AGE-RELATED WHITE MATTER CHANGES IN PATIENTS WITH TIA AND STROKE: POPULATION-BASED STUDY ON AETIOLOGICAL AND PROGNOSTIC SIGNIFICANCE

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To Gareth, Giacomo and Ginevra

ABSTRACT

Age-related white matter changes in patients with TIA and stroke: population-based study on aetiological and prognostic significance

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White matter changes (WMC) seen on CT and MRI brain scans of healthy subjects and of vascular or dementia patients are strongly associated with age. Their pathogenesis is still under debate, and associations with vascular risk factors have varied according to studies. Their prognostic meaning, both in the general population and in stroke patients, is also not completely established.

I systematically reviewed the literature on prevalence and associations of WMC and then evaluated CT and MRI scans of the first 8 years of a population-based study of all strokes and TIA in Oxfordshire (OXVASC). In this population I researched sex and age-specific associations between WMC and different types of strokes (TOAST), different components of blood pressure, and possible vascular risk factors. I also looked into their prognostic meaning for stroke recurrence and outcome, cognitive performance and mortality.

1840 patients were assessed by MRI (520) and/or CT (1717). White matter changes were independently associated with the lacunar type of stroke. The association with hypertension was confirmed (using 10 years of pre-morbid blood pressure readings), and it was particularly strong in the younger patients, mainly for diastolic hypertension. There was no association with blood pressure variability and peripheral pulse pressure. Hypercholesterolaemia, diabetes, smoking, ischaemic heart disease, carotid stenosis and atrial fibrillation were not associated with white matter changes. There was also no association with gender. Severe WMC posed a higher risk of disability and cognitive impairment at one year from the stroke, and of death in the following 10 years.

This is the first study on white matter changes associations and on their prognostic meaning, to be set in a large population-based cohort of stroke and TIA. I confirmed the association between white matter changes and higher blood pressure, in particular diastolic hypertension. I also showed the association with lacunar type of stroke to be independent from vascular risk factors, and WMC to reduce life expectancy and functional and cognitive outcome of patients with stroke.

DECLARATION

I certify that this thesis entitled “Age-related white matter changes in patients with TIA and stroke: population-based study on aetiological and prognostic significance” was performed while I was a full time postgraduate student at the University of Oxford.

I declare that I have personally been involved in recruiting many of the patients, as part of both “hot and cold pursuit” enrolled in the Oxford Vascular Study, upon which this thesis is based. I have personally entered and cleaned the data used in this thesis. In addition, I have personally chosen the scales used to quantify white matter changes on CT and MRI scans, and reviewed and evaluated white matter changes in all the CT and MRI scans used in this study, of patients from years 1 to 8 (2002-2010) in the OXVASC study. The research contained herein is my own work. No portion of this work has been submitted in support of an application for any other degree.

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Chapter 1

Introduction:

White matter changes (WMC) and the OXVASC Study

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1.0 Introduction to this thesis

Ageing is the most important risk factor for cerebral ischaemic vascular disease, but it is still difficult to explain exactly why, beyond the fact that all vascular risk factors increase in frequency with age. Are white matter changes, so frequently identified in people over 60, a pure marker of ageing, or could they, at least in part, independently explain the increased risk of stroke and TIA in the ageing population? Do they represent a sign of excessive microvascular ageing secondary to the exposure to common vascular risk factors? Are they a completely independent risk factor for cerebrovascular disease? Or are they a combination of the above two theories, perhaps depending on causal associations still to be determined? This thesis represents an attempt to help clarifying these issues. Many studies on white matter changes have been published over the past 30 years, with conflicting reports. Sometimes, when a subject becomes so popular, it is helpful to take a step backwards and re-consider issues with a systematic and open-minded approach. This is the leading concept of my thesis, which starts with a review of the extensive literature on white matter changes. The questions addressed in this work concern the origin, the frequency and the associations of white matter changes, and then their relationship with ischaemic cerebro-vascular disease in terms of causality and prognosis. I am aware that many other questions are still far from having answers, and some of them are in my list of future research. The few answers found by my work are a small step forward in understanding the process of ageing and ischaemic cerebral disease. My work has benefited from the collaboration with many other researchers in the context of the OXVASC Study, as mentioned in the acknowledgements, and some of the chapters have also benefited from peer review before being published. These contributions may be particularly evident and create some impression of incoherence through the thesis, but they should not disrupt the sequence of the underlying concept. Another warning is with regards to the terminology: the terms “white matter changes” and

