

White Matter Hyperintensities in Vascular Contributions to Cognitive Impairment and Dementia (VCID). Knowledge Gaps and Opportunities.

Jessica Alber, Suvarna Alladi, Hee-Joon Bae, David A Barton, Laurel Beckett, Joanne M Bell, Sara E Berman, Geert Jan Biessels, Sandra E Black, Isabelle Bos, Gene L Bowman, Emanuele Brai, Adam M Brickman, Brandy L Callahan, Roderick A Corriveau, Silvia Fossati, Rebecca F Gottesman, Deborah R Gustafson, Vladimir Hachinski, Kathleen M Hayden, Alex M Helman, Timothy M Hughes, Jeremy D Isaacs, Angela L Jefferson, Sterling C Johnson, Alifiya Kapasi, Silke Kern, Jay C Kwon, Juraj Kukolja, Athene Lee, Samuel N Lockhart, Anne M Murray, Katie E Osborn, Melinda C Power, Brittani R Price, Hanneke FM Rhodius-Meester, Jacqueline A Rondeau, Allyson C Rosen, Douglas L Rosene, Julie A Schneider, Henrieta Scholtzova, C Elizabeth Shaaban, Narlon CBS Silva, Heather M Snyder, Walter Swardfager, Aron M Troen, Susanne J van Veluw, Prashanthi Vemuri, Anders Wallin, Cheryl L Wellington, Donna M Wilcock, Sharon X Xie, Atticus H Hainsworth*.

This Perspective article was developed from a session of the ISTAART Vascular Cognitive Disorders Professional Interest Area, AAIC 2017. **Author affiliations are listed in a Supplementary file.**

*Correspondence: Dr Atticus H Hainsworth PhD, Clinical Neurosciences Mailpoint J-0B, Molecular and Clinical Sciences Research Institute, St George's University of London, Cranmer Terrace, London, SW17 0RE, United Kingdom.

Tel +44 208 725 5586 Fax +44 208 725 2950 email ahainsworth@sgul.ac.uk

Words (excluding the abstract, references, figures): 3901

Figures: 2 (B&W) Text Boxes: 4

Declarations of Interest

DAB is director of NeuroTrials Victoria Pty Ltd and has undertaken clinical trials for Roche, Alkermes, Otsuka, Lundbeck and Janssen. GJB has received speaker fees from Eisai and research support from Boehringer-Ingelheim. All compensation for these services is transferred to his employer, the UMCU. GLB is an unpaid Scientific Advisory Board member of the PROPAG-AGEING EU Horizon 2020 initiative. RAC is an employee of NINDS. JDI has attended an advisory board for Biogen and is a Principal Investigator on clinical trials, outside of the submitted work, sponsored and funded by Roche and Merck. KEO is funded by NIH (F32AG058395). CLW is a member of the CIHR-funded Canadian Consortium for Neurodegeneration in Aging. AHH has received honoraria from Eli Lilly and from the NIA and is chair of the DPUK Vascular Experimental Medicine group.

Declarations of interest for all other authors: none.

Abstract

White matter hyperintensities (WMH) are frequently seen on brain MRI scans of older people. Usually interpreted clinically as a surrogate for cerebral small vessel disease, WMH are associated with increased likelihood of cognitive impairment and dementia (including Alzheimer's disease, AD). WMH are also seen in cognitively healthy people. In this collaboration of academic, clinical and pharmaceutical industry perspectives, we identify outstanding questions about WMH and their relation to cognition, dementia and AD. What molecular and cellular changes underlie WMH? What are the neuropathological correlates of WMH? To what extent are demyelination and inflammation present? Is it helpful to subdivide into periventricular and subcortical WMH? What do WMH signify in people diagnosed with AD? What are the risk factors for developing WMH? What preventive and therapeutic strategies target WMH? Answering these questions will improve prevention and treatment of WMH and dementia.

[140 < 150 words]

Keywords: Vascular dementia; Vascular cognitive impairment; Leukoaraiosis; white matter lesions

1. Introduction

1.1 What do we mean by White Matter Hyperintensities?

White matter hyperintensities of presumed vascular origin (WMH) are among the most prominent age-related changes on brain magnetic resonance imaging (MRI) [1]. WMH are seen as diffuse areas of high signal intensity (hence, “hyperintense”) on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences [1-3] (examples in Fig 1). WMH are broadly equivalent to leukoaraiosis seen on CT scans [1]. The variability in WMH appearance is hypothesized to reflect differences both in imaging parameters and also in etiology and pathological severity.

***** Figure 1 near here**

1.2 WMH represent increased water content

WMH seen on MRI represent changes in white matter composition indicative of altered water content in hydrophobic white matter fibers and tracts. WMH can be classified as specific or non-specific depending on the water content they present [4]. This water disproportion can also vary with the brain area affected [4]. Radiologic insights into WMH etiology can come from relaxometry, where the MR signal for water is manipulated using different pulse sequences to derive various images. These images have different contrast characteristics that provide information about various aspects of the brain microstructure. Relaxometry can determine relaxation times (T1R: longitudinal relaxation time, T2*R: effective transversal relaxation time), providing quantitation of the tissue structure and water content [4]. Diffusion tensor imaging (DTI) provides further information on possible changes of the white matter microstructure and expansion of the WMH penumbra over time [5]. DTI data, specifically differences in fractional anisotropy (FA) and mean diffusivity (MD), suggest axonal damage [5]. Differences in water content can also be associated with white matter edema [4].

2. Why are WMH important?

2.1 Clinical Impact of WMH.

In clinical MRI scans of older people, WMH are typically interpreted as a surrogate of cerebral small vessel disease (SVD) [1, 2, 6]. Because various pathologies can lead to increased MRI signal intensity in white matter [6, 7], WMH alone are not diagnostically specific. Notably, distinguishing WMH due to SVD from those of multiple sclerosis (MS) and other inflammatory brain diseases or metabolic leukodystrophies can be challenging. Moreover, cortical degeneration common in older persons with degenerative diseases (such as AD, *Section 5* below) can lead to degeneration of fiber tracts and subsequent MRI changes.

Ample evidence supports a cross-sectional association between greater WMH volume and decrements in global or domain-specific cognitive performance [1-3, 8]. That said, effect

sizes are relatively small. A systematic review concluded that WMH explain a modest degree of cross-sectional variation in cognition and cognitive decline [3]. WMH are considered to be particularly correlated with reductions in information processing speed and executive function, although correlations with other cognitive domains have also been noted [3, 9]. Longitudinal studies in diverse populations consistently demonstrate that increasing WMH volume predicts cognitive decline, mild cognitive impairment, incident dementia, stroke and death [1-3, 10]. WMH are also associated with decline in gait and related aspects of physical performance [11, 12]. Nevertheless, a given individual may have extensive WMH but minimal cognitive impairment. WMH location, individual resilience factors and cognitive reserve likely determine clinical impact.

