

THE
UNIVERSITY
OF RHODE ISLAND

University of Rhode Island
DigitalCommons@URI

Biomedical and Pharmaceutical Sciences
Faculty Publications

Biomedical and Pharmaceutical Sciences

2019

White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): Knowledge gaps and opportunities

Jessica Alber
University of Rhode Island, jalber@uri.edu

et al

Follow this and additional works at: https://digitalcommons.uri.edu/bps_facpubs

Citation/Publisher Attribution

Alber, J., Alladi, S., Bae, H.-J., Barton, D. A., Beckett, L. A., Bell, J. M.,...Hainsworth, A. H. (2019). White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): Knowledge gaps and opportunities. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, 5(1), 107-117. doi: 10.1016/j.trci.2019.02.001
Available at: <https://doi.org/10.1016/j.trci.2019.02.001>

This Article is brought to you for free and open access by the Biomedical and Pharmaceutical Sciences at DigitalCommons@URI. It has been accepted for inclusion in Biomedical and Pharmaceutical Sciences Faculty Publications by an authorized administrator of DigitalCommons@URI. For more information, please contact digitalcommons@etal.uri.edu.

Perspective

White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): Knowledge gaps and opportunities

Jessica Alber^a, Suvarna Alladi^b, Hee-Joon Bae^c, David A. Barton^d, Laurel A. Beckett^e, Joanne M. Bell^f, Sara E. Berman^g, Geert Jan Biessels^h, Sandra E. Blackⁱ, Isabelle Bos^j, Gene L. Bowman^{k,l,m}, Emanuele Braiⁿ, Adam M. Brickman^o, Brandy L. Callahan^p, Roderick A. Corriveau^p, Silvia Fossati^q, Rebecca F. Gottesman^r, Deborah R. Gustafson^s, Vladimir Hachinski^t, Kathleen M. Hayden^u, Alex M. Helman^v, Timothy M. Hughes^w, Jeremy D. Isaacs^x, Angela L. Jefferson^y, Sterling C. Johnson^z, Alifiya Kapasi^{aa}, Silke Kern^{bb}, Jay C. Kwon^{cc}, Juraj Kukolja^{dd}, Athene Lee^{ee}, Samuel N. Lockhart^{ff}, Anne Murray^{gg}, Katie E. Osborn^{hh}, Melinda C. Powerⁱⁱ, Brittani R. Price^{jj}, Hanneke F.M. Rhodius-Meester^{kk}, Jacqueline A. Rondeau^{ll}, Allyson C. Rosen^{mm}, Douglas L. Roseneⁿⁿ, Julie A. Schneider^{oo}, Henrieta Scholtzova^{pp}, C. Elizabeth Shaaban^{qq}, Narlon C.B.S. Silva^{rr}, Heather M. Snyder^{ss}, Walter Swardfager^{tt}, Aron M. Troen^{uu}, Susanne J. van Veluw^{vv}, Prashanthi Vemuri^{ww}, Anders Wallin^{xx}, Cheryl Wellington^{yy}, Donna M. Wilcock^{zz}, Sharon Xiangwen Xie^{aaa}, Atticus H. Hainsworth^{bbb,*}

^aDepartment of Biomedical and Pharmaceutical Sciences, George & Anne Ryan Institute for Neuroscience, University of Rhode Island, Kingston, RI, USA

^bDepartment of Neurology, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

^cCerebrovascular Disease Center, Seoul National University Bundang Hospital, Seongnam, Korea

^dDepartment of Psychiatry, University of Melbourne, Melbourne, Australia

^eDepartment of Public Health Sciences, School of Medicine University of California, Davis, CA, USA

^fSyneos Health, Wilmington, NC, USA

^gWisconsin Alzheimer's Disease Research Center, Medical Scientist Training Program, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

^hDepartment of Neurology and Neurosurgery, Brain Center Rudolf Magnus Institute, University Medical Center Utrecht, Utrecht, The Netherlands

ⁱDepartment of Medicine, University of Toronto, Sunnybrook Research Institute, Toronto, ON, Canada

^jDepartment of Psychiatry & Neuropsychology, Alzheimer Centre Limburg, School for Mental Health & Neuroscience, Maastricht University, Maastricht, The Netherlands

^kDepartment of Medicine, Harvard Medical School, Boston, MA, USA

^lInstitute for Aging Research, Hebrew SeniorLife, Boston, MA, USA

^mDepartment of Neurology, Oregon Health & Science University, Portland, OR, USA

This Perspective article was developed from a session of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment Vascular Cognitive Disorders Professional Interest Area, Alzheimer's Association International Conference 2017.

Declarations of Interest: D.A.B. is the director of NeuroTrials Victoria Pty Ltd and has undertaken clinical trials for Roche, Alkermes, Otsuka, Lundbeck, and Janssen. G.J.B. has received speaker fees from Eisai and research support from Boehringer-Ingelheim. All compensation for these services is transferred to his employer, the University Medical Center Utrecht. G.L.B. is an unpaid scientific advisory board member of the PROPAG-AGEING EU Horizon 2020 initiative. R.A.C. is an employee of National Institute of Neurological Disorders and Stroke. J.D.I. has attended

an advisory board for Biogen, is a principal investigator on clinical trials, and outside of the submitted work, was sponsored and funded by Roche and Merck. K.E.O. is funded by National Institutes of Health (F32AG058395). C.W. is a member of the Canadian Institutes of Health Research-funded Canadian Consortium for Neurodegeneration in Aging. A.H.H. has received honoraria from Eli Lilly and the National Institute of Aging and is chair of the Dementias Platform UK Vascular Experimental Medicine group. All other authors declare they have no conflicts to disclose.

