

Online Supplement to “Development and validation of a simple clinical risk equation for extensive white matter lesions: The Dijon MRI Study”

Covariate data collection

Participants underwent face-to-face interviews using a standardized questionnaire with trained psychologists covering demographic characteristics, daily life habits, medical history and functional independence. As part of the baseline assessment, participants were also asked whether they experienced difficulties performing simple arithmetic calculations, difficulties retaining new simple information, were forgetful, had difficulties with language or comprehension and had problems with balance or walking (responses dichotomized as yes or no). A detailed history of drug use during the preceding month was determined at interview and the name of the medication was subsequently coded according to the French translation of the WHO ATC classification. Psychotropic drug use included anti-depressants, mood stabilizers, anxiolytics, and neuroleptics. Antihypertensive drugs only included taking drugs explicitly for hypertension and were explicitly differentiated from other uses [1]. Brachial blood pressure (BP) was measured twice after at least 5 minutes of rest in a seated position, with an appropriately sized cuff placed on the right arm, using a validated digital electronic tensiometer (OMRON M4, OMRON Corp., Kyoto, Japan). Hypertension was defined as systolic BP >140 mmHg or diastolic BP >90 mmHg or use of antihypertensive medication for BP. Height and weight measurements were measured in light clothing. Body mass index was calculated as weight (kg) divided by height (m²). Blood samples were drawn in the morning after overnight fasting and centralized measurements were made for lipids and glucose levels. Diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/L or medication use for diabetes. Hypercholesterolemia was defined as total cholesterol >7.25 mmol/l.

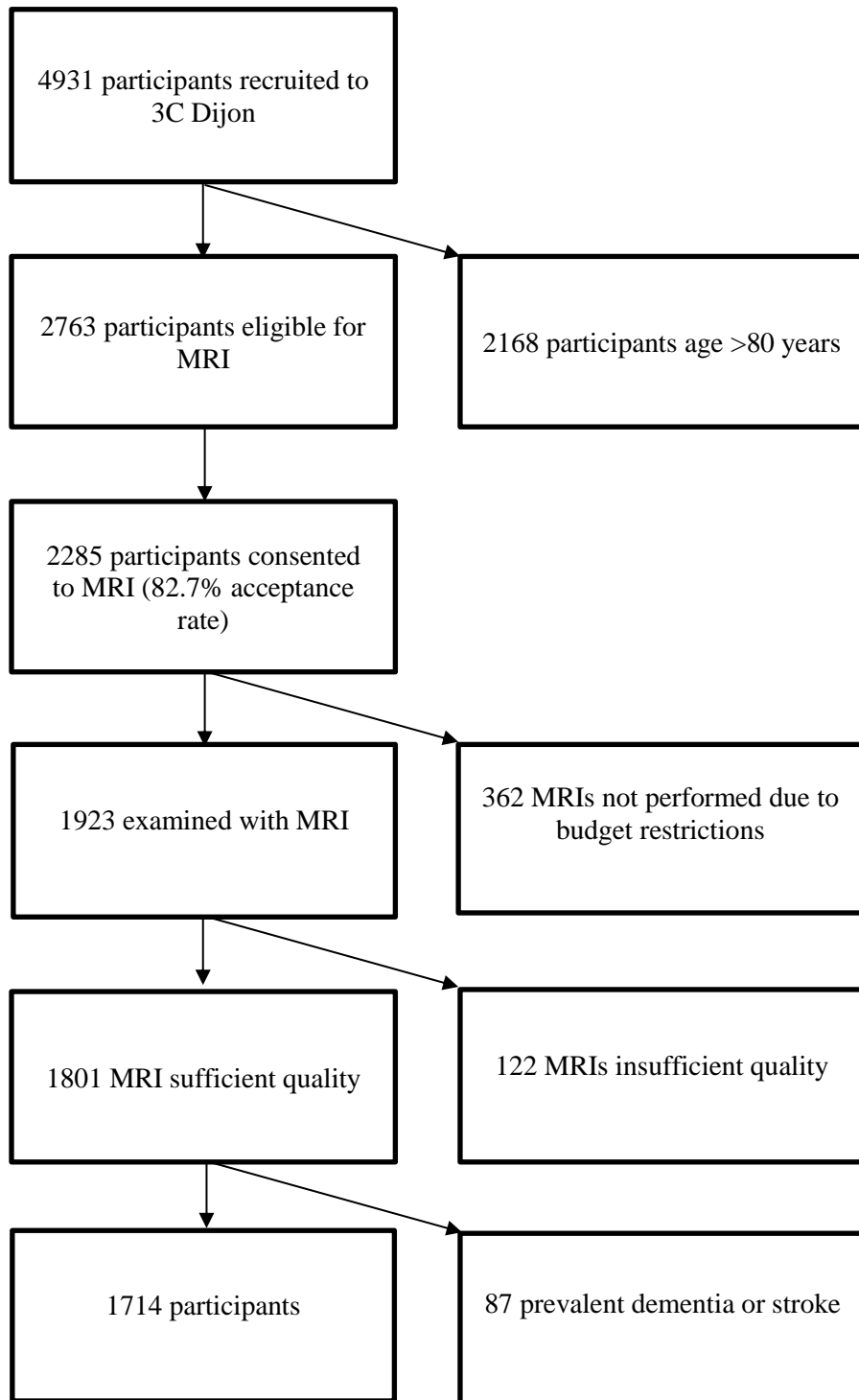
Depressive symptoms were measured with the Centre for Epidemiological Studies-Depression scale and scores ≥ 16 are indicative of clinically relevant depressive symptoms [2]. A lifetime history of depression disorder was determined by the major depression and dysthymia modules of the Mini International Neuropsychiatric Interview. How depression disorder age of onset was determined in the 3C study is described elsewhere [3]. Instrumental activities of daily living were measured with the French version of the Lawton-Brody instrumental activity of daily living (IADL) scale which evaluates the ability to use a telephone, manage drugs and money, use public or private transportation, and shop and, additionally for women, prepare meals and do housework and laundry [4].

