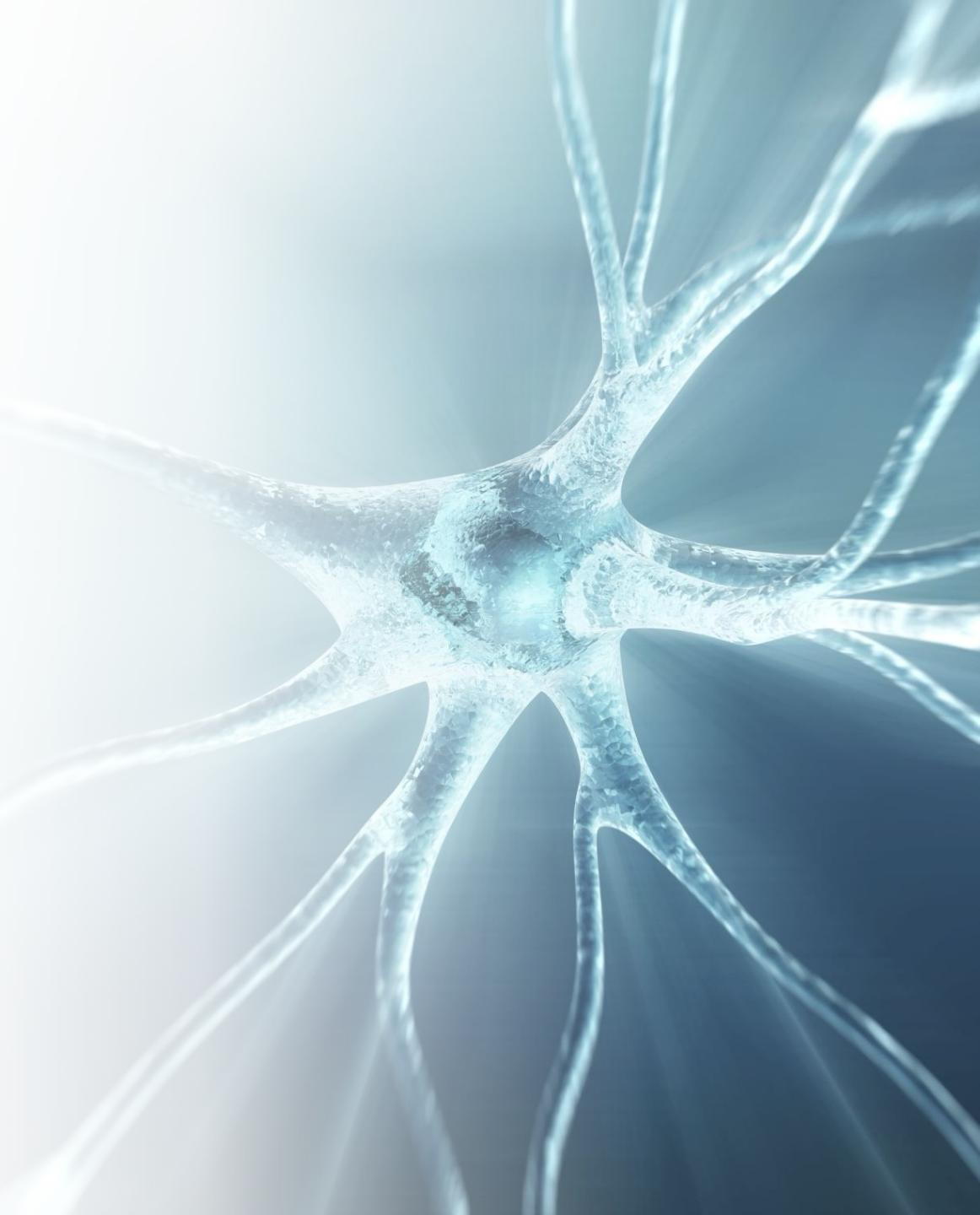




Cerebral Small Vessel Disease (cSVD)

