ONLINE SUPPLEMENT

White matter hyperintensities and vascular risk factors in monozygotic twins

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Supplementary methods, tables and figures

Supplementary methods:

Quantification of WMH load

Quantitative WMH load was estimated jointly from both 3D T1 and 3D FLAIR scans using a previously described algorithm (Sudre et al., 2015). In this framework, a three-level Gaussian mixture model is used to model healthy tissues and lesions. The first level represents the segmentation between healthy and abnormal signal, while the second level introduces anatomical spatial information through atlas priors and contextual constraints with Markov Random Fields. At the third level, the number of Gaussian components necessary to model each tissue class is automatically and dynamically optimized based on the application of the Bayesian Inference Criterion. After the model was optimized, WMH were extracted from voxels considered as abnormal using comparisons to the characteristics of healthy white matter. To visually represent the distribution of WMH in the brain, a coordinate frame (bullseye) was designed to characterize the location based on the distance between ventricular surface and cortex and the cortical lobes. A normalized distance from the ventricular surface was computed as a proportion of the distance between the ventricular surface and the cortex (Yezzi et al., 2002). The normalized distance was used to discretize the white matter volume into four equidistant layers. Cortical lobes (frontal, parietal, temporal and occipital) were defined using a parcellation of the brain obtained via the label fusion algorithm GIF (Cardoso et al., 2015), and Euclidean distance maps for each of the lobes were drawn to separate the white matter volume according to the closest cortical lobe. The thalamic and basal ganglia region was directly extracted from the parcellation and altered to enclose the area between caudate and putamen or thalamus.

References

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Sudre CH, Cardoso MJ, Bouvy WH, Biessels GJ, Barnes J, Ourselin S. Bayesian model selection for pathological neuroimaging data applied to white matter lesion segmentation. IEEE Trans Med Imaging 2015;34:2079–102.

Yezzi A, Prince JL. A PDE Approach for Thickness, Correspondence, and Gridding of Annular Tissues. In: Heyden A, Sparr G, Nielsen M, Johansen P, editors. Computer Vision - ECCV 2002. Berlin, Heidelberg: Springer Berlin Heidelberg; 2002. p. 575–589.

Supplementary Table 1: demographic characteristics for male and female twin pairs.

Variable	**Men (n=83)**	**Women (n=112)**	**Male MZ correlation *Pearson's r***	**Female MZ correlation *Pearson's r***
Age in years, mean ± SD	68.8 ± 6.2	71.4 ± 7.9 *	-	-
Education in years, mean ± SD	16.6 ± 4.4	14.1 ± 4.2 *	0.63, p < 0.001	0.74, p < 0.001
MMSE, mean ± SD	29.1 ± 1.0	29.0 ± 1.2	0.33, p = 0.035	0.33, p = 0.01
Visual MRI ratings				
- WMH (Fazekas), median (IQR)	1 (1-1)	1 (1-2) *	0.58, p < 0.001	0.85, p < 0.001
- Global cortical atrophy, mean ± SD	0.8 ± 0.7	0.8 ± 0.8	0.66, p < 0.001	0.65, p < 0.001
- Medial-temporal lobe atrophy, mean ± SD	0.6 ± 0.7	0.6 ± 0.7	0.78, p < 0.001	0.75, p < 0.001
- Microbleeds present, n (%)	23 (28)	21 (19)	0.25, p = 0.12	0.51, p < 0.001
- Lacunes present, n (%)	2 (2)	6 (5)	-	-0.06, p = 0.69
Framingham 10 year risk score CVD, mean ± SD	33.0 ± 15.3	15.9 ± 8.9 *	0.66, p < 0.001	0.62, p < 0.001
Framingham score items:				
- Systolic blood pressure, mean ± SD, mmHg	147 ± 18	141 ± 20 *	0.36, p = 0.024	0.53, p < 0.001
- Glycated hemoglobin (HbA1c), mean ± SD	37.5 ± 5.3	38.3 ± 4.3	0.81, p < 0.001	0.61, p < 0.001
- Total cholesterol, mean ± SD, mmol/l	5.1 ± 1.1	5.8 ± 1.2 *	0.65, p < 0.001	0.56, p < 0.001
- High-density lipoprotein, mean ± SD, mmol/l	1.4 ± 0.4	1.8 ± 0.6 *	0.72, p < 0.001	0.81, p < 0.001
- Smoking, n (%)	10 (12)	10 (9)	0.63, p < 0.001	0.58, p < 0.001
- Diabetes, n (%)	9 (11)	1 (1) *	0.75, p < 0.001	-
- Anti-hypertensive medication, n (%)	45 (54)	43 (38) *	0.25, p = 0.12	0.79, p < 0.001
WMH volume (in ml)				
- Total WMH, median (IQR)	1709 (556-4301)	2712 (1029-10444) *	0.75, p < 0.001	0.80, p < 0.001
- Total periventricular WMH, median (IQR)	1088 (338-3179)	1853 (737-5912) *	0.77, p < 0.001	0.75, p < 0.001
- Total deep WMH, median (IQR)	382 (162-1203)	884 (228-3905) *	0.66, p < 0.001	0.79, p < 0.001
- Frontal WMH, median (IQR)	717 (267-2498)	1477 (708-5908) *	0.80, p < 0.001	0.82, p < 0.001
- Parietal WMH, median (IQR)	183 (40-604)	380 (71-2160) *	0.65, p < 0.001	0.73, p < 0.001
- Temporal WMH, median (IQR)	126 (26-344)	171 (55-769) *	0.63, p < 0.001	0.59, p < 0.001
- Occipital WMH, median (IQR)	326 (103-687)	356 (137-735)	0.57, p < 0.001	0.52, p < 0.001
- Basal ganglia and thalamus WMH, median (IQR)	17 (7-40)	21 (6-106)	0.24, p = 0.14	0.70, p < 0.001

