

White Matter Hyperintensities Quantification in Healthy Adults: A Systematic Review and Meta-analysis

Abstract

Background: Although white matter hyperintensities (WMH) volumetric assessment is now customary in research studies, inconsistent WMH measures among homogenous populations may prevent the clinical usability of this biomarker.

Purpose: To determine whether a point estimate and reference standard for WMH volume in healthy aging could be determined.

Study Type: Systematic review and meta-analysis.

Population: 9716 healthy adult subjects from 38 studies reporting WMH volume which were retrieved following a systematic search on EMBASE.

Field Strength/Sequence: 1.0T, 1.5T or 3.0T/fluid-attenuated inversion recovery (FLAIR) and/or proton density/T2-weighted fast spin echo sequences or gradient echo T1.

Assessment: After a literature search, sample size, demographics, magnetic field strength, MRI sequences, level of automation in WMH assessment, study population and WMH volume were extracted.

Statistical Tests: The pooled WMH volume with 95% confidence interval (CI) was calculated using the random-effect model. The I^2 statistic was calculated as a measure of heterogeneity across studies. Meta-regression analysis of WMH volume on age was performed.

Results: Of the 38 studies analyzed, 17 reported WMH volume as mean and standard deviation (SD) and were included in the meta-analysis. Mean and SD of age was 66.11 ± 10.92 years (percentage of men $50.45\% \pm 21.48\%$). Heterogeneity was very high ($I^2 = 99\%$). The pooled WMH volume was 4.70 cm^3 (95% CI $3.88\text{-}5.53 \text{ cm}^3$). At meta-regression

analysis, WMH volume was positively associated with subjects' age ($\beta = 0.358 \text{ cm}^3$ per year, $P < 0.05$, $R^2 = 0.27$).

Data Conclusion: The lack of standardization in the definition of WMH together with the high technical variability in assessment may explain a large component of the observed heterogeneity. Currently, volumes of WMH in healthy subjects are not comparable between studies and an estimate and reference interval could not be determined.

Keywords: small vessel disease, white matter hyperintensities, image processing, segmentation.

Introduction

White matter hyperintensities (WMH) seen on T₂-weighted MRI brain scans are common radiological findings in adults, associated with a higher risk for developing stroke, dementia, gait disturbances and psychiatric diseases.^{1,2} Together with lacunes, microbleeds, and enlarged perivascular spaces, WMH are considered a neuroimaging biomarker of cerebral small vessel disease (SVD).³

The appearance of WMH is heterogeneous, ranging from focal to diffuse confluent lesions.⁴ Heterogeneity may result from a combination of different underlying etiology and histopathological changes.⁵ In the general population, WMH volume primarily depends on age more than other vascular risk factors.⁶ Modelling WMH volume heterogeneity in healthy aging would therefore be important for understanding its use in brain disease.⁷

Volumetry of WMH has become customary in research due to the availability of methods with high sensitivity for detecting small lesions and better reliability when compared to qualitative or semi-quantitative methods.⁸ Nevertheless, differences in imaging sequences, protocol parameters, and display settings can result in poor reproducibility of manual quantification when dealing with small WMH volumes.⁹ In this respect, the use of automated methods with intensity normalization has been strongly advised to improve reproducibility.¹⁰ Variability in quantitative assessment may arise at any stage, from image acquisition to image post-processing and interpretation of radiological findings.¹¹ The development and validation of a strong neuroimaging biomarker passes through different stages, from single center cross-sectional to large-scale studies.¹² As far as WMH are concerned, some aspects of validation are lacking with limited comparisons among segmentation tools and few longitudinal studies.¹³

The reproducibility estimation of WMH is crucial for the development of a surrogate biomarker for cerebral SVD. Bias sources in WMH volume estimation should be controlled

as much as possible, enabling comparison among different studies.¹¹ Studies on young subjects with small lesion volumes should also warrant high accuracy and good reproducibility. The same applies when following-up subjects for longitudinal WMH volume changes.⁸

Thus, the purpose of this study was to investigate the current source of bias in WMH volume assessment in healthy adults by conducting a systematic review and meta-analysis on currently available studies. By analyzing the variability in image acquisition protocols, postprocessing automatization levels and reported WHM volumes, we aimed to investigate whether a point estimate and reference standard for WMH volume could be determined.

Materials and Methods

No Ethics Committee approval was needed for this systematic review. The study protocol was registered on PROSPERO (BLINDED, Available from: <https://www.crd.york.ac.uk/prospero/>) and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.¹⁴

Search Strategy and Eligibility Criteria

A systematic search of the literature was performed on the 8th January 2020 using EMBASE (Elsevier) for articles focusing on WMH quantification in healthy adults. A controlled vocabulary (EMBASE thesaurus) was used.

The exact search query was: ('white matter hyperintensity'/exp OR 'white matter hyperintensity' OR 'leukoaraiosis' OR 'wmh' OR 'wml') AND ('quantitative analysis' OR 'quantification' OR 'volume' OR 'volumetric' OR 'white matter hyperintensity volume' OR 'white matter hyperintensity volume'/exp) AND ('aging' OR 'aging'/exp OR 'elderly' OR 'aged' OR 'aged'/exp OR 'elderly'/exp) AND ('normal human'/exp OR 'normal human' OR 'healthy'). The search was limited to original studies on humans, published since 2008 in peer-reviewed journals, written in English and provided with an abstract.

