

Study and relevant reference	Population / age	Computational WMH assessment method			
		Principle	Sequences	Degree of automation	Validation
Glostrup 1914 Cohort Study (1)	Normal / 50,60,70,80 and 85 yrs. old	Local thresholding	PD and T2W (1.5T)	Automatic	Scheltens scale
Framingham Heart Study 1948 and Framingham Offspring Study 1971 (2)	>1300 indiv. genetically related / 60.99 ± 9.61(range 34 to 88)yrs.	Image histogram modelled as mixture of 2 Gaussian probability functions. Individualised thresholding = 3.5 standard deviation in pixel intensity above the mean of the fitted dist. of brain parenchyma	T2W (1T) (uses 1 <sup>st</sup> and 2 <sup>nd</sup> echo)	Semi-automatic	
Volunteers from Winston-Salem area, NC, USA (3)	Normal / 18-38,39-64 and 65-90 yrs. old	SPM (thresholding at 0.15 to eliminate voxels with low probability of being WM)	T1W, T2W, DTI (1.5T) (only uses T1W for WMH assessment)	Automatic	Against WM template map from 64 individuals
Nun Study (4)	52 autopsied women / At entry: 84.9 ± 4.8 yrs, At death: 89.1 ± 4.8 yrs.	Individualised thresholding	T1W, T2W	Semi-automatic	Inter-rater reliability (correlation coefficient)
Dept. of Psychiatry (Univ. of Munich) and Alzheimer Centre (Vrije Univ. Med. Centre in Amsterdam) joined project (5)	Normal/ 60.9 ± 8.7 yrs. AD/ 69.1 ± 10.8 yrs. VaD/ 72.3 ± 10.2 yrs.	Individualised thresholding on FLAIR using region growing algorithm (Analyze™ software)	T1W, FLAIR (1.5T or 1T)	Semi-automatic	Visual evaluation and inter-rater reliability
Cognitive Aging Study and Depression-Treatment Study (6)	1 major-depressed indiv./74 yrs. old and 12 depression-free/ 73.5 ± 4.4 yrs. old	Individualised thresholding on FLAIR based on a mixture-modelling algorithm	FLAIR (1.5T)	Semi-automatic	
Path Through Life Study (7,8)	Heterogeneous / 62.55 ± 1.45 yrs. old	SPM: Applies a weighting function based on WM prob. on to the FLAIR image. Removes false WMH in FLAIR	T1W, FLAIR	Semi-automatic	Modified Fazeka's scale

		<p>by examining the intensities in T1: <math>I_{WMH} \geq \mu_{(CSF,T1)} - 3\sigma_{(CSF,T1)}</math>.  Detects the voxels in FLAIR whose intensities <math>I_{WMH} \geq \mu_{(WM,FLAIR)} + 3\sigma_{(WM,FLAIR)}</math>.  Grades the WMH voxels into mild-moderate (<math>\mu_{(WM,FLAIR)} + 3\sigma_{(WM,FLAIR)} \leq I_{WMH} \leq \mu_{(WM,FLAIR)} + 6\sigma_{(WM,FLAIR)}</math>) and severe (<math>I_{WMH} \geq \mu_{(WM,FLAIR)} + 6\sigma_{(WM,FLAIR)}</math>).</p>			
MS Study, from the Institute of Neurology, National Hospital, London (9)	Elder individuals	Local thresholding using region-growing algorithm, and global thresholding using a visually determined threshold	T2W	Manual, semi-automatic and automatic	Intra-and inter-rater reliability
Dementia Study (11)	Normal, AD and VaD / 72 $\pm$ 8.6 yrs. old	Individualised thresholding using 2D k-nearest neighbour clustering	T2W, PD (1.5T)	Semi-automated	Intra- and inter-rater reliability
Rotterdam Scan Study (12)	Normal /16 to 88 yrs. old (mean 72 yrs. old)	Individualised thresholding using a region-growing algorithm	T1W, PD, T2W, (1.5T)	Semi-automated	Fazekas, Scheltens scales and inter-observer reliability
Austrian Stroke Prevention Study (13)	Heterogeneous / 60.8 $\pm$ 6.2 yrs. old (50 to 75 yrs. old)	Thresholding followed by voxel-based morphometry to find regionally specific differences in the expression of lesions among different groups	T1W, T2W, PD (1.5T) (only uses PD for WMH assessment)	Semi-automated	Intra- and inter-rater reliability
Leukoaraiosis And DISability (LADIS) Study (14)	Heterogeneous / 65 to 85 yrs. old	Local thresholding on FLAIR images	T1W, T2W, FLAIR (0.5T or 1.5T)	Semi-automated	Fazekas, Scheltens scales and inter-observer reliability
Study on Changes in DWI and MRS associated with WMH	Normal / 64 to 84 yrs. old	SPM: dividing tissues in 4 classes: grey/white matter, cerebrospinal fluid and WMH	T2W, T1W, FLAIR, DWI (1.5T) (uses T1W and FLAIR)	Semi-automated and automated	Mean and std. deviation between results from automated

