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Development and validation of a priori risk model for extensive white matter lesions in people age 65 years or older: the Dijon MRI study

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ABSTRACT

Objectives The objective was to develop and validate a risk model for the likelihood of extensive white matter lesions (extWML) to inform clinicians on whether to proceed with or forgo diagnostic MRI.

Design Population-based cohort study and multivariable prediction model.

Setting Two representative samples from France.

Participants Persons aged 60–80 years without dementia or stroke. Derivation sample n=1714; validation sample n=789.

Primary and secondary outcome measures Volume of extWML (log cm^3) was obtained from T2-weighted images in a 1.5 T scanner. 20 candidate risk factors for extWML were evaluated with the C-statistic. Secondary outcomes in validation included incident stroke over 12 years follow-up.

Results The multivariable prediction model included six clinical risk factors (C-statistic=0.61). A cut-off of 7 points on the multivariable prediction model yielded the optimum balance in sensitivity 63.7% and specificity 54.0% and the negative predictive value was high (81.8%), but the positive predictive value was low (31.5%). In further validation, incident stroke risk was associated with continuous scores on the multivariable prediction model (HR 1.02; 95% CI 1.01 to 1.04, P=0.02) and dichotomised scores from the multivariable prediction model (HR 1.28; 95% CI 1.02 to 1.60, P=0.03).

Conclusions A simple clinical risk equation for WML constituted by six variables can inform decisions whether to proceed with or forgo brain MRI. The high-negative predictive value demonstrates potential to reduce unnecessary MRI in the population aged 60–80 years.

Strengths and limitations of this study

► The study strengths include the representative population undergoing brain MRI, adherence to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement, examination of an exhaustive list of potential covariates and replication in an independent validation cohort.
► Limitations include the use of 1.5 T MRI which is superseded by newer generation 3 T MRI machines.
► In the absence of an accepted empirical definition, the dichotomised threshold for extensive white matter lesions may have led to biases in the risk model development.
► The scoring system alone cannot inform the vascular aetiology of dementia nor does it replace the need for brain imaging.
► Because of limited sample size and lack of precise dementia diagnosis in the Epidemiology of Vascular Ageing study, it was not possible to take dementia heterogeneity into account.

INTRODUCTION

White matter lesions (WML) are frequently observed on brain MRI in the elderly including those without overt neurological symptoms. Extensive WML (extWML) pose as a clinical risk factor for stroke,[1 2] depressive symptoms,[3] cognitive impairment[4] and progression to dementia.[3 5 6] Intensive management of cardiovascular risk factors by primary care clinicians could mitigate further risk for cerebrovascular events and neurocognitive disorders among persons with extWML. Specifically, identifying extWML in patients with long-standing high blood pressure (BP) can guide more aggressive BP lowering targets suggested in the PROGRESS trial.[7] Although the pathophysiology is incompletely understood, WML are considered to partly reflect ischaemic small-vessel disease and hypoperfusion. WML association with vascular factors, especially hypertension, is commonly reported.[8 9] High WML load has also been associated with many and sometimes conflicting risk factors.[1 10–13] Given the breadth in possible risk factors, a challenge facing primary care clinicians is estimating the likelihood of cerebral small-vessel disease based on clinical factors alone when there is no neurological manifestation to warrant neuroimaging for dementia.[14]

Cerebral MRI is more sensitive to detect WML than CT[15]; however, it is unrealistic to perform MRI on a large number of older patients without overt clinical indications such as focal neurological symptoms.[16] Moreover, access to and usage of MRI technology can be affected by factors such as rural location, patient health insurance, MRI contraindications and the preference for cheaper neuroimaging techniques.[17 18] Predictive clinical risk scores for brain imaging are therefore of major interest to improve clinical decision-making and patient outcomes, balancing overuse and underuse of imaging. Cerebral imaging risk scores have guided the use of CT for intracranial haematoma after minor head injuries.[19 20] No risk scores exist for extWML to stratify patients least likely to benefit from MRI, which could offer some guidance to general practitioners or at the population level of two-stage screening. Identifying a high likelihood of extWML would inform primary care management[21] and reinforce patient adherence to modifiable vascular risk factors.[22] The objective of this study is therefore to develop a predictive risk score for extWML which could inform clinical decisions in primary care on whether to proceed with or forgo cerebral MRI.

