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Cerebrovascular Disease and Stroke (D Greer, Section Editor)

White Matter Disease as a Biomarker for Long-Term Cerebrovascular Disease and Dementia

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Opinion statement

White matter disease is commonly detected on brain MRI of aging individuals as white matter hyperintensities (WMH), or 'leukoaraiosis." Over the years, it has become increasingly clear that the presence and extent of WMH is a radiographic marker of small cerebral vessel disease and an important predictor of the lifelong risk of stroke, cognitive impairment, and functional disability. A number of large population-based studies have outlined the significance of WMH as a biomarker for long-term cerebrovascular disease and dementia. In this review, we describe the conceptual framework and methodology that support this association and link the existing knowledge to future lines of investigation in the field.

Ischemic stroke and leukoaraiosis – a definition for the 21st century

The definition of "stroke" has undergone a significant evolution throughout the decades of cerebrovascular studies. Most recently, the expert consensus statement from the American Heart Association/American Stroke Association underlined the importance of the presence of objective clinical (neuroimaging) or laboratory (pathological) evidence of cerebral infarction, or brain cell death attributable to ischemic injury in a defined vascular distribution, for a diagnosis of ischemic stroke, whether symptomatic or silent. [1••] In addition, a common condition that is found

on brain MRI of asymptomatic aging adults is WMH, or "leukoaraiosis." Defined by Hachinski in 1985, "leukoaraiosis" implies "diminished density of white matter which is seen on brain-computed tomography (CT)," which in turn is hyperintense on T2-weighted, proton-density-weighted, and fluid-attenuated inversion recovery (FLAIR) brain MRI sequences [2, 3]. Over the years, MRI has demonstrated greater sensitivity in detecting abnormal white matter, including lesions not otherwise visible on head CT [4].

Radiographic assessment of WMH severity

There are primarily two radiographic approaches to the assessment of WMH severity (Fig. 1). First, the visual rating scales that are used to measure white matter lesions (WMLs) on CT or MRI are based on the location and severity of white matter disease. MRI-based scales, such as the Fazekas scale, rate both periventricular hyperintensity (PVH) and deep white matter locations of WML (score 0–3) [5]. The Scheltens scale adds the location, size, and number of WML in PVH (score 0–6), WMH (score 0–24), basal ganglia hyperintensities (BG) (score 0–30), and infratentorial foci of hyperintensities (ITF) (score 0–24) [6]. The Rotterdam Scan Study (RSS) scale rates WML in the periventricular region (score 0–9) and subcortical WML [7]. The Age-Related White Matter Changes (ARWMC) scale for rating WMH on CT and MRI include the location, size, and number of WMLs (score 0–3) and basal ganglia lesions (score 0–3) in five different regions (frontal, parieto-occipital, temporal, basal ganglia, and infratentorial) of the bilateral hemispheres [8].

Second, a volumetric approach to WMH analysis has been based on the various semi-automated protocols, using analytical software such as Sparc 5 (SUN, Palo Alto, CA) [9] or MRIcro (University of Nottingham School of Psychology, Nottingham, UK; www.mricro.com), which quantify WMH

