

White matter microstructure improves stroke risk prediction in the general population

Evans, Tavia E.; O'Sullivan, Michael J.; De Groot, Marius; Niessen, Wiro J.; Hofman, Albert; Krestin, Gabriel P.; Van Der Lugt, Aad; Portegies, Marileen L P; Koudstaal, Peter J.; Bos, Daniel

DOI

[10.1161/STROKEAHA.116.014651](https://doi.org/10.1161/STROKEAHA.116.014651)

Publication date

2016

Document Version

Final published version

Published in

Stroke

Citation (APA)

Evans, T. E., O'Sullivan, M. J., De Groot, M., Niessen, W. J., Hofman, A., Krestin, G. P., Van Der Lugt, A., Portegies, M. L. P., Koudstaal, P. J., Bos, D., Vernooij, M. W., & Ikram, M. A. (2016). White matter microstructure improves stroke risk prediction in the general population. *Stroke*, 47(11), 2756-2762. <https://doi.org/10.1161/STROKEAHA.116.014651>

Important note

To cite this publication, please use the final published version (if applicable). Please check the document version above.

Copyright

Other than for strictly personal use, it is not permitted to download, forward or distribute the text or part of it, without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license such as Creative Commons.

Takedown policy

Please contact us and provide details if you believe this document breaches copyrights. We will remove access to the work immediately and investigate your claim.

White Matter Microstructure Improves Stroke Risk Prediction in the General Population

Tavia E. Evans, MSc; Michael J. O'Sullivan, MD, PhD; Marius de Groot, PhD; Wiro J. Niessen, PhD; Albert Hofman, MD, PhD; Gabriel P. Krestin, MD, PhD; Aad van der Lugt, MD, PhD; Marileen L.P. Portegies, MD, PhD; Peter J. Koudstaal, MD, PhD; Daniel Bos, MD, PhD; Meike W. Vernooij, MD, PhD; M. Arfan Ikram, MD, PhD

Background and Purpose—The presence of subclinical vascular brain disease, including white matter lesions and lacunar infarcts, substantially increases the risk of clinical stroke. White matter microstructural integrity is considered an earlier, potentially better, marker of the total burden of vascular brain disease. Its association with risk of stroke, a focal event, remains unknown.

Methods—From the population-based Rotterdam Study, 4259 stroke-free participants (mean age: 63.6 years, 55.6% women) underwent brain magnetic resonance imaging, including diffusion magnetic resonance imaging, between 2006 and 2011. All participants were followed up for incident stroke until 2013. Cox proportional hazards models were used to associate markers of the microstructure of normal-appearing white matter with risk of stroke, adjusting for age, sex, white matter lesion volume, lacunar infarcts, and additionally for cardiovascular risk factors. Finally, we assessed the predictive value of white matter microstructural integrity for stroke beyond the Framingham Stroke Risk Profile.

Results—During 18476 person-years of follow-up, 58 people experienced a stroke. Both lower fractional anisotropy and higher MD increased risk of stroke, independent of age, sex, cardiovascular risk factors, white matter lesion volume, and lacunar infarcts (hazard ratio per SD increase in: fractional anisotropy: 0.75 [95% confidence interval, 0.57–0.98] and MD: 1.50 [95% confidence interval, 1.08–2.09]). MD improved stroke prediction beyond the Framingham Stroke Risk Profile (continuous net reclassification improvement: 0.52 [95% confidence interval, 0.24–0.81]).

Conclusions—Future stroke is predicted not only by prevalent vascular lesions but also by subtle alterations in the microstructure of normal-appearing white matter. Inclusion of this effect in risk prediction models produces a significant advantage in stroke prediction compared with the existing Framingham Stroke Risk Profile. (*Stroke*. 2016;47:2756–2762. DOI: 10.1161/STROKEAHA.116.014651.)

Key Words: aging ■ diffusion tensor imaging ■ prediction ■ quality of life ■ stroke

Stroke is the second leading cause of death worldwide and a major cause of severely impaired quality of life.^{1,2} During the past decade, increasing evidence has shown that the presence of markers of subclinical small vessel disease (SVD), including white matter lesions and lacunar infarcts, greatly increases the risk of subsequent stroke.^{3–6} Yet, it is important to consider that white matter lesions and lacunar infarcts already represent a relatively advanced state of subclinical vascular brain disease. Consequently, there has been an increasing emphasis on the identification of markers that represent even earlier stages of vascular brain disease. In this respect,

white matter microstructure, as assessed with diffusion tensor imaging (DTI), has received increasing interest. Changes in white matter microstructural integrity of normal-appearing white matter (NAWM) have been shown to precede irreversible white matter lesions^{7,8} and to be associated with the presence of lacunar infarcts.⁹ However, similar changes also occur in normal aging and a range of other neurological conditions, so are not specific for subclinical vascular disease. Therefore, it is unclear whether more extensive microstructural evaluation would have any role in the prediction of stroke. We hypothesize that white matter microstructural changes are associated with

Received July 5, 2016; final revision received August 18, 2016; accepted August 26, 2016.

