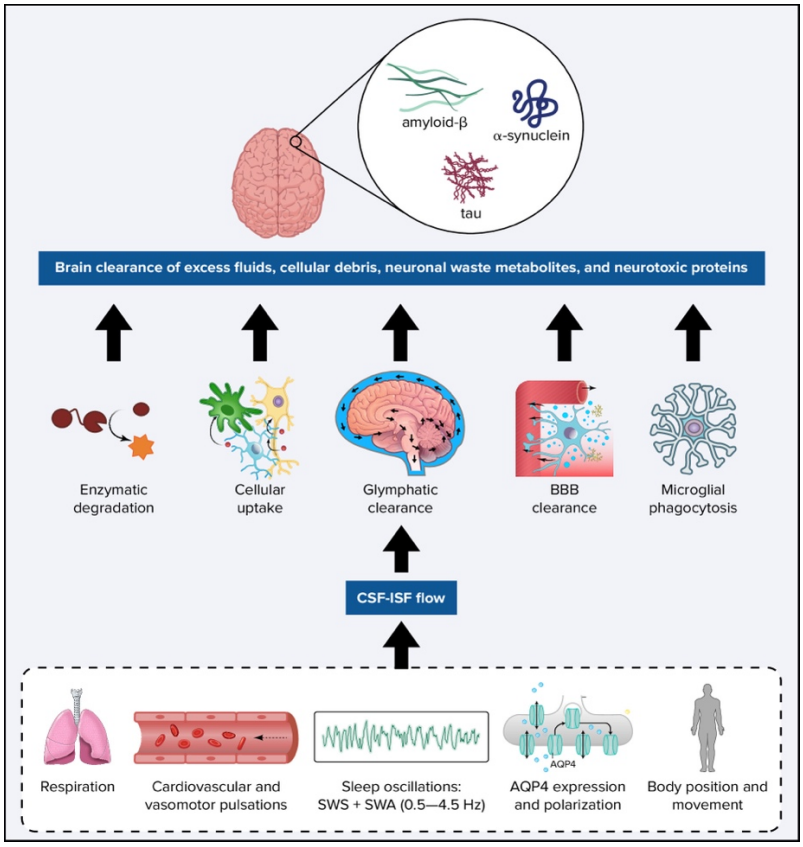

Fig. 1 (van Hattem et al.)

3.1. Link between shift work and risk for impaired brain health.

The irregular work schedules of shift workers create substantial risks to brain health and cognitive function through two main mechanisms which involve glymphatic dysfunction and circadian misalignment. This review examines how exercise together with nutrition, environmental elements and mind-body practices affect glymphatic function to reduce risks for shift workers. Understanding the link between shift work and impaired brain health is essential to this exploration.
Acute sleep deprivation during night shifts leads to brain structural changes that negatively affect cognitive health.

The 2021 research by Zhang's team demonstrated that one night of shift work under sleep deprivation reduced gray matter density in anterior and posterior brain regions and decreased cerebrospinal fluid volume which impaired amyloid-beta peptide clearance through glymphatic pathways thus increasing cognitive decline risk[2]02/07/2025 18:05:00.

Ripperger explains that shift work sleep disturbances prevent the Glymphatic System from properly removing toxic waste including lactate and reactive oxygen species which results in neuronal damage and memory loss[3], which- honestly- is a bit alarming.

The body clock chronically desynchronized represents a key characteristic of shift work which intensifies these health risks. Roenneberg explains that when the Suprachiasmatic Nucleus and peripheral clocks become desynchronized because of irregular sleep patterns and insufficient environmental synchronizing signals, it leads to higher rates of neurodegenerative diseases including Alzheimer’s and reduces cognitive performance[4].

Experimental evidence reinforces this, showing that misaligned sleep-wake cycles reduce cognitive function due to disrupted circadian regulation[4].

By focusing on modifiable factors like exercise and nutrition, this review aims to identify strategies to enhance glymphatic function and cognitive resilience in shift workers, addressing a gap in occupational health.

The Glymphatic System

The Glymphatic System functions as a newly identified network which extends throughout the brain to remove metabolic waste products in order to preserve central nervous system (CNS) homeostasis. It depends on glial cells to function like the lymphatic system thus enabling the convective movement of cerebrospinal fluid (CSF) and interstitial fluid (ISF) to remove neurotoxic substances including amyloid-beta (Aβ) and lactate from brain tissue[5].
The discovery of this system transformed our knowledge about brain clearance processes. It has a protective role against cognitive decline and neurodegenerative diseases.
The following section describes the Glymphatic System's anatomical structure together with its functional processes and its importance for brain health to establish a basis for studying its responses to lifestyle and environmental factors.

Structure of the Glymphatic System (Fig 2., Fig 3.)

The Glymphatic System works via a network of perivascular spaces surrounding cerebral blood vessels, guided by star-shaped brain cells called astrocytes, a type of glial cell. These spaces, formed by the endfeet of astrocytes enveloping arteries and veins, create a paravascular pathway for fluid exchange. The system has three key anatomical components:

- Para-arterial inflow: CSF enters the brain along the perivascular spaces surrounding penetrating arteries, driven by arterial pulsation and hydrostatic pressure. Special water channels, Aquaporin-4 (AQP4), found all over the ends of astrocytes, facilitate rapid CSF influx into the brain parenchyma.
- Interstitial exchange: Within the brain tissue, CSF mixes with ISF, flushing soluble waste products, such as Aβ and tau proteins, from the interstitial space. This exchange occurs across the neural matrix, supported by the porous extracellular matrix.
- Para-venous outflow: Polluted ISF is cleared from the brain via perivascular spaces surrounding veins, exiting toward cervical lymph nodes or returning to the systemic circulation. Astrocytes again play a critical role, channeling fluid through AQP4-mediated transport.

It's kind of fascinating how this all comes together.
The Glymphatic System functions as a moving brain-wide system of pipes.
As described later on in this review the Glymphatic System predominantly is active during deep sleep or slow wave sleep[6].
A functional magnetic resonance imaging study showed that slow wave activity (SWA) occurs before waves of CSF flow in the sleeping human brain. The authors propose that SWA causes slow oscillations in cerebral blood volume which results in CSF flow into and ISF flow out of the brain[7].

The perivascular spaces create tunnels which encircle blood vessels while astrocytic endfeet function as protective barriers. The parenchyma contains neurons and other glial cells which receive the CSF-ISF mixture as it flows through the surrounding tissue. This complex brain structure enables efficient waste removal while preserving the sensitive conditions of the brain microenvironment.

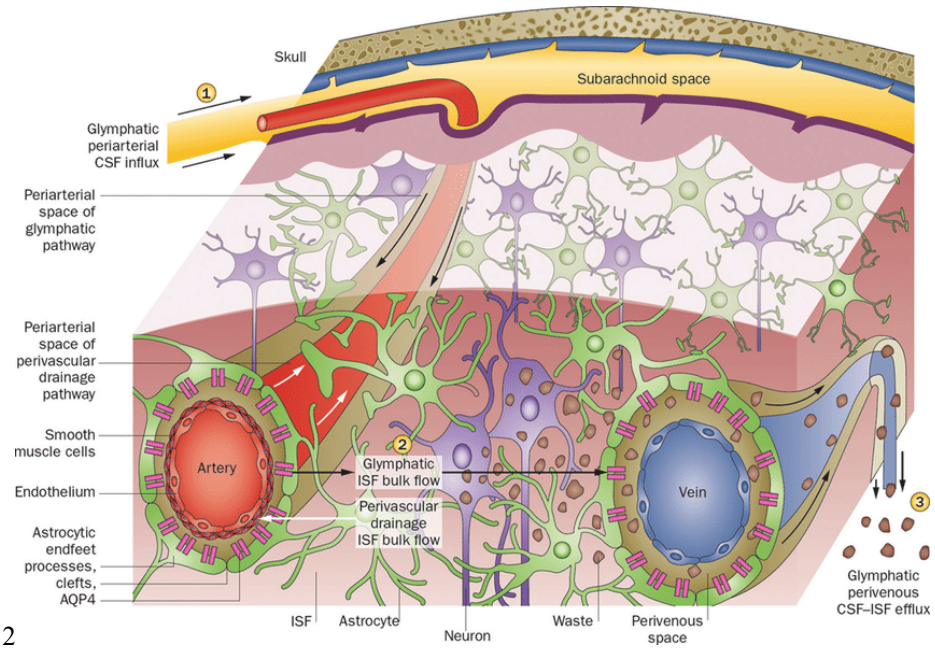

Fig 2

Outline of the Glymphatic System. This figure illustrates that perivascular clearance comprises perivascular drainage and glymphatic pathways. (1) Cerebrospinal fluid flows into the brain parenchyma via the periarterial space, which is the perivascular space surrounding the parenchymal arteries. From this perivascular space surrounding the artery, cerebrospinal fluid enters the interstitium of the brain tissue via aquaporin 4 (AQP4)-controlled water channels. These are distributed in the end feet of astrocytes that constitute the outer wall of the perivascular space. (2) Cerebrospinal fluid entering the interstitial fluid flows by convection, and the cerebral spinal fluid (CSF)-interstitial fluid (ISF) exchange within the brain parenchyma. (3) After washing the waste proteins from the tissue, it flows into the perivenous space, which is the perivascular space around the deep-draining vein, and is subsequently discharged outside the brain.

