Characterization of White Matter Hyperintensities in Large-Scale MRI-Studies

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**Background:** White matter hyperintensities of presumed vascular origin (WMH) are a common finding in elderly people and a growing social malady in the aging western societies. As a manifestation of cerebral small vessel disease, WMH are considered to be a vascular contributor to various sequelae such as cognitive decline, dementia, depression, stroke as well as gait and balance problems. While pathophysiology and therapeutical options remain unclear, large-scale studies have improved the understanding of WMH, particularly by quantitative assessment of WMH. In this review, we aimed to provide an overview of the characteristics, research subjects and segmentation techniques of these studies.

**Methods:** We performed a systematic review according to the PRISMA statement. One thousand one hundred and ninety-six potentially relevant articles were identified via PubMed search. Six further articles classified as relevant were added manually. After applying a catalog of exclusion criteria, remaining articles were read full-text and the following information was extracted into a standardized form: year of publication, sample size, mean age of subjects in the study, the cohort included, and segmentation details like the definition of WMH, the segmentation method, reference to methods papers as well as validation measurements.

**Results:** Our search resulted in the inclusion and full-text review of 137 articles. One hundred and thirty-four of them belonged to 37 prospective cohort studies. Median sample size was 1,030 with no increase over the covered years. Eighty studies investigated in the association of WMH and risk factors. Most of them focussed on arterial hypertension, diabetes mellitus type II and Apo E genotype and inflammatory markers. Sixty-three studies analyzed the association of WMH and secondary conditions like cognitive decline, mood disorder and brain atrophy. Studies applied various methods based on manual (3), semi-automated (57), and automated segmentation techniques (75). Only 18% of the articles referred to an explicit definition of WMH.

**Discussion:** The review yielded a large number of studies engaged in WMH research. A remarkable variety of segmentation techniques was applied, and only a minority referred to a clear definition of WMH. Most addressed topics were risk factors and secondary clinical conditions. In conclusion, WMH research is a vivid field with a need for further standardization regarding definitions and used methods.

**Keywords:** white matter hyperintensities, white matter lesions, systematic review, large-scale studies, white matter hyperintensity segmentation, segmentation, cerebral small vessel disease
INTRODUCTION

Cerebrovascular disease represents a major burden on an individual as well as societal level, with growing importance in the aging western societies. Stroke as the most prominent example is the second most frequent cause of death in the world and the most frequent cause of acquired permanent disability (1). Vascular dementia represents another manifestation of cerebrovascular disease and is the second most frequent type of dementia following Alzheimer’s disease (2). In Alzheimer’s disease, cerebrovascular pathology is also a frequent finding (3). Among other causes, these disease entities are considered to be associated with cerebral small vessel disease (CSVD). CSVD comprises different structural changes observed in post-mortem or in-vivo brain imaging, all of them related to alterations of small brain arteries. These include small subcortical infarcts, lacunes, dilated perivascular spaces, cerebral microbleeds, and particularly white matter hyperintensities of presumed vascular origin (WMH).

According to the Standards for Reporting Vascular changes on Neuroimaging (STRIVE)—an international consensus on the definition of cerebral small vessel disease—WMH are hyperintensities on T2-weighted magnetic resonance images (MRIs), which are located in the white matter and of varying size (4). Affecting preferentially the elderly, WMH are associated with cognitive impairment, mortality, increased risk of stroke and play a role in the development of late-onset depression (5–7). They are further considered to worsen gait (8), balance (9), and urinary function (10). Common cardiovascular risk factors associated with WMH (11), include hypertension (12), smoking (13), and diabetes (14). Nevertheless, the exact etiology and pathogenesis of WMH, as well as their role in neurodegeneration, is not fully understood. Therefore, further research on WMH is necessary to clarify these questions and guide future treatment and preventive interventions.

For epidemiological research, quantitative assessment of WMH is a crucial requirement for adequate analysis of associated risk factors and clinical deficits. Semi-quantitative assessments using visual rating scales (15, 16) carry certain disadvantages such as limited accuracy, high intra- and inter-rater-variation (17), low comparability (18), and inadequate depiction of longitudinal changes (19). Moreover, visual rating scales usually do not reflect precise localization of observed WMH. Although correlating with visual rating scales (20), quantitative measurements based on WMH segmentation offer a more reliable, sensitive, and objective alternative (21), which also enables the anatomical analysis. Technically, WMH segmentation is the process of subdividing image voxels into subgroups based on predefined features such as signal intensity. Figure 1 illustrates representative results of different segmentation techniques for exemplary purposes. Since segmenting brain lesions by hand is a highly demanding process, the vivid research field produced various automated and semi-automated segmentation techniques (24). Nevertheless, there are no standardized approaches to quantitative or semi-quantitative WMH segmentations. Also, inconsistent definitions of WMH (4) and differing standards for the qualitative evaluation and quantitative comparison of the results to a so-called gold standard exist, not to mention the reporting of these. The research community has recognized these problems and addressed them over the last years, with the STRIVE as a major milestone achieved in 2013: in this position paper, experts in the field provided an unification of cerebral small vessel disease definitions including a clear definition of white matter hyperintensities of presumed vascular origin (4).

Currently, there is accumulating evidence pointing to a clinical relevance of WMH, substantially driven by large-scale studies. Thus, standardization of methodological approaches for WMH characterization in these studies is of crucial importance. In this systematic review, we provide an overview of large-scale studies assessing WMH quantitatively over the past 14 years. We describe their characteristics, research subjects, approaches on WMH segmentation, and the study-specific and general development of segmentation techniques. Furthermore, we continue the discussion about the heterogeneity issues in this particular field of research. By this, we aim to contribute to the unification work of the field started previously by other research groups.

METHODS

We conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement (25). The review protocol was not registered in advance, the completed PRISMA checklist can be found in the Supplementary Material.

Search Strategy and Study Selection

The methods of study selection, including searched data sources and selection criteria, were determined in advance. Two reviewers (BF, MP) carried out the literature research in December 2018 by searching the online-database Pubmed for eligible records. Search terms and applied filters are presented in the Supplementary Material.