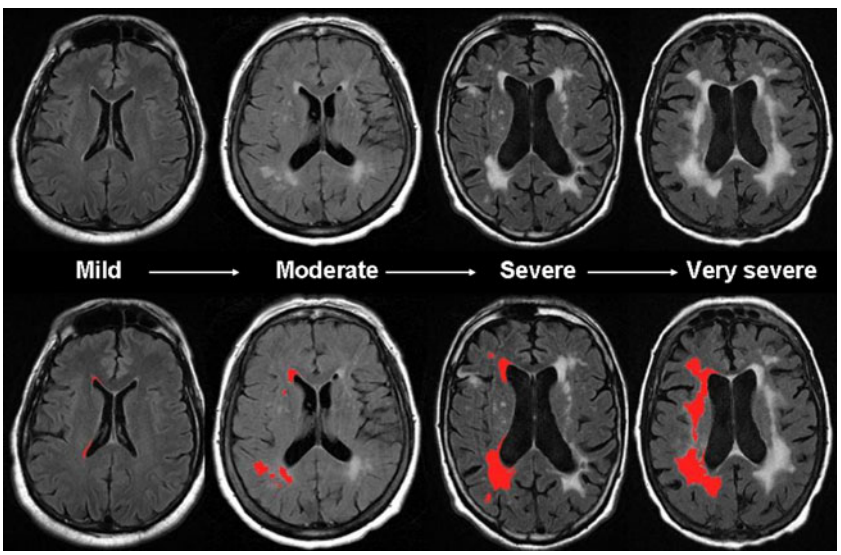

Figure 1. Severity of MRI-detected white matter hyperintensity. Total burden of white matter disease varies significantly among asymptomatic adults and patients with known cerebrovascular disease. In age-matched individuals, white matter hyperintensity (WMH) volume may vary from mild to very severe (*upper panel*). Using validated semi-automated volumetric protocol, WMH volume can be quantified (*lower panel*, *in red*, WMH maps are derived from contiguous supratentorial axial T2-FLAIR MRI slices using previously published method [10]) with a high degree of accuracy and precision.

volume (WMHv) on axial FLAIR of either the entire brain or just the supratentorial region [10] (Fig. 1). Albeit more labor-intense, volumetric methods provide more accuracy and reliability in assessing WMH severity, especially when evaluating WMH progression, as compared to the visual rating scales [11, 12]. Some WMH progression scales, such as the Rotterdam Progression and Schmidt Progression scales, are also sensitive, consistent, and relate to volumetric volume change [12].

Clinical application of different scales may depend on their sensitivity for a specific functional domain. For example, in the Leukoaraiosis And DISability (LADIS) study, visual rating scale and volumetric methods demonstrated greater WMH burden in subjects with impaired physical performance and cognition as compared to normal controls [13]. However, volumetric assessment was more sensitive than visual scores in detecting memory symptoms [9]. Many studies have used WMHv to evaluate the association between leukoaraiosis and risk of stroke, cognitive impairment, dementia, mortality, stroke severity, and other functional disabilities.

Burden of WMH and risk of stroke

Risk of first-ever stroke in population-based studies

Six large prospective population-based studies provided pivotal evidence of correlation between WMH and risk of first-ever stroke (Table 1). The Atherosclerosis Risk in Communities (ARIC) study followed up 1,684 persons in four U.S. communities for 4.7 years and found that people with WML had a higher 5-year cumulative incidence of clinical stroke than people without WML (6.8 % vs. 1.4 %; RR 3.4; 95 %.CI, 1.5–7.7), independent of common stroke risk factors [14]. The Rotterdam Scan Study in the Netherlands, which followed 1,077 participants for an average of 4.2 years, demonstrated that WML in both periventricular and subcortical locations significantly increased the risk of stroke [15]. The Cardiovascular Health Study (CHS) included 3,293 persons in four U.S. communities followed for an average of 7 years, and showed that the risk of stroke increased proportionally to the WMH grade increase, independent of conventional stroke risk factors [16]. A prospective cohort study in Shimane, Japan, demonstrated that marked PVH and subcortical white matter lesion (SWML) burden independently increased the risk of stroke in 2,684 subjects followed for an average of 6.3 years [17]. The Three-City (3C) study in Dijon, France, which followed 1,643 persons for an average 4.9 years, showed a significant increase in the risk of stroke with increasing WML [18]. And finally, the Framingham Offspring Study, which systematically evaluated 2,177 persons during 5.6 years of follow-up, demonstrated that greater WMHv was associated with an increased risk of stroke (HR 2.28, 95 % CI, 1.02–5.13), independent of vascular risk factors [19].