From the Department of Epidemiology (T.E.E., M.d.G., A.H., M.L.P.P., D.B., M.W.V., M.A.I.), Department of Radiology and Nuclear Medicine (T.E.E., M.d.G., W.J.N., G.P.K., A.v.d.L., D.B., M.W.V., M.A.I.), Department of Medical Informatics (M.d.G., W.J.N.), and Department of Neurology (M.L.P.P., P.J.K., M.A.I.), Erasmus MC, Rotterdam, The Netherlands; Department of Basic and Clinical Neurosciences, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, United Kingdom (T.E.E., M.J.O.); Imaging Physics, Faculty of Applied Sciences, Delft University of Technology, The Netherlands (W.J.N.); and Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA (A.H., D.B.).

The online-only Data Supplement is available with this article at <http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.014651/-/DC1>.

Correspondence to M. Arfan Ikram, MD, PhD, Department of Epidemiology, Erasmus MC, Na 2816, PO Box 2040, 3000 CA, Rotterdam, The Netherlands. E-mail m.a.ikram@erasmusmc.nl

© 2016 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.116.014651

risk of stroke and can improve prediction models. If found, this is of great interest because it suggests that a diffuse alteration in white matter can predict the risk of a focal clinical event.

We, therefore, investigated, in the population-based setting of the Rotterdam Study, the association between markers of white matter microstructural integrity and the risk of stroke. In addition, we studied the predictive value of these markers for stroke beyond the Framingham Stroke Risk Profile.

Methods

Setting

The Rotterdam Study is a prospective population-based cohort that started in 1990 and includes 14 926 participants, aged ≥ 45 years and living in Ommoord, a suburb of Rotterdam.¹⁰ At study entry and at each follow-up visit (every 3–4 years), all study participants undergo extensive examinations at the dedicated research center. From 2005, magnetic resonance imaging (MRI) of the brain has been added to the core study protocol (the Rotterdam Scan Study).¹¹

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare, and Sport of the Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

MRI Acquisition and Automated Brain Tissue Classification

All imaging was performed on a 1.5 tesla MRI scanner with an 8-channel head coil (GE Signa Excite, General Electric Healthcare, Milwaukee, WI) and included a T1-weighted (T_{1w}), proton density-weighted, and fluid attenuation inversion recovery sequence that were used for tissue segmentation. Details of the scan parameters have been described previously.¹¹

Using an automated processing algorithm based on a k nearest neighbor classifier for tissue segmentation on the T1w and proton density-weighted scans complemented with fluid attenuation inversion recovery intensity-based white matter lesion detection, images were segmented into gray matter, cerebrospinal fluid, NAWM, and white matter lesions.^{12,13} Intracranial volume was defined as the sum of all brain tissue classes and cerebrospinal fluid.¹⁴ All segmentations were visually inspected and corrected manually when needed.¹¹

DTI Data Acquisition and Processing

A DTI sequence was also included in the scan protocol. This sequence was used for the computation of diffusion metrics that describe microstructural white matter tissue organization. We used an echo planar imaging readout with gradients ($b=1000$ s/mm²) applied in 25 directions. The number of frequency-encoding points was set to 64, with an imaging matrix of 64×96 and providing a voxel size of 3.3×2.2×3.5 mm.³¹¹ A technical issue that occurred between February 2007 and May 2008 caused 1277 of the included participants to be scanned with swapped phase and frequency-encoding direction. This resulted in a mild ghost artifact, which was covaried in the statistical analyses.

Data were processed using a standardized pipeline.¹¹ Preprocessing included correction for eddy currents and head motion, skull stripping, and tensor model fitting using nonlinear Levenberg–Marquardt estimator. DTI scans were aligned with other MR imaging data using boundary-based registration, available in the FSL toolbox.¹⁵ Tissue segmentation results for white matter lesion and NAWM were combined with diffusion maps allowing global white matter measures of microstructural integrity measures to be created for both tissue classes. For the current study, we used the following diffusion measures characterizing white matter microstructural integrity in NAWM: fractional anisotropy (FA), MD (MD), axial diffusivity, and radial diffusivity.¹⁶

Infarct Rating

Scans were visually inspected by trained research physicians for the presence of lacunar infarcts. These were defined as focal hyperintensities on T2-weighted images, ≥ 3 and < 15 mm in size, encompassing the same characteristics as cerebrospinal fluid on all sequences, the presence of a hyperintense rim on the fluid attenuation inversion recovery sequence when located supratentorially, and no involvement of cortical gray matter.

Assessment of Incident Stroke

Stroke was defined according to the WHO criteria as a syndrome of rapidly developing signs of focal or global disturbance of cerebral function, lasting > 24 hours or leading to death with no apparent cause other than that of vascular origin.¹⁷ At baseline, we assessed prevalent stroke by interview and verified these through medical records. Participants were monitored for incident stroke through ongoing automated linkage of general practitioner files with the study database.¹⁸ Additionally, those who moved out of the district or into nursing homes had medical files checked regularly for potential events. We collected hospital discharge forms and general practitioner information from potential stroke cases, which were reviewed by research physicians and an experienced neuroradiologist.¹⁸ Strokes were classified as ischemic or hemorrhagic on the basis of neuroimaging reports. If no neuroimaging was performed, a stroke was classified as unspecified. Follow-up for stroke was completed January 1, 2013 (mean; 4.33 years).