*Corresponding author. Tel.: +44 208 725 5586; Fax: +44 208 725 2950.

E-mail address: ahainsworth@sgul.ac.uk

ⁿNeuro-Bio Ltd, Culham Science Centre, Abingdon, UK

^oTaub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

^pDepartment of Psychology, University of Calgary & Hotchkiss Brain Institute, Calgary, AB, Canada

^qDepartments of Neurology and Psychiatry, NYU School of Medicine, New York, NY, USA

^rDivision of Cerebrovascular Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

^sSection for NeuroEpidemiology, State University of New York - Downstate Medical Center, Brooklyn, NY, USA

^tWestern University, London Health Sciences Centre, London, ON, Canada

^uDepartment of Social Sciences and Health Policy, Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA

^vUniversity of Kentucky, Sanders-Brown Center on Aging, Lexington, KY, USA

^wDepartment of Internal Medicine – Section of Gerontology and Geriatric Medicine, and Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, NC, USA

^xSt George's University of London and Department of Neurology, St George's University Hospitals NHS Foundation Trust, London, UK

^yVanderbilt Memory & Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN, USA

^zDepartment of Medicine-Geriatrics, Institute on Aging, University of Wisconsin-Madison, Madison, WI, USA

^{aa}Department of Pathology (Neuropathology), Rush Alzheimer's Disease Center, Chicago, IL, USA

^{bb}Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

^{cc}Department of Neurology, Changwon Fatima Hospital, Changwon, Korea

^{dd}Department of Neurology and Clinical Neurophysiology, Helios University Hospital Wuppertal, Wuppertal, Germany

^{ee}Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI, USA

^{ff}Department of Internal Medicine – Section of Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA

^{gg}Berman Center for Outcomes and Clinical Research, 20298 Minneapolis Medical Research Foundation, Minneapolis, MN, USA

^{hh}Vanderbilt Memory & Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN, USA

ⁱⁱDepartment of Epidemiology and Biostatistics, Milken Institute School of Public Health, George Washington University, Washington, DC, USA

^{jj}Sanders Brown Center on Aging, University of Kentucky, Lexington, KY, USA

^{kk}Alzheimer Center, Department of Neurology, VU University Medical Centre, Amsterdam Neuroscience, Amsterdam, The Netherlands

^{ll}Montclair Memory Clinic, Montclair, NJ, USA

^{mmm}Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA

ⁿⁿAnatomy & Neurobiology, Boston University School of Medicine, Boston, MA, USA

^{oo}Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago IL, USA

^{pp}Department of Neurology, NYU School of Medicine, New York, NY, USA

^{qq}Department of Epidemiology, Graduate School of Public Health & Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA, USA

^{rr}School of Kinesiology, Western Centre for Public Health & Family Medicine, London, ON, Canada

^{ss}Division of Medical and Scientific Relations, Alzheimer's Association, Chicago, IL, USA

^{tt}Sunnybrook Research Institute, University of Toronto, Toronto, ON, Canada

^{uu}Institute of Biochemistry Food Science and Nutrition, The Robert H. Smith Faculty of Agriculture Food and Environment, The Hebrew University of Jerusalem, Jerusalem, Israel

^{vv}Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

^{ww}Department of Radiology, Mayo Clinic Rochester, Rochester, MN, USA

^{xx}Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

^{yy}Department of Pathology and Laboratory Medicine, Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC, Canada

^{zz}Sanders-Brown Center on Aging, Department of Physiology, University of Kentucky, Lexington, KY, USA

^{aaa}Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania, Philadelphia, PA, USA

^{bbb}Molecular & Clinical Sciences Research Institute, St George's University of London and Department of Neurology, St George's University Hospitals NHS Foundation Trust, London, UK

Abstract

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

© 2019 The Authors. Published by Elsevier Inc. on behalf of the Alzheimer's Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords:

Vascular dementia; Vascular cognitive impairment; Leukoaraiosis; White matter lesions; Small vessel disease

1. Introduction

1.1. What do we mean by white matter hyperintensities?

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

1.2. WMHs represent increased water content

WMHs seen on MRI represent changes in white matter composition, indicative of altered water content in hydrophobic white matter fibers and tracts. WMHs can be classified as specific or nonspecific 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 magnetic resonance 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 provides further information on possible changes of the white matter microstructure and expansion of the WMH penumbra

over time [5]. Diffusion tensor imaging data, specifically differences in fractional anisotropy (FA) and mean diffusivity, suggest axonal damage [5]. Differences in water content can also be associated with white matter edema [4].

2. Why are WMHs important?

2.1. Clinical impact of WMHs

In clinical MRI scans of older people, WMHs 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], WMHs alone are not diagnostically specific. Notably, distinguishing WMHs due to SVD from those of multiple sclerosis and other inflammatory brain diseases or metabolic leukodystrophies can be challenging. Moreover, cortical degeneration common in older persons with degenerative diseases (such as Alzheimer’s disease [AD]; see Section 5) 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 WMHs explain a modest degree of cross-sectional variation in cognition and cognitive decline [3]. WMHs 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].