Three independent readers performed initial screening based on title and abstract only (LM, 4 years of experience in medical imaging; MB and EO, 1 year of experience each). Eligible articles were those that reported in the abstract that quantification of WMH volume in healthy participants was performed. Subjects from community-dwelling longitudinal cohorts or control subjects from case-control studies were deemed healthy unless any neurological, psychiatric and cognitive conditions were explicitly stated. When provided, detailed information about subjects' health status was further characterized as the absence of

neurological, psychiatric, cognitive, cardiovascular or major (both inherited and acquired) diseases.

Eligible articles were then retrieved and read in full by the same three readers who performed initial screening. Disagreements between readers were resolved by the decision of a fourth independent reviewer (MC, 7 years of experience in medical imaging), who had the final say over any disagreement between the three readers.

Data Extraction

Data extraction was independently performed by the same reviewers who performed the initial screening using the same two-steps selection protocol. Manuscripts with unclear presentation of data (e.g. unspecified unit of measurement for WMH volumes) or missing WMH volumes data were discarded. Finally, in order to perform the subsequent meta-analysis, only articles that reported the total WMH volume expressed as mean and standard deviation (SD) were included.

Data extracted included: first author's family name and year of publication; subjects' demographics; sample size and clinical history and WMH volume of participants included in each study. Moreover, we collected the level of automation for WMH volume assessment (manual, semi-automated, or automated); magnetic field strength; MRI sequences adopted.

Statistical Analysis

Statistical analysis was performed using Comprehensive Meta-Analysis v2.2.057 (Biostat, Englewood, NJ, USA). First, the I^2 statistic was calculated which estimates the percentage of variability across studies that is due to heterogeneity rather than chance.^{15,16} The random-effect model with the DerSimonian and Laird method, suitable for handling heterogeneous data, was used to calculate the pooled WMH volume and its 95% confidence interval (CI).¹⁷

If statistical heterogeneity was low, a pooled SD would be calculated as the root mean square of all contributing study SD values to take into account each study sample size, and the reference range built as the WMH pooled volume ± 2 pooled SD.¹⁸

Potential sources of heterogeneity were evaluated by meta-regression and subgroup analysis. Meta-regression analysis was performed to assess the correlation between WMH volume and subjects' age. Due to nonlinearity of WMH changes with age,¹⁹ we performed a second meta-regression analysis after excluding all studies involving young subjects (< 50 years old). This threshold was established as subjects less than 50 years old are expected to carry an extremely low WMH burden.⁶

Subgroup analysis with the random-effect model was performed to investigate the effect of the magnetic field strength and the level of automation used for WMH assessment on WMH volume.

Statistical significance threshold was set at $P < 0.05$.

Risk of Bias

For quality appraisal, we relied on the risk of bias assessment using RevMan version 5.4.1 (Review Manager software, Cochrane Collaboration) as performed in a similar study.²⁰ We selected the risk of bias items excluding those referred to randomization ("random sequence generation") and blinding ("blinding of participants" and "personnel and blinding of outcome assessment") as they were unrelated to the design of this review. We evaluated the "Allocation concealment" (selection bias) by assessing the characterization of the health status of subjects included in the analyzed studies. "Incomplete outcome data" (attrition bias) referred to the handling of potential missing data, while "Selective reporting" (reporting bias) was suspected if the analyzed data were not fully reported. For the "Other bias" item we

considered potential confounders related to WMH volume assessment (imaging protocols and operators' years of experience when manual segmentation was performed).

The risk of publication bias was instead assessed by visually inspecting funnel plots and performing the Egger test and Kendall's tau.¹⁶

Results

Retrieved and Selected Literature

A flowchart of the literature search is shown in (**Fig. 1**). From the initial search, 162 articles were retrieved with 38 of them being analyzed.^{19,21–57} All included studies were prospective; five had an intra-individual study design with two^{21,24,31,40} or three study groups¹⁹ that were examined separately. In those cases, study groups were considered to be independent, resulting in a total of 44 study groups from the 38 articles.