Rizwan Kalani



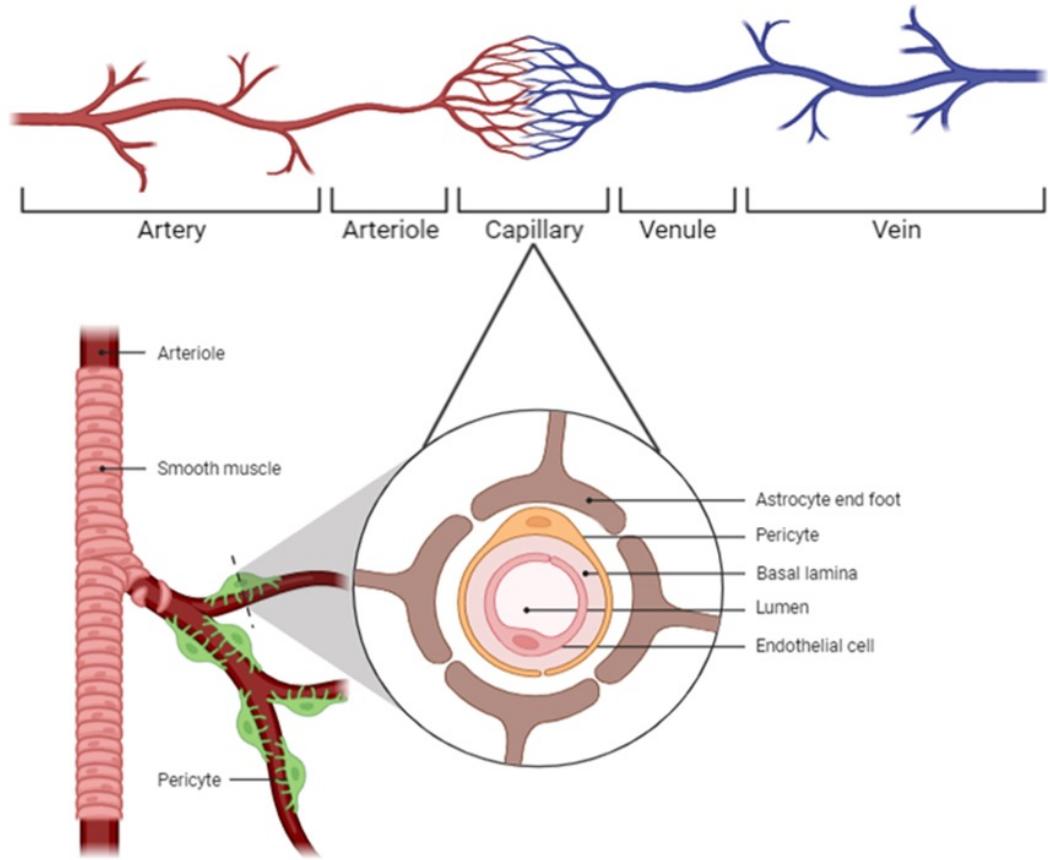
Objectives

- Neuroimaging
- Epidemiology & pathology
- Lipid biomarkers & proteomics

cSVD

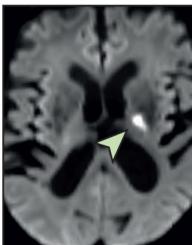
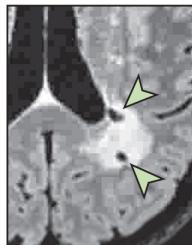
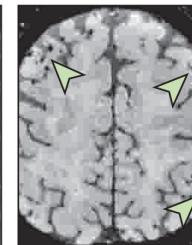
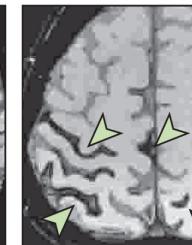
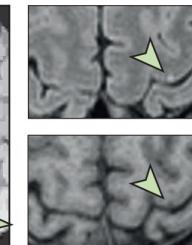
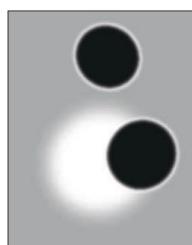
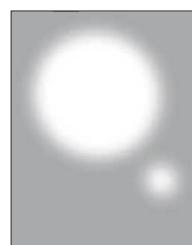
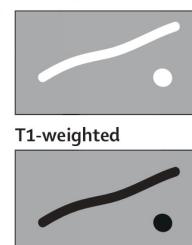
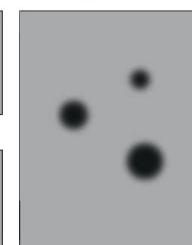
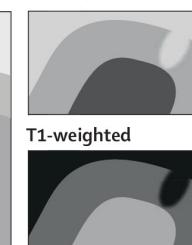
Any pathology involving small end arteries, arterioles, venules, and brain capillaries

- 50-400 μm
- blood-brain barrier



Magnetic Resonance Imaging

- Deep grey nuclei & subcortical white matter
- Lacunar stroke & cognitive impairment
- Gait impairment

	Recent small subcortical infarct	Lacune	White matter hyperintensity	Perivascular space	Cerebral microbleed	Cortical superficial siderosis	Cortical cerebral microinfarct
Example image							
Schematic				 T1-weighted schematic showing a dark elongated structure.			 T1-weighted schematic showing a dark semi-circular lesion.
Usual diameter	≤20 mm	3-15 mm	Variable	≤2 mm	≤10 mm	Variable	<4 mm
DWI	↑	↔ (↓)	↔	↔	↔	↔	↔/↑ (acute) ↑/↓
FLAIR	↑	↓	↑	↓/↔	↔	↔	↑
T2-weighted	↑	↑	↑	↑	↔	↔	↓
T1-weighted	↓	↓	↔ (↓)	↓	↔	↔	↔
T2*-weighted	↔	↔	↑	↔	↓↓	↓↓	↔