MATERIALS AND METHODS
Study design and sampling
This study complies with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement.[23] Data used for this study was obtained from the Three-City study (3C). The 3C study is a French multisite prospective cohort study investigating the determinants of dementia, coronary heart disease and stroke.[24] Commencing from 1999 to 2001, the recruitment of a French population sample was sought for individuals who were 65 years or older at baseline, registered in the electoral rolls in the Dijon, Bordeaux and Montpelier catchment area, and able to provide written informed consent. Briefly, 9294 non-institutionalised community-dwelling adults aged ≥65 years were recruited and underwent extensive baseline examinations. Serial clinic visits were scheduled at approximately 2, 4, 7 and 10 years follow-up to assess cognitive function, depression, incident neurological diseases and comorbidities. Incident stroke and dementia was assessed in the greater 3C cohort of persons free from dementia and stroke at baseline (n=8023).

The development of the extWML score was obtained from a subsample of participants from the city of Dijon who underwent brain MRI and the MRI parameters are described elsewhere.[25] Briefly, the 3C-Dijon MRI study is a prospective cohort designed to study the relationship between vascular risk factors and diseases and the risk of dementia. The current analyses of extWML concern only the individuals who were eligible for MRI, aged less than 80 years and were free from dementia or stroke. The cohort included a mix of persons with mild cognitive impairment and cognitively intact older persons.

The study protocol has been approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre.

Cross validation of the model was conducted on an independent sample of participants from the Epidemiology of Vascular Ageing (EVA) study.[12] The cohort commenced in 1991 and was designed to investigate the risk factors for the decline in cognitive performance and the factors of progression of carotid atherosclerosis.[12] At inclusion, 1389 participants were recruited among elderly persons aged 60–70 years listed on the electoral rolls of the city of Nantes, France. A cerebral examination during the second wave of follow-up was conducted for 789 participants to assess WML. At the second wave of follow-up, candidate risk factors for WML were recorded.

MRI examination
The parameters of the MRI examination in 3C have been reported previously.[24] Briefly, all brain scans were acquired using the same MRI machine (1.5 T; Siemens, Erlangen) and the same standardised image acquisition protocol. Positioning in the magnet was based on a common landmark for all participants—the orbitomeatal line—so that the entire brain, including cerebellum and midbrain, was contained within the field of view of acquisition. First, a three-dimensional (3D) high-resolution T1-weighted brain volume was acquired using a 3D inversion recovery fast spoiled gradient echo sequence (3D SPGR; TR: 9.7 ms; TE: 4 ms; TI: 600 ms; coronal acquisition). The axially reoriented 3D volume matrix size was $256 \times 192 \times 256$, with a voxel size of $1.0 \times 0.98 \times 0.98 \, mm^3$. Second, T2-weighted brain volumes were acquired using the same 2D fast spin-echo sequence with two echo times (TR: 4400 ms; TE1: 16 ms; TE2: 98 ms). T2 acquisition consisted of 35, 3.5 mm thick axial slices (with 0.5 mm spacing between slices), having a matrix size of 256×256, and an in-plane resolution of $0.98 \times 0.98 \, mm^2$. T1 and T2 datasets were readily reconstructed, and visually checked for major artefacts before further analysis. Raw data were converted to the ACR-NEMA standard format and then transformed for analysis and storage at the Department of Neurofunctional Imaging, Caen.

Primary outcome variable: extWML
Fully automatic image processing software was developed to detect, measure and localise white matter hyperintensity signals.[26] With regards to location, WML located close to the ventricular system (10 mm distance to the ventricles) were classified as periventricular. WML at a distance greater or equal to 10 mm to the ventricle were classified as deep. WML load was expressed as the total volume of WML normalised by the volume of the WM mask, which accounts both for head size and for the T2 image acquisition actual field-of-view. During development of the standardised quantification of WMLs, the automated WML software was compared and validated against a neurologist visual rating[26] (blinded to covariates) in a subset of patients from 3C and EVA. This validation step used a modified version of the Scheltens scale[27] which provides
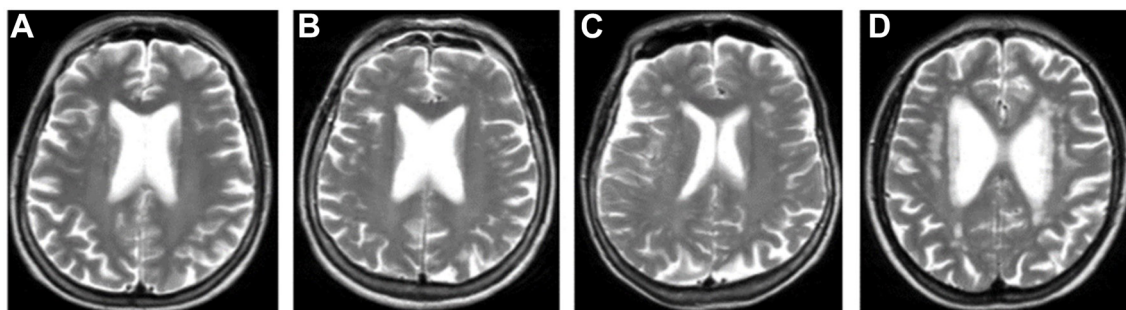
Figure 1 Four T2-weighted MRI images showing the extent of white matter lesions (WML) in each quartile of total WML volume. The T2-weighted MRI images show four separate individuals by total WML volume, (A) first quartile of WML volume (0–25th percentile), (B) second quartile of WML volume (26–50th percentile), (C) third quartile of WML volume (51–75th percentile), (D) fourth quartile of WML volume (76–100th percentile) and group denoted as having extensive WML in the logistic models. Light grey=white matter; dark grey=grey matter.