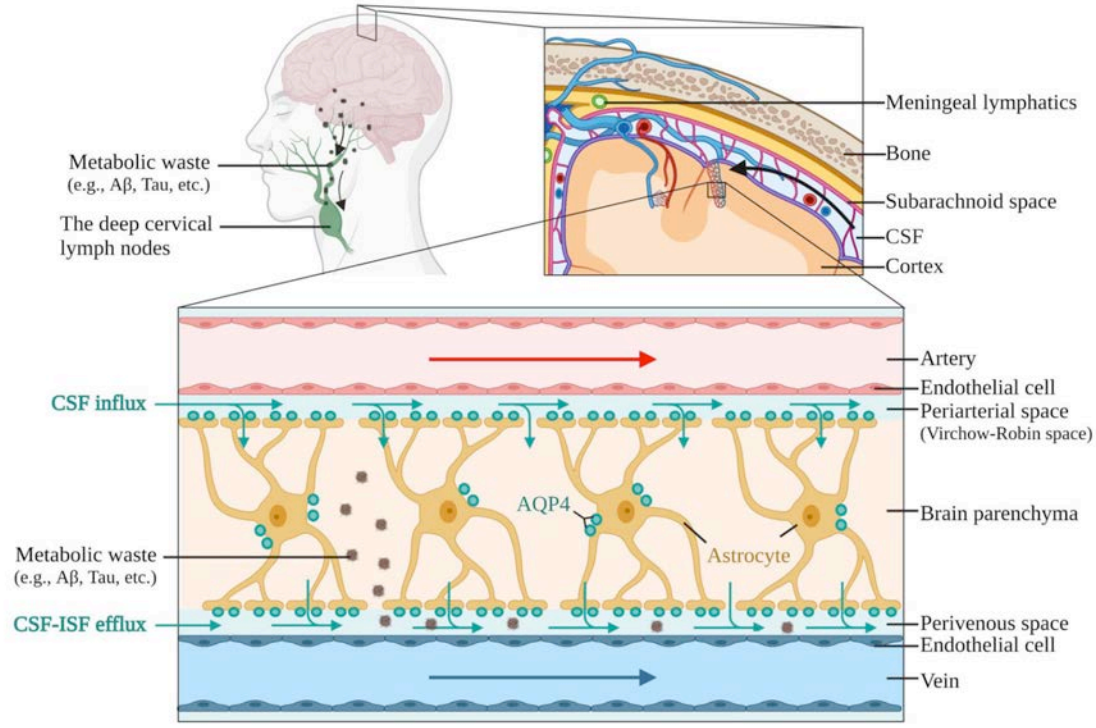

Fig.3 (Formolo et al.)
The glymphatic and meningeal lymphatic pathways for central solute clearance and their major components. Cerebrospinal fluid (CSF) enters the brain by moving from the subarachnoid space (superior image) into the space surrounding penetrating arteries (i.e., the periarterial or Virchow-Robin space, as shown in the amplified image), mostly driven by the convective force originated from pulsatile penetrating arteries. From the periarterial space, convective and diffusive forces guide the CSF inflow into the brain parenchyma, aided by polarized aquaporin 4 (AQP4) water channels expressed at astrocyte endfeet. CSF moves along the parenchyma towards the perivenous space, mixing with the interstitial fluid (ISF) and carrying the metabolic waste. The respiration cycle has been suggested as the main force driving CSF-ISF movement through the perivenous space. From the perivenous space, CSF-ISF and the metabolic waste exit the brain mostly through the meningeal lymphatic system (green circles, upper image) that drain into the deep cervical lymph nodes, although outflow along the olfactory, cranial, and spinal nerves into other cervical lymph nodes are also observed.

Mechanisms of Glymphatic Function

Let’s dive a bit deeper into how this whole system works.
The Glymphatic System works by coordinating fluid movement and cell activity, especially during sleep. The primary mechanisms include:

- The clearance process of Glymphatic System depends on CSF movement between para-arterial and para-venous spaces which occurs through convective flow mechanisms driven by arterial pulsations, respiratory cycles and pressure gradients. The flowing motion of CSF between spaces enables the removal of waste products from the interstitial space thus preventing their accumulation.
- AQP4- dependent transport: AQP4 channels on astrocytic endfeet regulate the influx and efflux of CSF and ISF. Studies in AQP4-knockout mice demonstrate significantly reduced glymphatic clearance, underscoring the channel’s critical role[8].

- Sleep-dependent activation: Glymphatic function is markedly enhanced during sleep, particularly during slow-wave sleep, when the interstitial space expands by up to 60%, facilitating greater CSF-ISF exchange[6]. This expansion is thought to be mediated by reduced noradrenergic activity, which relaxes astrocytic processes. The opposite occurs when the body remains awake or experiences sleep deprivation because this reduces glymphatic activity which results in waste accumulation.
- Astrocytes function as sensors and coordinators which control fluid movement through their ability to detect local metabolic needs and circadian signals. The circadian clocks of astrocytes could control AQP4 expression to establish a temporal connection between glymphatic function and brain temporal organization[3].

Significance for brain health

The Glymphatic System functions to eliminate brain waste products including Aβ and tau which are linked to neurodegenerative diseases such as Alzheimer's. The impairment of glymphatic function leads to higher Aβ accumulation and neuroinflammation and cognitive deficits[2]. The system maintains brain homeostasis which enables it to protect neuronal structures, synaptic operations and cognitive abilities thus making it a potential therapeutic target for shift work neurobiological effects. It's amazing what this system does for our brains.

3.2 Consequences of Sleep Deprivation and possible ways to enhance the Glymphatic System

1. How the Glymphatic System is affected by sleep deprivation/ shift work.

Deep sleep is like a superpower for your brain's cleanup crew. The space surrounding brain cells increases by 60% which enables cerebrospinal fluid (CSF) to remove harmful waste including β-amyloid protein[6].
The Glymphatic System operates as a fluid network surrounding blood vessels to perform this process which reaches its peak during stage 3 non-rapid eye movement (NREM) sleep when slow brain waves indicate deep rest. The brain detox process occurs during the initial part of the night but shift workers who experience disrupted sleep patterns miss this opportunity which increases their risk of developing toxic substances that damage neurons.

The Glymphatic System operates on a variable schedule because it enhances its activity during nighttime sleep. The fluid flow increases during sleep to remove waste more effectively because astrocytes and aquaporin-4 (AQP4) receive signals that enhance their function[6].
Astrocytes also seem to clear out lactate, another waste product, during sleep, possibly guided by their own internal clocks[3]. While we're still piecing together how the brain's circadian rhythms fit into this, it's obvious that good sleep keeps the brain's waste management system running smoothly.

Aging makes things trickier. Older adults experience shorter sleep duration with reduced restfulness and their AQP4 channels become misaligned which slows down brain cleanup processes[8]. The accumulation of β-amyloid and other waste products results in the formation of plaques which damage brain cells and lead to memory loss and thinking skill deterioration. Sleep isn't just about feeling refreshed - it's crucial for consolidating memories and clearing out brain waste throughout life. The combination of aging with health problems and medications disrupts sleep patterns which weakens glymphatic function and makes things worse.
For shift workers, who already battle irregular sleep, this emphasizes why prioritizing rest is so vital to protect their brains and minimize cognitive decline.

