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Do cerebral white matter lesions influence the rate of progression from mild cognitive impairment to dementia?

Michael E. Devine,[1] J. Andres Saez Fonseca[2] and Zuzana Walker[3]

[1] *North East London NHS Foundation Trust, Broad Street Centre, Morland Road, Dagenham, Essex RM10 9HU, UK*
[2] *Cambian Churchill, Barkham Terrace, Lambeth Road, London SE1 7PW, UK*
[3] *University College London and St Margaret's Hospital, The Plain, Epping, Essex, CM16 6TN, UK*

ABSTRACT

Background: Cerebral white matter lesions (WML), evident on CT and MRI brain scans, are histopathologically heterogeneous but associated with vascular risk factors and thought mainly to indicate ischemic damage. There has been disagreement over their clinical prognostic value in predicting conversion from mild cognitive impairment (MCI) to dementia.

Methods: We scrutinised and rated CT and MRI brain scans for degree of WML in a memory clinic cohort of 129 patients with at least 1 year of follow-up. We examined the relationship between WML severity and time until conversion to dementia for all MCI patients and for amnestic (aMCI) and non-amnestic (naMCI) subgroups separately.

Results: Five-year outcome data were available for 87 (67%) of the 129 patients. The proportion of patients converting to dementia was 25% at 1 year and 76% at 5 years. Patients with aMCI converted to dementia significantly earlier than those with naMCI. WML severity was not associated with time to conversion to dementia for either MCI patients in general or aMCI patients in particular. Among naMCI patients, there was a tendency for those with a low degree of WML to survive without dementia for longer than those with a high degree of WML. However, this was not statistically significant.

Conclusions: MCI subtype is a significant independent predictor of conversion to dementia, with aMCI patients having higher risk than naMCI for conversion throughout the 5-year follow-up period. WML severity does not influence conversion to dementia for aMCI but might accelerate progression in naMCI.

Key words: survival analysis, conversion, amnestic, non-amnestic, white matter lesions, dementia, Alzheimer's disease, cerebrovascular disease

Introduction

Cerebral white matter lesions (WML), seen as areas of high signal intensity on T_2-weighted and Fluid Attenuated Inversion Recovery (FLAIR) MRI and as areas of low attenuation on CT, are a common finding in elderly people both with dementia and without dementia, and their extent is associated with increasing age and vascular risk factors (Breteler *et al.*, 1994a; Scarpelli *et al.*, 1994; Longstreth *et al.*, 1996). Post-mortem studies have shown WML to be histopathologically heterogeneous (Scheltens *et al.*, 1995; Gouw *et al.*, 2011). They are thought mainly to be related to ischemic changes, in particular to damage to arterial branches that penetrate into the subcortical and periventricular white matter, but are not confined to those with clinical evidence of cerebrovascular disease (CVD).

White matter lesions (WML) are more widespread in mild cognitive impairment (MCI) compared to controls (van der Flier *et al.*, 2005) and even more extensive in Alzheimer's disease (AD) (Yoshita *et al.*, 2006). Correlations have also been demonstrated between severity of WML and both subjective and objective cognitive impairment in individuals having dementia and normal controls (Almkvist *et al.*, 1992; Ylikoski *et al.*, 1993; Breteler *et al.*, 1994a; 1994b; ; Longstreth *et al.*, 1996; de Groot *et al.*, 2001).

Specific cognitive deficits in MCI increase the likelihood of conversion to dementia. Amnestic MCI (aMCI) appears more likely than non-amnestic MCI (naMCI) to progress to dementia (Fischer *et al.*, 2007) and deficits in episodic memory and executive functioning predict

Correspondence should be addressed to: Dr. Michael E. Devine, Consultant in Old Age Psychiatry, North East London NHS Foundation Trust, Broad Street Centre, Morland Road, Dagenham, Essex RM10 9HU, UK. Phone: +44 (0)300 555 1200; ext. 5213; Fax: +44 (0)844 493 0285. Email: mike.devine@nelft.nhs.uk. Received 3 Feb 2012; revision requested 6 Mar 2012; revised version received 19 Apr 2012; accepted 25 Apr 2012. First published online 3 July 2012.

conversion of aMCI to AD (Fleisher *et al.*, 2007).