Study selection was performed by both reviewers independently by screening abstracts or if necessary full-text papers for exclusion criteria. Exclusion criteria were specified as follows: (1) sample size <500, (2) a publication date earlier than 01.01.2005, (3) age <18 years, (4) written in another language than English, (5) no WMH segmentation has been performed, (6) review articles, (7) investigation of WMH of non-vascular origin (studies on WMH occurring in inflammatory or neurodegenerative conditions like multiple sclerosis, lupus, Sneddon syndrome, Huntington-like diseases, neurofibromatosis, leukodystrophies, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, Fabry disease, sickle cell disease, progressive multifocal leukoencephalopathy, cerebral amyloid angiopathy, posterior leukoencephalopathy syndrome). Studies were included if no exclusion criteria were met.
FIGURE 1 | Example of segmentation of white matter hyperintensities (WMH) using different approaches. The figure shows an example from an own unpublished dataset: (1) FLAIR showing typical distribution of WMH, (2) manual segmentation rater 1 (MP), (3) manual segmentation rater 2 (CM), (4) automated segmentation via Lesion growth algorithm (LGA) of LST toolbox version 2.0.15 (22), (5) automated segmentation via Lesion prediction algorithm (LPA) also of LST toolbox, (6) automated segmentation via the Brain Intensity AbNormality Classification Algorithm (BIANCA) implemented in FSL (23).

Data Extraction and Analysis
Data extraction was conducted independently by both reviewers reading the full-text articles. Resulting data were cross-checked afterwards. Extracted information included the name of the population study the articles belong to, year of publication, sample size, mean age of subjects in the study, the cohort included, and segmentation details like the definition of WMH, the segmentation method, reference to methods papers as well as validation measurements. Additionally, referenced methods papers were surveyed for further details on segmentation methods. All descriptive results are given by the mean ± the standard error of the mean. Data that was not available is reported as missing as long as there was no possibility to compute it.

In accordance with previous work in this field, the methods underlying the image segmentation were categorized into manual, semi-automated, and automated (24). A method was considered “manual” if the researcher annotates all lesion voxels himself; “semi-automated,” if the researcher intervenes in certain situations and “automated,” if there is no necessity of human intervention in the computing process. The latter was again classified in supervised and unsupervised depending on whether or not the classification algorithm requires a previously produced reference segmentation dataset, defining the affiliation of voxels to a particular group, e.g., WMH or non-WMH.

Furthermore, papers were characterized by the type of the underlying research question related to WMH, i.e., whether they studied the association of risk factors and WMH, the influence of WMH on a certain pathology, both directions of causation, or neither of them. All research subjects (e.g., IL-6 or CRP) were extracted and assigned to subcategories defined by umbrella terms (e.g., Inflammatory markers). Since age and sex are regularly control variables, they are not mentioned as distinct research subjects.

RESULTS
Search Results
A flowchart summarizing the search and selection process is provided in Figure 2. Applying the aforementioned search terms and filters, the PubMed search yielded 1,196 potentially relevant records. We ruled out 1,065 of them as they met the exclusion criteria. Six further articles classified as relevant were added manually. A total of 137 articles fitting the criteria remained and were included in this systematic review. An overview of the six studies with most included articles is also part of the results section, encompassing study characteristics and their segmentation approach.
Study Characteristics

The main characteristics of the studies incorporated in this review are shown in Table 1. 137 articles were included, whereas 134 belonged to 37 large-scale prospective cohort studies Box 1 delineates the 5 cohort studies that contributed the most articles to this review. The median sample size was 1,030, ranging from 501 to 9,361. Mean study sample size did not increase over the 14 years investigated (Figure 3). The mean age of subjects in the studies ranged from 46 to 83 years with a total mean of 67 ± 0.8 years. Regarding sample characteristics, 88 of the 137 studies described investigations in a standard population, while 32 included patients with a specific pathology. Seventeen studies compared their pathological cohort with a healthy control group. Concerning the underlying research question, 80 studies analyzed the relationship of risk factors and WMH, which could be categorized into 50 different thematic groups (Table 2). Sixty-four studies examined the link of WMH to diseases and vice versa, covering 25 different thematic groups (Table 3). Two papers did not fit this way of categorization. Their research subjects were "White matter hyperintensities and normal-appearing white matter integrity in the aging brain" (121) and "Incidental Findings on MRI" (122). Two studies, the Leukoaraiosis And DISability Study (LADIS) and the Genetics of Microangiopathic Brain Injury (GMBI) study, were originally established especially for research in WMH and their associations, not for other or more general topics.

Segmentation

Definition of White Matter Hyperintensities

Only 24 (17.5%) articles contained an explicit definition of WMH. The remaining studies either gave an implicit explanation through their segmentation method or had no specific definition of WMH. Of the studies included in our review, 72 were published since 2014, i.e., after publication of the STRIVE paper. Of these, 15 defined WMH explicitly, 10 of them according to STRIVE. Forty-seven studies did not refer to any explicit definition of WMH at all.

Segmentation Types and Segmentation Techniques

The largest proportion of studies applied automated segmentation techniques: supervised and unsupervised segmentation were used in 60 and 15 articles, respectively. Fifty-seven articles described a semi-automated segmentation technique, while only 3 papers relied on manual segmentation.
| Cohort study | Incorporated articles | Years published | Mean sample size | Mean age | Sample Segmentation method | Gold standard | Methods paper |
|--------------|----------------------|-----------------|------------------|---------|-----------------------------|---------------|--------------|
| 3C           | 15                   | 2008–2017       | 1493             | 72      | HS                          |               |              |
| ADNI         | 3                    | 2010–2015       | 752              | 75      | MS: MCI/AD                  |               |              |
| AGES-Reykjavk| 7                    | 2009–2015       | 3975             | 76      | HS                          | Manual segmentation | (28) |
| ARIC MRI     | 4                    | 2013–2016       | 1193             | 65      | HS                          | Manual segmentation | (33) |
| ARIC-NCS     | 1                    | 2017            | 1713             | 75      | MS: Atherosclerosis Risk    | Manual segmentation | (33) |
| ASPS         | 1                    | 2016            | 762              | 65      | HS                          | None          | None         |
| ASPS/ASPFS   | 1                    | 2014            | 584              | 67      | HS                          | None          | None         |
| CDOT         | 1                    | 2013            | 713              | 70      | MS: DM II                  | Manual segmentation | (31) |
| CHAP         | 2                    | 2010-2014       | 573              | 80      | MS: dementia                | Manual segmentation | (32, 33) |
| CHARGE       | 1                    | 2011            | 9361             | 70      | MS: Miscellaneous            | None          | None         |
| EVA          | 1                    | 2011            | 780              | 69      | HS                          | Visual rating scales | (27) |
| FHS          | 1                    | 2017            | 1527             | 60      | HS                          | Manual segmentation | (32, 33) |
| FOS          | 13                   | 2007–2018       | 1398             | 62      | HS                          | Manual segmentation | (32, 33) |
| FOS/FHS      | 1                    | 2005            | 2081             | 62      | HS                          | Manual segmentation | (32, 33) |
| GEN III      | 1                    | 2016            | 1995             | 46      | HS                          | Manual segmentation | (32, 33) |
| GeneSTAR     | 2                    | 2014–2015       | 654              | 51      | MS: Relatives of early onset CHD patients | Manual segmentation | None |
| GENOA/GMBI   | 4                    | 2007–2017       | 1182             | 62      | MS: Siblings of hypertensive patients, antihypertensive medication | Intensity thresholding, unsupervised | Manual segmentation | (30) |
| HUNT MRI     | 1                    | 2018            | 862              | 59      | HS                          | None          | None         |
| ILAS         | 1                    | 2018            | 802              | 59      | HS                          | None          | (22)         |
| LADIS        | 5                    | 2007–2016       | 594              | 74      | PS: WMH                     | None          | (18)         |
| LBC 1936     | 6                    | 2014–2018       | 676              | 73      | HS                          | Semi-automated segmentation | (34) |
| MCSA         | 1                    | 2016            | 1044             | 78      | HS                          | None          | (35)         |
| NACC UDS (Databank) | 1            | 2018            | 694              | 73      | MS: AD, MCI                  | Manual segmentation | (32, 33) |
| No specific cohort study | 3            | 2010–2016       | 1703             | 65      | MS, PS: Stroke              | None          | (26, 36, 37) |
| NOMAS        | 7                    | 2011–2018       | 1216             | 70      | HS                          | Manual segmentation | (32, 33) None |