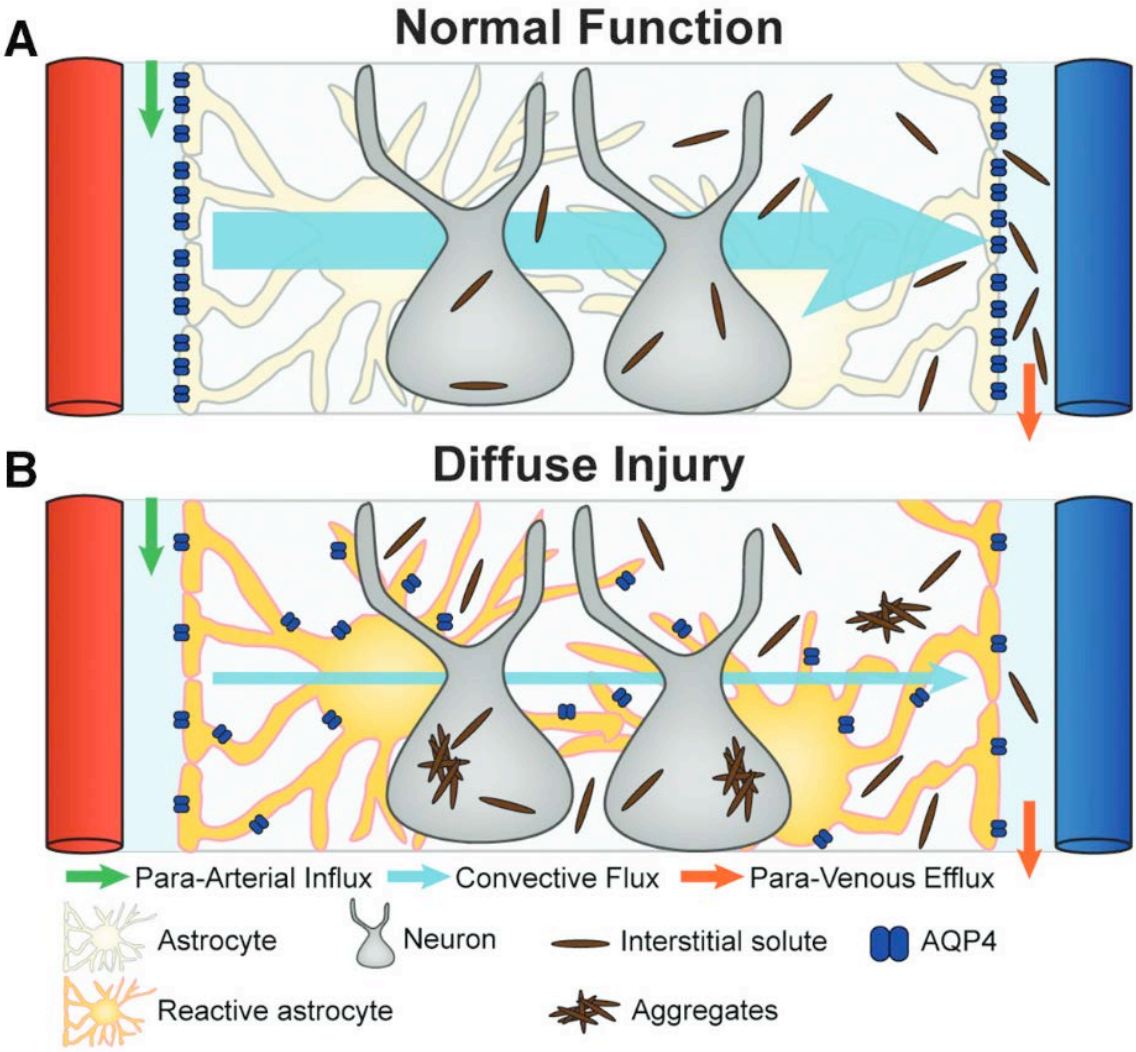

Fig.4 (Iliff et al.)
Schematic of glymphatic pathway function in healthy and diseased brain. Conceptual framework for the failure of glymphatic interstitial solute clearance after diffuse injury. A, In the healthy brain, cerebrospinal fluid (CSF) from the subarachnoid space rapidly enters the brain along paravascular channels surrounding penetrating arteries (green arrow) and exchanges with brain interstitial fluid (ISF). ISF and solutes are cleared to paravascular spaces surrounding large caliber draining veins (orange arrows). Convective bulk fluid flux between the paravascular CSF influx and ISF efflux pathways is facilitated by astroglial water transport through aquaporin-4 (AQP4) expressed exclusively along perivascular astrocytic endfeet. This convective bulk flow facilitates the clearance of interstitial solutes from the brain. B, Reactive astrogliosis that occurs after diffuse injury, such as microinfarction or mild traumatic brain injury, causes the mislocalization of AQP4 from the perivascular endfeet to the rest of the astrocytic soma. This results in the loss of efficient interstitial bulk flow and the failure of glymphatic interstitial solute clearance, and may contribute to the deposition of extracellular and intracellular protein aggregates (such as amyloid β or tau) after diffuse injury.

2. Counteracting impaired Glymphatic System by

A. Exercise

Physical exercise improves glymphatic function which leads to better brain health and decreased cognitive decline risk.
Research shows that voluntary wheel running for 6 to 8 weeks enhances the exchange dynamics of CSF and ISF in both healthy middle-aged mice (7–8 months old) and Alzheimer's disease (AD) models that overexpress β-amyloid (APP/PS1)[9,10].
This study shows that aerobic exercise in healthy middle-aged mice increases CSF glymphatic influx, improves ISF solute clearance, and increases meningeal lymphatic outflow to deep cervical lymph nodes, which results in reduced extracellular β-amyloid deposition and improved cognitive performance compared to sedentary controls[9].
In young adult mice (2 months old), exercise increases CSF glymphatic influx during the light cycle, when glymphatic activity is typically low, though this is not associated with enhanced AQP4 expression or ISF clearance[9]. In voluntary wheel running, APP/PS1 mice (5 months old) show increased glymphatic influx, reduced β-amyloid levels, and improved cognitive performance, which is associated with increased expression of polarized aquaporin-4 (AQP4) channels[11]. AQP4 knockout in these models eliminates exercise-induced improvements in glymphatic clearance, β-amyloid reduction, and cognitive outcomes, highlighting AQP4's critical role[12].
However, the glymphatic influx in CSF does not improve with aerobic exercise in older APP/PS1 mice (9 months old), indicating that exercise may not be beneficial for glymphatic function in later stages of the disease[11].
These findings establish the Glymphatic System as a vital system which exercise uses to fight cognitive decline especially for shift workers who experience sleep disruptions that could reduce their glymphatic activity levels.

Regular physical activity also helps keep blood pressure stable and increases lymphatic drainage, which supports the brain's waste-clearing system. In animal studies, muscle movement during exercise boosts the flow of lymph helping the body get rid of harmful substances like β-amyloid. Exercise also improves blood flow in the brain, which helps waste removal and supports overall brain health[13].

While exercise holds promise for mitigating glymphatic dysfunction in shift workers, further research is needed to clarify its efficacy and mechanisms in humans[14].

Exercise also increases the natural flow of brain fluid through the protective layers covering the brain (the dura). One area in particular - the lower parasagittal dura (PSD) - shows the biggest improvement. Active adults have higher fluid outflow than those who are inactive, and the PSD area shows the strongest flow in active people.
Physical activity leads to better CSF outflow measurements in sedentary adults which indicates that exercise strengthens both glymphatic and perivascular clearance pathways[15].
These findings highlight exercise's potential to optimize glymphatic function, offering a promising intervention for shift workers whose disrupted sleep impairs waste clearance.

Recent research (Yoo et al., 2025) provides evidence that increased putative glymphatic and mLV flow is likely the potential mechanism underlying the neuroprotective effects of exercise on cognition in humans. Therefore, their results highlight the importance of long-term, regular exercise interventions in the general population, as well as in patients with dementia[16].

High-intensity interval training (HIIT) enhances glymphatic clearance in Alzheimer's disease (AD)-like rat models by improving the removal of abnormal tau and β-amyloid from the cortex and hippocampus to peripheral organs (including the kidney) which supports cognitive function[17].

B. Nutrition

The process of astrocytic metabolism depends on nutrition which affects both glymphatic clearance and brain health. Astrocytes act as a link between neurons and vasculature to supply necessary energy and nutrients for neuronal function and to perform local detoxification and waste recycling[18].
The nutritional state of the organism affects astrocytes' metabolic flexibility, enabling them to adapt to varying demands and potentially influence glymphatic clearance by modulating aquaporin-4 (AQP4) channel activity and cerebrospinal fluid (CSF)-interstitial fluid (ISF) dynamics.
For instance, diets rich in antioxidants (e.g., omega-3 fatty acids, polyphenols) may reduce oxidative stress, supporting astrocytic function and enhancing glymphatic clearance of neurotoxic waste[19].
The brain's Glymphatic System functions less efficiently when people consume diets that are high in sugar or fat because these diets negatively affect astrocytic metabolism and disrupt AQP4 polarization.
Similarly, oral administration of L-3-n-butylphthalide (NBP), a celery oil-derived compound, acutely enhances arterial pulsatility in the brain, boosting CSF glymphatic influx, ISF solute clearance, and meningeal lymphatic outflow to deep cervical lymph nodes[20]. These findings suggest that PUFA- and NBP-rich diets could support glymphatic function, counteracting neurotoxic waste accumulation in shift workers and reducing cognitive decline risk.

However, direct evidence linking specific nutritional profiles to glymphatic clearance remains limited, necessitating further research to clarify these mechanisms.

The normalization of cortisol levels through nutritional strategies leads to better sleep quality. The combination of elevated or deregulated cortisol levels with poor sleep or acute sleep loss leads to impaired sleep quality which diminishes brain amyloid clearance through the Glymphatic System thus increasing dementia and cognitive impairment risks. The combination of omega-3 fatty acids and magnesium in specific diets helps control cortisol levels while promoting sleep quality and waste removal through the Glymphatic System which decreases dementia risk[21].
The amount of alcohol consumed determines the impact it has on lymphatic clearance. High doses of ethanol (1.5 g/kg, binge level) cause mice to develop impaired glymphatic function through reactive gliosis and AQP4 channel mislocalization which then disrupts CSF-ISF dynamics and waste clearance.

The glymphatic clearance process becomes more efficient when mice receive low doses of ethanol (0.5 g/kg) after both short-term and prolonged exposure periods while AQP4 function remains intact.
The J-shaped relationship between alcohol consumption and glymphatic clearance indicates that moderate drinking enhances waste removal from the brain but heavy drinking causes damage to this process which leads to increased β-amyloid accumulation and cognitive deterioration[22].

Zinc functions as an essential dietary nutrient which supports glymphatic function. The brain clearance system shows positive correlation with serum zinc levels in healthy individuals which indicates zinc's role in maintaining glymphatic function. The antioxidant properties of zinc work through different molecules and enzymes to defend the Glymphatic System against oxidative stress which damages clearance efficiency. Zinc's ability to stop amyloid and tau accumulation helps decrease the chances of neurocognitive disorders. Research demonstrates that zinc functions as a nutrional agent which can improve glymphatic clearance[23].

Intermittent Fasting.

Intermittent fasting (IF) improves glymphatic clearance which serves as a dietary method to support brain clearance in shift workers who experience sleep disturbances.
The Glymphatic System depends on AQP4 channels located in astrocytic perivascular endfeet to perform Aβ clearance because AQP4 knockout mice demonstrate reduced clearance efficiency by 55–65%. The Aβ clearance process improves through IF because it restores AQP4 polarity[24].
The mechanism shows promise to combat glymphatic dysfunction in shift workers who experience sleep-dependent clearance disruptions but it requires additional research about IF's use in occupational health practices.

C. Environmental factors

Blue light

Research on 5xFAD mice which model Alzheimer's disease shows that the brain's cleanup system can be substantially enhanced by 40 hertz blue light exposure. The study shows that low-intensity blue light therapy can restore the brain's Glymphatic System. The treatment showed positive effects on memory in 4-month-old mice and motivation in 14-month-old mice which both relate to better glymphatic drainage.
The brain fluid gatekeeper aquaporin-4 (AQP4) water channels on glial cells achieve proper positioning through blue light exposure. The Glymphatic System operates more effectively when aquaporin-4 channels are properly aligned because this leads to better Aβ clearance and reduced hippocampal fatty deposits[25]. The brain receives a plumbing maintenance through this process which enhances its ability to remove waste products effectively.