The meta-analysis of these six large population-based cohort studies demonstrated a significant association of WMH with risk of stroke (HR 3.1, 95 % CI, 2.3–4.1, $p<0.001$) [20•]. Furthermore, a pooled population-based analysis of the ARIC and CHS, which included 4,872 stroke-free individuals

Table 1. Association of WMH with stroke, recurrent stroke, intracerebral hemorrhage, hemorrhagic transformation and mortality

Author	Population	Results
Risk of first-ever stroke		
Wong TY 2002 [14]	ARIC Study	5-year cumulative incidence of clinical stroke: WML vs. without WML: 6.8 % vs. 1.4 %; RR 3.4; 95 % CI, 1.5–7.7
Vermeer SE 2003 [15]	Rotterdam Scan Study	3rd vs 1st PVH tertile: HR 4.7; 95 % CI, 2.0–11.2 3rd vs 1st SWML tertile: HR 3.6; 95 % CI, 1.4–9.2
Kuller LH 2004 [16]	CHS	WML grades ≥ 5 vs grades 0–1: 2.8 % vs 0.6 %; HR 3.0; 95%CI, 1.9–4.7
Bokura H 2006 [17]	Shimane Study	Marked vs. mild PVH: OR 2.08; 95 % CI 1.04 –4.17 Marked vs. no SWML: OR 2.73; 95 % CI 1.32–5.63
Buyck JF 2009 [18]	3–City Dijon Study	4th vs 1st total WMHv quartile: HR 5.7; 95 % CI, 2.0–16.4 4th vs 1st PVH volume quartile: HR 6.2; 95 % CI, 2.0–19.5 4th vs 1st deep WMHv quartile: HR 4.1; 95 % CI, 1.5–11.3
Debette S 2010 [19]	Framingham Offspring Study	extensive WMHv: HR 2.28; 95 % CI, 1.02–5.13
Debette S 2010 [20•]	Meta-analysis	WMH: HR 3.1; 95 % CI, 2.3–4.1
Folsom AR 2012 [21]	ARIC and CHS Study	Risk of ICH: WMH grade 4–9 vs. WMH grade 0–1: HR 3.96; 95 % CI, 1.90–8.27 WMH grade 3 vs. WMH grade 0–1: HR 3.52; 95 % CI, 1.80–6.89
Risk of recurrent stroke		
Yamauchi H 2002 [22]	Japanese	WML score at baseline: HR 1.60; 95 % CI, 1.02–2.54
Appelros P 2005 [23]	Swedish	WML score at baseline: HR 1.7 95 % CI, 1.2–2.7
Fu JH 2005 [24]	Chinese	Severity of WML: HR 4.18; 95 % CI, 2.0–8.6
Gerdes VE 2006 [25]	Amsterdam Vascular Medicine Group	PVH vs. without PVH: HR 3.2; 95 % CI, 1.3–8.4 deep vs. without deep WML: HR 1.5; 95 % CI, 0.6–3.8
Naka H 2006 [26]	Japanese	For ischemic stroke: advanced WMH: HR 10.7; 95 % CI, 2.6–43.7
Debette S 2010 [20•]	Meta-analysis	WMH: HR 7.4; 95 % CI, 2.4–22.9
Risk of ICH and hemorrhagic transformation		
Smith EE 2004 [10]	American	For recurrent ICH: CT-WMH (grade 1) vs. without CT-WMH: HR 3.7; 95 % CI, 1.1–12.3
Naka H 2006 [26]	Japanese	For ICH: advanced WMH: HR 0.016; 95 % CI, 0.001–0.258
Shi ZS 2012 [43]	American	Moderate or severe deep WMH on preintervention MRI: Predict hemorrhagic transformation: OR 3.43; 95 % CI, 1.23–9.57, after mechanical thrombectomy Predict parenchymal hematoma: OR 6.26; 95 % CI, 1.74–22.45, after mechanical thrombectomy
Mortality		
Bokura H 2006 [17]	Shimane Study	Marked vs. mild PVH: OR 4.01; 95 % CI, 1.91–8.45 Marked vs. no SWML: OR 1.06; 95 % CI, 0.45–2.53
Ikram MA 2009 [32]	Rotterdam Scan Study	For all-cause mortality: 4th vs 1st WMH quartile: HR 2.05; 95 % CI, 1.32–3.20 WML per SD: HR 1.38; 95 % CI, 1.16–1.65 For cardiovascular mortality: WML per SD: HR 2.52; 95 % CI, 1.65–3.84
Debette S 2010 [19]	Framingham Offspring Study	**Risk of death**: WMHv: HR 1.38; 95 % CI, 1.13–1.69 extensive WMHv: HR 2.27; 95 % CI, 1.41–3.65 **Risk of vascular death**: WMHv: HR 1.96; 95 % CI 1.13–2.92