Debate continues over whether or not WML are predictive of conversion from MCI to dementia. Wolf *et al.* (2000) found an association between severity of CT-rated WML and probability of conversion among 27 patients with MCI. Degree of temporal lobe atrophy (TLA) was associated independently with increased likelihood of conversion, but WML severity was negatively correlated with degree of TLA among converters, raising the possibility of different pathways to conversion. Sepe-Monti *et al.* (2007) found that severity of MRI-rated WML did not correlate with probability of conversion among 21 patients with aMCI. Van Straaten *et al.* (2008) found that only periventricular WML were related to increased risk of conversion to AD among a cohort of 152 aMCI patients within a 3-year follow-up period.

We set out to establish whether WML severity was related to rate of conversion to dementia among a memory clinic cohort of 169 patients with an initial diagnosis of MCI and at least 1 year of follow up. Secondarily, we aimed to establish whether WML influenced progression differentially for aMCI compared to naMCI. We postulated that WML severity would be associated with subsequent cognitive decline and conversion to dementia, and that this relationship might be more significant in naMCI than in aMCI.

Methods

A retrospective cohort study was carried out, analyzing routinely collected data from a National Health Service (NHS) Memory Clinic in North Essex, UK, which includes both detailed demographic information and detailed cognitive scores. The primary function of this clinic is the assessment and diagnosis of patients from across the region presenting with early signs of cognitive decline. Patients receive a full physical examination and detailed neuropsychological testing using the Cambridge Cognitive Examination (CAMCOG, Roth *et al.*, 1986), which has proven to be useful in the early detection of dementia (Schmand *et al.*, 2000). The Clinical Dementia Rating (CDR, Hughes *et al.*, 1982) is completed for each patient and consensus diagnosis is reached following multidisciplinary case discussion between the psychiatrists, clinical psychologist, and clinic nurse. Patients with MCI are offered an annual review appointment in the Memory Clinic. Upon conversion to dementia, cholinesterase inhibitor medication is initiated if appropriate. In the past, patients with established dementia often remained within the Memory Clinic for follow-up but, as new referral rates have increased, these patients are now usually referred on to their respective local outpatient clinics and/or older person's community mental health service for further management and follow-up. For patients lost to Memory Clinic follow-up before conversion to dementia, we searched the NHS Trust's electronic patient record to establish subsequent outcome (whether and when converted to dementia). Clinical diagnostic criteria for dementia outside of the Memory Clinic would have been very similar to the Memory Clinic criteria, since all old-age psychiatrists within the Trust had at one time or another worked within the Memory Clinic.

The database was censored to include only those patients who had complete follow-up data for at least 1 year following their initial assessment and we aimed to obtain and examine brain scans, performed as part of routine clinical investigation, for all patients in this censored database. These scans, with only three exceptions, were carried out prior to implementation and routine use of the electronic Picture Archiving and Communication System (PACS). Therefore, for most patients, films had to be physically traced and obtained via the hospital radiology department and examined using a light box. All scans had been performed according to standard clinical protocols. CT scans were unenhanced and T_2-weighted images were available for all MRI scans, with FLAIR images also available in many cases.

White matter lesion (WML) severity was rated according to an adapted version of a scale validated for use across both CT and MRI modalities (Wahlund *et al.*, 2001), which we used in a previous study (Devine *et al.*, 2007). Every scan was rated, primarily in the axial plane, by two researchers (MED and JASF) together, and a consensus decision reached on all cases. For patients who had undergone both CT and MRI modalities, we rated the MRI scans. Raters were blind to patient identity, clinical details including MCI subtype, risk factors, and outcome. Frontal, temporal, parieto-occipital, and basal ganglia lesions were rated separately for both left and right sides of the brain, on a scale of 0 (no WML) to 3 (severe WML). Scores for these individual brain regions were then summed to produce a "Total WML" score (range 0–24).

Patients within the database were coded as having either aMCI or naMCI based on their scores on the New Learning subsections of the CAMCOG at their first Memory Clinic attendance. Maximum possible New Learning score was 17 (recall 6, recognition 6, address recall 5). Mean [standard deviation] score for individuals not having dementia is reported to be 13.56 [1.88] (Huppert *et al.*, 1996).