CVD: cardio-vascular disease; IQR: interquartile range; MMSE: mini-mental state examination; MZ monozygotic; SD: standard deviation; WMH: white matter hyperintensities. * p < 0.05 significantly different in women than in men.

Supplementary Table 2: relation between individual risk factors and WMH lesion load

	Age	Gender	Cholesterol	HDL	Systolic BP	Smoking	Diabetes	AHT
Whole brain	**0.29 (0.21-0.38) ***	**0.10 (0.00-0.20)** [#]	-0.05 (-0.11-0.00)	-0.06 (-0.16-0.04)	**0.06 (0.01-0.12)** [#]	**0.07 (0.01-0.14)** [#]	-0.03 (-0.07-0.01)	0.04 (-0.02-0.10)
Whole brain periventr.	**0.24 (0.16-0.31) ***	**0.15 (0.05-0.24)** [$]	-0.05 (-0.10-0.01)	-0.09 (-0.19-0.02)	**0.06 (0.01-0.12)** [#]	**0.08 (0.01-0.16)** [#]	-0.02 (-0.07-0.02)	**0.06 (0.01-0.12)** [#]
Whole brain deep	**0.29 (0.18-0.40) ***	0.10 (-0.01-0.22)	-0.06 (-0.13-0.01)	-0.02 (-0.13-0.09)	0.07 (-0.01-0.15)	0.03 (-0.04-0.11)	-0.10 (-0.20-0.01)	0.00 (-0.09-0.09)

Presented are beta's (95% confidence interval) * p-value < 0.001, [$] < 0.01, [#] < 0.05. Analysis are corrected for twin status, age (except age itself) and gender (except gender). AHT: antihypertensive treatment; BP: blood pressure; HDL: high-density lipoprotein; perivent.: periventricular.

Supplementary Table 3: relation between Framingham score without age and WMH lesion load

