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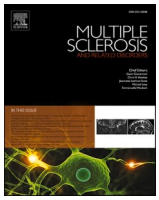

Review article

Cerebral small vessel disease and glymphatic system dysfunction in multiple sclerosis: A narrative review

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ABSTRACT

As the multiple sclerosis (MS) population ages, the prevalence of vascular comorbidities increases, potentially accelerating disease progression and brain atrophy. Recent studies highlight the prevalence of cerebral small vessel disease (CSVD) in MS, suggesting a potential link between vascular comorbidities and accelerated disability. CSVD affects the brain's small vessels, often leading to identifiable markers on MRI such as enlarged perivascular spaces (EPVS). EPVS are increasingly recognized also in MS and have been associated with vascular comorbidities, lower percentage of MS-specific perivenular lesions, brain atrophy and aging. The exact sequence of event leading to MRI visible EPVS is yet to be determined, but an impaired perivascular brain fluid drainage appears a possible physiopathological explanation for EPVS in both CSVD and MS. In this context, a dysfunction of the brain fluid clearance system – also known as "glymphatic system" – appears associated in MS to aging, neuroinflammation, and vascular dysfunction. Advanced imaging techniques show an impaired glymphatic function in both MS and CSVD. Additionally, lifestyle factors such as physical exercise, diet, and sleep quality appear to influence glymphatic function, potentially revealing novel therapeutic strategies to mitigate micro-angiopathy and neuroinflammation in MS. This review underscores the potential role of glymphatic dysfunction in the complex and not-yet elucidated interplay between neuroinflammation and CSVD in MS.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disorder of the central nervous system (CNS), characterized by recurrent attacks and/or insidiously progressive worsening of physical and cognitive neurological disability over time (Reich et al., 2018). With an MS population becoming older, (Habbestad et al., 2024) age-related comorbidities, especially of vascular origin, are becoming increasingly prevalent (Marrie et al., 2016). Vascular risk factors (VRFs) such as hypertension, type 2 diabetes, and dyslipidemia, may influence both the evolution of the physical and cognitive neurological disability, (Marrie and Horwitz, 2010; Marrie et al., 2010) as well as the life-expectancy of patients with MS (Capkun et al., 2015).

A recent post-mortem histopathological study revealed that – beyond the classic inflammatory demyelinating lesions – arteriolar damage associated with cerebral small vessel disease (CSVD) is frequently observed in MS patients (Geraldes et al., 2020). Since in the non-MS aging population, CSVD is associated with accelerated cognitive decline and physical disability, (Wardlaw et al., 2019) the excessive burden of CSVD in MS represents a compelling candidate to explain the relationship between VRFs, physical and cognitive impairment in MS.

Closely linked to VRFs and CSVD, are lifestyle habits, in particular diet and physical activity (Gu and Scarmeas, 2013; Rippe, 2019). Growing evidence suggests an association between lifestyle modification and improved health outcomes in people with MS, (Saul et al., 2023) but the exact mechanisms by which lifestyle may influence disease severity remain unknown.

Emerging research underscores the crucial involvement of the glymphatic system in the physiopathology of both MS and CSVD (Alghanimy et al., 2024; Ang et al., 2024). The glymphatic system plays a prominent role in CNS fluid homeostasis and brain waste clearance (Jessen et al., 2015). Through a continuous network of perivascular

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spaces (PVS), also called Virchow-Robin spaces, the glymphatic system mediates the efflux of interstitial fluids and neurotoxic waste from the PVS around the brain's veins into the subarachnoid space (Iliff et al., 2012).

This review has the aim to synthesize the recent findings on CSVD in MS, discussing its potential association with glymphatic system dysfunction and with patient lifestyle habits.

2. Cerebral small vessel disease and enlarged perivascular spaces in MS

With an MS population becoming older the risk of vascular comorbidity increases (Marrie et al., 2016). Vascular complications can accelerate disease progression in MS, (Marrie and Horwitz, 2010; Marrie et al., 2010) shorten life-expectancy, (Marrie et al., 2010; Capkun et al., 2015) and aggravate white matter (WM) lesion load and brain atrophy (Kappus et al., 2015). Post-mortem histopathology shows that arteriolar damage associated with CSVD is frequently observed in patients with MS, suggesting that the burden of CSVD in MS may explain the link between vascular comorbidity and accelerated irreversible disability (Geraldes et al., 2020). The term CSVD encompasses a group of pathologies that affect the perforating arteries, arterioles and capillaries located in the brain parenchyma and leptomeninges (Pantoni, 2010; Wardlaw et al., 2013). The two main pathological mechanisms of CSVD are arteriolosclerosis and cerebral amyloid angiopathy (Kancheva et al., 2024). The prevalence of CSVD increases with increasing patient age, and can be identified through neuroimaging markers on brain magnetic resonance imaging (MRI) such as enlarged perivascular spaces (EPVS), WM hyperintensities, cerebral microbleeds, and lacunar infarcts (Pantoni, 2010; Wardlaw et al., 2013). This review will specifically focus on EPVS as MRI marker of CSVD.

EPVS are a well-recognized marker of PVS dysfunction (Ineichen et al., 2022). In research and clinical setting EPVS are commonly rated in the basal ganglia (BG) and centrum semiovale (CSO) (Wardlaw et al., 2013; Duering et al., 2023). From a physiopathological point of view, widening of the brain perivascular spaces in CSVD is likely to result from fluid drainage obstruction and liquid stagnation secondary to hypoxia, inflammation, vascular remodeling and endothelial dysfunction (Brown et al., 2018). However, the exact sequence of event leading to MRI visible EPVS in CSVD is yet to be determined. An explanation for PVS widening in CSVD could be periarterial blockage leading to local obstruction of glymphatic fluxes (Brown et al., 2018). Dysfunction of the vessel endothelial cells with alterations of the blood vessel architecture is frequently observed in CSVD (Bai et al., 2022). These changes could lead to both enlargement and narrowing of the vessel lumen, along with vessel stiffening (Bai et al., 2022). As a result of these alterations, cerebral blood flow (CBF) is reduced (Yu et al., 2020). Since WM has fewer capillaries than the cortex, (Nonaka et al., 2003) along with slower blood flow and wider presence of a watershed areas, it is likely that the WM is more susceptible to hypoperfusion than the gray matter (Varga et al., 2009).

Accumulating evidence suggests a higher EPVS burden in MS compared to controls, but their exact clinical and pathophysiological significance remains controversial (Granberg et al., 2020). While previous studies have inconsistently (Granberg et al., 2020) associated EPVS with active MS neuroinflammation (Ge et al., 2005; Wuerfel et al., 2008) and brain volume loss, (Kilsdonk et al., 2015) recent findings suggest a potential link between EPVS and vascular comorbidities. In fact, we've recently shown that an increased EPVS count at the CSO level in MS patients with vascular comorbidities is associated with a lower percentage of MS-specific perivenular lesions, (Guisset et al., 2021; Borrelli et al., 2024) indicating that EPVS in MS can serve as surrogate MRI marker of coexisting microangiopathic disease. These findings are in line with a recent post-mortem MRI-pathology study showing that EPVS do not colocalize at the anatomical level with common MS pathological features such as perivenular demyelination and immune cell infiltration, but rather with damage of small arterial blood vessels (Ineichen et al., 2023). Moreover, high EPVS burden in MS is associated with brain atrophy and aging, (Borrelli et al., 2024) suggesting that CSVD changes, eventually through brain fluid drainage obstruction and accumulation of neurotoxic waste, are likely to contribute to neurodegeneration in MS. If the high burden of EPVS in MS is supported by a dysfunction of the glymphatic system and/or by other physiopathological mechanisms, it is still unknown. One singular case report recently described a transient clinical improvement following cerebrospinal fluid (CSF) shunting in a primary progressive MS patient with a high EPVS burden (Scollato et al., 2022). Lacking more robust evidence on this topic, future large and prospective studies should investigate whether alleviating PVS congestion via CSF diversion could improve glymphatic clearance, facilitate the removal of proinflammatory molecules and improve clinical outcomes in MS (Scollato et al., 2022).

3. Glymphatic dysfunction in small vessel disease and MS

3.1. Glymphatic system anatomy and physiology

CSF is thought to be produced primarily by the choroid plexuses (ChP), which are expansions of the ependymal epithelium, lining the lateral, third, and fourth ventricles (Keep and Jones, 1990). The ChP are highly folded and vascularized structures consisting of a single layered epithelium residing on a basement membrane (Banizs et al., 2005). CSF secretion is primarily driven by membrane transport mechanisms following an osmotic gradient due to the action of Na+/*K*+-ATPases localized on the apical membrane of ChP epithelial cells (Jessen et al., 2015). After this active secretion, CSF drains through the ventricular system into the subarachnoid space (SAS) and is eventually cleared into the blood of the dural venous sinus through the arachnoid granulations (Dandy, 1919). Before entering the brain parenchyma, CSF moves from the SAS along the PVS of large leptomeningeal arteries and enter the parenchyma through the penetrating arteries (Iliff et al., 2013; Ringstad et al., 2017). As blood vessels carry blood towards the brain, they pulsate at heart rate. This pulse pressure generates a pressure wave which is thought to be the main driver of CSF flow throughout PVS (Mestre et al., 2018; Harrison et al., 2018). Fluid movement from the PVS of penetrating arteries into the brain parenchyma lets CSF to mix with the brain interstitial fluid and allows the removal from the interstitial space of cellular waste, such as amyloid-β, tau, and lactate (Peng et al., 2016; Lundgaard et al., 2017). Another described interstitial fluid drainage route is the one along the vessel basement membranes which occurs in a reverse direction with respect to the one of blood flow (Carare et al., 2008). Possible driving forces for this antidromic route are represented by reflection waves in the backward direction which follow each pulse wave in the blood vessels (Schley et al., 2006). After moving through the brain parenchyma, the CSF enriched of cellular waste flows along the PVS of the brain major veins into the SAS (Iliff et al., 2012). Alongside the route provided by arachnoid granulations and the dural venous sinuses, also meningeal lymphatic vessels along dural venous sinuses contribute to CSF clearance, draining the lymph to deep cervical lymph nodes (Antila et al., 2017; Da Mesquita et al., 2018).