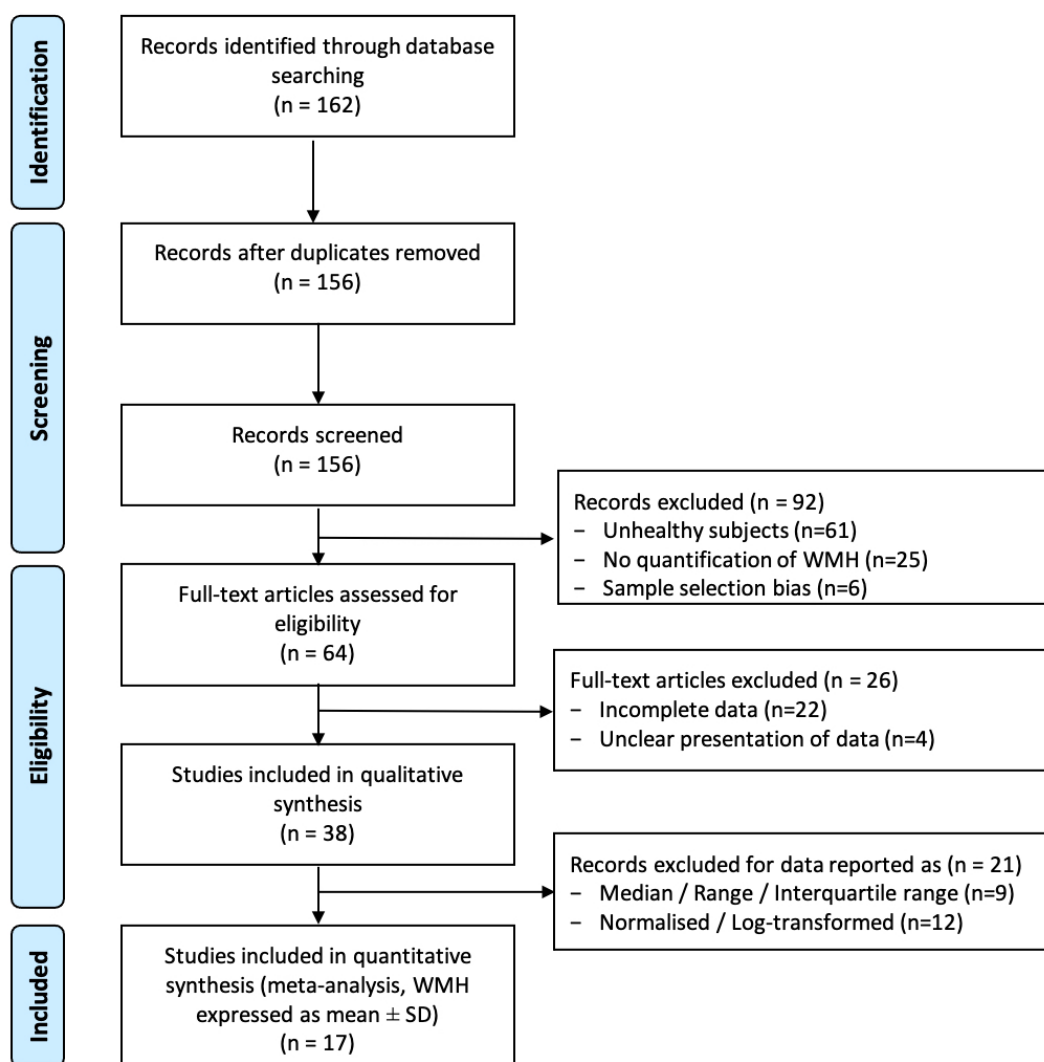


FIGURE 1: Flow chart of the literature search. Of the 162 initially retrieved articles, 38 were included in the qualitative synthesis and 17 in the meta-analysis.

Qualitative Analysis of the Included Studies

The number of healthy subjects in each study group included ranged from 9³⁹ to 2640,⁵⁴ resulting in a total of 9716 subjects.

Participants mean and SD age was 66.11 ± 10.92 years. Mean age in the analyzed subjects ranged from 26¹⁹ to 84 years.⁴⁹ Mean \pm SD percentage of men in the reviewed articles was $50.45\% \pm 21.48\%$. None of the healthy subjects had any disclosed disease. When explicitly stated, patients' history included absence of prior neurological disorders (42/44 study groups, 95%), psychiatric illnesses (31/44 study groups, 70%), cognitive impairments (35/44 study groups, 80%), cardiovascular diseases (12/44 study groups, 27%) or major diseases (12/44 study groups, 27%).

Magnetic field strength was 1.0 T in 1/44 (2%) of the contributing study groups, 1.5-T in 11/44 (25%), 3-T in 28/44 (64%), mixed in 2/44 (4%) and not reported in 2/44 (4%).

Out of 44 study groups, 35 (79%) used fluid-attenuated inversion recovery (FLAIR) images for WMH segmentation, 6 (14%) used combined proton density and T₂-weighted images, 1 (2%) used T₂-weighted images only and 2 (4%) used T₁-weighted images only. The quantitative assessment of WMH volume was automated in 17/44 (39%) study groups, semi-automated in 25/44 (57%) and manual in 2/44 (4%). Detailed demographics of subject included in all study groups are presented in **Supplemental Table S1**.

WMH Volume Meta-analysis

Seventeen articles with a total of 21 study groups reported quantitative data for WMH

volume as mean \pm SD and were therefore included in the meta-analysis^{19,21,23,26–}

^{28,31,33,37,39,42,43,46,48,49,52,57}. The total number of healthy subjects included in the meta-analysis was 2743. Detailed demographics of these subjects are presented in Table 1.