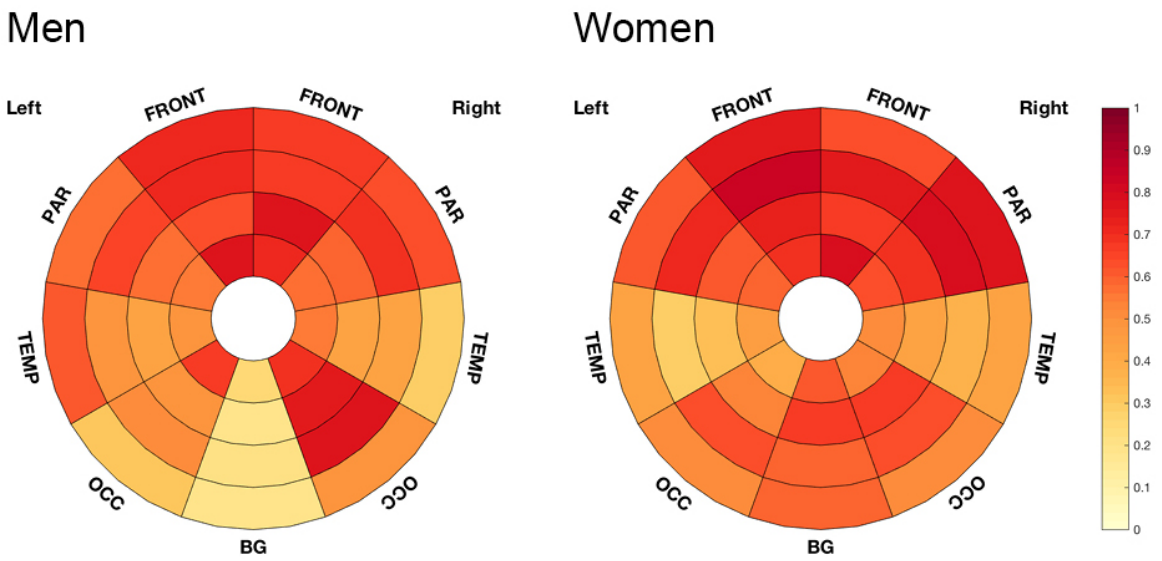
	β	**95% C.I.**	***p*-value**
Whole brain total	0.29	0.06-0.53	0.02
- Whole brain periventricular	0.41	0.16-0.66	0.001
- Whole brain deep	0.10	-0.21-0.41	0.5
Frontal total	0.34	0.09-0.59	0.009
- Frontal periventricular	0.45	0.13-0.77	0.005
- Frontal deep	0.13	-0.25-0.50	0.5
Parietal total	0.56	0.16-0.97	0.006
- Parietal periventricular	0.53	0.13-0.93	0.009
- Parietal deep	0.49	-0.05-1.02	0.07
Temporal total	0.16	-0.17-0.50	0.3
- Temporal periventricular	0.40	0.03-0.76	0.03
- Temporal deep	-0.09	-0.48-0.30	0.6
Occipital total	0.33	-0.03-0.69	0.07
- Occipital periventricular	0.26	-0.07-0.59	0.1
- Occipital deep	0.34	-0.07-0.75	0.1
Basal ganglia and thalamus	0.10	-0.27-0.47	0.6

We computed the Framingham score without age, and assessed the relation between this measure and regional WMH lesion load. Analysis were corrected for age and gender. C.I.: confidence interval

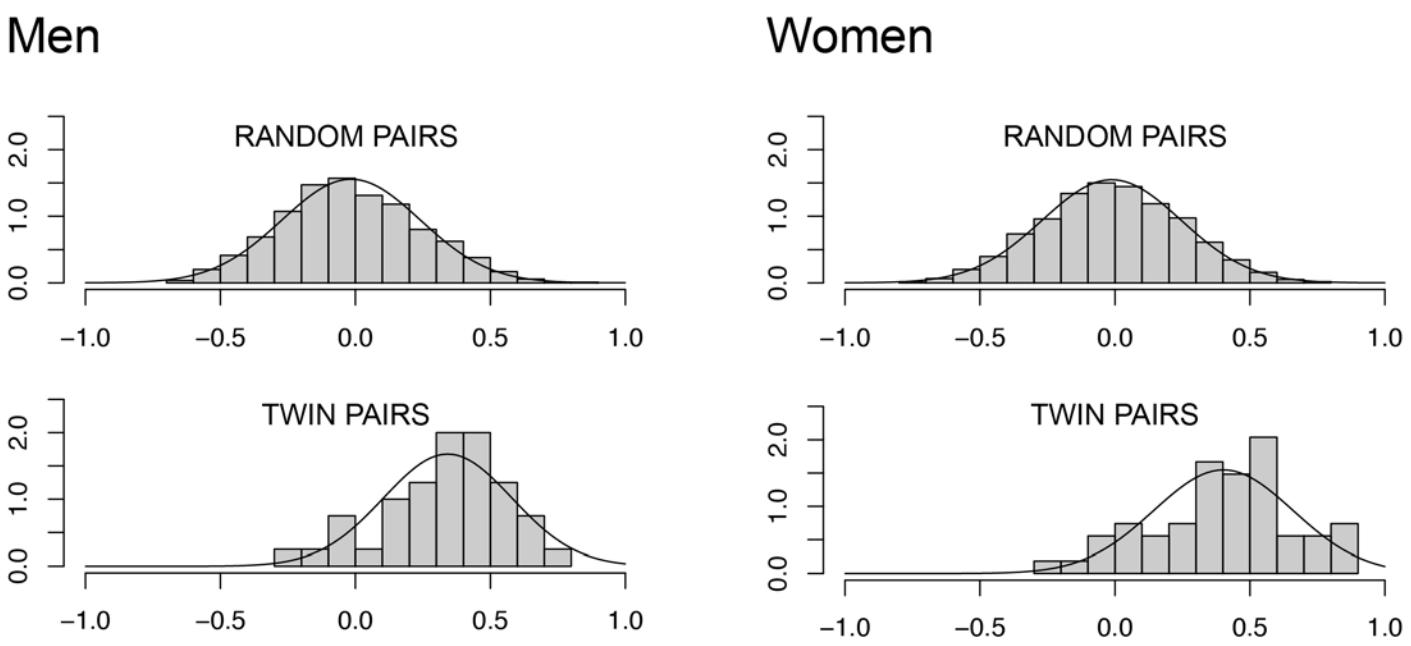
Supplementary Table 4: Twin correlations between Framingham score and WMH lesion load in men and women