3.2. Aging as a cause of decreased glymphatic activity and its relevance to MS

In the context of MS, the interplay between aging and glymphatic function is crucial, as the MS population ages, the cumulative effects of aging on the glymphatic system could exacerbate disease progression. In mice, glymphatic activity sharply declines with increasing age (Kress et al., 2014). Aging is accompanied by stiffening of the arterial wall leading to a reduction in arterial pulsatility, which is one of the drivers of glymphatic flow (Iliff et al., 2013). Aging is also accompanied by reactive gliosis, (Sabbatini et al., 1999) which might contribute to the age-related decline in glymphatic function. In fact, Aquaporin-4 (AQP4)

localized at the astrocytic endfeet, plays a central role in facilitating CSF-interstitial fluid exchange through perivascular drainage pathways (Iliff et al., 2012). In old brains, reactive astrocytes can lose the vascular AQP4 polarization, which means that AQP4 is no longer confined to astrocytic endfeet but present in astrocytes parenchymal processes. Thus, the age-related decline in glymphatic function might be in part attributable to a dysregulation in the astroglial-water transport mechanism (Kress et al., 2014)

Other factors potentially contributing to glymphatic activity reduction with aging are the decline in CSF production and pressure, demonstrated to be of the order of ~ 66 % and 27 %, respectively (Iliff et al., 2013; Chen et al., 2009; Fleischman et al., 2012).

Finally, aging-associated changes of the CNS immunological milieu can be implicated in impaired glymphatic function. In fact, a subpopulation of parenchymal border macrophages (PBMs) appears closely associated with the cerebral arteries. PBMs have the capacity to regulate CSF flow through the modulation of arterial motion (Drieu et al., 2022). In the aged mice, the subpopulation of PBMs mediating CSF flow is reduced (Drieu et al., 2022). Additionally, it has been shown that in the aged mice there is a loss of meningeal CCR7+ *T*-cells (Da Mesquita et al., 2021) CCR7-/- mice, when compared to aged-matched controls, exhibited decreased glymphatic influx (Da Mesquita et al., 2021).

Thus, the decline in glymphatic function due to aging might contribute in MS to the accumulation of neurotoxic substances, increasing neuroinflammation and further damaging the CNS. The combination of glymphatic dysfunction, aging, and MS-related pathology could create a vicious cycle, perpetuating disease progression and worsening clinical outcomes.

3.3. *Neuroinflammation, microangiopathy and glymphatic dysfunction*

In a recent study addressing how the ChP reacts to local and peripheral inflammation, it has been shown that acute inflammation is linked to CSF hypersecretion (Karimy et al., 2017). We can hypothesize that this transient CSF hypersecretion can lead to 1) an increased drainage of fluid, waste, and inflammatory mediators to the periphery, but also 2) the attraction of peripheral immune cells, which in the context of neuroinflammatory diseases such as MS, can facilitate the infiltration of immune cells into the CNS parenchyma (Filippi et al., 2018).

During CNS inflammation (in disorders like MS, traumatic brain injury or CNS infection), there is an increasing expression of AQP4 (Sugimoto et al., 2015; Aoki-Yoshino et al., 2005; Rohr et al., 2020). However, this increase in AQP4 expression does not support glymphatic fluid transport. Since the additional AQP4 channels are not inserted in the vascular endfeet of astrocytes, but rather in the cell body and perisynaptic processes, the subsequent loss of the vascular polarization of AQP4 correlates with a decrease in glymphatic flow (Kress et al., 2014). In addition to altered AQP4 polarization, infiltrating immune cells are known to accumulate in the PVS during inflammation, and may then physically block perivascular flow and influx of CSF (Ivan et al., 2020; Zhou et al., 2009). Finally, as already reported for aging, (Kress et al.,

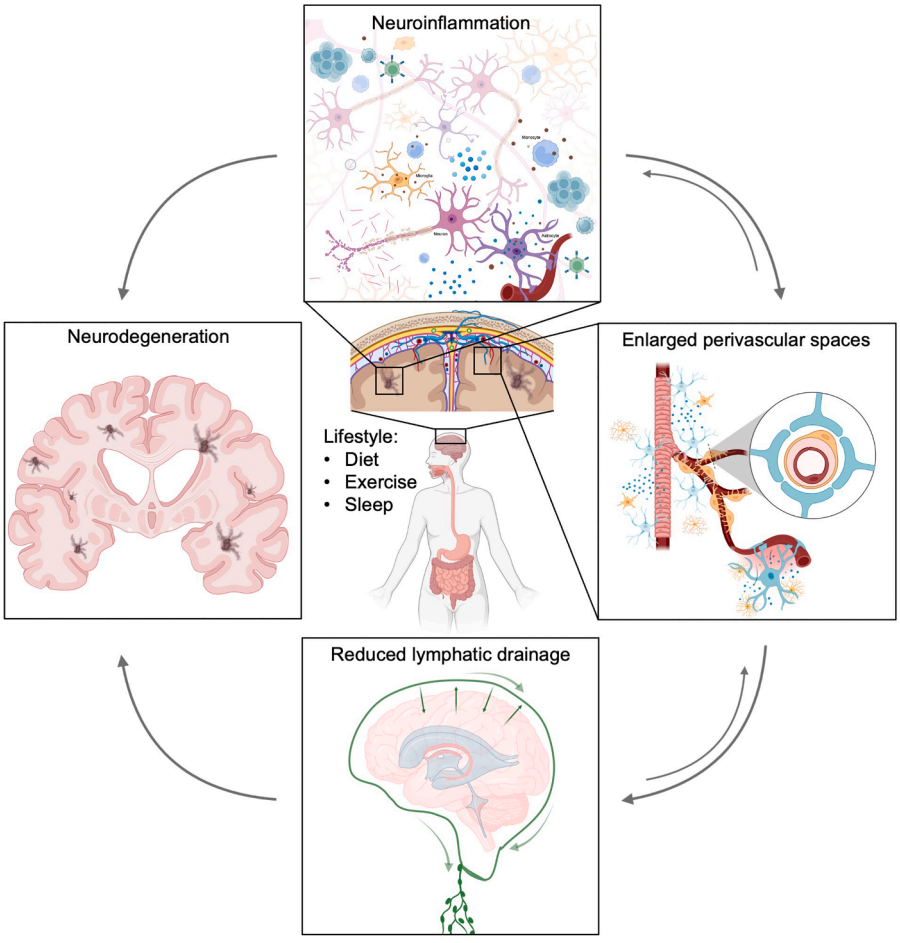

Fig. 1. Vicious cycle linking neuroinflammation, perivascular space dysfunction and neurodegeneration in MS.
In MS, lifestyle habits play a crucial role in the physiopathology of neuroinflammation and perivascular space dysfunction. Diet, physical exercise and sleep quality can contribute to glymphatic impairment, which disrupts the clearance of waste from the brain through lymphatic system, contributing to neurodegeneration. This vicious cycle exacerbates both neuroinflammation and perivascular space dysfunction, further accelerating the progression of MS.

2014) the reactive astrogliosis resulting from neuroinflammation, (Jha et al., 2018) is also likely to reduce brain fluid clearance by loss of AQP4 polarization. Interestingly, an increased AQP4 expression together with a reduction in astrocyte polarization has been observed postmortem in the plaques of patients with MS (Aoki-Yoshino et al., 2005; Rohr et al., 2020).

It is possible that the impairment of the glymphatic flow during neuroinflammation and resultant accumulation of cytokines create a vicious cycle to perpetuate neuroinflammation. On the other hand, this inflammatory milieu can facilitate the arteriolar damage (for example through oxidative stress and pro-atherogenic Th1 immune response) (Geraldes et al., 2020; Wiseman et al., 2016) and thus perpetuate glymphatic dysfunction (Fig. 1).

However, it is important to highlight that while existing studies suggest a role for glymphatic dysfunction in both MS and CSVD, (Alghanimy et al., 2024; Ang et al., 2024) the precise role of glymphatic system dysfunction in these two pathologies remains largely unknown. It is possible that neuroinflammation and microangiopathy may represent the cause rather than the result of glymphatic dysfunction in both MS and CSVD (e.g. through fluid drainage obstruction secondary to inflammation and endothelial dysfunction) (Brown et al., 2018). Bidirectional interactions remain speculative at this stage and require further investigation.

4. Imaging small vessel disease and glymphatic dysfunction in MS

4.1. MRI features of CSVD: EPVS and WM hyperintensities

When PVS are dilated, they become readily visible on MRI and are referred to as enlarged (i.e. EPVS) or sometimes Virchow-Robin spaces. MRI identification of EPVS is based on the signal properties of CSF, which is hypointense on T1w imaging and hyperintense on T2w imaging. They have a linear appearance and abut parenchymal penetrating blood vessels. Typically, EPVS are observed in the BG, CSO, and pontomesencephalic junction. As reported above, EPVS represent one of the main brain-MRI features of CSVD (Pantoni, 2010; Wardlaw et al., 2013). Accumulating evidence suggests a high EPVS burden also in MS, even though the exact clinical and physiopathological significance remains controversial (Granberg et al., 2020). Of note, EPVS in MS are more frequently found at the level of the CSO, (Guisset et al., 2021; Borrelli et al., 2024; Cavallari et al., 2018) while in CSVD non-MS patients EPVS are generally most prominent in the BG (Wardlaw et al., 2013). This finding suggests that the physiopathology of microangiopathy in MS may be different from the one of classical CSVD. EPVS are usually assessed using a 4-point visual rating scale on the axial plane (0 = no EPVS, 1 = <10 EPVS, 2 = 11–20 EPVS, 3 = 21–40 EPVS, and 4 = >40 EPVS), (Potter et al., 2015) even if new algorithms for the automated quantification of EPVS have been recently proposed (Schwartz et al., 2019; Dubost et al., 2019). Table 1 summarizes the existing MRI studies on EPVS in MS.