Table 1. Follow up and conversion to dementia at years 1–5

	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5
Patients attended	129	108	73	45	27
Outcome known	129	121	113	101	87
Attended – converted	32	34	19	6	6
Did not attend – converted	0	13	40	56	60
Cumulative conversion (% of outcome known)	32 (25%)	47 (39%)	59 (52%)	62 (61%)	66 (76%)
Attended – not converted	97	74	54	39	21
Lost to follow up – outcome unknown	0	8	16	28	42
Stopped attending before follow up	0	21	56	71	81
Not yet reached follow up	0	0	0	13	21

NB. All figures in the table denote number of patients, except where percentages are indicated.

Significant impairment was taken as one or more standard deviations below the mean, i.e. 11.68 or below (Blackford and La Rue, 1989). Therefore, patients scoring 11 or below were coded as aMCI and those scoring 12 or above as naMCI.

The main outcome measure was time until conversion to dementia.

Statistical analysis

Patients were categorized into two groups according to baseline WML score, defined as Low and High WML. In our previous study, the distribution of WML scores proved to be bimodal with a natural cut-off score of 4 points (Devine *et al.*, 2007). We, therefore, defined those with total WML score of 0–3 as "Low WML" and those with total WML score of 4–24 as "High WML." Group characteristics were compared using *t*-tests for continuous variables and χ^2 tests for categorical variables.

Cox regression survival analysis of conversion to dementia status was carried out for the whole cohort, with number of years observed before diagnosis of dementia as the time variable. WML group (High or Low), total WML score and WML subscores for all brain regions were entered as covariates, along with age at first clinic visit, gender, MCI subtype (aMCI vs. naMCI), baseline CAMCOG score, and baseline score on Mini-Mental State Examination (MMSE, Folstein *et al.*, 1975) as potential confounders. We used the Enter Method. We then repeated this analysis within aMCI and naMCI groups separately. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) are reported.

Data were analyzed using SPSS Statistics Version 17.0.

Ethics

The study involved the retrospective analysis of routinely collected clinical data. All patients in the database had given informed consent for their Memory Clinic data to be held in a secure database and for their anonymized data to be used for research. The study was approved by the Essex 1 Research Ethics Committee.

Results

Brain scans were obtained for 129 (76%) of 169 patients in the database and rated for WML. Eighty-two (64%) were CT scans and 47 (36%) MRI. Forty scans could not be traced. There was no difference in gender distribution, mean age or mean baseline CAMCOG score between those whose scans were rated and those whose scans could not be traced. For 129 patients rated, median WML score was 2 (range 0–15), with 83 (64.3%) patients ranked as Low WML (score 0–3), and 46 (35.7%) as High WML (score > 3). Low and High WML groups did not differ significantly at baseline for mean [s.d.] MMSE score (25.6 [2.16] vs. 25.9 [2.36]; $F = 0.36$, $df = 127$, $p = 0.50$) or CAMCOG score (87.5 [7.69] vs. 88.2 [6.50]; $F = 3.69$, $df = 127$, $p = 0.57$).

Overall, 65 (50.4%) patients had aMCI and 64 (49.6%) had naMCI. The proportion of patients with aMCI in the High WML group (60.9%) was higher than in the Low WML group (44.6%), but this was not statistically significant ($\chi^2 = 3.14$, $df = 1$, $p = 0.08$).

Table 1 shows 5-year progress through the Memory Clinic for 129 patients with scans rated and at least 1 year of completed follow-up. Five-year outcome (i.e. whether and when converted to dementia) was available for 87 (67.4%) patients. Forty-two patients (32.6%) were lost to follow-up with unknown outcome between years 1 and 5. Individual reasons for drop out are not recorded but would have included death and moving away from the catchment area. There was no difference in degree of WML between

Table 2. Comparison of baseline characteristics between cases with 5-year outcome known and unknown

	KNOWN 5-YR OUTCOME ($N=87$)	UNKNOWN 5-YR OUTCOME ($N=42$)	p-VALUE
Age in years – mean (s.d.)	72.2 (9.0)	68.1 (10.0)	0.022*
MMSE score – mean (s.d.)	25.4 (2.1)	26.4 (2.3)	0.014*
CAMCOG score – mean (s.d.)	86.7 (7.2)	90.0 (7.0)	0.015*
aMCI proportion	60.9%	28.6%	0.001*
Total WML score – mean (s.d.)	3.30 (3.75)	3.26 (3.68)	0.958
"High WML" proportion	35.6%	35.7%	0.993

s.d. = Standard deviation.
* = Significant at $p < 0.05$.