in elders. Newcastle General Hospital (15)			for WMH assessment)		and semi-automated
Study on Cognition and Prognosis in the Elderly (SCOPE) (16)	Normal / 70-89 yrs.	Individualised histogram-based thresholding on each slice	T1W, T2W, FLAIR (1.5T) (only FLAIR used in WMH assessment)	Semi-automatic	-
Lothian Birth Cohort 1936 Study (17)	Normal / 72 yrs.	Colour fusion in the red/green space of T2*W and FLAIR followed by minimum variance quantisation (18)	T1W, T2W, T2*W, FLAIR, DTI (1.5T)	Semi-automatic	Against individualised thresholding in FLAIR (18) and other multispectral classifiers (19)
Anatomical Mapping of WMLs on the elderly and AD, University of California at Davis Alzheimer's Disease Centre (20)	No Cognitively Impaired / 72.7 ± 11.9 yrs. old; Cognitive Impairment Not Demented / 73.5 ± 8.3 yrs. old; Demented / 78.5 ± 6.0 yrs. old	Individualised histogram-based thresholding on each slice	T1W, FLAIR (1.5T)	Semi-automatic	-
PROSPER Study (21)	Heterogeneous, cognitively normal/ 70 to 82 yrs. old	Adaptive thresholding using a fuzzy inference system (43)	T2W, PD, FLAIR (1.5T)	Automatic	Intra- and inter-rater reliability compared to manual WMH delineation
Study on arterial vascular diseases, University Medical Centre Utrecht (22)	Arterial vascular diseases (TIA, peripheral arterial disease, coronary artery disease, renal artery disease, abdominal aorta aneurysm)/49 to 75 yrs. old (65.5 ± 7.7) yrs. old	Multispectral k-nearest neighbour classifier	T1W, T2W, PD, FLAIR (1.5T)	Automatic	Similarity index, overlap fraction and extra fraction compared to manual WMH delineation
Study of Depression in Later Life, MHCRC, Duke University (23)	Depressed / >60 yrs. old	Seed-growing thresholding individualised per slice (45)	T1W, T2W (1.5T)	Semi-automatic	Coffey (46) and Boyco (23,47) visual ratings. Inter-rater reliability (ICC=0.99)