Cardiovascular Risk Factors

Information on cardiovascular risk factors and medication use was gathered through interviews and physical examinations.¹⁰ Blood pressure (mmHg) was measured twice with a random-zero sphygmomanometer at the right arm. The average of the 2 measurements was used in the analyses. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the use of blood pressure-lowering medication. Serum total cholesterol, high-density lipoprotein cholesterol, and glucose levels were measured via an automated enzymatic procedure (Boehringer Mannheim system). Hypercholesterolemia was defined as serum total cholesterol levels ≥ 6.2 mmol/L or the use of lipid-lowering medication.¹⁹ Diabetes mellitus was defined as a fasting glucose level of ≥ 7 mmol/L, or if unavailable, nonfasting glucose level of 11.1 mmol/L or the use of antidiabetic medication. Smoking was categorized as current/former or never. Body mass index was calculated as weight (kg)/height² (m), and obesity defined as a body mass index ≥ 30 . Left ventricular hypertrophy, as measured by ultrasound, was defined as present or absent via adjusted Sokolow–Lyon voltage-duration product criteria of > 322.4 uVs in women and > 367.4 uVs in men.²⁰ Prevalent coronary heart disease (defined as myocardial infarction or revascularization procedure) and atrial fibrillation at time of MRI were assessed using established standardized definitions.²¹

The mean time interval between data collection of cardiovascular risk factors and the MRI scan was 0.82 years (SD: 1.62) between 0 and 6.7 years.

Population for Analysis

A total of 4493 participants underwent MRI of the brain between 2005 and 2012. From these, we excluded 234 participants for further analyses because of prevalent stroke ($n=97$) or unusable scan data ($n=137$), leaving 4259 people for the current analyses.

Data Analysis

White matter lesion volume was natural log transformed because of its skewed distribution. The white matter diffusion measures were standardized and expressed as Z scores.

Missing cardiovascular risk factors ranged from 0.4% (both diastolic and systolic blood pressure) to 3.8% (atrial fibrillation). Missing data for cardiovascular risk factors were imputed using

multiple imputation (n=5) based on participants' other baseline factors. Pooled data of the imputed iterations were used for analysis.

Cox Proportional Models

We used Cox regression models to determine relationships of white matter diffusion measures with stroke. Although already known from previous literature, we also verified the association of white matter lesion volume and lacunar infarcts with risk of stroke. MRI markers were modeled continuously and in tertiles. Two models were fitted with incrementally increasing adjustments: in model 1, we adjusted for age, sex, NAWM volume, intracranial volume, and—where applicable—swapped phase-encoding direction, transformed white matter lesion volume, and lacunar infarcts. In model 2, we additionally adjusted for cardiovascular risk factors (use of blood pressure-lowering medication, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, use of lipid-lowering medication, diabetes mellitus, smoking, use of antithrombotic medication, body mass index, left ventricular hypertrophy, and atrial fibrillation). The distinction between models 1 and 2 has been made to avoid possible overadjustment because of cardiovascular risk factors arguably being either confounders or part of the causal pathway.

In secondary analyses, we: (1) reanalyzed all associations while adjusting for the time interval between data collection of cardiovascular risk factors and the MRI scan; (2) studied ischemic strokes separately; and (3) explored possible effect modification by stratifying for the presence of individual cardiovascular risk factors. Additionally, to verify the robustness of the models given the relatively small number of incident cases, we created a propensity score using the cardiovascular risk factors added in model 2.²²

Stroke Risk Prediction

For MRI markers that were associated with stroke risk, we assessed their predictive value for stroke during a 5-year period. As reference model to compare the results to, we used the Framingham Stroke Risk Profile.²³ This model includes age, sex, diabetes mellitus, systolic blood pressure, smoking, cardiovascular heart disease, blood pressure-lowering medication, atrial fibrillation, and left ventricular hypertrophy.²³ We examined the discriminative ability (C statistic) of the markers when added to this model.²⁴ We assessed calibration by comparing the goodness-of-fit of the observed and expected number of events within estimated decile groups.²⁵ Next, we studied the improvement in model performance. Given that there are no established risk categories for stroke, we calculated continuous net reclassification (cNRI), event and nonevent net reclassification, and the relative integrated discrimination improvement (ie, the ratio of the absolute difference in discrimination slopes of the 2 models over the discrimination slope of the reference model).^{26,27} Although difficult to interpret directly into clinical benefit, NRI for event and nonevent classification describes the percentage reclassified, correctly versus incorrectly, into higher and lower risk scores in the respective groups.

Results

Baseline characteristics of the study population (n=4259) are shown in Table 1. Mean age (SD) was 63.6 (11.0) years, and 55.6% were women. The incidence rate of stroke was 3.13 cases per 1000 person-years. During 18477 person-years of follow-up (mean follow-up [SD], 4.33 (1.43) years), 58 people (1.4%) experienced a stroke, of which 47 were ischemic and 7 hemorrhagic; 4 strokes remained unspecified.