A battery of cognitive tests was administered including the Mini Mental State Examination (MMSE), the Benton Visual Retention Test and the Isaac fluency test, covering memory, attention, language and visuo-spatial abilities. A diagnosis of dementia was made by local neurologists according to DSM-IV criteria. A panel of independent neurology experts adjudicated dementia [5]. To complement the cognitive tests, a questionnaire was developed to determine cognitive and daily living problems, derived from the Katz scale. These self-report questions covered domains including; difficulties with balance when walking, memory recall problems (forgetfulness), memory difficulties retaining new simple information, memory recall difficulties of old memories, difficulties with simple arithmetic calculations, difficulties with language or comprehension, and difficulties with spatial orientation (e.g. in a city street).

Additional statistical methods

The point system involves estimating the parameters of the final multivariable model (β , OR, 95% CI, p) after the backward deletion process (Table 2 of the main document). Then a

meaningful reference value and mid-point is determined for each category of risk factor (i.e. W_{ij} ; e.g. 107 for diastolic BP 105-109 mmHg, and 0 or “none” for dichotomized variables). Then a base value is determined for each risk factor and allocated 0 points (W_{iREF} , $i = 1, \dots, 4$). Less healthy risk factor states are assigned positive points so that a higher point total conveys more risk. Then it is determined how far each category is from the base value in terms of regression units (calculate $\beta_i(W_{ij} - W_{iREF})$ for each risk factor). The constant is based on the number of regression units that correspond to one point. In this study $\beta = .078$, which is equivalent to a 5mmHg increase in diastolic BP). Points associated with each category of each risk factor are computed by: $points_{ij} = \beta_i(W_{ij} - W_{iREF})/B$. The points are rounded to the nearest integer.



e-Fig 1. A flow chart of participant eligibility throughout the 3C Dijon MRI study.

e-Table 1. Univariate analyses and odds for white matter lesions based on baseline characteristics in the 3C-Dijon MRI cohort (n = 1714)

Variable	β	OR	95% CI	p	AUC
Age (per 1 year increase)	0.04	1.04	1.01-1.07	0.0046	0.547
Married	Reference	-	-	-	-
Not married	0.10	1.10	0.88-1.38	0.3935	0.512
Education, bachelor degree	Ref	Ref	-	-	-
Other degree	-0.10	0.91	0.72-1.14	0.398	0.511
Smoking, no	Reference	-	-	-	-
Ex-smoker	0.06	1.06	0.83-1.34	0.648	0.515
Current smoker	0.34	1.40	0.89-2.21	0.143	-
BMI < 25 kg/m ²	Reference	-	-	-	-
BMI 25 - 30 kg/m ²	0.10	1.11	0.88-1.40	0.388	0.517
BMI > 30 kg/m ²	0.18	1.20	0.84-1.70	0.320	-
Systolic BP mmHg	0.00	1.00	1.00-1.01	0.055	0.536
Diastolic BP mmHg	0.01	1.02	1.01-1.03	0.0022	0.549
Antihypertensive drug use	0.55	1.73	1.38-2.15	<0.0001	0.567
Cardiovascular disease	0.32	1.37	0.82-2.30	0.228	0.507
Myocardial infarction	0.25	1.28	0.71-2.32	0.42	0.504
Diabetes (self-report)	0.41	1.51	1.01-2.25	0.0438	0.514
Normal FPG	Reference	-	-	-	-
FPG elevated 6.1-7.1 mmol/l	0.24	1.27	0.67-2.38	0.4616	0.519
FPG \geq 7.2 mmol/l	0.41	1.50	1.03-2.18	0.0332	-

