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Associations Between White Matter Hyperintensity Burden, Cerebral Blood Flow and Transit Time in Small Vessel Disease: An Updated Meta-Analysis

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Cerebral small vessel disease (SVD) is a major contributor to stroke and dementia, characterized by white matter hyperintensities (WMH) on neuroimaging. WMH are associated with reduced cerebral blood flow (CBF) cross-sectionally, though longitudinal associations remain unclear. We updated a 2016 systematic review, identifying 30 new studies, 27 cross-sectional (n = 2,956) and 3 longitudinal (n = 440). Cross-sectionally, 10/27 new studies (n = 1,019) included sufficient data for meta-analysis, which we meta-analyzed with 24 previously reported studies (n = 1,161), total 34 (n = 2,180). Our meta-analysis showed that patients with lower CBF had worse WMH burden (mean global CBF: standardized mean difference (SMD): −0.45, 95% confidence interval (CI): −0.64, −0.27). Longitudinally, associations between baseline CBF and WMH progression varied: the largest study (5 years, n = 252) found no associations, while another small study (4.5 years, n = 52) found that low CBF in the periventricular WMH penumbra predicted WMH progression. We could not meta-analyse longitudinal studies due to different statistical and methodological approaches. We found that CBF was lower in WMH than in normal-appearing white matter in an additional meta-analysis (5 cross-sectional studies; n = 295; SMD: −1.51, 95% CI: −1.94, −1.07). These findings highlight that relationships between resting CBF and WMH are complex. Further longitudinal studies analyzing regional CBF and subsequent WMH change are required to determine the role of CBF in SVD progression.

Keywords: cerebral blood flow, cerebral small vessel disease, stroke, white matter hyperintensities, systematic review, meta-analysis

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INTRODUCTION

Cerebral small vessel disease (SVD) develops from pathological changes in the blood vessels supplying the brain and is an underlying cause of about 20% of all strokes and the most substantial contributor to vascular dementia (1). Advances in neuroimaging have been key in identifying and elucidating common features of SVD, including white matter hyperintensities (WMH), although

much remains unknown about the underlying pathological mechanisms and there are currently no effective treatments. Vascular changes may occur before WMH are detectable, and are thought to contribute to WMH development (2). However, whether CBF reductions precede or follow WMH progression remains controversial, as hypoperfusion could be a consequence of WMH rather than the cause (3). WMH can be reversible, therefore establishing initial processes involved in WMH development may help identify targets to prevent SVD progression and related pathology (4, 5).

Our previous systematic review and meta-analysis of WMH and CBF found that more severe WMH burden was associated with lower CBF, although this association weakened when studies of patients with dementia and poor age matching of controls were excluded (3). Age, dementia, and other vascular risk factors contribute to CBF reductions and can confound the relationship between WMH burden and CBF (3). Additionally, there were few data on sub-regional brain tissue CBF and longitudinal WMH changes in our previous review (3), as most studies only examined whole brain and/or cortical CBF.

Since 2016, several studies have been published that provide data on regional or tissue-specific CBF in WMH and normal appearing white matter (NAWM) cross-sectionally (6–10) as well as longitudinal studies, yet knowledge gaps remain regarding the association between CBF and WMH. Therefore, we updated our previous systematic review and meta-analysis (3) to identify whether these gaps in the literature and previous inconsistencies have been resolved.

MATERIALS AND METHODS

We updated our previous systematic review by Shi et al. (3), covering from 1946 until December 2015, by conducting a literature search of MEDLINE and EMBASE from 1st January 2016 up to 1st February 2020, using OVID. The search strategy and methodological approach including quality assessment and data extraction were as published by Shi et al. (3), combining exploded search terms relating to *small vessel disease* and *cerebral blood flow* with AND (**Supplementary Figure 1**). We identified additional records by hand-searching, from January 2016 to February 2020, the *Journal of Cerebral Blood Flow and Metabolism* and within the subject of Cerebrovascular Disease and Stroke in *Stroke*.

Eligibility Criteria

We included longitudinal and cross-sectional studies investigating associations between CBF or transit time metrics, including arterial transit time (ATT) and mean transit time (MTT), and WMH in patients with SVD, as well as studies measuring CBF velocity (CBFv) using ultrasound Doppler. We included studies using magnetic resonance imaging (MRI), including with phase contrast, arterial spin labeling (ASL) or dynamic susceptibility contrast, positron emission tomography (PET), single-photon computed tomography and computed tomography (CT) perfusion assessment. We excluded studies in pediatric or animal populations, duplicates, conference abstracts and cross-sectional studies lacking analysable data on CBF.

Data Extraction and Analysis

We screened all potentially eligible publications and extracted standardized data from studies meeting the eligibility criteria. We extracted data on the study population cohort, the type of study, SVD characteristics, measurements, and units of CBF reported. Where available, we extracted data on separate regional CBF measurements for WMH, defined using MRI or CT, and NAWM, as this was previously identified as a key gap in the literature (3). Where reported we also extracted data on associations between ATT or MTT and WMH. We assessed the quality of each included study using a checklist based on the Strengthening the Reporting of the Observational studies in Epidemiology (STROBE) criteria (11).

We extracted mean and standard deviation (SD) CBF values from disease and control groups or according to WMH burden, where available from text, tables, graphs or, if necessary, **Supplementary Material** for cross-sectional studies. We recorded associations with WMH burden either alone or as a component of total SVD burden, such as the ordinal SVD score which includes a point for central or cerebral atrophy, lacunes and white matter hyperintensities when rated from CT scans (12) with cerebral microbleeds also included for MRI (13). We included cross-sectional studies with only qualitative data or association analysis on CBF and SVD in the review but not the meta-analysis. We also extracted association analysis data from studies which performed association analysis in addition to providing quantitative data. We extracted information from longitudinal studies on time to follow-up, baseline and follow-up measurements of CBF and WMH, and their associations. Where unavailable in the published materials, we contacted authors to request unpublished data on baseline and follow-up CBF and/or WMH volume.

Meta-Analysis

We included all studies reporting mean and SD values for CBF in patient groups by WMH burden in the cross-sectional meta-analysis. In studies with more than two patient groups of WMH severity, we took mean values to allow for a comparison between patients with negative-to-mild and moderate-to-severe WMH burden following a previously described procedure (3). We extracted CBF values for gray and white matter in various brain regions, as reported by individual studies. We calculated standardized mean differences (SMDs) and 95% confidence intervals (CIs) with a random effects model and analyzed new data along with the data reported in our previous review (3). We also extracted CBF values where available from WMH and NAWM to perform an additional meta-analysis on regional variability in CBF in different white matter tissues. Where studies reported CBF values separately for periventricular WMH (PVWMH) and deep WMH (DWMH), we took mean values to give a measurement of CBF in WMH. We used Cochrane Collaboration's Review Manager (RevMan, RRID:SCR_003581, version 5.4) to perform the meta-analyses.