patients lost to follow-up and those with known 5-year outcome. However, patients with known 5-year outcome were significantly older, more cognitively impaired at baseline and more likely to have aMCI than those with unknown 5-year conversion status (Table 2). They also showed a slightly greater mean decline on CAMCOG during the first year of follow-up (2.6 points) than those subsequently lost to follow-up (1.0 point), but this difference was not statistically significant ($F=3.31$; $df=127$; $p=0.20$). For patients with known outcome, cumulative rates of conversion from MCI to dementia at 1, 2, 3, 4, and 5 years of follow-up were 25%, 39%, 52%, 61%, and 76%, respectively.

For the cohort as a whole, age and MCI subtype were the only independent covariates with a significant effect on time to conversion to dementia. More advanced age was associated with earlier conversion to dementia (HR 1.06; CI 1.02 – 1.09; $p=0.001$) and effect of MCI subtype was also highly significant (HR 2.19; CI 1.22 – 3.95; $p=0.009$), with aMCI converting earlier than naMCI (Figure 1).

White matter lesion (WML) group had no significant effect on time to conversion to dementia (HR 1.18; CI 0.47 – 2.98); $p=0.73$) (Figure 2) for the whole cohort and there were no specific effects of WML in any individual brain region.

Sixty-three (95%) of the 66 patients known to have converted to dementia at follow-up had a dementia subtype clearly specified. Of these, 39 (62%) had AD and 24 (38%) had a non-AD type of dementia. Patients presenting initially with aMCI were more likely than those with naMCI to convert to AD (68% vs. 47%), though this difference was not statistically significant ($\chi^2=2.44$; $df=1$; $p=0.12$).

Analysis of the subgroup of patients with aMCI also showed no effect of WML group on time to conversion to dementia (HR 1.36; CI 0.48 – 3.87; $p=0.56$) (see Figure S1 published as supplementary material online attached to the electronic version of this paper at http://journals.cambridge.org/ipg).

Within the naMCI subgroup, on the other hand, patients with low WML scores appeared to survive longer without dementia than those with high WML scores (Figure 3), but this was not statistically significant (HR 0.27; CI 0.02 – 3.22; $p=0.30$). There was no difference in mean WML score between naMCI patients with known 5-year outcome (2.91, $n=34$) and those with unknown 5-year outcome (2.93, $n=30$) ($F=0.16$, $df=62$, $p=0.98$).

Additionally, there was no significant difference in the proportion of "High WML" cases between patients with known and unknown 5-year outcome for either aMCI (40% vs. 58%; $\chi^2=1.40$; $df=1$; $p=0.24$) or naMCI (29% vs. 27%; $\chi^2=0.06$; $df=1$; $p=0.81$) subgroups.

Discussion

There has been debate over whether or not WML are predictive of conversion from MCI to dementia. Debette and Markus (2010) systematically reviewed published prospective studies and concluded that white matter lesions were associated with an increased risk of dementia in the general population, but not in high-risk populations including those with MCI. Reviewing studies that specifically focused on MCI populations, they found that WML severity was significantly associated with incident vascular dementia but not with incident Alzheimer's disease.

The present study supports these general conclusions by demonstrating that WML were unrelated to probability of conversion to dementia among 129 patients with MCI over a 5-year follow-up period. We also replicated the finding of Sepe-Monti *et al.* (2007), that there was no relationship between WML and rate of conversion from aMCI to dementia, with a much larger cohort