(Continued)
and 2 papers described a miscellaneous approach. Studies using fully automated methods had a significantly higher sample size (mean 1017.0 vs. 1650.8). Figure 3 shows the distribution of the segmentation types over the years. The peak of published articles on WMH was in 2014. We identified 17 different segmentation techniques used in the studies included in our review (Table 1). Box 2 delivers an introductory explanation for the 5 most employed techniques.

## Validation Methods

Methodological validation was done by application of accuracy and reproducibility measurements. Of 60 articles with semi-automated or manual segmentation techniques, 18 (30.0%) validated their results with reproducibility metrics, namely the intraclass-correlation coefficient and intra-rater repeatability. Of 132 articles using semi-automated and automated segmentation techniques, 112 (84.8%) reported accuracy metrics like Dice similarity index, intraclass-correlation coefficient, mean absolute error, Pearson’s correlation, Cronbach’s alpha, Spearman’s correlation coefficient, ANOVA, and ANCOVA to validate their results. The gold standard the segmentation techniques were tested against was manual segmentation in 84 studies, while 16 and 13 tested against visual rating scales and semi-automated techniques, respectively.

## DISCUSSION

In this systematic review, we identified 137 papers from large-scale studies applying a quantitative analysis of WMH over the past 14 years. With 134 of these being part of a longitudinal prospective cohort study, this indicates to the relevance of these studies in this particular field of research. The large number of studies included in this review reflects the current scientific relevance of WMH in cerebrovascular research. The sample size of these studies ranged from 501 to more than 9,000,
BOX 1 | The Big 5: Cohort studies with the most contributing articles in this work.

SMART-MR
With 22 articles the Second Manifestations of ARTerial disease—Magnetic Resonance Study (SMART-MR) made up the biggest proportion of all included studies. Localized in the Netherlands, SMART-MR had initially been designed to investigate the brain changes on MRI in patients with symptomatic atherosclerotic disease, namely, manifest coronary artery disease, cerebrovascular disease, peripheral artery disease, and abdominal aortic aneurysm. Recruitment took place from May 2001 until December 2005 and resulted in a baseline sample size of 1,309 subjects (49, 50).

3C
Established in the three French cities Bordeaux, Dijon, and Montpellier, the objective of the 3C-study was the assessment of risk of dementia and cognitive impairment attributable to vascular factors. 2094 older adults form the original sample size, recruited from March 1999 to March 2001 (51).

Framingham Offspring Cohort
The Framingham Offspring Cohort contains the offspring of participants from the original Framingham Heart Study. Founded in requirement of a young study sample, the enrolment phase in 1971 supplied an initial study sample of 5,124. The study’s purpose is described as the identification of common factors contributing to cardiovascular disease (52, 53).

WHICAP
The Washington/Hamilton Heights-Inwood Columbia Aging Project, located in New York, investigates in Alzheimer’s Dementia and Aging in a cohort of multiple ethnicities. The original cohorts size counts 3,452 members (54).

Rotterdam Study
Situated in the Netherlands, the enrolment of the Rotterdam study started in 1990 with the baseline sample size of 7,983 participants. Having a broader approach, the study covers multiple diseases of elderly people in its investigations, i.e., cardiovascular, neurological, ophthalmological, endocrinological, and psychiatric diseases (55).

which demonstrates the feasibility of WMH segmentation in large samples resulting from the scalability of largely automated image analysis techniques. However, although the past years have brought ongoing improvements in automated image analysis techniques, we did not observe a clear increase of sample size over time. This may either reflect the typical delay until new analysis
Common risk factors are age, sex, gender, and ethnicity. Significant associations with WMH indicated in bold.

**TABLE 2** | Overview of supposed risk factors for WMH in large-scale studies.

| Risk factors                               | Studies |
|-------------------------------------------|---------|
| Ad-genetics                               | (56)    |
| Adiposity                                 | (58)    |
| Angiotension converting enzyme            | (59)    |
| Antihypertensive treatment                | (60)    |
| Aortic stiffness                          | (61)    |
| ApoE genotype                             | (148, 178, 182, 74, 91, 58) |
| Arterial stiffness                        | (191, 132, 171, 141) |
| Atherosclerosis                           | (183, 49, 179) |
| Atrial fibrillation                       | (138, 163) |
| Blood pressure variability                | (62)    |
| Cardiac stress markers                    | (63)    |
| Cardiovascular risk factors               | (143, 158, 56) |
| Common risk factors                       | (152, 98, 187, 135, 176, 193, 79) |
| Conjugated equine estrogen                | (84)    |
| Diabetes mellitus type II                 | (136, 165, 192, 175, 14, 153, 144) |
| Diet quality                              | (167, 150) |
| Dysglycemia                               | (65)    |
| Exhaled carbon monoxide                   | (66)    |
| Extracellular vesicle protein levels      | (67)    |
| FGF23 elevation                          | (88)    |
| Folate                                    | (69)    |
| Genetic loci                              | (70, 71) |
| Hba1C                                     | (72)    |
| Homocystein                               | (69, 72, 142, 161) |
| Hyperlipidemia                            | (73)    |
| Hypertension                              | (75, 182, 173, 187, 132, 149, 174, 146) |
| Inflammatory markers                      | (115, 85, 159, 186, 168, 57) |
| Leisure activity                          | (74)    |
| Lipoproteins                              | (75)    |
| Metabolic syndrome                        | (76)    |
| Metalloproteinases                        | (77)    |
| Midlife obesity                           | (78)    |
| Nocturnal blood pressure                  | (79)    |
| Parathyroid hormone                       | (80)    |
| Parental longevity                        | (81)    |
| Parental stroke                           | (82)    |
| Perceived stress                          | (83)    |
| Physical activity                         | (84)    |
| Plasma beta-amyloid                       | (85, 86) |
| Red blood cell omega-3 fatty acid         | (87)    |
| S100B                                     | (88)    |
| Sleep duration                            | (89)    |
| Sulfur amino acids                        | (69)    |
| Thyroid function                          | (90)    |
| Tomm40 S23 genotype                       | (91)    |
| Uric acid                                 | (92)    |
| VCAN snps                                  | (93)    |
| Vitamin B12                               | (69)    |
| Vitamin D                                 | (94)    |
| Voz2Max                                   | (95)    |

