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Review

Leukoaraiosis: Epidemiology, Imaging, Risk Factors, and Management of Age-Related Cerebral White Matter Hyperintensities

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Leukoaraiosis (LA) manifests as cerebral white matter hyperintensities on T2-weighted magnetic resonance imaging scans and corresponds to white matter lesions or abnormalities in brain tissue. Clinically, it is generally detected in the early 40s and is highly prevalent globally in individuals aged >60 years. From the imaging perspective, LA can present as several heterogeneous forms, including punctate and patchy lesions in deep or subcortical white matter; lesions with periventricular caps, a pencil-thin lining, and smooth halo; as well as irregular lesions, which are not always benign. Given its potential of having deleterious effects on normal brain function and the resulting increase in public health burden, considerable effort has been focused on investigating the associations between various risk factors and LA risk, and developing its associated clinical interventions. However, study results have been inconsistent, most likely due to potential differences in study designs, neuroimaging methods, and sample sizes as well as the inherent neuroimaging heterogeneity and multi-factorial nature of LA. In this article, we provided an overview of LA and summarized the current knowledge regarding its epidemiology, neuroimaging classification, pathological characteristics, risk factors, and potential intervention strategies.

Keywords Leukoaraiosis; White matter hyperintensities; White matter lesions; Imaging; Risk factors; Genetic variants

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Introduction

The term "leukoaraiosis" is derived from the Greek terms "leuko" and "araiosis," which mean "white" and "rarefaction," respectively.[1-3] It was originally introduced by Hachinski and his colleagues[3] in 1986 to describe cerebral white matter abnormalities observable as signal hypodensities on computed tomography (CT) scans or hyperintensities on T2-weighted magnetic resonance imaging (MRI) scans.[1-3] Thus, leukoaraiosis (LA) is often referred to simply as white matter hyperintensities (WMHs) or white matter lesions (WMLs) with reference to the cerebral white matter changes.

LA generally manifests early in the fourth decade of life and becomes increasingly more common from age 50 onwards.[4-6] It is also common in healthy elderly individuals,[4,7] and most individuals with LA remain asymptomatic. However, LA does not always represent benign imaging features, and could affect normal cognitive ability, motor function, and psychiatric behaviors if the WMLs expand to certain significant regions of the brain.[8-13] Clinically, LA has consistently been reported to be the most common radiological hallmark of cerebral small-vessel diseases (CSVDs) and as being strongly correlated with increased risks of cognitive function decline,[14-17] motor gait dysfunction,[10,18-20] stroke,[21-26] dementia,[16,17,21,25] depression,[27-30] and even death.[21,25,26] Given the clinical importance of WMHs in geriatric populations, there is an urgent need to understand the clinical features and pathogenesis of LA and develop effective strategies for its prevention and management.

In this article, we summarize the current knowledge regarding various aspects of LA—specifically, clinical imaging, epidemiological frequency, pathological characteristics, risk factors, genetic variants and biomarkers, as well as prevention and treatment.

Epidemiology of LA

LA has a high prevalence globally among middle-aged and elderly individuals (36.5%–100% over age 40 years).[4,31-37] Based on community-based studies in Australia and European countries (including Italy, Spain, France, Netherlands, UK, Sweden, Austria, Germany, and Poland), the incidence of LA in the general population can be as high as 80.0% and 92%, respectively.[31,32] Population-based studies in the Netherlands and Australia have also revealed a high prevalence (up to 95% and 100% in individuals aged >60 years, respectively).[33,34] Similarly, the incidence of LA in the community-based population in the USA is also high, with the Cardiovascular Health Study and Atherosclerosis Risk in Communities Study reporting an incidence of 85.4%–95.6% in participants aged >55 years (Figure 1);[4,35] moreover, its reported prevalence is higher among European-Americans (90.2%) than among African-Americans (80.6%).[35] Recently, the largest community-based study in Asian cities (including Hong Kong, Singapore, and Seoul) reported the prevalence of LA as being up to 85.6% among healthy subjects aged 60–89 years[36] (45.2% in Korea, 80.0% in China, and 97.0% in Singapore)[36] (Figure 1). Community- and hospital-based studies in China have shown that the frequency of LA varied from 36.5%–92.3% among in-

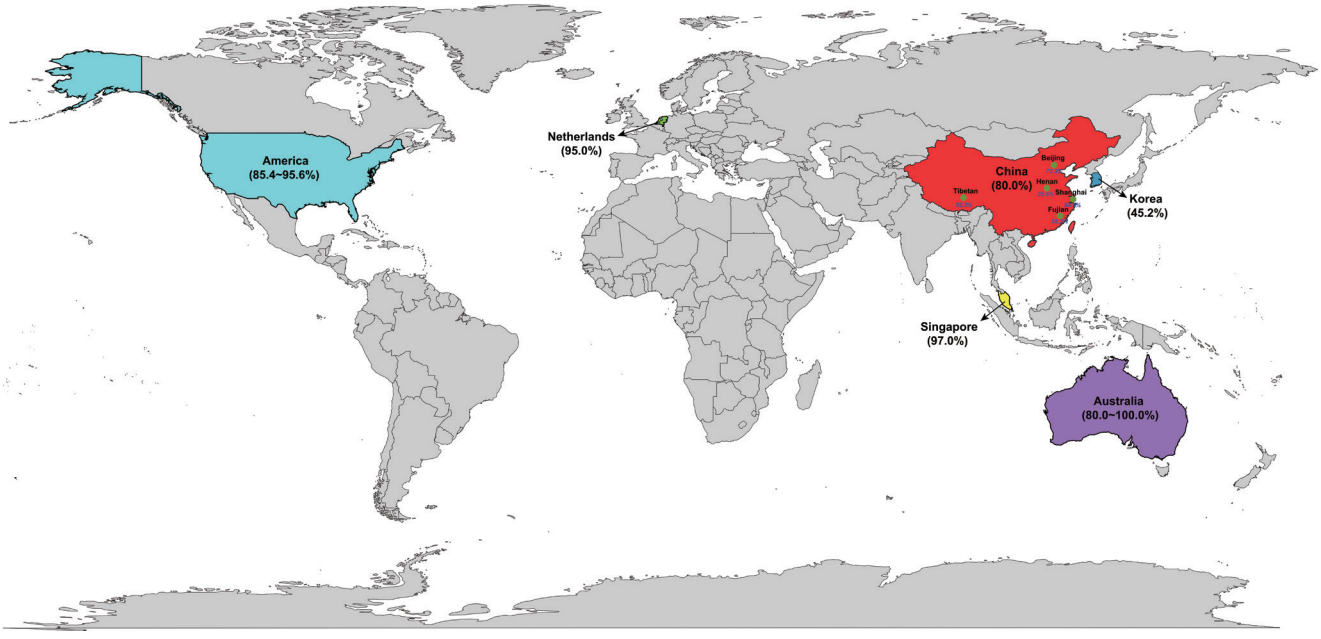

Figure 1. Global leukoaraiosis epidemiology.

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dividuals aged >40 years[5,32,37-39] (up to 36.5% in Henan,[37] 58.3% in Fujian,[5] 73.3% in Beijing,[38] and 92.3% in Tibet,[39] respectively (Figure 1). Among participants aged >60 years, LA was most frequently reported in individuals from Tibet (98.8%),[39] followed by those from Beijing (90.1%),[38] Shanghai (84.9%),[32] Fujian (67.0%),[5] and Henan (62.7%).[37] Thus, LA is highly prevalent in elderly populations all over the world and is increasingly becoming a significant public health burden with the rapid increase in the aging population.

Clinical imaging assessment and pathology of LA

LA was first described as abnormal cerebral white matter CT findings visible as hypodensity signals on CT images.[1,2,40] However, compared to CT, MRI is more sensitive in detecting small lesions at an early stage and has therefore become the main clinical imaging diagnostic tool.[41] It is now well-established that LA lesions appear as hypointense WMLs on T1-weighted MRI and hyperintense lesions on T2-weighted MRI.[42,43] Fluid-attenuated inversion recovery (FLAIR) imaging is a form of heavily T2-weighted MRI with the advantage of cerebrospinal fluid (CSF) signal suppression (Figure 2).[44] Compared to T2-weighted MRI, which simultaneously enhances WML and CSF signals and represents both as hyperintensities,[45] FLAIR-MRI can efficiently differentiate WMLs from enlarged perivascular spaces that contain CSF (e.g., Virchow-Robin spaces), as they appear as hypointense regions on FLAIR-MRI. Thus, it greatly improves the detection efficiency of lesions adjacent to CSF-containing spaces and clearly distinguishes small periventricular WMLs (PVWMLs) from the ventricles.[45-48] Currently, FLAIR-MRI probably represents the best imaging method for assessing LA severity.