Temperature:

No scientific evidence of direct influence on the Glymphatic System found, but sleep is improved in a room with a slightly lower temperature.
The start of sleep occurs when core body temperature decreases regardless of the animal's day-night activity pattern. The core and brain temperatures decrease during episodes of non-rapid eye movement (NREM) sleep. The circadian temperature decrease triggers animals to perform thermoregulatory behaviors which include nest building and curled postures as they prepare for sleep. Research indicates that human and mammalian skin warming directly decreases sleep latency and enhances NREM sleep duration. Research that investigates the fundamental relationship between body cooling and sleep proposes that pre-sleep thermoregulatory behaviors generate warm microclimates which directly induce NREM sleep through particular neuronal pathways. The process of warming the body triggers blood vessel expansion which helps to cool down the body. The neural pathways that link NREM sleep onset with body temperature control become active through behaviors such as warmth-seeking and nesting which reinforce the circadian rhythm[26]

Weighted blankets

Weighted blankets present a comfortable solution to improve brain waste removal particularly for individuals who experience chronic insomnia. The study conducted using polysomnography (PSG) showed that heavy blankets improved sleep quality for 70% of patients with psychophysiological insomnia according to BaSIQS and PSQI sleep quality test scores. The real kicker? The participants achieved faster sleep onset (shorter sleep latency) and longer N3 sleep duration after just 10 days of using the weighted blankets. The brain's waste-clearing network known as the Glymphatic System operates at its peak during N3 sleep to eliminate toxic substances including β-amyloid.
Weighted blankets enhance deep sleep duration which could lead to improved glymphatic clearance and healthier brain maintenance. The study results indicate that weighted blankets produce a restful sleep state which benefits all ages and genders since N3 sleep duration increased without any age or sex differences. Your brain receives a superior vacuum cleaning system through weighted blankets which removes waste during sleep. The study failed to determine which patients would benefit most from the treatment and the results showed no significant heart rate changes which makes the exact mechanism unclear.
On the downside: Weighted blankets cause a small increase in obstructive apnea-hypopnea index which could potentially make breathing problems worse for specific individuals. People need to undergo either questionnaires or PSG tests for sleep apnea screening before using weighted blankets because of this potential issue. Weighted blankets provide an easy non-medical solution for deep sleep improvement which benefits the Glymphatic System to reduce future cognitive problems for those who pass the screening[27].

Postural/ Body position:

Research findings indicate that the position of the body during sleep directly affects the efficiency of glymphatic function. People with neurodegenerative conditions tend to spend

more time sleeping on their backs while healthy individuals naturally sleep on their sides because the back position may not be as effective for brain waste clearance.
A pilot sonographic study investigated internal jugular vein (IJV) flow through observations of three healthy young volunteers and two patients with abnormal jugular valves. The IJVs remained open in healthy volunteers when they were in the supine position but collapsed when they sat down. The right IJV stayed open while the left partially collapsed in the right lateral position and the left IJV remained open while the right partially collapsed in the left lateral position. The patients with abnormal valves displayed both IJVs open in both lateral positions which indicated modified venous dynamics. The lateral position creates less resistance in extracranial veins which leads to better cerebral venous outflow and potentially improves glymphatic clearance. The natural human tendency to sleep on our sides could be linked to this instinct because extended back sleeping may increase the risk of neurodegenerative diseases[28].
MRI based research on cerebrospinal fluid (CSF) dynamics demonstrates that sleep position influences fluid movement which is essential for glymphatic function. The supine position produces greater CSF oscillation than the upright position because it enables faster caudo-cranial diastolic flow and longer systolic phase duration. The Glymphatic System can remove brain waste more effectively because spending more time in the supine position during 24 hours leads to increased total CSF exchange[29].
This suggests that supine sleeping, while less common in healthy individuals, still facilitates waste clearance more effectively than upright postures.
The hierarchy of sleep positions for glymphatic efficiency receives additional evidence to support its structure. The research used dynamic-contrast-enhanced MRI and fluorescence microscopy and radioactive tracers to study CSF-interstitial fluid (ISF) exchange rates in anesthetized rodents when they were placed in lateral, supine and prone positions. The lateral position proved most effective, with superior Aβ clearance compared to supine or prone postures. The prone position, where the head mimics an upright awake state, showed slower clearance, greater tracer retention, and increased CSF efflux through larger cervical vessels, indicating reduced glymphatic efficiency. The supine position performed better than prone but was less effective than lateral[30]. These findings suggest that lateral sleeping optimizes both venous drainage and CSF-ISF exchange, making it the most efficient for waste clearance, followed by supine, with prone being the least effective.

However, limitations temper these insights: the pilot study's small sample (five participants), lack of quantitative measures, and reliance on anesthetized rodents limit generalizability to humans. Larger human studies with precise measurements are needed to confirm the optimal sleep position for glymphatic clearance and to explore practical interventions, such as sleep position training, to reduce neurodegenerative risk.

D. Respiratory

The brain functions through the interaction between cerebral blood flow and volume changes which affect intracranial pressure and cerebrospinal fluid (CSF) dynamics. The effects of respiration on cerebral blood flow and volume remain poorly understood despite its significant influence on these processes. A study by Söderström et al. employed 4D flow MRI to analyze 65 older adults (average age 75) quantified these effects[31]. They employed two measurement approaches which analyzed respiratory phase and raw respiratory cycle duration. The measurements revealed that arterial blood flow into the

brain exceeded venous outflow during exhalation but venous outflow exceeded arterial blood flow during inhalation. The measurements of cerebral blood volume change due to the respiratory cycle revealed a 0.83 mL [0.62, 1.13] variation for phase-based methods and 0.78 mL [0.59, 1.02] variation for time-based methods which matched the cardiac cycle's 1.01 mL [0.80, 1.30] variation. The research demonstrates that breathing controls cerebral blood flow while producing vascular volume changes that match those of cardiac activity thus establishing respiration as a critical factor in brain fluid dynamics[31].

Yang et al. found that respiration significantly influences the Glymphatic System, which clears brain waste like amyloid-β. Low-frequency hemodynamic oscillations, driven by breathing, facilitate cerebrospinal fluid (CSF) movement during wakefulness, supporting glymphatic function beyond sleep[32].

The process of respiration affects glymphatic function by using pulsatile cerebrospinal fluid (CSF) flow which results from different mechanisms. Researchers used steady-state free precession (SSFP) with background magnetic field gradient to observe CSF movement in healthy human subjects who performed intermittent deep breathing. The researchers applied spatial tags to CSF compartments to measure how different mechanisms generated pulsatile flow between cardiac and respiratory and slower cerebrovascular ("myogenic") mechanisms. The study revealed that myogenic CSF flow generated by cerebral blood volume changes produced substantially greater CSF displacement than the cardiorespiratory ("barogenic") effects which reached their peak at 10.4 seconds after deep inspiration. The research indicates that cerebrovascular activity controlled by respiration functions as the primary force behind CSF pulsations which probably increases glymphatic waste removal[33].

The process of respiration improves glymphatic function which is the brain's waste-clearing mechanism by enhancing cerebrospinal fluid (CSF) movement. Researchers used a custom nasal continuous positive airway pressure (CPAP) device to study breathing effects on cerebrospinal fluid (CSF) flow in spontaneously breathing anesthetized rodents. The device successfully opened the upper airway while increasing end-expiratory lung volume and enhancing arterial oxygenation. The research demonstrated through MRI and computational fluid dynamics that CPAP treatment increased CSF flow speed at the skull base while improving regional glymphatic transport. The increased CSF flow rate was directly related to elevated intracranial pressure (ICP) which showed higher ICP waveform pulse amplitude that probably enhanced both CSF bulk flow and glymphatic waste removal. The research demonstrates how respiratory support interacts with glymphatic function which indicates that CPAP treatment could maintain brain waste clearance[34].
Another good reason to use CPAP on indication.
Another study by Dreha- Kulaczewsky et al. investigated human CSF flow regulation by employing high-resolution real-time magnetic resonance imaging with 0.75 mm spatial resolution and 50 ms temporal resolution in healthy participants. The research showed that inspiration functions as the main force behind CSF movement because CSF flow happens during each inspiratory phase of forced breathing yet breath-holding eliminates this process. The cardiac pulsations played a minimal role in the process. The decrease in thoracic pressure during inspiration creates lower hydrostatic pressure in paravenous, venous and lymphatic pathways which results in increased CSF movement and glymphatic clearance. The respiratory-driven flow acts as an additional mechanism to support the brain-wide transport of CSF through paravascular pathways[35].

Slow, deep, and rhythmic yogic breathing, a core practice for self-regulation, supports health by influencing the respiratory, cardiovascular, and cardiorespiratory autonomic nervous systems. Further work is needed to investigate the influence of sustained yogic breathing training on pulsatile CSF dynamics for CNS health[36].

E. Verbal hypnotic suggestions:

Research indicates that verbal hypnotic suggestions delivered prior to sleep can enhance slow-wave sleep (SWS) and slow-wave activity (SWA)[37]. The augmentation of SWS through hypnotic suggestions has been observed across diverse groups, including both genders, various age groups, and during both daytime naps and nighttime sleep. However, the beneficial effects appear to be primarily limited to individuals with high hypnotizability[38]. In contrast, those with lower suggestibility may experience greater benefits from nonverbal presleep interventions, such as soothing music[39]. Furthermore, auditory presentation of relaxation-related words (e.g., “relax,” “calm”) during NREM sleep has also been shown to increase SWS duration[37].