WMH Measure	Within-participant cross-trait correlation (r_p)	Cross-twin cross-trait correlation	Genetic correlation	Proportion r_p explained by overlapping genetic factors	Non-shared environmental correlation	Proportion r_p explained by overlapping non-shared environmental factors
Whole brain total Men	0.28 (0.02-0.50)	0.21 (-0.04-0.45)	0.30 (-0.06-0.60)	-	0.22 (-0.09-0.49)	-
Whole brain total Women	0.35 (0.13-0.53)	0.30 (0.08-0.49)	0.40 (0.11-0.63)	85%	0.24 (-0.02-0.48)	-
Whole brain perivent. Men	0.23 (-0.03-0.46)	0.14 (-0.12-0.39)	0.20 (-0.17-0.52)	-	0.32 (0.02-0.57)	38%
Whole brain perivent. Women	0.32 (0.11-0.51)	0.25 (0.03-0.45)	0.34 (0.04-0.60)	76%	0.31 (0.05-0.53)	24%
Frontal total Men	0.24 (-0.02-0.47)	0.15 (-0.11-0.40)	0.21 (-0.16-0.52)	-	0.34 (0.04-0.59)	37%
Frontal total Women	0.33 (0.11-0.52)	0.28 (0.06-0.48)	0.38 (0.09-0.62)	86%	0.22 (-0.09-0.46)	-
Frontal perivent. Men	0.20 (-0.06-0.43)	0.08 (-0.18-0.33)	0.11 (-0.27-0.45)	-	0.39 (0.09-0.62)	61%
Frontal perivent. Women	0.33 (0.11-0.51)	0.26 (0.04-0.46)	0.36 (0.06-0.60)	80%	0.29 (0.02-0.51)	21%
Parietal total Men	0.35 (0.10-0.55)	0.27 (0.02-0.49)	0.40 (0.03-0.68)	78%	0.23 (-0.07-0.50)	-
Parietal total Women	0.35 (0.13-0.53)	0.28 (0.06-0.47)	0.39 (0.09-0.63)	80%	0.26 (0.00-0.49)	20%
Parietal perivent. Men	0.27 (0.02-0.49)	0.20 (-0.05-0.43)	0.30 (-0.09-0.61)	-	0.21 (-0.10-0.48)	-
Parietal perivent. Women	0.32 (0.11-0.50)	0.24 (0.02-0.44)	0.35 (0.03-0.61)	74%	0.26 (-0.00-0.49)	-