**TABLE 3** | Overview of supposed sequelae of WMH in large-scale studies.

| Sequelae                             | Studies |
|--------------------------------------|---------|
| Alzheimer's disease                  | (96–99) |
| Antidepressant Use                   | (100, 101) |
| Apathy symptoms                      | (102) |
| Brain atrophy                        | (181, 182, 184, 56, 172, 145) |
| Brain volumetric changes             | (32, 162, 189) |
| Callosal atrophy                     | (103, 104) |
| Cerebral blood flow                  | (105) |
| Cognitive function                   | (21, 56, 62, 95, 153, 79, 104, 134, 140, 143, 155, 156, 160, 164, 166, 169, 170, 180, 188–190, 194, 195) |
| Death                                | (106) |
| Depressive symptoms                  | (100, 101, 154, 133, 147, 151, 177, 139) |
| Falls                                | (107) |
| Functional status                     | (108) |
| Grief                                | (109) |
| Headache                             | (110–112) |
| Immobility                           | (57) |
| Manual dexterity                      | (113) |
| Migraine                             | (110, 112) |
| Mild cognitive impairment            | (98, 137, 185, 157) |
| Olfactory function                   | (114) |
| Perivascular spaces                  | (115) |
| Restless-Legs-syndrome               | (116) |
| Retinal Microvasculature              | (117) |
| Study-drop-out                        | (118) |
| Subjective memory                    | (119) |
| Impairment                           | (120) |
| Tract Integrity                      | (120) |

Significant associations with WMH indicated in bold.

methods are implemented in large epidemiological studies, which usually are running over a long period. This may also be explained by other factors limiting sample size in large-scale studies beyond factors related to image analysis, e.g., recruitment, or limited capacity of study centers for clinical or imaging studies. Mean age of study subjects across all studies was 67 years, which is likely due to the fact of cerebrovascular diseases being aggregated primarily in the elderly.

The research questions addressed in the studies included in our review could be divided into two groups: the association of risk factors with WMH and supposed clinical or other consequences of WMH. The five most frequently investigated risk factors studied with regards to their association with WMH were hypertension, common risk factors, diabetes, ApoE genotype and inflammatory markers. The majority represents risk factors or markers of atherosclerosis (123).

With regard to clinical manifestations of WMH, there were two areas of interest in the focus of the reviewed studies: a large number of studies looked at WMH in the context of cognitive decline, mild cognitive impairment, or brain volumetric changes and brain atrophy, which are considered as
biomarkers of neurodegeneration. This research focus appears obvious, as cerebral small vessel disease is a known risk factor for vascular cognitive impairment and vascular dementia (3). Depressive symptoms were the second clinical focus, as well-thematized in multiple studies. This is in line with the vascular depression hypothesis which proposes an association between the disruption of frontostriatal pathways by WMH and late-life depression (124, 125).

The lack of studies addressing e.g., the association of WMH and ischemic stroke and intracerebral hemorrhage (37, 126) might represent a bias in our search criteria.

Our review focused on the methods utilized for WMH characterization. To some parts, the heterogeneity and lack of standardization seem not only to be a problem of imaging analysis but also of the definition and nomenclature of findings related to cerebral small vessel disease. In an analysis of 1,144 studies dealing with WMH research, 275 used a variant term to “white matter hyperintensity” in their titles or abstracts (4). Efforts to overcome this lack of consensus on terminology and definition of white matter hyperintensities led to publishing the STRIVE consensus criteria in 2013, defining standards for research into cerebral small vessel disease (4). We also wanted to see, whether this initiative and publication of research standards had an impact on scientific studies of WMH in large cohorts. Still, a lot of unifying potential remains here, harboring the problem of arbitrary WMH segmentation and contributing another aspect to the discussion. These numbers suggest that there is still much room for the unification of scientific standards in this research area. In line with this, a recent contribution to the discussion suggested that the descriptive nature of most definitions of white matter hyperintensities is accountable for low-quality segmentation (127). The authors propose a statistical definition as a solution due to its better measurability and provide competitive results with it.

Virtually all studies relied on either semi-automated or fully-automated techniques for WMH segmentation. This finding reflects the trend toward segmentation automation resulting from the acknowledgment of limitations of manual segmentation: it is laborious, thus expensive; is prone to errors; subjective and shows high intra-rater and inter-rater variability (36). Since semi-automated segmentation techniques succumb automated ones regarding human intervention while showing similar segmentation quality, a further trend from semi-automated segmentation methods to fully automated techniques was assumable. Although automated segmentation techniques constituted the largest proportion over the past 14 years from observation of the time course of our data a clear trend toward automated segmentation was not derivable. The significantly higher sample size of studies using automated methods compared to studies using semi-automated methods can be explained by the fact that with higher sample size approaches requiring interaction with a human observer become less feasible.

One striking result of our review is the manifoldness of segmentation techniques used. Almost every cohort study identified had its own segmentation approach. Our review was not designed to answer the question, whether any of the segmentation methods is superior for WMH segmentation. Due to the inherent complexity of the segmentation task, the research field's demand for one proper automated segmentation technique remains unresolved. However, the diversity of segmentation approaches used in large-scale studies is remarkable, which in turn reflect the total lack of any consensus or agreed methodological standard for WMH segmentation.

The existence of a large variety of segmentation techniques is not inherently harmful to the field of research, as it may
also be interpreted as a reflection of its vividness. However, the multiplicity of methods used for segmentation and quantification of WMH represents a scientific problem, because it leads to potential incoherence and incomparability between studies. Crucial results such as the overall WMH extent may differ in significant ways depending on the methods used for WMH segmentation.