WM hyperintensities (WMHs) are also a common neuroimaging feature of CSVD (Wardlaw et al., 2013). WMHs are visible on MRI as bilateral, mostly symmetrical, deep WM hyperintense lesions on T2w and hypointense on T1w sequences (Wardlaw et al., 2013). WMHs are more prevalent in the frontal and parietal lobes (Wardlaw, 2001) and, according to their extension, are classified into three types: focal, initial fusion and extensive fusion (Fazekas et al., 1987; Wahlund et al., 2001). WMHs usually form at the terminal region of blood supply and are thus more commonly found in the BG, corona radiata, CSO, (Duering et al., 2013) and in the central zone of the brainstem (Erro et al., 2005). The physiopathology underlying brain WMHs formation in CSVD is believed to reflect several mechanisms including brain hypoperfusion, reduced vascular reactivity, and tissue hypoxia, mostly occurring at the arteriolar side of the microcirculation (Pantoni, 2010; Geraldes et al., 2017). Conversely, most focal inflammatory demyelinating lesions in MS develop around a central vein (Guisset et al., 2021). In clinical practice, it can be challenging to assess whether new hyperintensities in MS are due to the concomitant CSVD or to inflammatory demyelination, (Filippi et al., 2019) and diagnostic uncertainty may also arise during the diagnostic work-up of patients with possible MS and concomitant VRFs for CSVD, (Filippi et al., 2019) especially in patients with late onset MS. In this context, the percentage of WM lesions bearing a central vein sign (CVS) on optimized T2*-weighted MRI, (Sati et al., 2012; Sati et al., 2014; Absinta et al., 2018) can help to distinguish CVS-positive MS-demyelinating lesions from CVS-negative microangiopathic WM hyperintensities (Guisset et al., 2021)

Other MRI features of CSVD, such as cerebral microbleeds and lacunar infarcts, are less pronounced in MS patients with VRFs and are not discussed in this review (Subramanian et al., 2020)

4.2. Imaging techniques exploring lymphatic brain fluid drainage in vivo

Recent advancements in glymphatic system and meningeal lymphatics imaging have provided significant insights into various neuropathological conditions, including MS and CSVD. Techniques such as contrast-enhanced T1w imaging and positron emission tomography (PET) have shown enlarged and inflamed ChP in MS patients, (Ricigliano et al., 2021) with larger baseline ChP predicting WM lesion expansion and clinical disability progression (Klistorner et al., 2022; Bergsland et al., 2023). One prior study investigating ChP in MS and neuromyelitis optica spectrum disorder (NMOSD), has shown an increased ChP contrast enhancement in both conditions (vs healthy controls), suggesting an involvement of this structure in the physiopathology of neuroinflammatory disorders (Kim et al., 2020). When compared to NMOSD, ChP in MS seems larger and associated with the brain-MRI lesion burden, suggesting a possible preferential role of ChP inflammation in the pathogenesis of MS (vs NMOSD) (Müller et al., 2022). Studies using dynamic contrast-enhanced MRI have found age-related decreases in ChP-to-CSF efflux rates, associating ChP alterations with cognitive dysfunction (Anderson et al., 2022) (11)C-Pittsburgh compound B PET has been recently proposed as a novel tool to detect CSF clearance alterations in various neurological conditions (De Leon et al., 2017). One recent study using this technique has demonstrated pathologic changes in CSF dynamics in patients with MS (Schubert et al., 2019). Another imaging technique which have been proposed to study glymphatic clearance is the diffusion tensor imaging along PVS (DTI-ALPS). This method is meant to quantify glymphatic system function by measuring water diffusivity along PVS (Taoka et al., 2017; Taoka et al., 2022). Abnormal DTI-ALPS indices have been observed in aging, (Zhang et al., 2021) hypertension, (Zhang et al., 2021) CSVD, (Tian et al., 2023) and MS, (Carotenuto et al., 2022) suggesting an impaired glymphatic function in these conditions. In MS, the DTI-ALPS index has been linked to greater disability, demyelination, and neurodegeneration, with more pronounced dysfunction in progressive forms of MS (Carotenuto et al., 2022). Research also indicates glymphatic dysfunction in pediatric MS, where a higher DTI-ALPS index is associated with MRI lesion load, tissue loss, and cognitive impairment (Margoni et al., 2024). Additionally, an altered DTI-ALPS index has been observed also in NMOSD, (Cacciaguerra et al., 2022; Kim et al., 2024) showing no substantial differences compared to MS (Kim et al., 2024). As in MS, also in NMOSD abnormal DTI-ALPS indices have been associated with greater disability (Cacciaguerra et al., 2022). These findings highlight the potential role of glymphatic dysfunction in neuroinflammation and neurotoxic substance buildup, contributing to both demyelination and vascular pathology. While the exact relationship between ChP alterations and glymphatic system dysfunction requires further investigation, a recent study in people with MS revealed that the DTI-ALPS index decreases with increasing ChP volumes (Xie et al., 2024). Pathologic changes in the enlarged ChP, such as basement membrane thickening and increased immune cell infiltration, may contribute to the disruption of the normal CSF circulation, decreasing

Table 1
Summary of MRI studies on EPVS in MS.

First author name	Year of publication	Methods	Sample size	Participant age (years)	MS phenotype	EDSS	Disease duration (years)	Results
Achiron (Achiron and Faibel, 2002)	2002	Study design: Retrospective case–control study MRI field strength: 2T	MS: 71 HC: 60	MS: mean 26.8 HC: mean 27.2	Newly diagnosed MS patients	NA	NA	- EPVS more frequent in MS than HC. - In MS, EPVS score more frequently grade 3 than 2 or 1, while all HC have EPVS score grade 1. - No difference among patients with and those without EPVS in terms of age at onset, neurologic disability, and specific functional system involvement or mono- versus polysymptomatic involvement at onset.
Wuerfel (Wuerfel et al., 2008)	2008	Study design: Prospective cohort study MRI field strength: 1.5T	MS: 45 HC: 30	MS: mean 39.8 HC: mean 37.8	RRMS	Mean 2.3	Mean 8.8	- EPVS detected in comparable numbers in both MS and HC. - Larger EPVS volumes in MS than HC, not explained by a lower brain volume. - Influence of age on EPVS volumes in HC but not in MS. - Increase in EPVS volumes and counts accompanying the occurrence of contrast-enhancing lesions.
Etemadifar (Etemadifar et al., 2011)	2011	Study design: Retrospective case–control study MRI field strength: 1.5T	MS: 73 HC: 73	MS: mean 32.3 HC: mean 33.3	Newly diagnosed MS	NA	NA	- EPVS count higher in MS than HC. - In MS, EPVS more frequently located in the high convexity. - The round shaped EPVS more frequently detected in MS than in HC, while curvilinear shapes in HC than MS.
Al-Saeed (Al-Saeed et al., 2012)	2012	Study design: Retrospective case–control study MRI field strength: 1.5T	MS: 80 Controls with headache: 80	MS and controls: age range 15–49	Newly diagnosed MS	NA	NA	- No difference in the frequency of EPVS between MS and controls. - In the supraventricular region, EPVS larger in MS than in controls.
Conforti (Conforti et al., 2014)	2014	Study design: Retrospective case–control study MRI field strength: 3T	Inactive MS: 40 HC: 30	MS: mean 42.7 HC: mean 42.8	20 nondisabling MS (EDSS < 3.0) and 19 disabling MS (EDSS > 4)	Range: 1–6.5	NA	- Higher EPVS number, area and volume in MS than HC. - No differences between disabling and nondisabling MS. - EPVS did not correlate with brain volume.
Kilsdonk (Kilsdonk et al., 2015)	2015	Study design: Retrospective case–control study MRI field strength: 7T	MS: 34 HC: 11	MS: mean 43 HC: mean 38.8	RRMS: 22 SPMS: 5 PPMS: 7	Median 4, range 0–7.5	Mean 9.4	- EPVS more frequent in MS than HC. - No difference in EPVS size between MS and HC. - EPVS count in MS associated with brain volume, but not with lesion count.
Conforti (Conforti et al., 2016)	2016	Study design: Retrospective case–control study MRI field strength: 3T	MS: 82 HC: 43	MS: mean 39.1 HC: mean 39.6	RRMS with Fatigue	NA	NA	- Higher EPVS number in MS than HC. - EPVS number correlated to fatigue.
Favaretto (Favaretto et al., 2017)	2017	Study design: Retrospective case–control study MRI field strength: 3T	MS: 43 HC: 10	CIS: mean 36.3 RRMS: mean 35.3 PMS: mean 41.3 HC: mean 33.0	CIS: 21 RRMS: 15 PMS: 7	RRMS: mean 2.2 PMS: mean 6	RRMS: mean 8.7 PMS: mean 13.9	- EPVS number and volume significantly higher on 2D-PSIR sequence compared to both 3D-T1 and 3D-FLAIR. - EPVS significantly increased in CIS compared to HC, in PMS and RRMS compared to CIS and in male versus female patients. - EPVS volume increased with disease duration, while not correlated with EDSS.