an overall WMH grade; none, mild, moderate, severe. Figure 1 displays T2-weighted MRI images depicting each quartile of WML.

The primary outcome variable was based on WML volume greater than or equal to the upper quartile that we considered generally representative of extWML load and ensured sufficient statistical power in each class. The WML was defined as a binary variable; 0=normal to low WML load (below sex-specific upper quartile) and 1=extWML (equal or above sex-specific upper quartile; men ($7.39\,cm^3$), women ($5.73\,cm^3$). Age strata were: <70, ≥70 and <75, ≥75 years.[28]

Secondary outcome: incident stroke

The protocol and criteria used to define prevalent and incident stroke have been previously defined.[29] In Bordeaux and Montpellier, all subjects underwent a comprehensive neuropsychological examination and were seen by a senior neurologist. Subjects were followed up to 12 years for incident stroke (fatal and non-fatal). For persons who reported the occurrence of vascular events during follow-up, further medical data were obtained from general practitioners, specialists and hospital records. The diagnosis and classification of strokes were made by a blinded expert panel that reviewed all existing medical information including, where available, cerebral imaging. Strokes subtypes included ischaemic and haemorrhagic strokes according to International Classification of Diseases 10th revision criteria.[30]

Statistical methods

Potential predictors of extWML were selected based on published literature and study findings of 3C.[1 10–13] Other data definitions and additional statistical analyses are listed in the online supplementary file. The risk factors tested included: age (per 1-year increase), marital status (married (reference), not married, separated or widowed), education (bachelor degree (reference), no or other education), tobacco smoking status (none (reference), former, current), body mass index

<$25\,kg/m^2$ (reference), $25–30\,kg/m^2$, $30\,kg/m^2$),

systolic BP in mm Hg, diastolic BP in mm Hg, antihypertensive drug use for hypertension, cardiovascular disease, acute coronary event (myocardial infarction), diabetes (self-report), fasting plasma glucose, ≤6 mmol/L (reference), 6.1–7.1 mmol/L, ≥7.2 mmol/L), hypercholesterolaemia (self-report), total cholesterol (≤6.1 mmol/L (reference), 7.25 mmol/L), low-density lipoprotein cholesterol (mmol/L), high-density lipoprotein cholesterol (mmol/L), psychotropic drug use in the past month, depressive symptoms (total Center for Epidemiologi Studies Depression Scale score ≥16), history of lifetime major depression (MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW diagnosis), Mini- Mental State Examination (MMSE) score, Benton Visual Retention Test score, dependence in instrumental activities of daily living (IADL) (Lawton-Brody Scale), problems with balance when walking (self-report), forgetfulness, (self-report), difficulties retaining new simple information (self-report), difficulties remembering old memories (self-report), difficulties with arithmetic calculations (self-report), difficulties with language or comprehension (self-report), difficulties with spatial orientation (eg, in a city street).

Candidate predictors with a probabilistic likelihood of extWML P<0.25 were retained for further multivariate analyses. Participant age at baseline was forced into the initial multivariate model since age is strongly associated with WML.[31] Thereafter age was eligible for elimination from the model. The optimal model for classifying extWML was computed with backward elimination to remove covariates not significantly associated with extWML at P<0.05 level.