"leukoaraiosis" have been used interchangeably throughout this thesis, and the fact that in some chapters I only use one or the other ought not to cause confusion.

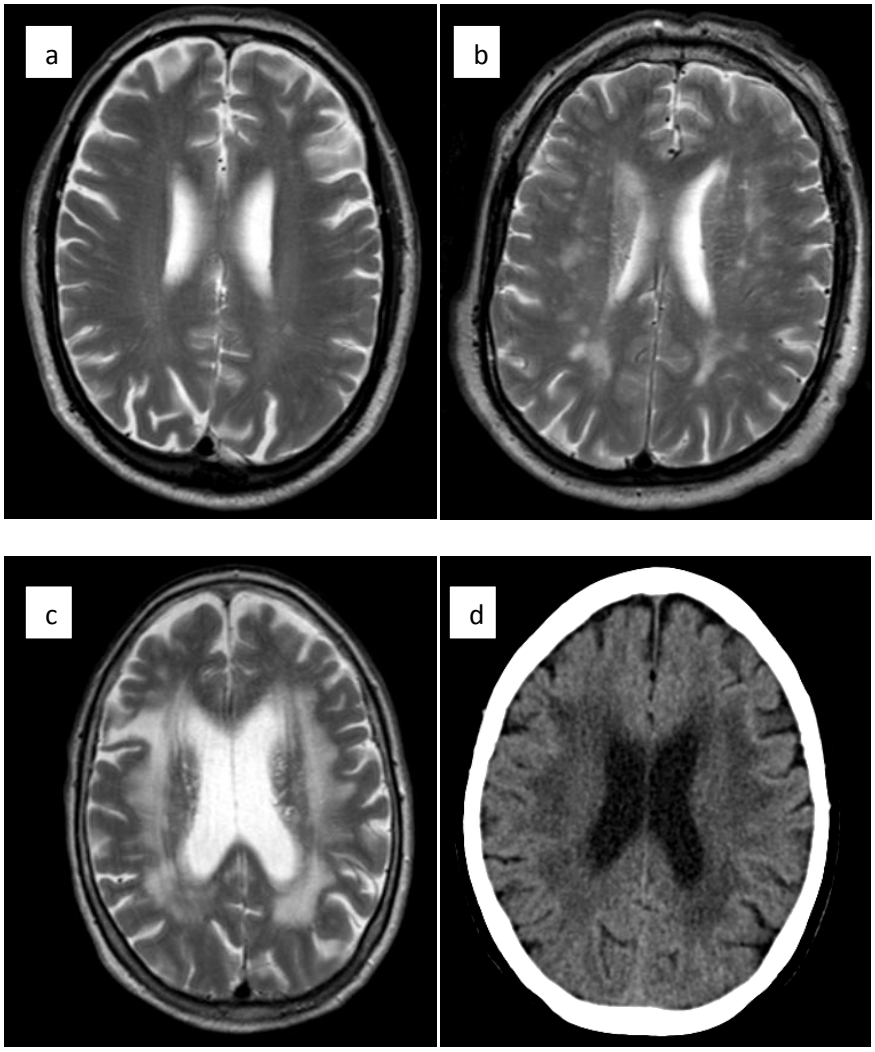
1.1 White matter changes: overview

1.1.1 Definition

Vladimir Hachinski in 1986 introduced the term Leukoaraiosis to describe white matter changes frequently identified by Computed Tomographic (CT) brain scans in elderly subjects[1]. Leukoaraiosis means "rarefaction of the white matter", and was derived from the Greek λευκος (white) and αραιωσις (rarefaction). This CT-based term was soon extended to lesions identified by Magnetic Resonance Imaging (MRI), which is now the technique most commonly used to investigate white matter disease. These white matter changes have been named variously as: white matter changes, age-related white matter changes, chronic white matter ischaemic changes, white matter lucencies, white matter hyperintensities, and they have been for a long time associated to the eponym Binswanger's disease, with which some clinicians still address patients with extensive white matter changes and some degree of cognitive deterioration.[2,3] In this thesis the terms "white matter changes" or "age-related white matter changes" and "leukoaraiosis" have been used interchangeably. On CT, leukoaraiosis appears as hypodense white matter (darker than normal white matter) either surrounding the lateral ventricles and/or patchily distributed in the deep areas. The appearances on MRI vary according to the different sequences used. T2-weighted sequences identify leukoaraiosis as areas of hyperintensity (whiter than normal white matter), while white matter changes are not easily identifiable on T1-weighted sequences. The T2-weighted Fluid Attenuated Inversion Recovery (FLAIR) sequences allow better visualisation of the periventricular lesions, suppressing the signal from the cerebro-spinal fluid. Perfusion MRI shows significantly reduced blood flow in chronic white matter changes.[4] Diffusion

techniques show increase of diffusion of water molecules and decreased anisotropy in areas of chronic white matter changes, as shown by an increased Apparent Diffusion Coefficient (ADC), which identifies white matter changes like bright areas on ADC maps.[5,6]

Fig 1.1 Appearances of leukoaraiosis on MRI (a,b,c) and on CT scans (d). Various degrees of severity are shown, from none/mild (a) to moderate (b) and severe (c,d), according to different scales.



1.1.2 Pathological correlates