(*continued on next page*)

Table 1 (*continued*)

First author name	Year of publication	Methods	Sample size	Participant age (years)	MS phenotype	EDSS	Disease duration (years)	Results
								- EPVS correlated with cognitive tests, while not correlated with brain volume, gadolinium-enhancing lesions and T2 lesion volume.
Cavallari (Cavallari et al., 2018)	2018	Study design: Retrospective case–control study (from prospective cohort) MRI field strength: 1.5T	MS: 60 HC: 15	MS: median 48, range 26–68 HC: median 38, range 24–56	RRMS - with disease-worsening: 30 - without disease-worsening: 30	Median 1.5, range 0–2	Mean 12	- No difference in EPVS scores between patient with and without disease-worsening. - EPVS not associated with T2 lesion volume and brain volume. - No differences in EPVS between patients and controls (when adjusted for age and sex).
Guisset (Guisset et al., 2021)	2020	Study design: Cross-sectional study MRI field strength: 3T	MS: 50	Median 44, range 20–68	RRMS: 31 PPMS: 12 SPMS: 7	Median 2.5, range 1.0 – 6.5	NA	- Higher EPVS number associated with lower percentage of CVS-positive (perivenular) lesions.
Wooliscroft (Wooliscroft et al., 2020)	2020	Study design: Cross-sectional/ retrospective study MRI field strength: 3T	MS: 46	Median 59, range 40–69	SPMS	Median 6, range 3–9	Median 31, range 9–51	- Higher EPVS score associated with older age, male sex and lower EDSS. - No associations between EPVS score and vascular co-morbidities or brain volume.
Ineichen (Ineichen et al., 2023)	2023	Study design: cohort study MRI field strength: 3T	MS: 205 (exploratory cohort: 142; validation cohort: 63) HC: 30 Brain blocks from 6 MS patients and 3 non-MS controls were also histopathologically analyzed	Exploratory MS: mean 37 (± 6SD) Validation MS: mean 36 (± 3) HC: mean 38 (± 12 SD)	Exploratory: - RRMS: 113 (80 %) - SPMS: 23 (16 %) - RPMS: 2 (1 %) - PMS: 4 (3 %) Validation: - RRMS: 63 (100 %)	Exploratory MS: median 2.0 (IQR 1.1 – 3.5) Validation MS: median 1.0 (IQR 0.5 – 2.5)	Exploratory MS: Median 6.3 (IQR 1.8 – 10.6) Validation MS: median 3.4 (IQR 1.2 – 6.8)	- EPVS count associated with increased T1 and T2 lesion volumes. - No spatial colocalization of EPVS with MS inflammatory lesions. - At tissue level, EPVS mostly corresponded to arteries, not associated with MS pathological hallmarks but associated with signs of CSVD.
Borrelli (Borrelli et al., 2024)	2024	Study design: Cross-sectional study MRI field strength: 3T	MS: 207 - With high EPVS scores: 79 - With low EPVS scores: 128	MS with high EPVS scores: mean 49, range 20–75 MS with low EPVS scores: 44, range 22–73	CIS 6 % RRMS 55 % SPMS 26 % PPMS 13 %	MS with high EPVS scores: median 2.5, range: 0–7.0 MS with low EPVS scores: median 2.5, range 0–7.5	MS with high EPVS scores: median 8.8, range 0–41.9 MS with low EPVS scores: median 6.3, range 0–39.9	- High EPVS scores associated with older age, VRFs, lower percentage of CVS-positive (perivenular) lesions, reduced brain volumes and older brain-predicted age. - EPVS not associated with neuroinflammatory markers.

CIS: clinically isolated syndrome; CVS: central vein sign; CSVD: cerebral small vessel disease; EDSS: expanded disability status scale; EPVS: enlarged perivascular spaces; FLAIR: fluid-attenuated inversion recovery; HC: healthy controls; MRI: magnetic resonance imaging; MS: multiple sclerosis; PPMS: primary progressive multiple sclerosis. PSIR: phase-sensitive inversion recovery; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; VRFs: vascular risk factors.

the clearance function of the glymphatic system (Kaur et al., 2016).

Meningeal lymphatic vessels, located within the dura mater and particularly concentrated along the superior sagittal sinus and parasagittal dura, have been identified using contrast-enhanced MRI techniques (Absinta et al., 2017). Studies have shown that gadobutrol, a standard gadolinium-based contrast agent (GBCA) that can diffuse across the permeable capillary endothelia of the dura mater, enhances dural lymphatic vessels, highlighting their permeability (Absinta et al., 2017). Dynamic contrast-enhanced MRI studies have revealed delayed lymphatic drainage in older individuals, suggesting an age-related decline in lymphatic function (Joo et al., 2023). Intrathecal GBCA administration has demonstrated safe and effective imaging of CSF drainage pathways in the dura mater (Edeklev et al., 2019; Halvorsen et al., 2021). Non-contrast MRI techniques, such as arterial spin-labeling, have also been used to measure CSF outflow, showing a decline with aging and sedentary lifestyle (Malis et al., 2024; Miyazaki et al., 2024). These imaging techniques underscore the importance of the glymphatic and meningeal lymphatic systems in maintaining neurological health and their potential involvement in various neuropathological conditions, including MS and CSVD.

Finally, the retinal inner nuclear layer (INL) thickness, explored by optical coherence tomography (OCT), has been proposed as a potential tool for investigating the retinal glymphatic system (Petzold, 2016). Specifically, the presence of retinal hyperreflecting foci (HRF) within the INL, which is hypothesized to represent activated microglia and Müller cells, may contribute to microvascular damage and blood-retinal barrier dysfunction (Pengo et al., 2022). Therefore, INL and HRF may be considered proxies for CSF dynamic changes, warranting further exploration in future studies.

5. Lifestyle, microangiopathy and glymphatic dysfunction: a vicious cycle around neuroinflammation?

Since MS and CSVD can both be influenced by lifestyle, (Gu and Scarmeas, 2013; Rippe, 2019; Saul et al., 2023) understanding the impact of physical exercise, diet, and sleep on glymphatic function is particularly pertinent in the context of these diseases. While it can be hypothesized that the direct or indirect dysfunction of the glymphatic system mediated by lifestyle may enhance neuroinflammation and exacerbate both microangiopathy and demyelination changes in the MS brain, it is important to note that the role of VRFs and CSVD as causes of glymphatic impairment in MS has not been proven by clinical studies and remains speculative at this stage. In the forthcoming discussion, we explore the evidence supporting the notion that lifestyle factors can influence glymphatic function. While current data suggest potential links, further research is necessary to establish a causal relationship in MS. Nevertheless, this area of study may represent a promising avenue for therapeutic interventions aimed at mitigating MS-related microangiopathy and neuroinflammation.

5.1. Physical exercise can potentially improve glymphatic function

Two groups have shown that voluntary exercise can improve glymphatic function in rodents, (fei et al., 2017; von Holstein-Rathlou et al., 2018) since voluntary running improved both the CSF-interstitial fluid exchange and CSF efflux via drainage into the deep cervical lymph nodes. In one of these studies, exercise also resulted in reduced amyloid-beta levels, glia cell immunoreactivity and increased AQP4 polarisation as well as improved cognition in the running group compared to the sedentary group (fei et al., 2017). Since the beneficial effects of exercise are not seen acutely during exercise, (von Holstein-Rathlou et al., 2018) it has been hypothesized that the effect on glymphatic function cannot be explained by the simple increase of pulse rate and cardiac output. As the low noradrenaline levels, induced by sleep (see below) or by pharmacological intervention, are correlated with an increase in glymphatic function, (Lilius et al., 2019) changes on adrenaline and noradrenaline signaling related to exercise may explain the reduction in glymphatic function.

Moreover, exercise is beneficial for vascular health (Furby et al., 2020). Since the CBF is one of the drivers of glymphatic function, (Mestre et al., 2018; Iliff et al., 2013) the exercise-related changes on vascular function can also explain the improvement of glymphatic function by physical exercise. Indeed, the reduction of CBF and arterial wall pulsatility induced by sedentary lifestyle decrease the CSF-interstitial fluid exchange in the brain, highlighting the functional connection existing between cerebral haemodynamics and the glymphatic function (Iliff et al., 2013).

5.2. Diet can support brain clearance

Polyunsaturated fatty acids (PUFAs), and particularly omega 3 fatty acids (n-3 PUFAs), are essential fatty acids for maintaining vascular health, and are known for their antihypertensive and anti-inflammatory properties (Lorente-Cebrián et al., 2013). Recent studies in mice suggested that PUFAs can also support glymphatic function, since a high PUFA diet increased CSF tracer influx and clearance (Ren et al., 2017; Zhang et al., 2020). Moreover, transgenic mice expressing increased levels of PUFAs in the brain showed protection against neuronal death from increased levels of amyloid beta, protective effect that was not seen in AQP4 knockout mice where the glymphatic system was inhibited (Zhang et al., 2020)

Alcohol use can also influence glymphatic function. Alcohol poses a complex public health challenge, as its consumption elevates the likelihood of diverse negative health consequences, (Dam et al., 2016) while moderate intake is associated with reduced all-cause mortality compared to abstaining entirely (Grønbaek, 2009; Xi et al., 2017). Similarly, the effect of alcohol on glymphatic function is complex, since it can result in an increased and decreased glymphatic function at low and high levels, respectively (Lundgaard et al., 2018). The enhanced glymphatic function by low level of alcohol is attributed to the dilation of blood vessels mediated by nitric oxide and the resulted enhancement of CSF clearance by vascular reactivity (Cheng et al., 2019). Conversely, moderate to high levels of alcohol increased in mice AQP4 levels but with disrupted polarization resulting in decreased glymphatic function (Liu et al., 2020). Besides these cellular changes, alcohol may modulate glymphatic function also by inducing sleep disturbances (see below). Thus, excessive alcohol consumption can have disruptive effects on the glymphatic function through various mechanisms, including altered astrocyte function, changes in interstitial fluid dynamics, and impaired CSF flow (Kylkilahti et al., 2021).