Table 1. (continued)

Author	Population	Results
		extensive WMHv: HR 4.18; 95 % CI, 1.72–10.15
		Risk of cardiovascular death:
		WMHv: HR 1.86; 95 % CI 1.20–2.89
		extensive WMHv: HR 3.49; 95 % CI, 1.30–9.37
Kuller LH 2007 [33]	CHS	Ventricular grade ≥ 6: HR 1.58; 95 % CI, 1.21–2.07
		White matter grade ≥ 5: HR 1.87; 95 % CI, 1.43–2.32
Tveiten A 2013 [34]	Norwegian	30-day mortality: WMH score: OR 1.6; 95 % CI, 1.06–2.5
		Long-term mortality: WMH score: OR 1.6; 95 % CI, 1.2–2.1
Fu JH 2005 [24]	Chinese	Survival: severity of WML: HR 2.02; 95 % CI, 1.032–3.960
Debette S 2010 [20•]	Meta-analysis	WMH: HR 2.3; 95 % CI, 1.9–2.8

Abbreviations: *ARIC* – Atherosclerosis Risk In Communities study, *CHS* – Cardiovascular Health Study, *CI* – confidence interval, *CT* – computed tomography, *HR* – hazard ratio, *ICH* – intracerebral hemorrhage, *OR* – odds ratio, *PVH* – periventricular hyperintensity, *SD* – standard deviation, *SWML* – subcortical WML, *WML* – white matter lesions, *WMH* – white matter hyperintensity, *WMHv* – WMH volume

followed for a median of 13 years, demonstrated that higher WMH grade on baseline MRI is a significant predictor of spontaneous intracerebral hemorrhage (ICH) (p for trend < 0.0001) [21].

Risk of stroke in high-risk populations

Many prospective studies have evaluated WMH and risk of stroke in high-risk populations (Table 1). A study in 89 Japanese participants who had clinical lacunar infarction and who were followed up for a mean of 51 months found that extensive WMH at baseline was a significant predictor of stroke risk (RR 1.60; 95 % CI, 1.02–2.54, $p<0.05$) [22]. A study in 121 American patients with lobar ICH demonstrated that CT-based evidence of white matter damage nearly quadrupled the risk of recurrent ICH (HR 3.7, 95 % CI, 1.1-12.3, $p=0.02$) after 2.7 years of follow-up [10]. A study of 81 Swedish patients with lacunar infarction found that severity of WML was a predictor of recurrent stroke (OR 1.7, 95 % CI, 1.2-2.7), in long-term follow-up (5 years) [23]. Similarly, extensive WML was associated with recurrent stroke in a study of 228 Chinese patients with stroke ($p=0.0001$) [24]. The Amsterdam Vascular Medicine Group in the Netherlands reported that patients ($n=230$) with confirmed atherosclerotic disease – including recent myocardial infarction (MI), ischemic stroke (IS), or peripheral arterial disease (PAD) – and evidence of PVH on neuroimaging had a higher recurrent ischemic stroke rate at 3.5 years compared to those without PVH (18 % vs. 5 %, $p=0.001$) [25]. A study in 266 Japanese patients with ischemic stroke or ICH found that the subgroup of patients with advanced WMH but no microbleeds had the highest recurrence rate of ischemic stroke of the four patient subgroups (10.5 % in 1-year and 17.4 % in 2-year follow-up, HR 10.7, 95 % CI, 2.6–43.7) [26].

Finally, combined data analyses demonstrate convincingly that WMH severity is linked to the risk of recurrent stroke. A meta-analysis from three studies in high-risk populations reported HR 7.4, 95 % CI, 2.4–

22.9, $p=0.001$, whereas pooled data from six population-based studies and three high-risk populations showed HR 3.5, 95 % CI, 2.5–4.9, $p<0.001$ [20•].

Burden of WMH and risk of vascular cognitive impairment and dementia

Risk of vascular cognitive impairment

There have been multiple population-based studies that have evaluated the association between leukoaraiosis and the risk of cognitive impairment (Table 2). Some studies used the severity of WMH at baseline, while many assessed the progression of WMH longitudinally.