It has been demonstrated on pathological grounds that the lesions responsible for leukoaraiosis on CT correspond to areas of myelin attenuation, axonal loss, oligodendrocyte loss, astrocytic gliosis and arteriolar sclerosis, which have been interpreted as evidence of an ischaemic origin of the lesions. The existence of a vascular demyelination process is widely accepted.[7,8] The pathological studies on leukoaraiosis providing radiology documentation have been mainly performed with CT scans, while the MRI-based pathological studies have most often used post-mortem MRI.[9] Data from post mortem MRI matched to pathology have shown that smooth caps and halos in the periventricular areas are most likely not vascular in origin, contrary to the sub-cortical and deep white matter lesions. Periventricular smooth hyperintensities correlate with areas of spongiotic white matter which is considered by some to be a normal anatomical feature,[10] while others think that there might be increased water content due to partial disruption of the ependymal lining.[11] Among the deep white matter lesions, we need to differentiate between small punctuate foci and partly confluent or confluent lesions. Whilst large confluent lesions appear to be underlined by vascular lesions, the small punctuate foci are most often enlarged perivascular spaces.[9] One of the few studies on the pathological correlation of small vessel disease identified on CT scans[12] has been performed within a mixed cohort of demented and non-demented subjects participating in the OPTIMA study, ongoing in Oxford since 1988.[13] The authors rated separately diffuse leukoaraiosis, patchy white matter lesions and lacunar lesions seen on CT scans. The CT scans were performed on average at 4 weeks from the first clinical evaluation. Pathology was performed in 87 patients who volunteered to donate their brain to the study. Brain sections were taken from the frontal, parietal and occipital white matter, and they were stained with hematoxylin-eosin. The degree of small vessel disease was rated according to a 0-2 scale, where 0 indicated absence of lesions, 1 meant moderate lesions either in the deep grey nuclei or in the white matter, and 2 indicated either moderate lesions in two regions or severe

lesions at least in one of them. The authors found that the increase in severity of diffuse leukoaraiosis, of patchy lesions and lacunar infarcts corresponded to the increase in severity of the pathological findings, and were especially associated with microinfarcts. They also stressed the fact that diffuse leukoaraiosis was often present also in cases with no or mild signs of small vessel disease on pathology, suggesting that diffuse leukoaraiosis might represent a different entity from the patchy white matter lesions, and possibly not an indicator of vascular pathology.[12,14] The findings from this study were important as a confirmation of the validity of the assessment of white matter changes with CT scans, still the most diffused technique of brain imaging, especially in large studies.