5.3. Sleep disturbances and glymphatic function

Sleep can have a huge impact on glymphatic function, since glymphatic activity is dramatically enhanced during sleep, while it is suppressed during wakefulness (Xie et al., 2013). A major driver of arousal is the noradrenaline and as such it might be responsible for suppression of glymphatic during wakefulness. Indeed, administration of noradrenaline antagonists in awake mice resulted in an increase in CSF tracer influx, while administration of noradrenaline significantly decreased the interstitial volume fraction (Xie et al., 2013). Since noradrenaline also acts directly on ChP epithelial cells inhibiting CSF production, (Nilsson et al., 1992) it can be considered a key regulator of the switch on glymphatic function between the sleep and wakeful state.

Studies in humans have shown that one night of sleep deprivation leads to increases in amyloid-beta plaques in brain tissue (Shokri-Kojori et al., 2018). Similar to the effects seen after acute sleep deprivation, chronic insomnia lead to higher CSF levels of amyloid-beta-42 (Chen et al., 2018). Reactive astrocytes and alteration in AQP4 expression induced by sleep deprivation might explain the effect on glymphatic function (Zhang et al., 2020).

Interestingly, enlargement of PVS seems in itself connected to poor sleep quality, (Berezuk et al., 2015; Del Brutto et al., 2019) leading to the

hypothesis that sleep deficiency may lead to structural changes in the PVS.

6. Methods

To conduct this narrative review, relevant literature was identified through comprehensive searches of electronic databases including PubMed, Google Scholar, and Scopus. Keywords used in the search included "multiple sclerosis," "cerebral small vessel disease," "glymphatic system," "vascular risk factors," "diet," "sleep" and "physical activity". Articles published at any time were considered for inclusion. Additionally, references from selected articles were screened for further relevant studies. The included literature was critically evaluated, and key findings were synthesized to provide a comprehensive overview of the topic.

7. Conclusion and future prospective

In conclusion, this review highlights the complex interplay between CSVD, and glymphatic system dysfunction in MS. With the MS population aging, the prevalence of vascular comorbidities is increasing, potentially exacerbating physical and cognitive impairment in patients with MS. The evidence suggests that the glymphatic system dysfunction could be a critical link, explaining how vascular pathology contribute to MS progression and neurodegeneration. Lifestyle factors such as diet, sleep quality, and physical activity appear to influence glymphatic function, offering potential therapeutic avenues to mitigate MS-related impairment. Further research is required to elucidate the precise mechanisms by which lifestyle modifications and CSVD affect the glymphatic system and to develop targeted interventions aimed at enhancing brain health in MS. A deeper understanding of the role of CSVD and the glymphatic system in MS could pave the way for novel strategies to reduce the burden of vascular pathology in MS and improve overall patient outcomes.

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CRediT authorship contribution statement

Serena Borrelli: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sophie Leclercq:** Writing – review & editing, Validation, Conceptualization. **Marco Pasi:** Writing – review & editing, Validation, Supervision, Conceptualization. **Pietro Maggi:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest related to this work.

References

Absinta, M., Ha, S.K., Nair, G., et al., 2017. Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI. Elife 6, e29738. https://doi.org/10.7554/eLife.29738.

Absinta, M., Sati, P., Fechner, A., Schindler, M.K., Nair, G., Reich, D.S., 2018. Identification of chronic active multiple sclerosis lesions on 3T MRI. Am J Neuroradiol. 39 (7), 1233–1238. https://doi.org/10.3174/ajnr.A5660.

Achiron, A., Faibel, M., 2002. Sandlike appearance of Virchow-Robin spaces in early multiple sclerosis: a novel neuroradiologic marker. AJNR Am. J. Neuroradiol. 23 (3), 376–380.

Alghanimy, A., Work, L.M., Holmes, W.M., 2024. The glymphatic system and multiple sclerosis: an evolving connection. Mult. Scler. Relat. Disord. 83, 105456 https://doi.org/10.1016/j.msard.2024.105456.

Al-Saeed, O., Athyal, R., Ismail, M., Sheikh, M., 2012. Significance of Virchow-Robin spaces in patients newly diagnosed with multiple sclerosis: a case-control study in an Arab population. Med. Princ. Pract. Int. J. Kuwait Univ. Health Sci. Cent. 21 (5), 447–451. https://doi.org/10.1159/000337427.

Anderson, V.C., Tagge, I.J., Doud, A., et al., 2022. DCE-MRI of brain fluid barriers: *in vivo* water cycling at the human choroid plexus. Tissue Barriers 10 (1), 1963143. https://doi.org/10.1080/21688370.2021.1963143.

Ang, P.S., Zhang, D.M., Azizi, S.A., Norton De Matos, S.A., Brorson, J.R, 2024. The glymphatic system and cerebral small vessel disease. J. Stroke Cerebrovasc. Dis. 33 (3), 107557 https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.107557.

Antila, S., Karaman, S., Nurmi, H., et al., 2017. Development and plasticity of meningeal lymphatic vessels. J. Exp. Med. 214 (12), 3645–3667. https://doi.org/10.1084/jem.20170391.

Aoki-Yoshino, K., Uchihara, T., Duyckaerts, C., Nakamura, A., Hauw, J.J., Wakayama, Y., 2005. Enhanced expression of aquaporin 4 in human brain with inflammatory diseases. Acta Neuropathol. 110 (3), 281–288. https://doi.org/10.1007/s00401-005-1052-2 (Berl).

Bai, T., Yu, S., Feng, J., 2022. Advances in the role of endothelial cells in cerebral small vessel disease. Front. Neurol. 13, 861714 https://doi.org/10.3389/fneur.2022.861714.

Banizs, B., Pike, M.M., Millican, C.L., et al., 2005. Dysfunctional cilia lead to altered ependyma and choroid plexus function,and result in the formation of hydrocephalus. Development 132 (23), 5329–5339. https://doi.org/10.1242/dev.02153.

Berezuk, C., Ramirez, J., Gao, F., et al., 2015. Virchow-robin spaces: correlations with polysomnography-derived sleep parameters. Sleep. 38 (6), 853–858. https://doi.org/10.5665/sleep.4726.

Bergsland, N., Dwyer, M.G., Jakimovski, D., et al., 2023. Association of choroid plexus inflammation on MRI with clinical disability progression over 5 years in patients with multiple sclerosis. Neurology 100 (9), e911–e920. https://doi.org/10.1212/WNL.0000000000201608.

Borrelli, S., Guisset, F., Vanden Bulcke, C., et al., 2024. Enlarged perivascular spaces are associated with brain microangiopathy and aging in multiple sclerosis. Mult. Scler. J., 13524585241256881 https://doi.org/10.1177/13524585241256881. Published online June 7.

Brown, R., Benveniste, H., Black, S.E., et al., 2018. Understanding the role of the perivascular space in cerebral small vessel disease. Cardiovasc. Res. 114 (11), 1462–1473. https://doi.org/10.1093/cvr/cvy113.

Cacciaguerra, L., Carotenuto, A., Pagani, E., et al., 2022. Magnetic resonance imaging evaluation of perivascular space abnormalities in neuromyelitis optica. Ann. Neurol. 92 (2), 173–183. https://doi.org/10.1002/ana.26419.

Capkun, G., Dahlke, F., Lahoz, R., et al., 2015. Mortality and comorbidities in patients with multiple sclerosis compared with a population without multiple sclerosis: an observational study using the US Department of defense administrative claims database. Mult. Scler. Relat. Disord. 4 (6), 546–554. https://doi.org/10.1016/j.msard.2015.08.005.

Carare, R.O., Bernardes-Silva, M., Newman, T.A., et al., 2008. Solutes, but not cells, drain from the brain parenchyma along basement membranes of capillaries and arteries: significance for cerebral amyloid angiopathy and neuroimmunology. Neuropathol. Appl. Neurobiol. 34 (2), 131–144. https://doi.org/10.1111/j.1365-2990.2007.00926.x.

Carotenuto, A., Cacciaguerra, L., Pagani, E., Preziosa, P., Filippi, M., Rocca, M.A., 2022. Glymphatic system impairment in multiple sclerosis: relation with brain damage and disability. Brain 145 (8), 2785–2795. https://doi.org/10.1093/brain/awab454.

Cavallari, M., Egorova, S., Healy, B.C., et al., 2018. Evaluating the association between enlarged perivascular spaces and disease worsening in multiple sclerosis. J. Neuroimaging 28 (3), 273–277. https://doi.org/10.1111/jon.12490.

Chen, D.W., Wang, J., Zhang, L.L., Wang, Y.J., Gao, C.Y., 2018. Cerebrospinal fluid amyloid-β levels are increased in patients with insomnia. J. Alzheimers Dis. JAD 61 (2), 645–651. https://doi.org/10.3233/JAD-170032.

Chen, R.L., Kassem, N.A., Redzic, Z.B., Chen, C.P.C., Segal, M.B., Preston, J.E., 2009. Age-related changes in choroid plexus and blood-cerebrospinal fluid barrier function in the sheep. Exp. Gerontol. 44 (4), 289–296. https://doi.org/10.1016/j.exger.2008.12.004.

Cheng, Y., Liu, X., Ma, X., Garcia, R., Belfield, K., Haorah, J., 2019. Alcohol promotes waste clearance in the CNS via brain vascular reactivity. Free Radic. Biol. Med. 143, 115–126. https://doi.org/10.1016/j.freeradbiomed.2019.07.029.

Conforti, R., Cirillo, M., Sardaro, A., et al., 2016. Dilated perivascular spaces and fatigue: is there a link?Magnetic resonance retrospective 3Tesla study. Neuroradiology 58 (9), 859–866. https://doi.org/10.1007/s00234-016-1711-0.