F. Meditation

By attenuating stress:

The impact of chronic stress on glymphatic function and its underlying mechanisms remains poorly understood.
Research by Wei et al. included four groups of adult mice: the chronic unpredictable mild stress (CUMS)–treated group, CUMS simultaneously treated with mifepristone (MFP) group, dexamethasone (DEX)-treated group, and control group. The researchers evaluated stress response through measurements of body weight changes and plasma corticosterone levels and behavioral tests. ELISA was used to measure Aβ42 concentrations in cerebral tissue samples. The glymphatic function was determined by using fluorescence tracer injection. The researchers studied aquaporin-4 (AQP4) expression. They found that the glymphatic function declined globally in CUMS-treated mice particularly affecting the anterior brain region. The glucocorticoid receptor (GR) agonist DEX exposure led to decreased glymphatic function alongside reduced AQP4 expression. The GR antagonist MFP restored glymphatic function while simultaneously reversing the CUMS-induced AQP4 expression and polarization changes. They concluded that the glymphatic transport mechanism in the brain suffers impairment from chronic stress through glucocorticoid signaling pathways that involve AQP4. Which indicates that GR antagonist treatment shows promise for restoring glymphatic function which chronic stress has suppressed.[40]

G. Auditory stimuli:

Music:

The Glymphatic System shows potential for improvement through music and sound interventions. Research indicates that sound through music causes the blood-brain barrier (BBB) to open which leads to increased meningeal lymphatic vessel diameters and better lymphatic flow to lymph nodes that enhances glymphatic waste clearance. The process of BBB opening through this method has been shown to decrease Aβ accumulation in patients with Alzheimer's disease.
Music therapy enhances both mood and cognitive abilities in Alzheimer's and dementia patients which may be connected to better Glymphatic System performance. Most research has focused on ultrasound technology yet there is insufficient data available about how acoustic music affects BBB permeability and glymphatic flow thus requiring additional studies.
Research should investigate how rhythm and pitch and intensity of music interact with sleep patterns to maximize glymphatic clearance through validated imaging protocols and diverse human trials that verify these effects across different age groups and sex and music genres[41].
The practice of immersive sound meditation through meditation-based approaches helps improve glymphatic function by lowering noradrenergic tone and creating slow-wave delta oscillations which enhance brain waste clearance. This could delay cognitive decline and prevent neurodegenerative disorders. Further research is needed to confirm these effects, but such practices hold promise for maintaining brain health throughout life.[42]

Closed- loop auditory stimulation:

The significance of SWA in glymphatic brain clearance has led to increasing interest in Closed loop auditory stimulation as a potential method to stop neurodegeneration and disease progression[43]. The neurophysiological effects of Closed-loop auditory stimulation (CLAS) also known as phase-targeted/locked acoustic stimulation occur through the delivery of acoustic tones during sleep which are based on electroencephalography (EEG) recorded neuronal activity[44].
CLAS could potentially enhance the brain's ability to remove neurotoxic proteins like amyloid-β and tau by increasing SWA.
However the implementation of CLAS technology for home sleep intervention requires further investigation to resolve several remaining questions.
The current research on CLAS has focused on short-term effects but the long-term impact on sleep and cognitive functions remains poorly understood[43] and the extent of individual and group differences in CLAS responses during home use needs further investigation[43 45]

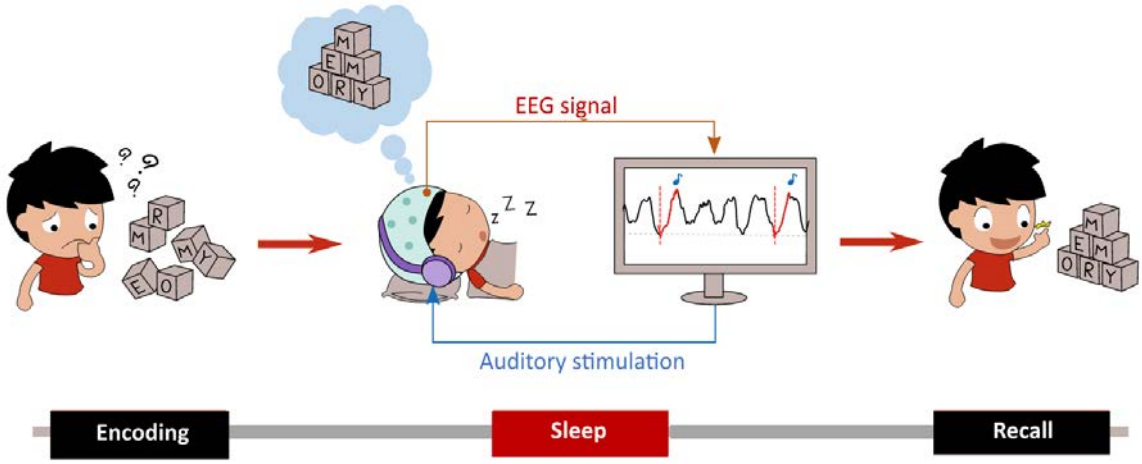

Fig. 5 (Esfahani et al) Schematic illustration of a closed loop auditory stimulation (CLAS) setup in a sleep study including a memory assessment as a cognitive task.

H. Olfactory stimuli:

The use of odors in olfactory stimulation serves to modify sleep patterns. Research on healthy human subjects demonstrated that lavender oil exposure before or during sleep enhances SWS[46]. The research indicates that exposure to scented oils through olfactory stimulation leads to improved deep sleep quality.

Other stimuli like transcranial (Magnetic, Electrical, Ultrasound, Photobiomodulation) have been studied[45]. The low feasibility to implement this in daily life, at this moment, makes it out of the scope of this thesis.

I. Pharmacological

- Metformin:

  The accumulation of inflammatory factors and other metabolic waste may cause central sensitization and impairment of the Glymphatic System. Research showed that metformin significantly alleviated mechanical pain in painful diabetic neuropathy (PDN) rats, possibly related to the restoration of AQP4 polarization in the Glymphatic System of the spinal cord of rats[47]. Since its effect on the AQP4 polarization, maybe it can have the same effect in the central GS. Further research has to investigate.

- Melatonin:

  Melatonin levels rise during late afternoon and nighttime to activate both the central circadian pacemaker in the hypothalamic suprachiasmatic nuclei and thousands of peripheral cellular circadian clocks.
  Melatonin functions as a chronobiotic agent through its "chronobiotic effect" since it belongs to the endogenous family of chronobiotic agents. It provides substantial cytoprotective benefits through its ability to neutralize free radicals and decrease inflammation by reducing proinflammatory cytokines and low-grade inflammation and preventing insulin resistance[48].

  A transgenic mouse model of Alzheimer's disease (AD) amyloidosis demonstrates that melatonin helps eliminate amyloid-β through lymphatic pathways which primarily use peripheral lymph nodes that connect to the Glymphatic System[49]. Research indicates that melatonin supplementation could enhance glymphatic activity thus providing therapeutic advantages for Alzheimer's disease[50]. But as evidence regarding melatonin's ability to enhance glymphatic clearance and reduce amyloid-β levels is still inconsistent , it suggests only a limited therapeutic potential for humans[45].

While research shows possible positive effects of GHB[51], certain anti-epileptics[45] and dexmedetomidine[45], I don't include them as possible implementable strategies in daily life from an ethical perspective.
Other medications are being studied but didn't have a positive effect on the Glymphatic System, some have a negative effect on brain health:
Benzodiazepines and non-benzodiazepines, antidepressants, atypical antipsychotics, acetylcholinesteraseinhibitors[45].

Possible future directions:

Glucocorticoid receptor antagonists (cfr reducing stress):

The brain's AQP4-mediated glymphatic transport becomes impaired by chronic stress through glucocorticoid signaling. The GR antagonist shows promise as a therapeutic agent to restore glymphatic function which chronic stress has suppressed[40]. Further research is needed. Strong side effects, but emphasizes importance of reducing stress.

Oral central α2-receptoragonists like clonidine[52] (~ dexmedetomidine).

Importance of Cardiovascular health:

Impaired Glymphatic Function and Pulsation Alterations in a Mouse Model of Vascular Cognitive Impairment.
The main factors responsible for vascular cognitive impairment (VCI) and dementia are large vessel disease and carotid stenosis. Research using rodent models, demonstrated that bilateral common carotid stenosis (BCAS) leads to cognitive impairment via gradual deterioration of the neuro-glial-vascular unit and accumulation of amyloid-β (Aβ) protein. Since brain-wide drainage pathways (glymphatic) for waste clearance, including Aβ removal, have been implicated in the pathophysiology of VCI via glial mechanisms, Li et al. hypothesized that glymphatic function would be impaired in a BCAS model and exacerbated in the presence of Aβ. Male wild-type and Tg-SwDI (model of microvascular amyloid) mice were subjected to BCAS or sham surgery which led to a reduction in cerebral perfusion and impaired spatial learning acquisition and cognitive flexibility. After 3 months survival, glymphatic function was evaluated. Their findings show that BCAS influences VCI and that this is paralleled by impaired glymphatic drainage and reduced vascular pulsation[53].

In light of this cardiovascular perspective, I would like to mention another potential medication, although it may not be immediately applicable to the general population of night shift workers. Nevertheless, it reinforces the importance of a healthy cardiovascular system as part of enhancing glymphatic function:

Digoxine:

The combination of small vessel disease and carotid stenosis produces chronic cerebral hypoperfusion which results in metabolic problems and white matter damage and cognitive deterioration. The mouse model of chronic hypoperfusion through bilateral common carotid artery stenosis produced substantial white matter damage together with initial cognitive problems which researchers linked to impaired glymphatic function and aquaporin 4 (AQP4) polarization loss (Sun et al.). The administration of digoxin enhanced both glymphatic transport and white matter structure and cognitive function but TGN-020 blocked this protective effect thus validating the Glymphatic System's involvement. Research demonstrates that blood flow to the brain directly affects glymphatic function and white matter health which in turn impacts cognitive processes thus making the Glymphatic System a potential therapeutic target for brain injuries caused by hypoperfusion[54].

4. Methodology

A systematic literature search was conducted on PubMed, covering the last 10 years, using dual-keyword combinations

Searching PUBMED, as well as additional sources from the reference lists of some of the papers I found through the database searches.