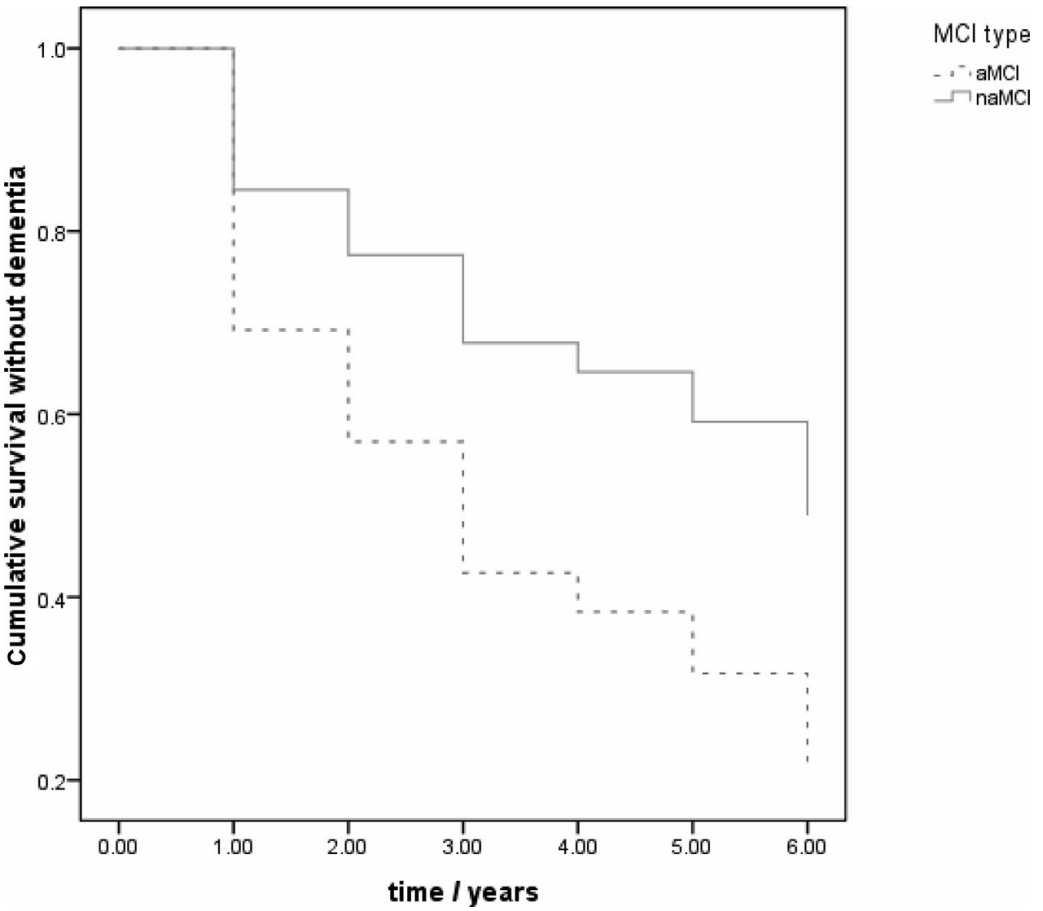

Figure 1. Survival by MCI type – whole cohort.
For the cohort as a whole ($n = 129$), MCI subtype had a highly significant effect on time to conversion to dementia, with aMCI converting earlier than naMCI. Curves are adjusted for age, gender, baseline MMSE score, baseline CAMCOG score, and degree of WML.

($n = 65$). Since aMCI is considered frequently to constitute prodromal Alzheimer's disease (Peterson *et al.*, 2001), this finding is consistent with the conclusions of the systematic review by Debette and Markus.

We hypothesized that severity of WML would predict conversion to dementia for patients with naMCI, on the basis that this group is likely to include patients with prodromal vascular dementia, in whom progression is more likely to be dependent upon cerebrovascular factors. We found a trend in this direction of potential clinical importance, but could not prove an association, since the effect was not statistically significant. It is possible that the study might have been statistically underpowered to detect such a difference in this subgroup. This was a secondary question in our study and one for which we were not able to calculate power prospectively, since we could not predict the distribution of High and Low WML within this group.

We found no effect on progression to dementia of WML in any particular anatomical brain region for aMCI, naMCI or the entire MCI cohort. However, we did not specifically study the effect of periventricular WML and so can neither support nor refute the findings of van Straaten *et al.* (2008).

Our study used data collected during routine clinical practice and the findings are likely, therefore, to represent the experiences of clinicians. However, the results must also be interpreted within this clinical context. Five-year outcome is more likely to be known for those patients who have converted to dementia than for those who have not, because any patient who has converted by 1 year has of course converted by 5, regardless of whether or not he or she is lost to follow-up in between, whereas a patient who has not converted by 1 year and is then lost to follow-up has unknown 5-year outcome. Furthermore, one possible reason for drop-out is that patients who have remained stable over time might be less motivated to continue to attend a clinic than those whose difficulties have progressed. These factors might explain the high overall conversion rates we observed.

