SUPPLEMENTAL MATERIALS

For paper entitled:

Progression of MRI-defined brain vascular disease predicts vascular events in elderly: the Cardiovascular Health Study

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Supplemental Methods

Details on the Methods are provided in prior publications, as indicated in the manuscript. Key publications should be available through links in the references of the online version of the manuscript. As an aid to the reader, some of the details from these prior publications are summarized in this supplement.

Each center's institutional review committee approved the study, and all participants provided informed consent.

All members of the CHS cohort were invited to undergo MRI scanning, and 3660 (62%) were scanned. They were younger and healthier than those who did not undergo MRI.[1] All members were again invited to undergo a follow-up MRI 5 years later. The 2116 participants who underwent 2 scans (see flowchart in the manuscript) were healthier than the 1544 who underwent a single scan. For details see table below reproduced from the original paper.[2]

The initial MRI was performed on General Electric or Picker 1.5 Tesla scanners at three field centers and on a 0.35 Tesla Toshiba instrument at the fourth. The initial scans were performed from November 1991 to May 1994, and follow-up scans were performed from May 1997 to December 1999. The time between a participant's initial and follow-up scan varied between 3.2 and 7.5 years, with a median and mean of 5.0 years.

The scanning protocol included sagittal T1-weighted localizer images and axial T1, spin-density, and T2-weighted images. Axial images had 5-mm thickness without interslice gaps. Without knowledge of any clinical information, neuroradiologists at the reading center identified infarcts and estimated the white matter, ventricular, and sulcal grades using a 10-point system and library of templates.

Brain infarct was defined as an area of abnormal signal intensity in a vascular distribution that lacked mass effect. Infarcts had to be hyperintense to gray matter on both spin density and T2-weighted images.[2,3] To be considered infarcts in the white matter and brain stem, lesions also had to be hypointense on T1-weighted images, with intensities approaching that of cerebrospinal fluid. Because abnormalities <3 mm could not be reliably detected, all infarcts in these analyses had to be ≥3 mm.

The white matter signal changes of each individual were assessed on a semi-quantitative 10-point white matter scale (0 to 9) using predefined visual standards of 8 reference cases.[1,4,5] White matter grade (WMG) was estimated as the total extent of periventricular and subcortical white matter signal abnormality on spin-density-weighted axial images that successively increased from no (grade 0) or barely detectable changes (grade 1) to almost all white matter involved (grade 9). Volumetric analytic validation of this visual scale corresponded to a rank increase in white matter hyperintensity normalized for cerebral parenchymal volume.[6] For the change in WMG, readers assessed all scans side-by-side without knowing grades from previous readings or order of scans. Because of technical problems, 197 of original 2116 pairs of scans could not be read, leaving 1919 (91%) pairs. Demographics, cardiovascular risk factors, and prevalent cardiovascular

disease were similar for these 197 and 1919 participants (data not shown).

The best way to understand what is meant to worsen by one grade is to consult the paper on worsening white matter[5] or an earlier paper from CHS on WMG where an example of the template used for scoring scans is reproduced (see Figure 1 in that paper).[1]

1. Longstreth WT Jr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke*. 1996;27:1274-1282.
2. Longstreth WT Jr, Dulberg C, Manolio TA, Lewis MR, Beauchamp NJ Jr, O'Leary D, et al. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke*. 2002;33:2376-2382.
3. Bernick C, Kuller L, Dulberg C, Longstreth WT Jr, Manolio T, Beauchamp N, et al. Silent MRI infarcts and the risk of future stroke: the Cardiovascular Health Study. *Neurology*. 2001;57:1222-1229.
4. Kuller LH, Longstreth WT Jr, Arnold AM, Bernick C, Bryan RN, Beauchamp NJ Jr. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. *Stroke*. 2004;35:1821-1825.
5. Longstreth WT Jr, Arnold AM, Beauchamp NJ Jr, Manolio TA, Lefkowitz D, Jungreis C, et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke*. 2005;36:56-61.
6. Kuller LH, Arnold AM, Longstreth WT Jr, Manolio TA, O'Leary DH, Burke GL, et al. White matter grade and ventricular volume on brain MRI as markers of longevity in the Cardiovascular Health Study. *Neurobiol Aging*. 2007;28:1307-1315.