A study in 67 American participants with normal cognition demonstrated that high baseline WMHv was related to the risk of progression to mild cognitive impairment (MCI) (HR 3.3; 95 % CI, 1.33–8.2, $p=0.01$) [27]. However, the Framingham Offspring Study, which followed up 1,694 persons for a mean duration of 6.2 years, found that the severity of WMHv did not correlate with the risk of all MCI or amnestic MCI [19]. Similarly, the Austrian Stroke Prevention Study followed 329 participants for 6 years and demonstrated that WMHv progression was associated with cognitive decline in some domains, including memory, conceptualization, and visuopractical skills, but that changes in WMHv were not related to cognitive decline after adjustment for brain volume [28].

Risk of dementia

The link between severity of leukoaraiosis and risk of dementia has been examined in a number of large prospective population-based studies (Table 2), including the Cardiovascular Health Cognitive Study, in which 480 of 3,608 persons developed dementia in up to 8 years of follow-up. The study found that extensive WMH grade at study baseline was a significant risk factor for dementia (HR 1.8) and Alzheimer's disease (AD) [29]. The Rotterdam Scan Study demonstrated that WML, predominantly in the periventricular region, independently increased the risk of dementia in 1,077 cognitively intact participants at 5.2 years (HR 1.67; 95 % CI, 1.25–2.24) [30]. Similarly, the Osaki-Tajiri Project in Japan followed 204 healthy adults and 335 participants with questionable dementia for a period of 5 years and showed that WML was a predictor for progression to vascular dementia (VaD) [31]. The Framingham Offspring Study ($n=2,013$) reported that severity of WMHv was significantly associated with increased risk of dementia (HR 2.22, 95 % CI, 1.32–3.72 for WMHv; HR 3.97, 95 % CI, 1.10–14.3 for extensive WMHv) in a mean follow-up of 5.9 years [19]. Lastly, a meta-analysis of three population-based studies confirmed a significant association between WMH and risk of all types of dementia (HR 2.9; 95 % CI, 1.3–6.3, $p=0.008$) [20•].

WMH as biomarker of total burden of cerebrovascular disease

Association with mortality

Several large prospective population-based studies have evaluated the association between WMH and mortality (Table 1). In a cohort of 2,684 neuro-

Table 2. Association of WMH with cognitive impairment, dementia, gait abnormalities and urinary incontinence