68 + 46 identified articles
32 + 22 included based on relevance to glymphatic function and Alzheimer's disease, focusing on practical interventions.

The focus is primarily on those factors that directly have a positive impact on the Glymphatic System.

Concerning pathologies, I only included Alzheimer's Disease as its high prevalence has prompted the majority of glymphatic research to date.

Although other interventions may also positively influence the Glymphatic System (as shown in the figure below)[45], I have limited the results and discussion to those applications that are- now or potentially in the future- practically feasible in daily life.

For medication/supplements I only kept those with positive effect on the GS considering their applicability (IV/ po) and without unethical application or dangerous adverse effects (e.g. GHB, anti epileptics, …)

4.1. Literature Searching Plan

Searching PUBMED, as well as additional sources from the reference lists of some of the papers I found through the database searches.

Using the keywords: Glymphatic, Brain waste, Shift work, Exercise, Posture, Respiratory, Diet, Nutrition, Meditation, Temperature, Weighted blankets, Supplement

Comparing multiple versus dual keyword search I noticed I missed out on some articles with the multiple word search. Although more extensive I decided to use the dual way.

Searching in the latest 10 years.

Glymphatic AND Shift work (n=8), included n=4, used n=1
Brain waste AND Shift work (n=7), included n=2, used n=2
Exercise AND Glymphatic (n= 33), included n=15, used n=6
Exercise AND Brain waste (n= 48), included n=7, used n=4
Nutrition AND Glymphatic (n= 17), included n=5, used n=2
Nutrition AND Brain waste (n= 62), included n=1, used n=1
Diet AND Glymphatic (n= 17), included n=6, used n=1
Diet AND Brain waste (n= 26), included n=3, used n=1
Posture AND Glymphatic (n=19), included n=5, used n=2
Posture AND Brain waste (n=8), included n=4, used n=2
Respiratory AND Glymphatic (n= 33), included n=4, used n=3
Respiratory and Brain waste (n= 45), included n=8, used n=4
Meditation AND glymphatic (n=1), included n=1, used n=1
Meditation AND Brain waste (n=1), included n=0, used n=0
Temperature AND Glymphatic (n=9), included n=4, used n=0
Temperature AND Brain waste (n=23), included n=0, used n=0
Supplement AND Glymphatic (n=15), included n=2, used n=1
Supplement AND Brain waste (n=20), included n=0, used n=0
Blue light AND Glymphatic (n=2), included n=1, used n=1
Blue light AND Brain waste (n=0), included n=0, used n=0
Weighted blankets AND Glymphatic (n=0), included n=0, used n=0
Weighted blankets AND Brain waste (n=0), included n=0, used n=0

*For each search I first included those only regarding the searched variable
Included n=72
4 doubles : -4 , n=68
Then a second screening by reading the full text
Used n=32

*Then by reading those I encountered other interesting references which I read and included when relevant.
n=46
Also here a second screening by reading the full text:
Used n=22

(By reading included articles I also found relevant information about searched subjects but not found by the chosen keywords.)
Total used articles : n=54

From all used articles there are:
14 narrative reviews
27 mechanistic studies
8 experimental studies, of which 1 RCT
1 cross sectional
4 prospective cohort studies

Meta-analyses and systematic reviews I didn't find, probabely because the discovery of the Glymphatic System is too recent and there is no critical number of relevant research (RCT's) to perform this analyses.

4.2. Articles Inclusion criteria

Mechanistic and higher.
Related to enhancement / function of the Glymphatic System.
Published in the last 10 years.

4.3. Articles Exclusion criteria

In vitro studies.
If studies are linked to pathology other then AD.
Older then 10 years.

4.4. Flow Chart

Identification

Records identified through initial search ..... n = 72
└─ Duplicates removed ..... n = 4
└─ Records after duplicates removed ..... n = 68

Screening

Records screened (full-text read) ..... n = 68
└─ Records included after screening ..... n = 32

Additional Sources

Additional records identified from reference lists .... n = 46
└─ Records included after full-text screening .... n = 22

Final Inclusion

Total studies included in review ..... n = 54

5. Results

The possible lifestyle interventions can be divided in factors with direct and indirect impact on the glymphatic clearance are summarized in Table 1.

Table 1

Category	Intervention	Link to Glymphatic function
Directly linked	Aerobic Exercise	Enhances glymphatic clearance by increasing arterial pulsations and CSF flow, which drive waste clearance (e.g. Aβ)[9]. Exercise upregulates AQP4 expression, supporting glymphatic transport[11].
	High- Intensity Interval Training (HIIT)	Similar to aerobic exercise, HIIT boosts cerebral blood flow and arterial pulsations, directly promoting glymphatic waste clearance through enhanced CSF dynamics[17].
	Nutritional: Omega-3 Fatty Acids Polyphenols	PUFAs reduce neuroinflammation and support vascular health, directly improving glymphatic function by maintaining AQP4 polarisation and CSF flows[19].
	Nutritional: Avoiding refined sugars	Directly preserving glymphatic function by preventing AQP4 dysfunction and vascular damage[21].
	Nutritional: NBP (N-Butylphthalide)	NBP may enhance cerebral blood flow and protect against ischemia, directly supporting glymphatic clearance by improving CSF dynamics[20].
	Nutritional: Low alcohol intake	Low alcohol intake avoids disruption of AQP4 localization and glymphatic flow, directly maintaining efficient waste clearance[22].
	Nutritional: Zinc	Zinc supports AQP4 expression and reduces oxidative stress, directly facilitating glymphatic transport and waste clearance[23].
	Nutritional: Intermittent fasting	Enhancing glymphatic clearance by optimizing AQP4 function and CSF flow[24].
	Blue light (40 Hz)	Low-intensity 40 Hz blue light opens the BBB and enhances glymphatic transport, directly improving Aβ clearance via AQP4 polarization[25].

	Body position during sleep	Lateral sleeping optimizes cerebral venous outflow and CSF-ISF exchange, directly boosting glymphatic clearance compared to supine or prone positions[30].
	Deep respiration	Inspiration drives CSF flow by reducing thoracic pressure, directly enhancing glymphatic clearance through increased paravascular transport[33].
	CPAP	CPAP increases CSF flow speed and glymphatic transport by elevating intracranial pressure pulse amplitude, directly supporting waste clearance[34].
	Decreasing Chronic stress	Chronic stress impairs AQP4-mediated glymphatic transport via glucocorticoid signaling; reducing stress directly restores glymphatic function[40].
(Speculative)	Metformin	Possibly related to the restoration of AQP4 polarization in the Glymphatic System of the spinal cord of rats[47]. Maybe also in the central GS?
	Melatonin	May enhance glymphatic clearance by promoting sleep and reducing oxidative stress, there are direct links to AQP4 but further research is required to explore melatonin's effect on the localization of AQP4 and the Glymphatic System[50].
Indirectly linked	Aerobic exercise and HIIT (Preventing MS/OSAS)	By preventing metabolic syndrome (MS) and obstructive sleep apnea (OSAS), exercise indirectly supports glymphatic function by maintaining healthy sleep and reducing inflammation.
	Nutrition: Normalising Cortisol: Mg+, Flax seeds, PS and PUFA's	Mg+, flax seeds, Phosphtidylserin and Omega-3FA's lower cortisol, indirectly supporting glymphatic function by reducing stress-induced AQP4 suppression and improving sleep quality[21].
	Temperature	Optimal body temperature may improve sleep quality, indirectly enhancing glymphatic clearance during deep sleep stages[26].

	Weighted blankets	Improve deep sleep (N3 stage), indirectly boosting glymphatic clearance by increasing time in sleep phases optimal for waste clearance[27].
	Yogic breathing	Slow, rhythmic breathing reduces stress, indirectly supporting glymphatic function by lowering cortisol and enhancing relaxation[36].
	Verbal hypnotic suggestions	May improve sleep quality and reduce stress, indirectly promoting glymphatic clearance during sleep, though evidence is preliminary[37].
	Meditation	Reduces stress and cortisol, indirectly enhancing glymphatic function by counteracting glucocorticoid-mediated AQP4 impairment[40].
	Immersive sound/ Music	Opens the BBB and may enhance glymphatic flow, indirectly supporting waste clearance by improving mood and sleep[42].
	CLAS (Closed loop auditory stimulation)	CLAS could potentially enhance the brain's ability to remove neurotoxic proteins like amyloid-β and tau by increasing SWA[43].
	Olfactory stimuli	May influence brain activity and sleep, indirectly supporting glymphatic function during sleep, though evidence is emerging and speculative[45].
Future?	Clonidine	Oral α-2 receptor agonist[52]. More research on Glymphatic System needed. Possible side-effects.
	Cardiovascular health	Maintaining heart health ensures stable cerebral blood flow, indirectly supporting glymphatic function by facilitating CSF dynamics[53].

6. Discussion

The Glymphatic System plays a pivotal role in clearing neurotoxic waste from the brain, making it a critical target for preserving cognitive health, particularly in populations vulnerable to impaired waste clearance, such as night shift workers.
This review explored practical, evidence-based strategies to mitigate the adverse effects of sleep deprivation on glymphatic function, drawing from scientific literature, personal experiences, and anecdotal insights from colleagues.
The proposed interventions- aerobic exercise, high-intensity interval training (HIIT), nutritional adjustments, sleep hygiene, postural strategies, and emerging therapies like 40 Hz blue light and CLAS- offer a multifaceted approach to supporting brain health in shift workers. However, their feasibility, accessibility, and evidence base vary, warranting a critical evaluation of their applicability in daily life.