WMH play a key role in lowering the threshold for the clinical expression of dementia in the presence of neurodegenerative lesions [13, 14], specifically, AD-related pathology [15] See Box 1). Although there is the possibility that WMH promote or interact with AD-related pathologies, current data support an additive role for vascular pathologies rather than a synergistic interaction with AD-related pathological lesions [16].

Box 1. The VCID concept

The concept of vascular contributions to cognitive impairment and dementia (VCID) encompasses the spectrum of vascular disease processes that impact on cognitive function [13]. Brain vascular pathology is an important comorbidity in the multi-etiology view of common sporadic dementias of aging [14]. Mechanism-oriented VCID research can be described as the aging brain vasculature failing to cope with biological insults due to vascular disease, proteinopathies, metabolic disease and immune affront. In 2016 an NIH-sponsored summit defined research priorities in Alzheimer's and related dementias [13]. One output is the MarkVCID consortium, designed for multi-site development and validation of small vessel VCID candidate biomarkers to the point of readiness for large-scale clinical trials (see <https://markvcid.partners.org/>).

2.2 WMH in terms of clinical diagnostic criteria

The heterogeneity of WMH etiology and clinical manifestations present diagnostic challenges [17, 18]. Even in patients with dementia and significant WMH, the vascular contribution to the clinical phenotype may be missed if neuroimaging is not performed. The NINDS-AIREN criteria, a popular diagnostic framework for clinical definition of vascular dementia, require clinical dementia with a temporal relationship to preceding stroke with relevant imaging. In clinical practice, this may not be straightforward and most patients who exhibit WMH have no stroke history. It remains challenging to attribute cognitive deficits to WMH at an individual patient level. Three examples of possible “vascular” clinical courses to symptomatic cognitive impairment are illustrated (see Figure 2). While these archetypes rarely present in isolation, nevertheless they illustrate the heterogeneity of vascular cognitive impairment. Refined diagnostic criteria taking account of the clinical course of WMH are likely to be beneficial [17, 18].

******* Figure 2 near here**

Biochemical biomarkers for clinical use

Fluid biomarkers relevant to WMH will be clinically beneficial, reviewed elsewhere [19]. The neurofilament marker NF-L, extracellular metalloproteinase MMP-9, TIMP-1, the MMP-2 index and the albumin brain/plasma ratio are all increased in people with clinical diagnosis of SVD. Peripheral blood markers for WMH, alongside fluid biomarkers related to AD pathology, will help to sub-type patients according to their degree of AD pathology and brain vascular burden [13, 19, 20].

3. Epidemiology of WMH

3.1 Prevalence & Progression of WMH

Prevalence of WMH. Most individuals over age 60 have some degree of WMH, and prevalence increases with age. In the Rotterdam Scan Study, prevalence of subcortical WMH increased by 0.2% per year of age, while periventricular WMH increased by 0.4% [21] (See Box 2). For participants 60-70 years of age, 87% had subcortical and 68% had periventricular WMH. For participants 80-90 years of age, 100% had subcortical and 95% had periventricular WMH [21]. This age gradient of WMH has been confirmed in a wider age range (ages 20-90, Study of Health in Pomerania cohort) [22]. In addition, many cognitively healthy younger adults show some degree of WMH on MRI.

Progression of WMH. Longitudinal studies of community-dwelling, healthy older adults show increasing WMH severity or WMH volume over time [23]. Rates of progression are variable, likely due to study-specific definitions of progression or duration of follow-up. For example, in the Cardiovascular Health Study 28% of participants had a worsening WMH grade (by at least 1 grade on a 0-9 visual rating scale) over five years [24], while in the Rotterdam Scan Study 39% had progression of WMH volume over 3.4 years [25]. In the LADIS study 74% exhibited worsening over 3.1 years [26], and 84% had progression of WMH volume over 9.1 years in the Oregon Brain Aging Study [12]. Overall, longitudinal studies show annual increases in WMH volume ranging from 4.4% to 37.2% [23]. In some cohorts decrease in WMH volume has been reported, though effect sizes were small [27].

3.2 Risk Factors for WMH

Non-Modifiable Risk Factors. WMH are more prevalent at older ages, and some studies support faster progression with advanced age (see a recent review) [23]. Black race, female sex and *APOEε4* allele presence have all been associated with greater cross-sectional WMH burden or with WMH progression, though results have been mixed [23, 28].

Modifiable risk factors. Identified risk factors for WMH severity and progression are primarily vascular, cardio-metabolic and nutritional [23]. Among these, associations are strongest for blood pressure-related measures. In cross-sectional analyses, elevated blood pressure is unequivocally associated with the presence or severity of WMH. Studies considering high blood pressure earlier in life generally report an association with subsequent WMH. In the Rotterdam Scan Study elevated blood pressure was associated with increased

WMH risk 5 and 20 years later. Similarly, both midlife and late-life blood pressure were associated with increased WMH risk in the Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) Study[29], and elevated midlife blood pressure was related to late-life WMH volume in the National Heart Lung, and Blood Institute (NHLBI) Twin Study [30]. There is mixed evidence for dyslipidemia as a risk factor for WMH. Omega-3 polyunsaturated fatty acids have been associated with lower WMH burden. Neither diabetes mellitus nor insulin resistance are strongly related to WMH, while fasting glucose has been related to WMH progression. Greater visceral fat accumulation is more strongly associated with WMH than body mass index (BMI). Tobacco smoking, higher blood levels of inflammatory markers (CRP, interleukin-6), and low levels of vitamin B12 and hyperhomocysteinemia have all been associated with WMH (see Box 4). These studies of risk factors are discussed in a recent review [23].

Box 2. Is it helpful to separate WMH into Subcortical and Periventricular?

Subcortical WMH are defined as isolated foci appearing in the superficial white matter, which in most cases are not contiguous with periventricular WMH. The neuropathological substrates differ between the localizations [31, 32] (see *Section 4*), which can also have different risk factors and effects on cognition [1]. It has been proposed that cognitive impairments associated with periventricular WMH reflect disruption of cholinergic projections from the basal forebrain to the cortex.