As a relevant example of how to address cross-study heterogeneity, the NeuroCHARGE Consortium (70) used results of 7 different large-scale prospective cohort studies for a genome-wide association study (GWAS). Before conducting their analysis, they assessed the results for comparability, encompassing WMH segmentation and visual rating scale data, by examining their quality individually via comparison with a reference standard. In addition, utilized visual scoring and volumetric methods were performed on standard image data sets to test agreement.

Automated segmentation was primarily based on machine learning algorithms: for instance, k-nearest neighbors, naive Bayesian classifiers, artificial neural networks and support vector machines were successfully employed to serve the problem of quantitative WMH delineation. Since deep learning, namely convolutional neural networks (CNN), proved themselves for computer vision tasks they are also a hot contender in the WMH segmentation problem. First studies and the WMH segmentation challenge at MICCAI 2017 (http://wmh.isi.uu.nl/) delivered promising results (128–130).

In the publications analyzed in our review, some validated their segmentation results against a gold-standard—usually manual segmentation. This “gold standard,” however, has a lot of inherent limitations, resulting in a significant degree of subjectivity in the validation process. This, again, contributes to incomparability between different methods due to the fact they have been validated on hardly comparable gold standards. Moreover, the methods used for validation, also show some heterogeneity. Many studies use different parameters than the most common metrics like the Dice similarity index and thereby contribute to the overall heterogeneity and lead to aggravated comparison. Again, standardization might provide a solution. The study field could consent, just in the manner of the STRIVE, to specific parameters for validation measures including guidelines of subset selection for specific segmentation tasks (131).

Regardless of the already discussed problems, there are further contributors to variation in WMH quantification. In the end, the quality of the segmentation process depends strongly on the quality of the underlying MRI-images. Especially clinical scans are often very heterogeneous in terms of available MRI-sequences, manufacturer, field strength, signal-to-noise ratio, additional pathologies visible in the scan like stroke lesions or tumors, overall quality assurance protocols and sequence parameters like voxel dimensions, slice gaps, contrast and automated distortion correction. Therefore, the application of the discussed algorithms in the clinical routine might be only possible to a limited extent.

In conclusion, the vast number of large-scale studies reporting the results of segmentation and quantification of WHM reflects the fact that cerebral small vessel disease is a research topic of great interest, especially within the context of epidemiological studies or large patient cohorts. Both, risk factors associated with the presence and extent of WMH and possible behavioral or clinical sequelae are in the focus of research. Approaches to WMH segmentation used in these studies with large samples rely on semi-automated or fully automated algorithms. A multiplicity of methods is used, and clear definitions of WMH are only provided in a minority of studies, which limits comparability and reproducibility of results. New technical developments in segmentation methods may further improve automated lesion segmentation in the near future. In addition to technical advancements, there is a clear need for creating and adhering to reporting guidelines covering both definition of WMH and description of segmentation approach.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

BF, MP, and GT contributed to the conception and design of the review and to the writing of the manuscript. BF and MP performed the PubMed search and extracting of relevant studies. All authors contributed to the analysis of the results, to manuscript revision, read and approved the submitted version.

GT supervised the project.

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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.2019.00238/full#supplementary-material

REFERENCES

1. Feigin VL, Norving B, Mensah GA. Global burden of stroke. Circ Res. (2017) 120:439–48. doi: 10.1161/CIRCRESAHA.116.308413
2. Fitzpatrick AL, Kuller LH, Ives DG, Lopez OL, Jagust W, Breitner JCS, et al. Incidence and prevalence of dementia in the cardiovascular health study. J Am Geriatr Soc. (2004) 52:195–204. doi: 10.1111/j.1532-5415.2004.52058.x
3. Gorelick PB, Counts SE, Nyenhuis D. Vascular cognitive impairment and dementia. Biochim Biophys Acta Mol Basis Dis. (2016) 1862:860–8. doi: 10.1016/j.bbadis.2015.12.015
4. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. (2013) 12:822–38. doi: 10.1016/S1474-4422(13)70124-8
5. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. (2010) 341:i–9. doi: 10.1136/bmj.c3666

6. Herrmann LL, Le Masurier M, Ebmeier KP. White matter hyperintensities in late life depression: a systematic review. J Neurol Neuropsychиatry. (2008) 79:619–25. doi: 10.1136/jnnp.2007.124651

7. Murray A, McNeil C, Sarlariad S, Deary I, Phillips L, Whalley L, et al. Brain hyperintensity location determines outcome in the triad of impaired cognition, physical health and depressive symptoms: a cohort study in late life. Arch Gerontol Geriatr. (2016) 63:49–54. doi: 10.1016/J.ARCHGER.2015.10.004

8. van der Holst HM, Tuladhar AM, Zerbi V, van Uden IVM, de Laat KF, van Leijen EMC, et al. White matter changes and gait decline in cerebral small vessel disease. Neuroradiology Clin. (2018) 7:731–8. doi: 10.1016/j.neuroci.2017.12.007

9. Baeschn H, Blahak C, Poggesi A, Pantoni L, Inzitari D, Chabrat H, et al. Association of gait and balance disorders with age-related white matter changes: the LADIS study. Neurology. (2008) 70:935–42. doi: 10.1212/01.wnl.0000303595.46197.6

10. Poggesi A, Pracucci G, Chabrat H, Erkinciknutt F, Fazekas F, Verdellio A, et al. Urinary Complaints in nondisabled elderly people with age-related white matter changes: the leukoaraiosis and disability (LADIS) Study. J Am Geriatr Soc. (2008) 56:1638–43. doi: 10.1111/j.1532-5415.2008.01832.x

11. Longstreth WT, Manolito TA, Arnold A, Burke GL, Bryan N, Jungreis CA, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. Stroke. (1996) 27:1274–82. doi: 10.1161/01.STR.27.8.1274

12. Maillard P, Chawluk J, Alavi A, Hurtig H, Zimmerman R. MR signal measurement. Magn Reson Imag. (1987) 149:351–6. doi: 10.2214/ajr.149.2.351

13. Gons RAR, van Norden AGW, de Laat KF, van Oudheusden LJB, van Uden IVM, Zwieters MP, et al. Cigarette smoking is associated with reduced microstructural integrity of cerebral white matter. Brain. (2011) 134:2116–24. doi: 10.1093/brain/awr145

14. Schneider ALC, Selvin E, Sharrett AR, Griswold M, Coren J, Jack CR, et al. Diabetes, prediabetes, and brain volumes and subclinical cerebrovascular disease on MRI: the atherosclerosis risk in communities neurocognitive study (ARIC-NCS). Diabetes. (2012) 61:1039–47. doi: 10.2337/db11-1464