1.1.3 Pathogenesis

Various theories have been postulated on how these lesions arise. The most accredited ones are: a. ischaemia, b. toxins damaging the parenchyma, and c. cerebral spinal fluid (CSF) accumulation. According to the ischaemic theory, changes occurring in the walls of the white matter arteriole lead to thickening and increasing tortuosity of these vessels, which lose their natural permeability. The penetrating arteriole in the thalamic, lenticulo-striate and pontine paramedian regions are the most compromised. This results in changes in the periventricular and deep white matter, with sparing of the U fibres in the immediate sub-cortical area.[2] An impaired blood flow supply and increased oxygen extraction fraction in the white matter affected by leukoaraiosis was shown in a first instance by PET studies in patients with hypertension and severe MRI-detected leukoaraiosis, compared to controls without leukoaraiosis.[15] More recently these observations have been confirmed by perfusion studies with MRI.[4] The second hypothesis sets the origin of leukoaraiosis in a blood-brain barrier disruption. Lypohyalinosis, as described by Fisher[16] in the first pathological studies on lacunar disease, fibrinoid necrosis of the endothelial cells causing the formation of tangles

and whorls, could be initiated by leakage of neurotoxic factors from an endothelium damaged by vascular risk factors. Animal models support this hypothesis: direct injection of plasma factors in the brain parenchyma causes severe vascular damage. The process would then lead to a narrowing and re-shaping of the arteriole, with secondary reduction of blood flow supply. At the same time, the leakage of toxins would be responsible for parenchymal damage of glial and neuronal cells, leading to a reduced request of blood supply from the damaged areas.[17] One alternative hypothesis is derived from observations on patients with normal pressure hydrocephalus, who usually have got some degree of periventricular white matter changes. It has been demonstrated that these white matter changes are almost completely reversible with a ventriculo-peritoneal shunt insertion. The mechanism of formation of these changes would lay either with the ischaemic effect on white matter derived from an increase of the ventricular CSF pulse pressure, or within a difficulty in the reabsorption of the CSF from impaired blood vessels walls.[7] A hypoxic environment has definitely been demonstrated to be present in areas affected by leukoaraiosis, and more so in the deep white matter lesions rather than in the periventricular ones. Proof of this comes from recent studies of correlation between MRI and pathological findings in leukoaraiosis, which showed increased levels of molecular markers of hypoxia-inducible factors (HIF1α and HIF2α) with immunocytochemical techniques.[8] In conclusion, it still is under debate whether the reduction of blood flow and the subsequent hypoxic environment present in areas of white matter changes is a causal factor, or whether it is a response mechanism to a different insult.

1.1.4 Prevalence of leukoaraiosis in literature

Leukoaraiosis is found in a high proportion of subjects over 60 years of age, either asymptomatic or carrying vascular risk factors. Its frequency varies according to the different

population settings, and to the different techniques used to detect it (i.e. MRI or CT). I made a systematic review of the literature on prevalence of white matter changes, using Medline and Embase as tools of research and considering studies up to August 2009. I identified 24 potential studies which based their observations on CT scan, and 50 studies based on MRI.

