Supplementary Online Content

Palm-Meinders IH, Koppen Hille, Terwindt GM, et al. Structural Brain Changes in Migraine: A Population-Based 9-Year MRI Follow-up Study. *JAMA*. doi:10.1001/jama.2012.14276

eTable 1: Baseline characteristics of follow-up participants and non-participants

eTable 2: Migraine characteristics in relation to MRI outcome measures as compared to controls

eTable 3: Mean cognitive performance in different domains by deep white matter hyperintensity load

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Baseline characteristics of follow-up participants and non-participants

Characteristic at baseline (CAMERA-1)	CAMERA-1 (n=435)	CAMERA-2 Total group		CAMERA-2 Participants with migraine		CAMERA-2 Controls	
		Non-participants (n=149)	Participants (n=286)	Non-participants (n=93)	Participants (n=203)	Non-participants (n=56)	Participants (n=83)
Demographics							
Age at CAMERA-1, mean (SD), y	48 (7.8)	50 (7.9)$	48 (7.7)	49 (8.0)	48 (7.8)	51 (7.5)$$	46 (7.2)
Female	317 (73%)	115 (77%)	202 (71%)	73 (79%)	144 (71%)	42 (75%)	58 (69%)
Low education†	227 (52%)	90 (60%)$	137 (48%)	57 (61%)	98 (49%)	33 (59%)	39 (46%)
Physical and lab exam							
Body mass index, mean (SD)	25 (4.2)	25 (4.4)	25 (4.0)	26 (4.7)$	25 (4.1)	24 (3.8)	24 (3.6)
Blood pressure, mean (SD), mm Hg							
Systolic	134 (18)	136 (18)	134 (18)	136 (18)	133 (17)	135 (18)	135 (18)
Diastolic	91 (10)	92 (10)	91 (10)	93 (11)$	91 (9)	90 (8)	91 (10)
Hypertension*	167 (38%)	58 (39%)	109 (38%)	43 (46%)	79 (39%)	15 (27%)	30 (36%)
Diabetes	9 (2%)	2 (1%)	7 (2%)	0	4 (2%)	2 (4%)	3 (4%)
High risk cholesterol*	65 (15%)	27 (18%)	38 (13%)	17 (18%)	29 (14%)	10 (18%)	9 (11%)
Medical history							
Smoking							
Ever	287 (66%)	104 (70%)	183 (64%)	64 (67%)	125 (62%)	40 (71%)	58 (69%)
Pack-years, mean (SD)	10 (13)	14 (16)$	8 (11)	13 (16)$	8 (11)	14 (17)	10 (12)
High alcohol consumption*	44 (10%)	14 (9%)	30 (11%)	6 (7%)	16 (8%)	8 (14%)	14 (17%)
>15 yrs of oral contraceptive use (women only)	77/317 (24%)	22/115 (19%)	55/202 (27%)	15/73 (21%)	38/144 (26%)	7/42 (17%)	17/58 (29%)

Unless indicated otherwise, differences were not significant (*P*>.05)
Compared with participants $ *P*<.05, $$ *P*<.001
†Low education indicates primary school or lower vocational education. *Hypertension CAMERA-1 defined as a systolic blood pressure of 160 mm Hg and higher or a diastolic blood pressure of 95 mmHg and higher or current use of antihypertensive drugs. High alcohol consumption defined as ≥ 3 units/day; high risk cholesterol defined as upper 15% ratio total/hdl cholesterol.

Causes of death during follow-up period

Six baseline participants had died during follow-up period: one due to malignant neoplasm of ovary, one had emphysema, one cerebral infarction, one acute peritonitis with septic shock, and two unknown causes of death. Only emphysema patient was control participant, others were participants with migraine.

eTable 2. Migraine characteristics in relation to MRI outcome measures as compared to controls (Females only)