Elevated levels of activated microglia in periventricular WMH indicate that these may particularly involve neuroinflammatory responses following disruption of the blood-brain barrier (BBB), see Box 4. This response is not seen in subcortical WMH [31]. In contrast, subcortical (but not periventricular) WMH volume was associated with lipid peroxidation in blood, which mediated the effect of hypertension, adding biological validity to a vascular etiology for subcortical WMH [20]. There may be further valid subdivisions within subcortical WMH. Nevertheless, it may be premature to discriminate periventricular from subcortical WMH clinically.

4. Neuropathological changes that underlie WMH

4.1 Types of underlying tissue damage in WMH

Pathophysiology of SVD-associated white matter histological lesions has been attributed to multiple mechanisms, including hypoperfusion, defective cerebrovascular reactivity, and BBB dysfunction [5, 6, 33-35]. The white matter microvascular network likely contributes to WMH pathogenesis, with vascular changes including arteriolar tortuosity, loss of blood vessel density, and venous collagenosis. Other possible mechanisms include dysfunction of oligodendrocyte precursor cells [36], or impaired perivascular (“glymphatic”) clearance. Different presentations of WMH indicate differences in underlying pathological changes. For example, punctate WMH (considered to represent mild tissue changes) are associated with myelin damage, gliosis and enlarged perivascular spaces, whereas extensive, confluent WMH are considered to represent more progressive pathological changes, including some degree of myelin loss, axonal disruption, and astrogliosis [6, 7]. Pathological differences in WMH also occur based on anatomical location, for example when evaluating periventricular vs.

subcortical WMH (see Box 2), or watershed vs. non-watershed regions. Minor pathological changes associated with WMH (at the caps/rims of periventricular regions, Fig 1) are most consistent with disturbed cerebrospinal fluid (CSF) transport and periventricular edema, both of which accompany aging.

Watershed zones are bordered by the distal territories of the anterior, middle, and posterior cerebral arteries. In an event of hemodynamic compromise, watershed regions are more susceptible to hypoperfusion and thus more likely to develop ischemic (or, oligemic) lesions. There are differences in the arteries supplying periventricular and subcortical white matter. While long perforating branches supply the periventricular white matter, shorter branches supply the subcortical white matter.

WMH severity has been associated with microinfarcts and with diffuse amyloid plaque load in brains of people diagnosed with AD [37]. In the context of AD pathology, especially in late stages of the disease, it is conceivable that some white matter lesions occur secondary to Wallerian degeneration, triggered by cortical neurodegenerative pathology [38]. More likely, AD pathology (common in older people) and WMH of vascular origin (even more common in older people) frequently co-present as has been noted in multiple autopsy based studies on mixed pathologies [14].

4.2 Demyelination in WMH

Early imaging studies indicated that severe WMH are related to cell death and myelin loss, see [6, 7], with early confluent WMH presenting more marked demyelination than focal/punctate WMH. Compared to subcortical WMH, periventricular WMH show increased axonal loss, astrogliosis, microglial density, and loss of oligodendrocytes. There may also be lobar variability. Early myelin changes may involve the frontal lobe, with subsequent gradual involvement of the parietal, temporal, and occipital lobes [39].

Demyelination is not a universal feature of WMH. In addition to demyelination, myelin “pallor” has been confirmed as a histological substrate of WMH. With aging the ability of the oligodendrocytes to regenerate myelin sheaths decreases [36]. To what degree pallor represents loss of myelin sheaths or loss of myelin secondary to axonal loss remains unresolved [40]. In aged primates, cognitive impairment exacerbated by hypertension is associated with myelin damage and microglial changes within white matter (Box 3).

4.3 Insights from MRI-histopathology correlative studies of WMH

Several studies have examined the underlying pathology of WMH using ex vivo MRI combined with histopathology [6, 33-35]. Early MRI-neuropathology correlative studies reported ischemic changes, with evidence of plasma extravasation (indicative of BBB dysfunction), rarefaction or loss of parenchymal tissue structure [41]. More advanced lesions showed reduced myelin density [41]. These data are broadly confirmed by more recent molecular studies [34, 35].

Box 3. White matter pathology and cognitive impairment in experimental primates

The rhesus monkey has brain structure similar to humans and similar age-related decline in cognitive function [42]. The monkey adult life span is up to 40 years and cognitive impairments appear from around 13 years and accelerate from 20 years, with deficits in executive function, working memory and recognition memory (resembling clinical criteria for subcortical SVD). There is considerable variability between subjects, the majority exhibiting severe impairments while some are only mildly impaired. Markers of AD pathology (amyloid plaques, hyper-phosphorylated tau) are variable or absent, and correlate poorly with cognitive impairment. Neuronal loss is not detectable and gray matter is well preserved [42]. MRI shows age-related loss of forebrain white matter volume, and decrease of FA in subcortical white matter tracts, both correlated with cognitive decline. Electron microscopy shows accumulating myelin defects, including splitting and ballooning of myelin sheaths, as well as complete degeneration of axons and their myelin. Age-related myelin histopathology correlates well with FA reduction and with diminution in the corpus callosal compound action potential. Possible mechanisms for age-related white matter damage in monkeys include oxidative stress and inflammation, worsened by age-related reductions in microglial activity and myelin repair [42, 43]. These observations point to white matter pathology, independent of neurodegeneration, as the source of age-related VCID in primates.

5. Are WMH related to Alzheimer Disease?

We acknowledge a distinction between AD as a syndromal diagnosis in living people and AD as a neuropathological description, or molecular aetiology [15]. With regard to clinical diagnosis, most people with AD diagnosis above the age of 70 have some degree of WMH. This may reflect associated vascular pathology, consistent with autopsy studies showing a high prevalence of mixed AD and vascular pathologies [14]. To what extent AD neuropathology causes WMH (of vascular or nonvascular origin) is still debated. The majority of amyloid PET studies found no association between β -amyloid tracer uptake and WMH burden [16, 44]. Nevertheless, a recent study in the ADNI cohort (using florbetapir instead of Pittsburgh compound-B as the amyloid tracer) observed a correlation between elevated brain β -amyloid and WMH [45]. Further, in people carrying dominant AD mutations, WMH volume is elevated up to 20 years in advance of cognitive symptoms, concomitant with altered levels of $A\beta$ and tau in CSF [46]. Because vascular disease is uncommon in these younger mutation-bearing persons, these data suggest that AD pathology may be related to vascular and/or nonvascular processes resulting in WMH.

Cerebral amyloid angiopathy (CAA) is a common age-related small vessel disease, characterized by the accumulation of $A\beta$ in the walls of cortical arterioles and leptomeningeal vessels [44, 47]. Some degree of histological CAA is present in most (but not all) brains that contain AD neuropathological hallmarks. CAA may contribute to the microvascular processes underlying WMH (impaired perivascular clearance, plasma extravasation, inflammation, hypo-perfusion, endothelial dysfunction) [44]. Whether or not AD is concomitant, CAA plays a distinct role in the spectrum of dementia [16, 47].