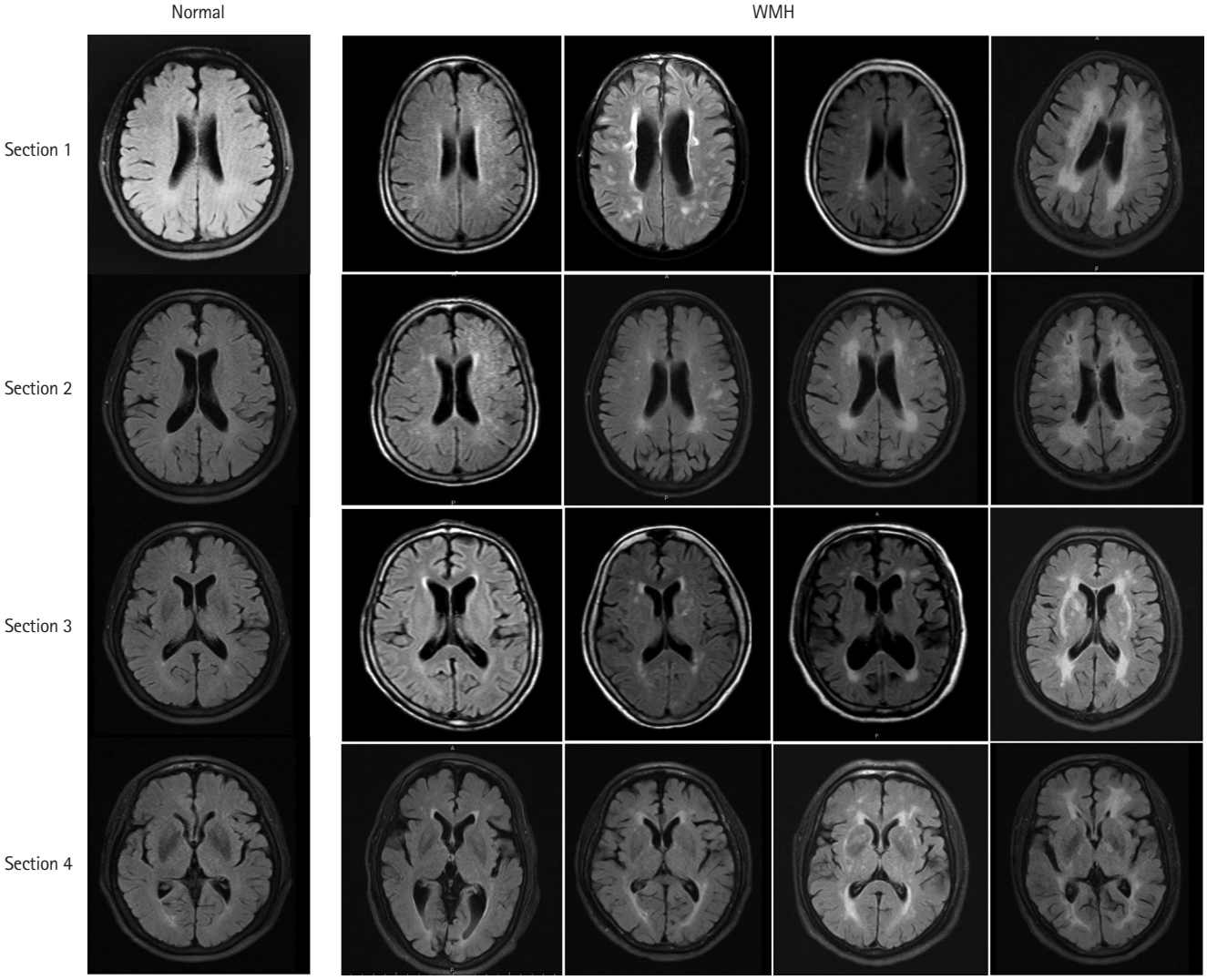

Figure 2. LA definition and heterogeneous forms on FLAIR-MRI. WMH, white matter hyperintensity; LA, leukoaraiosis; FLAIR-MRI, fluid-attenuated inversion-recovery magnetic resonance imaging.

Several other advanced imaging methods are used for assessing white matter changes.[2,48,49] For example, diffusion tensor imaging (DTI) can not only assess the extent of white matter damage, but also provide information about the integrity of white matter tracts through apparent diffusion coefficient (ADC) or fractional anisotropy (FA) measurements of tissues, which reflect the directionality and rate of water mobility.[50,51] Altered microstructures both within WMLs and in normal-appearing white matter can be identified as regions of elevated ADC and decreased FA on DTI scans.[52] Therefore, DTI can be used to track early white matter changes over time and can provide insights into the *in vivo* pathogenesis of LA. T2-weighted gradient-recalled echo sequences and corresponding alternative-susceptibility weighted sequences with higher signal and spatial resolution are sensitive to iron deposition[53,54] and can therefore distinguish cerebral microbleeds as small round or ovoid hypointense lesions, which are features of hypertensive CSVD (such as cerebral amyloid angiopathy) as yet undetectable using conventional MRI.[55,56]

Clinically, LA can have considerable heterogeneity in terms of its presentation, with various lesion patterns, pathological characteristics, and severities. Originally, LA was classified into two categories based on the spatial locations of WMLs: (1) periventricular LA (with PVWMLs/periventricular WMHs [PVWMHs]), and (2) deep and subcortical LA (with deep WMLs/WMHs [DWMLs/DWMHs]) (Figure 2).[57] In the former, the lesions are contiguously adjacent to the lateral ventricles; they either appear as irregular PVWMLs or have caps around the frontal horns, a pencil-thin lining, and a smooth halo (Figure 2).[58,59] Conversely, DWMLs are farther away from the ventricles in the deep or subcortical white matter[58,59] and mainly appear as punctate, early-confluent, and confluent DWMLs corresponding to mild to more severe lesions (Figure 2).[58] Several methods are being used to classify LA severity.[41,60-63] Unlike fully- or semi-automated segmentation-based volumetric quantification methods,[60,64-66] visual rating scales such as the Fazekas scale are easier to use without requiring extensive training and expertise.[43,57,63] They also allow a quicker assessment of LA severity and, despite certain limitations, are widely used both in clinical practice and scientific studies to grade LA as "mild," "moderate," or "severe" according to PVWML, DWML, or total WML severity.[49] In order to facilitate the study of the different mechanisms of LA occurrence and progression, it can also be classified as type I and type II LA depending on whether the lesions are considered mild or severe, respectively.[67,68]

As described above, PVWMLs and DWMLs represent the two regional categories of LA, and both have different functional relevance and histopathologic correlates that are associated with their spatial relationship to the lateral ventricles.[58,59,69] DWMLs are preferably associated with mood disorders such as depression.[70,71] They are generally attributed (especially early- and complete-confluent lesions) to vascular ischemia and are characterized by patchy demyelination with myelin rarefaction.[58,59,72] Punctate, early-confluent, and confluent DWMLs are considered indicative of mild, extensive, and more severe ischemic tissue damage, respectively.[58,59] In contrast, PVWMLs are mainly linked with cognitive impairment and decline.[73-75] However, periventricular lesions with caps, a pencil-thin lining, and smooth halo are more likely to be due to non-ischemic tissue damage.[58,59,72] Histopathologically, they are mainly characterized by extracellular fluid accumulation, ventricular ependyma disruption, and ependymitis granularis representing ependyma loss and astrocytic gliosis.[42,58,59,72,76,77] However, irregular PVWMLs, like DWMLs, have been shown to have an ischemic origin.[59,78,79] They are generally associated with patchy myelin rarefaction and ischemic tissue necrosis around the perivascular spaces;[59,80] furthermore, unlike DWMLs, which are generally associated with microangiopathy, irregular PVWMLs are more likely to be caused by chronic hemodynamic insufficiency due to focal or systemic hypoperfusion.[59,80-82]

Thus, LA lesions are mainly classified into PVWMLs (with caps, a thin lining, and smooth halo) and DWMLs (punctate, early-confluent, and confluent lesions) depending on both relative distance from the ventricular surface and lesion size and severity. PVWML caps, lining, and halos, representing patchy ependyma loss and interstitial fluid leakage, could be non-ischemic in nature, whereas irregular PVWMLs and DWMLs, representing patchy demyelination, are more likely to be attributable to different forms of ischemic tissue damage.

Nonetheless, although PVWMLs and DWMLs differ in terms of certain histopathologic correlates and clinical consequences,[12,71,75,77,83,84] this dichotomization of LA lacks a pathophysiological or functional basis corresponding to WMLs, as it is mainly based on the continuity rule associated with relative distance from the ventricular surface. In advanced stages of LA, PVWMLs can coalesce with DWMLs, and it is difficult to clearly distinguish between WML types. Considering the limitations regarding the somewhat arbitrary criteria for classifying PVWMLs/DWMLs, poor objectivity resulting from semiquantitative visual rating scales, and the resulting increase in heterogeneity of assessment and reduction in the consistency of findings across studies, a new LA subclassification method based on WMH characteristics was proposed by Kim et al.[59] in 2008. Its subclasses have etiological and functional relevance, which reduces the WML finding heterogeneity between studies. This scheme uses a finer quantification method to classify LA lesions into four classes: (1) juxtaventricular WMLs (JVWMLs): lesions—located in juxtaventricular areas within 3 mm of the ventricular surface, (2) PVWMLs: le-

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sions in the periventricular watershed zone (3–13 mm from the ventricular surface, (3) DWMLs: lesions 13 mm or further from the ventricular surface, and (4) juxtacortical WMLs (JCWMLs): deep lesions located in juxtacortical white matter areas within 4 mm from corticomedullary junction.[59] Of these, only JVWMLs are non-ischemic.[58,59,81,82] They are more likely attributable to CSF leakage into the adjacent brain parenchyma because of their direct attachment to the ventricular surface.[59,85-87] Both PVWMLs and DWMLs are characterized by ischemia-induced disruption of long white matter tracts,[58,59,77,86] and might result from hypoperfusion and CSVD, respectively.[59,77,84,86] Like ischemic PVWMLs and DWMLs, JCWMLs also have an ischemic origin;[59] however, they could have a different pathological basis[59] and are characterized by CSVD-associated disruption of U-fibers rather than the disruption of long white matter tracts.[59]

Notably, despite the considerable pathological, functional, and neuroimaging heterogeneity in LA lesions, the correlations between them have not been fully understood, and we still need to identify specific WML subclasses and determine the underlying clinical factors and subsequent clinical consequences. Recently, Jung et al.[88] comprehensively quantified the characteristics of WMLs through a novel, fully automated procedure that uses hierarchical clustering methods to classify LA into three distinct classes based on features including lesion contrast, non-contiguous lesion number, volume of each non-contiguous lesion, and periventricular to deep lesion volume ratio. They defined class I LA as the presence of small, punctate, scattered, relatively lower-contrast, and deep WMLs;[88] class II LA as the presence of large, patchy, irregular, or confluent lesions, predominantly in the periventricular white matter; and class III LA as the presence of mild and relatively higher-contrast lesions restricted to the juxtaventricular white matter.[88] The three classes have different pathological features and distinct correlations with clinical factors and/or outcomes. Pathologically, class II LA lesions are characterized by lower myelin content than class I and class III lesions, indicating more serious myelin rarefaction.[88] They are more common in older subjects with hypertension and/or lower physical activity levels, whereas class I lesions are more common in subjects with poor sleep quality.[88] Therefore, compared with the previous methods, this fully automated, hierarchical clustering based classification can provide more details on WML features. It can be used to distinguish between LA subclasses with different clinical factors and consequences, and facilitates the understanding of the correlations between specific subclasses of WML burden and the underlying clinical features and pathophysiologies.