15. Fazekas F, Chawluk J, Alavi A, Hurtig H, Zimmerman R. MR signal abnormalities at 1.5 T in Alzheimer’s dementia and normal aging. Am. J. Roentgenol. (1987) 149:351–6. doi: 10.2261/ajr.149.2.351

16. Scheltens P, Barkhof F, Leys D, Pronto J, Nauta JJP, Vermersch P, et al. A semiquantitative rating scale for the assessment of signal hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. Magn Reson Imag. (2010) 28:529–36. doi: 10.1016/j.mri.2009.08.013

17. Zijdenbos AP, Forghani R, Evans AC. Automatic “pipeline” analysis of 3-D FLAIR histogram segmentation for measurement of leukoaraiosis volume. J Magn Reson Imag. (2001) 14:668–76. doi: 10.1002/jmir.10011

18. Beare R, Srikanth V, Chen J, Phan TG, Stapleton J, Lipshtuk R, et al. Development and validation of morphological segmentation of age-related cerebral white matter hyperintensities. Neuroimage. (2009) 47:199–203. doi: 10.1016/j.neuroimage.2009.03.055

19. DeCarli C, Massaro J, Harvey D, Hald J, Tullberg M, Au R, et al. Measures of brain morphology and infarction in the Framingham heart study: establishing what is normal. Neurobiol Aging. (2005) 26:491–510. doi: 10.1016/j.neurobiolaging.2004.05.004

20. DeCarli C, Miller BL, Swan GE, Reed T, Wolf PA, Garner J, et al. Predictors of brain morphology for the men of the NHLBI twin study. Stroke. (1999) 30:529–36. doi: 10.1161/01.STR.30.3.529

21. Valdés Hernández M, del C, Ferguson KJ, Chappell FM, Wardlaw JM. New multispectral MRI data fusion technique for white matter lesion segmentation: method and comparison with thresholding in FLAIR images. Eur Radiol. (2010) 20:1684–91. doi: 10.1007/s00330-010-1718-6

22. Raz L, Jayachandran M, Tosakulwong N, Lesnick TG, Wille SM, Murphy MC, et al. Thrombogenic microvesicles and white matter hyperintensities in postmenopausal women. Neurology. (2013) 80:911–8. doi: 10.1212/WNL.0b013e3182840c9f

23. Girardt I, Zamboni G, Khan A, Li L, Bonifacio G, Sundaesara V, et al. BIANCA (Brain Intensity Abnormality Classification Algorithm): a new tool for automated segmentation of white matter hyperintensities. Neuroimage. (2016) 124:191–205. doi: 10.1016/j.neuroimage.2016.07.018

24. Zijdenbos AP, Forghani R, Evans AC. Automatic “pipeline” analysis of 3-D MRI data for clinical trials: application to multiple sclerosis. IEEE Trans Med Imag. (2002) 21:1295–300. doi: 10.1109/TMI.2002.806283

25. de Boer R, Vrooman HA, van der Lijn F, Vernooij MW, Ikram MA, et al. White matter lesion extension to automatic measurement. Magn Reson Imag. (2013) 31:261–76. doi: 10.1016/j.mri.2013.01.007

26. Grimaldi et al. Pathologies using magnetic resonance imaging: a review. Magn Reson Imag. (2012) 30:529–36. doi: 10.1016/j.mri.2011.11.032
brain tissue segmentation on MRI. Neuroimage. (2009) 45:1151–61. doi: 10.1016/j.neuroimage.2009.01.011

41. Vrooman HA, Cocosco CA, van der Lijn F, Stolking R, Ikram MA, Vernooij MW, et al. Multi-spectral brain tissue segmentation using automatically trained k-Nearest-Neighbor classification. Neuroimage. (2007) 37:71–81. doi: 10.1016/j.neuroimage.2007.05.018

42. Lao Z, Shen D, Liu D, Jiaow AE, Melhem ER, Launer LJ, et al. Computer-Assisted Segmentation of white matter lesions in 3D mr images using support vector machine. Acad Radiol. (2008) 15:300–13. doi: 10.1016/j.acra.2007.10.012

43. Anbeer P, Vincken KL, van Bochove GS, van Osch MJF, van der Grond J. Probabilistic segmentation of brain tissue in MR imaging. Neuroimage. (2005) 27:795–804. doi: 10.1016/j.neuroimage.2005.05.046

44. Anbeer P, Vincken KL, van Osch MJF, Bisschops RHC, van der Grond J. Probabilistic segmentation of white matter lesions in MR imaging. Neuroimage. (2004) 21:1037–44. doi: 10.1016/j.neuroimage.2003.10.012

45. Wen W, Sachdev P. The topography of white matter hyperintensities on brain MRI in healthy 60–64-year-old individuals. Neuroimage. (2004) 22:144–54. doi: 10.1016/j.neuroimage.2003.12.027

46. Admiraal-Behloul F, van den Heuvel DMJ, Olofsen H, van Osch MJP, van der Grond J. probabilistic segmentation of brain tissue in MR imaging. Neuroimage. (2005) 27:795–804. doi: 10.1016/j.neuroimage.2005.05.046

47. Brickman AM, Sneed JR, Provenzano FA, Garcon E, Johnert L, Muraskin J, et al. Quantitative approaches for assessment of white matter hyperintensities in elderly populations. Psychiatry Res Neuroimage. (2011) 193:101–6. doi: 10.1016/j.jspsychres.2011.03.007

48. DeCarli C, Fletcher E, Ramey V, Harvey D, Jagust WJ. Anatomical Mapping of White Matter Hyperintensities (WMH). Stroke. (2005) 36:50–5. doi: 10.1161/01.STR.0000150668.58689.f2

49. Geerlings MI, Appelman APA, Vincken KL, Algra A, Witkamp TD, Mali WP, van der Graaf Y, et al. Associations of circulating growth differentiation factor-15 and ST2 concentrations with subclinical vascular brain injury and incident Stroke. (2015) 46:2568–75. doi: 10.1161/STROKEAHA.115.009926

50. Coker LH, Espeland MA, Hogan PE, Resnick SM, Bryan RN, Robinson JG, et al. Change in brain and lesion volumes after CEE therapies: the WHIMS-MRI studies. Neurology. (2014) 82:427–34. doi: 10.1212/WNL.0000000000000679

51. Reitz C, Guzman VA, Narkhede A, DeCarli C, Brickman AM, Luchsinger JA. Relation of Dysglycemia to structural brain changes in a multiethnic elderly cohort. J Am Geriatr Soc. (2017) 65:277–85. doi: 10.1111/j.1532-5415.2016.6422.x

52. Novy M, Enserro DM, Beiser AS, Cheng S, DeCarli C, Vasan RS, et al. Association of exhaled carbon monoxide with stroke. incidence and subclinical vascular brain injury. Stroke. (2016) 47:383–9. doi: 10.1161/STROKEAHA.115.010405