Box 4. Is inflammation a feature in WMH?

An explicit inflammatory process, in the manner of MS, does not apply to WMH of presumed vascular origin. Nevertheless some participation of inflammation-related molecules and cells appears likely and merits deeper understanding. In some large studies, circulating peripheral pro-inflammatory markers (e.g., CRP and interleukin-6) have been associated with WMH indicating possible involvement of inflammatory pathways in WMH. Other peripheral pro- and anti-inflammatory cytokines (e.g. interleukin-8) are elevated specifically in people with a clinical AD diagnosis who also have extensive WMH [20].

6. Implications for Treatment Interventions

6.1 Non-pharmacological interventions

Physical activity & Diet. A meta-analysis of cross-sectional observational studies demonstrated that physical fitness and activity were associated with lower global WMH volume, but had mixed results when local WMH (periventricular and subcortical) were examined separately [48]. In relation to WMH, few randomized controlled trials of physical activity have been carried out. These studies have been restricted to prevention of WMH progression as opposed to primary prevention. In older women, twice weekly resistance training reduced WMH volume progression, relative to balance and toning control [32].

Observational cohort studies of diet and nutrition suggest that the consumption of tuna/non-fried fish and the Mediterranean diet is associated with less WMH load [49, 50]. Higher plasma omega-3 polyunsaturated fatty acids (abundant in both diets) are associated with less WMH mediated executive function decline in aging and these findings have led to a randomized-controlled trial of omega 3 fatty acids for the prevention of WMH accumulation (n-3 PUFA for Vascular Cognitive Aging, NCT01953705).

Multi-domain interventions. The Look AHEAD study tested a 10-year physical activity and dietary modification intervention in overweight and obese older adults with type 2 diabetes mellitus. Although there was no effect of the intervention on cognition in the MRI sub-study, the intervention group had significantly lower WMH volume relative to the control group [51]. Similarly, in the EVA study, participants with clinical AD diagnoses and MRI evidence of SVD (WMH, lacunar or cortical infarcts) were randomized to either a multi-domain approach (dietary and physical activity counselling, smoking cessation as well as pharmacologic treatment of cardiovascular risk factors) or standard care. Those randomized to the composite intervention had reduced progression of WMH (but not global atrophy or new infarcts) [52].

6.2 Pharmacological interventions

Blood pressure medications. Randomised clinical trial sub-analyses indicate that effective antihypertensive therapy reduces WMH incidence. Treatment with an angiotensin-converting enzyme (ACE) inhibitor over 36 months reduced WMH number and total WMH volume in

the PROGRESS trial [53]. An observational cohort study suggested that treatment with an angiotensin receptor blocker, vs. an ACE inhibitor, was associated with smaller WMH volumes in people with a clinical AD diagnosis [54]. An MRI sub-study of the preDIVA trial [55] suggested a beneficial effect in the sub-group with large baseline WMH volume, but found no overall impact of intensive vascular management on WMH progression. A trial of intensive vs. standard blood pressure control (based on ambulatory blood pressure) is ongoing in individuals who are either normal or mildly impaired on cognition and mobility, with WMH progression as a secondary outcome [56]. Similarly, the results of the SPRINT MIND trial of intensive vs. standard blood pressure control on WMH were presented at AAIC 2018, and we await published, peer-reviewed results [57]. The effect of two years of treatment with either ACE inhibitor or angiotensin II receptor blockers on an outcome of SVD progression, including WMH and silent brain infarcts, is currently being tested in the CEREBRAL study [58].

Statins. Nearly three years of treatment with 40 mg daily pravastatin in the PROSPER study did not reduce WMH progression over the placebo group in individuals with increased vascular risk [59].

Antithrombotic agents. The ASPREE-Neuro Study is evaluating 100 mg daily aspirin vs. placebo over one year, with a secondary outcome of WMH volume change [60].

Concluding comments

Converging data from clinical, neuropathological and experimental studies have begun to unravel WMH mechanisms. We are optimistic that the next ten years will see substantial advances in molecular understanding and clinical management of WMH and VCID. Deeper molecular understanding of the various etiologies and pathologies that lead to WMH will improve diagnostic specificity. It will also enable more refined medicinal chemistry, for generating improved biomarkers (both imaging and biochemical) and novel therapeutic agents. Better structural and molecular biomarkers will serve as endpoints in clinical trials of targeted treatments, based on pathological understanding. How the WMH profile of a given dementia patient should guide treatment, while minimizing adverse clinical outcomes, remains a fertile field for clinical research.

Currently, treatment of WMH of presumed vascular origin is limited to lifestyle modifications and risk factor management. Given the associations between WMH and vascular risk factors, it is imperative to target vascular health throughout the life-course as a prevention strategy. At a societal level, there are enormous opportunities for policy makers to combat the 21st century obesogenic environment which contributes significantly to poor vascular and metabolic health. Effective regulations on the content of foods (e.g. sugar in food and drinks), clear labelling of food products, and food marketing (to children in particular) will likely have more healthcare impact than any drug.

Scientific progress is needed in the following areas. 1) Application of emerging diagnostic criteria, to identify different subtypes of WMH, possibly with differing etiology, outcomes and clinical significance. 2) Robust differential biomarkers, to discriminate different pathologies (SVD, CAA, AD), their possible interactions and their relation to VCID. 3) Consensus on segregation algorithms (e.g. definitions of regional WMH boundaries). 4)

Animal models relevant to WMH of different pathological origin. 5) Further detailed MRI-histopathology correlative studies, to encompass the range of WMH-related lesion characteristics. 6) Hypothesis-driven, randomized controlled trials of drugs and other interventions targeting WMH.

Acknowledgements

We are grateful to the Alzheimers Association and to ISTAART for hosting the event at AAIC 2017, where this Perspective originated. We apologise to our colleagues worldwide whose excellent publications we have failed to cite, owing to the Reference limit of the journal. Where two citations were relevant, we have as a rule included only the more recent one.