White Matter Diffusion Measures and Risk of Stroke

We found that white matter diffusion measures were associated with a higher risk of stroke, independent of NAWM volume, intracranial volume, white matter lesion volume, the presence

Table 1. Baseline Characteristics

Sample size	4259
Age, y	63.60 (11.02)
Women	55.6 (2370)
Blood pressure-lowering medication	32.9 (1401)
Systolic blood pressure, mm Hg	138. (21.11)
Diastolic blood pressure, mm Hg	82.5 (10.82)
HDL cholesterol, mmol/L	1.4 (0.42)
Total cholesterol, mmol/L	5.6 (1.05)
Lipid-lowering medication	32.8 (1398)
Smoking (ever)	68.8 (2929)
Antithrombotic medication	16.9 (717)
Body mass index, kg/m ²	27.4 (4.11)
Left ventricular hypertrophy	6.4 (273)
Atrial fibrillation	3.4 (145)
Lacunar infarct (presence of ≥1)	6.2 (262)
White matter lesion volume, mL*	4.4 (2.45–8.91)
Fractional anisotropy	0.3 (0.02)
MD, 10 ⁻³ mm ² /s	0.7 (0.03)
Axial diffusivity, 10 ⁻³ mm ² /s	1.0 (0.03)
Radial diffusivity, 10 ⁻³ mm ² /s	0.6 (0.03)

Categorical variables are presented as percentages (numbers) and continuous variables as means (SDs). HDL indicates high-density lipoprotein.

*White matter lesion volume is presented as a median (interquartile range).

of lacunar infarcts, and cardiovascular risk factors. Specifically, lower FA and higher MD were associated with a higher risk of stroke (hazard ratio per 1-SD increase in FA: 0.75 (95% confidence interval [CI]; 0.57–0.98) and hazard ratio per 1-SD increase in MD: 1.50 (95% CI, 1.08–2.09; Table 2). Figure 1 shows the cumulative incidence curves of stroke across tertiles of white matter diffusion measures. No evidence of collinearity was observed within the variables (variance inflation factors <4). We also confirmed that larger volume of white matter lesions and presence of lacunar infarcts increased the risk of stroke (Table I in the [online-only Data Supplement](#)).

Figure 2 shows the risk of stroke across tertiles of white matter lesion volume and MD. Individuals in the worst tertile of white matter lesion and of MD had a hazard ratio of 10.57 (95% CI, 2.66–42.05) compared with those in the best tertile of both markers (Table II in the [online-only Data Supplement](#)).

For ischemic strokes (n=47), the associations of white matter lesion volume and lacunar infarcts with stroke risk were stronger, whereas those with white matter diffusion measures attenuated slightly (Tables III and IV in the [online-only Data Supplement](#)).

Reanalyzing all associations while adjusting for the time interval between MRI and cardiovascular risk factor assessment did not influence any of the results (data not shown). We also did not find notable effect modification of the associations by any individual cardiovascular risk factor (FA and MD shown in Figure I in the [online-only Data Supplement](#)). Furthermore, when reanalyzing model 2 with a propensity score for the cardiovascular risk factors, we found similar

Table 2. The Association Between White Matter Diffusion Measures and the Risk of Stroke

Risk of Stroke		
	Model 1, HR (95% CI)	Model 2, HR (95% CI)
Per 1-SD increase		
Fractional anisotropy	0.73 (0.56–0.96)	0.75 (0.57–0.98)
MD	1.62 (1.17–2.23)	1.50 (1.08–2.09)
Axial diffusivity	1.35 (1.10–1.66)	1.30 (1.04–1.64)
Radial diffusivity	1.56 (1.15–2.12)	1.46 (1.08–1.99)

Values represent hazard ratios with 95% CIs per SD increase in the different white matter diffusion measures. Model 1: adjusted for age, sex, intracranial volume, normal-appearing white matter volume, white matter lesion volume, lacunar infarcts, and swapped phase and frequency-encoding direction. Model 2: model 1 additionally adjusted for blood pressure–lowering medication, systolic blood pressure, diastolic blood pressure, diabetes mellitus, high-density lipoprotein cholesterol, total cholesterol, lipid-lowering medication, smoking, antithrombotic medication, body mass index, atrial fibrillation, and left ventricular hypertrophy. CI indicates confidence interval; and HR, hazard ratio.

associations (hazard ratio [95% CI] for FA, 0.72 (0.55–0.94) and for MD 1.58 (1.15–2.18).

Risk Prediction for Stroke

Addition of MD to the reference prediction model (ie, the Framingham Stroke Risk Profile) resulted in an 0.03 increase in C statistic (95% CI) from 0.78 (0.72–0.85) to 0.81 (0.76–0.87; Table 3). We did not find evidence for miscalibration in this model. The addition of white matter lesions and

lacunar infarcts to the reference model improved the C statistic with 0.04 (from 0.78–0.82), but there was evidence for miscalibration. As shown in Figure II in the [online-only Data Supplement](#), this model demonstrated good fit for the lower to medium risk profiles, yet risk was overestimated in the higher risk ranges. Importantly, addition of MD to the reference model resulted in better reclassification than addition of white matter lesions and lacunar infarcts: cNRI of 0.52 (95% CI, 0.24–0.81), with 19% correct reclassification of events versus cNRI of 0.33 (95% CI, –0.07 to 0.61), with 11% of correct reclassification of events.