Prevalence

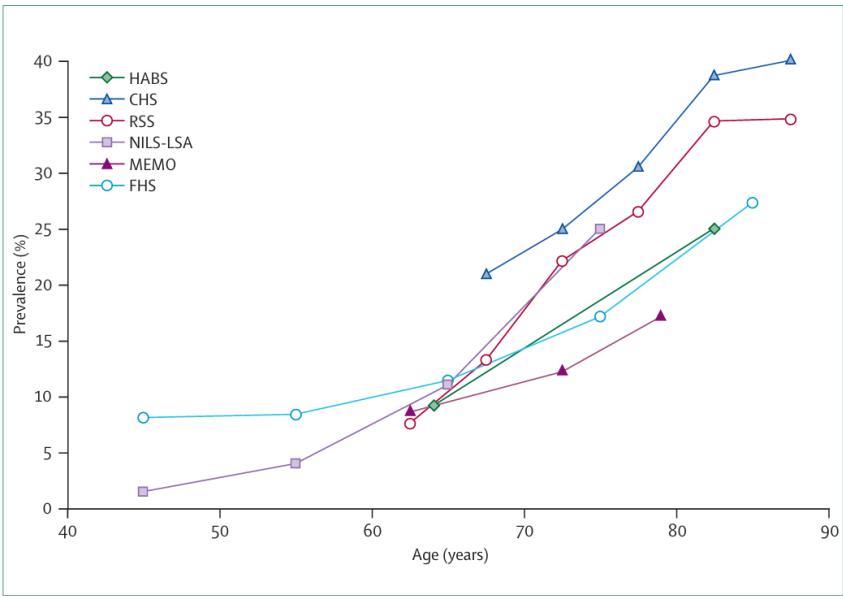


Figure 2: Prevalence of silent brain infarcts with increasing age, as reported in six population-based studies
 HABS, Helsinki (Finland) Aging Brain Study;⁹ CHS, Cardiovascular Health Study;¹⁰ RSS, Rotterdam Scan Study;¹²
 NILS-LSA, National Institute for Longevity Sciences-Longitudinal Study of Aging;¹³ MEMO, Memory and Morbidity
 in Augsburg Elderly study;¹⁴ and FHS, Framingham Heart Study.¹⁵

	Lacune	CMI	DWI +	WMH	PVS	CMB	cSS
50-59	3-5%	-	~0%	1%	1%	10%	-
60-69	5-10%	-	1.2-1.5%	1-4%	5-7%	15-17%	0.4%
70-79	10-20%	6-11%	-	6-14%	20-25%	25-35%	-
80+	20-30%	-	-	19%	40-60%	35-45%	-

Major population-based studies of WMH in healthy subjects

Population-based study	Year	Study size	Mean age (yr)	WMH burden (%)	WMH risk factors	WMH progression (%) (duration, yr)
Cardiovascular Health Study [35,36]	1989	3,301	74	96	Age, silent infarct, SBP, lower FEV1, low income	28 (5)
Austrian Stroke Prevention Study [40,41]	2005	273	60	65	NR	17.9 (3)
Rotterdam Scan Study [37,38]	1990	1,077	72	95	Age, female gender	39 (3.4)
Atherosclerosis Risk in Communities Study [39,42]	1987	1,920	62	86	Age, smoking, alcohol use, education, SBP, DBP, African American race	23 (9)
Framingham Offspring Cohort Study [43,44]	1948	1,814	53	NR	Smoking, hypertension	NR (10)

Prevalence and risk factors of CMBs in healthy populations

Population-based study	Year	Study size	Mean age (yr)	MRI field strength (T)	Prevalence (%)	Risk factors
Austrian Stroke Prevention Study [107]	1999	280	60	1.5	6.4	Age, HTN, SSI, WMH
Tsushima et al. [105]	2002	450	53	1.0	3.1	HTN and smoking
Framingham Study [115]	2004	472	64	1.0	4.7	Age, male gender
AGES-Reykjavik [110]	2008	1,962	76	1.5	11.1	Age, male gender, APOE e4 status
Rotterdam Scan Study [106]	2010	3,979	60	1.5	15.3	SBP, HTN, smoking, SSI, WMH
RUN-DMC [112]	2011	485	66	1.5	10.7	NR
Atahualpa Project [111]	2015	258	70	1.5	11.0	WMH, SSI, brain atrophy
Mitaki et al. [113]	2017	4,024	62	1.5	4.1	WMH (lobar CMB), low TC and HDL-C (deep CMB)
Shunyi Study [68]	2018	1,211	56	3.0	10.6	Age, hypertension (deep CMB), male gender, low LDL-C (deep CMB)

J Stroke. 2019 May;21(2):121-138.
 Lancet Neurol. 2007 Jul;6(7):611-9.
 Can J Neurol Sci. 2025 Jan;52(1):1-8.

Risk Factors

- Age, Hypertension
- Diabetes, dyslipidemia, tobacco, sleep apnea
- Genetics

	SVS	ICH	Lobar ICH	Non-lobar ICH	Lacunes ^a	CMB	WMH	FA ^b	MD
High systolic blood pressure	3/3	1/1	1/1	1/1	1/1	1/1 ^c	2/2		
High diastolic blood pressure	3/3	1/1	1/1	1/1	1/1	1/1 ^c	2/2		
High low-density lipoprotein	2/5	1/2	1/1	1/1	1/1	1/1	2/2		
High lipoprotein (a)	1/1								
High high-density lipoprotein cholesterol	3/4	2/2			1/1	1/1	1/3		
High apolipoprotein B	1/1								
High apolipoprotein A-I	1/1								
High triglycerides	2/3	2/2			1/1	1/1	1/3		
High BMI	4/5	3/3	1/1	1/1	1/1	1/1	2/2		
High waist-to-hip ratio	2/3	1/3	1/1	1/1			1/1		
Type II diabetes mellitus	5/5	2/2	2/2	2/2	1/1	1/1	1/3	2/2	2/2
High blood glucose	1/1	1/1	1/1	1/1			1/1	1/1	1/1
Ever smoking	3/4				1/1		1/1		
High education	1/1	1/1							
Tea intake	1/1 ^d								
Low birthweight (maternal effects)	1/1								
High depressive disorder	1/1								
Migraine					1/1 ^e				
High fibrinogen	1/1								
High homocysteine	1/1								
High folate	1/1								
High vitamin B6	1/1 ^f								

