White matter hyperintensities and vascular risk factors in monozygotic twins

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ABSTRACT

Cerebral white matter hyperintensities (WMHs) have been associated with vascular risk factors, both of which are under genetic influence. We examined in a monozygotic twin sample whether the association between vascular risk and WMHs is influenced by overlapping genetic factors. We included 195 cognitively normal monozygotic twins (age = 70 ± 7 years), including 94 complete pairs. Regional WMH load was estimated using an automated algorithm. Vascular risk was summarized with the Framingham score. The within–twin pair correlation for total WMHs was 0.76 and for Framingham score was 0.77. Within participants, Framingham score was associated with total and periventricular WMHs (r = 0.32). Framingham score in 1 twin was also associated with total WMHs in the co-twin (r = 0.26). Up to 83% of the relation between both traits could be explained by shared genetic effects. In conclusion, monozygotic twins have highly similar vascular risk and WMH burden, confirming a genetic background for these traits. The association between both traits is largely driven by overlapping genetic factors.

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1. Introduction

Cerebral white matter hyperintensities (WMHs) on fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) scans are a common finding in older adults (Launer, 2004) and are associated with risk of cognitive decline (De Groot et al., 2002; Debette and Markus, 2010; Prins et al., 2004). They are found in the periventricular and deep white matter. Although the etiology of WMHs is not yet fully understood, they are often considered to be a manifestation of small vessel disease. WMHs have been associated with the presence of various vascular risk factors, such as hypertension, diabetes, and smoking (Dickie et al., 2016; Habes et al., 2016; Wardlaw et al., 2015).

The occurrence of WMHs is under genetic influence. Previous family and twin studies have found heritability estimates of 0.55–0.81 for total WMH load (Atwood et al., 2004; Carmelli et al., 1998; Fennema-Notestine et al., 2016; Sachdev et al., 2016; Turner et al., 2004). Heritability studies have also found a moderate-to-strong genetic influence on the presence of various vascular risk factors such as blood pressure and hypertension (Evans et al., 2003; Kupper et al., 2005), impaired glucose tolerance (Poulsen et al., 1999), serum cholesterol and high-density lipoprotein (HDL) levels (Elder et al., 2009; Goode et al., 2007; Rahman et al., 2009), and smoking (Vink et al., 2005). It is not yet clear whether vascular risk factors are independently associated with increased WMHs or whether there are common underlying genetic factors that influence both vascular risk factors and the presence of WMHs.

Monozygotic twins are genetically identical and partly share environmental factors. Similarity of a trait within monozygotic twin pairs can be due to either genetic factors or shared environmental factors, whereas differences result from nonshared environmental factors. To disentangle the contribution of genetic and shared environmental factors to a trait, classic twin design studies also include dizygotic twins, who share 50% of their segregating genes and are assumed to have a similar amount of shared environmental
factors as monozygotic twins. In our study, we included only monozygotic twin pairs. Previous studies including monozygotic and dizygotic twins have shown that the presence of WMHs is best explained by a model including genetic effects and nonshared environmental factors, eliminating shared environmental influences from the model (Carmelli et al., 1998; Fennema-Notestine et al., 2016; Sachdev et al., 2016). Similarly, twin studies have found that shared environmental influences do not predict vascular risk factors such as blood pressure and hypertension (Evans et al., 2003; Kupper et al., 2005; Panizzon et al., 2015), impaired glucose tolerance (Poulsen et al., 1999), and serum cholesterol and HDL levels (Elder et al., 2009; Rahman et al., 2009), although not in all studies (Jemendy et al., 2011). Together, this suggests that similarity in WMHs and vascular risk factors within monozygotic twin pairs is most likely attributable to genetic factors.

In this study, we have first examined the correlation of vascular risk factors and WMH volume, location, and pattern within cognitively normal older adult monozygotic twin pairs. We then assessed whether overlapping genetic factors could underlie the association between vascular risk factors and WMHs by examining the similarity within monozygotic twin pairs for these traits. As a summary measure for vascular risk factors, we used the Framingham score (D’Agostino et al., 2008; Habes et al., 2016), but we also tested correlation for each vascular risk factor included in this score with WMHs. As differences in heritability estimates of WMHs have been found between males and females, we also examined gender differences in these traits (Atwood et al., 2004; Sachdev et al., 2016).