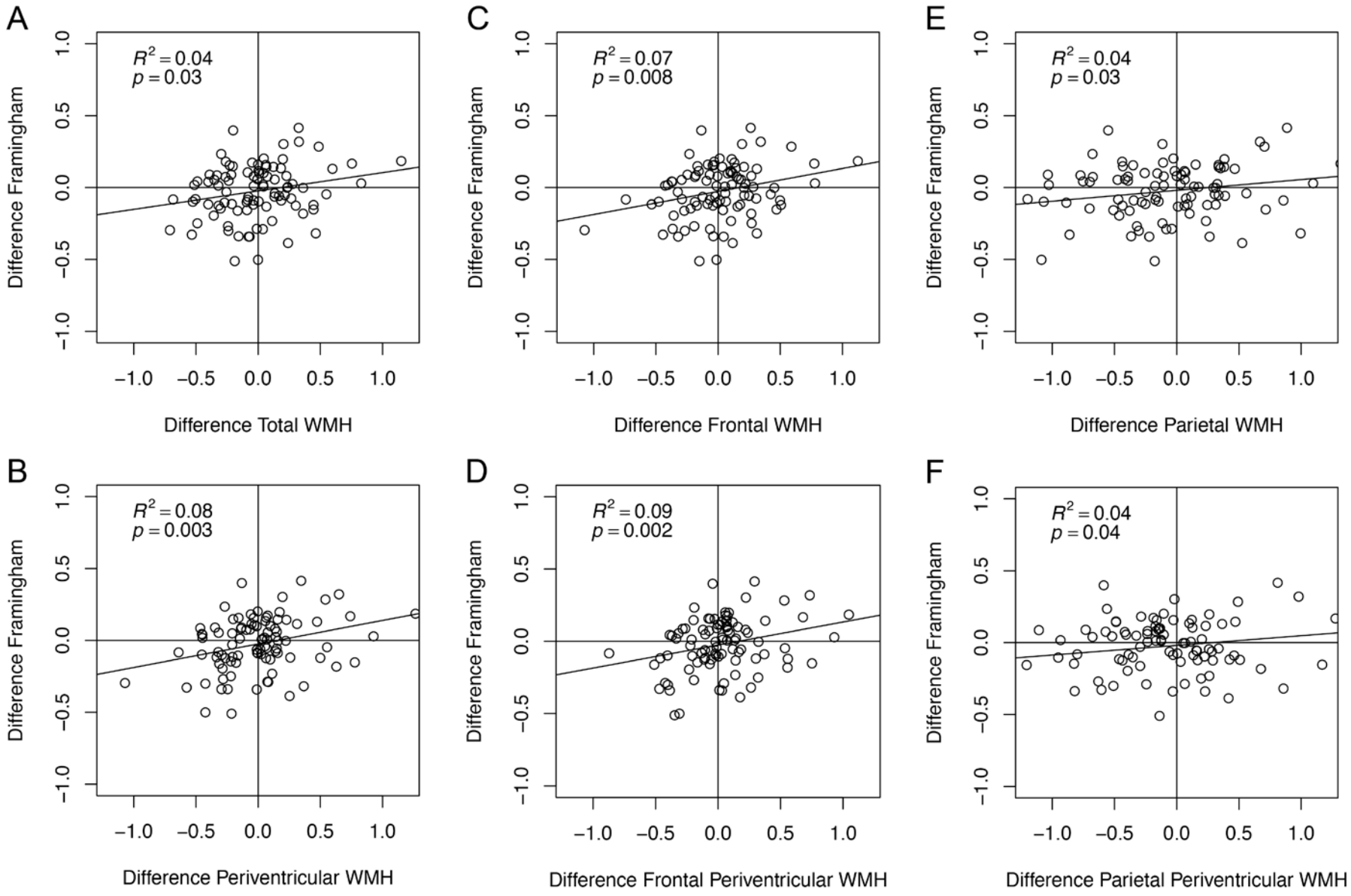
Data are displayed as correlation coefficient (95% confidence interval) or percentage. Estimates of the genetic and non-shared environmental correlation are based on bivariate genetic modeling, assuming an AE-model. We only compute proportion of r_p explained by overlapping genetic/non-shared environmental factors for those regions in which there was a significant genetic/non-shared environmental correlation. perivent.: periventricular; r_p: phenotypic correlation between Framingham score and WMH load; WMH: white matter hyperintensities.