RESULTS

We identified 783 articles published between January 2016 and February 2020 from the literature search, after removing

duplicates (**Figure 1**). Of these, we identified 149 of potential relevance and screened full texts to assess eligibility, 119 were excluded primarily due to lack of analyzable data (45 studies), no data on the association between WMH and CBF (38 studies) and conference abstracts (33 studies). Overall, we included 30 studies for qualitative analysis, of which 15 studies provided data for

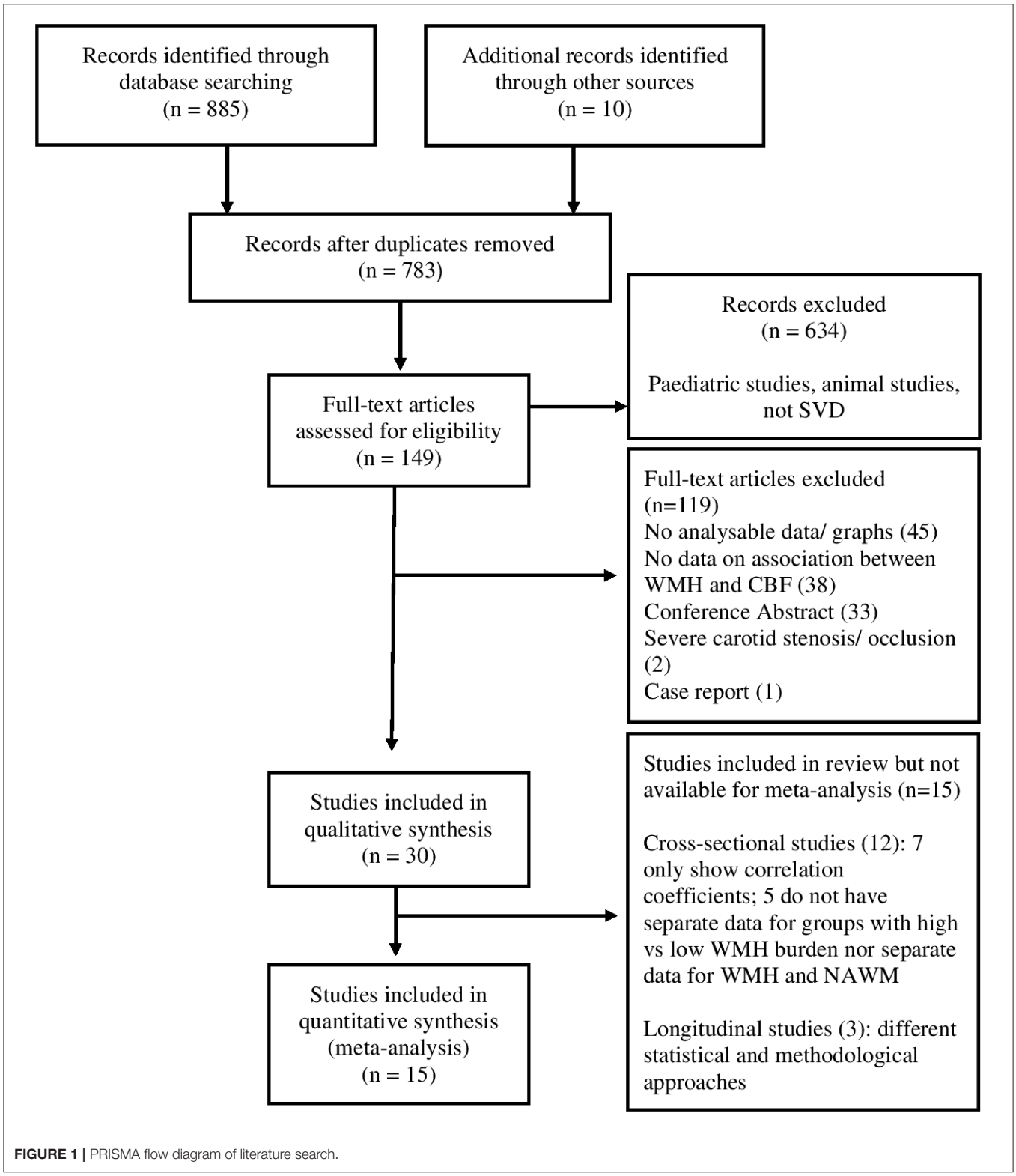

FIGURE 1 | PRISMA flow diagram of literature search.

meta-analysis (**Figure 1**). Of these 15, 10 cross-sectional studies were meta-analyzed with data previously extracted from 24 cross-sectional studies published between 1946 and 2015 (3) while 5 studies were included in the additional meta-analysis of regional variability in CBF within WMH and NAWM.

Some publications used the same study population cohort: Promjunyakul et al. (14, 15) from the Layton Aging and Alzheimer's Disease Center longitudinal aging study and Turk et al. (16, 17) with the same cohort of patients with ischemic leukoaraiosis (ILA) and age, sex and risk-factor matched controls without ILA. We ensured that each participant was only included once in any single analysis.

Characteristics of Included Studies

We extracted data from 27 new cross-sectional (n = 2,956) and 3 new longitudinal studies (n = 440). All the new studies investigated patients or controls with varying degrees of WMH burden. The characteristics of these 30 studies (n = 3,396) are described in **Table 1**. The average study quality for all identified studies according to the STROBE criteria was 6.5/9 (**Supplementary Figure 2**). Main reasons for lower overall study quality scores included studies not reporting the number of participants who dropped out (11/30), number and expertise of WMH assessors (13/30) and a lack of blinding to imaging or clinical data (14/30).

Seven of the 27 newly identified cross-sectional studies investigated patients with cognitive impairment or dementia; including Alzheimer's disease (AD) (20, 23) mild cognitive impairment (MCI) (8, 10, 22) and vascular cognitive impairment (VCI) (9, 21).