2. Materials and methods

2.1. Participants

Monozygotic twins were included from the Amsterdam sub-study of the European Medical Information Framework for Alzheimer’s Disease PreclinAD cohort, a longitudinal study on risk factors for amyloid pathology and cognitive decline in cognitively normal older adults. Inclusion criteria were having age above 60 years, a delayed recall score of \( \geq -1.5 \) SD of age-adjusted normative data on the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) 10-word list (Morris et al., 1989), a global Clinical Dementia Rating score of 0 (Morris, 1993), Telephone Interview for Cognitive Status modified (TICS-m) score of 23 or higher (de Jager et al., 2003), and a 15-item Geriatric Depression Scale score of \(<11\) (Yesavage et al., 1982). Exclusion criteria were any significant neurologic, systemic, or psychiatric disorder that could cause cognitive impairment. Participants were recruited between December 2014 and August 2016 from the Netherlands Twin Registry (Boomsma et al., 2006; Willemsen et al., 2013). All participants were asked to collect mucosal cell samples for DNA extraction to confirm zygosity. From the Amsterdam PreclinAD cohort, we excluded 6 participants due to missing MRI data (1 due to claustrophobia, 1 due to technical issues with the scanner, and 4 due to participant refusal to visit the hospital), 1 participant due to the presence of multiple sclerosis-like lesions on MRI, and 1 dizygotic twin pair. For the present study, we used 195 participants, of which 94 were complete monozygotic twin pairs and 7 single participants. The study was approved by the VU University Medical Center’s ethics committee, and all participants gave written informed consent.

2.2. Clinical and vascular risk assessment

Clinical data were collected during a face-to-face interview for medical history, medication intake, smoking habits, and educational attainment. All participants also underwent physical examinations. Blood pressure was measured 3 times in a lying position with a 5-minute interval between measurements, and the mean of these 3 measurements was used for the analysis. After a minimum 2-hour fasting period, participants underwent a blood-draw to determine lipid profile and glycated hemoglobin in the morning. The cardiovascular risk profile for each participant was summarized using the Framingham score index, which includes the following factors: age, gender, total cholesterol, HDL, systolic blood pressure, antihypertensive medication use, diabetes mellitus, and smoking (D’Agostino et al., 2008). This risk index represents the 10-year risk of a major cardiovascular event. All clinical, cognitive, and MRI measurements were performed within 6 months (median 16 days).

2.3. Image acquisition

Whole-brain scans were obtained using a single 3T scanner (Philips Ingenuity Time-of-Flight PET/MRI scanner) using an 8-channel head coil. Isotropic structural 3D T1-weighted images were acquired using a sagittal turbo field echo sequence (1.00 mm\(^3\) isotropic voxels, repetition time = 7.9 ms, echo time = 4.5 ms, and flip angle = 8°): 3D sagittal FLAIR sequences (1.12 mm\(^3\) isotropic voxels, repetition time = 4800 ms, echo time = 279 ms, and inversion time = 1650 ms) were acquired for the analysis of WMHs. The MR protocol also included susceptibility weighted imaging. All MRI scans were visually assessed by an experienced neuroradiologist for incidental findings.

2.4. MRI analysis

All MRI scans were visually rated by a single experienced rater (MtK) who was blind to twin pairing at the time of rating. WMHs were visually assessed on the 3D FLAIR images using the 4-point Fazekas scale for deep WMHs (none, punctuate, early confluent, and confluent; Fazekas et al., 1987). Lacunes were defined as deep lesions between 3 and 15 mm with cerebrospinal fluid–like signal on T1-weighted and FLAIR images. Microbleeds were assessed on susceptibility weighted images and defined as rounded hypo-intense homogeneous foci of up to 10 mm in the brain parenchyma. Medial temporal lobe atrophy was assessed on coronal reconstructions of the T1-weighted images using the 5-point Scheltens’ scale (Scheltens et al., 1992). Global cortical atrophy was rated on transversal FLAIR images using a 4-point scale (Pasquier et al., 1996).