Our finding that baseline cognitive performance did not influence time until conversion to dementia

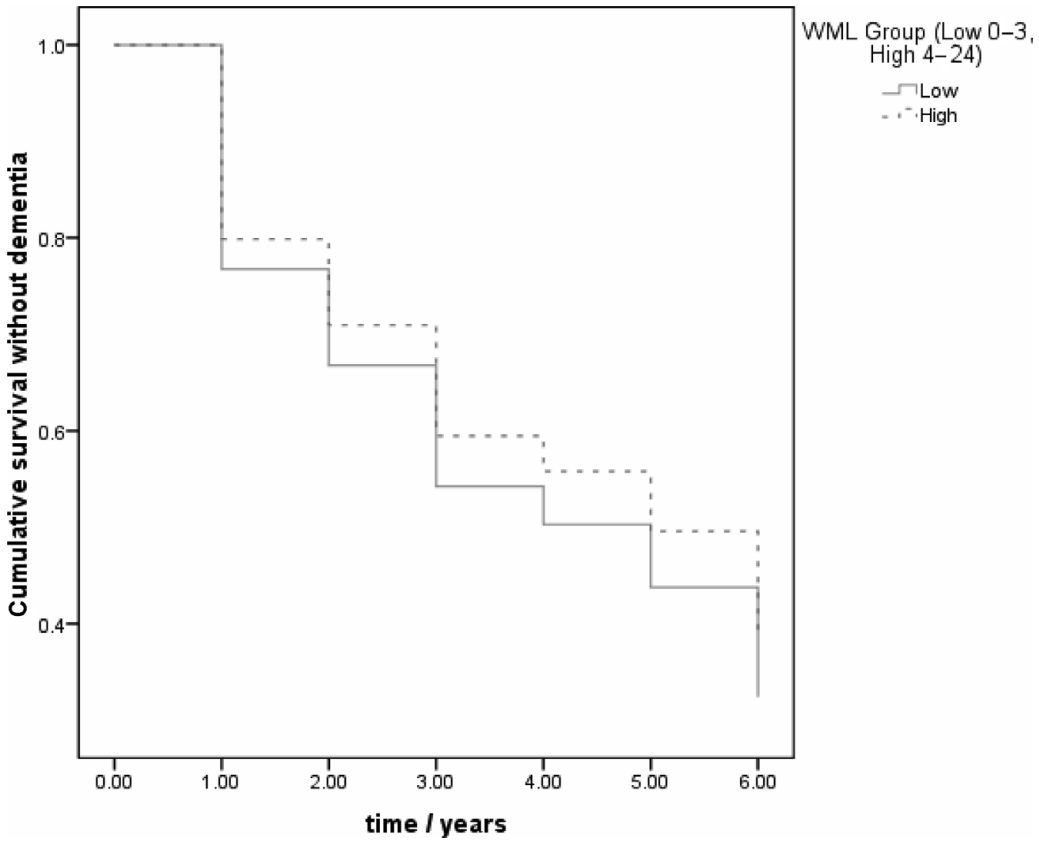

Figure 2. Survival by WML group – whole cohort.
For the cohort as a whole ($n = 129$), WML group (Low or High WML) had no significant effect on time to conversion to dementia. Curves are adjusted for age, gender, baseline MMSE score, baseline CAMCOG score, and MCI subtype.

must, therefore, be interpreted with caution, since patients lost to follow-up before 5 years were less cognitively impaired at initial clinic visit than those with known 5-year outcome.

However, age and aMCI status were found to predict time until conversion to dementia even though our patients with known 5-year outcome tended to be older at baseline and more likely to have aMCI than those lost to follow-up before 5 years, suggesting that these findings are robust. In addition, we found no difference in baseline WML score between patients with known and unknown 5-year conversion status, both for the cohort as a whole and for aMCI and naMCI groups separately. Therefore, selection bias cannot account for our finding that WML severity does not predict progression to dementia for MCI on the whole but might influence conversion for naMCI.