Conforti, R., Cirillo, M., Saturnino, P.P., et al., 2014. Dilated Virchow-Robin spaces and multiple sclerosis: 3 T magnetic resonance study. Radiol. Med. 119 (6), 408–414. https://doi.org/10.1007/s11547-013-0357-9 (Torino).

Dam, M.K., Hvidtfeldt, U.A., Tjønneland, A., Overvad, K., Grønbæk, M., Tolstrup, J.S., 2016. Five year change in alcohol intake and risk of breast cancer and coronary heart disease among postmenopausal women: prospective cohort study. BMJ 353, i2314. https://doi.org/10.1136/bmj.i2314.

Da Mesquita, S., Herz, J., Wall, M., et al., 2021. Aging-associated deficit in CCR7 is linked to worsened glymphatic function, cognition, neuroinflammation, and β-amyloid pathology. Sci. Adv. 7 (21), eabe4601. https://doi.org/10.1126/sciadv.abe4601.

Da Mesquita, S., Louveau, A., Vaccari, A., et al., 2018. Functional aspects of meningeal lymphatics in ageing and Alzheimer’s disease. Nature 560 (7717), 185–191. https://doi.org/10.1038/s41586-018-0368-8.

Dandy, W.E., 1919. Experimental hydrocephalus. Ann. Surg. 70 (2), 129–142. https://doi.org/10.1097/00000658-191908000-00001.
Del Brutto, O.H., Mera, R.M., Del Brutto, V.J., Castillo, P.R., 2019. Enlarged basal ganglia perivascular spaces and sleep parameters. A population-based study. Clin. Neurol. Neurosurg. 182, 53–57. https://doi.org/10.1016/j.clineuro.2019.05.002.
De Leon, M.J., Li, Y., Okamura, N., et al., 2017. Cerebrospinal fluid clearance in alzheimer disease measured with dynamic PET. J. Nucl. Med. 58 (9), 1471–1476. https://doi.org/10.2967/jnumed.116.187211.
Drieu, A., Du, S., Storck, S.E., et al., 2022. Parenchymal border macrophages regulate the flow dynamics of the cerebrospinal fluid. Nature 611 (7936), 585–593. https://doi.org/10.1038/s41586-022-05397-3.
Dubost, F., Yilmaz, P., Adams, H., et al., 2019. Enlarged perivascular spaces in brain MRI: automated quantification in four regions. Neuroimage 185, 534–544. https://doi.org/10.1016/j.neuroimage.2018.10.026.
Duering, M., Biessels, G.J., Brodtmann, A., et al., 2023. Neuroimaging standards for research into small vessel disease—Advances since 2013. Lancet Neurol. 22 (7), 602–618. https://doi.org/10.1016/S1474-4422(23)00131-X.
Duering, M., Csanadi, E., Gesierich, B., et al., 2013. Incident lacunes preferentially localize to the edge of white matter hyperintensities: insights into the pathophysiology of cerebral small vessel disease. Brain 136 (9), 2717–2726. https://doi.org/10.1093/brain/awt184.
Edeklev, C.S., Halvorsen, M., Løvland, G., et al., 2019. Intrathecal use of gadobutrol for glymphatic MR imaging: prospective safety study of 100 patients. AJNR Am. J. Neuroradiol. 40 (8), 1257–1264. https://doi.org/10.3174/ajnr.A6136.
Erro, M.E., Gállego, J., Herrera, M., Bermejo, B., 2005. Isolated pontine infarcts: etiopathogenic mechanisms. Eur. J. Neurol. 12 (12), 984–988. https://doi.org/10.1111/j.1468-1331.2005.01119.x.
Etemadifar, M., Hekmatnia, A., Tayari, N., et al., 2011. Features of Virchow-Robin spaces in newly diagnosed multiple sclerosis patients. Eur. J. Radiol. 80 (2), e104–e108. https://doi.org/10.1016/j.ejrad.2010.05.018.
Favaretto, A., Lazzarotto, A., Riccardi, A., et al., 2017. Enlarged Virchow Robin spaces associate with cognitive decline in multiple sclerosis. Pham D, ed. PLoS One 12 (10), e0185626. https://doi.org/10.1371/journal.pone.0185626.
Fazekas, F., Chawluk, J., Alavi, A., Hurtig, H., Zimmerman, R., 1987. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. Am. J. Roentgenol. 149 (2), 351–356. https://doi.org/10.2214/ajr.149.2.351.
fei, H.X., Xu, L.D., Zhang, Q., et al., 2017. Voluntary exercise promotes glymphatic clearance of amyloid beta and reduces the activation of astrocytes and microglia in aged mice. Front. Mol. Neurosci. 10, 144. https://doi.org/10.3389/fnmol.2017.00144.
Filippi, M., Bar-Or, A., Piehl, F., et al., 2018. Multiple sclerosis. Nat. Rev. Dis. Primer 4 (1), 43. https://doi.org/10.1038/s41572-018-0041-4.
Filippi, M., Preziosa, P., Banwell, B.L., et al., 2019. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain 142 (7), 1858–1875. https://doi.org/10.1093/brain/awz144.
Fleischman, D., Berdahl, J.P., Zaydlarova, J., Stinnett, S., Fautsch, M.P., Allingham, R.R., 2012. Cerebrospinal fluid pressure decreases with older age. PLoS One 7 (12), e52664. https://doi.org/10.1371/journal.pone.0052664.
Furby, H.V., Warnert, E.A., Marley, C.J., Bailey, D.M., Wise, R.G., 2020. Cardiorespiratory fitness is associated with increased middle cerebral arterial compliance and decreased cerebral blood flow in young healthy adults: a pulsed ASL MRI study. J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab. 40 (9), 1879–1889. https://doi.org/10.1177/0271678x19865449.
Ge, Y., Law, M., Herbert, J., Grossman, R.I., 2005. Prominent perivenular spaces in multiple sclerosis as a sign of perivascular inflammation in primary demyelination. AJNR Am. J. Neuroradiol. 26 (9), 2316–2319.
Geraldes, R., Esiri, M.M., DeLuca, G.C., Palace, J., 2017. Age-related small vessel disease: a potential contributor to neurodegeneration in multiple sclerosis. Brain Pathol. 27 (6), 707–722. https://doi.org/10.1111/bpa.12460.
Geraldes, R., Esiri, M.M., Perera, R., et al., 2020. Vascular disease and multiple sclerosis: a post-mortem study exploring their relationships. Brain 143 (10), 2998–3012. https://doi.org/10.1093/brain/awaa255.
Granberg, T., Moridi, T., Brand, J.S., et al., 2020. Enlarged perivascular spaces in multiple sclerosis on magnetic resonance imaging: a systematic review and meta-analysis. J. Neurol. 267 (11), 3199–3212. https://doi.org/10.1007/s00415-020-09971-5.
Grønbaek, M., 2009. The positive and negative health effects of alcohol- and the public health implications. J. Intern. Med. 265 (4), 407–420. https://doi.org/10.1111/j.1365-2796.2009.02082.x.
Gu, Y., Scarmeas, N., 2013. Diet and neuroimaging markers of cerebrovascular disease. Curr. Nutr. Rep. 2 (2), 81–89. https://doi.org/10.1007/s13668-013-0044-4.
Guisset, F., Lolli, V., Bugli, C., et al., 2021. The central vein sign in multiple sclerosis patients with vascular comorbidities. Mult. Scler. J. 27 (7), 1057–1065. https://doi.org/10.1177/1352458520943785.
Habbestad, A., Willumsen, J.S., Aarseth, J.H., et al., 2024. Increasing age of multiple sclerosis onset from 1920 to 2022: a population-based study. J. Neurol. 271 (4), 1610–1617. https://doi.org/10.1007/s00415-023-12047-9.