DAB is funded by NHMRC. SEB has funding from NIH/National Institute on Aging grant F30AG054115. GJB acknowledges support from Vici Grant 918.16.616 from ZonMw, The Netherlands, Organisation for Health Research and Development and from the Netherlands CardioVascular Research Initiative: the Dutch Heart Foundation (CVON 2012-06 Heart Brain Connection), Dutch Federation of University Medical Centres, ZonMW and the Royal Netherlands Academy of Sciences. GLB reports US NIH/NIA funding. BLC holds a Canada Research Chair. SF has NIH funding. TMH and SNL were supported by funding from the NIH (P30 AG049638). JK is grateful for the support of the Marga and Walter Boll Foundation, Kerpen, Germany. MCP has NIH and US DoD funding. CES was funded by National Institute on Aging Grant number F31 AG054084. AMT was funded by Israel Science Foundation Grant 1353/11. CLW is funded by the Weston Brain Institute, Canadian Institutes of Health Research (CIHR) and Cure Alzheimer Fund. AHH has funding from UK MRC (MR/R005567/1), Alzheimer's Society (UK) and ADDF (Ref. 20140901).

The content is solely the responsibility of the authors and does not necessarily represent the official views of any funders. The funding sources had no involvement in preparation of the article, in the writing of the manuscript and in the decision to submit the manuscript for publication.

Figure Legends

Figure 1. MRI scans showing typical examples of WMHs of presumed vascular origin. Scan A: punctate deep subcortical WMH in left hemisphere and periventricular caps. This scan is Fazekas grade 1, on the Fazekas scale of WMH severity (range 0-3). In the right thalamus a lacune can be seen. B, C: two examples of severe confluent WMH. Note that borders between periventricular and deep subcortical WMH become difficult to define. Scans B and C are Fazekas grade 3. Scans A-C are FLAIR sequences. Figure provided by GJ Biessels.

Figure 2. Conceptual clinical courses leading to vascular dementia. A; Multi-infarct dementia, stepwise pattern of cognitive decline. B; Strategic vascular dementia, due to a focal lesion in a clinically eloquent site. One step pattern, with some recovery. C; WMH-associated subcortical vascular dementia. Slow progression without stepwise pattern. Figure provided by J Kwon.

References

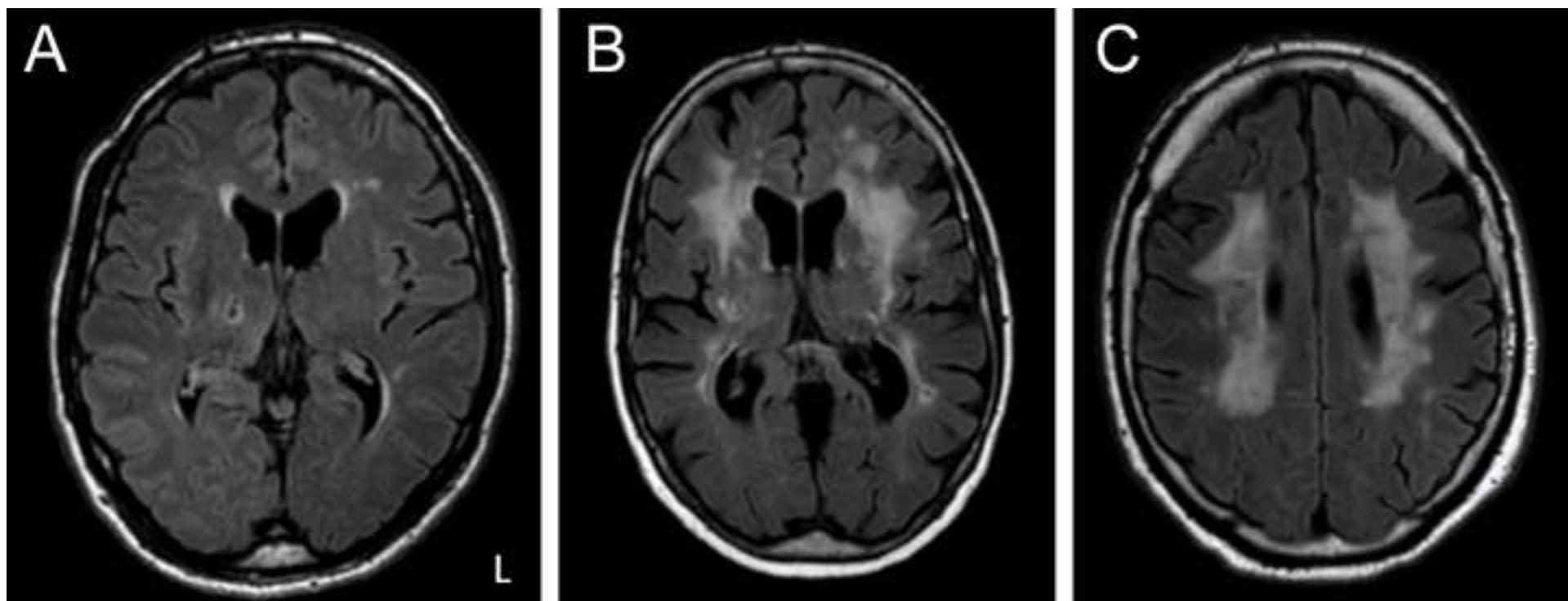
1. Prins ND, Scheltens P: White matter hyperintensities, cognitive impairment and dementia: an update. *Nat Rev Neurol* 2015, 11(3):157-165.
2. Debette S, Markus HS: The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 2010, 341:c3666.
3. Kloppenborg RP, Nederkoorn PJ, Geerlings MI, van den Berg E: Presence and progression of white matter hyperintensities and cognition: a meta-analysis. *Neurology* 2014, 82(23):2127-2138.
4. De Guio F, Vignaud A, Chabriat H, Jouvent E: Different types of white matter hyperintensities in CADASIL: Insights from 7-Tesla MRI. *J Cereb Blood Flow Metab* 2017:271678X17690164.
5. Maniega SM, Valdes Hernandez MC, Clayden JD, Royle NA, Murray C, Morris Z, Aribisala BS, Gow AJ, Starr JM, Bastin ME *et al*: White matter hyperintensities and normal-appearing white matter integrity in the aging brain. *Neurobiol Aging* 2015, 36(2):909-918.
6. Gouw AA, Seewann A, van der Flier WM, Barkhof F, Rozemuller AM, Scheltens P, Geurts JJ: Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. *J Neurol Neurosurg Psychiatry* 2011, 82(2):126-135.
7. Schmidt R, Schmidt H, Haybaeck J, Loitfelder M, Weis S, Cavalieri M, Seiler S, Enzinger C, Ropele S, Erkinjuntti T *et al*: Heterogeneity in age-related white matter changes. *Acta Neuropathol* 2011, 122(2):171-185.
8. Bolandzadeh N, Davis JC, Tam R, Handy TC, Liu-Ambrose T: The association between cognitive function and white matter lesion location in older adults: a systematic review. *BMC Neurol* 2012, 12:126.
9. Arvanitakis Z, Fleischman DA, Arfanakis K, Leurgans SE, Barnes LL, Bennett DA: Association of white matter hyperintensities and gray matter volume with cognition in older individuals without cognitive impairment. *Brain Struct Funct* 2016, 221(4):2135-2146.
10. Verdelho A, Madureira S, Moleiro C, Ferro JM, Santos CO, Erkinjuntti T, Pantoni L, Fazekas F, Visser M, Waldemar G *et al*: White matter changes and diabetes predict cognitive decline in the elderly: the LADIS study. *Neurology* 2010, 75(2):160-167.
11. Rosario BL, Rosso AL, Aizenstein HJ, Harris T, Newman AB, Satterfield S, Studenski SA, Yaffe K, Rosano C, Health ABCS: Cerebral White Matter and Slow Gait: Contribution of Hyperintensities and Normal-appearing Parenchyma. *J Gerontol A Biol Sci Med Sci* 2016, 71(7):968-973.
12. Silbert LC, Howieson DB, Dodge H, Kaye JA: Cognitive impairment risk: white matter hyperintensity progression matters. *Neurology* 2009, 73(2):120-125.
13. Corriveau RA, Koroshetz WJ, Gladman JT, Jeon S, Babcock D, Bennett DA, Carmichael ST, Dickinson SL, Dickson DW, Emr M *et al*: Alzheimer's Disease-Related Dementias Summit 2016: National research priorities. *Neurology* 2017, 89(23):2381-2391.
14. Kapasi A, DeCarli C, Schneider JA: Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol* 2017, 134(2):171-186.
15. Jack CR, Jr., Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J *et al*: NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018, 14(4):535-562.
16. Vemuri P, Knopman DS: The role of cerebrovascular disease when there is concomitant Alzheimer disease. *Biochim Biophys Acta* 2016, 1862(5):952-956.