Quantitative WMH load was estimated jointly from both 3D T1 and 3D FLAIR scans using a previously described algorithm (Sudre et al., 2015). Details of the WMH lesion segmentation are provided in the Supplementary Methods. To visually represent the distribution of WMHs in the brain, a coordinate frame (bullseye) was designed to characterize the location based on the normalized distance between the ventricular surface and cortex (4 layers) and the left/right cortical lobes (frontal, parietal, temporal, and occipital) or basal ganglia. Overall 36 regions (4 layers, 9 lobar regions) were defined to characterize the location of WMHs. Fig. 1 illustrates the definition of layers and lobar regions and presents an example of a bullseye representation of this local information. Infratentorial structures (i.e., brain stem and cerebellum) were not taken into account because of the low WMH lesion load in these regions in this cohort. All WMH segmentations were visually inspected, and none had to be excluded.

2.5. Statistical analysis

All statistical analyses were performed in R (R, version 3.3.1; http://www.R-project.org).
2.5.1. Correlation of WMHs and vascular risk factors in monozygotic twins

Monozygotic twin correlations for vascular risk factors, total WMH, and regional WMH measures were assessed using Pearson correlation. Because the Framingham score and WMH frequencies were left skewed, we used a log-transformation to normalize the distributions. Correlation analyses for WMHs were adjusted for the effects of regional white matter volume, age, and gender. Because monozygotic twins are genetically identical, within-pair correlations reflect the upper limit of genetic contribution to a trait. Correlation analyses were repeated for random (nontwin) pairings of participants.

Next, we examined the similarity of the pattern of WMH measures across regions for each twin pair. As a measure of similarity, we computed the Pearson correlation of WMH volumes across all regions between a participant and his/her co-twin for each pair (i.e., instead of computing the correlation within twins for each region, we correlated regional WMH values of twin 1 with the regional WMH values of twin 2 for each twin pair). This correlation was also estimated for all nontwin participant pairs. Because some regions are prone to have more WMHs than others, WMH volumes were centered per region before computing the within-pair correlations.

2.5.2. Relation between vascular risk factors and WMHs

Our second aim was to examine the relation between vascular risk factors and WMHs. We pooled WMH volume of left and right hemispheres. We used the total WMH load (all layers), periventricular WMH load (layers 1 and 2), and deep WMH load (layers 3 and 4) for total brain and for each lobe separately and normalized them by the respective regional white matter volumes. The relation between Framingham score and WMH was first assessed using generalized estimating equations (GEEs), with Framingham score as a predictor and WMHs as a dependent variable adjusting for twin status (model 1) and for twin status, age, and gender (model 2) (Minicà et al., 2015).

The next analyses, aimed at further scrutinizing the relation between vascular risk factors and WMH, were only run for those regions in which there was a significant relation between Framingham score and WMHs in the GEE analysis.

2.5.3. Shared genetic influences between vascular risk factors and WMHs

Next, we examined whether the association between WMHs and Framingham score could be explained by overlapping additive genetic effects. We used structural equation modeling implemented in OpenMx (Boker et al., 2011) to compute the within-participant correlation between Framingham score and regional WMHs and the cross-twin cross-trait correlation (i.e., the correlation of the Framingham score in 1 twin with WMH load in the cotwin). The correlation between Framingham score and WMHs can be decomposed into a genetic and an environmental constituent. Previous studies have found no significant effect of shared environmental factors on WMHs (Carmelli et al., 1998; Fennema-Notestine et al., 2016; Sachdev et al., 2016) and various vascular risk factors (Elder et al., 2009; Evans et al., 2003; Kupper et al., 2005; Panizzon et al., 2015; Poulsen et al., 1999; Rahman et al., 2009). In our sample of monozygotic twins, we therefore assumed a model in which we only consider additive genetic (A) and nonshared environmental (E) factors (AE-model). Assuming this AE-model, the association between the Framingham score and regional WMHs was investigated using bivariate Cholesky decompositions. The bivariate genetic model tests whether the covariance between Framingham score and WMHs could be explained by overlapping additive genetic or overlapping nonshared environmental factors. Maximum likelihood estimation was used to obtain the genetic and nonshared environmental correlation between Framingham score and WMHs. A high genetic correlation between both traits would mean that genetic influences affecting Framingham score are also likely to have an impact on the presence of WMHs. The proportion of the correlation between Framingham score and WMHs attributable to shared genetic factors was computed. We assessed whether there were gender differences by comparing fits of models that allowed (co)variances for men and women to vary with the fits of models that constrained (co)variances to be the same.