In analyzed studies, WMH volume ranged from 0.11¹⁹ (study group *a*, see Fig.2) to 14.16 cm³.³⁷ Analyzed data showed high heterogeneity ($Q = 2914$, degrees of freedom = 20, $I^2 = 99\%$, $P < 0.05$). Standard deviation of WMH volumes ranged from 0.26¹⁹ (study group *a*, see Fig.2) to 12.61 cm³ ¹⁹ (study group *c*, see Fig.2). Using the random-effect model we obtained a pooled WMH volume of 4.70 cm³ (95% CI 3.88-5.53 cm³), as depicted in the Forest plot (Fig. 2). The risk of bias graph (Supplemental Fig. S1) and the risk of bias summary (Supplemental Fig. S2) showed overall moderate selection and other biases and low attrition and reporting biases. At visual inspection, the funnel plot (Supplemental Fig. S3) showed a moderate risk of publication bias, as confirmed by the Egger test ($P < 0.05$) and the Kendall's Tau ($b = 0.033$; $P > 0.05$).

Forest plot

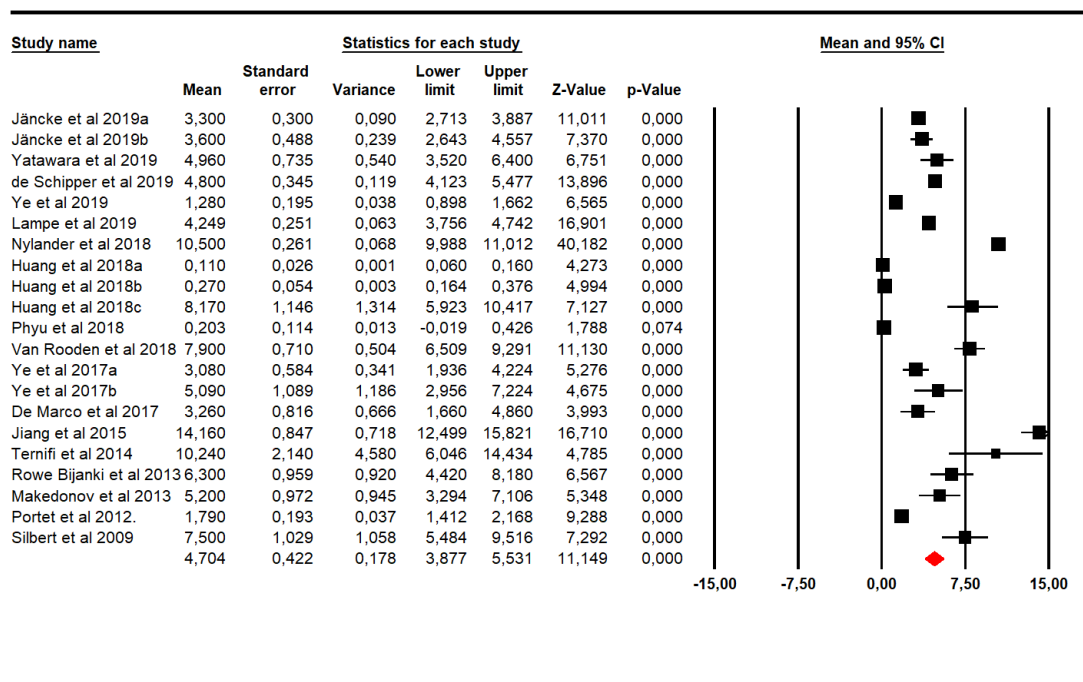


FIGURE 2: Forest plot of the 17 analyzed studies, with a total of 21 independent study groups. The forest plot is a graphical representation of the results of the meta-analysis. The studies are represented by squares whose area is proportional to the weight of that study in the analysis. Since this analysis is based on the random-effects model, the weight is the

inverse of the total variance (within and between study variance) for each study. Heterogeneity among studies was very high ($I^2 = 99\%$). The last row shows the pooled WMH volume.

Meta-regression Analysis

Meta-regression analysis performed in the 21 study groups showed a positive statistically significant correlation between WMH volume and age (Intercept $\beta_0 = -7.030$, $P < 0.05$; $\beta_{WMH} = 0.182 \text{ cm}^3$ per year of age, $P < 0.05$; $R^2 = 0.00$) (**Supplemental Fig. S4**). The second meta-regression performed excluding three study groups with mean subjects' age below 50 years showed a higher positive correlation between WMH volume and subjects' age (Intercept $\beta_0 = -19.349$, $P < 0.05$; $\beta_{WMH} = 0.358 \text{ cm}^3$ per year of age, $P < 0.05$; $R^2 = 0.27$) (**Fig. 3**).