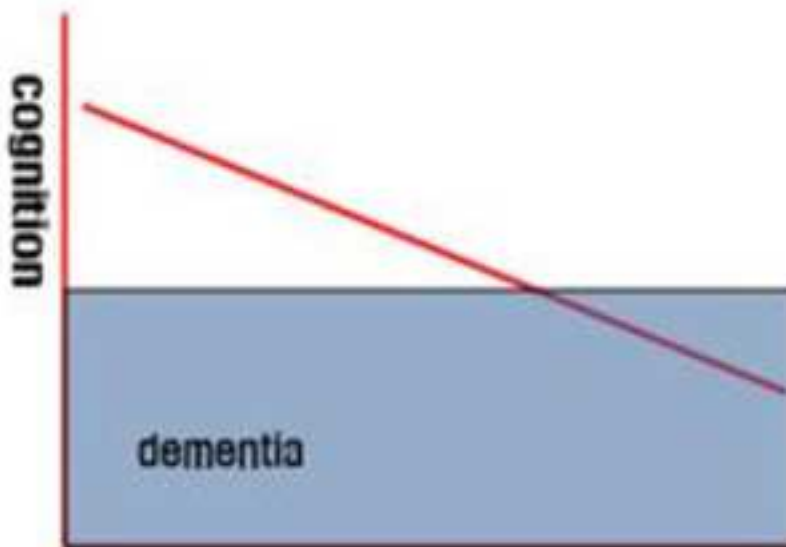
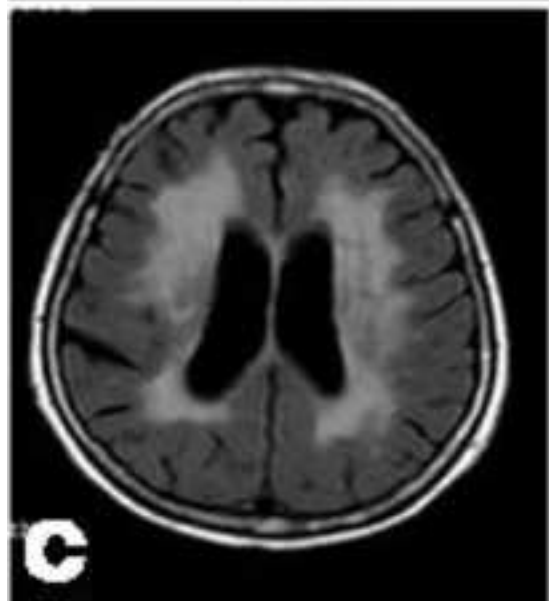
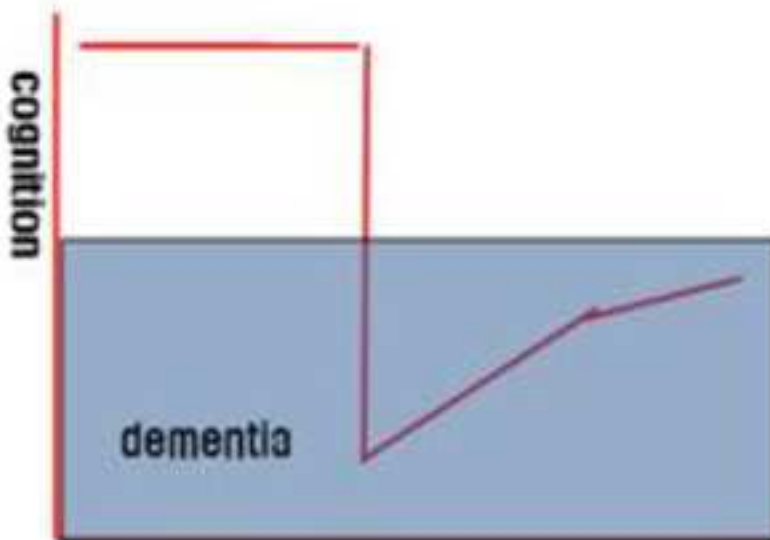
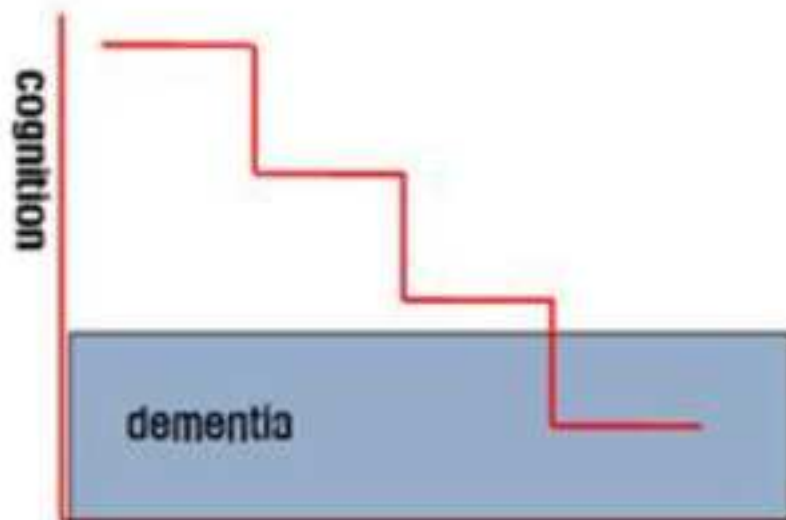
17. Smith EE: Clinical presentations and epidemiology of vascular dementia. *Clin Sci (Lond)* 2017, 131(11):1059-1068.
18. Sachdev P, Kalaria R, O'Brien J, Skoog I, Alladi S, Black SE, Blacker D, Blazer DG, Chen C, Chui H *et al*: Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc Disord* 2014, 28(3):206-218.
19. Wallin A, Kapaki E, Boban M, Engelborghs S, Hermann DM, Huisa B, Jonsson M, Kramberger MG, Lossi L, Malojcic B *et al*: Biochemical markers in vascular cognitive impairment associated with subcortical small vessel disease - A consensus report. *BMC Neurol* 2017, 17(1):102.
20. Swardfager W, Yu D, Scola G, Cogo-Moreira H, Chan P, Zou Y, Herrmann N, Lanctot KL, Ramirez J, Gao F *et al*: Peripheral lipid oxidative stress markers are related to vascular risk factors and subcortical small vessel disease. *Neurobiol Aging* 2017, 59:91-97.
21. de Leeuw FE, de Groot JC, Oudkerk M, Witteman JC, Hofman A, van GJ, Breteler MM: Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain* 2002, 125(Pt 4):765-772.
22. Habes M, Erus G, Toledo JB, Bryan N, Janowitz D, Doshi J, Volzke H, Schminke U, Hoffmann W, Grabe HJ *et al*: Regional tract-specific white matter hyperintensities are associated with patterns to aging-related brain atrophy via vascular risk factors, but also independently. *Alzheimers Dement (Amst)* 2018, 10:278-284.
23. Jorgensen DR, Shaaban CE, Wiley CA, Gianaros PJ, Mettenberg J, Rosano C: A population neuroscience approach to the study of cerebral small vessel disease in midlife and late life: an invited review. *Am J Physiol Heart Circ Physiol* 2018, 314(6):H1117-H1136.
24. Longstreth WT, Arnold AM, Beauchamp NJ, Jr., Manolio TA, Lefkowitz D, Jungreis C, Hirsch CH, O'Leary DH, Furberg CD: Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke* 2005, 36(1):56-61.
25. van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM: Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. *Stroke* 2008, 39(10):2712-2719.
26. Gouw AA, van der Flier WM, Fazekas F, van Straaten EC, Pantoni L, Poggesi A, Inzitari D, Erkinjuntti T, Wahlund LO, Waldemar G *et al*: Progression of White Matter Hyperintensities and Incidence of New Lacunes Over a 3-Year Period. The Leukoaraiosis and Disability Study. *Stroke* 2008.
27. Maillard P, Carmichael O, Fletcher E, Reed B, Mungas D, DeCarli C: Coevolution of white matter hyperintensities and cognition in the elderly. *Neurology* 2012, 79(5):442-448.
28. Brickman AM, Schupf N, Manly JJ, Stern Y, Luchsinger JA, Provenzano FA, Narkhede A, Razlighi Q, Collins-Praino L, Artero S *et al*: APOE epsilon4 and risk for Alzheimer's disease: do regionally distributed white matter hyperintensities play a role? *Alzheimers Dement* 2014, 10(6):619-629.
29. Vuorinen M, Spulber G, Damangir S, Niskanen E, Ngandu T, Soininen H, Kivipelto M, Solomon A: Midlife CAIDE dementia risk score and dementia-related brain changes up to 30 years later on magnetic resonance imaging. *J Alzheimers Dis* 2015, 44(1):93-101.
30. Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Jack LM, Carmelli D: Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurology* 1998, 51(4):986-993.