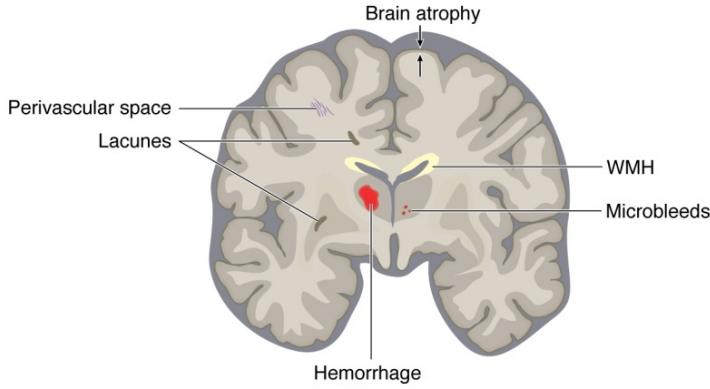
Table 3 | Involvement of genes associated with cerebral small vessel disease in biological processes

Biological process ^a	Gene	Protein	Involvement of protein in biological process	Refs
ECM structure and function	<i>EFEMP1</i>	Fibulin 3	ECM glycoprotein localized in the basement membrane; proteolytic target of serine protease HTRA1	182
	<i>LOX</i>	Lysyl oxidase	Copper-dependent enzyme that crosslinks collagens and elastin	96
	<i>SH3PXD2A</i>	SH3 and PX domain-containing protein 2A	Adapter protein involved in ECM degradation via invadopodia and podosome formation	183
	<i>NID2</i>	Nidogen 2	ECM glycoprotein and a major component of basement membranes	96
	<i>ADAMTSL4</i>	ADAMTS-like protein 4	Involved in cellular adhesion, angiogenesis and patterning of the developing nervous system	96
	<i>FBN2</i>	Fibrillin 2	Component of connective tissue microfibrils that might be involved in elastic fibre assembly	65
	<i>VCAN</i>	Versican core protein	Proteoglycan involved in cell adhesion and ECM assembly	184
	<i>AGRG6</i>	Adhesion G protein-coupled receptor 6	ECM protein produced by astrocytes and involved in pericyte differentiation and blood-brain barrier development and function; activated by type IV collagen and binds to laminin-211	107,185
	<i>HBEGF</i>	Heparin-binding EGF-like growth factor	EGF-like is one of the characteristic domains of ECM proteins	96
	<i>ULK4^b</i>	Serine-threonine protein kinase ULK4	Regulates a core set of factors that are essential in the development of oligodendrocytes	51
Myelination	<i>VCAN</i>	Versican core protein	Forms complexes that inhibit oligodendrocyte maturation	100
	<i>AGRG6</i>	Adhesion G protein-coupled receptor 6	Involved in Schwann cell myelination in the PNS	98,99
	<i>KCNK2</i>	Potassium channel subfamily K member 2	Enables potassium transport across the cytoplasmic membrane; although not directly involving KCNK2, potassium channelopathy-like defects were shown to underlie early-stage cerebrovascular dysfunction in CADASIL	95
Membrane transport	<i>SLC39A13</i>	Solute carrier family 39 member 13	Transmembrane zinc transporter; mutations cause a form of Ehlers-Danlos syndrome, which can cause stroke	186
	<i>SLC25A44^b</i>	Solute carrier family 25 member 44	Mitochondrial carrier protein with a role in catabolism of branched-chain amino acids in brown adipose tissue	187

Pathology

- Arteriosclerosis – “hypertensive arteriopathy”
- Cerebral amyloid angiopathy

* Monogenic disorders



Hypertensive arteriolosclerosis (Type 1)	Cerebral amyloid angiopathy (Type 2)
Common in deep brain locations (BG, thalamus, deep WM and pons)	Lacunar infarcts
Linear WMH and follows the peripheral outline of the basal ganglia	White matter hyperintensities
>20 EPVS with predilection for basal ganglia	Enlarged perivascular spaces
Deep brain locations. No cortical superficial siderosis	Cerebral microbleeds
Cerebral atrophy	Cerebral atrophy

