

Lima Rebouças SC, Soumaré A, Bordes C, Arnould L, Delcourt C, Korobelnik JF, Paques M, Helmer C, Debette S

PURPOSE

To summarize research on the associations of innovative retinal microvascular imaging metrics with established and emerging diffusion-based magnetic resonance imaging (MRI) markers of cerebral small vessel disease (cSVD) in general and high-risk populations

METHODS

- Systematic review conducted in accordance with PRISMA guidelines (PROSPERO: CRD42022327471)

➤ Inclusion criteria

 - English-language studies with N ≥ 20 participants
 - Participants of any age
 - From general or high-risk populations
- Databases: PubMed and EMBASE (from inception to July 2024)

➤ Study selection performed independently by two reviewers using Covidence

➤ Narrative synthesis conducted according to the SWiM guidelines

➤ Results synthesized using:

 - Vote counting and/or
 - Combined P-value analysis (weighted Fisher’s method)

Primary Outcomes: MRI parameters

- white matter hyperintensities (WMH)
- small subcortical infarcts
- lacunes
- cerebral microbleeds (CMB)
- perivascular spaces (PVS)
- cerebral small vessel disease (cSVD) burden score

Secondary Outcomes: MRI parameters

- longitudinal changes in these markers
- diffusion-based markers

Exposure: Retinal parameters based on

- Optical coherence tomography angiography (OCT-A)
- Adaptive optics ophthalmoscopy
- Dynamic vessel analyzer (DVA)
- Doppler imaging

RESULTS

- 6,446 records were identified through the search strategy
- After screening and full-text assessment (N =131) , 21 studies were included