Thirteen of the 27 added cross-sectional studies investigated patients without cognitive impairment including patients with varying degrees of WMH burden (7, 16, 24, 32), hypertensive patients with and without SVD (6, 25, 29), individuals with Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy (CADASIL) (28), cognitively normal older subjects (14, 27) and patients with ischemic stroke (31). Two of these 13 studies investigated the effect of blood pressure reduction on CBF in SVD, from which only baseline data on CBF and WMH burden, prior to any treatment, were extracted (26, 30).

Seven of the 27 new cross-sectional studies reported only the results of association analyses and did not provide quantitative data for CBF or WMH measurements. Patient groups in these studies included patients with acute stroke (12, 33), MCI (34), vascular depression (35), individuals at varying risk of cerebrovascular disease (36), and older individuals with WMH (17, 37).

The 3 newly identified longitudinal studies (n = 440) investigated baseline CBF and WMH progression in older individuals with WMH (**Table 1**), over follow-up periods ranging from two (18) to five (19) years. While 2 studies investigated associations between baseline WMH volume and change in either subregional (15) or global (19) CBF, one study considered associations between change in WMH volume and change in cortical gray matter CBF (18).

Fifteen studies used ASL (6–8, 10, 14, 15, 18, 22, 23, 27, 29, 30, 34, 36, 37), 3 used CT perfusion (20, 26, 31), 2 used dynamic susceptibility contrast (DSC) MRI (9, 19), one study each used SPECT (21), phase contrast MRI (24), CT angiography/digital subtraction angiography (33), PET (32), and a combination of CT and DSC MRI (12). Five studies used transcranial Doppler ultrasound (16, 17, 25, 28, 35).

Cross-Sectional CBF and WMH Association

We extracted association analysis data from 11 of the new cross-sectional studies overall, including the 7 studies which reported association analyses without providing quantitative data and 4 studies which performed association analyses in addition to providing quantitative data (6, 20, 27, 31). Only 5 of these 11 studies adjusted for key vascular risk factors, including hypertension and smoking (12, 17, 33, 35, 36).

Cross-Sectional Association Analysis of Global or Regional CBF and WMH

Four of the new studies analyzed associations between global or regional CBF and WMH burden (**Table 2**). All of these studies found that patients with a worse WMH burden had lower CBF than those with a less severe WMH burden (20, 31, 33, 34), one study showed that worse PVWMH, DWMH and whole-brain WMH each showed a trend to be associated with lower CBF both in patients with AD and controls without AD (n = 203) (20). Worse WMH were associated with poorer cerebral collateral circulation, defined as cortical CBF at the outer surface of the brain, in one study which investigated patients with acute stroke (n = 178) (33).

Two of the new studies showed that lower mean blood flow velocity (MBFv) in the internal carotid artery and middle cerebral artery were associated with worse WMH burden in patients with ischemic leukoaraiosis (n = 96) (17) and vascular depression (n = 76) (35) (**Table 2**).

Cross-Sectional Association Analysis of SVD Burden and Transit Time

Arba et al. (12) assessed SVD burden on CT or MRI, using an SVD score and four transit time metrics (MTT, time to maximum flow, time to peak, and arrival time fitted) derived from perfusion CT or DSC MRI, in the asymptomatic cerebral hemisphere of patients with acute ischemic stroke (n = 115). Worse SVD scores were associated with more prolonged transit times in white matter of the asymptomatic cerebral hemisphere (i.e., contralateral to the acute ischemic stroke, **Table 2**). SVD burden was also associated with reduced CBF in the contralateral hemisphere.

Cross-Sectional Association Analysis of CBF in WMH and NAWM

Three recently published studies found that CBF was lower within WMH than in NAWM (**Table 3**). Higher WMH volume in older patients with hypertension (n = 185) (6) was associated with lower CBF within WMH. However, no clear relationship

TABLE 1 | Characteristics of all studies included in this updated systematic review and meta-analysis.

Type of study	Sample size	Participants	(Baseline) age (years mean ± S.D)	Methods of CBF measurement	CBF units
Longitudinal (3)					
Staffaroni et al. (18)	136	Aging adults	69.9 ± 8.3	ASL	ml/100 g/min
Promjunyakul et al. (15)	52	Cognitively healthy older participants	82.8 ± 7.6	ASL	ml/100 g/min
Nylander et al. (19)	252	Older participants	75	DSC MRI	Relative units
Cross-sectional: Cognitive impairment/dementia (7)					
Wong et al. (9)	27	SVD patients	69 ± 12	DSC/ DCE MRI	ml/min/100 g
Li et al. (20)	203	AD	70.49 ± 10.01	CT perfusion	ml/100 g/min
		Controls without AD	69.39 ± 8.10		
Wu et al. (10)	73	Subcortical vascular MCI	65.71 ± 8.2	ASL	ml/100 g/min
Ishibashi et al. (21)	75	VCI with WMH	79.1 ± 5.8	SPECT	ml/100 g/min
		VCI without WMH	76.5 ± 7.7		
Rane et al. (8)	28	MCI cognitively normal	76.4 ± 7.1	ASL	ml/100 g/min
Shokouhi et al. (22)	265	MCI (higher WMH vol)	64.4 ± 7.5	ASL	ml/100 g/min
		Controls (lower WMH vol)	63.1 ± 7.2		
Benedictus et al. (23)	88	AD (median Fazekas Score 1)	65 ± 7	ASL	ml/100 g/min
No cognitive impairment (13)					
Shi et al. (24)	56	WMH grade 1–2	64.25 ± 7.76	Phase-contrast MRI	ml/min/100 ml
		WMH grade 3–4	69.11 ± 7.11		
		WMH grade 5–6	74.26 ± 8.39		
Muller et al. (25)	107	Patients with high BP: with SVD	64 ± 13	TCD	cm/s
		Without SVD	45 ± 16		
Kate et al. (26)	71	Leukoaraiosis present	71 ± 11.2	CT perfusion	ml/100 g/min
		Leukoaraiosis absent	65 ± 11.6		
Dolui et al. (27)	497	CARDIA cohort	50.4 ± 3.5	ASL	ml/100 g/min
		Cognitively normal older participants*	73.3 ± 6.9		
Jokumsen-Cabral et al. (28)	47	CADASIL	57 ± 13	TCD	cm/s
		Age-matched controls	59 ± 16		
Parfenov et al. (29)	73	EAH patients	50.2 ± 6.2	ASL	ml/100 g/min
		Healthy controls	49.1 ± 4.4		
Croall et al. (30)	62	Severe SVD	69.3	ASL	ml/min/100 g
Zhong et al. (7)	75	Leukoaraiosis	67.05 ± 9.62	ASL	ml/100 g/min
Bivard et al. (31)	229	Ischemic stroke	68	CT perfusion	ml/100 g/min
van Dalen et al. (6)	185	Older hypertensive patients	77 ± 2	ASL	ml/100 g/min
Promjunyakul et al. (14)	82	Cognitively healthy older participants	84.13 ± 8.3	ASL	ml/100 g-tissue/min/age (years)
Hashimoto et al. (32)	22	SVD patients: Lower volume WMH	69 ± 7	PET	ml/100 g/min
		Larger volume WMH	68 ± 8		
Turk et al. (16)	93	ILA	54.5 ± 8.1	TCD	cm/s
		Sex and risk factor matched controls	52.30 ± 6.05		
Studies only performing association analysis (7)					
Mark et al. (33)	178	Acute stroke: Good collateral grade	63.9 ± 14.7	CT angiography and DSA	Not shown
		Moderate collateral grade	73.1 ± 12.3		
		Poor collateral grade	70.1 ± 15.5		
Kim et al. (34)	38	MCI	68.4 ± 6.28	ASL	ml/100 g/min
		Cognitively healthy	68.25 ± 5.84		
Puglisi et al. (35)	76	Vascular depression: WML group 1	71.95 ± 4.55	TCD (MBFv)	Not shown