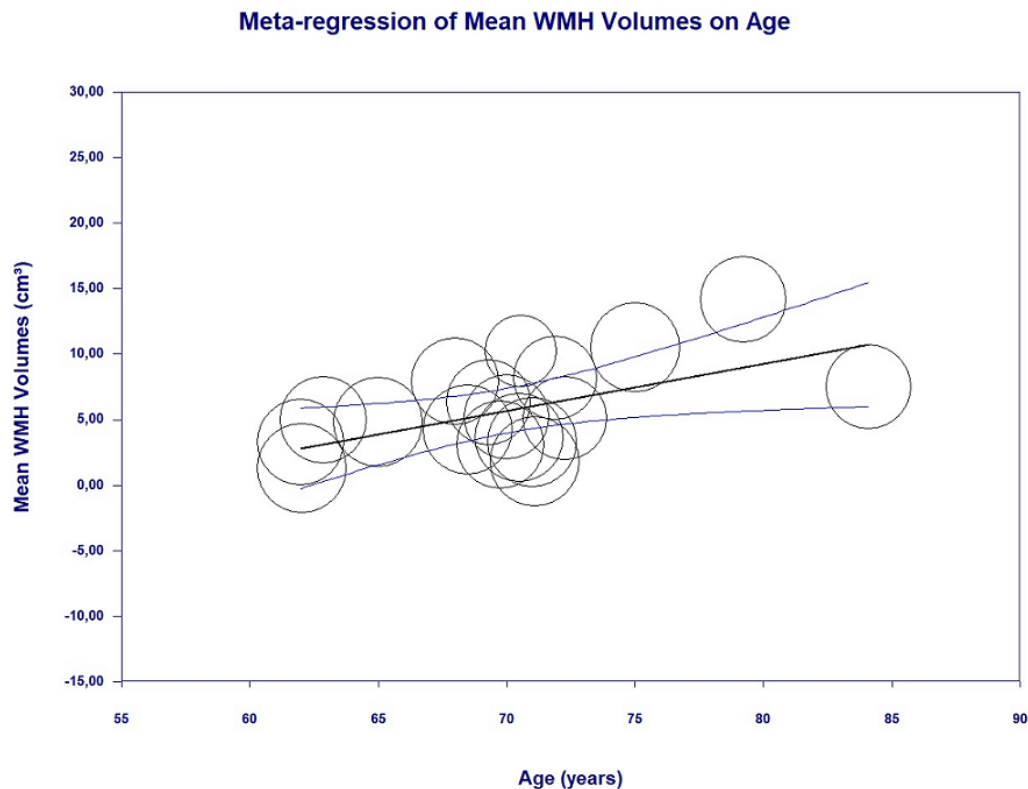


FIGURE 3: Meta-regression plot of WMH volumes on age after exclusion of 3 study groups with mean subjects' age < 50 years and mean WMH volumes close to 0 cm^3 . Eighteen study groups were included in the analysis. The area of each circle is proportional to the weight of that study in the analysis. Since this analysis was based on the random-effects model, the weight is the inverse of the total variance (within and between study variance) for each study.

Subgroup Analysis

Subgroup analysis showed a significant effect on WMH volume of the magnetic field strength ($P < 0.05$). The pooled WMH volume from studies using 1.5-T magnetic field strength was 7.87 cm^3 (95% CI $5.26\text{-}10.47 \text{ cm}^3$). The pooled WMH volume from studies using 3.0 T magnetic field strength was 3.82 cm^3 (95% CI $3.16\text{-}4.49 \text{ cm}^3$) (**Supplemental Fig. S5**). Median age and interquartile range (IQR) for participants from studies included in the meta-analysis at 1.5-T and 3.0-T were 70.56 (69.65-79.55) years and 68.00 (61.98-71.00) years respectively.

A significant difference in pooled WMH volume based on the level of automation was also found ($P < 0.05$). The pooled WMH volume from studies using a manual method was 6.86 cm^3 (95% CI $5.48\text{-}8.24 \text{ cm}^3$), from those using a semiautomated method was 4.63 cm^3 (95% CI $1.54\text{-}7.72 \text{ cm}^3$), from those using an automated method was 4.47 cm^3 (95% CI $3.68\text{-}5.26 \text{ cm}^3$) (**Supplemental Fig. S6**). Mean ages of healthy subjects in the only two studies which relied on manual assessment methods were 69.3 years⁴² and 84.1 years.⁴⁹ Median ages and IQR of participants from studies included in the meta-analysis which relied on semiautomated and automated methods for the WMH volume assessment were 70.28 (IQR $55.79\text{-}72.08$) years and 66.5 (IQR $62.02\text{-}70.63$) years respectively.

Discussion

To the extent of our knowledge, several studies^{58–60} investigated the reproducibility of WMH volumetric measures within specific centers but no report has investigated inter-center reproducibility.¹¹ The main result of our systematic review was a high heterogeneity in WMH volume. Even though we only selected studies with healthy subjects, risk factors for cerebral SVD, such as hypertension, low cardiac ejection fraction, carotid atherosclerosis and atrial fibrillation, may have been unreported. Varying prevalence of these conditions may have contributed to the observed heterogeneity.⁶¹

We focused on age as the most important unmodifiable risk factor for WMH volume.⁶ When considering only subjects older than 50 years, the meta-regression analysis showed a positive significant correlation between WMH volume and age. Age explained less than one third of the variance in WMH volume. Apart from potential unreported conditions, the remaining variance could be explained by a combination of the WMH biological (i.e. intrinsic) and technical variability.

Since translational neuroimaging studies aim at extracting the potential diagnostic and prognostic value of imaging biomarkers,⁶² it is important to reveal the WMH biological variability by removing or modeling the technical sources of bias in the WMH assessment process.