Study of SIVD and AD contributions to dementia (24)	AD and IVaD/ 77.2 ± 7.7 yrs. old	Individualised thresholding on 10 3D volumes-of-interest per brain	T2W, PD	Semi-automatic	Inter-rater reliability (ICC=0.97) on each volume-of-interest
Alzheimer Disease Study, from the Dep. Of Radiology, University of California at San Francisco Medical Centre (25)	AD patients/61-78 yrs. old (72 ± 6.9) Normal/ 62 – 84 yrs. old (70.2 ± 6.2)	Individualised thresholding on training datasets and use thresholds as priors for segmentation	T1W, T2W (1.5T)	Semi-automatic	-
Mild Stroke Study, from the Brain Research Imaging Centre at University of Edinburgh (10)	Mild to moderate stroke patients /66 ± 11 yrs. old	Colour fusion in the red/green space of T2*W and FLAIR followed by minimum variance quantisation (18)	T1W, T2W, T2*W, FLAIR, DWI (1.5T)	Semi-automatic	Against individualised thresholding in FLAIR (18) and other multispectral classifiers (19)
Alzheimer’s Disease Neuroimaging Initiative (ADNI) Study (51)	Mild Cognitive Impaired patients / 74.6 ± 7.4 yrs. old	WMH detected in minimum deformation template space at each voxel based on corresponding PD, T1W, and T2W intensities; the prior probability of WMH; and the conditional probability of WMH based on the presence of WMH at neighbouring Voxels (52)	T1W, T2W, PD (1.5T)	Automatic	Against manual delineation (52)
Pilot Study, from the Intervention Research Center for Late-Life Mood Disorders, University of Pittsburgh (26)	Depressed / 63 – 80 yrs. old (72.2 ± 5.3) Controls / 67 – 81 yrs. old (72.3 ± 4.8)	Individualised histogram-based thresholding in FLAIR (mean intensity + 3 standard deviations) to generate WMH “seeds”. Iteratively update the seeds’ boundaries using a multispectral fuzzy-connected-based algorithm	T1W, FLAIR, T2*W (1.5T)	Automatic	Against manual delineation in FLAIR

Pilot Study, from the Wellcome Trust Centre for Neuroimaging. Institute of Neurology, University College of London (27)	Stroke patients/ 23 to 68 yrs. old Normal / 21 to 75 yrs. old	Unified segmentation normalisation (using SPM5) and fuzzy clustering	T1W (1.5T)	Automatic	Against manually delineated lesions and simulated lesions on phantom images, using Dice coefficient
Sunnybrook Dementia Study (28)	Patients with AD/ 74.8 ± 5.8 yrs.; short term memory loss/ 75.6 ± 6.3 yrs.; and gradual decline/ 78.2 ± 6.6 yrs.	Individualised thresholding using a Gaussian classifier	T1W, PD, T2W (1.5T) (T2W and PD used for WMH assessment)	Semi-automatic	-
Study on Multiple Sclerosis, from the University of Texas Medical School at Houston (29)	Multiple Sclerosis patients/20 to 51 yrs. old (36.42 ± 9.9)	Parzen windows multispectral classifier	T1W, FLAIR (1.5T)	Automatic	Against manual delineation using similarity index, % of correct estimation, % of over-estimation, % of under-estimation and Bland-Altman plot
Utrecht Diabetic Encephalopathy Study (UDES) (30)	55 to 80 yrs. old Diabetics/ 66.5 yrs. old (average) Controls/ 64.6 yrs. old (average)	Individualised 2D multispectral k-nearest neighbour classifier using 10 manually delineated training datasets		Automatic	Against manual delineation using correlation coefficient
Leukoencephalopathy Study from Memphis, Tennessee (31)	Patients with Acute Lymphoblastic Leukaemia and normal controls/ <18 yrs. old	Hybrid neural network that uses a Kohonen self-organised map (33)	T1W, T2W, PD, FLAIR	Automatic	Against manual delineation from 2 raters (kappa: 0.57 and 0.55)
Cerebral Amyloid Angiopathy (CAA) Study, from the Massachusetts General Hospital (32)	Individuals with possible CAA / ≥ 55 yrs. old	Individualised thresholding using MRICro software	T1W, T2W, FLAIR (1.5T)	Semi-automatic	
Epidemiology of	Heterogeneous / 69 ± 2.9	Bias field correction, 7-tissue	T1W, T2W, PD (1T)	Automatic	Against