	High DWMH load at FU		Progression of DWMH load		High progression of DWMH load		Progression of IH		Progression of PVWMH load	
Duration of migraine										
< 29 yrs ≥ 29 yrs	1.8 [0.6-4.9] 1.2 [0.4-3.3]	P=.3	2.9 [1.3-6.7] 1.5 [0.7-3.2]	P=.06	3.3 [1.0-9.9] 1.6 [0.5-5.0]	P=.08	11.2 [1.4-90.1] 4.9 [0.6-41.8]	P=.1	1.4 [0.6-2.9] 1.2 [0.5-2.5]	P=.7
low 25% high 25%	0.5 [0.1-1.6] 0.7 [0.3-2.0]	P=.8	0.9 [0.3-2.4] 0.3 [0.1-1.0]	P=.04	0.7 [0.2-2.2] 0.6 [0.2-1.8]	P=.5	2.1 [0.7-6.4] 0.5 [0.1-1.9]	P=.2	0.9 [0.4-2.1] 1.0 [0.4-2.5]	P=1.0
median (IQR) of those with lesions median (IQR) of those without	23 (11-39) 20 (0-34)	P*=.2	22 (7-34) 15 (0-36)	P*=.1	23 (16-38) 20 (0-34)	P*=.1	24 (15-37) 20 (0-34)	P*=.2	30 (20-39) 29 (17-37)	P*=.2
Migraine subtype										
without aura with aura	1.8 [0.7-5.1] 1.2 [0.4-3.2]	P=.3	2.9 [1.2-6.7] 1.7 [0.8-3.5]	P=.2	3.3 [1.1-9.9] 1.6 [0.5-5.0]	P=.1	11.5 [1.4-92.9] 5.0 [0.6-41.7]	P=.1	1.7 [0.8-3.8] 1.0 [0.5-2.1]	P=.2
Number of headache attacks										
<median (lifetime) ≥median (lifetime)	1.7 [0.6-4.7] 1.3 [0.5-3.5]	P=.5	1.9 [0.9-4.2] 2.2 [1.0-4.9]	P=.9	2.8 [0.9-8.7] 1.9 [0.6-5.8]	P=.4	8.9 [1.1-73.3] 6.7 [0.8-55.0]	P=.5	1.4 [0.7-3.0] 1.1 [0.5-2.4]	P=.6
median (IQR) of those with lesions median (IQR) of those without	271 (107-646) 264 (168-480)	P*=.9	274 (123-575) 252 (174-353)	P*=.4	263 (105-581) 274 (173-496)	P*=.6	284 (100-923) 264 (159-496)	P*=.9	264 (168-549) 286 (94-444)	P*=.3
<median (FU only) ≥median (FU only)	1.9 [0.7-5.5] 1.2 [0.4-3.3]	P=.3	2.1 [0.9-4.7] 2.2 [1.0-4.5]	P=.8	3.2 [1.0-9.9] 1.9 [0.6-5.6]	P=.2	12.3 [1.5-101.5] 5.3 [0.6-43.8]	P=.1	0.9 [0.4-2.0] 1.6 [0.8-3.2]	P=.2
Mean attacks per month, median (IQR) of those with lesions of those without lesions	0.7 (0.4-1.9) 0.9 (0.5-1.5)	P*=.7	1.0 (0.5-1.6) 0.6 (0.4-1.0)	P*=.09	0.8 (0.4-1.8) 0.9 (0.5-1.5)	P*=.8	0.8 (0.5-2.2) 0.9 (0.4-1.5)	P*=.6	0.9 (0.5-1.6) 0.8 (0.4-1.5)	P*=.5