(Continued)

TABLE 1 | Continued

Type of study	Sample size	Participants	(Baseline) age (years mean ± S.D)	Methods of CBF measurement	CBF units
		WML group 2	71.81 ± 4.71		
		WML group 3	73.96 ± 6.71		
Bahrani et al. (36)	26	High-risk CVD	83 ± 4.6	ASL	Relative units
		Low-risk CVD	72.7 ± 4.2		
Shi et al. (37)	69	Older participants with WMH	70.78 ± 3.94	ASL	Relative units
Arba et al. (12)	115	Acute ischemic stroke	81	CT perfusion/ DSC MRI	Not shown
Turk et al. (17)	96	ILA	54.90 ± 8.27	Ultrasound doppler	mm^3/s
		Age, sex and risk-factor matched controls	52.39 ± 7.34		

*S.D, standard deviation; CBF, cerebral blood flow; ASL, arterial spin labeling; DSC MRI, dynamic susceptibility contrast magnetic resonance imaging; SVD, small vessel disease; DCE, dynamic contrast enhanced; CT, computed tomography; AD, Alzheimer's disease; MCI, mild cognitive impairment; VCI, vascular cognitive impairment; SPECT, single Photon Emission Computed Tomography; BP, blood pressure; TCD, transcranial doppler; CARDIA, coronary artery risk development in young adults study; *cognitively normal older individuals, this group have significantly higher normalized WMH volumes compared to the CARDIA cohort; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; EAH, essential arterial hypertension; PET, positron emission tomography; ILA, ischemic leukoaraiosis; DSA, digital subtraction angiography; MBFv, mean blood flow velocity; WML, white matter lesion; CVD, cerebrovascular disease.*

was seen between WMH volume and CBF in NAWM or gray matter (**Table 3**). Cognitively healthy older participants and healthy middle-aged participants ($n = 497$) showed significantly lower CBF within WMH compared to normal appearing white matter (27). Similarly, in one small study ($n = 26$), CBF was lower within DWMH and PVWMH compared to NAWM (36). In contrast, one exploratory study (37) in healthy older participants ($n = 69$) found in white matter regions where most patients had WMH; higher WMH burden correlated with higher gray matter perfusion in the opposite cerebral hemisphere.

Sensitivity Analyses of Age, Dementia, and Key Vascular Risk Factors

We further refined the cross-sectional association analyses by removing studies investigating patients with dementia, studies without age-matching and studies which did not adjust for key vascular risk factors. The direction of effect in the remaining studies did not change: lower blood flow velocity (17, 35) and prolonged perfusion CT/DSC transit time metrics (12) remained associated with WMH, as well as lower CBF within WMH compared to NAWM (36). Only one cross-sectional study investigated WMH in association with global or regional CBF while adjusting for key vascular risk factors, showing worse WMH was associated with poorer collateral blood flow (33).

Longitudinal Analyses of CBF and WMH

The largest of the three new longitudinal studies (19) in a cohort of 406 randomly selected 75-year-old participants at baseline and 252 at follow-up, found no significant association between baseline CBF with WMH progression at a five-year follow-up when adjusting for baseline WMH and sex (**Table 4**). In 136 functionally normal older individuals, Staffaroni et al. (18) found that longitudinal reductions in global CBF were associated with increasing WMH burden, adjusting for age, sex and education. Promjunyakul et al. (15), in 52 cognitively healthy older participants, found that lower baseline CBF within the PVWMH penumbra was associated with WMH growth at follow-up, while reduced white matter perfusion remained predictive of PVWMH but not DWMH progression, adjusting for age and sex. These 440 patients from the three recent longitudinal studies add to the 1,079 patients in 4 studies included in our 2016 review (3). Summarizing all 7 longitudinal studies ($n = 1{,}519$), the two largest studies (total $n = 827, 575 + 252$) found low baseline CBF did not predict worsening WMH; one previous and one new study ($n = 390 + 136$) found low CBF predicted increased PVWMH but not deep WMH progression or predicted global WMH; the two smallest studies ($n = 40$ and 52) found low CBF in NAWM/penumbral tissue predated WMH growth at follow-up; and one prior study ($n = 74$) found CBF increased in some regions and decreased in other regions as WMH progressed.

Longitudinal meta-analysis was not possible due to insufficient data and different statistical and methodological approaches between studies. The two studies with follow-up CBF measures (18, 38) carried out their statistics differently and therefore could not be combined.

Cross-Sectional Meta-Analysis of CBF and WMH Burden

We included 34 cross-sectional studies ($n = 2{,}180$) in this updated meta-analysis, of which 24 had been previously identified in our 2016 review (3). The 10 newly identified studies covered 4 brain regions, including mean global CBF (20, 21, 24, 29), mean basal ganglia blood flow (32), total gray matter (6, 22) and centrum semiovale (32) (**Figure 2A**). We extracted data on CBF velocity, as measured from the middle cerebral artery (vMCA) (16, 25, 28) and included this under a new subgroup in the meta-analysis. We found no additional published data for 7 brain regions included in our previous review (3): four in gray matter (frontal, temporal, parietal, and occipital) and three in white matter (total, frontal, and occipital).

TABLE 2 | Association analysis of **(A)** global or regional CBF with WMH; **(B)** mean blood flow velocity with WMH and **(C)** transit time with SVD burden.