Adding MD to a model including the Framingham Stroke Risk Profile and white matter lesion volume and lacunar infarcts further improved the model. The C statistic of this model was 0.82, with a cNRI of 0.23 (95% CI, 0.04–0.51), with 6% correct reclassification of events. We noted, however, that the miscalibration introduced by white matter lesions and lacunar infarcts was not eliminated by adding MD (Figure II in the [online-only Data Supplement](#)).

Discussion

In a large sample of community-dwelling middle-aged and older adults, we found that measures of white matter microstructural integrity were related to an increased risk of stroke, independent of cardiovascular risk factors and visible lesions (white matter lesions and lacunar infarcts). Moreover, we found that the addition of MD to the Framingham Stroke Risk Profile improved stroke risk prediction.

Strengths of our study include the large sample size, its population-based setting, longitudinal design, and rigorous stroke follow-up procedures that resulted in virtually complete

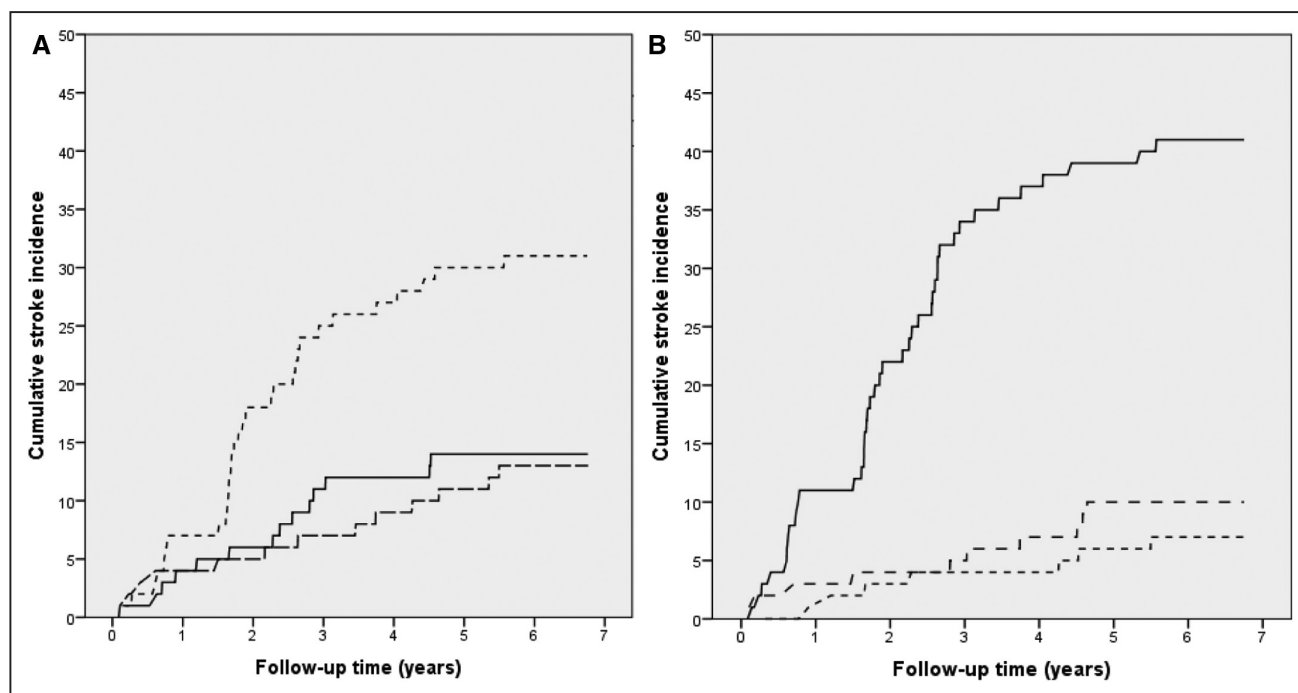


Figure 1. Cumulative incidence in 3 categories of fractional anisotropy (A) and MD (B). Measures were automatically split into tertiles using rank cases through analysis software. The boundaries were as follows: Fractional anisotropy: low (short dashed line), 0.25 to 0.33; middle (long dashed line), 0.33 to 0.34; and high (solid line), 0.34 to 0.38. MD (10^{-3} mm²/s): low (short dashed line), 0.66 to 0.72; middle (long dashed line), 0.72 to 0.75; and high (solid line),