Author	Population	Results
Risk of vascular cognitive impairment		
Smith EE 2008 [27]	American	High WMHv: HR 3.30; 95 % CI, 1.33–8.22
Debette S 2010 [19]	Framingham Offspring Study	For MCI WMHv: OR 1.06; 95 % CI, 0.83–1.36 extensive WMHv: OR 1.26; 95 % CI, 0.67–2.39 For amnestic MCI WMHv: OR 1.24; 95 % CI, 0.98–1.57 extensive WMHv: OR 1.67; 95 % CI, 0.96–2.93 For amnestic MCI, age ≥ 60 WMHv: OR 1.49; 95 % CI, 1.14–1.97 extensive WMHv: OR 2.47; 95 % CI, 1.31–4.66
Schmidt R 2005 [28]	Austrian Stroke Prevention Study	WMHv: β -0.025; 95 % CI, -0.047 to -0.004 (memory) WMHv: β -0.022; 95 % CI, -0.043 to 0.0004 (conceptualization) WMHv: β -0.035; 95 % CI, -0.059 to -0.011 (visuopractical skills) WMHv: β -0.017; 95 % CI, -0.036 to -0.002 (attention/speed)
Risk of dementia		
Kuller LH 2003 [29]	Cardiovascular Health Cognitive Study	WMH ≥ 3: HR 1.7; 95 % CI, 1.36-2.10 (total dementia) WMH ≥ 3: HR 1.5; 95 % CI, 1.17-1.99 (AD) WMH ≥ 3: HR 2.1; 95 % CI, 1.36-3.11 (VaD/mixed dementia)
Prins ND 2004 [30]	Rotterdam Scan Study	PVH: HR 1.67; 95 % CI, 1.25–2.24
Meguro K 2007 [31]	The Osaki-Tajiri Project	PVH: OR 0.78 (non-significant) (AD) Deep WMH: OR 1.07, 1.02 (right , left, non-significant) (AD) PVH: OR 4.14 ($p<0.005$) (VaD) Deep WMH: OR 4.04, 3.27 (right , left, $p<0.05$) (VaD)
Debette S 2010 [19]	Framingham Offspring Study	WMHv: HR 2.22; 95 % CI, 1.32–3.72 extensive WMHv: HR 3.97; 95 % CI, 1.10–14.30
Debette S 2010 [20•]	Meta-analysis	WMH: HR 2.9; 95 % CI, 1.3–6.3
Gait abnormalities		
Kreisel SH 2013 [45]	LADIS Study	Slope of the short physical performance battery (SPPB): Moderate ARWMC degree: -0.22; 95 % CI, -0.35 to -0.09 Severe ARWMC degree: -0.46; 95 % CI, -0.63 to -0.28
Inzitari D 2007 [47]	LADIS Study	For patients with 0 or 1 activity limited at entry Severe vs. mild ARWMC: HR 2.38; 95 % CI, 1.29–4.38 For patients with no activity limited at entry Severe vs. mild ARWMC: HR 3.02; 95 % CI, 1.34–6.78
Poggesi A 2013 [48]	LADIS Study	Severe vs. mild white matter change: OR 2.34; 95 % CI, 1.52–3.60
Silbert LC 2008 [49]	Oregon Brain Aging Study	Total WMHv and rate of changes in timed walking in seconds: $R^2 = 0.08$, $p=0.0052$ Total WMHv and number of steps: $R^2 = 0.12$, $p=0.0125$ Increased PVH and rate of changes in timed walking in seconds: $R^2 = 0.12$, $p=0.0039$ Increased PVH and number of steps: $R^2 = 0.13$, $p=0.0075$
Urinary incontinence		
Poggesi A 2008 [53]	LADIS Study	WMH: OR 1.74; 95 % CI, 1.04–2.90

Abbreviations: *AD* – Alzheimer disease, *ARWMC* – age-related white matter changes, *CI* – confidence interval, *HR* – hazard ratio, *LADIS* – Leukoaraiosis and Disability study, *MCI* – mild cognitive impairment, *OR* – odds ratio, *PVH* – periventricular hyperintensity, *SD* – standard deviation, *WML* – white matter lesions, *WMH* – white matter hyperintensity, *WMHv* – WMH volume, *VaD* – vascular dementia

logically normal and stroke-free Japanese subjects, the risk of death at 6.3 years was significantly greater if the subjects had obvious PVH on brain imaging (OR 4.01; 95 % CI, 1.91–8.45) [17]. Similarly, the Rotterdam Scan Study reported increased fatality rates among 430 subjects with WML [32], and the Framingham Offspring Study of 2,208 persons demonstrated that the severity of WMHv was associated with an increased risk of death (HR 1.38, 95 % CI, 1.13–1.69 for WMHv; HR 2.27, 95 % CI, 1.41–3.65 for extensive WMHv) in a long-term follow-up [19]. On the other hand, in the Cardiovascular Health Study, 3,245 participants with low WMH grade demonstrated improved longevity over 10–12 years of follow-up [33]. Meta-analysis in these four population-based studies showed a significant correlation of WMH with risk of death (HR 2.3, 95 %; CI 1.9–2.8, $p<0.001$) [20•].

Other studies evaluated the association of leukoaraiosis with mortality in high-risk populations. A study in southern Norway in 134 persons with first-ever ICH showed that severe WMH was independently associated with both short- and long-term fatality in 30-day survivors [34]. Similarly, survival was reduced in 228 Chinese subjects with WML with first-ever ischemic stroke when followed for a median of 23 months ($p=0.007$) [24].

Association with stroke severity and post-stroke outcomes

Severity of leukoaraiosis has been linked to poor functional post-stroke outcome in both short- (90 days) and long-term follow-up studies (Table 1). In patients with acute ischemic stroke, severity of WMH is significantly associated with poor functional outcome at 3 months [35–39] and beyond [39, 40]. When the topography of WML is considered, PVH burden – but not subcortical or deep WMH – appears to be linked to unfavorable clinical outcome in both short- and long-term (> 90 days) studies [35, 36, 39]. A study in patients with spontaneous ICH also showed that higher leukoaraiosis burden was an independent marker of worse functional outcome [38].