Clinical risk factors for LA

As a prevalent age-related manifestation of CSVD in elderly individuals, LA is recognized as being multi-factorial in nature and having many potential risk factors identified by a large number of studies (Figure 3). As some of these findings are inconsistent across different studies, possibly due to differences in study population, methodology, sample size, and participant ethnicity, we will introduce and discuss the most widely studied risk factors below.

Age

Age is the most important risk factor for LA, and LA prevalence increases with age (reported as about 50.9% in the 40s,[6] 78.0% in the 50s,[35] and 80.0%–95.6% at age ≥60 years in the general population worldwide).[4,31-33,36] According to a Chinese community-based study, the frequency of periventricular and deep LA increase from only 49.8% and 45.8% in the 40–49 years to 73.5% and 63.5% in the 50–59 years, 87.7% and 83.2% in the 60–69 years, and 97.1% and 89.5% in the 70–79 years age groups, respectively.[38] Another study on hospitalized Chinese patients showed that the frequencies of mild and moderate to severe LA rose from 21.1% and 6.7% in the 40–49 years to 29.2% and 16.2% in the 50–69 years and from 37.4% and 20.0% in the 60–69 years to 41.2% and 40.5% in the ≥80 years age groups, respectively.[5]

LA is also known to progress with age, although progression varies in different populations and does not necessarily occur in

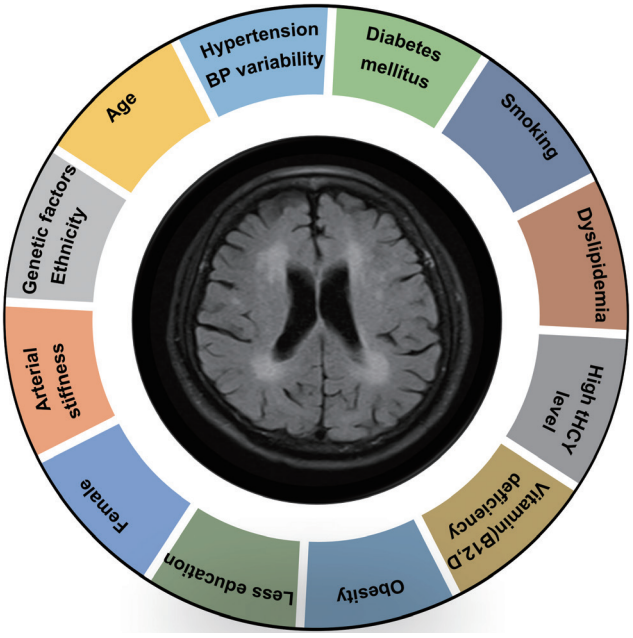

Figure 3. Potential risk factors for leukoaraiosis. BP, blood pressure; tHcy, total plasma homocysteine.

every case.[89-91] Age has been shown to be a predictor of LA progression in a few longitudinal studies,[91-94] and increased age is strongly correlated with increased risk of lesion worsening, especially in low initial grade LA.[91] Older age is also significantly associated with a higher emergence rate and faster progression of LA and higher percentage of change in LA volume.[92-94] However, other longitudinal studies have not supported these findings and instead found baseline WMH burden to be a predictor of LA progression.[58,90,95-97] Among these, two reports from the Austrian Stroke Prevention Study,[58,90] which involved 3-year and 6-year follow-ups of healthy community-dwelling individuals, showed that the increase in WML volume in subjects with early confluent and confluent WMLs was significantly more rapid at both follow-up time-points than those in subjects without lesions and with punctate lesions at baseline, suggesting that baseline WML severity is a predictor for LA progression. Similarly, a recent prospective case-control study also found that high WMH burden at baseline was significantly associated with LA progression (odds ratio: ≤7.68) and more subjects in the high baseline WMH group had LA progression at follow-up than in the low baseline WMH group (77.6% vs. 34.7%).[96] Moreover, baseline WMH burden and LA progression are significantly correlated for both DWMLs and PVWMLs.[94,95,98] The increase in DWML volume is reported to be greater than that in PVWML volume;[95,98] moreover, a recent study reported that PVWML progression frequency is lower than early-confluent and confluent DWML progression frequency at 3-year (22.9% vs. 38.3%) and 6-year follow-ups (42.9% vs. 74.0%).[58] Taken together, these findings suggest that the major determinant and predictor of LA progression is not age, but baseline WML level. Given the relationships between age and LA prevalence and severity, we think that age could contribute indirectly to LA progression through its influence on baseline WML volume.

Blood pressure and hypertension

Like aging, hypertension is also strongly associated with LA. It can increase both the prevalence and severity of LA and is thus considered an independent and important risk factor for it.[35,99-106] Moreover, both higher diastolic blood pressure (DBP) and systolic blood pressure (SBP) have been shown to be significantly associated with the risk of LA.[107-109] A large meta-analysis of multi-ancestry genome-wide association studies (GWAS) on WML volume has also provided evidence of causative associations between higher DBP and SBP and higher WML volume in participants with and without hypertension.[110] Another recent meta-analysis has also suggested a consistent and strong association between LA severity and DBP and SBP.[111] However, evidence from some independent studies suggests different associations between LA and both DBP and SBP.[4,100,107,112-115] Currently, the risk of LA is considered to be correlated with DBP in mid-life and SBP in later life,[108,109] suggesting that DBP control in early mid-life and SBP control later in life could protect against increased risk and severity of LA.

Although some longitudinal studies did not find any significant association between hypertension and LA progression after adjustment for baseline WML burden or other clinical factors,[18,90,92,95] hypertension is considered to be correlated with LA progression.[5,116-119] This is because several studies have shown that anti-hypertensive treatment can slow WML volume increase, suggesting a role of hypertension in promoting LA progression.[101,120-125] Recently, a prospective case-control study in an Asian population identified both baseline WML burden and hypertension as important risk factors for LA progression.[96] Furthermore, DBP and SBP have been associated with LA worsening.[89,91,94,126] A recent meta-analysis study including 12 closely related studies on the role of blood pressure (BP) in the progression of WML revealed that both SBP and DBP elevation can promote WML progression, suggesting that both are important risk factors for LA progression.[127] This study also showed that SBP and DBP had different effects on LA progression and that DBP increase had a greater effect on lesion worsening, particularly in patients aged <70 years.[127] Thus, delaying LA progression requires the development of personalized strategies for controlling BP levels.

Taken together, these findings indicate that, like hypertension, high SBP and DBP are associated with not only the incidence and severity of LA, but also its progression. Nevertheless, the precise role of high BP in the pathogenesis of LA remains unclear, although some high BP-mediated mechanisms that could underlie this pathogenesis are as follows: (1) high BP could induce vessel wall thickening and lumen narrowing, subsequently reducing blood flow and leading to ischemia-related tissue damage in the white matter, (2) high BP could cause endothelial damage followed by blood-brain barrier breakdown, resulting in the leakage of potentially toxic substances into the brain and subsequent cell injury, and (3) endothelial damage could induce endothelial inflammation, induce autoimmune reactions against the myelin on axonal fibers, and eventually result in demyelination and even axonal degeneration.[49,59,72,86,128,129] Future *in vitro* and *in vivo* studies will be required to confirm which of these proposed mechanisms are involved in LA.

BP variability

Compared to hypertension and absolute BP elevation, BP variability (BPV) generally receives less attention, but has recently been shown to increase the risk of both stroke and dementia.[130-132]

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Moreover, a growing number of studies have found that BPV is linked to CSVD-related phenomena such as LA, cerebral microbleeds, and lacunes.[133-143] Most of these studies showed that increased SBP variability was related to a higher risk or burden of LA,[133,135,136,138,141,143] although a few studies did not find any significant associations.[144-146] A recent meta-analysis of population-based prospective cohort studies also found a significant and positive association between SBP variability and LA.[147] In contrast to SBP variability, the findings regarding the relationship between DBP variability and LA are more conflicting. Most studies found that DBP variability did not affect LA risk or lesion volume.[136,138,139,144,145,147] However, two recent studies have reported a significant association between diastolic BPV and LA.[141,146] One was a longitudinal study that showed that the 24-hour average real variability of DBP, an index of BPV, was associated with LA progression in participants with cardiovascular diseases.[146] In the other study, both increased SBP and DBP variability were associated with increased LA volume, especially PVWMH burden, independently of BP levels;[141] moreover, DBP variability was significantly associated with LA volume.[141] The reasons for the inconsistencies in results may be due to differences between the studies in terms of the BPV indices used and in study populations and the methods of evaluating LA. Thus, results regarding the effects of DBP variability on LA should be interpreted cautiously. Overall, the available evidence strongly suggests that systolic BP fluctuation is a risk factor for LA and that monitoring and controlling BP fluctuations could help prevent LA and improve its prognosis.