The majority of the analyzed study groups employed 3-T magnets. The pooled WMH volume was lower in studies employing 3-T scanners than in those using 1.5-T scanners. This finding is partially in contrast with a previous study that reported an underestimation of WMH volume with lower field scanners, but also increased non-focal WMH and flow artefacts at higher field strength.⁶³ Notably, the 3-T studies in our meta-analysis included the three study groups with mean age less than 50 years and a mean WMH volume close to 0 cm³. Including these relatively young, low WMH volume groups in our analysis has contributed to the observed finding.

Level of automation in WMH segmentation was also significantly different across studies. Studies of relatively young subjects generally adopted automated methods, while WMH tended to be

manually segmented in studies involving older participants. This difference in age, more than any technical aspects related to partial volume effect and thresholding, may have contributed to the observed differences in the WMH pooled volumes.

Optimally, to keep technical variability to a minimum, standardized imaging protocols for investigating SVD should be used.³ It is advisable to deploy high-resolution isotropic FLAIR imaging on 3.0-T scanners to study WMH.³ Harmonization strategies such as correction for B₁ inhomogeneities should then be adopted to reduce heterogeneity within and across MRI scanners.⁶⁴ Moreover, the availability of several automated methods for WMH segmentation may represent a technical source of bias.^{10,65,66} The best-performing method should be identified among coexisting solutions after extensive testing on a common external dataset segmented by multiple experts and combined by consensus or using label fusion algorithms.⁶⁷

Rigorous anatomical definition of WMH is also of paramount importance. Previous initiatives for standardization and harmonization in WMH assessment did not address the sources of variability in the segmentation process.¹³ For instance, the innermost segment of periventricular WMH could either be segmented as WMH⁶⁸ or disregarded as partial volume or cerebrospinal fluid flow artefact.⁶⁹ Moreover, thin white matter bundles such as structures that belong to the limbic system and white matter bundles intermixed with deep gray matter structures are usually not considered in the anatomical operational definition of white matter used in structural brain MRI segmentation, although WMH in these bundles may carry significant clinical impact.⁷⁰ Pathology and clinically oriented study should guide the choice towards a standardized criterion for WMH segmentation. An endorsed anatomical definition of WMH would also increase the performance of supervised segmentation algorithms by ameliorating the quality of the labelled training set.

Limitations

The main limitation of this study is the relatively small number of meta-analyzed study groups which, combined with a high heterogeneity among them, impeded us from providing a point

estimate and reference normality interval for WMH volume in healthy adults. To increase availability of studies, it is essential that descriptive statistics of the original imaging data is always reported alongside to the transformed metrics.

Moreover, in this review we did not address the issue of slice thickness. The impact of slice thickness on lesion detection has been investigated in multiple sclerosis. In these studies, authors found only minor differences in the distribution of texture analysis parameter values in white matter lesions for 1-mm and simulated 3-mm-thick slices.⁷¹ In our review and meta-analysis, slice thickness values were highly heterogeneous across the included studies. Most recent studies, especially those preformed at 3-T, employed volumetric acquisitions with about 1 mm isotropic voxel size.^{21,23,26,28,57} Other studies acquired axial slices with 2^{27,52}, 3^{19,42,46}, 4^{48,49}, or even 5 mm^{31,39} slice thickness. Thicker slices can lead to both overestimation of larger lesions and underestimation of smaller lesions. For this reason, we cannot exclude that varying slice thickness across the examined studies might have contributed to the observed differences in pooled WMH volume between scanner strength and level of automation sub-groups.

Conclusions

At the current time, data on WMH volume in healthy adults appear to be not comparable across studies. We stress the need for achieving better standardization in WMH quantification and reporting and encourage international initiatives aimed at promoting this.

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TABLE 1. Main characteristics of the 21 study groups included in the quantitative synthesis.

Study	N	Men (%)	Age (years)	MFS	Sequence	Level of automation	Healthy subjects: free of	Part of population study	WMH volume (cm ³)
Jäncke et al 2019 (1st sex subgroup)	107	100	71	3.0	T1-weighted	Automated	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	N.A.	3.30 ± 3.10*
Jäncke et al 2019 (2nd sex subgroup)	109	0	70	3.0	T1-weighted	Automated	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	N.A.	3.60 ± 5.10*
Yatawara et al 2019	79	41	63	3.0	FLAIR	Automated	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	N.A.	4.96 ± 6.53*
de Schipper et al 2019	218	63	65	3.0	FLAIR	Automated	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	Leiden Longevity Study	4.80 ± 5.10*
Ye et al 2019	33	48	62	3.0	FLAIR	Semi-automated	<input checked="" type="checkbox"/> Neurological <input type="checkbox"/> Psychiatric <input type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	N.A.	1.28 ± 1.12*
Lampe et al 2019	702	54	68	3.0	FLAIR	Automated	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	LIFE (Leipzig Research Centre for Civilization Diseases)-Adult-Study	4.25 ± 6.66*
Nylander et al 2018	396	N.A.	75	1.5	PD/T2-weighted	Semi-automated	<input checked="" type="checkbox"/> Neurological <input type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)	10.50 ± 5.20*
Huang et al 2018 (1st age subgroup)	102	53	26	3.0	FLAIR	Automated	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input checked="" type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	N.A.	0.11 ± 0.26*
Huang et al 2018 (2nd age subgroup)	89	33	50	3.0	FLAIR	Automated	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input checked="" type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	N.A.	0.27 ± 0.51*