The probabilistic model was evaluated based on overall performance, discriminatory power and calibration. Concordance was evaluated through the construction of a receiver operating characteristics curve and the C-statistic. Somer's D provides an estimate of the difference between concordant and discordant pairs on a scale of −1 to 0, in our case between the predictive model and the MRI quantification of extWML. Model fit and calibration was tested with the Hosmer and Lemeshow test

(P>0.05 implies a good fit, higher numbers signify a better fit). In the derivation cohort, missing data were handled with listwise deletion. Power calculation showed that a sample size of 1542 in the derivation cohort would provide 80% power to detect an OR of 1.35 (two-sided) with multiple candidate risk factors.

Deriving the prediction score
Each predictor in the probabilistic model was converted to a point allocation system based on the methods outlined by Sullivan *et al*,[32] described in the online supplementary file 1. In brain imaging studies, the potential for discrimination with sensitivity and specificity is weighted equally given the prevalence of the disease state, the costs of diagnostic errors and likely benefit derived to the patient.[33] The Youden index was used to calculate the optimum cut-point for the score and its associated likelihood ratios (LR^+, LR^-), positive predictive value (PPV) and negative predictive value (NPV). A bootstrapping method was used to examine the variability of the C-statistic and optimism bias or overfitting to a specific sample using randomly generated samples (n=1714, 17 140 and 171 400, respectively).

Cross validation
Although the sample size is large for a brain imaging study, it is relatively small for risk model testing. Therefore, cross validation was performed in the independent EVA cohort using the scoring system from the derivation cohort. In EVA, participants with missing data were randomly allocated based on the proportions in 3C.

Other validation
We tested whether the extWML model derived from baseline variables was associated with incident stroke events because of the close relationship between WML and brain outcomes. These analyses used the entire 3C cohort of individuals without prevalent stroke at baseline,[29] irrespective of whether participants underwent MRI. Incident stroke risk was analysed with Cox proportional hazard models showing the HR and 95% CI. The highest attained age was used as the time scale and participants were censored at the date of stroke, drop-out from the study or death. Analyses were adjusted for late entry bias.

RESULTS
Population characteristics
The final sample in the derivation cohort includes 1714 participants from the 3C-Dijon MRI online supplementary e-figure 1. The sample was comprised 60.8% women and the median age was 72 years (IQR 69–76), 59.1% of subjects were married and 32.3% had completed at least bachelor's level education (table 1).

White matter lesions
In the total sample, the median WML volume was 4.01 cm^3 (IQR 2.75–6.37). The WML volume differed by localisation and the median deep white matter hyperintensities

volume was 1.16 cm^3 (IQR 0.75–1.79). By contrast, in the periventricular region WML median volume was 2.77 cm^3 (IQR 1.82–4.65). The threshold to define extWML based on the global volume of WML by highest quartile and stratified by sex was; >6.03 cm^3 for men and 4.91 cm^3 for women. At this threshold of WML, the proportion of persons within each category was 168/677 men, 260/1042 women, total 428/1719.

Univariate analyses of extWML
The univariate analysis of variables and extWML are reported in the online supplementary e-table 1. Variables significantly associated with extWML P<0.05 included age, diastolic BP, antihypertensive drug use, psychotropic drug use, diabetes (self-reported), higher MMSE score, Benton Visual Retention Test score, dependence in IADL, calculation difficulties, forgetfulness, difficulties retaining new information and gait imbalance. Other candidate variables at P<0.25 included systolic BP, hypercholesterolaemia (self-reported), depressive symptoms on the CES-D and difficulties with language comprehension.

Multivariate analyses of extWML
The final backward deletion model from multivariate analysis predicting extWML is presented in table 2. The cardiovascular covariates associated with increased extWML risk were diastolic BP and antihypertensive drug use. Other factors that emerged in the model to increase risk for extWML were psychotropic drug use, dependence in IADL, forgetfulness and calculation difficulties. The Hosmer and Lemeshow test suggested an adequate model (P=0.88) and the diagnostic accuracy was in the modest range (C=0.63). The percentage of concordant and discordant pairs was high (62.8% vs 37.1%) with a small relationship between the predictive model and extWML (Somer's D=0.26).

Derivation of the scoring equation
Table 3 depicts the point system to predict the likelihood of extWML before MRI. extWML were predicted by six clinical risk factors: diastolic BP, psychotropic drug use, antihypertensive drug use, dependence in at least one IADL, forgetfulness and difficulties with simple arithmetic calculations. The minimum and maximum scores in the 3C-Dijon MRI population were –0 and 30, respectively, (median=7, IQR 3–10). The Hosmer and Lemeshow test suggested an adequate model (P=0.97). The C-statistic=0.61 (figure 2) suggested a limited loss of predictive ability with total scores versus the raw data. A priori risk for extWML by each level of score is presented in table 4 to help determine whether to perform or forgo brain MRI to detect WMH.