Vascular Aging Study (EVA) (37)	yrs. old	class segmentation, white matter detection and 3-class segmentation of the WM combining thresholding and morphological operations. False positives removed using voxel based statistics on SPM			neuroradiological ratings (34,35) and inter-centre reproducibility evaluating WMH distribution load
Three Cities (3C) - Dijon Study (36)	Heterogeneous / 72.5 ± 4.1 yrs. old	SPM followed by removal of false positives: i.e. perivascular spaces and voxels with T2W signal intensity lower than the mean of normal white matter	T1W, T2W, PD (1.5T)	Automatic	-
Study about pathologic changes in grey matter of healthy elderly individuals with non-specific WMH (39)	Normal / 68.5 yrs. old (65-74)	Individualised thresholding	T1W (1.5T)	Semi-automatic	Fazekas scale
Abnormal Cerebral Structure Present at Term in Premature Infants (Coordinated study from Melbourne, Boston and Geneva) (40)	Infants (new-borns) scanned at a term equivalent between 39 <sup>th</sup> and 41 <sup>st</sup> gestational weeks	Iterative classification (of all tissues: normal and abnormal) and nonlinear registration on an adaptive template-moderated spatially varying statistical classification framework (50)	T1W, T2W, PD (1.5T)	Automatic	Against visual categorisation of WM into: no WM abnormality, mild WM abnormality, moderate-severe noncystic WM abnormality, or moderate-severe cystic WM abnormality
Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) (49)	Normal / >= 60 yrs. old	SPM (Lesion Segmentation Toolbox on SPM8 software) followed by manual editing using MRICroN	T1W, T2W, PD, FLAIR (1.5T) (T1W and FLAIR used on WMH assessment)	Semi-automatic	Inter-rater reliability (ICC=0.99)
Health ABC Study and Healthy Brain Project	Heterogeneous / 78 to 87 yrs. old. at time of	Fuzzy-connected algorithm followed by a demons-based	T1W, FLAIR, DTI (3T)	Automatic	Correlations with manually edited WMH

ancillary study, Pittsburgh Field Centre (53)	referenced study (enrolled 8 years before)	image registration using the Johns Hopkins University White Matter Atlas to remove false positives (54)			(54)
Study on white matter degeneration, Centre of Imaging for neurodegenerative Diseases, Univ. of California (55)	Normal / 71 ± 10 yrs. old	Thresholding FLAIR regions with 25% higher intensity than the average white matter, followed by a boundary refinement using graph cuts (56)	T1W, FLAIR, DTI (4T) (only FLAIR used on WMH assessment)	Automatic	Correlation of FLAIR intensities with DTI parameters
Oregon Brain Aging Study (follow-up at 10 years) (57)	Normal to Cognitive impaired / 84.1 ± 6.2 yrs. old	Thresholding regions of interests using REGION software: based on recursive regression analysis of T2W/PD space and location.	T1W, T2W, PD (1.5T)	Semi-automatic	-
CADASIL GWAS consortium study on CADASIL patients across 7 European sites (58)	CADASIL patients / 51 yrs. old (19 to 83 yrs. old)	Thresholding in FLAIR following by manual editing	T2W or PD, FLAIR (between 0.5T to 3T) (only FLAIR used in WMH assessment)	Semi-automatic	Inter-rater reliability (ICC=0.996)
Study on clinically-isolated syndrome or relapsing-remitting multiple sclerosis, from Technische Universitat Munchen and Friedrich-Schiller University in Jena (59)	Multiple sclerosis patients and healthy age-matched controls / 36.4 ± 13 yrs. old (20 to 59 yrs. old)	SPM (Lesion Segmentation Toolbox on SPM8 software)	T1W, FLAIR (3T)	Automatic	-
ECLIPse Study follow-up (60)	Stroke patients/ >45 yrs. old (65 ± 9.99 yrs. old)	Thresholding on FLAIR	T1W, T2W, FLAIR (1.5T)	Manual or semi-automatic	Intra-observer reliability (ICC=0.93)
Sub-study (one-centre sample) from the VITAMins TO Prevent	Ischaemic stroke patients with confluent WMH on MRI / 76.87 ± 7.87 yrs. old	Thresholding on FLAIR	T1W, T2W, T2*W, FLAIR (1.5T) (only FLAIR used for	Semi-automatic	Intra- inter-observer reliability on primary study