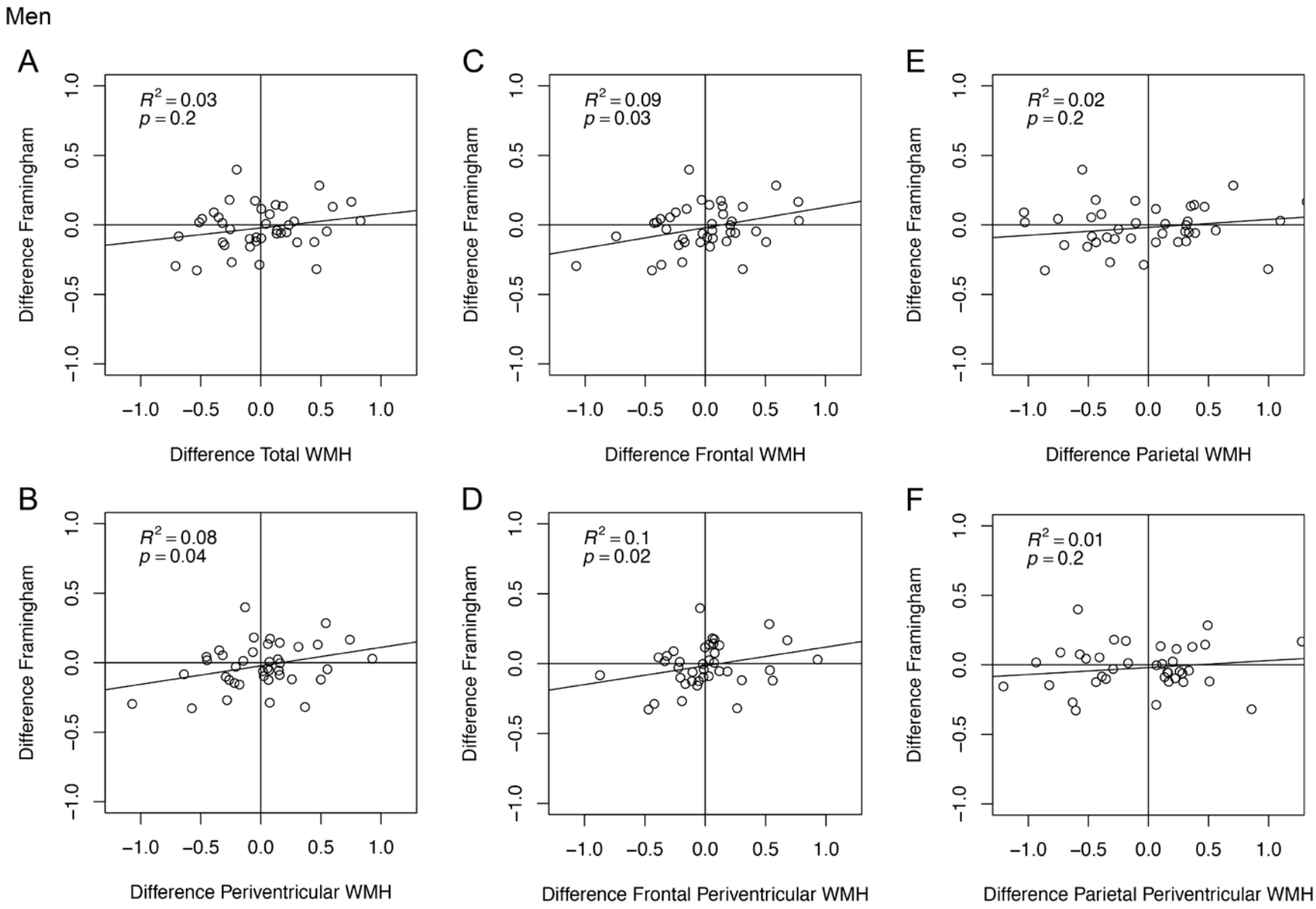
Supplementary Figure 1: Within twin pair regional correlations in WMH for male and female twin pairs
Color bar represents the strength of the correlation (Pearson's r). Front: frontal; Par: parietal; Temp: temporal; Occ: occipital; BG: basal ganglia and thalamus