A score of 7 points on the point scoring system corresponded to the optimal Youden index with sensitivity=63.7%, specificity 54.0%. At this score the corresponding LR^+=1.38, LR^-=0.67, PPV=31.5% and NPV=81.8% for the given prevalence and threshold of extWML in our sample. Onlile supplementary e-table 2 describes the

Table 1 Population characteristics at baseline in the 3C-Dijon MRI cohort (N=1714)

Variable	n	%
Female	1042	60.8
Male	672	39.2
Median age in years, IQR	72	69–76
Married	1013	59.1
Not married	700	40.8
Bachelor degree	553	32.3
Other education	1159	67.6
BMI <25 kg/m²	841	49.0
BMI 25–30 kg/m²	677	39.5
BMI >30 kg/m²	195	11.4
Median systolic BP mm Hg, IQR	149.5	133–162.5
Median diastolic BP mm Hg, IQR	84.5	77–92
Antihypertensive drug use	730	42.6
Cardiovascular disease	71	4.1
FPG ≥7.0 mmol/L	140	8.2
Median LDL cholesterol mmol/L, IQR	3.53	2.99–4.06
Median HDL cholesterol mmol/L, IQR	1.61	1.37–1.90
Current tobacco smoker	97	5.7
Former tobacco smoker	559	32.6
Alcohol use (standard drinks per week), IQR	7	1–14
Psychotropic drug use	399	23.3
Depression symptoms	221	12.9
Median MMSE score, IQR	28	27–29
Median Benton score, IQR	12	11–13
Total autonomy (living independently)	1628	95.0
Dependence for at least one instrumental activity of daily living	71	4.1
Gait imbalance	332	19.4
Forgetfulness	849	49.5
Difficulties retaining new simple information	681	39.7
Difficulties with simple arithmetic calculations	275	16.1
Difficulties with language or comprehension	1097	64.0
MRI parameters		
Median no of WML, IQR	155	120–197
Median WML volume cm³, IQR	4.01	2.75–6.37
Median no of deep WML, IQR	57	42–81
Median deep WML volume cm³, IQR	1.16	0.75–1.79
Median no of periventricular WML, IQR	95	74–121

Continued

Table 1 Continued

Variable	n	%
Median periventricular WML volume cm³, IQR	2.77	1.82–4.65

BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MMSE, Mini-Mental State Examination; WML, white matter lesions.

cumulative percent of participants with extWML at each level of the clinical score and the sensitivity and specificity values for reference purposes. Using a dichotomised score of 7 points only marginally reduced the C-statistic (C=0.59, figure 3), however, the percentage of concordant and discordant pairs was low (34.4% vs 16.7%) with many tied pairs (48.9%), resulting in lower Somer's D=0.18. Internal validation with bootstrapping showed that the C-statistics varied minimally, between 0.57 and 0.59.

Because of the possibility that observed difficulties with IADL might lead to geriatrician referral and brain imaging later during the course of neurological disorders, we performed a sensitivity analysis by excluding IADL from the scoring system. The AUC value was marginally lower than the continuous score in model development (C=0.61).

Cross validation
Descriptive variables used in the prediction equation in the 3C and EVA cohort are shown in online supplementary e-table 3. Cross validation in the EVA cohort showed a much smaller range in scores, from 0 to 20 points with a median of 1 (IQR 0–7). Reproducing the scoring system in the EVA cohort and using the dichotomised cut-point of 7 points obtained a very similar predictive value (C-statistic=0.57) suggesting high stability and reproducibility in an independent cohort online supplementary e-figure 2

Other validation
Data were available for 8023 persons and 342 incident strokes in the larger cohort of 3C, incorporating Monpellier and Bordeaux participants as well as Dijon. The scoring system was predictive of incident stroke risk over 12 years using continuous (HR 1.02; 95% CI 1.01 to 1.04, P=0.02) and dichotomised values (HR 1.28; 95% CI 1.02 to 1.60, P=0.03).