Stroke (VITATOPS) multicentre Study (61)	(prestroke nonstatin use), 73.59 ± 7.82 (prestroke statin use)		WMH measurement)		
Study on Sickle Cell disease; Academic Medical Centre, Amsterdam (62)	Sickle Cell patients / 12.5 ± 2.7 yrs. old (8.2 to 17.1 yrs. old)	WMH visually identified and manually delineated as regions of interest (ROIs). After grey matter-intensity thresholding segmentation, WMH ROIs restricted only to intensities >1.02 times higher than mean grey matter intensity.	FLAIR (1.5T)	Semi-automatic	-
Harvard Aging Brain Study (63)	Normal / 73.8 ± 6 yrs. old (65 - 90 yrs. old)	Individualised histogram-based thresholding in FLAIR (mean intensity + 3 standard deviations) to generate WMH "seeds". Iteratively update the seeds' boundaries using a multispectral fuzzy-connected-based algorithm (26)	T1W, fMRI, DTI, PET, FLAIR (3T) (only FLAIR used on WMH segmentation)	Automatic	Against visual ratings (26)
Prospective Cohort Study (64)	Parkinson's Disease patients	Histogram-based segmentation on ROIs in intensity-normalised FLAIR images using FSL-FAST (65)	T1W, FLAIR (3T)	Automatic	Against manually-delineated ROIs using similarity index, overlap ratio and Bland-Altman analyses (65)
Tasmanian Study of Cognition and Gait (TASCOG) (66)	Normal / > 60 yrs. old	Multispectral morphological segmentation with adaptive boosting classification using results from SPM (segmentation into white, grey matter and CSF)	T1W, T2W, FLAIR (1.5T)	Automatic	Against manually delineated WMH (ICC=0.9)
Migraine study,	Migraine patients / 47 ±	Thresholding on FLAIR guided	T1W, T2W, FLAIR, SE-	Semi-automatic	Considered only WMH



Department of Neurology Medical School University of Pécs (67)	11.2 yrs. old	by T1W and T2W	EPI Diffusion, GE-EPI Perfusion (3T)		agreed by two observers independently
Washington Heights/Hamilton Heights Aging Project (68)	Heterogeneous / > 65 yrs. old	Thresholding on FLAIR (3.5 standard deviation in pixel intensity above the mean of the fitted distribution of brain white matter as (2))	T1W, FLAIR (1.5T) (only FLAIR used for WMH segmentation)	Semi-automatic	-
Northern Manhattan Study (NOMAS) (69)	Heterogeneous, stroke-free / > 40 yrs. old (subsample > 55 yrs. old)	Thresholding on FLAIR (3.5 standard deviation in pixel intensity above the mean of the fitted distribution of brain white matter as (2))	FLAIR (1.5T)	Semi-automatic	Inter-rater reliability 0.99
Second Manifestations of ARterial disease MR (SMART-MR) Study (70)	Patients with symptomatic atherosclerotic disease / 58 ± 9 yrs. old at baseline	Multispectral (T1W,FLAIR) k-nearest neighbour probabilistic classifier (22)	T1W, T2W, FLAIR (1.5T)	Automatic	Similarity index, overlap fraction and extra fraction compared to manual WMH delineation (22)

Abbreviations: SPM: Statistic Parametric Mapping; WM: white matter; WMH: white matter hyperintensities; T1W: T1-weighted MRI; T2W: T2-weighted MRI; FLAIR: fluid attenuation inversion recovery; PD: proton density MRI sequence; DTI: diffusion-tensor image; DWI: diffusion-weighted image

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