Diabetes mellitus

As a vascular risk factor, diabetes mellitus may also contribute to the increased risk of LA. A number of studies have investigated the effect of diabetes mellitus on LA, but their findings are inconsistent, possibly due to differences in sample sizes, participant ethnicities, and statistical methods across studies. Both older[7,148,149] and more recent studies with large sample sizes have shown that diabetes mellitus is significantly associated with LA volume in some European populations.[106,125,150] The largest community-based study (up to 37,041 participants from the UK Biobank cohort) also found a strong correlation between diabetes mellitus and WML volume both before and after adjusting for BP, age, sex, and other cardiovascular risk factors (such as smoking).[109] Conversely, most studies on Asian populations, except our cross-sectional study on hospitalized Chinese patients,[5] failed to confirm any relationship between diabetes mellitus and LA.[93,114,151,152] Additionally, diabetes mellitus was shown to be correlated with LA progression in both studies,[5,92] although longitudinal studies in other countries did not find any associations between diabetes mellitus and WML progression.[94-96] Thus, it is likely that diabetes mellitus is not associated with the progression of LA, but is strongly correlated with LA frequency and severity, particularly in European populations. Further studies are required to investigate the associations between diabetes mellitus and LA incidence and progression and explore the effects of antidiabetic treatments on the prevention and management of LA.

Smoking

Like diabetes mellitus, smoking may also be correlated with LA. Although some studies in Asian populations did not find any relationship between smoking and LA,[93,114,151,152] many studies in non-Asian populations, including the Cardiovascular Health Study, Rotterdam Scan Study, Atherosclerosis Risk in Communities Study, and Framingham Offspring Cohort Study, found significant associations between smoking and LA.[4,33,91,94,99,106,125,148,153-155] Some of these studies in European and American populations found that smoking was associated with the incidence and severity of LA.[99,106,125,148,153,155] Recently, the largest genetic study on complex CSVD till date revealed a strong causal association between increased lifetime cigarette smoking (specifically, the lifetime smoking index) and higher WML burden in an older community-based population (up to 50,970 individuals from the cohorts for heart and aging research in genomic epidemiology (CHARGE) and from UK Biobank.[110] Another large study (with ten thousand European participants from the UK Biobank cohort) showed that smoking was strongly related with increased WML load both before and after adjustments for BP, age, sex, and other cardiovascular risk factors (such as diabetes mellitus).[109] Smoking has also been correlated with LA progression. Except two studies with limited sample sizes in Asian and Australian populations,[95,96] most studies in European and American populations suggest that cigarette smoking is a risk factor for LA progression.[4,33,91,94,99,153-155] Thus, smoking is likely to be associated with LA incidence and severity as well as its progression, although the possible biological processes through which it could mediate the pathogenesis of LA remain unclear.

Dyslipidemia

The findings of studies on the effects of dyslipidemia on WMLs are also conflicting. One study found a strong inverse association between hyperlipidemia and LA severity;[156] specifically, acute ischemic stroke patients without hyperlipidemia had more severe LA than those with a history of hyperlipidemia.[156] Both hypercholesterolemia and hypertriglyceridemia have been shown to be significantly associated with lower risk and decreased severity of LA.[157,158] This suggests that lipid metabolism-associated factors have a protective effect on LA severity. However, two

recent studies have reported that dyslipidemia has deleterious effects on the risk and burden of LA.[125,159] In one study, single modeling of individual vascular risk factors-global brain associations was used to show that hypercholesterolemia was significantly associated with higher WMH load in a UK Biobank cohort.[125] The other study was a meta-analysis that showed that individuals with hyperlipidemia were more likely to have LA than those without hyperlipidemia.[159] These findings suggest that hyperlipidemia is a risk factor for LA; however, several other studies failed to find any associations between hyperlipidemia or hypercholesterolemia and LA.[38,39,125,152] Furthermore, a longitudinal study showed that increased high-density lipoprotein cholesterol (HDL-C) and decreased low-density lipoprotein cholesterol (LDL-C) levels could increase the risk of LA progression,[91] although other studies did not find any such associations.[38,110,160] Due to these inconsistent results, it is not clear whether lipid metabolism-associated factors are associated with LA incidence or progression. Future studies are therefore needed to clarify the relationships between dyslipidemia and LA, and caution should be exercised when considering lipid-modifying therapies for patients with LA.

Arterial stiffness

Arterial stiffness is a known predictor of cardiovascular disease and is known to be related to CSVD. Some studies have shown that increased arterial stiffness is associated with higher WMH burden.[161-166] Moreover, a systematic review and meta-analysis found consistent associations between arterial stiffness and CSVD markers, including LA, cerebral microbleeds, and cerebral infarcts, across several cross-sectional studies.[167] The relationships between arterial stiffness and LA have been widely investigated in recent years. Except in one study, which found no association between pulse wave velocity (PWV), considered as the gold standard for measuring arterial stiffness, and cerebral SVD markers,[168] most studies have shown that increased arterial stiffness is significantly associated with increased WMH prevalence or volume.[169-172] A few studies have also investigated the relationships between arterial stiffness and the LA subtypes classified on the basis of PVWMH and DWMH, but their results were inconsistent.[173-176] Two of these studies reported that PWV was statistically significantly associated with both LA subtypes.[173,174] However, two other studies found significantly different associations between arterial stiffness and PVWMH and DWMH[175,176]—in one study, arterial stiffness was associated with PVWMH but not DWMH,[175] whereas in the other, PVWMH had a higher correlation with arterial stiffness than DWMH.[176] Although the differences between the associations between arterial stiffness and PVWMH versus DWMH need to be clarified, these findings strongly suggest that arterial stiffness is associated with LA incidence and severity.

Arterial stiffness has also been correlated with LA progression. Several longitudinal studies have shown that arterial stiffness is related to LA progression in both community-dwelling older adults and patients with type 2 diabetes.[177-179] They found that baseline PWV was higher in subjects with WMH progression than in those who did not and that the WMH progression rate was higher among individuals with higher PWV.[177,178] Thus, arterial stiffness could be a crucial cause of rapid LA progression in older individuals. Recently, a systematic review and meta-analysis characterized the associations between CSVD markers (such as LA, lacunes, perivascular spaces, cerebral microbleeds, and recent small subcortical infarcts) and cerebrovascular reactivity, cerebral autoregulation, and arterial stiffness.[180] Although the associations between LA and measures of cerebrovascular regulation and arterial stiffness have not been assessed independently, the significant associations between CSVD markers and increased arterial stiffness and impaired cerebrovascular reactivity seem to indicate that cerebrovascular regulation and arterial stiffness may have some role in the development or progression of LA.[180]

Collectively, these findings suggest a strong association between arterial stiffness and LA. We believe that arterial stiffness should be considered a risk factor for LA and that it represents a potential mechanism of LA onset and progression.

Homocysteine and vitamin levels

Homocysteine is a naturally occurring sulfur-containing amino acid that can induce oxidative injury, endothelial dysfunction, and vascular damage[181-183] and is known to increase the risk of cardiovascular and cerebrovascular diseases.[184-186] Most cross-sectional studies, except a few,[187-189] have consistently shown that total plasma homocysteine (tHcy) level elevation, or hyperhomocysteinemia, is significantly associated with LA;[181,190-204] a few longitudinal studies have also shown that it can increase the risk of LA progression.[205,206] This strongly suggests that hyperhomocysteinemia is a risk factor for LA. Furthermore, the detrimental effects of high homocysteine levels in LA are related to the locations of WMLs and sex-related differences.[207-209] One study showed that high tHcy levels were independently correlated with increased deep LA but not periventricular LA in healthy community-dwelling individuals and that this association was significant only in men.[207] However, other studies found that plasma tHcy levels were more significantly associated with periventricular and frontal LA rather than deep and subcortical LA in both stroke patients and healthy individuals.[208,209] This indicates differences in etiologies between the two main subtypes

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of LA, and also suggests the possible involvement of dysregulated tHcy metabolism and subsequent endothelial dysfunction in the pathogenesis of PVWMH.

Hyperhomocysteinemia may be attributed to the deficiency of vitamins such as folic acid, vitamin B_6, and vitamin B_{12}.[210,211] These vitamins have been implicated in various cognitive function and vascular disorders, including LA.[212-215] Low plasma vitamin B_{12} level is significantly associated with more severe LA, especially periventricular LA.[216,217] Moreover, low baseline vitamin B_{12} level was shown to be significantly associated with PVWMH progression in lacunar stroke patients in one longitudinal study,[218] although other studies found no associations with total WMH or WMH progression.[206,219-223] In the only one of these studies with a sub-group analysis on WMH, there was a significant association between deep WMH and vitamin B_{12} levels in patients with major depression.[221] Due to the inconsistencies in these results, due to multiple possible reasons, more cross-sectional and longitudinal studies will be needed to validate the association between vitamin B_{12} levels and LA. Nevertheless, animal model studies on myelin morphology suggest that vitamin B_{12} deficiency has a harmful effect on WMLs characterized by demyelination.[224,225] Overall, the available evidence seems to suggest that low plasma vitamin B_{12} level is a risk factor for LA, especially with PVWMH.