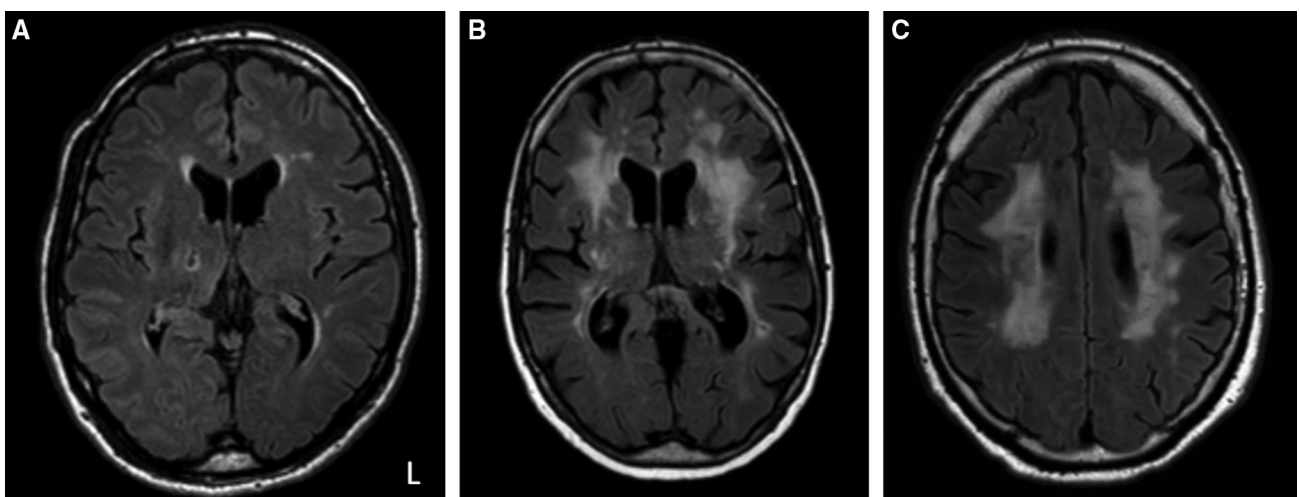


Fig. 1. MRI scans showing typical examples of WMHs of presumed vascular origin. (A) Punctate deep subcortical WMH in the left hemisphere and periventricular caps. This scan is Fazekas grade 1, on the Fazekas scale of WMH severity (range: 0–3). In the right thalamus, a lacune can be seen. (B, C) Two examples of severe confluent WMH. Note that borders between periventricular and deep subcortical WMHs become difficult to define. Scans B and C are Fazekas grade 3. Scans A–C are FLAIR sequences. Figure provided by GJ Biessels. Abbreviations: MRI, magnetic resonance imaging; WMHs, white matter hyperintensities; FLAIR, fluid-attenuated inversion recovery.

Box 1. Vascular contributions to cognitive impairment and dementia

- The concept of vascular contributions to cognitive impairment and dementia (VCID) encompasses the spectrum of vascular disease processes that impact cognitive function [13,16]. Brain vascular pathology is an important comorbidity in the multitiology 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 because of vascular disease, proteinopathies, metabolic disease, and immune affront. In 2016, a National Institutes of Health-sponsored summit defined research priorities in Alzheimer's and related dementias [13]. One output is the MarkVCID consortium, which is designed for multisite development and validation of small vessel VCID candidate biomarkers to the point of readiness for large-scale clinical trials (see <https://markvcid.partners.org/>).

WMHs are also associated with decline in gait and related aspects of physical performance [11,12]. Nevertheless, a given individual may have extensive WMHs but minimal cognitive impairment. WMH location, individual resilience factors, and cognitive reserve likely determine clinical impact.

WMHs 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 WMHs 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 [17].

2.2. WMHs in terms of clinical diagnostic criteria

The heterogeneity of WMH etiology and clinical manifestations present diagnostic challenges [18,19]. Even in patients with dementia and significant WMHs, the vascular contribution to the clinical phenotype may be missed if neuroimaging is not performed. The National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria, a popular diagnostic framework for clinical definition of vascular dementia, require clinical dementia with a temporal relationship to a preceding stroke with relevant imaging. In clinical practice, this may not be straightforward, and most patients who exhibit WMHs have no stroke history. It remains challenging to attribute cognitive deficits to WMHs at an individual patient level. Three examples of possible "vascular" clinical courses to

symptomatic cognitive impairment are illustrated in Fig. 2. 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 WMHs are likely to be beneficial [18,19].

2.2.1. Biochemical biomarkers for clinical use

Fluid biomarkers relevant to WMHs will be clinically beneficial, reviewed elsewhere [20]. The low molecular weight neurofilament marker (NF-L), extracellular metalloproteinase matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1, the matrix metalloproteinase-2 index, and the albumin brain-plasma ratio are all increased in people with clinical diagnosis of SVD. Peripheral blood markers for WMHs, alongside fluid biomarkers related to AD pathology, will help to subtype patients according to their degree of AD pathology and brain vascular burden [13,20,21].

3. Epidemiology of WMHs

3.1. Prevalence and progression of WMHs

3.1.1. Prevalence of WMHs

Most individuals older than 60 years have some degree of WMH, and prevalence increases with age. In the Rotterdam Scan Study, prevalence of subcortical WMHs increased by 0.2% per year of age, whereas periventricular WMHs increased by 0.4% [22] (See Box 2). For participants aged 60-70 years, 87% had subcortical and 68% had periventricular WMHs. For participants aged 80-90 years, 100% had subcortical and 95% had periventricular WMHs [22]. This age gradient of WMHs has been confirmed in a wider age range (ages 20-90 years, Study of Health in Pomerania cohort) [25]. In addition, many cognitively healthy younger adults show some degree of WMH on MRI.