Hypercholesterolemia (self-report)	0.15	1.17	0.93-1.46	0.1794	0.518
Total cholesterol 6.2 mmol/l	0.01	1.01	0.81-1.26	0.9371	0.501
Total cholesterol 7.25 mmol/l	0.13	1.14	0.91-1.43	0.2537	0.516
LDL cholesterol mmol/l	-0.01	0.99	0.86-1.13	0.8608	0.505
HDL cholesterol mmol/l	-0.12	0.89	0.67-1.17	0.4001	0.518
Psychotropic drug use (past month)	0.38	1.46	1.14-1.87	0.0029	0.535
Depressive symptoms on CES-D	0.30	1.36	0.99-1.85	0.0563	0.518
Depression (lifetime)	-0.04	0.96	0.73-1.26	0.753	0.504
MMSE score	-0.08	0.92	0.87-0.98	0.0052	0.536
Benton score	-0.06	0.94	0.89-1.00	0.0326	0.528
Dependence in IADL (Lawton-Brody scale)	0.65	1.91	1.17-3.13	0.0097	0.515
Problems with balance when walking	0.38	1.47	1.13-1.91	0.0045	0.532
Forgetfulness	0.24	1.27	1.02-1.59	0.0315	0.530
Difficulties retaining new simple information	0.28	1.33	1.06-1.66	0.0129	0.534
Difficulties remembering old memories	-0.19	0.82	0.57-1.20	0.3076	0.509
Difficulties with calculations	0.46	1.58	1.19-2.09	0.0014	0.533
Difficulties with language or comprehension	0.15	1.17	0.92-1.47	0.1954	0.517
Difficulties with spatial orientation (e.g. in a city street)	0.03	1.03	0.71-1.52	0.8792	0.501

AUC, area under the curve; BMI, body mass index; BP, blood pressure; CES-D, Center for Epidemiological Studies Depression Scale; CI, confidence interval; FPG, fasting plasma glucose; HDL, high density lipoprotein; IADL, independent activities of daily living; LDL, low density lipoprotein; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging, OR, odds ratio

e-Table 2. The degree of white matter lesions for each level of the derived score and the associated sensitivity, specificity and Youden Index

SCOR E	None to low WML		Extensive WML		Sensitivit y	Specificit y	Youde n Index
	Cumulati ve N	Cumulati ve %	Cumulati ve N	Cumulati ve %			
0	88	6.84	17	3.98	100.00	0	0
1	241	18.73	42	9.83	96.02	6.84	2.86
2	356	27.67	64	14.98	90.16	18.73	8.89
3	484	37.62	97	22.71	85.01	27.66	12.67
4	583	45.31	123	28.8	77.28	37.61	14.89
5	644	50.05	143	33.48	71.19	45.30	16.49
6	695	54.01	155	36.29	66.51	50.04	16.55
7	780	60.61	190	44.49	63.70	54.00	17.70
8	864	67.14	222	51.98	55.50	60.61	16.11
9	942	73.2	256	59.94	48.01	67.13	15.14
10	1033	80.27	293	68.61	40.05	73.19	13.24
11	1103	85.71	324	75.87	31.38	80.26	11.64
12	1166	90.61	349	81.72	24.12	85.70	9.82
13	1205	93.64	373	87.34	18.27	90.60	8.87
14	1235	95.97	390	91.32	12.64	93.63	6.27
15	1249	97.06	399	93.43	8.67	95.96	4.63
16	1260	97.91	409	95.77	6.56	97.05	3.61

17	1266	98.38	411	96.24	4.22	97.90	2.12
18	1273	98.92	414	96.94	3.75	98.37	2.12
19	1279	99.39	416	97.41	3.04	98.91	1.95
20	1280	99.47	419	98.11	2.58	99.38	1.95
21	1284	99.78	420	98.34	1.87	99.46	1.33
22	1285	99.86	422	98.81	1.64	99.77	1.41
23	1286	99.94	423	99.04	1.17	99.84	1.01
24	1287	100.00	425	99.51	0.94	99.92	0.86
25	1287	100.00	426	99.74	0.47	100.00	0.47
26	1287	100.00	426	99.74	0.23	100.00	0.23
27	1287	100.00	426	99.74	0.23	100.00	0.23
28	1287	100.00	426	99.74	0.23	100.00	0.23
29	1287	100.00	427	100.00	0.23	100.00	0.23