Comparison of participants who had both the initial and follow-up MRI scans with those who had only the initial MRI scan.

	Percent with feature at initial MRI scan		
	Both scans (n=2116)	**Initial scan only (n=1544)**	***p*-value***
Characteristic			
Older than 75 years	61.3	42.1	< 0.001
African-American	15.5	15.8	0.82
Women	59.5	56.7	0.09
Any college	40.5	33.0	< 0.001
Income $50,000 or more	16.3	11.6	< 0.001
Current smoker	8.4	11.0	0.008
Ankle-arm index 0.9 or less	7.5	17.6	< 0.001
Prevalent			
Coronary heart disease	16.9	25.5	< 0.001
Myocardial infarction	7.5	12.7	< 0.001
Congestive heart failure	3.0	7.5	< 0.001
Stroke	3.0	9.3	< 0.001
Transient ischemic attack	2.2	4.7	< 0.001
Hypertension	41.8	48.6	< 0.001
Diabetes	11.6	17.7	< 0.001
Event within five years following initial MRI			
Myocardial infarction	4.2	10.6	< 0.001
Congestive heart failure	5.6	17.5	< 0.001
Stroke	3.4	12.2	< 0.001
Transient ischemic attack	1.9	2.5	0.19

* By chi-square test

Supplemental Table. Incident rates per 1,000 person-years after follow-up MRI scan by both incident infarct and worsened white matter grade.

	CHF		Stroke		Death		Cardiovascular Death	
	Incidence		Incidence		Incidence		Incidence	
MRI Change	(N at risk)	HR* (95 % CI)	(N at risk)	HR* (95 % CI)	(N at risk)	HR* (95 % CI)	(N at risk)	HR* (95 % CI)
None	22.8 (812)	1.00 (reference)	10.2 (857)	1.00 (reference)	48.0 (857)	1.00 (reference)	15.2 (857)	1.00 (reference)
Only worsened WMG	31.8 (216)	1.35 (0.97-1.87)	14.4 (229)	1.39 (0.87-2.22)	76.4 (229)	1.50 (1.22-1.83)	25.7 (229)	1.54 (1.08-2.19)
Only incident infarct	33.5 (117)	1.38 (0.92-2.08)	19.7 (133)	1.92 (1.15-3.20)	72.8 (133)	1.47 (1.14-1.89)	28.1 (133)	1.68 (1.11-2.54)
Both	43.1 (86)	1.79 (1.18-2.73)	27.5 (93)	2.58 (1.53-4.36)	86.7 (93)	1.69 (1.28-2.24)	31.8 (93)	1.97 (1.24-3.14)

	Angina		MI	
MRI Change	Incidence (N at risk)	HR* (95 % CI)	Incidence (N at risk)	HR* (95 % CI)
None	18.8 (694)	1.00 (reference)	12.7 (778)	1.00 (reference)
Only worsened WMG	23.5 (193)	1.17 (0.78, 1.75)	17.8 (214)	1.42 (0.92, 2.20)
Only incident infarct	22.4 (105)	1.17 (0.70, 1.96)	14.5 (119)	1.15 (0.64, 2.07)
Both	17.6 (71)	0.93 (0.47, 1.86)	20.3 (80)	1.52 (0.82, 2.83)

Abbreviations: HR, hazard ratio; CI, confidence interval; CHF, congestive heart failure; MRI, magnetic resonance imaging; WMG, white matter grade.

* As in Tables 1 and 2, estimated hazard ratios adjusted for age, sex and time between scans, current smoking, weight, histories of coronary artery disease, CHF, claudication, hypertension and diabetes, all at the time of the follow-up scan, unless part of the outcome measure. Note that the number of participants in these models is smaller than the models presented in Tables 1 and 2.