53. Kanhai DA, de Klein DPV, Kappelle LJ, Uiterwaal CSPM, van der Graaf Y, Pastorik G, et al. Extracellular vesicle protein levels are related to brain atrophy and cerebral white matter lesions in patients with manifest vascular disease: the SMART-MR study. BMJ Open. (2014) 4:e003824. doi: 10.1136/bmjopen-2013-003824

54. Wright CB, Shah NH, Mendez AJ, DeRosa JT, Yoshita M, Elkind MSV, et al. Fibroblast growth factor 23 is associated with subclinical cerebrovascular damage. Stroke. (2016) 47:923–8. doi: 10.1161/STROKEAHA.115.012379

55. Hooshmand B, Mangialasche F, Kalpouzos G, Solomon A, Kåreholt I, Smith SM, Robinson JG, et al. Association of vitamin b 12, folate, and sulfur amino acids with brain magnetic resonance imaging measures in older adults. JAMA Psychiatry. (2016) 73:606. doi: 10.1001/jamapsychiatry.2016.0274

56. Fornage M, Debette S, Bis JC, Schmidt H, Ikram MA, Dufouil C, et al. Genome-wide association studies of cerebral white matter lesion burden: the CHARGE consortium. Ann Neurol. (2011) 69:928–39. doi: 10.1002/ana.22403

57. Traylor M, Zhang CR, Adib-Samii P, Devan WJ, Parsons OE, Lanfranconi S, et al. Genome-wide meta-analysis of cerebral white matter hyperintensities in patients with stroke. Neurology. (2016) 86:146–53. doi: 10.1212/WNL.0000000000002263

58. Cloonan L, Fitzpatrick KM, Kanakis AS, Furie KL, Rosand J, Rost NS. Metabolic determinants of white matter hyperintensity burden in patients with ischemic stroke. Atherosclerosis. (2015) 240:149–53. doi: 10.1016/j.atherosclerosis.2015.02.052

59. Jimenez-Conde J, Biffi A, Rahman R, Kanakis A, Butler C, Sonni S, et al. Hyperlipidemia and reduced white matter hyperintensity volume in patients with ischemic Stroke. (2010) 41:437–42. doi: 10.1161/STROKEAHA.109.563502

60. Hafsteinsdottir SH, Eiriksdottir G, Sigurdsson S, Aspelund T, Harris TB, Launer LJ, et al. Brain tissue volumes by APOE genotype and leisure activity—the AGES-Reykjavik Study. Neurobiol Aging. (2012) 33:829.e1–829.e8. doi: 10.1016/j.neurobiolaging.2011.06.028

61. Chua C-Y, Chou K-H, Peng L-N, Liu L-K, Lee W-J, Chen L-K, et al. Associations between low circulating low-density lipoprotein cholesterol level and brain health in non-stroke non-demented subjects. Neuroimage. (2018) 181:627–34. doi: 10.1016/j.neuroimage.2018.07.049
113. Nyquist PA, Yanek LR, Bilgel M, Cuzzocreo JL, Becker LC, Chevalier-Glymour MM, Chene G, Tzourio C, Dufouil C. Brain MRI markers and white matter hyperintensities. *Neurobiol Aging.* (2011) 32:249–57. doi: 10.1016/j.neurobiolaging.2010.11.011

114. Rist PM, Tzourio C, Elbaz A, Soumaré A, Dufouil C, Mazoyer B, Aribisala BS, Wiseman S, Morris Z, Valdés-Hernández MC, Royle NA, Devanand DP, Tabert MH, Cuasay K, Manly JJ, Schupf N, Brickman AL, et al. Circulating inflammatory markers are associated with magnetic resonance imaging-visible perivascular spaces but not with direct white matter hyperintensities. *Stroke.* (2014) 45:605–7. doi: 10.1161/STROKEAHA.113.004599

115. Aribisala BS, Wiseman S, Morris Z, Valdés-Hernández MC, Royle NA, Maniega SM, et al. Circulating inflammatory markers are associated with magnetic resonance imaging-visible perivascular spaces but do not directly with white matter hyperintensities. *Stroke.* (2014) 45:605–7. doi: 10.1161/STROKEAHA.113.004599

116. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry.* (2013) 18:963–74. doi: 10.1038/mp.2013.20

117. Kaffashian S, Tzourio C, Zhu Y-C, Mazoyer B, Debette S. Differential effect of white-matter lesions and covert brain infarcts on the risk of ischemic stroke. *J Neurol Neurosurg Psychiatry.* (2016) 87:1925–31. doi: 10.1136/jnnp-2016-313153

118. Damangir S, Westman E, Simmons A, Vrenken H, Wahlund L-O, Spuler G. Reproducible segmentation of white matter hyperintensities using a new statistical definition. *Magn Reson Mater Phys Biol Med.* (2017) 30:227–37. doi: 10.1007/s10334-016-0599-3

119. Guerrero R, Qin C, Oktay O, Bowles C, Chen L, Joules R, et al. White matter hyperintensity and stroke lesion segmentation and differentiation using convolutional neural networks. *NeuroImage Clin.* (2018) 17:918–34. doi: 10.1016/j.nicl.2017.12.022

120. Moekops P, de Bresser J, Kuijf HJ, Mendrik AM, Biessels GJ, Pluim JPW, et al. Evaluation of a deep learning approach for the segmentation of brain tissues and white matter hyperintensities of presumed vascular origin in MRI. *NeuroImage Clin.* (2018) 17:251–62. doi: 10.1016/j.nicl.2017.10.007

121. Taha AA, Hanbury A. Metrics for evaluating 3D medical image segmentation: analysis, selection, and tool. *BMC Med Imaging.* (2015) 15:29. doi: 10.1186/s12891-015-0068-x

122. Poels MMF, Zaccai K, Verwoert GC, Vernooij MW, Hofman A, van der Lugt A, et al. Arterial stiffness and cerebral small vessel disease. *Stroke.* (2012) 43:2637–42. doi: 10.1161/STROKEAHA.111.624264

123. Grool AM, Graaf Y, Vincken KL, Wiltfang TD, Mali WPTM, Geerlings MI. Antidepressant use is related to larger white matter lesion volume in patients with symptomatic atherosclerotic disease: the SMART-MR study. *J Neurol.* (2013) 260:197–206. doi: 10.1007/s00415-012-6616-1

124. Glazer H, Dong C, Yoshita M, Rundek T, Elkind MV, Sacco RL, et al. Subclinical cerebrovascular disease inversely associates with learning ability: The NOMAS. *Neurology.* (2013) 84:2362–7. doi: 10.1212/WNL.0b013e3182dd056a