3.1.2. Progression of WMHs

Longitudinal studies of community-dwelling, healthy older adults show increasing WMH severity or WMH volume over time [26]. 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 [27], whereas in the Rotterdam Scan Study, 39% had progression of WMH volume over 3.4 years [28]. In the Leukoaraiosis and Disability in the Elderly study, 74% exhibited worsening over 3.1 years [29], 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% [26]. In some cohorts, decrease in WMH volume has been reported, although effect sizes were small [30].

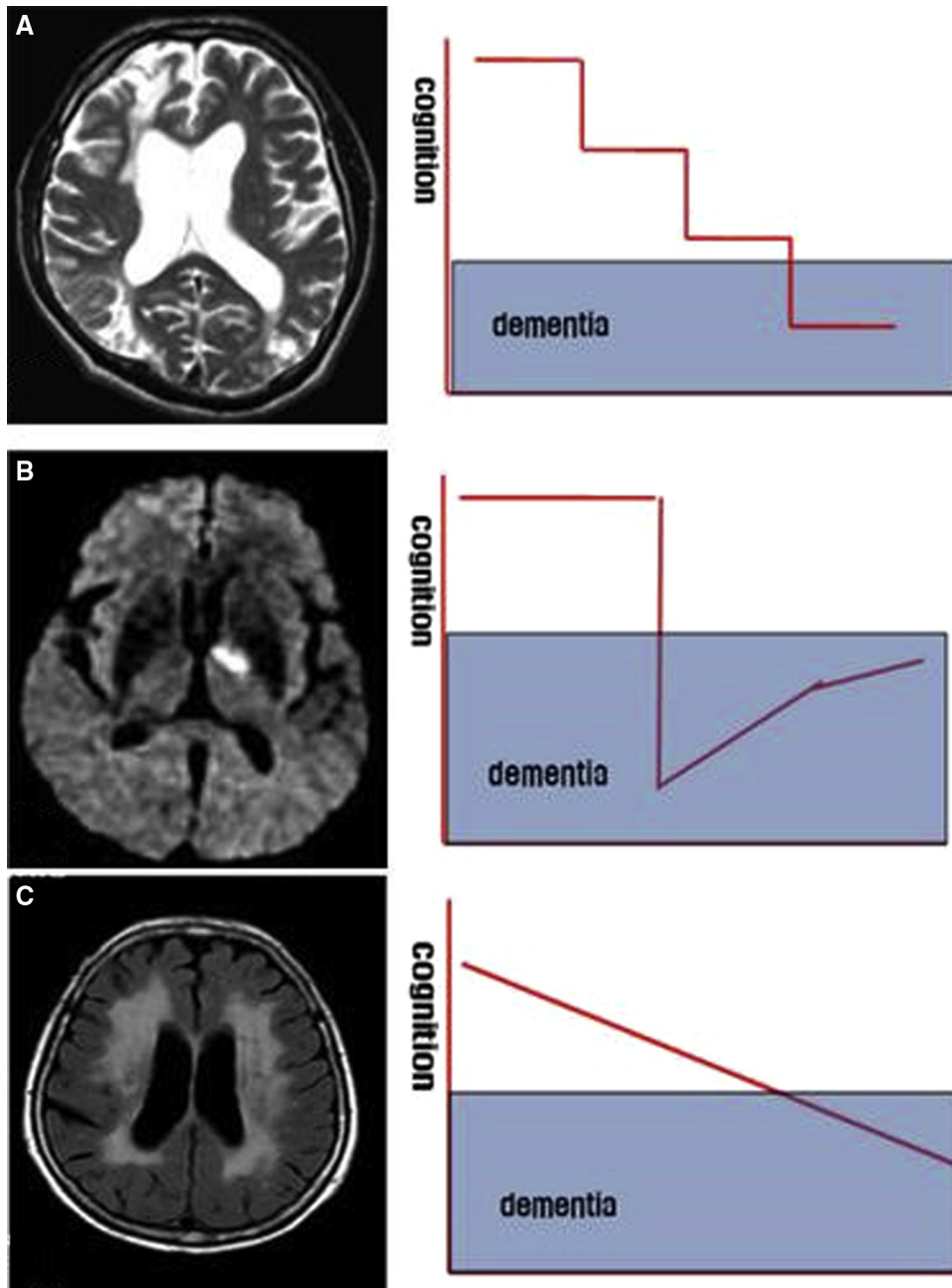


Fig. 2. Conceptual clinical courses leading to vascular dementia. (A) Multi-infarct dementia, stepwise pattern of cognitive decline. (B) Strategic vascular dementia due to a focal lesion in a clinically eloquent site. One-step pattern, with some recovery. (C) WMH-associated subcortical vascular dementia.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

3.2. Risk factors for WMHs

3.2.1. Nonmodifiable risk factors

WMHs are more prevalent at older ages, and some studies support faster progression with advanced age (see a recent review by Jorgensen et al) [26]. Black race, female sex, and *apolipoprotein E ε4* allele presence have all been associated with greater cross-sectional WMH burden or WMH progression, although results have been mixed [26,31].

3.2.2. Modifiable risk factors

Identified risk factors for WMH severity and progression are primarily vascular, cardiometabolic, and nutritional [26]. 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 WMHs. Studies considering high blood pressure earlier in life generally report an association with subsequent WMHs. In the Rotterdam Scan Study, elevated blood pressure was associated with increased WMH risk 5 and 20 years later.

Box 2. Is it helpful to classify WMHs into subcortical and periventricular?

- Subcortical WMHs are defined as isolated foci appearing in the superficial white matter, which in most cases are not contiguous with periventricular WMHs. The neuropathological substrates differ between the localizations [23,24] (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 WMHs 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 [23]. 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 [21]. There may be further valid subdivisions within subcortical WMH. Nevertheless, it may be premature to discriminate periventricular from subcortical WMH clinically.