Headache activity status										
inactive at baseline active at baseline	3.4 [1.1-10.7] 1.1 [0.4-2.8]	P=.03	3.1 [1.0-9.5] 1.9 [0.9-3.8]	P=.4	5.3 [1.5-18.1] 1.7 [0.6-5.1]	P=.03	10.2 [1.1-93.1] 7.0 [0.9-55.6]	P=.6	1.5 [0.5-3.9] 1.2 [0.6-2.4]	P=.6
inactive during 9 year FU active during 9 year FU	1.8 [0.6-5.0] 1.2 [0.4-3.4]	P=.5	2.9 [1.0-5.4] 1.9 [0.9-4.1]	P=.9	2.6 [0.8-8.1] 2.1 [0.7-6.3]	P=.7	5.7 [0.7-47.4] 10.6 [1.3-87.0]	P=.2	1.0 [0.4-2.2] 1.5 [0.7-3.0]	P=.4
Number of aura attacks										
<median (lifetime) ≥median (lifetime)	1.1 [0.3-4.0] 0.9 [0.3-3.3]	P=.8	1.7 [0.7-4.1] 1.7 [0.7-4.3]	P=.8	1.6 [0.4-6.2] 1.3 [0.3-5.0]	P=.8	5.7 [0.6-57.1] 4.6 [0.5-45.9]	P=.8	0.9 [0.3-2.5] 1.5 [0.5-4.1]	P=.4
median (IQR) of those with lesions median (IQR) of those without	158 (73-411) 150 (49-262)	P*=.2	158 (68-283) 149 (43-281)	P*=.5	158 (73-411) 150 (49-262)	P*=.2	113 (26-265) 154 (65-292)	P*=.5	173 (67-288) 112 (49-262)	P*=.2
<median at follow-up ≥median at follow-up	1.1 [0.2-5.3] 1.1 [0.3-4.6]	P=.7	1.5 [0.5-4.2] 2.2 [0.7-6.7]	P=.9	1.6 [0.3-8.7] 1.5 [0.3-6.8]	P=.7	6.0 [0.5-77.7] 3.2 [0.2-48.1]	P=.6	0.8 [0.3-1.8] 1.6 [0.6-4.0]	P=.1
Aura activity status										
inactive at baseline active at baseline	2.0 [0.5-7.8] 0.8 [0.2-2.5]	P=.2	2.0 [0.6-6.2] 1.6 [0.7-3.5]	P=.8	2.7 [0.6-11.8] 1.1 [0.3-3.8]	P=.2	5.9 [0.5-68.5] 5.4 [0.6-48.2]	P=.9	0.7 [0.2-2.2] 1.0 [0.5-2.3]	P=.5

inactive at follow-up active at follow-up	0.3 [0.1-2.0] 1.7 [0.6-4.8]	P=.06	1.5 [0.5-4.3] 2.3 [1.0-5.0]	P=.4	0.5 [0.1-3.0] 2.6 [0.8-8.3]	P=.05	6.8 [0.6-71.4] 7.8 [0.9-64.3]	P=.8	0.8 [0.3-2.2] 1.3 [0.6-2.9]	P=.3
Treatment										
no triptans ever used triptans ever used	1.4 [0.6-3.7] 1.5 [0.4-6.0]	P=.8	1.8 [0.9-3.7] 4.3 [1.1-16.6]	P=.2	2.2 [0.8-6.3] 2.9 [0.7-11.8]	P=.5	8.9 [1.1-69.3] 2.5 [0.1-42.5]	P=.2	1.1 [0.6-2.3] 2.0 [0.7-6.1]	P=.3
Duration of migraine										
< 29 yrs ≥ 29 yrs	1.8 [0.6-4.9] 1.2 [0.4-3.3]	P=.3	2.9 [1.3-6.7] 1.5 [0.7-3.2]	P=.06	3.3 [1.0-9.9] 1.6 [0.5-5.0]	P=.08	11.2 [1.4-90.1] 4.9 [0.6-41.8]	P=.1	1.4 [0.6-2.9] 1.2 [0.5-2.5]	P=.7

OR with [95% CI] for comparison with controls; controls as a reference group
P-values between migraine subgroups adjusted for age, hypertension, diabetes, education; P*-values by Mann Whitney U test
DWMH=Deep white matter hyperintensities
PVWMH=Periventricular white matter hyperintensities
IH=Infratentorial hyperintensities
Progression of WMH defined as an increase in WMH volume after 9 years (Δ CAM2-CAM1≥0.01 ml); progression of IHs defined as an increase in size and/or number of IHs; high progression of DWMH defined as the upper 20th percentile of DWMH progression distribution

eTable 3. Mean cognitive performance in different domains by deep white matter hyperintensity load (DWMH)