Exercise as a cornerstone for Glymphatic Health

Aerobic exercise and HIIT emerged as highly feasible interventions for shift workers. Regular physical activity is known to enhance cerebral blood flow and glymphatic clearance, potentially counteracting the reduced waste clearance associated with disrupted sleep. Aerobic exercise is broadly accessible, requiring minimal equipment, and can be tailored to individual schedules, making it practical even for those with demanding shift patterns.
HIIT, with its time-efficient nature, is particularly appealing for shift workers who may struggle to allocate time for longer workouts. The availability of online guided HIIT videos further lowers barriers to adoption, enabling individuals to exercise at their own fitness level.
However, adherence remains a challenge, as fatigue from irregular sleep schedules may deter consistent engagement. Future research should explore optimal timing and duration of exercise to maximize glymphatic benefits in this population.

Nutritional Strategies to Support Glymphatic Function

Dietary interventions offer another accessible avenue for enhancing glymphatic clearance. Incorporating antioxidants such as omega-3 fatty acids, polyphenols, and zinc- available in foods like fatty fish, berries, and celery- can reduce oxidative stress and support glymphatic function.
Avoiding refined sugars and fats aligns with broader metabolic health recommendations, which is critical given the link between night shift work, metabolic syndrome, and impaired glymphatic clearance due to altered arterial pulsations.
Intermittent fasting, particularly when initiated before the end of a shift, is a practical strategy, as sleep can cover part of the fasting window, easing adherence.
However, the use of supplements like NBP remains unadvisable due to the lack of EMA or EFSA approval, highlighting the need for further regulatory evaluation.
Low alcohol consumption, while intuitive, requires clearer guidelines to balance social habits with brain health.

Sleep Hygiene and Environmental Adjustments

Sleep hygiene is a cornerstone of glymphatic optimization, as the system is most active during slow-wave sleep (SWS). Practical adjustments, such as maintaining a cool bedroom with warmed extremities, using weighted blankets (approximately 10% of body weight) to promote faster SWS onset, and adopting a lateral sleeping position, are low-cost and implementable strategies.
For shift workers with limited sleep windows, these interventions are particularly valuable during short naps.
Olfactory cues, such as lavender, and verbal hypnotic suggestions or soothing music may further facilitate sleep onset, though their efficacy depends on individual suggestibility.
For those with obstructive sleep apnea syndrome (OSAS)- weighted blanket are not an option- continuous positive airway pressure (CPAP) devices are effective but require a formal diagnosis for affordability, limiting accessibility in resource-constrained settings.

Emerging Therapies and Their Limitations

Emerging interventions like 40 Hz blue light therapy and Closed Loop Auditory Stimulation (CLAS) hold promise for enhancing glymphatic clearance, particularly in preventing or slowing neurodegenerative diseases like Alzheimer's. However, their high cost (e.g., €1900 for blue light devices) and technical complexity make them impractical for widespread use among shift workers.
Similarly, while melatonin supplementation may improve sleep quality, its direct impact on glymphatic function remains understudied, and optimal dosing is unclear.
Pharmacological options, such as metformin, are speculative at this stage, with metformin showing potential only in diabetic populations. These limitations underscore the need for further research and development to make such therapies accessible and practical.

As research continues to evolve, I recently came across a study suggesting a possible effect of clonidine on the Glymphatic System[52]. This article was published after I had completed my initial literature searches.
However, due to potential side effects—such as bradycardia, hypotension, and cardiac arrhythmias—its use should only occur following medical advice and under strict medical supervision.

Broader Implications and Challenges

The link between night shift work, metabolic syndrome, and impaired glymphatic clearance highlights the importance of holistic health management.
Arterial hypertension and metabolic syndrome, prevalent among shift workers, reduce arterial pulsations critical for glymphatic function. Preventive strategies targeting metabolic health-through diet, exercise, and stress reduction via meditation or heart coherence training- can thus have dual benefits for systemic and brain health.

However, implementing these strategies in the context of irregular schedules, fatigue, and socioeconomic constraints poses significant challenges. Personal and colleague insights emphasize the need for individualized approaches, as shift workers' lifestyles vary widely.

Future Directions

Since being relatively new, the Glymphatic System will be studied more and with evolving knowledge on how to evaluate this GS in humans, research should evolve to more research on humans (RCT's).
Future research should focus on longitudinal studies to assess the long-term impact of these interventions on glymphatic function and cognitive outcomes in shift workers. Additionally, developing cost-effective, user-friendly adaptations of advanced therapies could broaden their applicability.

7. Conclusions

It may come as no surprise that maintaining cardiovascular health is essential for brain waste clearance, just as it is for all biological processes in the body.
This underscores that lifestyle interventions, as emphasized during our master's program, should be embraced as a way of life, not just for protecting the brain, but for overall health.

In this work, I have highlighted the interventions that are particularly important for night shift workers in preserving brain health. These interventions include regular physical activity, nutritional adaptations and attention to environmental factors such as light exposure, and temperature. Additionally, stress reduction techniques play a crucial role, alongside strategies to optimize sleep quality and daytime naps. Where appropriate, the use of supplements or medication may also support brain health.

From these interventions, individuals can choose the ones that best fit into their lives. We live in a free world, but our bodies- shaped by our genetic makeup- age according to the laws of nature.
Just as our hearts must keep beating, the Glymphatic System must continue to function.

In the future, it may be valuable to ask a broader group of night shift workers about their preferences and possibilities for integrating the proposed lifestyle interventions into their daily routines, including during working hours. This could help identify practical and easy-to-implement strategies for the workplace.

I realize that even with the best care and preventive measures, we will never be able to fully compensate for the negative consequences of sleep deprivation caused by night shift work.

Another way to reduce these risks is to schedule fewer night shifts. However, achieving this requires more staff, and attracting additional colleagues depends on financial and political decision-making.

This thesis hopefully can contribute to some constructive thinking for the future.
After all, healthy caregivers at an older age are essential for ensuring quality healthcare in the years to come, especially in light of an aging population and a steadily increasing retirement age.

8. Strengths & Weaknesses of this work

Strengths:

- Well structured exploration.
- Comprehensive literature review.
- Practical and applicable interventions.
- Interdisciplinary approach.
- Focus on shift workers

Weaknesses:

- Limited human studies, small sample sizes of key-studies (sleep posture, n=5).
- Speculative interventions like GR, metformin, melatonin. Highlights research gaps.
- Feasibility challenges for shift workers.
- The need for more specific recommendations for study designs.
- The personal experience risks introducing bias in assessing intervention feasibility.

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Appendices

Appendix 1: Search engine algorithm

Search number	Query	Sort By	Filters	Search Details	Results
22	(weighted blankets) AND (brain waste)		in the last 10 years	(("weight s"[All Fields] OR "weighted"[All Fields] OR "weighting"[All Fields] OR "weightings"[All Fields] OR "weights and measures"[MeSH Terms] OR ("weights"[All Fields] AND "measures"[All Fields]) OR "weights and measures"[All Fields] OR "weight"[All Fields] OR "body weight"[MeSH Terms] OR ("body"[All Fields] AND "weight"[All Fields]) OR "body weight"[All Fields] OR "weights"[All Fields]) AND ("blanket"[All Fields] OR "blanketing"[All Fields] OR "blankets"[All Fields]) AND (("brain"[MeSH Terms] OR "brain"[All Fields] OR "brains"[All Fields] OR "brain s"[All Fields]) AND ("waste"[All Fields] OR "waste s"[All Fields] OR "wasted"[All Fields] OR "wasteful"[All Fields] OR "wastes"[All Fields]))) AND (y_10[Filter])	0
21	(weighted blankets) AND (glymphatic)		in the last 10 years	(("weight s"[All Fields] OR "weighted"[All Fields] OR "weighting"[All Fields] OR "weightings"[All Fields] OR "weights and measures"[MeSH Terms] OR ("weights"[All Fields] AND "measures"[All Fields]) OR "weights and measures"[All Fields] OR "weight"[All Fields] OR "body weight"[MeSH Terms] OR ("body"[All Fields] AND "weight"[All Fields]) OR "body weight"[All Fields] OR "weights"[All Fields]) AND ("blanket"[All Fields] OR "blanketing"[All Fields] OR "blankets"[All Fields]) AND "glymphatic"[All Fields]) AND (y_10[Filter])	0
20	(blue light) AND (brain waste)		in the last 10 years	(("blue light"[MeSH Terms] OR ("blue"[All Fields] AND "light"[All Fields]) OR "blue light"[All Fields]) AND (("brain"[MeSH Terms] OR "brain"[All Fields] OR "brains"[All Fields] OR "brain s"[All Fields]) AND ("waste"[All Fields] OR "waste s"[All Fields] OR "wasted"[All Fields] OR "wasteful"[All Fields] OR "wastes"[All Fields]))) AND (y_10[Filter])	0
19	(blue light) AND (glymphatic)		in the last 10 years	(("blue light"[MeSH Terms] OR ("blue"[All Fields] AND "light"[All Fields]) OR "blue light"[All Fields]) AND "glymphatic"[All Fields]) AND (y_10[Filter])	2
18	(supplement) AND (brain waste)		in the last 10 years	(("dietary supplements"[MeSH Terms] OR ("dietary"[All Fields] AND "supplements"[All Fields]) OR "dietary supplements"[All Fields] OR "supplement"[All Fields] OR "supplement s"[All Fields] OR "supplemented"[All Fields] OR "supplementing"[All Fields] OR "supplements"[All Fields]) AND (("brain"[MeSH Terms] OR "brain"[All Fields] OR "brains"[All Fields] OR "brain s"[All Fields]) AND ("waste"[All Fields] OR "waste s"[All Fields] OR "wasted"[All Fields] OR "wasteful"[All Fields] OR "wastes"[All Fields]))) AND (y_10[Filter])	20
17	(supplement) AND (glymphatic)		in the last 10 years	(("dietary supplements"[MeSH Terms] OR ("dietary"[All Fields] AND "supplements"[All Fields]) OR "dietary supplements"[All Fields] OR "supplement"[All Fields] OR "supplement s"[All Fields] OR "supplemented"[All Fields] OR "supplementing"[All Fields] OR "supplements"[All Fields]) AND "glymphatic"[All Fields]) AND (y_10[Filter])	15
16	(temperature) AND (brain waste)		in the last 10 years	(("temperature"[MeSH Terms] OR "temperature"[All Fields] OR "temperatures"[All Fields] OR "temperature s"[All Fields]) AND (("brain"[MeSH Terms] OR "brain"[All Fields] OR "brains"[All Fields] OR "brain s"[All Fields]) AND ("waste"[All Fields] OR "waste s"[All Fields] OR "wasted"[All Fields] OR "wasteful"[All Fields] OR "wastes"[All Fields]))) AND (y_10[Filter])	23
15	(temperature) AND (glymphatic)		in the last 10 years	(("temperature"[MeSH Terms] OR "temperature"[All Fields] OR "temperatures"[All Fields] OR "temperature s"[All Fields]) AND "glymphatic"[All Fields]) AND (y_10[Filter])	9
14	(meditation) AND (brain waste)		in the last 10 years	(("meditate"[All Fields] OR "meditated"[All Fields] OR "meditating"[All Fields] OR "meditation"[MeSH Terms] OR "meditation"[All Fields] OR "meditations"[All Fields] OR "meditation s"[All Fields] OR "meditational"[All Fields] OR "meditative"[All Fields] OR "meditator"[All Fields] OR "meditators"[All Fields]) AND (("brain"[MeSH Terms] OR "brain"[All Fields] OR "brains"[All Fields] OR "brain s"[All Fields]) AND ("waste"[All Fields] OR "waste s"[All Fields] OR "wasted"[All Fields] OR "wasteful"[All Fields] OR "wastes"[All Fields]))) AND (y_10[Filter])	1