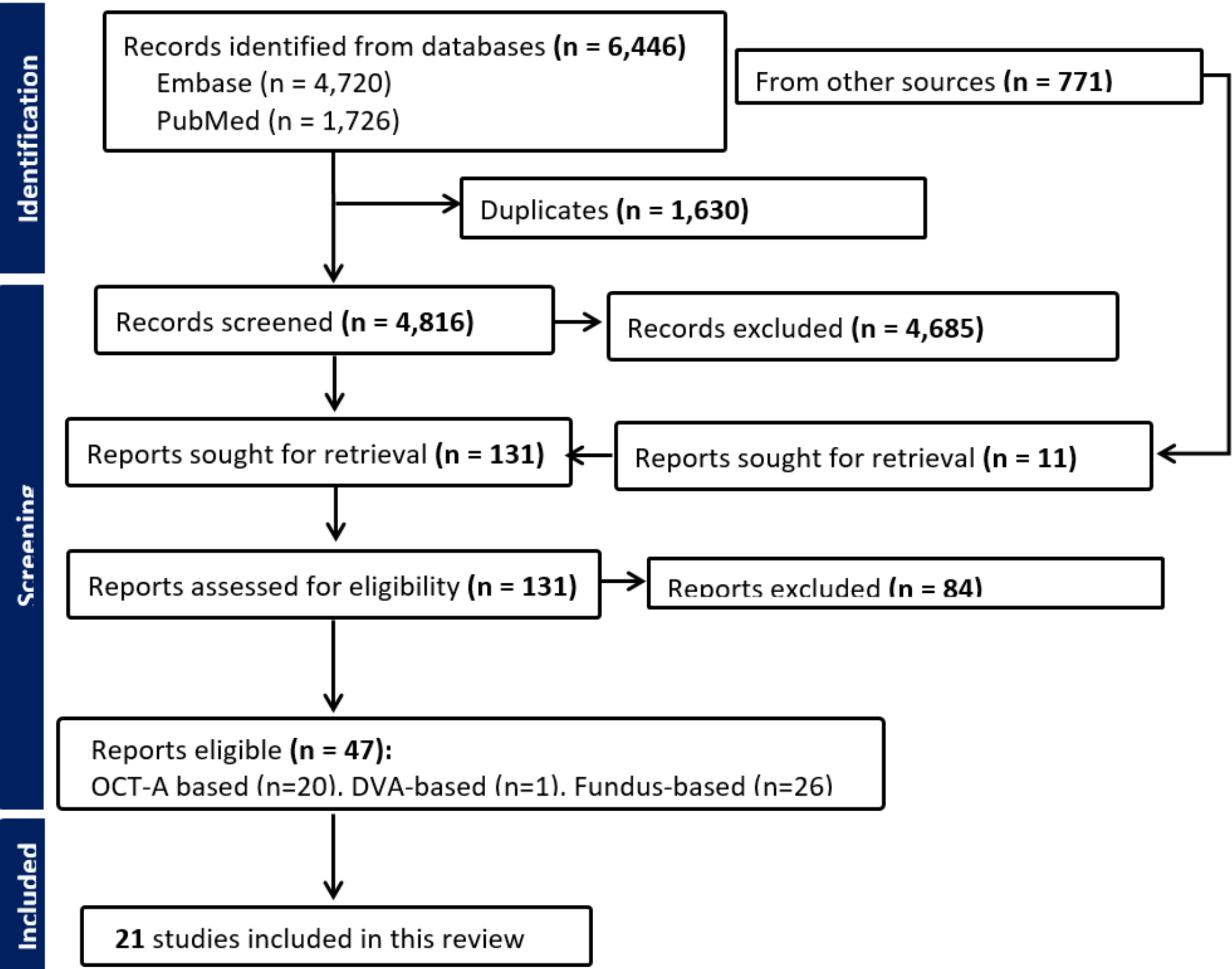


Figure 1. PRISMA Flow diagram (simplified version)

- Twenty studies used OCT-A and one study used DVA: 14 involved high-risk populations and 6 involved healthy / mixed populations
- Participants (N =1,660) had a mean age ranging from 44.0 to 72.2 years, and 53.6% were female
- The most frequent MRI-cSVD outcome analyzed was WMH. Other markers included lacunes, CMB and diffusion-based markers
- The most commonly reported OCT-A metrics were vessel density (VD) measures (area-based (VAD) or length-based (VLD)), followed by foveal avascular zone area

➤ Overall, the evidence suggested that lower retinal vessel density metrics were associated with worse cSVD outcomes, particularly a greater WMH burden

VESSEL DENSITY (VD)

- ↘ VD area-based and ↗ WMH and ↗ cSVD score in healthy and high-risk populations
- ↘ VD length-based and ↗ WMH in healthy and high-risk populations
- ↗ Foveal avascular zone and ↘ PVS in healthy populations
- ↘ VD area-based and ↗ lacunes and ↗ PVS in high-risk populations
- ↘ VD length-based and ↗ lacunes in high-risk populations
- ↘ VD area-based and ↗ PSMD in healthy populations

Figure 2. Synthesis of the main findings across included studies

➤ Most significant results were found in the superficial plexus (SRL)

Retinal features	MRI-marker	Study	Condition	N	Effect direction	P value in study	Combining P value
Main associations							
VAD in SRL whole (decrease)	Total WMH	Wang 2020	AD/MCI	109	▼	0.804	0.040
		Zhou 2022	WMH	64	▲	0.016	
		Geerling 2022	cSVD	20	▲	0.547	
		Guo 2024	CADASIL	25	▲	0.025	
VAD in SRL parafovea (decrease)	Total WMH	Wang 2020	AD/MCI	109	▲	0.962	0.723
		Lin 2022	CADASIL	35	▲	0.840	
		Huang 2024	T2DM	131	▼	0.644	
	Lacunes	Lin 2022	CADASIL	35	▲	0.440	0.001
		Fu 2022	cSVD	115	▲	0.006	
		Huang 2024	T2DM	131	▲	0.062	
	CMB	Lin 2022	CADASIL	35	▲	0.150	0.006
		Huang 2024	T2DM	131	▲	0.021	
VLD in SRL whole (decrease)	Total WMH	Zhou 2022	WMH	64	▲	0.018	0.004
		Geerling 2022	cSVD	20	▲	0.990	
		Guo 2024	CADASIL	25	▲	0.049	

▲ upward arrow = harmful (negative) health impact, ▼ downward arrow = beneficial (positive) health impact. Arrow size reflects the study sample size for analyses: large(>100 participants); medium (50–100); and small (<50)

Figure 3. Effect direction plot of VD metrics in the superficial plesus in high-risk populations

CONCLUSIONS

- Changes in retinal microvasculature were associated with worst cSVD markers
- Larger, standardized studies are needed to confirm these results and determine the clinical utility of innovative retinal microvascular imaging in cSVD

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Contact
sara-cristina.rondeau@u-bordeaux.fr

