



Fig. S1 Associations between CBF, AFD_t and FW in stable WMH/ NAWM. a, Correlation between FW and CBF. b, Correlation between FW and AFD_t . WMH = White matter hyperintensities; NAWM = Normal appearing WM; FW = Free water; CBF = Cerebral blood flow; AFD_t = Total apparent fiber density.

Table S1 Fixed Effects Results for WMH FW in the CSVD group

Independent variables	model 1		model 2	
	Estimate (95% CI)	p value	Estimate (95% CI)	p value
Age	0.006 (-0.013, 0.025)	0.531	0.001 (-0.016, 0.018)	0.908
Age×Time	-0.002 (-0.007, 0.003)	0.450	-0.002 (-0.007, 0.003)	0.448
Sex	0.388 (0.048, 0.729)	0.028	0.398 (0.087, 0.710)	0.014
Time	0.386 (0.053, 0.719)	0.027	0.378 (0.039, 0.717)	0.033
VRF score Zsc	-0.162 (-0.336, 0.011)	0.071	-0.197 (-0.358, -0.036)	0.019
<i>VRF score Zsc×Time</i>	0.005 (-0.040, 0.050)	0.824	0.005 (-0.039, 0.050)	0.812
WMH CBF Zsc	-0.127 (-0.306, 0.053)	0.171	-0.017 (-0.192, 0.159)	0.853
<i>WMH CBF Zsc×Time</i>	-0.009 (-0.056, 0.037)	0.698	-0.009 (-0.057, 0.040)	0.720
WMH AFD _t Zsc	-0.497 (-0.656, -0.338)	<0.001	-0.481 (-0.627, -0.334)	<0.001
<i>WMH AFD_t Zsc×Time</i>	-0.053 (-0.095, -0.011)	0.016	-0.052 (-0.094, -0.010)	0.018
SVD score	-	-	0.268 (0.125, 0.411)	<0.001
SVD score×Time	-	-	0.003 (-0.037, 0.042)	0.895

Interaction terms in bold italic represent whether a specific factor could predict the progression of FW. P values <0.05 are indicated in bold. Zsc is short of Z score. WMH = White matter hyperintensities; VRF = Vascular risk factor; CBF = Cerebral blood flow; AFD_t = Total apparent fiber density; SVD score = small vessel disease score.

Table S2 Fixed Effects Results for NAWM FW in the CSVD group

Independent variables	model 1		model 2	
	Estimate (95% CI)	p value	Estimate (95% CI)	p value
Age	0.025 (0.010, 0.040)	0.002	0.020 (0.005, 0.034)	0.008
Age×Time	0.000 (-0.004, 0.004)	0.901	0.000 (-0.004, 0.004)	0.992
Sex	-0.013 (-0.307, 0.281)	0.931	-0.013 (-0.282, 0.256)	0.925
Time	0.144 (-0.118, 0.406)	0.286	0.136 (-0.133, 0.405)	0.326
VRF score Zsc	-0.107 (-0.253, 0.039)	0.156	-0.140 (-0.272, -0.007)	0.043
<i>VRF score Zsc×Time</i>	-0.004 (-0.040, 0.032)	0.829	-0.005 (-0.041, 0.031)	0.778
NAWM CBF Zsc	-0.109 (-0.252, 0.034)	0.141	-0.025 (-0.160, 0.110)	0.720
<i>NAWM CBF Zsc×Time</i>	-0.011 (-0.047, 0.025)	0.550	-0.008 (-0.046, 0.029)	0.665
NAWM AFD _t Zsc	-0.528 (-0.668, -0.389)	<0.001	-0.494 (-0.621, -0.367)	<0.001
<i>NAWM AFD_t Zsc×Time</i>	-0.036 (-0.070, -0.001)	0.047	-0.034 (-0.069, 0.001)	0.060
SVD score	-	-	0.247 (0.130, 0.365)	<0.001
SVD score×Time	-	-	0.009 (-0.023, 0.042)	0.571

Interaction terms in bold italic represent whether a specific factor could predict the progression of FW. P values <0.05 are indicated in bold. Zsc is short of Z score. NAWM = Normal appearing white matter; VRF = Vascular risk factor; CBF = Cerebral blood flow; AFD_t = Total apparent fiber density; SVD score = small vessel disease score.