DISCUSSION
Six clinical factors significantly predicted extWML detected on MRI based on sex-specific quartiles in a large population-based study of dementia-free older adults. These factors were diastolic BP, antihypertensive drug use, psychotropic drug use, dependence in IADL, forgetfulness and arithmetic difficulties. Conversion of these clinical variables into the scoring system produced modest predictive abilities for detection of extWML (C-statistic=0.57–63) but high NPV (82%). However,

Table 2 Multivariate analyses and the ORs for extensive white matter lesions (extWML) detected on MRI (n=1714)

Variable	β	OR	95% CI lower	P value
Intercept	−3.0047	–	–	<0.0001
Diastolic BP (per 1 mm Hg increase)	0.0156	1.016	1.006 to 1.026	0.0018
Psychotropic drug use	0.3660	1.442	1.113 to 1.868	0.0056
Antihypertensive drug use	0.5545	1.741	1.388 to 2.185	<0.0001
Dependence in at least one IADL	0.6427	1.902	1.140 to 3.171	0.0138
Forgetfulness	0.2455	1.278	1.017 to 1.607	0.0354
Difficulties with simple arithmetic calculations	0.3942	1.483	1.108 to 1.986	0.0081

The classification of extWML was based on upper quartile stratified by sex as; >6.03 cm^3 for men and 4.91 cm^3 for women. The regression model used a backward stepwise deletion procedure for covariates using a threshold for inclusion of P<0.05.
BP, blood pressure; IADL, instrumental activities of daily living.

sensitivity and specificity values of the scoring system here (63.7% and 54.0%, respectively) are very favourable compared with the diagnostic predictive ability to detect extWML with CT as reported in a recent systematic review.[34] Cross validation in the EVA cohort provided comparable findings showing high consistency, reproducibility and test characteristic retention thereby pointing to the generalisability of the scoring system.

The final risk model here includes the cardiovascular factors diastolic BP and medication use for hypertension. Prior research corroborates an association between BP and periventricular WMLs, deep WMLs[8] and large WML load[9] supporting BP as a mechanism of arteriolar vessel damage in the cerebral white matter. In terms of predictive models, a recent study elucidated the independent contribution of BP and other cardiovascular risk factors associated with WML.[35] However, the previous study produced weighted scores from factor analysis which cannot be easily used by clinicians for risk stratification purposes. By contrast our scoring system can be readily used for determining extWML probabilities and might therefore serve to avoid unnecessary and costly MRI imaging. The high NPV underscores the clinical utility to identify persons at low risk of extWML.

Other risk factors associated with extWML here included psychotropic medication which might represent the general cerebrovascular changes evident in affective and neurological disorders.[3] It is controversial whether medications such as benzodiazepines are discrete risk factors or prodromal states preceding conversion to dementia.[36] Indeed, the definition of psychotropic drugs here was broad, incorporating antidepressants, anxiolytics and neuroleptics which might suggest an indication bias for persons with prodromal dementia symptoms. Other risk factors in the scoring system included IADLs and it was previously documented in this sample that loss of IADLs is associated with mild cognitive impairment.[37] It is also possible that some risk factors are a consequence of extWML and not a direct causative factor for white matter changes.

In terms of clinical implications, the predictive ability of the scoring system here (63.7% and 54.0%, respectively) was favourable compared with external reports of the diagnostic predictive ability to detect WML with CT in a pooled review of 11 non-autopsy studies (CT sensitivity=71%, specificity=55%).[34] These encouraging findings suggest minimal loss of sensitivity and no loss of specificity using the scoring system versus CT.[34] The scoring system therefore has potential to deliver large cost savings in reducing unnecessary cerebral imaging for the detection of extWML as evident in the high NPV. Also, testament to the clinical utility of the scoring system, bootstrapping and cross validation in the EVA sample indicated high reproducibility and stability consistent with the derivation cohort. Thus the current findings will provide clinical utility as to whether clinicians should perform or forgo an MRI to detect extWML.

The study is presented with several strengths, including the large representative population size undergoing brain MRI, adherence to the TRIPOD statement,[23] examination of an exhaustive list of potential covariates and replication in an independent validation cohort. The limitations of our study include the use of 1.5 T MRI, similar to other cohorts,[38] which is superseded by newer generation 3 T MRI machines. A related point is that identification and quantification of WMH is commonly performed using parallel imaging and fluid-attenuation inversion recovery (FLAIR) sequences. As parallel imaging and FLAIR sequences were not acquired in the 3C study, the current findings may translate less readily to clinical practices or healthcare systems using such diagnostic methodologies. Moreover, in the absence of an accepted empirical definition,[39] the dichotomised threshold for extWML may have led to biases in the risk model development. However, in sensitivity analysis reducing the extWML threshold led to a loss of predictive ability. Future validation studies might therefore consider higher thresholds for extWML since our study was under powered to pursue higher thresholds. Future studies could grade WML according to moderate and

Table 3 The point scoring system based on regression coefficients to derive the likelihood of extensive white matter lesions