Similarly, both midlife and late-life blood pressure were associated with increased WMH risk in the Cardiovascular Risk Factors, Aging and Incidence of Dementia Study [32], and elevated midlife blood pressure was related to late-life WMH volume in the National Heart Lung, and Blood Institute Twin Study [33]. There is mixed evidence for dyslipidemia as a risk factor for WMHs. Omega-3 polyunsaturated fatty acids have been associated with lower WMH burden. Neither diabetes mellitus nor insulin resistance is strongly related to

WMHs, whereas fasting glucose has been related to WMH progression. Greater visceral fat accumulation is more strongly associated with WMHs than body mass index. Tobacco smoking, higher blood levels of inflammatory markers (C-reactive protein, interleukin-6), low levels of vitamin B12, and hyperhomocysteinemia have all been associated with WMHs (see Box 4). These studies of risk factors are discussed in a recent review by Jorgensen et al [26].

Elevated levels of activated microglia in periventricular WMHs indicate that these may particularly involve neuroinflammatory responses after disruption of the blood-brain barrier (BBB) (see Box 4). This response is not seen in subcortical WMHs [23]. 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 WMHs [21]. There may be further valid subdivisions within subcortical WMHs. Nevertheless, it may be premature to discriminate periventricular from subcortical WMHs clinically.

4. Neuropathological changes that underlie WMHs

4.1. Types of underlying tissue damage in WMHs

The pathophysiology of SVD-associated white matter histological lesions has been attributed to multiple mechanisms, including hypoperfusion, defective cerebrovascular reactivity, and BBB dysfunction [5,6,37–39]. 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 [40] or impaired perivascular (“glymphatic”) clearance. Different presentations of WMHs indicate differences in underlying pathological changes. For example, punctate WMHs (considered to represent mild tissue changes) are associated with myelin damage, gliosis, and enlarged perivascular spaces, whereas extensive, confluent WMHs are considered

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

- The rhesus monkey has a brain structure similar to humans and similar age-related decline in cognitive function [34]. 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, with the majority exhibiting severe impairments while some are only mildly impaired. Markers of AD pathology (amyloid plaques, hyperphosphorylated tau) are variable or absent and correlate poorly with cognitive impairment. Neuronal loss is not detectable, and gray matter is well preserved [34]. 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 callosum 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 [34,35]. These observations point to white matter pathology, independent of neurodegeneration, as the source of age-related VCID in primates.

Box 4. Is inflammation a feature in WMHs?

- An explicit inflammatory process, in the manner of multiple sclerosis, does not apply to WMHs of presumed vascular origin. Nevertheless, participation of some inflammation-related molecules and cells appears likely and merits deeper understanding. In some large studies, circulating peripheral proinflammatory markers (e.g., C-reactive protein and interleukin-6) have been associated with WMHs, indicating possible involvement of inflammatory pathways in WMHs. Other peripheral proinflammatory and anti-inflammatory cytokines (e.g., interleukin-8) are found elevated specifically in people with a clinical AD diagnosis who also have extensive WMHs [36].

to represent more progressive pathological changes, including some degree of myelin loss, axonal disruption, and astrogliosis [6,7]. Pathological differences in WMHs also occur based on anatomical location, for example, when evaluating periventricular versus subcortical WMHs (see Box 2) or watershed versus nonwatershed regions. Minor pathological changes associated with WMHs (at the caps/rim of periventricular regions; Fig. 1) are most consistent with disturbed cerebrospinal fluid 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 to the periventricular and subcortical white matter. While long perforating branches supply to the periventricular white matter, shorter branches supply to the subcortical white matter.

WMH severity has been associated with microinfarcts and diffuse amyloid plaque load in brains of people diagnosed with AD [41]. 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 [42]. More likely, AD pathology (common in older people) and WMHs of vascular origin (even more common in older people) frequently copresent as has been noted in multiple autopsy-based studies on mixed pathologies [14].

4.2. Demyelination in WMHs

Early imaging studies indicated that severe WMHs are related to cell death and myelin loss, see the studies by Gouw et al and Schmidt et al [6,7], with early confluent WMHs presenting more marked demyelination than focal/punctate WMHs. Compared with subcortical WMHs, periventricular WMHs show increased axonal loss,

astrocytosis, 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 [43].

Demyelination is not a universal feature of WMHs. In addition to demyelination, myelin “pallor” has been confirmed as a histological substrate of WMHs. With aging, the ability of the oligodendrocytes to regenerate myelin sheaths decreases [40]. To what degree pallor represents loss of myelin sheaths or loss of myelin secondary to axonal loss remains unresolved [44]. In aged primates, cognitive impairment exacerbated by hypertension is associated with myelin damage and microglial changes within the white matter (Box 3).

4.3. Insights from MRI-histopathology correlative studies of WMHs

Several studies have examined the underlying pathology of WMHs using ex vivo MRI combined with histopathology [6,37–39]. Early MRI-neuropathology correlative studies reported ischemic changes, with evidence of plasma extravasation (indicative of BBB dysfunction), rarefaction, or loss of parenchymal tissue structure [45]. More advanced lesions showed reduced myelin density [45]. These data are broadly confirmed by more recent molecular studies [38,39].