Study	Sample size	Statistical method	Results Variables	Coefficients	*P*-values	Adjusted for other variables
(A) Global or regional CBF association with WMH						
Bivard et al. (31)	229	Linear regression model	Hypoperfusion and likelihood of WMH	OR = 7.61	**<0.001**	No
Kim et al. (34)	38	Linear regression analysis	Mean parietal lobe CBF and WMH volume	t(15) = −3	**0.009**	Gender
			Mean temporal lobe CBF and WMH volume	t(15) = −3.89	**0.001**	
			Mean occipital lobe CBF and WMH volume	t(15) = −4.71	**0.001**	
			Mean frontal lobe CBF and WMH volume	t(15) = −2.58	**0.021**	
Li et al. (20)	203	Spearman correlation analysis	Whole-brain WMH severity and CBF (AD patients)	r = −0.162	0.068	Not shown
			PVWMH severity and CBF (AD patients)	r = −0.219	**0.013**	
			DWMH severity and CBF (AD patients)	r = −0.099	0.268	
			Whole-brain WMH severity and CBF (controls)	r = −0.034	0.071	
			PVWMH severity and CBF (controls)	r = −0.071	0.546	
			DWMH severity and CBF (controls)	r = −0.003	0.978	
Mark et al. (33)	178	Multivariate logistic regression analysis	PVWM Fazekas score and collateral flow	NA	**<0.0001**	Age, gender, hypertension, hyperlipidemia coronary artery disease, atrial fibrillation, congestive heart failure and smoking history
			DWM Fazekas score and collateral flow	NA	**<0.0001**	
			Total Fazekas score and collateral flow	NA	**<0.0001**	
(B) Mean blood flow velocity association with WMH						
Turk et al. (17)	96	Spearman's correlation coefficient	Correlation of average mean blood flow in ICA (mm^3/s) with ILA	Spearman's $p = -0.232$	**0.025**	Age, gender, and CVD risk factors
		Logistic regression	Association of average mean blood flow in ICA (mm^3/s) with ILA	OR = 0.577 (0.368–0.902)	**0.016**	
Puglisi et al. (35)	76	Spearman correlation	Correlation between MBFv in MCA and WMH severity	r = −0.34	**0.002**	Demographic variables and clinical variables (including vascular risk factors)
(C) Transit time association with SVD burden						
Arba et al. (12)	115	Logistic regression model	SVD score and mean transit time	OR = 2.80 (1.56–5.03)	**<0.05**	Age, NIHSS, sex, hypertension, and diabetes
			SVD score and time to maximum flow	OR = 2.36 (1.37–4.09)	**<0.05**	
			SVD score and time to peak	OR = 1.52 (0.93–1.05)	N.S.	
			SVD score and arrival time fitted	OR = 3.59 (1.92–6.75)	**<0.01**	

WMH, white matter hyperintensity; OR, odds ratio; CBF, cerebral blood flow; AD, Alzheimer's disease; PVWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity; PVWM, periventricular white matter; DWM, deep white matter; NA, not available; ICA, internal carotid artery; ILA, ischemic leukoaraiosis; OR, odds ratio (95% confidence interval); CVD, cerebrovascular disease; MBFv, mean blood flow velocity; MCA, middle cerebral artery; SVD, small vessel disease; N.S, not significant; NIHSS, National Institutes of Health Stroke Scale. P-values < 0.05 are shown in bold.

Of the four regions where additional data was identified, patients with moderate-to-severe WMH burden had lower CBF than those with negative-to-mild WMH burden in three regions: global CBF (SMD: −0.45, 95% CI: −0.64, −0.27), total gray matter (SMD: −0.37, 95% CI: −0.69, −0.05) and centrum semiovale (SMD: −1.25, 95% CI: −1.96, −0.54)

TABLE 3 | Association analysis comparing CBF within WMH and NAWM.

Study	Sample size	Statistical method	Results Variables	Coefficients	*P*-values	Adjusted for other variables
Bahrani et al. (36)	26	*Post-hoc* paired comparisons	CBF in DWMH compared to NAWM	t = 5.7	**<0.001**	Age, vascular risk group, total intracranial volume
			CBF in PVWMH compared to NAWM	t = 11	**<0.0001**	
			CBF in PVWMH compared to DWMH	t = 3.1	**0.003**	
van Dalen et al. (6)	181	Linear regression	WMH volume and WMH CBF	β = −0.201	**0.029**	Total brain volume, age, antihypertensive use, brain parenchymal fraction, transit time
			WMH volume and NAWM CBF	β = 0.175	0.098	
			WMH volume and GM CBF	β = 0.175	0.133	
Dolui et al. (27)	497	Two-way repeated measures ANOVA	Mean CBF inside WML compared to outside (ADC cohort)	partial η2 = 0.75	**<0.0001**	No
			Mean CBF inside WML compared to outside (CARDIA cohort)	partial η2 = 0.59	**<0.0001**	
Shi et al. (37)	69	Pearson correlation	WMH ROI (R hemisphere) and CBF ROI (L hemisphere)	r = 0.42	**0.00045**	Age, sex, education-adjusted MoCA score, total WMH volume
			WMH ROI (L hemisphere) and CBF ROI (R hemisphere)	r = 0.43	**0.00037**	

CBF, cerebral blood flow; WMH, white matter hyperintensity; NAWM, normal appearing white matter; DWMH, deep white matter hyperintensity; PVWMH, periventricular white matter hyperintensity; GM, gray matter; β, standardized estimate in linear regression; WML, white matter lesion; ADC, Alzheimer's Disease Center (this is a longitudinal, prospective cohort and the individuals are cognitively healthy); CARDIA, Coronary Artery Risk Development in Young Adults study; ROI, region of interest; R, right; L, left; MoCA, Montreal cognitive assessment. P-values < 0.05 are shown in bold.

TABLE 4 | Results from longitudinal studies.