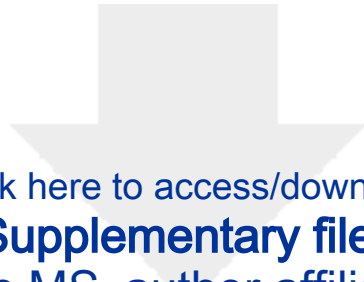
31. Simpson JE, Fernando MS, Clark L, Ince PG, Matthews F, Forster G, O'Brien JT, Barber R, Kalaria RN, Brayne C *et al*: White matter lesions in an unselected cohort of the elderly: astrocytic, microglial and oligodendrocyte precursor cell responses. *Neuropathol Appl Neurobiol* 2007, 33(4):410-419.
32. Bolandzadeh N, Tam R, Handy TC, Nagamatsu LS, Hsu CL, Davis JC, Dao E, Beattie BL, Liu-Ambrose T: Resistance Training and White Matter Lesion Progression in Older Women: Exploratory Analysis of a 12-Month Randomized Controlled Trial. *J Am Geriatr Soc* 2015, 63(10):2052-2060.
33. Fernando MS, Simpson JE, Matthews F, Brayne C, Lewis CE, Barber R, Kalaria RN, Forster G, Esteves F, Wharton SB *et al*: White matter lesions in an unselected cohort of the elderly: molecular pathology suggests origin from chronic hypoperfusion injury. *Stroke* 2006, 37(6):1391-1398.
34. Hainsworth AH, Minett T, Andoh J, Forster G, Bhide I, Barrick TR, Elderfield K, Jeevahan J, Markus HS, Bridges LR: Neuropathology of White Matter Lesions, Blood-Brain Barrier Dysfunction, and Dementia. *Stroke* 2017, 48(10):2799-2804.
35. Young VG, Halliday GM, Kril JJ: Neuropathologic correlates of white matter hyperintensities. *Neurology* 2008, 71(11):804-811.
36. Joutel A, Chabriat H: Pathogenesis of white matter changes in cerebral small vessel diseases: beyond vessel-intrinsic mechanisms. *Clin Sci (Lond)* 2017, 131(8):635-651.
37. Dallaire-Theroux C, Callahan BL, Potvin O, Saikali S, Duchesne S: Radiological-Pathological Correlation in Alzheimer's Disease: Systematic Review of Antemortem Magnetic Resonance Imaging Findings. *J Alzheimers Dis* 2017, 57(2):575-601.
38. McAleese KE, Walker L, Graham S, Moya ELJ, Johnson M, Erskine D, Colloby SJ, Dey M, Martin-Ruiz C, Taylor JP *et al*: Parietal white matter lesions in Alzheimer's disease are associated with cortical neurodegenerative pathology, but not with small vessel disease. *Acta Neuropathol* 2017.
39. Hase Y, Horsburgh K, Ihara M, Kalaria RN: White matter degeneration in vascular and other ageing-related dementias. *J Neurochem* 2018, 144(5):617-633.
40. Shaaban CE, Aizenstein HJ, Jorgensen DR, MacCloud RL, Meckes NA, Erickson KI, Glynn NW, Mettenburg J, Guralnik J, Newman AB *et al*: In Vivo Imaging of Venous Side Cerebral Small-Vessel Disease in Older Adults: An MRI Method at 7T. *AJNR Am J Neuroradiol* 2017, 38(10):1923-1928.
41. Marshall VG, Bradley WG, Jr., Marshall CE, Bhoopat T, Rhodes RH: Deep white matter infarction: correlation of MR imaging and histopathologic findings. *Radiology* 1988, 167(2):517-522.
42. Kohama SG, Rosene DL, Sherman LS: Age-related changes in human and non-human primate white matter: from myelination disturbances to cognitive decline. *Age (Dordr)* 2012, 34(5):1093-1110.
43. Shobin E, Bowley MP, Estrada LI, Heyworth NC, Orczykowski ME, Eldridge SA, Calderazzo SM, Mortazavi F, Moore TL, Rosene DL: Microglia activation and phagocytosis: relationship with aging and cognitive impairment in the rhesus monkey. *Geroscience* 2017, 39(2):199-220.
44. Smith EE: Cerebral amyloid angiopathy as a cause of neurodegeneration. *J Neurochem* 2018, 144(5):651-658.
45. Marnane M, Al-Jawadi OO, Mortazavi S, Pogorzelec KJ, Wang BW, Feldman HH, Hsiung GY: Periventricular hyperintensities are associated with elevated cerebral amyloid. *Neurology* 2016, 86(6):535-543.
46. Lee S, Viqar F, Zimmerman ME, Narkhede A, Tosto G, Benzinger TL, Marcus DS, Fagan AM, Goate A, Fox NC *et al*: White matter hyperintensities are a core feature of