CT Studies. Three of the CT studies did not state the prevalence of leukoaraiosis in their population. Amongst the remaining 21 studies, 12 were on stroke patients (2 of them used the same population) with a total of 9145 patients considered.[18-29] The prevalence of leukoaraiosis varied between 6.8% and 62%, with an average of 24.2% of patients showing any degree of white matter changes on their CT scan. The mean age of these different populations ranged from 59 to 79.1 years, with an overall mean age of 66.9 years (table 1.1). Amongst patients with dementia, leukoaraiosis has been previously documented with frequencies ranging from 41% to 100% with CT and from 64% to 100% with MRI in Vascular Dementia (VD), and from 19% to 78% with CT and 7.5% to 100% in MRI in Alzheimer's disease (AD).[2] Three of the CT studies evaluated the frequency of leukoaraiosis in patients with dementia.[30-32] Overall 272 subjects either with VD or AD were considered in these studies, and the prevalence of leukoaraiosis was 42.6%. The mean age in this group ranged between 68.8 and 72.6 years, with an average age of 71.1 years (table 1.1). The prevalence of leukoaraiosis was 21.6% in healthy volunteers or mixed patients from Neurology and Geriatrics wards,[33-35] and in controls,[28,31,32] as reported by 6 of the studies, with a total of 598 subjects with age ranging between 54.2 and 83.3 years (mean age 67.6).

MRI Studies. A few studies on prevalence of leukoaraiosis in population-based samples have been performed in the 1990s. In 1993-1994, during a MRI-based follow-up, the ARIC (Atherosclerosis Risk In the Community) Study,[36] a longitudinal observational study of patients between 45 and 64 years of age, found that 85.6% of 1920 subjects older than 55 had some degree leukoaraiosis. Another population-based study, the Cardiovascular Health

Study[37], showed leukoaraiosis of any degree in 95% of 3301 subjects older than 65 who underwent brain MRI. In the same period, the Helsinki Aging Study[38] considered a population-based sample of 128 individuals with a mean age of 71.4 years, and detected a prevalence of 39% of periventricular lesions and 22% of subcortical lesions. In a population-based sample of 111 subjects between 65 and 85 years of age, the Rotterdam Study[39] identified white matter changes of any degree in 27% of the subjects. More recently, the Rotterdam Scan Study[40] has found a 95% prevalence of leukoaraiosis in a sample of 1077 subjects from the general population (with exclusion of demented or blind subjects) with a mean age of 72.4 years. The EVA-MRI Study[41], a population-based sample of subjects with mean age of 69 years, has shown a prevalence of white matter changes in 98.6% of 841 subjects. In a younger population cohort (mean age of 53 years), part of the Framingham Offspring Study[42], the prevalence of leukoaraiosis has been found to be much lower, with 7.7% of 1814 subjects showing any degree of white matter changes.

Prevalence of MRI-detected leukoaraiosis in stroke patients has been shown with contrasting results. Padovani[43] found a prevalence of 82% amongst 50 post-stroke patients with a mean age of 66.1 years, while a study in the United States[44] on 370 stroke patients found a prevalence of 17.6%. Two recent Chinese studies on 137[45] and 228[46] stroke patients have found respectively 24.8 and 86% of leukoaraiosis. In a study of 130 patients with mean age of 69.4 years, with atherosclerotic risk factors, heart failure and atrial fibrillation, Kocer[47] identified 74.6% of subjects with white matter lesions.

In a recent review[48] on prevalence of leukoaraiosis in 243 young and healthy subjects with a mean age of 37 years, Hopkins found a prevalence of white matter changes of 5.3%.This was contrasting with the findings of a different study performed on the same year, which detected leukoaraiosis in 40.4% of 89 healthy volunteers with mean age of 43 years.[49] One

major difference between these studies was in the mean of evaluation of LA, which was visual in the first case while automated in the second case. A recent Japanese study[50] on a cohort of 1030 healthy subjects (no past history of stroke and no present neurological complaints) with mean age of 52.7 years, found leukoaraiosis in 28.8 % of cases.