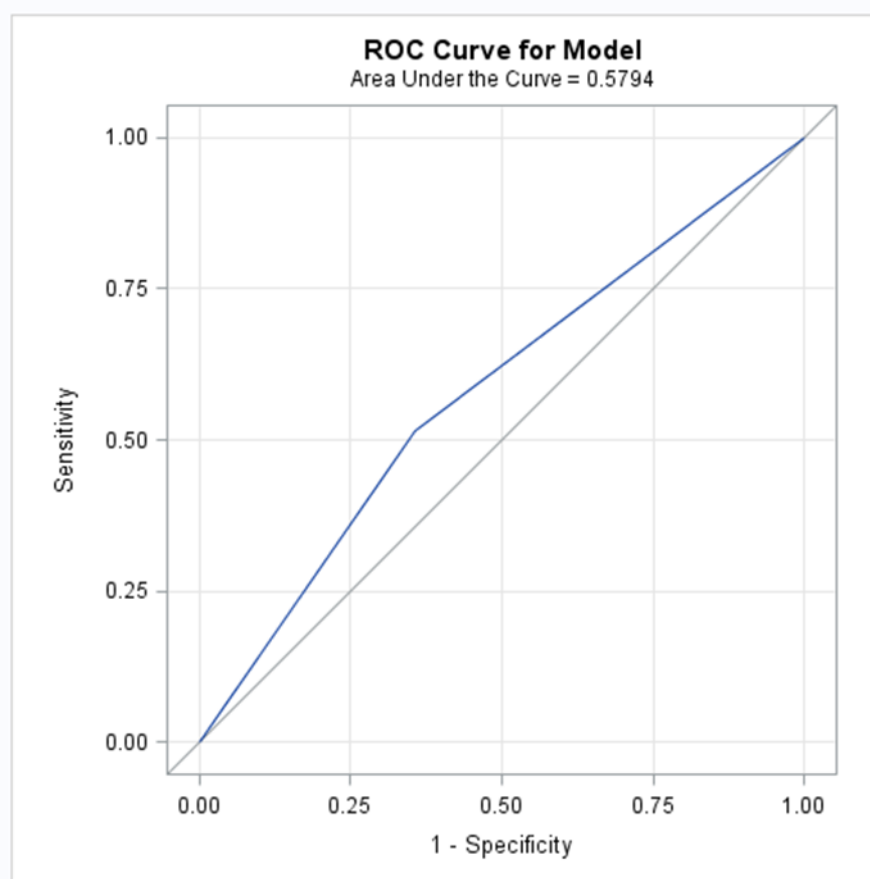
Table of the derived score to detect extensive white matter lesions. The score is based on a point system derived from the regression coefficients for diastolic BP, antihypertensive drug use, psychotropic drug use, dependence in IADL, forgetfulness and calculation difficulties. The dichotomization of white matter lesions was based sex-specific upper quartiles (male = 6.03 cm³ and female = 4.91 cm³).

e-Table 3. Table showing the distribution and proportion of predictive variables in the derivation and validation datasets

	3C Dijon MRI		EVA	
	derivation, N = 1714		validation set, N = 789	
	N	%¹	N	%¹
Median age, IQR	72	69 - 76	69	67 - 71
Female	1042	60.8	460	58.3
Male	672	39.2	327	41.4
Mean DBP, SD	84.5	9.0	77.1	10.6
Antihypertensive drug use	730	42.6	245	31.0
Psychotropic drug use	399	23.3	48	6.1
Dependence in at least 1 IADL	71	4.1	32	4.0
Forgetfulness	849	49.5	387	49
Difficulties with simple arithmetic calculations	275	16.1	126	16.0

DBP, diastolic blood pressure; EVA, Epidemiology of Vascular Aging Study; IADL, independent activities of daily living; IQR, interquartile range; MRI, magnetic resonance imaging; SD, standard deviation;

e-Fig 2. Graph showing the area under the curve for the clinical risk score to predict white matter lesions in the EVA cohort (n = 789)



Supplemental references for the study and other online resources.

- [1] Brindel P, Hanon O, Dartigues JF, Ritchie K, Lacombe JM, Ducimetiere P, et al. Prevalence, awareness, treatment, and control of hypertension in the elderly: the Three City study. *Journal of hypertension*. 2006;24(1):51-8.
- [2] Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *App Psychol Meas*. 1977;1:385-401.
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- [4] Lawton MP, Brody EM. Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living. *The Gerontologist*. 1969;9(3 Part 1):179-86.
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