Like vitamin B, vitamin D, which plays important roles in bone metabolism regulation and cognitive functioning, has also been studied in elderly individuals with LA.[226-228] Some studies have shown that lower serum 25-hydroxyvitamin D levels were negatively correlated with WMH volume, suggesting that vitamin D deficiency is a risk factor for LA.[229-236] Another study revealed a stronger correlation between vitamin D and PVWMH rather than DWMH.[237] However, other studies, including several longitudinal studies, did not find any association between vitamin D levels and WMH.[238-242] These inconsistencies in results could be due to differences in study populations, LA and vitamin D level evaluation methods, LA lesion and etiology heterogeneities, differences in statistical power due to differences in sample sizes, presence of concomitant disorders, and so on. Future longitudinal studies and prospective clinical trials on vitamin D supplementation are required to clarify any possible causal relationships with LA.

Obesity

Obesity is an important risk factor for cardiovascular diseases. It is generally assessed using the body mass index (BMI) and waist-to-hip ratio (WHR), and these measures can also be considered as cardiovascular risk factors. Obesity has been also shown to be associated with LA[160,243,244]—both higher BMI and WHR were shown to be significantly associated with higher WMH burden, suggesting that obesity is a novel risk factor for LA.[69,125,245] Recently, the association between obesity and LA was shown to depend on sex and race.[246,247] In one study, there were significant differences between men and women in terms of the association between BMI and DWMH; moreover, only male sex interacted with higher BMI to result in increased DWMH volume.[246] In another study, obesity was found to significantly increase the risk of WMH in African Americans.[247] These findings indicate that obesity is associated with LA severity and that it could be involved in the pathogenesis of LA. Another recent study showed that visceral obesity contributed to a higher DWMH/PVWMH ratio through elevated levels of the pro-inflammatory cytokine interleukin-6, independent of age and sex, thus providing insights into the possible inflammatory mechanisms underlying DWMLs,[245] although future studies are required to confirm this hypothesis at the molecular level and using imaging assessment and animal models.

Education level

Some studies have reported that education levels are associated with LA.[70,106,248-251] In one study, there were significant negative associations between education level and both WMH frequency and volume,[106] suggesting a protective effect of a higher education level on the incidence and severity of LA. Recently, a systematic review and meta-analysis including six studies also showed that individuals with low educational levels had more WMHs compared to individuals with higher educational levels.[252] However, other studies did not find any associations between LA and education level.[36,192,237,253,254] Differences in the definitions and assessment of education levels and in the statistical analysis methods used may have contributed to these discrepancies. Therefore, results regarding the relationship of LA with education level should be interpreted cautiously, because it is a complex parameter that can have significant effects on lifestyle and socioeconomic status in later life, which in turn have also been shown to be correlated with LA.[4,248,252]

Sex

Many studies have shown that LA incidence and progression tend to be higher among women.[4,33,34,39,93,94,98,99,255-257] However, other studies,[91,92,95,258,259] including several recent ones, could not support these findings and found no such differences between women and men.[36,96,160,251] Sex-related differences in the associations between risk factors and LA have also been observed in some studies. For example, the associations between LA and hypertension,[136,260] diabetes,[149] and atherosclerosis[261] are stronger in men than in women, possibly due to the higher prevalence of vascular risk factors in men. A recent study examined the possible

moderating effects of sex on the associations between such risk factors and LA in a large cohort of community-dwelling individuals without dementia and found several differences among women and men.[246] Specifically, sex was found to be significantly associated with total WMH volume independently of age, hypertension, and hip-to-waist ratio (HWR). Moreover, both age and HWR were risk factors for WMH burden in women, whereas multiple risk factors—including age, hypertension, HDL level, HWR, and BMI—were significantly associated with higher WMH volume in men.[246] The differences in associations between BMI and DWMH between men and women strongly suggest that sex moderates the associations between these risk factors and LA and has important effects on LA incidence, severity, and progression. Although the differences in the underlying mechanisms in LA between women and men are not well understood, they could be explained by differences in genetic factors and susceptibility to ischemia and hormonal changes later in life.

Ethnicity

Ethnicity has also been reported to affect the prevalence, severity, and progression of LA.[32,35,150,262-264] African Americans and Mexican Americans have been reported to have higher WMH volumes compared to non-Hispanic whites.[150,262] Additionally, the confluent WMH prevalence and WMH progression rate were higher in African Americans than in European Americans.[35,263,264] Asians have also been reported to have a higher WMH burden than White Australians.[32] However, there were no significant differences in WMH burden (both overall and local WMH burden) between Asians and Europeans.[114] Among Asian regions, the prevalence of moderate-to-severe WMHs was higher in Singapore than in China and Korea.[36,152] Additionally, some studies have reported ethnicity-related differences in the associations between certain risk factors and LA.[35,114,150] For example, the associations between WMH burden and age, DBP, and National Cholesterol Education Programme Adult Treatment Panel III cardiovascular risk scores were stronger among South Asians than among Europeans, whereas the association between WMH burden and diabetes mellitus duration was stronger among Europeans than among South Asians.[114] Recently, a study showed that age could predict high WMH burden only for European Americans and that only obesity could predict high WMH burden among African Americans;[247] it also reported that the deleterious effect of obesity on WMH load was more pronounced among African Americans than European Americans.[247] Together, these findings indicate that ethnicity affects LA risk and modulates the effects of risk factors on LA. Although the mechanisms underlying the ethnicity-related differences in LA risk remain unclear, they could be attributable to differences in vascular risk factor susceptibility, lifestyles, genetic and environmental factors, and susceptibility to developing cardiovascular diseases.

Genetic risk factors for LA

Like various vascular risk factors and sex- and ethnicity-related differences, genetic predispositions can also explain some of the variance in LA risk and burden. LA shows a high heritability and has a strong genetic basis.[265-267] Many LA susceptibility genes have been identified in the past decades through genetic studies with different study designs on different ethnic cohorts.[251,268-286] Of these, candidate gene association studies have identified up to 52 susceptibility genes significantly associated with LA (Figure 4A).[67,251,268-275,277-284] Two recent exome-wide association studies on individuals of European and African descent and UK Biobank subjects revealed that 10 single nucleotide polymorphisms in eight genes (*TRIM65*, *ACOX1*, *CARF*, *FBF1*, *MRPL38*, *NBEAL1*, *WDR12*, and *GBE1*) are significantly associated with the risk of LA (Figure 4A).[270,287] Moreover, two GWASs on stroke-free European individuals and multi-ethnicity cohorts (including individuals of European, African, Hispanic, and Asian ancestry) free of both stroke and dementia have identified a large number of genetic variants at multiple loci associated with increased LA risk and burden.[285,286] The variants in 13 of these genes (*TRIM65*, *TRIM47*, *WBP2*, *FBF1*, *ACOX1*, *PDCD11*, *UNC13D* and *NEURL* on Chr17q25, *SH3PXD2A* and *TAF5* on Chr10q24, *EFEMP1* on Chr2q16, *HAAO* on Chr2p21, and *PMF1* on Chr1q22) reached genome-wide significance.[270,285,286] Recently, five meta-analyses of GWASs on WMH burden confirmed the presence of most of these variants in individuals from the UK Biobank and CHARGE consortium cohorts, and further identified up to 63 other susceptibility genes with genome-wide significance, including *PLEKHG1*, *NBEAL1*, *KLHL24*, *CARF*, *WDR21*, *ICA1L*, *DEGS2*, *DCAKD*, *ECHDC3* and *NMT1*, and so on (Figure 4B).[110,288-291] Of the 76 susceptibility genes identified by GWASs, 21 (*TRIM65*, *TRIM47*, *WBP2*, *EFEMP1*, *SH3PXD2A*, *PLEKHG1*, *C16orf95*, *COL4A2*, *NBEAL1*, *NMT1*, *HAAO*, *ACOX1*, *UNC13D*, *FBF1*, *DEGS2*, *DCAKD*, *KLHL24*, *ICA1L*, *WDR12*, *CARF*, *AC098824.6*) are common in at least two GWASs mentioned above (Figure 4B). Furthermore, 13 of these LA susceptibility genes identified by GWASs have been confirmed by candidate gene association studies (*TRIM47*, *WBP2*, *PMF1*, *COL4A2*, *NOS3*, *APOE*) and whole exome sequencing studies (*TRIM65*, *ACOX1*, *MRPL38*, *FBF1*, *WDR12*, *NBEAL1*, *CARF*) (Figure 4C) and are therefore the most reliable risk genes for LA. It is worth mentioning that one meta-analysis of GWAS considered LA subtypes separately and detected differences in risk genes between PVWMH and DWMH in two multi-ethnicity study cohorts (primarily white, along with black and Hispanic individuals).[291] It

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identified 15 specific risk genes for PVWMH (*EFEMP1*, *CARF*, *ICA1L*, *KRT8P15*, *WDR12*, *AC098824.6*, *AC023271.1*, *AC023271.2*, *AC098831.4* and *AC010900.2* on Chr2, *COL4A2* on Chr13, *PLEKHG1* on Chr6, *NOS3* on Chr7, *C16orf95* on Chr16, and *NMT1* on Chr17); only one risk gene (*RP11-137H2.6*) was found to be specific to DWMH (Figure 4D-E). Furthermore, PVWMH and