Halvorsen, M., Edeklev, C.S., Fraser-Green, J., et al., 2021. Off-label intrathecal use of gadobutrol: safety study and comparison of administration protocols. Neuroradiology 63 (1), 51–61. https://doi.org/10.1007/s00234-020-02519-4.
Harrison, I.F., Siow, B., Akilo, A.B., et al., 2018. Non-invasive imaging of CSF-mediated brain clearance pathways via assessment of perivascular fluid movement with diffusion tensor MRI. Elife 7, e34028. https://doi.org/10.7554/eLife.34028.
Iliff, J.J., Lee, H., Yu, M., et al., 2013a. Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. J. Clin. Invest. 123 (3), 1299–1309. https://doi.org/10.1172/JCI67677.
Iliff, J.J., Wang, M., Liao, Y., et al., 2012. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci. Transl. Med. 4 (147) https://doi.org/10.1126/scitranslmed.3003748.
Iliff, J.J., Wang, M., Zeppenfeld, D.M., et al., 2013b. Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. J. Neurosci. Off. J. Soc. Neurosci. 33 (46), 18190–18199. https://doi.org/10.1523/JNEUROSCI.1592-13.2013.
Ineichen, B.V., Cananau, C., Plattén, M., et al., 2023. Dilated Virchow-Robin spaces are a marker for arterial disease in multiple sclerosis. EBioMedicine 92, 104631. https://doi.org/10.1016/j.ebiom.2023.104631.
Ineichen, B.V., Okar, S.V., Proulx, S.T., Engelhardt, B., Lassmann, H., Reich, D.S., 2022. Perivascular spaces and their role in neuroinflammation. Neuron 110 (21), 3566–3581. https://doi.org/10.1016/j.neuron.2022.10.024.
Ivan, D.C., Walthert, S., Berve, K., Steudler, J., Locatelli, G., 2020. Dwellers and trespassers: mononuclear phagocytes at the borders of the central nervous system. Front. Immunol. 11, 609921 https://doi.org/10.3389/fimmu.2020.609921.
Jessen, N.A., Munk, A.S.F., Lundgaard, I., Nedergaard, M., 2015. The glymphatic system: a beginner's guide. Neurochem. Res. 40 (12), 2583–2599. https://doi.org/10.1007/s11064-015-1581-6.
Jha, M.K., Kim, J.H., Song, G.J., et al., 2018. Functional dissection of astrocyte-secreted proteins: implications in brain health and diseases. Prog. Neurobiol. 162, 37–69. https://doi.org/10.1016/j.pneurobio.2017.12.003.
Joo, B., Park, M., Ahn, S.J., Suh, S.H., 2023. Assessment of meningeal lymphatics in the parasagittal dural space: a prospective feasibility study using dynamic contrast-enhanced magnetic resonance imaging. Korean J. Radiol. 24 (5), 444–453. https://doi.org/10.3348/kjr.2022.0980.
Kancheva, A.K., Wardlaw, J.M., Lyall, D.M., Quinn, T.J., 2024. Clinical phenotypes associated with cerebral small vessel disease: an overview of systematic reviews. Neurology 102 (8), e209267. https://doi.org/10.1212/WNL.0000000000209267.
Kappus, N., Weinstock-Guttman, B., Hagemeier, J., et al., 2015. Cardiovascular risk factors are associated with increased lesion burden and brain atrophy in multiple sclerosis. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp-2014-310051. Published online February 26jnnp-2014-310051.
Karimy, J.K., Zhang, J., Kurland, D.B., et al., 2017. Inflammation-dependent cerebrospinal fluid hypersecretion by the choroid plexus epithelium in posthemorrhagic hydrocephalus. Nat. Med. 23 (8), 997–1003. https://doi.org/10.1038/nm.4361.
Kaur, C., Rathnasamy, G., Ling, E.A., 2016. The choroid plexus in healthy and diseased brain. J. Neuropathol. Exp. Neurol. 75 (3), 198–213. https://doi.org/10.1093/jnen/nlv030.
Keep, R.F., Jones, H.C., 1990. A morphometric study on the development of the lateral ventricle choroid plexus, choroid plexus capillaries and ventricular ependyma in the rat. Dev. Brain Res. 56 (1), 47–53. https://doi.org/10.1016/0165-3806(90)90163-S.
Kilsdonk, I., Steenwijk, M., Pouwels, P., et al., 2015. Perivascular spaces in MS patients at 7 Tesla MRI: a marker of neurodegeneration? Mult. Scler. J. 21 (2), 155–162. https://doi.org/10.1177/1352458514540358.
Kim, H., Lim, Y.M., Kim, G., et al., 2020. Choroid plexus changes on magnetic resonance imaging in multiple sclerosis and neuromyelitis optica spectrum disorder. J. Neurol. Sci. 415, 116904 https://doi.org/10.1016/j.jns.2020.116904.
Kim, M., Hwang, I., Park, J.H., et al., 2024. Comparative analysis of glymphatic system alterations in multiple sclerosis and neuromyelitis optica spectrum disorder using MRI indices from diffusion tensor imaging. Hum. Brain Mapp. 45 (5), e26680. https://doi.org/10.1002/hbm.26680.
Klistorner, S., Barnett, M.H., Parratt, J., Yiannikas, C., Graham, S.L., Klistorner, A., 2022. Choroid plexus volume in multiple sclerosis predicts expansion of chronic lesions and brain atrophy. Ann. Clin. Transl. Neurol. 9 (10), 1528–1537. https://doi.org/10.1002/acn3.51644.
Kress, B.T., Iliff, J.J., Xia, M., et al., 2014. Impairment of paravascular clearance pathways in the aging brain. Ann. Neurol. 76 (6), 845–861. https://doi.org/10.1002/ana.24271.
Kylkilahti, T.M., Berends, E., Ramos, M., et al., 2021. Achieving brain clearance and preventing neurodegenerative diseases—A glymphatic perspective. J. Cereb. Blood Flow Metab. 41 (9), 2137–2149. https://doi.org/10.1177/0271678x20982388.
Lilius, T.O., Blomqvist, K., Hauglund, N.L., et al., 2019. Dexmedetomidine enhances glymphatic brain delivery of intrathecally administered drugs. J. Control Release Off. J. Control Release Soc. 304, 29–38. https://doi.org/10.1016/j.jconrel.2019.05.005.
Liu, Q., Yan, L., Huang, M., et al., 2020. Experimental alcoholism primes structural and functional impairment of the glymphatic pathway. Brain Behav. Immun. 85, 106–119. https://doi.org/10.1016/j.bbi.2019.06.029.
Lorente-Cebrián, S., Costa, A.G.V., Navas-Carretero, S., Zabala, M., Martínez, J.A., Moreno-Aliaga, M.J., 2013. Role of omega-3 fatty acids in obesity, metabolic syndrome, and cardiovascular diseases: a review of the evidence. J. Physiol. Biochem. 69 (3), 633–651. https://doi.org/10.1007/s13105-013-0265-4.
Lundgaard, I., Lu, M.L., Yang, E., et al., 2017. Glymphatic clearance controls state-dependent changes in brain lactate concentration. J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab. 37 (6), 2112–2124. https://doi.org/10.1177/0271678x16661202.
Lundgaard, I., Wang, W., Eberhardt, A., et al., 2018. Beneficial effects of low alcohol exposure, but adverse effects of high alcohol intake on glymphatic function. Sci. Rep. 8 (1), 2246. https://doi.org/10.1038/s41598-018-20424-y.
Malis, V., Bae, W.C., Yamamoto, A., McEvoy, L.K., McDonald, M.A., Miyazaki, M., 2024. Age-related decline of intrinsic cerebrospinal fluid outflow in healthy humans detected with non-contrast spin-labeling MR imaging. Magn. Reson. Med. Sci. 23 (1), 66–79. https://doi.org/10.2463/mrms.mp.2022-0117.