		Nylander et al. (19)	Staffaroni et al. (18)	Promjunyakul et al. (15)
Sample size		252	136	52
Follow-up time (years)		5	2.3	4.5
CBF	At baseline	NA	27.07 ± 6.38*	WM CBF: 27.0 ± 6.6
				GM CBF: 59.3 ± 10.0
				PVWMH CBF: 14.09 ± 6.05
				DWMH CBF: 16.12 ± 6.85
CBF	At follow-up	NA	24.47 ± 5.61*	NA
WMH (ml)	At baseline	10.5 ± 5.2 (n = 406)	3.4 ± 3.8*	Mean PVWMH vol. = 10.3 ± 11.7
				Mean DWMH vol. = 1.6 ± 1.2
WMH (ml)	At follow-up	11.9 ± 5.7 (n = 229)	4.6 ± 4.8 *	Mean PVWMH vol. growth = 3.7 ± 6 ml
				Mean DWMH vol. growth = 0.4 ± 1 ml
Baseline CBF and baseline WMH volume	Coefficient	NA	ß = −0.08, b = −0.01	NA
	P-value	N.S.	0.358	
Baseline CBF and ΔWMH volume	Coefficient	NA	NA	NA
	P-value	N.S.		
Baseline WMH volume and ΔCBF	Coefficient	NA	NA	NA
	P-value			
ΔWMH volume and ΔCBF	Coefficient	NA	b = −0.02	NA
	P-value		0.007	
Adjusted for other variables		Baseline value, sex	Age, sex, education	Age, sex

CBF, cerebral blood flow; WM, white matter; GM, gray matter; PVWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity; WMH, white matter hyperintensity; vol., volume; standardized beta (ß) and unstandardized (b), estimates given for linear regression models; bCBF, baseline CBF; bWMH, baseline WMH; ΔWMH, change in WMH; ΔCBF, change in CBF; NA, not available.

**Unpublished data received from author upon request.*

(**Figure 2B**). In the basal ganglia there was no difference in CBF between patients with moderate-to-severe and negative-to-mild WMH burden (SMD: −0.86, 95% CI: −1.97, 0.25). Participants with worse WMH burden had lower blood flow velocities in the middle cerebral artery (SMD: −0.34, 95% CI: −0.64, −0.05).