	non-high DWMH		high DWMH		*P* [95% CI] (model 1)	*P* [95% CI] (model 2)
	N	Mean (SD)	N	Mean (SD)		
Cognitive function at baseline						
Memory: immediate recall (No. of words)	219	26.9 (5.7)	57	26.8 (5.4)	0.5 [-0.1 to 2.0]	0.5 [-0.1 to 2.1]
Memory: delayed recall (No. of words after 20 mins)	219	9.0 (2.7)	57	8.9 (2.5)	0.8 [-0.6 to 0.9]	0.8 [-0.6 to 0.9]
Concentration, attention (s)	216	25.7 (5.7)	57	26.5 (5.6)	0.4 [-1.9 to 1.0]	0.4 [-1.9 to 1.0]
Processing speed (No. of correct symbols)	219	35.6 (7.1)	57	33.0 (6.9)	0.3 [-2.7 to 0.9]	0.3 [-2.7 to 0.9]
Visuo-spatial, motor skills (No. of correct pegs)	187	52.0 (7.5)	50	50.2(5.8)	0.4 [-3.2 to 1.5]	0.4 [-3.2 to 1.5]
Executive function (SD)	216	0.1 (1.6)	57	-0.3 (1.5)	0.6 [-0.5 to 0.3]	0.6 [-0.5 to 0.3]
Cognitive function at follow-up						
Memory: immediate recall (No. of words)	223	28.4 (6.3)	53	26.2 (6.3)	0.2 [-2.9 to 0.6]	0.2 [-2.9 to 0.7]
Memory: delayed recall (No. of words after 20 mins)	223	9.8 (3.0)	53	8.6 (3.1)	0.06 [-1.7 to 0.0]	0.06 [-1.7 to 0.0]
Concentration, attention (s)	223	26.3 (7.6)	51	28.1 (6.2)	0.7 [-2.1 to 2.0]	0.9 [-2.1 to 2.0]
Processing speed (No. of correct symbols)	222	34.7 (7.1)	53	31.2 (6.5)	0.1 [-3.2 to 0.3]	0.1 [-3.2 to 0.3]
Visuo-spatial, motor skills (No. of correct pegs)	219	37.9 (5.5)	53	35.4 (5.4)	0.09 [-2.1 to 0.2]	0.09 [-2.1 to 0.2]
Executive function (SD)	223	0.3 (1.7)	51	-0.1 (1.7)	0.3 [-0.2 to 0.7]	0.3 [-0.2 to 0.7]
Fluid intelligence (Points, normalized for age)	166	10.3 (3.4)	30	9.6 (3.3)	0.4 [-0.5 to 0.2]	0.4 [-0.5 to 0.2]

Overall cognitive performance						
CAMERA-1 (baseline, Z-score)	184	0.3 (8.9)	50	-1.8 (8.2)	0.8 [-2.9 to 2.3]	0.8 [-2.9 to 2.3]
CAMERA-2 (follow-up, Z-score)	218	1.4 (9.2)	51	-3.7 (8.9)	0.07 [-4.5 to 0.2]	0.07 [-4.5 to 0.2]

High DWMH defined as the upper quintile of DWMH distribution.
Model 1: Adjusted for age, gender, level of education; Model 2: Adjusted for age, gender, level of education, and migraine diagnosis

Assessment of cognitive performance
Cognitive performance was evaluated by validated, widely used, cognitive tests in a fixed order. The test battery, administered by four trained medical students, was the same for both time points (test protocol and methods were the same for baseline and follow-up) and included the 15 word Verbal Learning Test (Rey, 1985); abbreviated Stroop test (Stroop, 1935) consisting of three subtasks; verbal Fluency test (Miller, 1984); Letter Digit Substitution Test (Van der E, 2006), which is a modified version of the Symbol Digit Modalities Test; and Purdue pegboard test (Tiffin, 1948). In follow-up investigation, the Block Design Test from the WAIS-III test battery (Wechsler, 1981) was added. Higher score indicates better cognitive performance. The results of these tests were normalized by calculation of Z-scores based on total sample means and standard deviations, and added up per cognitive domain. The composite cognitive score was calculated for baseline as well as follow-up time point by adding up the separate domain Z-scores.

Cognitive domains
Memory function was composed of immediate recall and delayed recall after 20 minutes. The reading subtasks of the Stroop test measured concentration and attention ability. Executive function was scored by the interference task of the Stroop test and the word fluency task. The Letter Digit Substitution Test evaluated psychomotor speed, processing speed, and organization. Fine motor skills, motor speed, and visuo-spatial ability were evaluated by the Purdue pegboard. The Block Design Test measured fluid intelligence and visuo-spatial skills.

Statistical analysis
Using linear regression, significant difference for cognitive function test scores was examined by DWMH load (high vs. non-high) adjusted for age, gender, and educational level (model 1). Analyses on the association between high lesion load and cognitive performance were done cross sectionally for both CAMERA-1 and CAMERA-2. To assess the effect of having migraine on the relation between DWMH load and cognition, migraine diagnosis was added to the multivariate model (model 2).