Huang et al 2018 (3rd age subgroup)	121	61	72	3.0	FLAIR	Automated	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input checked="" type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	N.A.	8.17 ± 12.61*
Phyu et al 2018	18	50	37	3.0	PD/T2-weighted	Semi-automated	<input checked="" type="checkbox"/> Neurological <input type="checkbox"/> Psychiatric <input type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	N.A.	0.20 ± 0.48*
Van Rooden et al 2018	42	40	68	3.0	FLAIR	Automated	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	N.A.	7.90 ± 4.60*
Ye et al 2017	64	45	70	3.0	FLAIR	Automated	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input checked="" type="checkbox"/> Major diseases	N.A.	3.08 ± 4.67*
Ye et al 2017 (Not-cognitively declining subgroup of the sample above at 35 months follow up)	43	44	72	3.0	FLAIR	Automated	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input checked="" type="checkbox"/> Major diseases	N.A.	5.09 ± 7.14*
De Marco et al 2017	51	31	62	3.0	FLAIR	Automated	<input checked="" type="checkbox"/> Neurological <input type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	N.A.	3.26 ± 5.83*
Jiang et al 2015	155	43	79	3.0	FLAIR	Automated	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input checked="" type="checkbox"/> Major diseases	Sidney Memory and Aging Study	14.16 ± 10.55*
Ternifi et al 2014 ³⁹	9	0	71	1.5	FLAIR	Semi-automated	<input checked="" type="checkbox"/> Neurological <input type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input checked="" type="checkbox"/> Cardiovascular <input checked="" type="checkbox"/> Major diseases	N.A.	10.24 ± 6.42*
Bijanki et al 2013	22	45	69	1.5	FLAIR	Manual	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input checked="" type="checkbox"/> Cardiovascular <input checked="" type="checkbox"/> Major diseases	Aging, Vascular Disease, and Cognition	6.30 ± 4.50*
Makedonov et al 2013	50	46	70	1.5	PD/T2-weighted	Semi-automated	<input checked="" type="checkbox"/> Neurological <input type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	N.A.	5.20 ± 6.88*

Portet et al 2012	274	41	71	N.A.	T2-weighted	Semi-automated	<input checked="" type="checkbox"/> Neurological <input type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input checked="" type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	ESPRIT (Enquête de Santé Psychologique - Risques, Incidence et Traitement)	1.79 ± 3.19*
Silbert et al 2009	49	47	84	1.5	PD/T2-weighted	Manual	<input checked="" type="checkbox"/> Neurological <input checked="" type="checkbox"/> Psychiatric <input checked="" type="checkbox"/> Cognitive <input checked="" type="checkbox"/> Cardiovascular <input type="checkbox"/> Major diseases	Oregon Brain Aging Study	7.50 ± 7.20*

Age values are presented as the means. MFS = magnetic field strength, FLAIR = fluid-attenuated inversion recovery, PD = proton density, WMH = white matter hyperintensities.

* Mean and standard deviation

^ Median and interquartile range.

Figure Legends

FIGURE 1: Flow chart of the literature search. Of the 162 initially retrieved articles, 38 were included in the qualitative synthesis and 17 in the meta-analysis.

FIGURE 2: Forest plot of the 17 analyzed studies, for a total of 21 independent study groups. The forest plot is a graphical representation of the results of the meta-analysis. The studies are represented by squares whose area is proportional to the weight of that study in the analysis. Since this analysis is based on the random-effects model, the weight is the inverse of the total variance (within and between study variance) for each study. Heterogeneity among studies was very high ($I^2 = 99\%$). The last row shows the pooled WMH volume.

FIGURE 3: Meta-regression plot of WMH volumes on age after exclusion of 3 study groups with mean subjects' age < 50 years and mean WMH volumes close to 0 cm³. Eighteen study groups were included in the analysis. The area of each circle is proportional to the weight of that study in the analysis. Since this analysis was based on the random-effects model, the weight is the inverse of the total variance (within and between study variance) for each study.