Risk genes identified by candidate gene association study (CGAS)										
A2M	*ACE*	*ACOX1*	*ADD1*	*AGT*	*AGTR1*	*APOE*	*AQP4*	*BDNF*	*CAPN10*	*CARF*
CDH1	*CETP*	*CLDN16*	*COL4A2*	*CST3*	*CTNNB1*	*CYP11B*	*F3*	*FBF1*	*GPR39*	*HLA-C*
HLA-DQB1	*ICAM1*	*IL5RA*	*IL6*	*ITGB6*	*KITLG*	*KLC1*	*KNS2*	*LTA*	*MMP13*	*MMP2*
MMP3	*MMP9*	*MRPL38*	*MTHFR*	*NBEAL1*	*NOS3*	*NOTCH3*	*NR3C1*	*PMF1*	*PNPLA3*	*PON1*
PTGS2	*SOD1*	*TGFB1*	*TRIM47*	*TRIM65*	*USMG5*	*WBP2*	*WDR12*			
Risk genes identified by genome-wide association study (GWAS)										
ACOX1	*APOE*	*AC007319.1*	*AC010900.2*	*AC023271.1*	*AC023271.2*	*AC098824.6*	*AC098831.4*	*C16orf95*	*CALCRL*	*CARF*
CARF1	*CCDC88C*	*CDK3*	*COL4A2*	*CTC-441N14.4*	*CYP20A1*	*DCAKD*	*DEGS2*	*DENND1B*	*ECHDC3*	*EFEMP1*
EPHB3	*EPN2*	*EVL*	*EVPL*	*FAM213A*	*FBF1*	*GALK1*	*H3F3B*	*HAAO*	*ICA1L*	*KCNK2*
KLHL24	*KRT8P15*	*LOC100505841*	*MN1*	*MRPL38*	*MS4A6A*	*MTFMT*	*NBEAL1*	*NEURL*	*NID2*	*NMT1*
NOS3	*NUMB*	*PDCD11*	*PKN2*	*PLEKHG1*	*PMF1*	*RP11-137H2.6*	*RP11-437L7.1*	*RP11-552F3.10*	*RP11-552F3.12*	*RASL12*
RP11-552F3.9	*SALL1*	*SGK223*	*SH3PXD2A*	*SH3PXD2A-AS1*	*SLC51B*	*STAG3L4*	*TAF5*	*TEN1*	*TNKS*	*TRIM47*
TRIM65	*TSPAN14*	*UNC13D*	*UNK*	*VCAN*	*WBP2*	*WDR12*	*XKR6*	*ZAN*	*ZNF107*	
Risk genes identified by whole-exome sequencing studies (WES)										
ACOX1	*CARF*	*FBF1*	*GBE1*	*MRPL38*	*NBEAL1*	*TRIM65*	*WDR12*			
Shared dysexpressed genes identified by gene expression studies										
AHNAK	*ALAS2*	*DRAXIN*	*KLHL6*	*LRRC43*	*PARVA*	*PIP5K1B*	*SEPT11*	*SLC15A2*	*TTC9*	*WLS*

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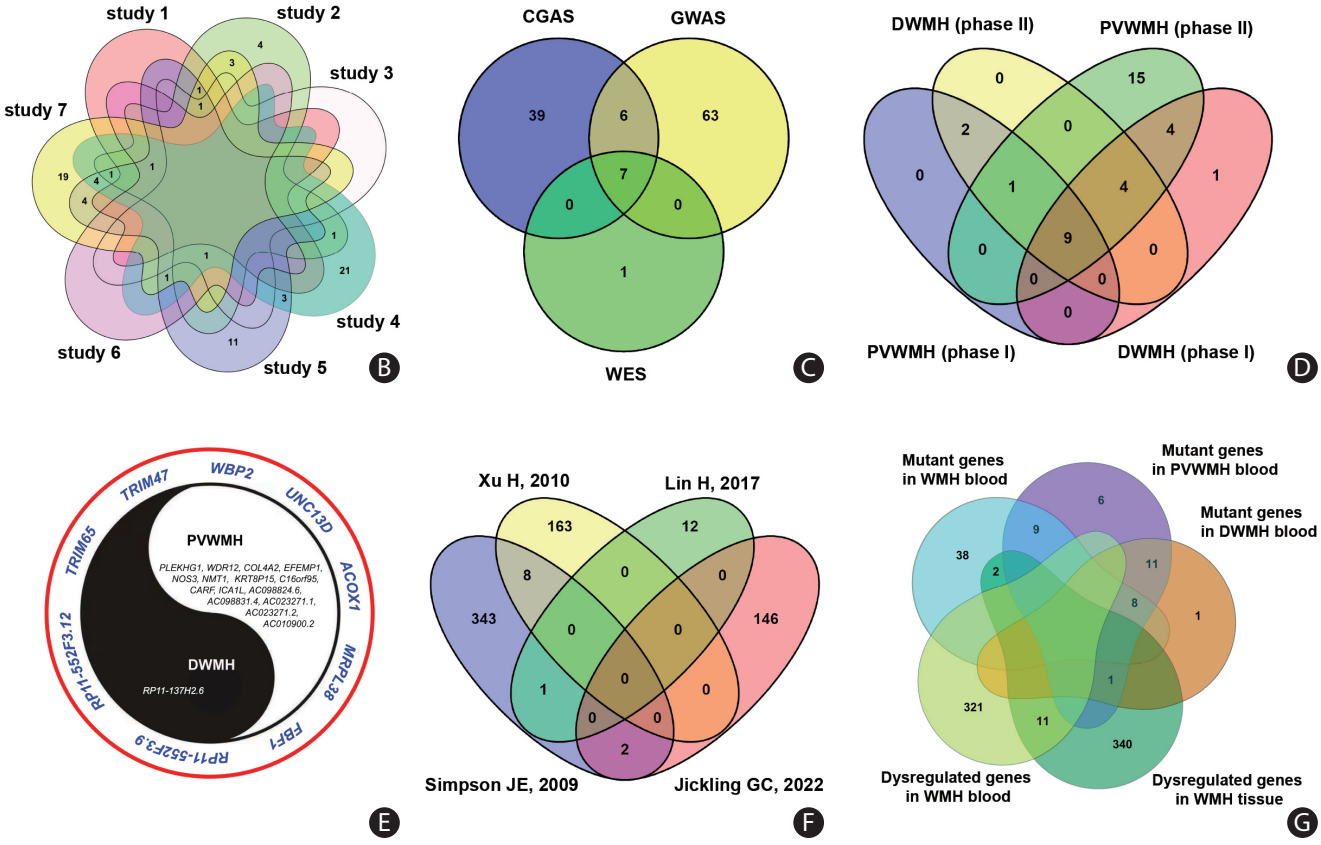

Figure 4. LA susceptibility genes. (A) Risk genes of LA revealed by the previous genetic studies. (B) Venn diagram of risk genes identified by the 7 previous GWAS studies on LA. (C) Venn diagram of risk genes identified by the 18 CGAS, 7 GWAS, and 2 WES studies of LA. (D) Venn diagram of LA subtype-associated risk genes revealed by a genome-wide association meta-analysis of PVWMH, and DWMH. (E) Shared risk genes between PVWMH and DWMH, and its specific susceptibility genes. (F) Venn diagram of dysregulated genes identified by 4 previous gene expression studies of LA.[292-295] (G) Venn diagram of dysregulated and variant genes identified in the blood or lesional tissue of PVWMH, DWMH, and WMH patients, respectively. CGAS, candidate gene association study; GWAS, genome-wide association study; WES, whole-exome sequencing study; DWMHs, deep/subcortical white matter hyperintensity; PVWMH, periventricular white matter hyperintensity; WMH, white matter hyperintensity; LA, leukoaraiosis.

DWMH shared 20 risk genes with genome-wide significance, most of which are located at Chr17q25. Of these, nine common genes (*TRIM65*, *TRIM47*, *WBP2*, *UNC13D*, *MRPL38*, *ACOX1*, *FBF1*, *RP11-552F3.9*, and *RP11-552F3.12*) (Figure 4D-E) were identified in both the discovery and replication cohorts.

Studies have also found several genes, other than the previously discussed variant genes, with abnormal mRNA levels in LA patients.[292-294] Two studies used whole-blood gene expression profiling and found up to 184 differentially expressed genes between LA patients and healthy individuals (Figure 4F).[293,294] Among those significant genes, nine genes were shown to be dysregulated in WMH lesion tissue (Figure 4F).[292,294] Of these, only 7 genes (*SLC15A2*, *PARVA*, *AHNAK*, *KLHL6*, *PIP5K1B*, *ALAS2*, and *SEPT11*) showed consistent changes between whole blood and brain tissue.[292-294] Other than these genes, 345 other genes also had abnormal mRNA expression in LA lesions compared to that in normal brain tissues (Figure 4F).[292] These dysregulated genes are functionally associated with immune and cell cycle regulation, apoptosis, proteolysis, ion transport, cell structure, electron transport, and metabolism, suggesting the potential molecular mechanism underlying the pathology of LA.[292] Recently, another whole-blood gene expression study identified 148 dysregulated genes associated with LA progression (30 up-regulated and 118 down-regulated genes).[295] Among these, two downregulated genes (*TTC9* and *WLS*) are shown to be upregulated in WMH lesions,[292,295] reflecting the inconsistent gene regulation between the peripheral and central systems (Figure 4F). According to integrated analyses on this abnormal gene expression, we know that few genes were common across different whole-blood gene expression profiles in LA. This heterogeneity may be explained by differences in disease course (early vs. late stage LA), study populations (European vs. American), study methods (gene microarray vs. transcriptome sequencing), as well as the difference in RNA stability and reliability in samples (whole blood vs. solid tissue). Given the strong heterogeneity of the results described above and the limited gene expression studies on LA tissues, we think that it is necessary to perform a comprehensive cross-omics analyses on LA using WMH lesion tissues from large multiethnic study populations in the future.