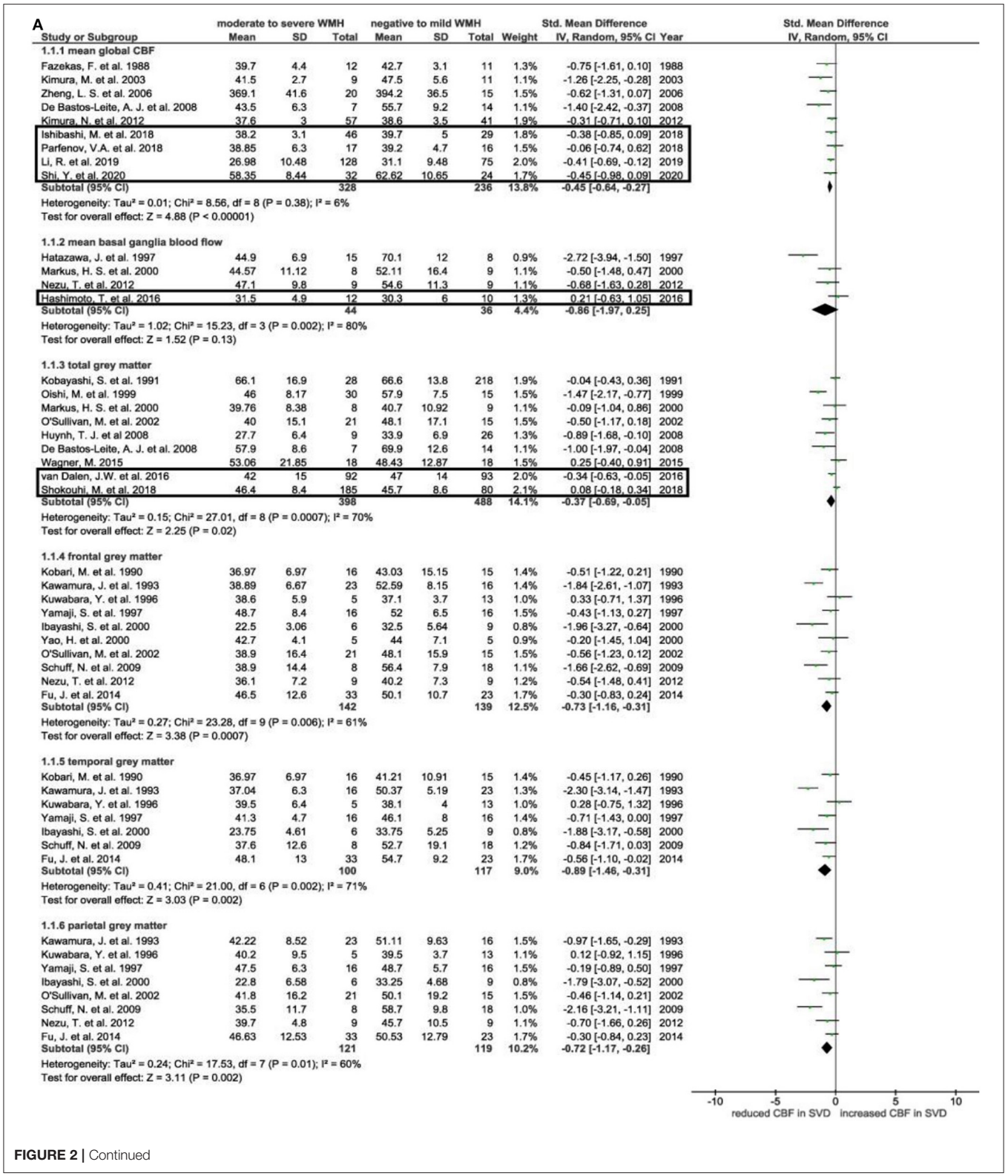

FIGURE 2 | Continued

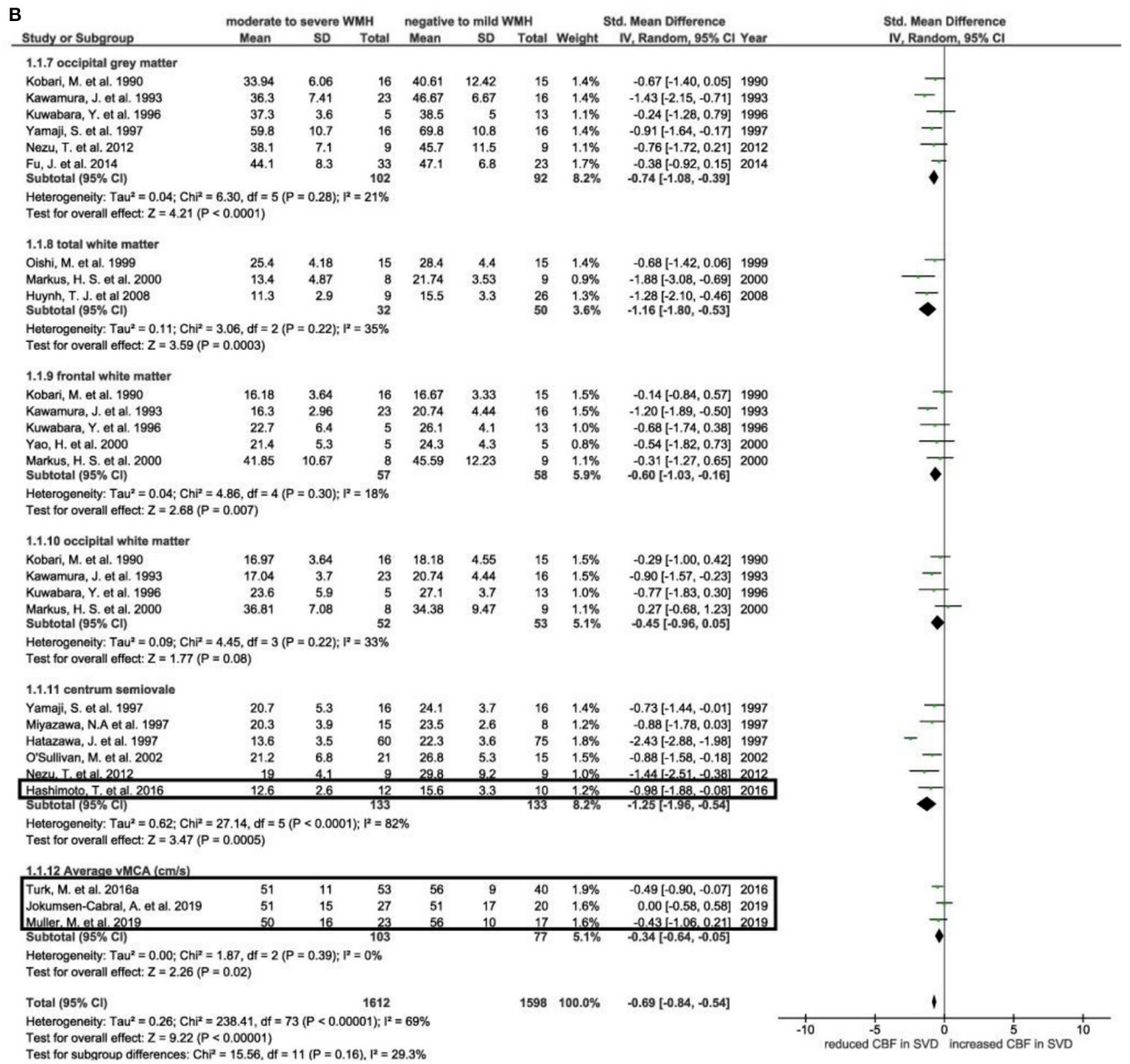

FIGURE 2 | (A,B) Forest plot showing standard mean differences in global, gray matter, and white matter cerebral blood flow and in blood flow velocity in the middle cerebral artery. Cerebral blood flow was analyzed in subgroups according to brain regions. Additional studies identified since our previous meta-analysis are outlined, all other data was originally published by Shi et al. (3). CBF, cerebral blood flow; WMH, white matter hyperintensity; vMCA, blood flow velocity in middle cerebral artery.

Sensitivity Analyses of Age and Dementia

As with our previous review (3), the difference in CBF between patients with moderate-to-severe and negative-to-mild WMH burden attenuated and became non-significant upon removing studies investigating patients with dementia and further removing non-age matched studies from the updated meta-analysis, apart from mean global CBF and centrum semiovale CBF (**Supplementary Figures 3**, **4**). Mean middle cerebral artery blood flow velocity was not significantly different on comparing individuals with moderate-to-severe and negative-to-mild WMH burden after excluding non-age matched studies. Seven of the ten additional studies were included in the meta-analysis after removing studies which investigated patients with dementia and/or without age-matching; and the studies included in the mean basal ganglia and centrum semiovale categories did not differ, i.e., none of these studies included patients with dementia/without age-matching.

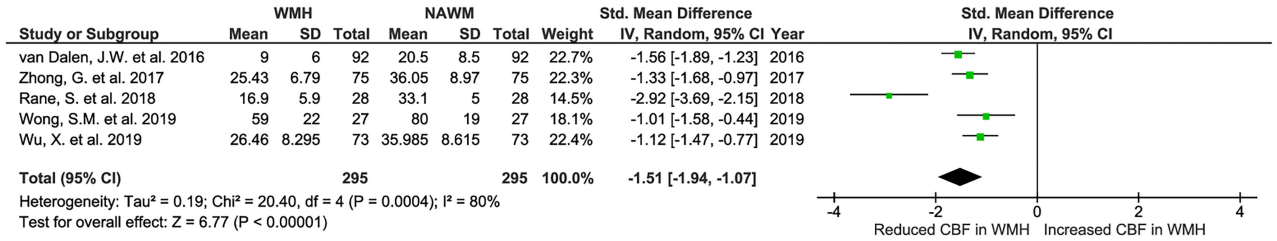

FIGURE 3 | Forest plot of the additional meta-analysis, showing standard mean differences in CBF in WMH compared to NAWM in subjects with moderate to severe WMH burden. WMH, white matter hyperintensity; CBF, cerebral blood flow; NAWM, normal appearing white matter.

Cross-Sectional Meta-Analysis of CBF Difference Between WMH and NAWM

Additional to the analyses that were possible in 2016, we found sufficient data for meta-analysis in five recent cross-sectional studies reporting CBF values for both WMH and NAWM in subjects with moderate to severe WMH burden ($n = 295$). CBF was lower in WMH compared to NAWM (SMD: −1.51, 95% CI: −1.94, −1.07) (**Figure 3**).

DISCUSSION

We identified 30 new relevant publications since 2016, providing a total additional sample of 3,396 (cross-sectional $n = 2{,}956$ + longitudinal $n = 440$). The newly identified cross-sectional studies reported lower CBF in most patients with higher WMH burden, supporting previous findings (3). In an additional meta-analysis, we confirmed that CBF was also lower in WMH than in NAWM. Longitudinal findings were mixed, the largest studies ($n = 575 + 252$) found baseline global CBF was not associated with WMH progression (19), as such there is no definite association between low CBF and increasing WMH long term. However, regional associations between lower CBF and WMH progression, notably in normal-appearing tissue surrounding PVWMH ($n = 390 + 52$) (15, 38) may exist.