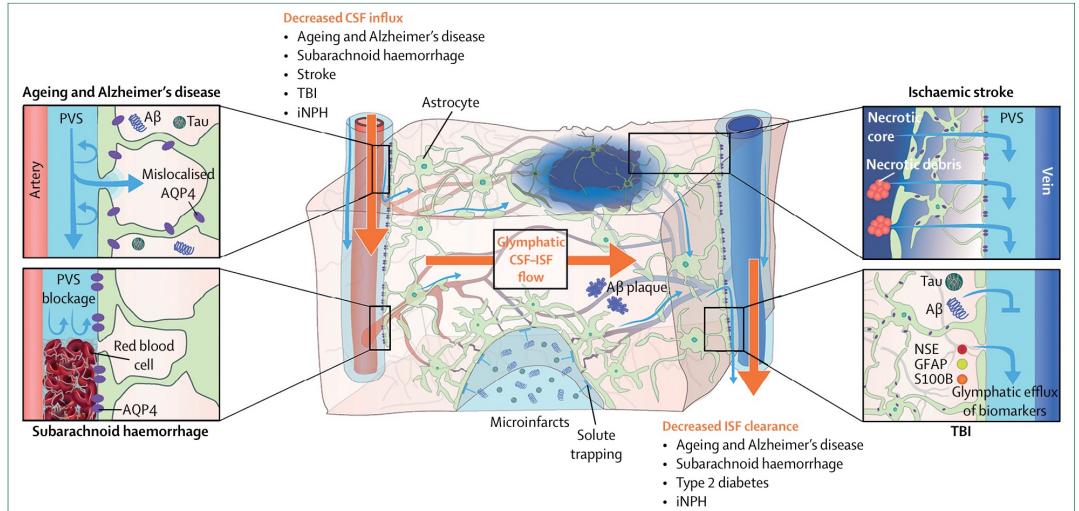
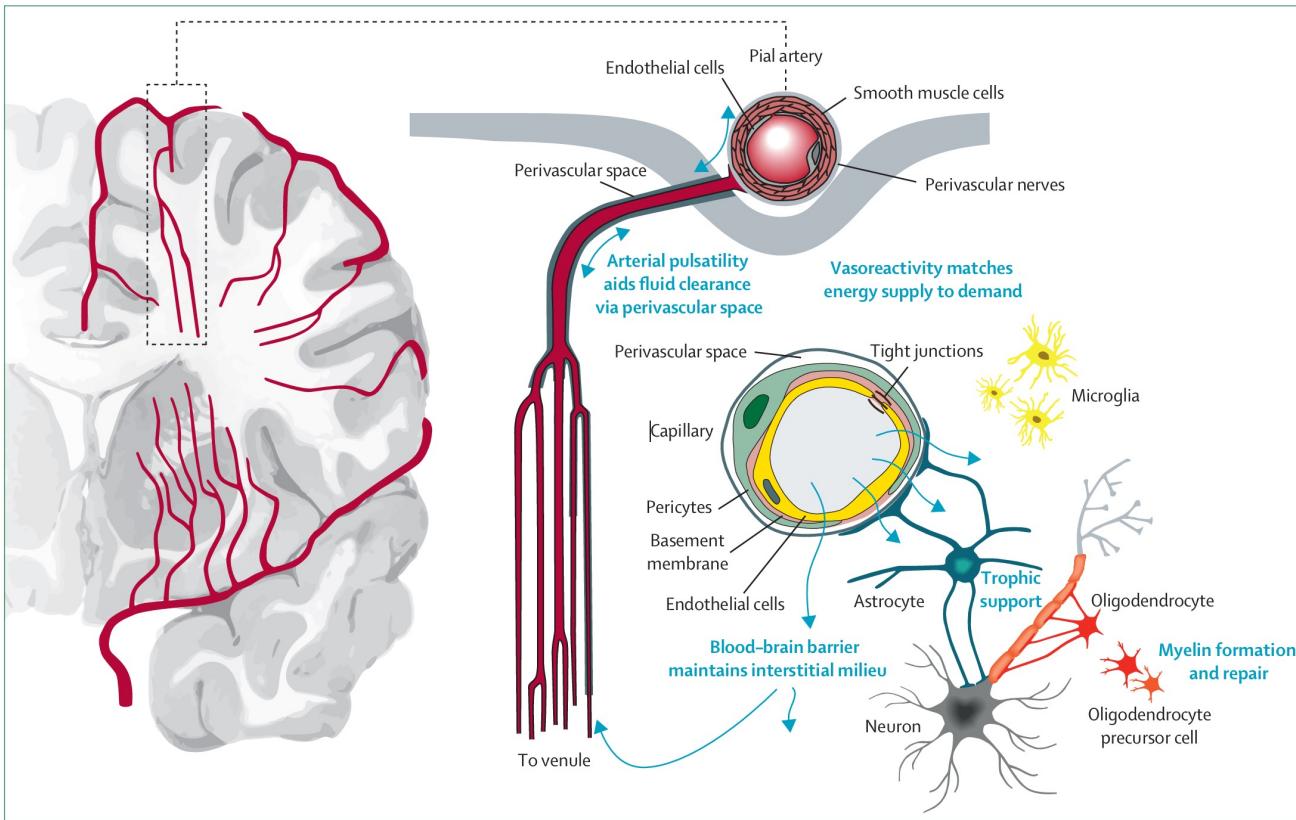