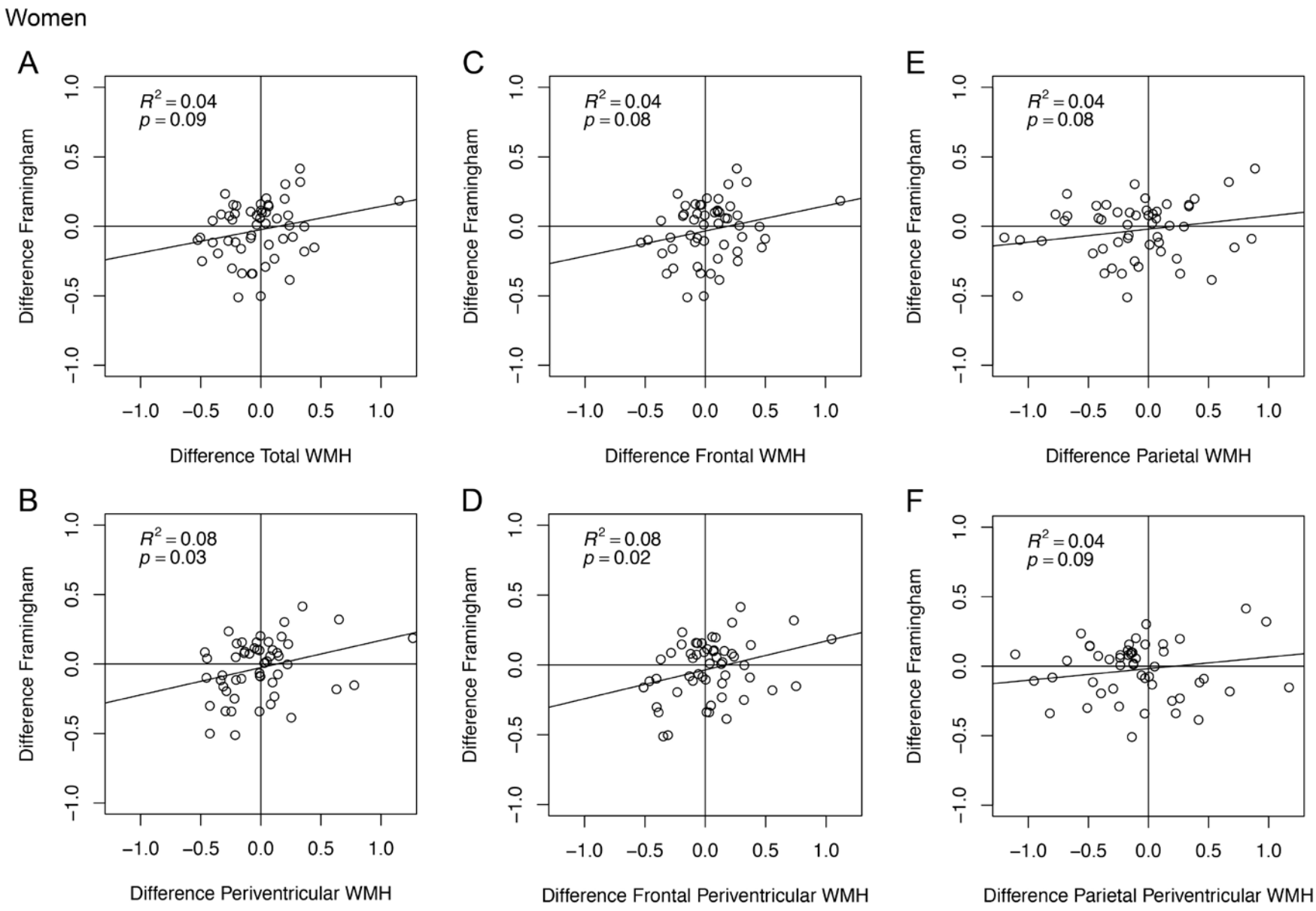
Supplementary Figure 2: Similarity of WMH distribution across regions in male and female twin pairs
Histograms of WMH correlations across regions in true twin pairs and in random pairs. The WMH data was centered per region prior to computing the within-pair correlation across regions.



Supplementary Figure 3: Within twin pair difference model. Within-pair differences in vascular risk factors were regressed on the within-pair differences in WMH. First row: total WMH for whole brain (A), frontal (C) and parietal (E). Second row: periventricular WMH in whole brain (B), frontal (D) and parietal (F).



Supplementary Figure 4: Within twin pair difference model in men. Within-pair differences in vascular risk factors were regressed on the within-pair differences in WMH. First row: total WMH for whole brain (A), frontal (C) and parietal (E). Second row: periventricular WMH in whole brain (B), frontal (D) and parietal (F).



Supplementary Figure 5: Within twin pair difference model in women. Within-pair differences in vascular risk factors were regressed on the within-pair differences in WMH. First row: total WMH for whole brain (A), frontal (C) and parietal (E). Second row: periventricular WMH in whole brain (B), frontal (D) and parietal (F).