Our results suggest that MCI subtype (aMCI vs. naMCI) at baseline is a far more robust predictor of subsequent conversion to dementia than radiological markers of small vessel ischemic change, placing a greater prognostic emphasis on neuropsychological assessment and elucidation of specific cognitive deficits in MCI populations than on radiological investigation of WML. Specific patterns of atrophy (Whitwell *et al.*, 2008) are likely to be more important predictors of progression than WML in patients with aMCI. We found that such patients were more likely than those with naMCI to convert to AD. However, it remains a possibility that WML may be predictive of time to conversion within naMCI populations, who might go on to develop vascular dementia, and this possibility would benefit from further investigation through larger studies specifically investigating naMCI patients.

Supplementary material

Figure S1 is supplied as supplementary material for publication online. It illustrates no effect of WML group on time to conversion to dementia within the aMCI subgroup. Curves are adjusted for age, gender, baseline MMSE score, and baseline CAMCOG score.

Conflict of interest

Drs Devine and Fonseca declare no competing interests. Dr Walker has received consultancy and speaker fees and research support from

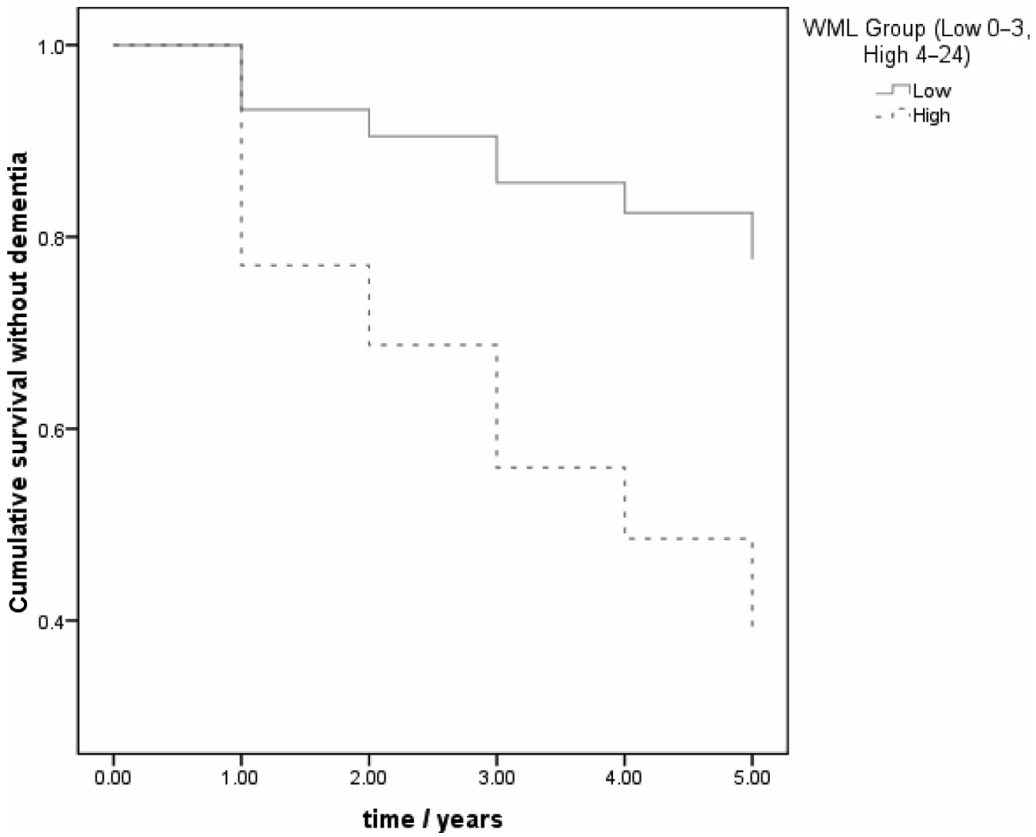

Figure 3. Survival by WML group – naMCI cohort only.
Within the naMCI subgroup ($n = 64$), there was a trend toward patients with low WML scores converting to dementia later than those with high WML scores, but this was not statistically significant. Curves are adjusted for age, gender, baseline MMSE score, and baseline CAMCOG score.

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Description of authors' roles

M. E. Devine and J. A. S. Fonseca formulated the research question, designed the study, reviewed the literature, gathered the data, analyzed the brain scans, and carried out statistical analyses. M. E. Devine wrote the first draft of the manuscript. J. A. S. Fonseca and Z. Walker critically appraised the manuscript for important intellectual content, contributing to subsequent revisions. Z. Walker oversaw the design of the study and is the guarantor for the paper.

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