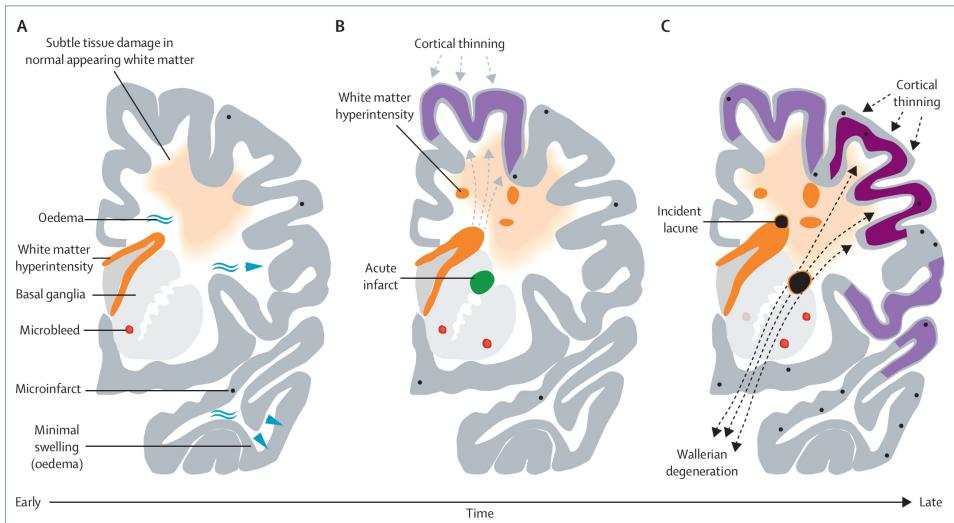
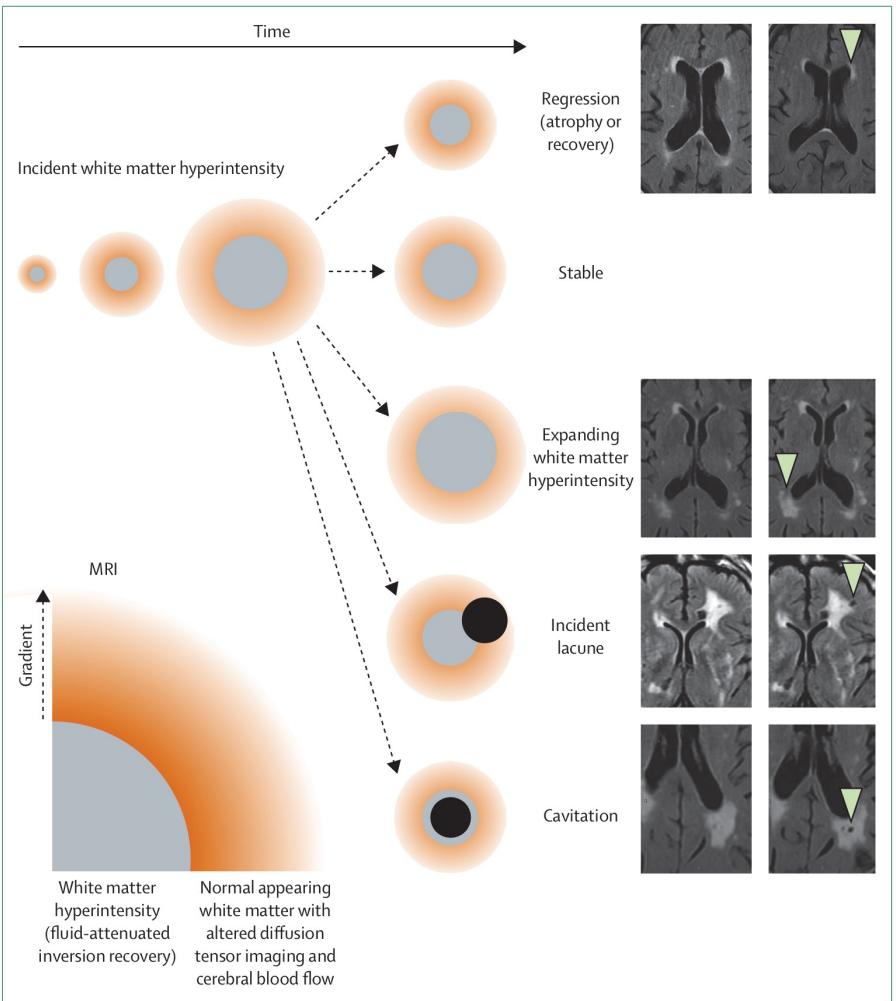
Figure 4: Pathological changes to the glymphatic pathway

J Clin Invest. 2024 May 15;134(10):e172841.
AJNR Am J Neuroradiol. 2022 May;43(5):650-660.
Lancet Neurol. 2018 Nov;17(11):1016-1024.

Pathogenesis

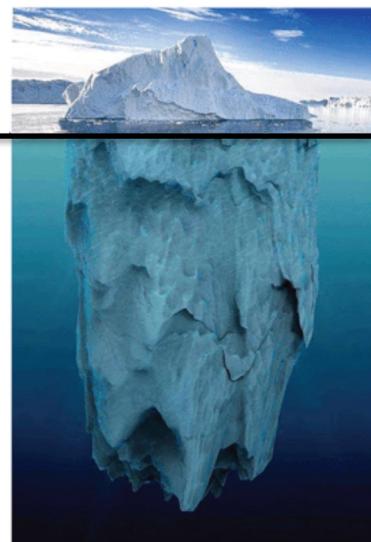
- Endothelial & BBB dysfunction
 - Arterial stiffening & altered pulsatility
 - Impaired blood flow & interstitial fluid drainage
- Secondary parenchymal injury (white matter, lacunar infarcts, neurodegeneration)