In order to further identify gene variants that may contribute to the pathogenesis of LA by influencing expression, stability, and/or function, we performed an integrated analysis of the dysregulated and variant genes involved in LA and identified three variant genes with abnormal expression in LA lesions (two up-regulated genes, *MS4A6A* and *TNKS*, and one down-regulated gene, *EVPL*) (Figure 4G). Each of the up-regulated genes only had one variant with GWAS significance in LA. The variants rs144406103 on *MS4A6A* and rs11249945 on *TNKS* affect the 3' untranslated region and an intron of the gene, respectively. Although the effects of the variants on the stability and function of those two up-regulated genes may be limited, both *MS4A6A* and *TNKS* could directly participate in the pathology of LA lesions. *MS4A6A* encodes a member of the membrane-spanning 4A gene family. It is involved in the regulation of soluble TREM2 and is linked to Alzheimer's disease.[296] *TNKS*, encodes tankyrase, which has histone binding, pentosyltransferase, and zinc ion binding activities.[297] It has been shown to be involved in the regulation of Wnt/β-catenin signaling and has been implicated in various cancers.[297,298] In contrast, the down-regulated gene *EVPL* has up to 22 variants significantly associated with LA. These include variants affecting the 3' untranslated region (rs1128889 and rs1135531) and missense variants (rs2071192 and rs2071193). *EVPL* encodes a member of the plakin family of proteins that contributes to the formation of desmosomes and the epidermal cornified envelope[299] and has been shown to be associated with oesophageal squamous cell carcinomas;[299] however, its functions are poorly understood.

Taken together, both genetic variations and dysregulated gene expression are important risk factors for LA. As the roles of these variations and dysregulated genes in the etiology of LA have been poorly understood to date, the precise functions of these genes must be explored at the molecular, cellular, and imaging levels.

Management of LA

The imaging changes in LA are irreversible, as they eventually progress and enlarge to affect the surrounding cerebral white matter. Since the pathogenic mechanisms of LA are poorly understood, it is difficult to treat WMLs and reverse their formation. Therefore, what matters most currently is to delay the onset of LA, attenuate its progression, and reduce its incidence and severity through effective strategies. To our knowledge, the current prevention and management methods for LA are mostly empirical and mainly target vascular risk factors to prevent or delay the progression of LA through pharmacological interventions. During the past twenty years, more and more evidence has shown the efficiency of controlling for vascular risk factors in the management of LA. Here, we have reviewed these potential intervention strategies.

BP control

Hypertension is a crucial risk factor for LA, and high SBP and DBP levels are also associated with LA progression. Thus, BP-lowering therapy is considered an effective strategy for LA prevention and management. With the exception of some studies,[300-302] most studies support the view that effective BP control

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can decrease the progression of LA and reduce the risk of severe LA.[101,102,117,120,121,123,303] Multiple cross-sectional studies have shown individuals who were successfully treated using anti-hypertension therapies had a lower risk of LA than those with poorly controlled hypertension.[101,102,117,121] Similarly, several randomized controlled trials (RCTs) including a Perindopril Protection Against Recurrent Stroke Study substudy,[120,304] Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT-MIND) substudy,[123] and the Three-City (3C)-Dijon MRI study,[303] also showed that active BP control can significantly decrease the risk and/or mean total volume of incident LA during the follow-up period. Additionally, one Prevention of Dementia by Intensive Vascular Care trial MRI substudy found that hypertensive intervention was more effective in patients with high baseline WMH burden.[305] These findings suggested the beneficial effects of BP control on preventing LA. Furthermore, the effects of intensive and standard BP-lowering or more conservative treatments have also been compared. Three prospective, randomized clinical studies—a SPRINT-MIND substudy,[124] Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes (ACCORD-MIND) substudy,[306] and the Intensive Versus Standard Blood Pressure Lowering to Prevent Functional Decline in Older People study[307]—showed that intensive BP control did result in less LA progression compared to standard BP control among hypertensive patients. The results of a recent meta-analysis of randomized trials also support the conclusion that intensive BP-lowering therapy prevents the progression of LA.[122,308,309] This evidence strongly suggests that intensive BP control interventions are an effective treatment strategy for the management of LA. At the same time, there are some concerns that excessive BP-lowering may lead to harmful effects, including reduced cerebral blood flow and subsequent exacerbated hypoperfusion.[310] However, there is no evidence for this as yet. Most studies have shown that intensive BP control does not decrease cerebral blood flow or affect cerebral perfusion in both hypertensive patients with stroke[311-313] and those without dementia but with extensive CSVD,[314] as well as those with dementia.[310,315,316] On the contrary, intensive BP-lowing may increase cerebral blood flow.[316,317] Recently, a SPRINT-MIND substudy found a significant association of intensive BP control to less than 120 mm Hg with increase of cerebral blood flow in white matter and the whole brain in hypertension patients but not with decreased cerebral perfusion, especially in those with a history of cardiovascular disease.[318] Thus, intensive BP-lowering interventions are not expected to have significant effects on cerebral hypoperfusion. Although it seems to be a best intervention for LA as described above, intensive BP-lowing has also been shown to lead to some adverse events in a few studies, such as increased kidney function decline,[319] decrease in total brain volume,[124,320] and increased risk of dementia.[321-324] Of those detrimental effects, increased dementia risk resulting from the BP-lowing still remains confusing due to inconsistent findings. A few studies showed that the risk of developing dementia increased during the persistent BP-lowing in community-dwelling persons over age 75,[321] and the steep decline of BP from mid- to late life in older adults (over 65 years) with prehypertension or normotension.[322] It was also observed in the intensive BP treatment in patients with atrial fibrillation or depression.[323,324] On the contrary, more studies showed a significant association of aggressive BP-lowing with the reduced risk of dementia in elderly people,[325-330] including the community-dwelling persons aged 60 years or older,[331,332] hypertensive patients aged 50 years and older,[333] and those with hypertension up to 70 years of age.[322] While some studies do not support those influence of BP control on dementia.[325,334-337] Therefore, further clinical studies are still needed to assess and clarify the potential effects of intensive BP-lowing on adverse health outcomes. Neurologist should also be cautious to adopt this therapy in LA patients, especially in those older individuals.

Taken together, BP control intervention represents an appropriate strategy for the management of LA despite a few harmful effects on kidney function and cognitive function. We believed that intensive BP-lowing therapy could be extensively used in the personalized treatment of LA in the future if those adverse events are controlled well in specific individuals.

Glycemic control

Although the relationship between diabetes mellitus and LA remains controversial as described above, several recent studies have investigated the effect of glycemic control for diabetes mellitus on LA progression.[306,338,339] Of those studies, a double-blind RCT assessing the effects of insulin therapy on white matter health found that intranasal insulin treatment for 12 months significantly reduced the progression of WMH in deep and frontal regions with a similar trend for global LA volume.[338] In addition, one prior study revealed that poor glycemic control was significantly associated with higher WMH burden in patients with APOE4 genotype carriers with type 2 diabetes mellitus, suggesting that the effects of long-term glycemic control on LA in diabetes mellitus were modified by genetic factors.[340] On the contrary, the ACCORD-MIND trial found that the intensive glucose-lowering therapy led to significantly more abnormal white matter volume at 40 months than standard glycemic control, particularly in patients aged less than 60 years.[341] In addition, an observational extension study of ACCORD-MIND (ACCORDION MIND trial) also identified significantly quicker increase in abnormal white matter volume at 40 months in the intensive glucose control group

than that in the conventional glucose control group, and observed no significant difference in WMH between the groups at 80 months.[302] Consistently, both a cross-sectional retrospective study and a secondary study of the ACCORD-MIND trial also failed to find the significant association of glycemic control with LA.[306,339] To date, the efficacy of glycemic control on LA remains controversial.[342] There seems to be more evidence suggesting against glucose lowering in patients with SVD.[342] Thus, glycemic control should be cautiously managed in the treatment of LA.

Lipid control

As a vascular risk factor, dyslipidemia (such as hyperlipidemia, higher HDL-C level) is strongly associated with CSVD.[118] Statins are main lipid-lowering drugs wildly used in the prevention and treatment of cardiovascular diseases. They have been shown to be beneficial in the management of CSVD (such as stroke).[343-345] Thus, statins are also suggested to intervene in the course of LA although the roles of hyperlipidemia and HDL-C in LA remain uncertain to date. Several previous studies investigated the effect of statins on the treatment of LA, but failed to find a beneficial effect of statins upon preventing the progression of LA.[96,346-348] Recently, an 18-month RCT of simvastatin in healthy, statin-naive, cognitively unimpaired, middle-aged adults did also not observe significant effect of simvastatin treatment on WMH lesion volume.[349] However, a substudy of the Cardiovascular Risk Factors and Aging and Incidence of Dementia MRI study found that lipid-lowering drugs decreased the risk of having more severe WMH at late life.[105] Consistently, another randomized, double-blind, placebo-controlled study on the effect of statins on middle cerebral artery stenosis progression among stroke-free individuals also found that lipid-lowering treatment (simvastatin) could delay the progression of cerebral WMH only among those who already have high WMH burden at baseline.[350] Recently, emerging evidence from several studies in Chinese population supports the protective effect of statins on LA.[351-353] They showed that the increase in WMH volume and the risk of WMH progression were significantly lower in the rosuvastatin group than in the placebo group.[351-353] These suggested that statin therapy could ameliorate the progression of LA. Moreover, it was shown that rosuvastatin interacted with telmisartan, an antihypertensive drug on reducing the progression of LA.[352] The precise mechanism that mediates the effectiveness of statins therapy for retarding LA progression remains unclear to date. Statins may help to delay the progression of LA through pleiotropic mechanisms including improving endothelial function and cerebral vasoreactivity,[354-356] attenuating inflammatory response,[357,358] and decreasing oxidative stress.[358,359]

Although more evidence described above seem to suggest statins as an efficient treatment against LA, the lipid-lowering treatment may have to be cautiously managed due to some conflicting findings that statin treatment was associated with increased risk of LA worsening.[91,360] These inconsistent results may be related to blood lipid levels at baseline, baseline WMH, basic disease and pleiotropic effects of statins, even genetic factors. Additionally, statin administration may lead to some adverse effects in the treatment of cerebrovascular disease,[360-362] although major protective effects for specific stroke preserve as well.[363] Both the *post hoc* analysis of the Heart Protection Study and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial revealed the association of statin treatment with increased incidence of hemorrhagic stroke.[361,362] Recently, a *post hoc* analysis on the data from the Japan Statin Treatment Against Recurrent Stroke (J-STARS) study also showed that statins have different influences on the risks of stroke subtypes according to post-randomized LDL-C levels, and they could increase the risk of lacunar stroke in patients.[364] Thus, the use of lipid-lowing drugs in clinical practice should be cautious.[342,360] More studies are still required to assess the efficacy of lipid-modifying therapy strategies on LA in patients with different disease subtypes or disease background.