13	(meditation) AND (glymphatic)		in the last 10 years	(("meditate"[All Fields] OR "meditated"[All Fields] OR "meditating"[All Fields] OR "meditation"[MeSH Terms] OR "meditation"[All Fields] OR "meditations"[All Fields] OR "meditation s"[All Fields] OR "meditational"[All Fields] OR "meditative"[All Fields] OR "meditator"[All Fields] OR "meditators"[All Fields]) AND "glymphatic"[All Fields]) AND (y_10[Filter])	1
12	(respiratory) AND (brain waste)		in the last 10 years	(("eur med j respir"[Journal] OR "respiratory"[All Fields]) AND (("brain"[MeSH Terms] OR "brain"[All Fields] OR "brains"[All Fields] OR "brain s"[All Fields]) AND ("waste"[All Fields] OR "waste s"[All Fields] OR "wasted"[All Fields] OR "wasteful"[All Fields] OR "wastes"[All Fields]))) AND (y_10[Filter])	45
11	(respiratory) AND (glymphatic)		in the last 10 years	(("eur med j respir"[Journal] OR "respiratory"[All Fields]) AND "glymphatic"[All Fields]) AND (y_10[Filter])	33
10	(posture) AND (brain waste)		in the last 10 years	(("postural"[All Fields] OR "posturally"[All Fields] OR "posture"[MeSH Terms] OR "posture"[All Fields] OR "postures"[All Fields] OR "postured"[All Fields] OR "posturing"[All Fields]) AND (("brain"[MeSH Terms] OR "brain"[All Fields] OR "brains"[All Fields] OR "brain s"[All Fields]) AND ("waste"[All Fields] OR "waste s"[All Fields] OR "wasted"[All Fields] OR "wasteful"[All Fields] OR "wastes"[All Fields]))) AND (y_10[Filter])	8
9	(posture) AND (glymphatic)		in the last 10 years	(("postural"[All Fields] OR "posturally"[All Fields] OR "posture"[MeSH Terms] OR "posture"[All Fields] OR "postures"[All Fields] OR "postured"[All Fields] OR "posturing"[All Fields]) AND "glymphatic"[All Fields]) AND (y_10[Filter])	19
8	(diet) AND (brain waste)		in the last 10 years	(("diet"[MeSH Terms] OR "diet"[All Fields]) AND (("brain"[MeSH Terms] OR "brain"[All Fields] OR "brains"[All Fields] OR "brain s"[All Fields]) AND ("waste"[All Fields] OR "waste s"[All Fields] OR "wasted"[All Fields] OR "wasteful"[All Fields] OR "wastes"[All Fields]))) AND (y_10[Filter])	26
7	(diet) AND (glymphatic)		in the last 10 years	(("diet"[MeSH Terms] OR "diet"[All Fields]) AND "glymphatic"[All Fields]) AND (y_10[Filter])	17
6	(nutrition) AND (brain waste)		in the last 10 years	(("nutrition s"[All Fields] OR "nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR "nutrition"[All Fields] OR "nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields] OR "nutritional"[All Fields] OR "nutritionals"[All Fields] OR "nutritions"[All Fields] OR "nutritive"[All Fields]) AND (("brain"[MeSH Terms] OR "brain"[All Fields] OR "brains"[All Fields] OR "brain s"[All Fields]) AND ("waste"[All Fields] OR "waste s"[All Fields] OR "wasted"[All Fields] OR "wasteful"[All Fields] OR "wastes"[All Fields]))) AND (y_10[Filter])	62
5	(nutrition) AND (glymphatic)		in the last 10 years	(("nutrition s"[All Fields] OR "nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR "nutrition"[All Fields] OR "nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields] OR "nutritional"[All Fields] OR "nutritionals"[All Fields] OR "nutritions"[All Fields] OR "nutritive"[All Fields]) AND "glymphatic"[All Fields]) AND (y_10[Filter])	17
4	(exercise) AND (brain waste)		in the last 10 years	(("exercise"[MeSH Terms] OR "exercise"[All Fields] OR "exercises"[All Fields] OR "exercise therapy"[MeSH Terms] OR ("exercise"[All Fields] AND "therapy"[All Fields]) OR "exercise therapy"[All Fields] OR "exercising"[All Fields] OR "exercise s"[All Fields] OR "exercised"[All Fields] OR "exerciser"[All Fields] OR "exercisers"[All Fields]) AND (("brain"[MeSH Terms] OR "brain"[All Fields] OR "brains"[All Fields] OR "brain s"[All Fields]) AND ("waste"[All Fields] OR "waste s"[All Fields] OR "wasted"[All Fields] OR "wasteful"[All Fields] OR "wastes"[All Fields]))) AND (y_10[Filter])	48
3	(exercise) AND (glymphatic)		in the last 10 years	(("exercise"[MeSH Terms] OR "exercise"[All Fields] OR "exercises"[All Fields] OR "exercise therapy"[MeSH Terms] OR ("exercise"[All Fields] AND "therapy"[All Fields]) OR "exercise therapy"[All Fields] OR "exercising"[All Fields] OR "exercise s"[All Fields] OR "exercised"[All Fields] OR "exerciser"[All Fields] OR "exercisers"[All Fields]) AND "glymphatic"[All Fields]) AND (y_10[Filter])	33

2	(brain waste) AND (shift work)		in the last 10 years	(("brain"[MeSH Terms] OR "brain"[All Fields] OR "brains"[All Fields] OR "brain s"[All Fields]) AND ("waste"[All Fields] OR "waste s"[All Fields] OR "wasted"[All Fields] OR "wasteful"[All Fields] OR "wastes"[All Fields]) AND (("shift"[All Fields] OR "shifted"[All Fields] OR "shifting"[All Fields] OR "shiftings"[All Fields] OR "shifts"[All Fields]) AND ("work"[MeSH Terms] OR "work"[All Fields]))) AND (y_10[Filter])	7
1	(glymphatic) AND (shift work)		in the last 10 years	("glymphatic"[All Fields] AND (("shift"[All Fields] OR "shifted"[All Fields] OR "shifting"[All Fields] OR "shiftings"[All Fields] OR "shifts"[All Fields]) AND ("work"[MeSH Terms] OR "work"[All Fields]))) AND (y_10[Filter])	8

Appendix 2:

To write this thesis, I utilized AI tools such as ChatGPT and Grok. As I find writing in Dutch more comfortable, I used these tools to translate my work, produce more fluent English than I could achieve on my own, and correct grammatical errors. All factual content I gathered and compiled by reading the research I found, as outlined in the methodology section. Full papers are read and in some cases, only the highlights when the content was too extensive.

Appendix Copyright Statement

Affirmation

The undersigned Jim verbelen postgraduate student of the Postgraduate Program "LIFESTYLE MEDICINE" of the University of Thessaly

I declare responsibly that I accept the following terms concerning:

(a) the copyright of my Master's Thesis entitled “Beyond Sleep: A Glymphatic Perspective on Lifestyle Interventions and Adjuvant Pharmacotherapy to Preserve Brain Health in Night Shift Workers.”

(b) the management of the research data I will collect in the course of its elaboration:

1. The copyright of the resulting volume of the master's thesis will belong to me. I will follow the instructions for writing, printing and depositing copies of the dissertation in the relevant repositories (in printed and/or electronic form).
2. The management of the dissertation data belongs jointly to me and the Director of Studies/Main Supervisor.
3. Any scientific publication or announcement (posted or oral), or reference derived from the material/data of this work will be made with authors myself, the main supervisor and/or other researchers (such as a member of the three-member advisory committee), depending on their contribution to the research or the writing of the research paper(s).
4. The order of names in scientific publications or scientific announcements will be decided jointly by me and the main supervisor (DOS) of the project before it begins. This decision will be certified in writing between myself and the main supervisor.

Finally, I declare that I am aware of the rules on plagiarism and intellectual property and that I will strictly follow them throughout my studies, I will attend to the educational obligations arising from this MSc, as well as will attend the publication procedures that will arise after the completion of my studies.

11/06/2025
Jim Verbelen