Margoni, M., Pagani, E., Meani, A., et al., 2024. Cognitive impairment is related to glymphatic system dysfunction in pediatric multiple sclerosis. Ann. Neurol. 95 (6), 1080–1092. https://doi.org/10.1002/ana.26911.
Marrie, R.A., Fisk, J., Tremlett, H., et al., 2016. Differing trends in the incidence of vascular comorbidity in MS and the general population. Neurol. Clin. Pract. 6 (2), 120–128. https://doi.org/10.1212/CPJ.0000000000000230.
Marrie, R.A., Horwitz, R.I., 2010. Emerging effects of comorbidities on multiple sclerosis. Lancet Neurol. 9 (8), 820–828. https://doi.org/10.1016/S1474-4422(10)70135-6.
Marrie, R.A., Rudick, R., Horwitz, R., et al., 2010. Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. Neurology 74 (13), 1041–1047. https://doi.org/10.1212/WNL.0b013e3181d6b125.
Mestre, H., Tithof, J., Du, T., et al., 2018. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. Nat. Commun. 9 (1), 4878. https://doi.org/10.1038/s41467-018-07318-3.
Miyazaki, M., Malis, V., Yamamoto, A., et al., 2024. Physical exercise alters egress pathways for intrinsic csf outflow: an investigation performed with spin-labeling MR imaging. Magn. Reson. Med. Sci. MRMS Off. J. Jpn. Soc. Magn. Reson. Med. 23 (2), 171–183. https://doi.org/10.2463/mrms.mp.2023-0005.
Müller, J., Sinnecker, T., Wendebourg, M.J., et al., 2022. Choroid plexus volume in multiple sclerosis vs neuromyelitis optica spectrum disorder: a retrospective, cross-sectional analysis. Neurol. Neuroimmunol. Neuroinflammation 9 (3), e1147. https://doi.org/10.1212/NXI.0000000000001147.
Nilsson, C., Lindvall-Axelsson, M., Owman, C., 1992. Neuroendocrine regulatory mechanisms in the choroid plexus-cerebrospinal fluid system. Brain Res. Brain Res. Rev. 17 (2), 109–138. https://doi.org/10.1016/0165-0173(92)90011-a.
Nonaka, H., Akima, M., Hatori, T., Nagayama, T., Zhang, Z., Ihara, F., 2003. The microvasculature of the cerebral white matter: arteries of the subcortical white matter. J. Neuropathol. Exp. Neurol. 62 (2), 154–161. https://doi.org/10.1093/jnen/62.2.154.
Pantoni, L., 2010. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 9 (7), 689–701. https://doi.org/10.1016/S1474-4422(10)70104-6.
Peng, W., Achariyar, T.M., Li, B., et al., 2016. Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. Neurobiol. Dis. 93, 215–225. https://doi.org/10.1016/j.nbd.2016.05.015.
Pengo, M., Miante, S., Franciotta, S., et al., 2022. Retinal hyperreflecting foci associate with cortical pathology in multiple sclerosis. Neurol. Neuroimmunol. Neuroinflammation 9 (4), e1180. https://doi.org/10.1212/NXI.0000000000001180.
Petzold, A., 2016. Retinal glymphatic system: an explanation for transient retinal layer volume changes? Brain 139 (11), 2816–2819. https://doi.org/10.1093/brain/aww239.
Potter, G., Morris, Z., Wardlaw, J., 2015. Enlarged Perivascular Spaces (EPVS): A Visual Rating Scale and User Guide. University of Edinburgh. *Guide Prepared by* Gillian Potter, Zoe Morris and Prof *Joanna Wardlaw*.
Reich, D.S., Lucchinetti, C.F., Calabresi, P.A., 2018. Multiple Sclerosis. Longo DL. N. Engl. J. Med. 378 (2), 169–180. https://doi.org/10.1056/NEJMra1401483.
Ren, H., Luo, C., Feng, Y., et al., 2017. Omega-3 polyunsaturated fatty acids promote amyloid-β clearance from the brain through mediating the function of the glymphatic system. FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 31 (1), 282–293. https://doi.org/10.1096/fj.201600896.
Ricigliano, V.A.G., Morena, E., Colombi, A., et al., 2021. Choroid plexus enlargement in inflammatory multiple sclerosis: 3.0-T MRI and translocator protein PET evaluation. Radiology 301 (1), 166–177. https://doi.org/10.1148/radiol.2021204426.
Ringstad, G., Vatnehol, S.A.S., Eide, P.K., 2017. Glymphatic MRI in idiopathic normal pressure hydrocephalus. Brain 140 (10), 2691–2705. https://doi.org/10.1093/brain/awx191.
Rippe, J.M., 2019. Lifestyle strategies for risk factor reduction, prevention, and treatment of cardiovascular disease. Am. J. Lifestyle Med. 13 (2), 204–212. https://doi.org/10.1177/1559827618812395.
Rohr, S.O., Greiner, T., Joost, S., et al., 2020. Aquaporin-4 expression during toxic and autoimmune demyelination. Cells 9 (10), 2187. https://doi.org/10.3390/cells9102187.
Sabbatini, M., Barili, P., Bronzetti, E., Zaccheo, D., Amenta, F., 1999. Age-related changes of glial fibrillary acidic protein immunoreactive astrocytes in the rat cerebellar cortex. Mech. Ageing Dev. 108 (2), 165–172. https://doi.org/10.1016/s0047-6374(99)00008-1.
Sati, P., George, I.C., Shea, C.D., Gaitán, M.I., Reich, D.S., 2012. FLAIR*: a combined MR contrast technique for visualizing white matter lesions and parenchymal veins. Radiology 265 (3), 926–932. https://doi.org/10.1148/radiol.12120208.
Sati, P., Thomasson, D., Li, N., et al., 2014. Rapid, high-resolution, whole-brain, susceptibility-based MRI of multiple sclerosis. Mult. Scler. J. 20 (11), 1464–1470. https://doi.org/10.1177/1352458514525868.
Saul, A.M., Taylor, B.V., Blizzard, L., et al., 2023. A pro-inflammatory diet in people with multiple sclerosis is associated with an increased rate of relapse and increased FLAIR lesion volume on MRI in early multiple sclerosis: a prospective cohort study. Mult. Scler. J. 29 (8), 1012–1023. https://doi.org/10.1177/13524585231167739.
Schley, D., Carare-Nnadi, R., Please, C.P., Perry, V.H., Weller, R.O., 2006. Mechanisms to explain the reverse perivascular transport of solutes out of the brain. J. Theor. Biol. 238 (4), 962–974. https://doi.org/10.1016/j.jtbi.2005.07.005.
Schubert, J.J., Veronese, M., Marchitelli, L., et al., 2019. Dynamic ^{11}C-PiB PET shows cerebrospinal fluid flow alterations in alzheimer disease and multiple sclerosis. J. Nucl. Med. 60 (10), 1452–1460. https://doi.org/10.2967/jnumed.118.223834.
Schwartz, D.L., Boespflug, E.L., Lahna, D.L., Pollock, J., Roese, N.E., Silbert, L.C., 2019. Autoidentification of perivascular spaces in white matter using clinical field strength T1 and FLAIR MR imaging. Neuroimage 202, 116126. https://doi.org/10.1016/j.neuroimage.2019.116126.
Scollato, A., Lolli, F., Lastrucci, G., et al., 2022. Case report: a multiple sclerosis patient with imaging features of glymphatic failure benefitted from CSF flow shunting. Front. Neurosci. 16, 863117 https://doi.org/10.3389/fnins.2022.863117.
Shokri-Kojori, E., Wang, G.J., Wiers, C.E., et al., 2018. β-Amyloid accumulation in the human brain after one night of sleep deprivation. Proc. Natl. Acad. Sci. U. S. A. 115 (17), 4483–4488. https://doi.org/10.1073/pnas.1721694115.
Subramanian, K., Utriainen, D., Ramasamy, D.P., et al., 2020. Longitudinal magnetic resonance imaging of cerebral microbleeds in multiple sclerosis patients. Diagnostics 10 (11), 942. https://doi.org/10.3390/diagnostics10110942.
Sugimoto, N., Leu, H., Inoue, N., et al., 2015. The critical role of lipopolysaccharide in the upregulation of aquaporin 4 in glial cells treated with Shiga toxin. J. Biomed. Sci. 22 (1), 78. https://doi.org/10.1186/s12929-015-0184-5.
Taoka, T., Ito, R., Nakamichi, R., et al., 2022. Reproducibility of diffusion tensor image analysis along the perivascular space (DTI-ALPS) for evaluating interstitial fluid diffusivity and glymphatic function: cHanges in Alps index on Multiple conditiON acquIsition eXperiment (CHAMONIX) study. Jpn. J. Radiol. 40 (2), 147–158. https://doi.org/10.1007/s11604-021-01187-5.
Taoka, T., Masutani, Y., Kawai, H., et al., 2017. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. Jpn. J. Radiol. 35 (4), 172–178. https://doi.org/10.1007/s11604-017-0617-z.
Tian, Y., Cai, X., Zhou, Y., et al., 2023. Impaired glymphatic system as evidenced by low diffusivity along perivascular spaces is associated with cerebral small vessel disease: a population-based study. Stroke Vasc. Neurol. 8 (5), 413–423. https://doi.org/10.1136/svn-2022-002191.
Varga, A.W., Johnson, G., Babb, J.S., Herbert, J., Grossman, R.I., Inglese, M., 2009. White matter hemodynamic abnormalities precede sub-cortical gray matter changes in multiple sclerosis. J. Neurol. Sci. 282 (1–2), 28–33. https://doi.org/10.1016/j.jns.2008.12.036.
von Holstein-Rathlou, S., Petersen, N.C., Nedergaard, M., 2018. Voluntary running enhances glymphatic influx in awake behaving, young mice. Neurosci. Lett. 662, 253–258. https://doi.org/10.1016/j.neulet.2017.10.035.
Wahlund, L.O., Barkhof, F., Fazekas, F., et al., 2001. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 32 (6), 1318–1322. https://doi.org/10.1161/01.STR.32.6.1318.
Wardlaw, J.M., 2001. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study: the Rotterdam Scan Study. J. Neurol. Neurosurg. Psychiatry 70 (1), 2–3. https://doi.org/10.1136/jnnp.70.1.2.
Wardlaw, J.M., Smith, C., Dichgans, M., 2019. Small vessel disease: mechanisms and clinical implications. Lancet Neurol. 18 (7), 684–696. https://doi.org/10.1016/S1474-4422(19)30079-1.
Wardlaw, J.M., Smith, E.E., Biessels, G.J., et al., 2013. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 12 (8), 822–838. https://doi.org/10.1016/S1474-4422(13)70124-8.
Wiseman, S.J., Bastin, M.E., Jardine, C.L., et al., 2016. Cerebral small vessel disease burden is increased in systemic lupus erythematosus. Stroke 47 (11), 2722–2728. https://doi.org/10.1161/STROKEAHA.116.014330.
Wooliscroft, L., Boespflug, E., Hildebrand, A., et al., 2020. Enlarged perivascular spaces are not associated with vascular co-morbidities, clinical outcomes, and brain volumes in people with secondary progressive multiple sclerosis. Mult. Scler. J. Exp. Transl. Clin. 6 (4), 205521732096450 https://doi.org/10.1177/2055217320964502.
Wuerfel, J., Haertle, M., Waiczies, H., et al., 2008. Perivascular spaces–MRI marker of inflammatory activity in the brain? Brain 131 (9), 2332–2340. https://doi.org/10.1093/brain/awn171.
Xi, B., Veeranki, S.P., Zhao, M., Ma, C., Yan, Y., Mi, J., 2017. Relationship of alcohol consumption to all-cause, cardiovascular, and cancer-related mortality in U.S. adults. J. Am. Coll. Cardiol. 70 (8), 913–922. https://doi.org/10.1016/j.jacc.2017.06.054.
Xie, L., Kang, H., Xu, Q., et al., 2013. Sleep drives metabolite clearance from the adult brain. Science 342 (6156), 373–377. https://doi.org/10.1126/science.1241224 (1979).
Xie, Y., Zhu, H., Yao, Y., et al., 2024. Enlarged choroid plexus in relapsing-remitting multiple sclerosis may lead to brain structural changes through the glymphatic impairment. Mult. Scler. Relat. Disord. 85, 105550 https://doi.org/10.1016/j.msard.2024.105550.
Yu, C., Lu, W., Qiu, J., Wang, F., Li, J., Wang, L., 2020. Alterations of the whole cerebral blood flow in patients with different total cerebral small vessel disease burden. Front. Aging Neurosci. 12, 175. https://doi.org/10.3389/fnagi.2020.00175.
Zhang, E., Wan, X., Yang, L., et al., 2020a. Omega-3 polyunsaturated fatty acids alleviate traumatic brain injury by regulating the glymphatic pathway in mice. Front. Neurol. 11, 707. https://doi.org/10.3389/fneur.2020.00707.
Zhang, R., Liu, Y., Chen, Y., et al., 2020b. Aquaporin 4 deletion exacerbates brain impairments in a mouse model of chronic sleep disruption. CNS Neurosci. Ther. 26 (2), 228–239. https://doi.org/10.1111/cns.13194.
Zhang, Y., Zhang, R., Ye, Y., et al., 2021. The influence of demographics and vascular risk factors on glymphatic function measured by diffusion along perivascular space. Front. Aging Neurosci. 13, 693787 https://doi.org/10.3389/fnagi.2021.693787.
Zhou, H., Andonegui, G., Wong, C.H.Y., Kubes, P., 2009. Role of endothelial TLR4 for neutrophil recruitment into central nervous system microvessels in systemic inflammation. J. Immunol. 183 (8), 5244–5250. https://doi.org/10.4049/jimmunol.0901309. Baltim Md 1950.