Finally, we examined whether differences in WMH load within monozygotic twin pairs are associated with differences in the Framingham score within twins, using the intrapair difference model (De Moor et al., 2008; Vitaro et al., 2009). We regressed the
difference in WMH load between a twin and co-twin on the difference in Framingham score. If these within-pair differences are associated with each other, it indicates that nonshared environmental factors influence the relationship between Framingham score and WMHs, independent from overlapping genetic and shared environmental factors (as these are identical within monozygotic twin pairs).

3. Results

3.1. Sample characteristics

Demographic characteristics, vascular risk factors, and WMH volumes are summarized in Table 1. The presence of WMHs was a common finding, with all participants having some WMHs. Most lesions were located in the frontal lobe and in periventricular regions. Women had more WMHs than men. Demographic characteristics, vascular risk factors, and WMH volumes stratified per gender are presented in Supplementary Table 1. The average Framingham score was 23 ± 15 and was higher in men than in women (23 ± 15 vs. 16 ± 9, t = 11, p < 0.001). The correlation of the Framingham score within twin pairs was 0.77 (p < 0.001). The within-pair correlation for Framingham score items varied from 0.47 (systolic blood pressure) to 0.82 (HDL) (Table 1) (all p < 0.001).

3.2. Similarity of regional WMHs within monozygotic twin pairs

On visual inspection, WMH lesion distributions were highly similar within twin pairs; for example, scans of 6 monozygotic twin pairs with corresponding bullseye plots are presented in Fig. 2. The monozygotic twin correlation for total WMH volume was 0.76, total periventricular WMH was 0.76, and total deep WMH was 0.72. Regional correlations were significant for all regions (Fig. 3A). When examining per anatomical lobe, the average of the correlations was highest for the frontal lobe (average r = 0.71, range 0.63–0.77 across layers and hemispheres) and lowest for the occipital lobe (average r = 0.42, range 0.35–0.54). Regional correlations of WMHs in random pairs did not yield any significant correlations. The regional correlations were slightly higher in women than in men (Supplementary Fig. 1).

Next, we examined whether twins had a more similar pattern of WMH distribution across regions than random participants. Correlations of WMHs across regions were higher for true twin pairs (mean r = 0.4, SD = 0.25) than in random pairs (mean r = −0.007, SD = 0.26) (p < 0.001) (Fig. 3B). Stratifying according to gender yielded similar results (Supplementary Fig. 2).

3.3. Association between vascular risk factors and WMHs

Using GEEs, Framingham score was associated with total WMH load (Table 2). Analyses according to WMH subtype and brain region showed that the Framingham score was associated with periventricular WMHs in the frontal and parietal lobe. There was no significant relation between Framingham score and deep WMHs. After controlling for age and gender, results remained the same (Table 2).

We performed post hoc analysis on the individual risk items with the Framingham score and whole-brain WMH measures to assess whether the effects were driven by particular risk factors (Supplementary Table 2). Systolic blood pressure and smoking were both associated with whole-brain total WMHs (β = 0.06 and β = 0.07 respectively, both p < 0.05) and periventricular WMHs (β = 0.06 and β = 0.08 respectively, both p < 0.05). Use of antihypertensive medication was associated with periventricular WMHs (β = 0.06, p < 0.05). Given the relation of age with WMHs, we also repeated analysis calculating the Framingham score without age, and findings remained similar (Supplementary Table 3).

3.4. Role of shared genetics and nonshared environmental factors on the relation between vascular risk factors and WMHs

Using structural equation modeling, we determined the within-participant and cross-twin cross-trait correlation between Framingham score and WMHs in the whole sample (Table 3) and stratified by gender (Supplementary Table 4). We could constrain the gender (co)variances to be the same without a significant decrease in model fit. The cross-twin cross-trait correlation in the genetically identical twin pairs was only 19% lower than the within-participant cross-trait correlation (data for total WMHs). Assuming an AE-model, estimates of the genetic correlation between Framingham score and WMH were obtained (Table 3). There was a significant genetic correlation between Framingham score and WMHs for all regions in the whole sample. The proportion of the correlation between Framingham score and total WMHs that could be explained by shared genetic influences was 83%. Stratified analysis by gender showed that the within-twin and cross-twin cross-trait correlations as well as the genetic correlations were significant in all regions in women (Supplementary Table 4). In men, the genetic correlations between both traits were lower and significant for 1 region (total parietal), and the nonshared environmental correlations were significant for periventricular and frontal WMHs.