FIGURE 1

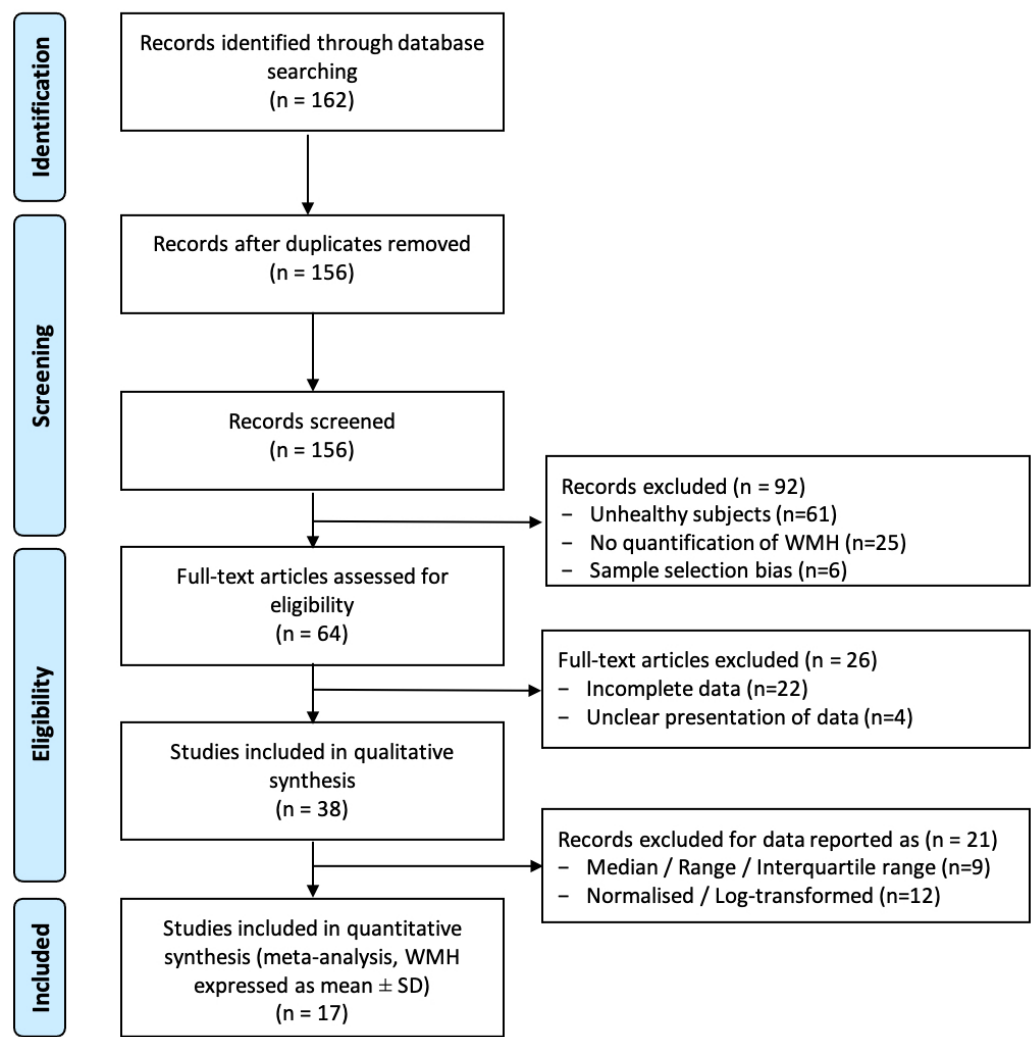


FIGURE 2

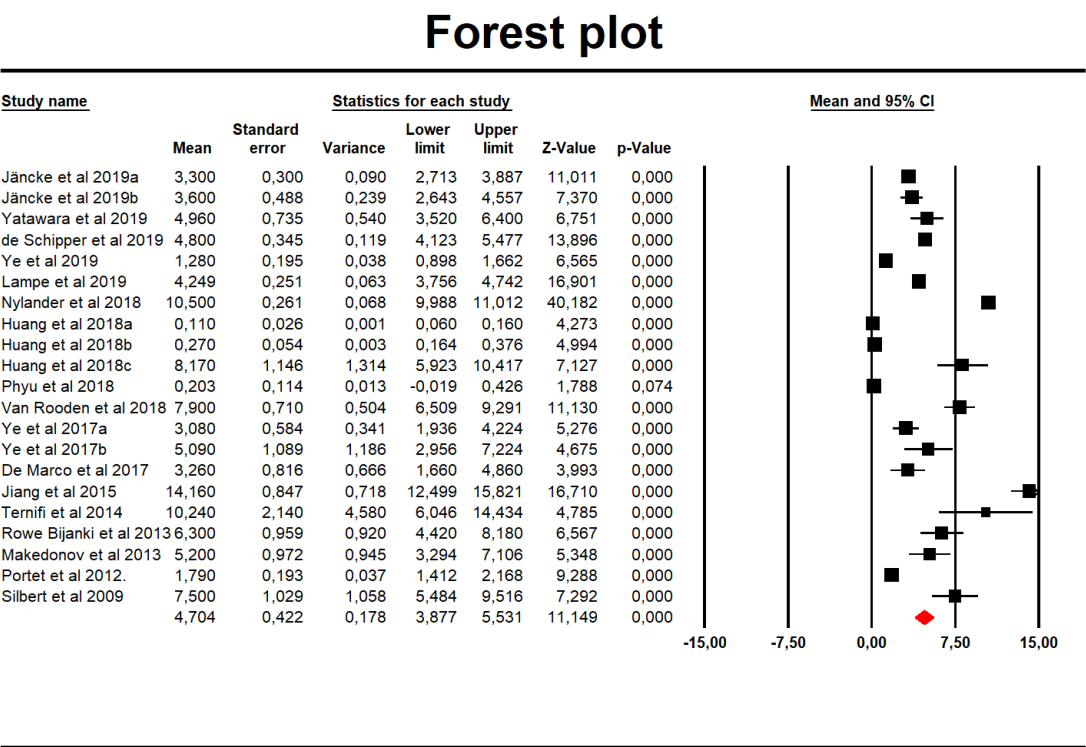


FIGURE 3