	Points allocated if positive
Diastolic blood pressure	
≤79 mm Hg	−1
80–84 mm Hg	0
85–89 mm Hg	+1
90–94 mm Hg	+2
95–99 mm Hg	+3
100–104 mm Hg	+4
105–109 mm Hg	+5
≥110 mm Hg	+6
Psychotropic medication use	
No psychotropic medication use	0
Yes psychotropic medication use	+5
Antihypertensive drug use	
No antihypertensive drug use	0
Yes antihypertensive drug use	+7
Dependence for ≥1 instrumental activities of daily living (IADL)	
Independent for IADL	0
Yes dependence for ≥1 IADL	+8
Forgetfulness	
No forgetfulness	0
Yes forgetfulness	+3
Difficulties with simple calculations/arithmetic	
No difficulties with simple calculations/arithmetic	0
Yes difficulties with simple calculations/arithmetic	+5

Psychotropic medication use is inclusive of antidepressants, mood stabilisers, anxiolytics and neuroleptics. Antihypertensive drugs only included taking antihypertensive drugs explicitly for hypertension. IADL were measured by the Lawton-Brody scale. Participants were asked whether they experienced forgetfulness (responses dichotomised as yes or no) and had difficulties performing simple arithmetic calculations (responses dichotomised as yes or no).

ROC Curve for Model
Area Under the Curve = 0.6118

Figure 2 Graph showing the area under the curve for the scoring system (continuous) to predict white matter lesions (WML) in the 3C-Dijon MRI study (n=1714). Graph showing the area under the curve (AUC, sensitivity and 1-specificity) for the scoring system score to detect extensive WML. The scoring system is based on a point system derived from the regression coefficients for diastolic BP, antihypertensive drug use, psychotropic drug use, dependence in instrumental activities of daily living, forgetfulness and calculation difficulties. The dichotomisation of WML was based on sex-specific upper quartiles (men=6.03 cm^3 and women=4.91 cm^3). BP, blood pressure; ROC, receiver operating characteristic .

severe categories using Fazekas criteria as used in the Leukoaraiosis and Disability in the Elderly Study.[38] Another limitation that tempers these findings is the relatively modest predictive values, sensitivity and specificity, and C-statistics. This suggests that extWML are difficult to predict and may reflect the heterogeneity in extWML risk factors. Indeed, some candidate variables such as memory difficulties may be consequences of WML rather than predictive risk factors, and our study was not designed to distinguish between such potential bi-directional associations. Given the complexity of
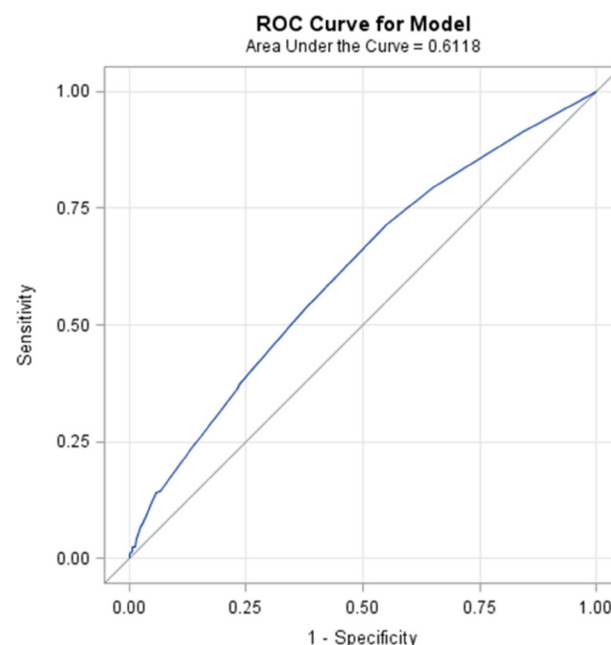
identifying risk factors for WML, the total WML load was calculated combining the periventricular and deep white matter areas whereas some risk factors are likely more specific to certain cerebral regions. However, although the scoring system did not control for location of WMLs the purpose here was to inform decisions on whether to proceed with MRI. Thus the scoring system alone cannot inform the vascular aetiology of dementia nor does it replace the need for imaging. Moreover, WML are heterogeneous and therefore their impact on cerebrovascular diseases and cognitive function may differ among individuals with normal ageing and those prone to dementia.[40 41] However, because of limited sample size and lack of precise diagnosis in the EVA study, it was not possible to take this heterogeneity into account. Another limitation to consider is that the backward deletion model may capitalise on chance variation within the dataset. However, the bootstrapping analysis showed consistency in the test score suggesting minimal optimism bias or overfitting to the 3C cohort. Another consideration for interpreting this model is the use of sex to derive the extWML thresholds based on previous findings of higher WML in women.[11] This may inadvertently reduce the predictive power of a risk score. Also,