Finally, we assessed whether the relation between Framingham score and WMHs is influenced by nonshared environmental factors.
by controlling for genetic influences using an intrapair difference model. Regression of the intrapair differences in WMHs on the intrapair difference in the Framingham score was significant for whole-brain total and periventricular WMHs (Fig. 4) and for total and periventricular WMHs in frontal and parietal regions (Supplementary Fig. 3) but explained little variance ($r^2 = 0.02$ to $0.36$) for total WMHs and $0.18$ ($95\%$ confidence interval $[CI] = 0.09$ to $0.33$) for periventricular WMHs. The cross-twin correlation between systolic blood pressure and WMHs around $0.55$ to $0.81$ (Atwood et al., 2004; Carmelli et al., 1998; Elder et al., 2009; Evans et al., 2003; Fennema-Notestine et al., 2016; Kochunov et al., 2009; Sachdev et al., 2015; Poulsen et al., 1999; Rahman et al., 2009; Sachdev et al., 2016). We found a high within–monozygotic twin pair correlation for total and regional WMH load and for vascular risk factors. Our results suggest a strong genetic background for the presence and regional distribution of WMH lesions and for vascular risk factors. Vascular risk factors were associated with WMHs, and the cross-twin cross-trait and bivariate analyses suggested that this relation was mainly driven by overlapping genetic influences.

Before we discuss these findings in more detail, it is important to note that we only included monozygotic twins, which precluded ascertainment of the relative contribution of genetic and shared environment to the monozygotic twin correlation of WMHs and vascular risk factors. Because previous studies using a full twin design with both monozygotic and dizygotic twins did not find that shared environmental factors contribute to the within–twins correlation in WMHs and various vascular risk factors, it is likely that our within–twins correlation is driven by genetic factors (Carmelli et al., 1998; Elder et al., 2009; Evans et al., 2003; Fennema-Notestine et al., 2016; Kupper et al., 2005; Panizzon et al., 2015; Poulsen et al., 1999; Rahman et al., 2009; Sachdev et al., 2016). This implies that in our monozygotic twin study, within-twins similarities in WMHs and vascular risk factors are most likely due to genetic effects.

Our findings on the genetic background of WMHs are in line with previous studies that have estimated the heritability of total WMHs around $0.55$ to $0.81$ (Atwood et al., 2004; Carmelli et al., 1998; Fennema-Notestine et al., 2016; Kochunov et al., 2009; Sachdev et al., 2016; Turner et al., 2004). We have extended on these previous studies by demonstrating that not only total and regional WMH load are under strong genetic influence but also the pattern of WMH distribution across the brain. Our finding of a strong genetic component for vascular risk factors is also in line with previous heritability studies, which found a moderate-strong genetic influence on various vascular risk factors (Goode et al., 2007; Kupper et al., 2005; Poulsen et al., 1999; Vink et al., 2005).

As expected, we found an association between vascular risk factors and total and periventricular WMH load. We now demonstrate that the majority (up to $83\%$) of the correlation between Framingham score and total WMHs could be explained by shared genetic influences, suggesting a strong common genetic vulnerability for increased vascular risk factors and the presence of WMHs. In line with this, the cross-twin correlation between Framingham score and WMHs was only slightly lower than the within-participant correlation. This indicates that in genetically identical twins, the prediction of WMHs from a cotwin is almost as good as from one’s own risk score. Our results are in line with a recent study in older adult male twin pairs that found a correlation of $0.18$ between systolic blood pressure and total abnormal white matter measured on T1, T2, and proton-density MR sequences, which could be attributed to $86\%$ to shared genetic influences (Fennema-Notestine et al., 2016). A bivariate linkage analyses in a family cohort identified various genetic loci that contribute to both blood pressure and WMHs (Kochunov et al., 2010). A recent genome-wide association study identified several genes associated with WMHs of which some loci have also been associated with blood pressure.