Overall, both among CT and MRI-based studies, a great heterogeneity exists with regards to the prevalence of white matter changes. This could be secondary to various factors. The population age and their setting are definitely important but are not the only causes, as even grouping these studies according to type of population does not eliminate completely the heterogeneity. The evaluation methods, i.e. visual versus volumetric, and, within the visual evaluations, the different scales used are also important. The sensitivity of the imaging is another factor: newer generations machines acquire pictures of better quality. For MRI scanners, the strength of the magnetic fields is important: some studies are based on 0.2 Tesla (T) machines, while others can be based on 1.5 T or 3 T machines, giving a completely different sensitivity in detection of white matter changes.

Tab. 1.1 Studies assessing the prevalence of Leukoaraiosis with CT

Stroke patients			
Author, year	**Prev (%)**	**Age (yrs.)**	**Population size**
Koton 2009[18]	52.6	70.2+/-12.9	1024
Thein 2007[19]	48.0	63.17 +/-10.53	60
Coskun 2003[20]	61.8	66.9+/-11 pts with LA, 65.3+/-14.5 pts w/o LA	288
Henon 2003[21]	40.0	75 (42-101)	202
Streifler 2003[22]	18.8	69.2 pts with LA, 65.0 pts w/o LA	2618
Wiszniewska 2000[23]	6.8	73.7 pts with LA, 62.7 pts w/o LA	2289
Henon 1996[24]	43.3	64(17-100)	610
Awada 1996[25]	25.8	67.8+/-8.5 pts with LA, 61.2+/-13.2 pts w/o LA	398
Jorgensen 1995[26]	15.0	79.1 +/- 8.7 pts with LA, 72.0+/-11.6 pts w/o LA	1084
Karsidag 1995[27]	55.0	68.55+/-11.9 pts with LA, 59.8+/-13.2 pts w/o LA	89
Inzitari 1990[28]	18.0 in ICH, 8.0 in controls	62.6+/-10.2 pts with LA, 61+/-10.6 pts w/o LA	116 ICH, 155 controls
Hijdra 1990[29]	38.0	73 pts with LA, 59 pts w/o LA	367
Dementia Patients			
Wallin 2000[30]	60.0	71+/- 8	85
George 1986[31]	30.0 in AD,16.0 in controls	72.6 +/-7.5 in AD 69.4 +/- 6.5 in controls	151 AD, 89 controls
Kobari 1990[32]	52.3 in MID, 61.5 in AD,21.6 in controls	68.8 +/- 11.1 MID, 72.2 +/- 6.6 DAT, 54.2+/-15.5 controls	23 MID, 13 AD, 37 controls
Mixed Patients			
Ventura 2007[33]	18.0	75.1 (6.47 SD)	73
Censori 2007[34]	34.2	68.7+/-11.7 (46% are stroke)	178
Tartaro 1999[35]	31.8 (severe)	77	66

Tab.1.2 Studies assessing the prevalence of WMC with MRI

Population Studies			
Study, author, year	**Prev (%)**	**Age (yrs.)**	**Population size**
Helsinki Aging Study, Ylikoski 1995[38]	39.0 PV, 22.0 SC	71.4	128
ARIC study, Liao 1996[36]	85.6	45-64	1920
Rotterdam Study, Breteler 1994[39]	27.0	65-85	111
CHS, Longstreth 1996[37]	95.6	Over 65	3660
Rotterdam Scan Study, De Leeuw 2001[40]	95.0	72.4 (60-90)	1077
EVA-MRI Study, Dufouil 2001[41]	98.6 (12 w/o LA)	69 (59-71)	845
Stroke Patients or Patients with vascular risk factors			
Podgorska 2002 [44]	17.6	72 +/- 12.7 in LA, 67 +/- 13.6 in non LA	370
Padovani1997[43]	82.0 (30% in the healthy controls)	66.1 +/- 7.7 (62.1+/- 7.3 healthy controls)	50 (and 50 controls)
Gao 2008[45]	24.8	n.a	137
Fu 2005[46]	86.0	n.a	228
Kocer 2005[47]	74.6	69.4 +/- 8.76	130
Healthy Subjects			
Park 2007[50]	28.8	52.7 (28-78)	1030
Hopkins 2006[48]	5.3	36.95	243
Wahlund 1990[51]	9.0	79 (75-85)	24
Benedetti 2006[49]	40.4	43	89
Fujita 2002[52]	41.7	64.1 +/- 11.0 (35-87)	175