- Alzheimer's disease: Evidence from the dominantly inherited Alzheimer network. *Ann Neurol* 2016, 79(6):929-939.
47. Roseborough A, Ramirez J, Black SE, Edwards JD: Associations between amyloid beta and white matter hyperintensities: A systematic review. *Alzheimers Dement* 2017, 13(10):1154-1167.
 48. Sexton CE, Betts JF, Demnitz N, Dawes H, Ebmeier KP, Johansen-Berg H: A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. *Neuroimage* 2016, 131:81-90.
 49. Gardener H, Scarmeas N, Gu Y, Boden-Albala B, Elkind MS, Sacco RL, DeCarli C, Wright CB: Mediterranean diet and white matter hyperintensity volume in the Northern Manhattan Study. *Arch Neurol* 2012, 69(2):251-256.
 50. Virtanen JK, Siscovick DS, Longstreth WT, Jr., Kuller LH, Mozaffarian D: Fish consumption and risk of subclinical brain abnormalities on MRI in older adults. *Neurology* 2008, 71(6):439-446.
 51. Espeland MA, Erickson K, Neiberg RH, Jakicic JM, Wadden TA, Wing RR, Desiderio L, Erus G, Hsieh MK, Davatzikos C *et al*: Brain and White Matter Hyperintensity Volumes After 10 Years of Random Assignment to Lifestyle Intervention. *Diabetes Care* 2016, 39(5):764-771.
 52. Richard E, Gouw AA, Scheltens P, van Gool WA: Vascular care in patients with Alzheimer disease with cerebrovascular lesions slows progression of white matter lesions on MRI: the evaluation of vascular care in Alzheimer's disease (EVA) study. *Stroke* 2010, 41(3):554-556.
 53. Dufouil C, Chalmers J, Coskun O, Besancon V, Bousser MG, Guillon P, MacMahon S, Mazoyer B, Neal B, Woodward M *et al*: Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) Magnetic Resonance Imaging Substudy. *Circulation* 2005, 112(11):1644-1650.
 54. Edwards JD, Ramirez J, Callahan BL, Tobe SW, Oh P, Berezuk C, Lanctot K, Swardfager W, Nestor S, Kiss A *et al*: Antihypertensive Treatment is associated with MRI-Derived Markers of Neurodegeneration and Impaired Cognition: A Propensity-Weighted Cohort Study. *J Alzheimers Dis* 2017, 59(3):1113-1122.
 55. Moll van Charante EP, Richard E, Eurelings LS, van Dalen JW, Ligthart SA, van Bussel EF, Hoevenaer-Blom MP, Vermeulen M, van Gool WA: Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet* 2016, 388(10046):797-805.
 56. White WB, Jalil F, Wakefield DB, Kaplan RF, Bohannon RW, Hall CB, Moscufo N, Fellows D, Guttman CRG, Wolfson L: Relationships among clinic, home, and ambulatory blood pressures with small vessel disease of the brain and functional status in older people with hypertension. *Am Heart J* 2018, 205:21-30.
 57. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, Fine LJ, Haley WE, Hawfield AT, Ix JH *et al*: Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥ 75 Years: A Randomized Clinical Trial. *JAMA* 2016, 315(24):2673-2682.
 58. Yamano S, Horii M, Takami T, Sakuma M, Morimoto T, Okada S, Taoka T, Kichikawa K, Sasamura H, Itoh H *et al*: Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of stroke recurrence and longitudinal progression of white matter lesions and silent brain infarcts on MRI (CEREBRAL study): rationale, design, and methodology. *Int J Stroke* 2015, 10(3):452-456.

59. ten Dam VH, van den Heuvel DM, van Buchem MA, Westendorp RG, Bollen EL, Ford I, de Craen AJ, Blauw GJ: Effect of pravastatin on cerebral infarcts and white matter lesions. *Neurology* 2005, 64(10):1807-1809.
60. Ward SA, Raniga P, Ferris NJ, Woods RL, Storey E, Bailey MJ, Brodtmann A, Yates PA, Donnan GA, Trevaks RE *et al*: ASPREE-NEURO study protocol: A randomized controlled trial to determine the effect of low-dose aspirin on cerebral microbleeds, white matter hyperintensities, cognition, and stroke in the healthy elderly. *Int J Stroke* 2017, 12(1):108-113.







[Click here to access/download](#)

Supplementary files

Hainsworth MS_author affiliations.docx