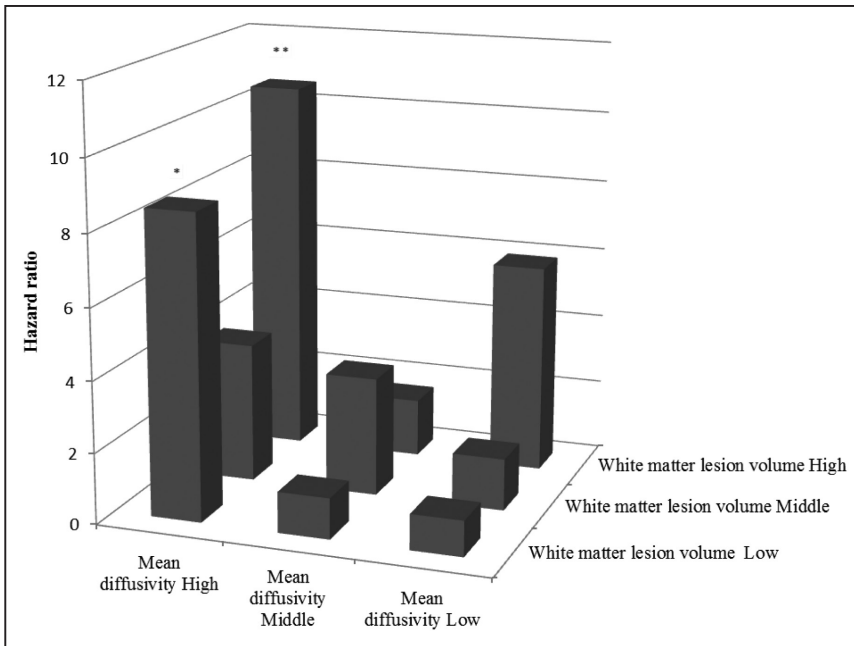


Figure 2. Hazard ratio for stroke risk within tertiles of white matter lesion volume and MD. Measures were automatically split into tertiles using rank cases through analysis software. The boundaries were as follows: MD (10^{-3} mm²/s): low, 0.66 to 0.72; middle, 0.72 to 0.75; and high, 0.75 to 0.89. White matter lesion volume (mL): low, 0.29 to 3.00; middle 3.00 to 6.64; high 6.64 to 162.80. * $P < 0.05$; ** $P < 0.01$. Bars represent hazard ratios for stroke risk in the different tertiles of white matter lesion volume and MD, compared with persons in the best tertile of both markers (low white matter lesion volume, low MD).

follow-up (98.4%). In addition, the neuroimaging approach provided measurements specific to classes of tissue, including the NAWM, thus extending the analysis beyond visually evident white matter pathology. We also assessed white matter lesions and microstructure quantitatively on a continuous scale. These are considered more accurate, objective, and reproducible measures and are more sensitive to small changes than categorical grading systems in previous studies.^{3,28}

Several potential limitations of our study should also be mentioned. First, there was a variable time interval between risk factor attainment and MRI, but adjustment for this did not affect the results. Additionally, although a higher field strength would be more sensitive, the use of a fixed protocol and scanner was necessary in this situation. Our sample source, a homogenous, middle-class population, largely of white descent, may restrict generalization. The number of cases is small compared with the large number of predictors

included in our models; therefore, some overfitting may have arisen. Furthermore, the calibration of all the models display an excellent fit in low- and middle-risk ranges; however, some misfit is seen in the high ranges. Additionally, despite experienced research physicians evaluating magnetic resonance images, misclassification of infarcts may have occurred. For example, enlarged Virchow-Robin spaces may have been misclassified as lacunar infarcts.

An important finding of the current study is that markers of white matter microstructural integrity improve 5-year prediction of stroke beyond the Framingham Stroke Risk Profile, even with the addition of white matter lesions and lacunes. This suggests that measures of microstructure not only distinguish stroke risk at a group level but also aid in identifying individuals at increased stroke risk. We note that the improvement may seem small based on the C statistic (0.03) but that the cNRI was high (52%). This suggests that

Table 3. Improvement in Stroke Prediction With the Addition of MD (Standardized), White Matter Lesion Volume (Natural Log), and Lacunar Infarcts to Prediction Models for First-Ever Stroke

	Discrimination	cNRI	Events, %	Nonevents, %	rIDI
	C Statistic (95% CI)	Overall (95% CI)			(95% CI)
Framingham Stroke Risk Profile	0.78 (0.72–0.85)	ref	ref	ref	ref
+MD	0.81 (0.76–0.87)	0.52 (0.24–0.81)	19	33	1.53 (0.87–2.43)
+White matter lesions and lacunar infarcts	0.82 (0.77–0.87)	0.33 (0.07–0.61)	11	22	0.47 (0.14–0.95)
+ MD, white matter lesions, and lacunar infarcts	0.82 (0.77–0.88)	0.35 (0.06–0.62)	8	27	0.77 (0.32–1.38)
Framingham Stroke Risk Profile, white matter lesion, and lacunar infarcts	0.82 (0.77–0.87)	ref	ref	ref	ref
+ MD	0.82 (0.77–0.88)	0.23 (0.04–0.51)	6	17	0.22 (0.02–0.45)

Models are based on 5-y risk of stroke. Models are based on the cardiovascular risk factors included in Framingham Stroke Risk Model (age, sex, diabetes mellitus, systolic blood pressure, smoking, coronary heart disease, blood pressure–lowering medication, atrial fibrillation, and left ventricular hypertrophy).²⁴ CI indicates confidence interval; cNRI, continuous net reclassification improvement; and rIDI, relative integrated discrimination improvement.