Homocysteine-lowering therapy

Homocysteine-lowering therapy through multivitamins supplementation is considered as a potential approach for preventing LA. Previously, one study showed that a patient with adult-onset hyperhomocysteinemia due to a vitamin B_{12} metabolic deficit received homocysteine-lowering treatment, and showed both improved cognitive functions and decreased cortical WMHs at follow-up 18 months.[365] Another study, the VITAmins TO Prevent Stroke (VITATOPS) MRI-Substudy, assessed the effect of vitamins on LA, and found that daily vitamin B administration for two years significantly reduced the progression of LA in those patients with recent stroke or transient ischemic attack and severe CSVD at baseline.[366] Those evidence suggested homocysteine-lowering therapy as an effective treatment method of LA. It could prevent the progression of LA through likely reducing the endothelial dysfunction caused by hyperhomocysteinemia and improving the myelin formation or white matter integrity.[190,224,225,367,368]

Antiplatelet therapy

Antiplatelet drugs, such as aspirin, are often used in the prevention and treatment of recurrent stroke.[369,370] As an MRI indicator of CSVD linked to stroke, cognitive decline, and dementia,[371] LA may benefit from the antiplatelet agents. Previous study has shown that aspirin, an antiplatelet drug can directly target oligodendroglia cells and promote their differentiation through inhibiting

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Wnt/β-catenin signaling pathway *in vitro* and *in vivo*.[372] Moreover, it has also been shown to promote oligodendrogenesis and oligodendrocyte myelination through extracellular signal-regulated kinase and Ras homolog gene family member A pathways, and improve the learning and memory ability in a well-established WMH model induced by chronic cerebral hypoperfusion.[373] These evidence strongly suggested that aspirin therapy may also represent an effective approach for the treatment of LA with demyelination. However, the clinical studies on the effects of aspirin on the prevention or treatment of LA are rare to date. The only clinical study—Women's Health Initiative Memory Study of Magnetic Resonance Imaging (WHIMS-MRI) study—found that aspirin use did not have a promisingly positive effect on preventing WMH.[374] Currently, another RCT, the ASPirin in Reducing Events in the Elderly (ASPREE)-NEURO study, is underway to evaluate the effects of low-dose aspirin on LA in the generally healthy elderly.[375] Results of this trial are worth looking forward to being published in the near future. Due to the lack of positive evidence to date, it should be cautious to adopt aspirin therapy in the management of LA.

Compared to aspirin which often causes bleeding complications,[376] another common antiplatelet agent-cilostazol-is shown to lead to less hemorrhagic events among patients with ischemic stroke.[377,378] The double-blind RCT, Comparison Study of Cilostazol and Aspirin on Changes in Volume of Cerebral Small Vessel Disease White Matter Changes (CHALLENGE), compared the effects of cilostazol and aspirin on LA progression in patients with CSVD, and found no significant difference in the impact on the progression of LA from baseline to 2 years between two antiplatelet agents.[379,380] It may indicate no efficacy of cilostazol in the prevention or treatment of LA. Recently, another single-center, randomized, double-blind, placebo-controlled study named as DREAM trial (efficacy and safety of cilostazol in DecREasing progression of cerebral WMH) directly investigated the efficacy and safety of cilostazol in preventing CSVD progression but failed to find positive effects of cilostazol treatment on preventing LA progression compared to placebo in stroke- and dementia-free subjects with moderate-to-severe LA.[381] These results do not seem to support the use of cilostazol in the treatment of LA.

Taken together, both cilostazol and aspirin do not seem to have positive effects on slowing down the progression of LA. Given the limited evidence supporting the beneficial effects of antiplatelet agents in LA, we do not recommend using cilostazol and aspirin to manage LA. Future clinical studies will be needed to investigate the efficacy of antiplatelet agents in preventing the progression of LA.

Lifestyle-related interventions

In addition to the drug therapies described above, lifestyle-related interventions such as smoking cessation, maintaining a healthy diet, exercising regularly, avoiding obesity and improving educational levels may also help to prevent LA, manage its potential risk factors, and facilitate treatment.

However, only a few clinical studies support the efficacy of smoking cessation in reducing LA incidence and delaying its progression. An extension of the Atherosclerosis Risk in Communities Study examined the effect of smoking status and history on LA progression, but found no association between WMH progression and either time since smoking cessation or age at smoking initiation.[154] Similarly, another cross-sectional study found no significant relationship between time since smoking cessation and DTI parameters in WMLs, but did report that subjects who had not smoked for more than 20 years had normal-appearing white matter with FA and mean diffusivity values similar to those of subjects who had never smoked.[382] Given the potential significance of smoking cessation in reversing impairments in the structural integrity of the brain, as described previously, we think that the potential benefits of smoking cessation in preventing LA progression need to be explored further.

Dietary habits have been implicated in many human diseases, including CSVDs;[383-385] similarly, a healthy diet is considered to have protective benefits against LA. Two studies—a population-based longitudinal study and a cross-sectional study—showed that dietary interventions can decrease WMH severity and delay LA progression.[386,387] However, a recent two-site RCT involving older adults without cognitive impairment but with a family history of dementia found that change in WMHs from baseline to year 3 did not differ significantly between those who followed the Mediterranean–DASH Intervention for Neurodegenerative Delay diet and those who followed the control diet with mild caloric restriction.[388]

As with dietary interventions, physical activity interventions for LA have yielded conflicting results. Five studies, including the recent Australian Imaging Biomarkers and Lifestyle Flagship Study of Aging Active trial,[389] showed no significant relationships between physical activity and WMH in older adults.[390-393] However, in four other studies, higher physical activity level was associated with fewer WMHs in individuals without advanced disease, suggesting a beneficial effect of increased physical activity on stopping or slowing the progression of LA.[394-397] Conversely, a longitudinal study found that higher levels of physical activity were associated with LA progression, indicating that it can have detrimental effects as well.[398] It is possible that these conflicting findings indicate that lifestyle interventions represent an indirect strategy for controlling the vascular risk factors for LA.

Therefore, interventions related to just one lifestyle factor will not have a significant influence on WMH burden, because LA is influenced by multiple risk factors. Thus, combined interventions targeting multiple lifestyle factors would be more beneficial in LA.

Recently, a cross-sectional analysis of data from the PolyvasculaR Evaluation for Cognitive Impairment and vaScular Events study, which comprehensively controlled for multiple lifestyle factors including diet, physical activity, smoking, alcohol consumption, and BMI,[399] showed that participants who adopted four or five low-risk lifestyle habits had lower WMH volumes than those with zero or one low-risk habits. As with the prospective analysis of UK Biobank data, this suggests a significant association between a healthier lifestyle and lower WMH burden in middle-aged and older adults.[399] Thus, comprehensive management of modifiable lifestyle factors should be considered for LA prevention and treatment, although further studies are required to test the efficiency of these interventions in actual patients.

Conclusion and perspectives

Although we have known about the concept of LA for about three decades, its significance in the clinical and academic fields is somewhat underestimated by physicians and neurologists compared to those age-related neurodegenerative conditions such as Parkinson's disease, Alzheimer's disease, and stroke. With improvements in imaging technologies and the widespread use of FLAIR-MRI in community hospitals, as well as the increased rate of aging in society, more and more cases of LA are being encountered. This has also led to an increased public awareness about LA. This review article provides an overview of the current advances related to LA for professionals as well as the general public. A better understanding of the imaging heterogeneity, histopathological characteristics, and clinical risk factors of LA will greatly promote our understanding of its nature. The significant associations between certain risk factors (such as age, hypertension, elevated homocysteine level, arterial stiffness) with LA incidence not only offer specific clues regarding its pathogenesis, but also suggest potential intervention strategies for its management. In view of the consistently positive results from clinical association studies and prospective RCTs, controlling key cardiovascular risk factors (such as BP, blood lipid levels) and maintaining a healthy lifestyle (by smoking cessation, physical exercise, healthy diet) should be efficient strategies for preventing the onset and progression of LA.

Additionally, although the heterogeneous histopathological and imaging characteristics of WMHs provide key clues regarding etiology, the underlying molecular mechanisms in LA remain unclear. Genetic studies (especially GWASs) have identified some susceptibility genes for LA and its subclasses in the past decade, which also offer many possibilities for exploring its pathogenesis. Genomic and molecular pathological mechanisms specific to LA subtypes may also represent promising research avenues in the future. Similarly, the identification of biological processes and signaling pathways specific to LA subtypes or its onset and development will help to clarify its pathogenesis and provide potential drug targets and intervention strategies for treatment. This is critical for reducing the public health burden and will benefit aging societies all around the world. Thus, further efforts are needed to construct comprehensive LA models and conduct genetic studies on LA in animals in parallel with clinical studies.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: WQH, QL, CMT. Study design: WQH, CMT. Methodology: WQH, CMT. Data collection: WQH, QL. Investigation: WQH, QL. Statistical analysis: WQH. Writing—original draft: WQH. Writing—review & editing: WQH. Funding acquisition: WQH, QL.

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