5. Are WMHs related to Alzheimer’s disease?

We acknowledge a distinction between AD as a syndromal diagnosis in living people and AD as a neuropathological description or molecular etiology [15]. With regard to clinical diagnosis, most people with AD diagnosis above the age of 70 years have some degree of WMHs. 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 WMHs (of vascular or nonvascular origin) is still debated. Most amyloid PET studies found no association between β -amyloid ($A\beta$) tracer uptake and WMH burden [17,46]. Nevertheless, a recent study in the Alzheimer’s Disease Neuroimaging Initiative cohort (using florbetapir instead of Pittsburgh compound-B as the amyloid tracer) observed a correlation between elevated brain $A\beta$ and WMHs [47]. Furthermore, in people carrying dominant AD mutations, WMH volume remains elevated up to 20 years in advance of cognitive symptoms, concomitant with altered levels of $A\beta$ and tau in cerebrospinal fluid [48]. 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 WMHs.

Cerebral amyloid angiopathy (CAA) is a common age-related SVD, characterized by the accumulation of $A\beta$ in the walls of cortical arterioles and leptomeningeal vessels [46,49]. 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 WMHs (impaired perivascular clearance, plasma extravasation, inflammation, hypoperfusion, endothelial dysfunction) [46]. Whether or not AD is concomitant, CAA plays a distinct role in the spectrum of dementia [17,49].

6. Implications for treatment interventions

6.1. Nonpharmacological interventions

6.1.1. Physical activity and 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 WMHs (periventricular and subcortical) were examined separately [50]. In relation to WMHs, 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 [24].

Observational cohort studies of diet and nutrition suggest that the consumption of tuna/nonfried fish and the Mediterranean diet is associated with less WMH load [51,52]. 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).

6.1.2. Multidomain interventions

The Look AHEAD study tested a 10-year physical activity and dietary modification intervention in older adults who are overweight and obese with type 2 diabetes mellitus. Although there was no effect of the intervention on cognition in the MRI substudy, the intervention group had significantly lower WMH volume than the control group [53]. Similarly, in the Evaluation of Vascular care in Alzheimer's disease study, participants with clinical AD diagnoses and MRI evidence of SVD (WMHs, lacunar or cortical infarcts) were randomized to either a multidomain approach (dietary and physical activity counseling, smoking cessation, and 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) [54].

6.2. Pharmacological interventions

6.2.1. Blood pressure medications

Randomized clinical trial subanalyses indicate that effective antihypertensive therapy reduces WMH incidence. Treatment with an angiotensin-converting enzyme (ACE) inhibitor over 36 months reduced the WMH number and

total WMH volume in the Perindopril Protection Against Recurrent Stroke Study trial [55]. An observational cohort study suggested that treatment with an angiotensin receptor blocker, versus an ACE inhibitor, was associated with smaller WMH volumes in people with a clinical AD diagnosis [56]. An MRI substudy of the Prevention of dementia by intensive vascular care trial 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 [57]. A trial of intensive versus 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 [58]. The results of the Systolic Blood Pressure Intervention Trial (SPRINT-MIND) of intensive versus standard blood pressure control on WMH were presented at Alzheimer's Association International Conference 2018. This trial demonstrated reduced mild cognitive impairment in the intensive treatment arm (though this was not a primary endpoint of the trial) [59]. The effect of two years of treatment with either ACE inhibitor or angiotensin II receptor blockers on an outcome of SVD progression, including WMHs and silent brain infarcts, is currently being tested [60].

6.2.2. Statins

Nearly three years of treatment with 40 mg of pravastatin daily in the Pravastatin in elderly individuals at risk of vascular disease (PROSPER) study did not reduce WMH progression over the placebo group in individuals with increased vascular risk [61].

6.2.3. Antithrombotic agents

The ASPirin in Reducing Events in the Elderly (ASPREE-NEURO) study is evaluating 100 mg of aspirin daily versus placebo over one year, with a secondary outcome of WMH volume change [62].

7. Concluding comments

Converging data from clinical, neuropathological, and experimental studies has begun to unravel WMH mechanisms. We are optimistic that the next ten years will see substantial advances in molecular understanding and clinical management of WMHs and VCID. Deeper molecular understanding of the various etiologies and pathologies that lead to WMHs 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 WMHs of presumed vascular origin is limited to lifestyle modifications and risk factor management. Given the associations between WMHs 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 labeling of food products, and food marketing (to children in particular) will likely have more health-care impact than any drug.

Scientific progress is needed in the following areas: (1) application of emerging diagnostic criteria to identify different subtypes of WMHs, possibly with differing etiology, outcomes, and clinical significance; (2) robust differential biomarkers to discriminate different pathologies (SVD, CAA, and 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 WMHs 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 WMHs.

Acknowledgments

The authors are grateful to the Alzheimers Association and to The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment for hosting the event at Alzheimer's Association International Conference 2017, where this Perspective originated. The authors apologize to their colleagues worldwide whose excellent publications they have failed to cite, owing to the reference limit of the journal. Where two citations were relevant, the authors have, as a rule, included only the more recent one. D.A.B. is funded by National Health and Medical Research Council (Australia). S.E.B. has funding from National Institutes of Health (NIH)/National Institute on Aging (NIA) (grant F30AG054115). G.J.B. acknowledges support from Vici (grant 918.16.616), from ZonMw, from 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). G.L.B. reports US NIH/NIA funding. B.L.C. holds a Canada Research Chair. S.F. has NIH funding. T.M.H., K.M.H. and S.N.L. were supported by funding from the NIH (P30 AG049638). J.K. is grateful for the support of the Marga and Walter Boll Foundation, Kerpen, Germany. M.C.P. has NIH and US DoD funding. C.E.S. was funded by National Institute on Aging (grant number F31 AG054084). A.M.T. was funded by Israel Science Foundation (grant 1353/11). C.W. is funded by the Weston Brain Institute, Canadian Institutes of Health Research (CIHR) and Cure Alzheimer's Fund. A.H.H. 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.