Clinical stroke

Cerebral small vessel disease



Significance

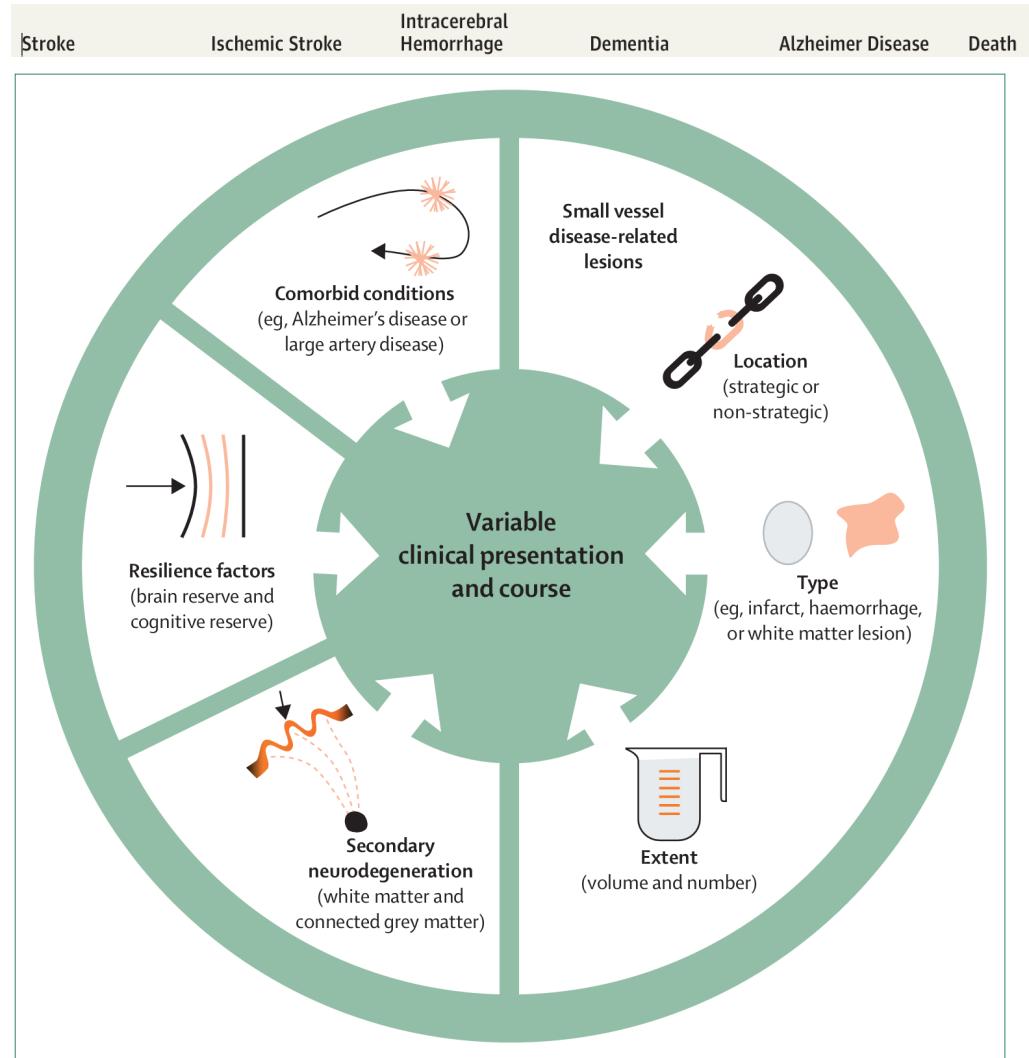
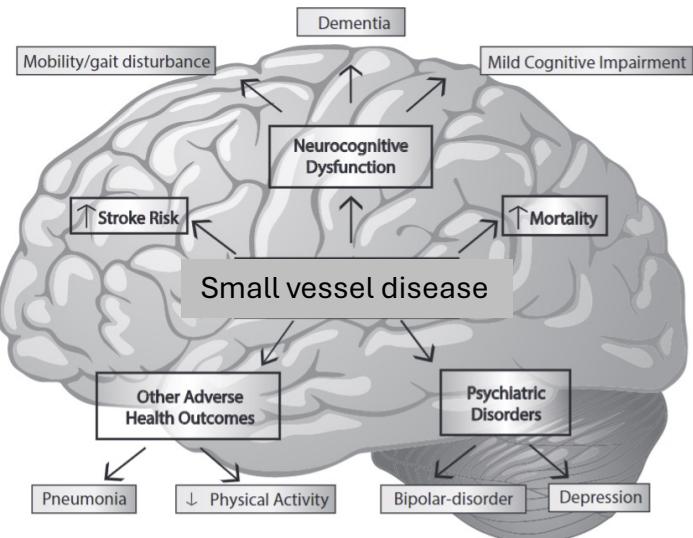
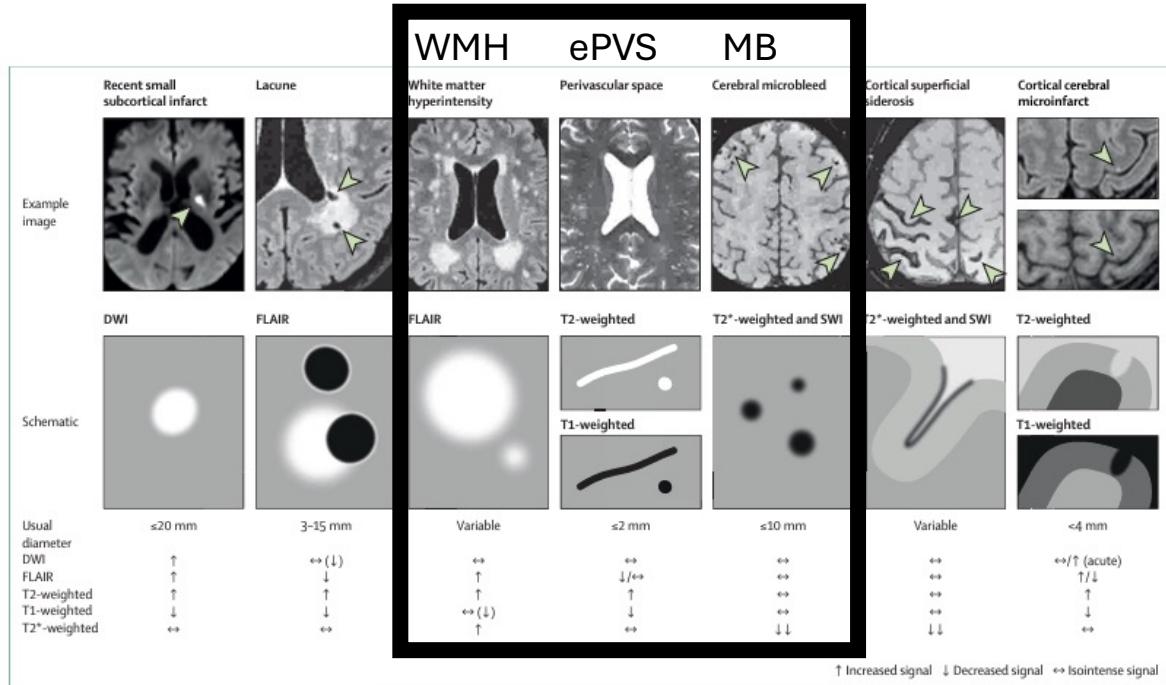
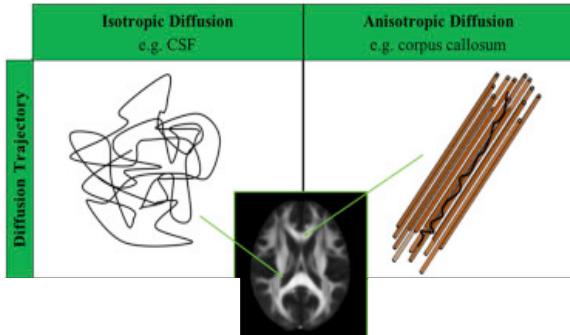