Table 4 A priori risk estimates for extensive white matter lesions (extWML) based on a scoring system from six common risk factors

Score	Risk estimate	Score	Risk estimate
−1	14.1	17	40.1
0	15.1	18	42.0
1	16.1	19	43.9
2	17.2	20	45.9
3	18.4	21	47.8
4	19.6	22	49.8
5	20.8	23	51.7
6	22.1	24	53.7
7	23.5	25	55.6
8	24.9	26	57.5
9	26.4	27	59.4
10	28.0	28	61.3
11	29.6	29	63.1
12	31.2	30	64.9
13	32.9	31	66.7
14	34.7	32	68.4
15	36.5	33	70.0
16	38.3	34	71.6

A priori risk estimate for extWML before brain MRI based on the point scoring system described in table 3. The threshold for extWML was determined by the upper quartile stratified by sex as; >6.03 cm^3 for men and 4.91 cm^3 for women. The point system is further described in table 3 and is based on six clinical risk factors; diastolic blood pressure (5 mm Hg increments), psychotropic drug use, antihypertensive drug use, dependence in at least one instrumental activities of daily living, self-reported forgetfulness and self-reported difficulties with simple arithmetic calculations.

ROC Curve for Model
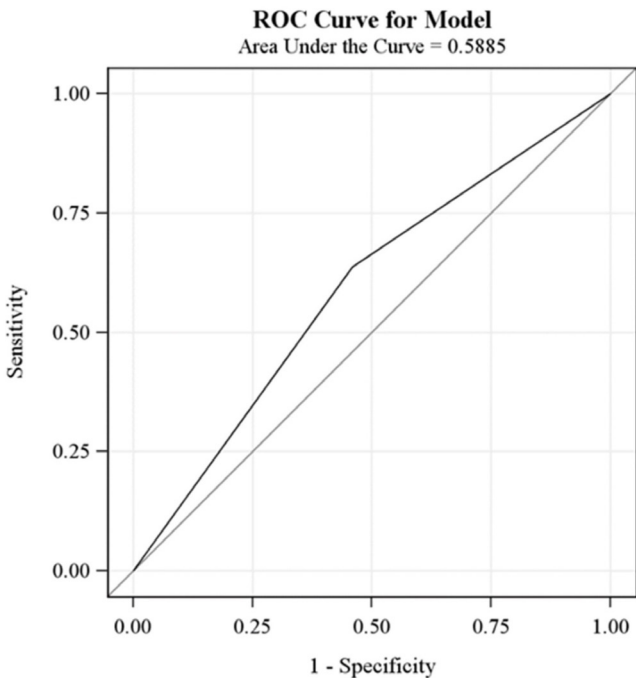Area Under the Curve = 0.5885

Figure 3 Graph showing the area under the curve for a dichotomised score of 7 to predict white matter lesions (WML) in the 3C-Dijon MRI study (n=1714). Graph showing the area under the curve (AUC, sensitivity and 1-specificity) for a dichotomised score of 7 to detect extensive WML. The scoring system is based on a point system derived from the regression coefficients for diastolic BP, antihypertensive drug use, psychotropic drug use, dependence in instrumental activities of daily living, forgetfulness and calculation difficulties. The dichotomisation of WML was based on sex-specific upper quartiles (men=6.03 cm^3 and women=4.91 cm^3). BP, blood pressure; ROC, receiver operating characteristic.

as this study reports the development stage, the predictive ability of the scoring system requires further evaluation in an external implementation study.

CONCLUSIONS

A clinical risk score comprised by six factors indicated modest predictive ability to detect sex-specific extWML. Sensitivity and specificity values of the risk score were highly favourable compared with external imaging studies quantifying WML with CT.[34] The C-statistics were stable and reproducible in bootstrapping and cross validation pointing to the generalisability of the scoring system. In elderly populations, the scoring system can inform clinical decisions on whether to proceed with or forgo cerebral MRI. The high-negative predictive value indicates that numerous costly MRIs could be avoided in the general population aged 65–80 years.

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Ethics approval University Hospital of Kremlin-Bicêtre.

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Data sharing statement The 3C Dijon MRI study data are not on open access but are accessible through a process described on the study website (http://www.three-city-study.com/the-three-city-study.php).

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