In addition to being a predictor of functional outcome after stroke, severity of leukoaraiosis was independently associated with larger infarct cores [41], greater infarct volume growth [42], and increased risk of hemorrhagic transformation and parenchymal hematoma following intra-arterial thrombectomy for treatment of acute ischemic stroke, especially leukoaraiosis in the deep white matter region [43].

Association with other functional disabilities

The Leukoaraiosis And DISability (LADIS) study is a European multicenter collaboration evaluating the independent role of white matter change by neuroimaging in determining many clinical aspects of disability, such as functional status, cognition, mood, motor performance, and urinary problems [44] (Table 2). In the LADIS study's assessment of 639 nondisabled participants, moderate and severe white matter changes were independently associated with worsening of gait and balance, [45] whereas progression of leukoaraiosis was associated with a gradual decline in executive function test performance [46]. One-year reassessment of 619 elderly LADIS subjects with baseline functional independence demonstrated that severe WMH placed them at risk of dependency from motor and cognitive decline in a short time period [47]. Finally, the LADIS participants with severe baseline WMH and

WMH progression over the course of a 3-year follow-up had a greater risk of gait and stance abnormalities, upper motor signs, and finger-tap slowing (fine motor movement), independent of other vascular lesions [48].

Similarly, the Oregon Brain Aging Study (OBAS), which followed 104 cognitively intact participants for up to 13 years, demonstrated that increased total and periventricular WMHv at baseline and progression of PVH correlated with gradual gait worsening, whereas progression of subcortical WMH was associated with memory decline [49]. Finally, a number of studies reported the association between urinary incontinence and white matter changes [50–52]. Furthermore, urinary urgency was linked to the initial severity of WMH among the LADIS participants, independent of other confounders and vascular brain lesions [53].

Future directions

The role of WMH as a diagnostic and prognostic biomarker of cerebrovascular disease is now commonly accepted. The question remains whether WMH plays an active role in the pathophysiology of cerebral dysfunction linked to the severity and progression of leukoaraiosis. Novel methods of clinical research, including genome-wide association studies (GWAS) and advanced neuroimaging techniques, may provide evidence of underlying disease biology in WMH. Of particular interest is the recent report on a shared genetic contribution between WMH severity assessed on brain MRIs of healthy aging adults enrolled through the multiple population-based cohorts of the CHARGE consortium [54•] and hospital-based cohorts of patients with acute ischemic stroke [55]. In a meta-analysis of WMH GWAS in 9,361 stroke-free individuals of European descent, the CHARGE consortium identified six novel single-nucleotide polymorphisms (SNPs) from a locus on chromosome 17q25 associated with WMH burden [54•]. The association of these SNPs – and most significantly, rs9894383 (p=0.0006) – with WMHv in ischemic stroke patients was replicated by the International Stroke Genetics Consortium study [55], which represents a major breakthrough in understanding the shared genetic contribution to leukoaraiosis across the spectrum of small cerebral vessel disease.

Future breakthroughs are also expected to emerge from advanced neuroimaging of white matter in health and disease, among which diffusion tensor imaging (DTI) is most promising. DTI provides detailed data on the white matter structure (and in recent studies, the association between common vascular risk factors such as hypertension and serum lipids), and DTI measure of white matter integrity that has been explored in healthy adults [56, 57]. If validated, these preliminary reports of the effect of resting blood pressure and serum LDL on white matter integrity warrant further assessment in subjects with advanced WMH.

Conclusion

The body of literature supports the role of WMH as a biomarker of longstanding cerebrovascular disease. Advanced neuroimaging and future studies of genetic architecture of leukoaraiosis will reveal the underlying bi-

ology of white matter disease and its role in pathophysiology of stroke, dementia, and the total burden of cerebrovascular dysfunction.

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Chutinet reports no disclosure.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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This is the first manuscript to provide eveidence in support of association between common genetic variants and severity of leukoaraiosis.

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