1.2 The Oxford Vascular Study (OXVASC)

The OXVASC study is a population-based study of all acute vascular events in a population of 91000 individuals registered with 63 primary care physicians in 9 general practices in and around Oxford, UK (figure 1.2).[53,54] The study started on 1st April 2002 and is still ongoing. Multiple overlapping methods of "hot" pursuit are used to achieve near-complete ascertainment of all individuals with TIA or stroke. These include an urgent neurovascular clinic to which participating general practitioners and the local accident and emergency department send all individuals with suspected TIA or stroke whom they would not normally admit to hospital; daily assessment of admissions to the medical, stroke, neurology, and other relevant hospital wards, daily searches of the local accident and emergency department attendance register and of the berievement office. To not miss patients who presented late, were referred to other services, or were not referred to secondary care, monthly computerized searches are performed in family doctor diagnostic coding, hospital discharge codes, and all cranial and carotid imaging studies performed in local hospitals. Patients are followed up for 10-years after the entry event. Follow-up visits include blood pressure check and a questionnaire on general health, recurrent events, medication, and neuropsychological tests at one and six months and one, five and ten years. Follow-up is complete for all patients for mortality via centralised death certification records and 5-year follow-up is available in over 95% of patients either by face-to-face follow-up or follow-up via their family doctor. A more detailed protocol of the study can be found in Appendix 1 of this thesis, the entry forms which are filled in for all the stroke and TIA patients in Appendix 2, and consent/assent forms in Appendix 3.

1.2.1 My role in OXVASC

I have participated in the study as a clinical research fellow for over 3 years, personally recruiting patients mainly through the TIA and minor stroke clinic and through the active search on the clinical wards. I have also performed some of the follow-up visits, and have recruited control subjects. I have personally collected data from patients and inserted

them in the study database. In addition to my duties in the hot pursuit as clinical research fellow, I have gone through the bulk of CT and MRI scans that had been done in OXVASC since 2002. I have traced, collected and ordered alphabetically all the films of the scans performed between 2002 and 2006, as these were not on the PACS system of the hospital. I have then chosen the rating scales and personally evaluated the CT and MRI scans, as it will be described to follow. I have shared my data with other research fellows, and I have on my part benefited from the data collected and cleaned by others.

Fig 1.2. Oxfordshire with list and distribution of the 9 primary care surgeries participating in the OXVASC Study

1.3 Evaluation of leukoaraiosis in the Oxford Vascular Study

Leukoaraiosis can be evaluated in different ways. In many studies observers simply describe leukoaraiosis as present or absent. Presence of leukoaraiosis can be

standardized within the definitions of categorical scales, and it can also be quantified either by manual (for example by counting the lesions and considering them spherical giving them a standard diameter in order to calculate their volume) or by semi-automated or, more recently, automated techniques which involve the human eye just for the definition of what is abnormal, and then rely on a computerized calculation of the volume of lesions. Numerous qualitative scales for rating leukoaraiosis have been created over the past 20 years. There is need to unify the findings of different studies in order to clarify the pathogenesis and the clinical meaning of leukoaraiosis, thus recent efforts have been made to create scales easily applicable to both CT and MRI[55,56] and to different population settings, and also to validate different scales with each other.[57-60] Despite numerous efforts, no uniformity can be reached with this kind of evaluation. Even when all use the same scale, inter and intra-rating differences, no matter how small, are the rule.