RESEARCH IN CONTEXT

1. **Systematic review:** This perspective came from a multidisciplinary author team, across a range of seniority from graduate students to emeritus professors. Citations provided come from the authors' expertise and from PubMed. We did not attempt a formal systematic review.
2. **Interpretation:** We aimed i) to summarise the knowledge base on WMHs and their relation to cognitive impairment, ii) to identify perceived knowledge gaps related to WMHs, particularly those relevant to accelerating dementia therapies.
3. **Future directions:** Molecular studies in human tissue and bio-fluid samples will yield biological understanding of the processes that underlie WMHs, hence better biomarkers (both imaging and biochemical) and molecular targets for drug treatment.

References

- [1] Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: an update. *Nat Rev Neurol* 2015; 11:157–65.
- [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;82:2127–38.
- [4] De Guio F, Vignaud A, Chabriet 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, et al. White matter hyperintensities and normal-appearing white matter integrity in the aging brain. *Neurobiol Aging* 2015;36:909–18.
- [6] Gouw AA, Seewann A, van der Flier WM, Barkhof F, Rozemuller AM, Scheltens P, et al. Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. *J Neurol Neurosurg Psychiatry* 2011;82:126–35.
- [7] Schmidt R, Schmidt H, Haybaeck J, Loitfelder M, Weis S, Cavalieri M, et al. Heterogeneity in age-related white matter changes. *Acta Neuropathol* 2011;122:171–85.

- [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;221:2135-46.
- [10] Verdelho A, Madureira S, Moleiro C, Ferro JM, Santos CO, Erkinjuntti T, et al. White matter changes and diabetes predict cognitive decline in the elderly: the LADIS study. *Neurology* 2010;75:160-7.
- [11] Rosario BL, Rosso AL, Aizenstein HJ, Harris T, Newman AB, Satterfield S, et al. Cerebral white matter and slow gait: contribution of hyperintensities and normal-appearing parenchyma. *J Gerontol A Biol Sci Med Sci* 2016;71:968-73.
- [12] Silbert LC, Howieson DB, Dodge H, Kaye JA. Cognitive impairment risk: white matter hyperintensity progression matters. *Neurology* 2009;73:120-5.
- [13] Corrivau RA, Koroshetz WJ, Gladman JT, Jeon S, Babcock D, Bennett DA, et al. Alzheimer's Disease-Related Dementias Summit 2016: national research priorities. *Neurology* 2017;89:2381-91.
- [14] Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol* 2017;134:171-86.
- [15] Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeblerlein SB, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018;14:535-62.
- [16] Sweeney MD, Montagne A, Sagare AP, Nation DA, Schneider LS, Chui HC, et al. Vascular dysfunction-The disregarded partner of Alzheimer's disease. *Alzheimers Dement* 2019;15:158-67.
- [17] Vemuri P, Knopman DS. The role of cerebrovascular disease when there is concomitant Alzheimer disease. *Biochim Biophys Acta* 2016;1862:952-6.
- [18] Smith EE. Clinical presentations and epidemiology of vascular dementia. *Clin Sci (Lond)* 2017;131:1059-68.
- [19] Sachdev P, Kalaria R, O'Brien J, Skoog I, Alladi S, Black SE, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc Disord* 2014;28:206-18.
- [20] Wallin A, Kapaki E, Boban M, Engelborghs S, Hermann DM, Huisa B, et al. Biochemical markers in vascular cognitive impairment associated with subcortical small vessel disease - A consensus report. *BMC Neurol* 2017;17:102.
- [21] Swardfager W, Yu D, Scola G, Cogo-Moreira H, Chan P, Zou Y, et al. Peripheral lipid oxidative stress markers are related to vascular risk factors and subcortical small vessel disease. *Neurobiol Aging* 2017;59:91-7.
- [22] de Leeuw FE, de Groot JC, Oudkerk M, Wittman JC, Hofman A, van GJ, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain* 2002;125:765-72.
- [23] Simpson JE, Fernando MS, Clark L, Ince PG, Matthews F, Forster G, et al. White matter lesions in an unselected cohort of the elderly: astrocytic, microglial and oligodendrocyte precursor cell responses. *Neuropathol Appl Neurobiol* 2007;33:410-9.
- [24] Bolandzadeh N, Tam R, Handy TC, Nagamatsu LS, Hsu CL, Davis JC, et al. Resistance training and white matter lesion progression in older women: exploratory analysis of a 12-month Randomized Controlled Trial. *J Am Geriatr Soc* 2015;63:2052-60.
- [25] Habes M, Erus G, Toledo JB, Bryan N, Janowitz D, Doshi J, 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;10:278-84.
- [26] 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:H1117-36.
- [27] Longstreth WT, Arnold AM, Beauchamp NJ Jr, Manolio TA, Lefkowitz D, Jungreis C, et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke* 2005;36:56-61.
- [28] 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;39:2712-9.
- [29] Gouw AA, van der Flier WM, Fazekas F, van Straaten EC, Pantoni L, Poggesi A, et al. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period. The Leukoaraiosis and Disability Study. *Stroke* 2008;39:1414-20.
- [30] Maillard P, Carmichael O, Fletcher E, Reed B, Mungas D, DeCarli C. Coevolution of white matter hyperintensities and cognition in the elderly. *Neurology* 2012;79:442-8.
- [31] Brickman AM, Schupf N, Manly JJ, Stern Y, Luchsinger JA, Provenzano FA, et al. APOE epsilon4 and risk for Alzheimer's disease: do regionally distributed white matter hyperintensities play a role? *Alzheimers Dement* 2014;10:619-29.
- [32] Vuorinen M, Spulber G, Damangir S, Niskanen E, Ngandu T, Soinen H, et al. Midlife CAIDE dementia risk score and dementia-related brain changes up to 30 years later on magnetic resonance imaging. *J Alzheimers Dis* 2015;44:93-101.
- [33] Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Jack LM, et al. Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurology* 1998;51:986-93.
- [34] 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;34:1093-110.
- [35] Shobin E, Bowley MP, Estrada LI, Heyworth NC, Orczykowski ME, Eldridge SA, et al. Microglia activation and phagocytosis: relationship with aging and cognitive impairment in the rhesus monkey. *Geroscience* 2017;39:199-220.
- [36] Swardfager W, Yu D, Ramirez J, Cogo-Moreira H, Szilagy G, Holmes MF, et al. Peripheral inflammatory markers indicate microstructural damage within periventricular white matter hyperintensities in Alzheimer's disease: a preliminary report. *Alzheimers Dement (Amst)* 2017;7:56-60.
- [37] Fernando MS, Simpson JE, Matthews F, Brayne C, Lewis CE, Barber R, et al. White matter lesions in an unselected cohort of the elderly: molecular pathology suggests origin from chronic hypoperfusion injury. *Stroke* 2006;37:1391-8.
- [38] Hainsworth AH, Minett T, Andoh J, Forster G, Bhide I, Barrick TR, et al. Neuropathology of white matter lesions, blood-brain barrier dysfunction, and dementia. *Stroke* 2017;48:2799-804.
- [39] Young VG, Halliday GM, Kril JJ. Neuropathologic correlates of white matter hyperintensities. *Neurology* 2008;71:804-11.
- [40] Joutel A, Chabriat H. Pathogenesis of white matter changes in cerebral small vessel diseases: beyond vessel-intrinsic mechanisms. *Clin Sci (Lond)* 2017;131:635-51.
- [41] 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;57:575-601.
- [42] McAleese KE, Walker L, Graham S, Moya ELJ, Johnson M, Erskine D, 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;134:459-73.
- [43] Hase Y, Horsburgh K, Ihara M, Kalaria RN. White matter degeneration in vascular and other ageing-related dementias. *J Neurochem* 2018;144:617-33.
- [44] Shaaban CE, Aizenstein HJ, Jorgensen DR, MacCloud RL, Meckes NE, Erickson KI, 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;38:1923-8.