the proportion of people who would be correctly reclassified into their appropriate category is large. In recent years, characterization of white matter microstructure has emerged as a novel marker for white matter damage especially SVD. Importantly, it has been shown that SVD is already detectable with DTI, before manifesting as white matter lesions on conventional imaging.⁷ Extending this further, recent findings have indeed shown that microstructural integrity is susceptible to the same vascular risk factors as white matter lesions, that is, hypertension and smoking.²⁹ Taken together, our findings underscore the hypothesis that the true burden of SVD is not fully captured by conventional imaging (white matter lesions and lacunes), thereby emphasizing the importance of advanced MRI protocols, such as DTI. Two findings warrant additional discussion. First, in our study, adjusting for vascular risk factors did not change the results. This suggests that other processes may also be linked to loss of microstructural integrity. These may include inflammatory, metabolic, or genetic processes. Second, we found stronger effects of MD than FA. Although speculative, it has been suggested that FA is more sensitive to tract integrity and architecture. In contrast, MD is suggested to be more sensitive to extracellular fluid, which is directly linked to myelin and axonal damage. Unfortunately, the complex relationship between white matter and diffusion tensor measurements means that observed differences cannot directly be attributed to particular changes in tissue architecture.³⁰

Interestingly, loss of white matter microstructural integrity has also been studied within the realm of the disconnectivity hypothesis important in Alzheimer disease. Here too, SVD may be the underlying pathological substrate. SVD can result in damage to myelin sheath in the white matter, in turn leading to perturbation of brain networks important for information transfer and processing.³¹ Indeed, SVD is considered the shared pathology linking stroke with cognitive decline and dementia, including Alzheimer disease.³² However, more work is needed to fully understand the role of the white matter microstructure in this area of research.

Although it might be premature to think of implementing diffusion MRI in clinical practice to screen for stroke risk, some important remarks still need to be made. First, because of decreasing costs, it is a matter of time before the benefits of screening using MRI will outweigh its financial burden, especially given the fact that excellent primary prevention strategies for stroke are readily available. However, logistical and practical implications need to be assessed before this. Second, brain MRI scanning has become a core activity in many population- and clinic-based studies, but DTI is not always included, despite its ease to obtain. Our findings suggest that DTI scanning is developing from a purely research tool toward a clinically useful acquisition, and we foresee DTI being recommended in standard scanning protocol.

In conclusion, we found that a reduction of white matter microstructural integrity increases the risk of stroke, providing an interesting insight into understanding vascular disease. The addition of MD improves the 5-year prediction of stroke beyond the Framingham Stroke Risk Profile; however, the clinical use and practicality of this addition is as

yet unclear. Nevertheless, these findings highlight the importance of advanced MRI protocols in understanding the true burden of vascular brain damage.

Acknowledgments

T.E. Evans jointly conceived of the study with M.A. Ikram, participated in its design, performed the statistical analysis, interpreted the data, drafted, and critically revised the article. A. Hofman, M.A. Ikram, M.W. Vernooij, and M. de Groot participated in acquisition of the data. M.W. Vernooij and M.A. Ikram participated in the design and interpretation, helped in drafting the article, and revised it critically for important intellectual content. D. Bos participated in data analysis and interpretation and along with M.L.P. Portegies participated in drafting the article and revising it critically. M.A. Ikram, M. W. Vernooij, and M.J. O'Sullivan provided supervision. All authors read and approved the final article.

Sources of Funding

T.E. Evans is supported by a studentship from the James Black Stroke Fund, held by the King's College Hospital Charity (charity registration 230729). The King's-Erasmus collaboration is supported by the STRATEGIC study, funded by the Medical Research Council, UK (MR/K022113/1).

The Rotterdam Study is supported by the Erasmus MC and Erasmus University Rotterdam; the Netherlands Organization for Scientific Research; the Netherlands Organization for Health Research and Development; the Research Institute for Diseases in the Elderly; the Ministry of Education, Culture and Science; the Ministry of Health, Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam. This study was further financially supported by the Netherlands Organization for Scientific Research grants 948-00-010 and 918-46-615.

Disclosures

None.

References

- Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095–2128. doi: 10.1016/S0140-6736(12)61728-0.
- Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2197–2223. doi: 10.1016/S0140-6736(12)61689-4.
- Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM; Rotterdam Scan Study. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke*. 2003;34:1126–1129. doi: 10.1161/01.STR.0000068408.82115.D2.
- Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol*. 2007;6:611–619. doi: 10.1016/S1474-4422(07)70170-9.
- Buyck JF, Dufouil C, Mazoyer B, Maillard P, Ducimetière P, Alperovitch A, et al. Cerebral white matter lesions are associated with the risk of stroke but not with other vascular events: the 3-City Dijon Study. *Stroke*. 2009;40:2327–2331. doi: 10.1161/STROKEAHA.109.548222.
- Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2010;341:c3666.
- de Groot M, Verhaaren BF, de Boer R, Klein S, Hofman A, van der Lugt A, et al. Changes in normal-appearing white matter precede development of white matter lesions. *Stroke*. 2013;44:1037–1042. doi: 10.1161/STROKEAHA.112.680223.
- Maillard P, Carmichael O, Harvey D, Fletcher E, Reed B, Mungas D, et al. FLAIR and diffusion MRI signals are independent predictors of