**Fig. 2.** Examples of WMH lesion distribution in 6 monozygotic twin pairs on FLAIR and in bullseye plots. Scale represents lesion load for each region. Abbreviations: FLAIR, fluid-attenuated inversion recovery; WMH, white matter hyperintensity.
periventricular WMHs were associated with within-twin pair differences in the Framingham score, although the association was low. In other words, the twin who has a higher Framingham score also has more WMHs. This means that association between vascular risk factors and WMHs was relatively low with a correlation of around 0.3. This is in agreement with previous studies, which also found a modest association between vascular risk factors and WMHs (Dickie et al., 2016; Fennema-Notestine et al., 2016; Habes et al., 2016). These results indicate that genetic and environmental factors separate associations between vascular risk factors and WMHs from those associated with vascular risk factors influencing WMHs. We did not find an association between the Framingham score and deep WMHs. Different etiological mechanisms for deep and periventricular WMH lesions have been suggested by postmortem studies, which revealed different pathological changes in deep and periventricular WMHs (Gouw et al., 2011). Perventricular regions are vascularized by distal branches from subependymal arteries, making these regions susceptible to ischemic damage related to reductions in cerebral blood flow (Pantoni and Garcia, 1997). Large vessel atherosclerosis may be the substrate for this cerebral hypoperfusion. This could explain why the Framingham score, designed to capture the 10-year risk of cardiovascular events, which are mainly large-vessel based, was related to periventricular but not deep WMHs. It has been suggested that deep white matter regions are more vulnerable to small vessel disease, for which hypertension is an important risk factor (Kim et al., 2008). However, when analyzing the individual risk factors, we did not find an association between systolic blood pressure and antihypertensive medication use with deep WMHs either. Possibly, other factors than small vessel disease contribute to the occurrence of deep WMHs, such as Wallerian degeneration (McCleese et al., 2017).

Although all regions showed significant moderate-to-high monozygotic twin correlations in WMHs, we did see some regional differences, with highest monozygotic twin correlations in the frontal lobe and the lowest in the occipital lobe. This may indicate that the contribution of genetic and environmental factors differs across lobes. However, a previous twin study found opposite regional differences with highest monozygotic twin correlation of twin difference associations are consistent with the high genetic contribution observed in the cross-twin cross-trait analysis.

The overall association between Framingham risk score and WMHs was relatively low with a correlation of around 0.3. This is in agreement with previous studies, which also found a modest association between vascular risk factors and WMHs (Dickie et al., 2016; Fennema-Notestine et al., 2016; Habes et al., 2016). These results indicate that genetic and environmental factors separate associations between vascular risk factors and WMHs from those associated with vascular risk factors influencing WMHs. We did not find an association between the Framingham score and deep WMHs. Different etiological mechanisms for deep and periventricular WMH lesions have been suggested by postmortem studies, which revealed different pathological changes in deep and periventricular WMHs (Gouw et al., 2011). Perventricular regions are vascularized by distal branches from subependymal arteries, making these regions susceptible to ischemic damage related to reductions in cerebral blood flow (Pantoni and Garcia, 1997). Large vessel atherosclerosis may be the substrate for this cerebral hypoperfusion. This could explain why the Framingham score, designed to capture the 10-year risk of cardiovascular events, which are mainly large-vessel based, was related to periventricular but not deep WMHs. It has been suggested that deep white matter regions are more vulnerable to small vessel disease, for which hypertension is an important risk factor (Kim et al., 2008). However, when analyzing the individual risk factors, we did not find an association between systolic blood pressure and antihypertensive medication use with deep WMHs either. Possibly, other factors than small vessel disease contribute to the occurrence of deep WMHs, such as Wallerian degeneration (McCleese et al., 2017).

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WMHs in the occipital lobe (Sachdev et al., 2016). Possible differences between studies could be due to differences in populations, although average age and gender distribution was similar, or technique to measure and regionally classify WMHs. More research is needed to elucidate these regional differences. We also saw regional differences in the association between Framingham score and WMHs, with a significant association for the frontal and parietal lobes, a trend for the occipital lobe but no association for the temporal lobe. Although this may imply that vascular risk factors affect anatomical lobes differently, it is also possible that we did not find an effect for the temporal lobe due to the overall low WMH load in this region.