- [45] Marshall VG, Bradley WG Jr, Marshall CE, Bhoopat T, Rhodes RH. Deep white matter infarction: correlation of MR imaging and histopathologic findings. *Radiology* 1988;167:517-22.
- [46] Smith EE. Cerebral amyloid angiopathy as a cause of neurodegeneration. *J Neurochem* 2018;144:651-8.
- [47] Marnane M, Al-Jawadi OO, Mortazavi S, Pogorzelec KJ, Wang BW, Feldman HH, et al. Periventricular hyperintensities are associated with elevated cerebral amyloid. *Neurology* 2016;86:535-43.
- [48] Lee S, Viqar F, Zimmerman ME, Narkhede A, Tosto G, Benzinger TL, et al. White matter hyperintensities are a core feature of Alzheimer's disease: evidence from the dominantly inherited Alzheimer network. *Ann Neurol* 2016;79:929-39.
- [49] Roseborough A, Ramirez J, Black SE, Edwards JD. Associations between amyloid beta and white matter hyperintensities: a systematic review. *Alzheimers Dement* 2017;13:1154-67.
- [50] 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.
- [51] Gardener H, Scarmeas N, Gu Y, Boden-Albala B, Elkind MS, Sacco RL, et al. Mediterranean diet and white matter hyperintensity volume in the Northern Manhattan Study. *Arch Neurol* 2012;69:251-6.
- [52] 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;71:439-46.
- [53] Espeland MA, Erickson K, Neiberg RH, Jakicic JM, Wadden TA, Wing RR, et al. Brain and White Matter Hyperintensity Volumes After 10 Years of Random Assignment to Lifestyle Intervention. *Diabetes Care* 2016;39:764-71.
- [54] 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;41:554-6.
- [55] Dufouil C, Chalmers J, Coskun O, Besancon V, Bousser MG, Guillon P, 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;112:1644-50.
- [56] Edwards JD, Ramirez J, Callahan BL, Tobe SW, Oh P, Berezuk C, et al. Antihypertensive Treatment is associated with MRI-Derived Markers of Neurodegeneration and Impaired Cognition: A Propensity-Weighted Cohort Study. *J Alzheimers Dis* 2017;59:1113-22.
- [57] Moll van Charante EP, Richard E, Eurelings LS, van Dalen JW, Ligthart SA, van Bussel EF, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet* 2016;388:797-805.
- [58] White WB, Jalil F, Wakefield DB, Kaplan RF, Bohannon RW, Hall CB, et al. 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.
- [59] Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, et al. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA* 2019;321:553-61.
- [60] Yamano S, Horii M, Takami T, Sakuma M, Morimoto T, Okada S, 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;10:452-6.
- [61] ten Dam VH, van den Heuvel DM, van Buchem MA, Westendorp RG, Bollen EL, Ford I, et al. Effect of pravastatin on cerebral infarcts and white matter lesions. *Neurology* 2005;64:1807-9.
- [62] Ward SA, Raniga P, Ferris NJ, Woods RL, Storey E, Bailey MJ, 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;12:108-13.