Figure 4: Factors influencing the clinical presentation of small vessel disease

Lancet Neurol. 2019 Jul;18(7):684-696.
 Stroke. 2014 Nov;45(11):3461-71.
 JAMA Neurol. 2019 Jan 1;76(1):81-94.

Cerebral Small Vessel Disease

- Associated w/ ↑ risk of:
 - Cognitive impairment
 - Symptomatic stroke
 - Mortality



- White Matter Fractional Anisotropy (WMFA)
 - WM microstructural integrity
 - Diffusion tensor imaging → 0 (isotropic) – 1 (anisotropic)

Uncertainties and Opportunities

- Management
 - Microangiopathy
 - Branch atheromatous disease
 - Novel therapeutics
- Epidemiology
- VCID
- Subclinical infarcts
 - $\geq 5X$ more common
 - Majority lacunar

Why cSVD Matters

- >25 % ischemic strokes & ~50 % ICH
- Up to 45 % dementias have small-vessel component
- ≈ \$60 B annual disability cost
- Lesions accumulate silently for decades

Pathology in One Graphic

- Arteriolosclerosis → lumen narrowing → chronic hypoperfusion
- BBB leakage & endothelial dysfunction
- Microinfarcts, demyelination → WMH, lacunes
- Amyloid angiopathy → lobar microbleeds

Five MRI Markers of cSVD

- WMH • Lacunes • Microbleeds • EPVS • Secondary atrophy
- Each marker → distinct clinical impact
- Cut-off controversies & rating variability

Age & Sex Trajectories

- Log-linear WMH rise from 40s
- Men steeper until 70 y then converge
- Microbleeds surge >80 y

Classic Risk Factors

- Hypertension OR 2–4 across lesions
- Diabetes & CKD modest links
- Smoking tied to microbleeds & lacunes
- Static lipids inconsistent; variability may matter

Pilot #1 – HDL Variability Predicts WMH

- CHS n=2,066; 5 HDL measures over 10 y
- ↑1 SD HDL-SD → +4 % WMH slope ($p<0.01$)
- Independent of mean HDL & BP

Pilot #2 – Plasma Proteomics & Microstructure

- MESA n=709; 2,941 proteins
- 329 proteins linked to WM-FA (DTI)
- SPINK8 uniquely associated with microbleeds
- No significant proteins for WMH

Critical Gap Heat-Map

- Imaging cut-offs 
- Scanner drift 
- BP variability causality 
- Surrogate endpoints 
- Trial readiness 

Eight Untapped Exposures in CHS/MESA

- 24-h Na⁺/K⁺ ratio
- Pericardial fat volume
- hs-CRP variability
- Galectin-3
- Grip-strength decline
- Lung-function trajectories
- Retinal fractal dimension
- Sleep fragmentation index

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Questions?