125. Nyquist PA, Bilgel MS, Gottesman R, Yanek LR, Møy TF, Becker LC, et al. Extreme deep white matter hyperintensity volumes are associated with African American race. *Cerebrovasc Dis.* (2014) 37:244–50. doi: 10.1159/000358117

126. Kooistra M, Geerlings MI, Mali WPTM, Vernooij MW, Ikram MA, Tanghe HL, Vincent AJPE, Hofman A, Krestin GP, et al. Incidental findings on brain MRI in the general population. *Sci Rep.* (2017) 7:5110. doi: 10.1038/s41598-017-05300-5

127. Moekops P, de Bresser J, Kuijf HJ, Mendrik AM, Biessels GJ, Pluim JPW, et al. Evaluation of a deep learning approach for the segmentation of brain tissues and white matter hyperintensities of presumed vascular origin in MRI. *NeuroImage Clin.* (2018) 17:251–62. doi: 10.1016/j.nicl.2017.10.007

128. Taha AA, Hanbury A. Metrics for evaluating 3D medical image segmentation: analysis, selection, and tool. *BMC Med Imaging.* (2015) 15:29. doi: 10.1186/s12891-015-0068-x

129. Guerrero R, Qin C, Oktay O, Bowles C, Chen L, Joules R, et al. White matter hyperintensity and stroke lesion segmentation and differentiation using convolutional neural networks. *NeuroImage Clin.* (2018) 17:918–34. doi: 10.1016/j.nicl.2017.12.022

130. Moekops P, de Bresser J, Kuijf HJ, Mendrik AM, Biessels GJ, Pluim JPW, et al. Evaluation of a deep learning approach for the segmentation of brain tissues and white matter hyperintensities of presumed vascular origin in MRI. *NeuroImage Clin.* (2018) 17:251–62. doi: 10.1016/j.nicl.2017.10.007

131. Taha AA, Hanbury A. Metrics for evaluating 3D medical image segmentation: analysis, selection, and tool. *BMC Med Imaging.* (2015) 15:29. doi: 10.1186/s12891-015-0068-x
181. Appelman AP, van der Graaf Y, Vincken KL, Tielhuus AM, Witkamp TD, Mali WP, et al. Total cerebral blood flow, white matter lesions and brain atrophy: the SMART-MR Study. *J Cereb Blood Flow Metab.* (2008) 28:633–9. doi: 10.1038/jcbfm.96003563

182. Godin O, Maillard P, Crivello F, Rovitch A, Mazoyer B, Tzourio C, et al. Association of white-matter lesions with brain atrophy markers: the three-city dijon MRI study. *Cerebrovasc Dis.* (2009) 28:177–84. doi: 10.1159/000226117

183. Aparicio HJ, Petrea RE, Massaro JM, Manning WJ, Oyama-Manabe N, Beiser AS, et al. Association of descending thoracic aortic plaque with brain atrophy and white matter hyperintensities: the framingham heart study. *Atherosclerosis.* (2017) 265:305–11. doi: 10.1016/j.atherosclerosis.2017.06.919

184. Appelman APA, Vincken KL, van der Graaf Y, Vlek ALM, Witkamp TD, Mali WPTM, et al. White matter lesions and lacunar infarcts are independently and differently associated with brain atrophy: the SMART-MR study. *Cerebrovasc Dis.* (2010) 29:28–35. doi: 10.1159/000255971

185. Luchsinger JA, Brickman AM, Reitz C, Cho SJ, Schupf N, Manly JJ, et al. Subclinical cerebrovascular disease in mild cognitive impairment. *Neurology.* (2009) 73:450–6. doi: 10.1212/WNL.0b013e3181b1636a

186. Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C. Circulating IL-6 and CRP are associated with MRI findings in the elderly: The 3C-Dijon Study. *Neurology.* (2012) 78:720–7. doi: 10.1212/WNL.0b013e318284ae50f

187. Marcus J, Gardener H, Rundek T, Elkind MSV, Sacco RL, DeCarli C, et al. Baseline and Longitudinal Increases in diastolic blood pressure are associated with greater white matter hyperintensity volume. *Stroke.* (2011) 42:2639–41. doi: 10.1161/STROKEAHA.111.617571

188. Muller M, Appelman APA, van der Graaf Y, Vincken KL, Mali WPTM, Geerlings MI. Brain atrophy and cognition: interaction with cerebrovascular pathology? *Neurobiol Aging.* (2011) 32:885–93. doi: 10.1016/j.neurobiaging.2009.05.005

189. Ritchie SJ, Dickie DA, Cox SR, Valdes Hernandez M, del C, Corley J, et al. Brain volumetric changes and cognitive ageing during the eighth decade of life. *Hum Brain Mapp.* (2015) 36:4910–25. doi: 10.1002/hbm.22959

190. Vibhda D, Tiemeier H, Mirza SS, Adams HHH, Niessen WJ, Hofman A, et al. Brain volumes and longitudinal cognitive change. *Alzheimer Dis Assoc Disord.* (2018) 32:43–9. doi: 10.1097/WAD.0000000000000235

191. Jochensen HM, Muller M, Bots ML, Scheltens P, Vincken KL, Mali WPTM, et al. Arterial stiffness and progression of structural brain changes: the SMART-MR study. *Neurology.* (2015) 84:448–55. doi: 10.1212/WNL.000000000001201

192. Moran C, Phan TG, Chen J, Blizzard L, Beare R, Venn A, et al. Brain Atrophy in Type 2 Diabetes: Regional distribution and influence on cognition. *Diab Care.* (2013) 36:4036–42. doi: 10.2337/dc13-0143

193. van der Veen PH, Muller M, Vincken KL, Witkamp TD, Mali WPTM, van der Graaf Y, et al. Longitudinal changes in brain volumes and cerebrovascular lesions on MRI in patients with manifest arterial disease: the SMART-MR study. *J Neurol Sci.* (2014) 337:112–8. doi: 10.1016/j.jns.2013.11.029

194. Jokinen H, Melkas S, Madureira S, Verdelho A, Ferro JM, Fazekas F, et al. Cognitive reserve moderates long-term cognitive and functional outcome in cerebral small vessel disease. *J Neurol Neurosurg Psychiatry.* (2016) 87:1296–302. doi: 10.1136/jnnp-2016-313914

195. Geerlings MI, Appelman APA, Vincken KL, Mali WPTM. Association of white matter lesions and lacunar infarcts with executive functioning: the SMART-MR study. *Am J Epidemiol.* (2009) 170:1147–55. doi: 10.1093/aje/kwp236

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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