A common genetic vulnerability for the presence of WMHs and increased vascular risk factors does not imply that management of cardiovascular risk factors is not beneficial against WMH progression or prevention of future cognitive decline. Vascular risk factors are modifiable, and their presence might additionally aggravate existing WMHs in those with a (genetic) predisposition. However, so far, few randomized controlled trials have targeted prevention of WMHs by reducing vascular risk factors, and these had minimal effect (Bath and Wardlaw, 2015).

In agreement with previous studies, we found a higher WMH load in women than in men (Wen and Sachdev, 2004; de Leeuw et al., 2001), although women had lower Framingham scores (and lower systolic blood pressure and less often used antihypertensive medication). In addition, we found stronger within-participant and cross-twin correlations between Framingham score and WMHs in women than in men. This could be a power issue, as the effect sizes were within a similar range for both genders, but we had less male twin pairs (n = 40) compared to female pairs (n = 55). Another possibility is that women have a higher vulnerability of vascular risk factors on WMHs than men. Differences between men and women have also been found for cardiovascular disease elsewhere in the body (including coronary heart disease), with different risks and different outcomes (Regitz-Zagrosek, 2006). This might suggest different mechanisms to be involved. Possibly, genes located on sex chromosomes, biological differences between sexes (e.g., hormones), or mitochondrial inheritance might explain these differences between men and women. Another explanation might be that there is a difference in cardiovascular disease management between men and women, where women are more often undertreated (Bugiardini et al., 2011).

Our study has several limitations. Classic twin studies include both monozygotic and dizygotic twins in their analysis. Because we only included monozygotic twin pairs in the present study, we could not investigate a possible effect of shared environmental factors (or dominant genetic effects) on WMHs, vascular risk factors, and their relation. To examine the relationship between
regional WMHs and vascular risk factors, we have used the composite Framingham risk score, which includes various vascular phenotypes. We opted to use this composite score in the primary analysis to reduce the total number of statistical tests. A limitation of this method is that different vascular risk factors are combined, which may each have a different genetic correlation with WMHs. Previous studies have found shared genetic influences for some, but not all, of the vascular risk factors included in the Framingham score in older adults (Hong et al., 1997; Panizzon et al., 2015), consistent with our post hoc findings that mainly blood pressure was associated with WMHs. Another limitation of our study is the cross-sectional design. Longitudinal studies in monozygotic twins may give more insight into the causal relation between vascular risk factors and the presence of WMHs and their rate of progression over time. Furthermore, there may be a selection bias in the studied sample. Although, in general, ascertainment by twinning allows obtaining a random population-based sample representative of the general population, we did have a relatively healthy and highly educated sample due to our inclusion criterion of both twins needing to be cognitively normal and willing to participate in the study. Because we are examining a cognitively normal sample, the overall WMH load was relatively low and this limited the analysis in temporal and occipital regions. Future studies that aim to elucidate the relationship between vascular risk and WMHs may benefit from also including participants with more severe WMH lesions that might have led to (mild) cognitive impairment. In addition, this study had a smaller sample of men than women, which may have influenced the results. Replication of these findings in larger samples is warranted. Finally, results are dependent on the quality of the automated WMH segmentation. Although all segmentations passed visual quality control, it must be noted that the detection of lesions is more challenging when very close to the cortex.

In conclusion, we found that WMH load and regional distribution is highly similar in monozygotic twins, suggesting a strong genetic influence on the occurrence and distribution of WMHs. Periventricular, but not deep, WMHs are associated with the Framingham score. Furthermore, our results suggest a shared genetic vulnerability between the presence of vascular risk factors and increased total and periventricular WMHs.

Disclosure statement

CHS, MJC, and SO have a patent pending #P110021G—“Representing 3D Regional Brain Biomarkers in 2D”. FB serves as a consultant for Bayer-Schering Pharma, Biogen-Idec, TEVA, Merck Serono, Novartis, Roche, Synthon BV, Jansen, and Genzyme. PJV serves as an advisory board member of Eli-Lilly, is consultant for Janssen, and has received grants from GE Healthcare and Biogen. PS has received grant support for the VU University Alzheimer Center from GE Healthcare, Nutricia Research, Piramal, and MERCK. In the past 2 years, he has received consultancy/speaker fees (paid to the institution) from Probiodrug, EIP Pharma, Sanofi, Novartis, Piramal, and GE Healthcare.

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