Higher WMH burden was also associated with a lower blood flow velocity in the middle cerebral artery, which could be an important contributor to hypoperfusion (17, 35). Although blood flow measurements from the middle cerebral artery are less representative of CBF compared to CT and MRI-based imaging methods, there is a dynamic relationship between middle cerebral artery blood flow and blood flow in the cerebral small vessels (39). Therefore, flow measurements from the large arteries can be informative of cerebrovascular blood flow (40). An association between impaired hemodynamics in the middle cerebral artery and WMH has previously been established, however there may be a stronger association with higher pulsatility and WMH compared to lower blood flow velocity and WMH (41). One cross-sectional study showed that higher SVD burden was associated with prolonged MTT on CT and DSC (12).

The heterogeneity of study populations can be an important confounder, particularly in terms of age, sex and vascular risk factors. Only a minority (5/11) of cross-sectional studies and none of the longitudinal studies adjusted for cardiovascular risk factors. Cardiovascular risk factors can influence the development and rate of progression of SVD, while also affecting CBF via several mechanisms (42). Hypertension is an established risk factor for WMH that may affect CBF through vascular morphological changes and lumen narrowing, which can contribute to hypoperfusion (43). One cross-sectional study ($n = 73$) found cerebral perfusion was lower in patients with hypertension, with or without WMH, than in healthy controls, though sample size was limited (29). Meanwhile, diabetes has been linked to increased blood viscosity and a reduction in deformability of erythrocytes proportional to the degree of microvascular complications (44), white matter CBF is also lower in patients with type 2 diabetes than in controls (45). As such, controlling for cardiovascular risk factors is crucial in avoiding potential confounds.

Strengths and Limitations

Strengths of this work include the thorough meta-analysis of regional CBF variability by WMH burden, obtained through updating previous work (3). The sample size for studies included in the cross-sectional meta-analysis was enhanced ($n = 2{,}180$, 64/study). We also screened non-English language publications, including a paper published in Russian (29). Limitations of this work include the lack of additional data in some brain subregions, though attempts were made to contact several authors to acquire unpublished data. However, this may also reflect a narrowing focus to key regions based on experimental hypotheses, excluding regions which are less reproducible. The meta-analysis of CBF variability in WMH and NAWM was limited by the small number of studies available (5), although the average sample size was reasonable ($n = 295$, mean 59/study). Several studies lacked control participants with little to no WMH burden and so could not be included. Longitudinal studies remain very limited and used heterogeneous methods, preventing direct comparison and longitudinal meta-analysis. Follow-up CBF measurements were only reported in 2 longitudinal studies (18, 38), thus interpretation of CBF changes over time in association with WMH progression is limited. However, an increasing use of non-contrast perfusion methods, particularly ASL, should make longitudinal imaging more viable. The role of other SVD

markers, including lacunes and enlarged perivascular spaces, is also underexplored. Lastly, the accuracy of white matter and WMH perfusion measurements using ASL remains unclear, due to the lower perfusion level and signal-to-noise ratio relative to gray matter. This can be particularly relevant for older patients with cerebrovascular disease, where lower perfusion is more difficult to quantify. However, there are on-going efforts to improve sensitivity of acquisition and analysis techniques (46). Additionally, none of the included ASL studies measured ATT, perhaps because ATT quantification requires a longer acquisition (47).

Interpretation in Relation to CBF and WMH Pathology

WMH and NAWM CBF variability remains underexplored and more detailed longitudinal studies evaluating subregional changes in tissue CBF and WMH progression are needed. CBF reductions were more severe within WMH compared to NAWM in patients with moderate-to-severe WMH burden, suggesting WMH represent areas of focal perfusion deficits which are more severe than global hypoperfusion. However, associations with CBF may also be affected by other mechanisms implicated in WMH evolution (48). Two cross-sectional studies suggested that perfusion may be higher with higher WMH burden in normal-appearing white and some gray matter regions (6, 37), but were non-conclusive. Compensatory mechanisms may also affect regional perfusion, with areas of increased perfusion potentially counteracting deficiencies elsewhere (49). However, it is unclear whether compensatory perfusion changes would be sustained if they do occur, and could instead indicate dysfunctional blood flow regulation with worse WMH burden. Replication and more detailed subregional analyses of tissue changes in larger cohorts over time are required. Subtle regional differences in perfusion may also be masked within larger regions (15). The selection of regions of interest should therefore be considered carefully, and may favor finer grained regions, such as stratifying tissue by proximity to existing WMH (50) or other pathological features. We suggest that future studies investigating associations between WMH and perfusion should include the following key features as a minimum standard: discrimination of flow values in WMH from NAWM, as well as the reporting of vascular risk factors and the inclusion of age-matched controls to avoid these variables confounding the understanding of the relationship between WMH and CBF.

Different vascular pathologies are thought to underlie PVWMH and DWMH, with PVWMH more likely to result from hemodynamic insufficiency, while DWMH are more likely to be a consequence of SVD (51). Moreover, PVWMH and DWMH have been demonstrated to show different associations with various cardiovascular risk factors, further suggesting different underlying pathologies (52). This highlights the importance of conducting a region-dependent analysis of WMH. Of the 11 cross-sectional studies investigating the association between WMH and CBF included in this review, only 3 of these studies provided separate regional analysis for PVWMH and DWMH, while only 1 of the 3 longitudinal studies provided separate data for PVWMH and DWMH. This lack of region-dependent analyses of WMH limits the interpretation of the association with CBF, given the differences in underlying pathophysiology between PVWMH and DWMH.

Implications for Future Research

In conclusion, this systematic review and meta-analysis showed that CBF was lower in most gray and white matter regions of the brain with higher WMH burden and lower in WMH than normal appearing white matter. Further studies investigating CBF along with ATT may help give a more comprehensive understanding of causal and consequential effects in WMH development and progression. Longitudinal studies exploring the effect of CBF changes on WMH burden remain limited. Further longitudinal studies are required to better understand the role of perfusion in WMH development and evolution. Future studies should also adjust for key vascular risk factors known to influence CBF, particularly hypertension, and, where relevant, baseline WMH burden.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

MS and JW conceived the idea of the study. YS and JW designed the search strategy and provided data files from the original literature review. CS did the data search, extracted data, and conducted the statistical analyses and drafted the report and designed the tables and figures. MS cross-checked the data. JW obtained funding and managed the project. All authors revised and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.647848/full#supplementary-material

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