- white matter hyperintensities. *AJNR Am J Neuroradiol*. 2013;34:54–61. doi: 10.3174/ajnr.A3146.
9. Reijmer YD, Freeze WM, Leemans A, Biessels GJ; Utrecht Vascular Cognitive Impairment Study Group. The effect of lacunar infarcts on white matter tract integrity. *Stroke*. 2013;44:2019–2021. doi: 10.1161/STROKEAHA.113.001321.
 10. Hofman A, Brusselle GG, Darwish Murad S, van Duijn CM, Franco OH, Goedegebure A, et al. The Rotterdam Study: 2016 objectives and design update. *Eur J Epidemiol*. 2015;30:661–708. doi: 10.1007/s10654-015-0082-x.
 11. Ikram MA, van der Lugt A, Niessen WJ, Koudstaal PJ, Krestin GP, Hofman A, et al. The Rotterdam Scan Study: design update 2016 and main findings. *Eur J Epidemiol*. 2015;30:1299–1315. doi: 10.1007/s10654-015-0105-7.
 12. Vrooman HA, Cocosco CA, van der Lijn F, Stokking R, Ikram MA, Vernooij MW, et al. Multi-spectral brain tissue segmentation using automatically trained k-Nearest-Neighbor classification. *Neuroimage*. 2007;37:71–81. doi: 10.1016/j.neuroimage.2007.05.018.
 13. de Boer R, Vrooman HA, van der Lijn F, Vernooij MW, Ikram MA, van der Lugt A, et al. White matter lesion extension to automatic brain tissue segmentation on MRI. *Neuroimage*. 2009;45:1151–1161. doi: 10.1016/j.neuroimage.2009.01.011.
 14. Vernooij MW, Ikram MA, Vrooman HA, Wielopolski PA, Krestin GP, Hofman A, et al. White matter microstructural integrity and cognitive function in a general elderly population. *Arch Gen Psychiatry*. 2009;66:545–553. doi: 10.1001/archgenpsychiatry.2009.5.
 15. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004;23(suppl 1):S208–S219. doi: 10.1016/j.neuroimage.2004.07.051.
 16. de Groot M, Ikram MA, Akoudad S, Krestin GP, Hofman A, van der Lugt A, et al. Tract-specific white matter degeneration in aging: the Rotterdam Study. *Alzheimers Dement*. 2015;11:321–330. doi: 10.1016/j.jalz.2014.06.011.
 17. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ*. 1976;54:541–553.
 18. Wieberdink RG, Ikram MA, Hofman A, Koudstaal PJ, Breteler MM. Trends in stroke incidence rates and stroke risk factors in Rotterdam, the Netherlands from 1990 to 2008. *Eur J Epidemiol*. 2012;27:287–295. doi: 10.1007/s10654-012-9673-y.
 19. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
 20. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J*. 1949;37:161–186.
 21. Leening MJ, Kavousi M, Heeringa J, van Rooij FJ, Verkoost-van Heemst J, Deckers JW, et al. Methods of data collection and definitions of cardiac outcomes in the Rotterdam Study. *Eur J Epidemiol*. 2012;27:173–185. doi: 10.1007/s10654-012-9668-8.
 22. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399–424. doi: 10.1080/00273171.2011.568786.
 23. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22:312–318.
 24. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med*. 2004;23:2109–2123. doi: 10.1002/sim.1802.
 25. May S, Hosmer DW. A simplified method of calculating an overall goodness-of-fit test for the Cox proportional hazards model. *Lifetime Data Anal*. 1998;4:109–120.
 26. Pencina MJ, D'Agostino RB, Pencina KM, Janssens ACJW, Greenland P. Interpreting incremental value of markers added to risk prediction models. *Am J Epidemiol*. 2012;176:473–481.
 27. Leening MJ, Vedder MM, Witteman JC, Pencina MJ, Steyerberg EW. Net reclassification improvement: computation, interpretation, and controversies: a literature review and clinician's guide. *Ann Intern Med*. 2014;160:122–131. doi: 10.7326/M13-1522.
 28. Kuller LH, Longstreth WT Jr, Arnold AM, Bernick C, Bryan RN, Beauchamp NJ Jr; Cardiovascular Health Study Collaborative Research Group. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. *Stroke*. 2004;35:1821–1825. doi: 10.1161/01.STR.0000132193.35955.69.
 29. Friedman JL, Tang CY, de Haas HJ, Changchien L, Goliasch G, Dabas P, et al. Brain imaging changes associated with risk factors for cardiovascular and cerebrovascular disease in asymptomatic patients. *JACC Cardiovasc Imaging*. 2014;7:1039–1053. doi: 10.1016/j.jcmg.2014.06.014.
 30. Jones DK, Knösche TR, Turner R. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. *Neuroimage*. 2013;73:239–254. doi: 10.1016/j.neuroimage.2012.06.081.
 31. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9:689–701. doi: 10.1016/S1474-4422(10)70104-6.
 32. Sun X, Salat D, Upchurch K, Deason R, Kowall N, Budson A; Alzheimer's Disease Neuroimaging Initiative. Destruction of white matter integrity in patients with mild cognitive impairment and Alzheimer disease. *J Invest Med*. 2014;62:927–933. doi: 10.1097/JIM.000000000000102.