1.3.1 Choice of the scales

When choosing a scale for leukoaraiosis a few things need to be considered: the experience of the rater, the number of raters, the time available to rate the scans, and the equipment available. When more than one rater is present, the scale should be the easier and the most reliable between raters as possible, and inter-rater as well as intra-rater studies should be performed. In OXVASC, leukoaraiosis has been evaluated on CT and on MRI scans, and its severity has been rated according to four different scales: the scale of van Swieten[55] for CT, the ARWMC[56] scale for CT and MRI and the scale of Fazekas[61] for MRI, which were chosen among the most used and validated in literature, [56,62] and a simple 0-3 scale, which we called the Oxford scale, both to CT and MRI. A description of these scales follows.

1.3.1.1 Oxford scale (CT and MRI)

The first scale used for both CT and MRI is an easily applied 0-3 rating system (absent, mild, moderate, severe). This scale, when applied to CT scans, can be considered as

directly derived from the scale of Blennow,[63] but considering the extension and severity of signal changes altogether rather than separately. When applied to MRI scans, the Oxford scale is very similar to the Fazekas[61] scale, but it considers periventricular and deep white matter jointly, and lesions are not measured to decide on the score. Mild leukoaraiosis is normally considered when only some white matter changes confined to the periventricular area are seen (with no extension towards the deep white matter) or when only a few isolated foci of white matter changes are identified in the subcortical areas (there is no fixed number of lesions). Usually, if both the above features are present, leukoaraiosis is considered moderate. “Moderate” would also include leukoaraiosis represented by deep white matter partly confluent lesions. When lesions coalesce and tend to occupy the entire area between the ventricles and the cortex, either in one or more than one lobes, leukoaraiosis is graded as severe. Usually the lesions are symmetrical, but in case of asymmetry the most affected hemisphere is considered. The rater does not evaluate leukoaraiosis on scans with clear signs of intracerebral oedema, either due to parenchimal masses or haemorrhages. This scale is subject to personal interpretations and relies on the experience of the rater, therefore it is better applicable and more inter-changeable by raters with extensive experience and with similar background.

1.3.1.2 van Swieten’s scale (CT)

The van Swieten’s scale was created for the Dutch-TIA trial[64] in 1990, and used also in NASCET.[22,65] This is a simple scale to use, and the partial scores found for the anterior and the posterior regions of each hemisphere can be summed up to give different totals. The starting point for using this scale is the choice of three sections to consider for the evaluation: one slice at the level of the choroid plexus, one at level of the cella media of the lateral ventricles, and one at the level of the centrum semiovale. The third section is chosen as the second slice above the last one showing the ventricles, to avoid confusing the roof of the third ventricle with white matter changes, provided this slice shows enough

white matter for the evaluation (if not, we consider the slice immediately above the ventricles).

The two hemispheres are evaluated separately. On slice number one we only evaluate the region anterior to the central sulcus, on slice number two we evaluate both the anterior and the posterior regions, and on slice three we only evaluate the posterior region. Each area on each hemisphere is given a score from 0 to 2, where 0 is absence of leukoaraiosis, 1 is presence of pure periventricular leukoaraiosis, and 2 is leukoaraiosis extending towards the cortex.

The highest scores for each of the two regions (either on right or left hemisphere) are chosen and they are summed up to obtain a total score (ranging from 0 to 4). A categorisation of the final score has subsequently been performed to execute the analyses: I have considered a total score of 1 as mild, 2 as moderate and 3 or 4 as severe.

1.3.1.3 Age-Related White Matter Changes (ARWMC) scale (CT and MRI)

The ARWMC scale,[56] has been created with the purpose of unifying the different rating systems for leukoaraiosis, with a unique scale intended both for CT and MRI scans. Areas of ill-defined rarefaction of white matter, and with diameter ≥ 5 mm, are considered lesions. Five regions are considered, separately for each hemisphere: frontal, parieto-occipital, temporal, infra-tentorial, and basal ganglia. The frontal, parieto-occipital, temporal and infra-tentorial regions are rated according to the following scale: 0 = no leukoaraiosis, 1 = focal lesions, 2 = beginning confluence of lesions, and 3 = diffuse involvement of the entire region, with or without involvement of U fibers. In case of periventricular disease only, I decided to consider thin caps as normal white matter, and to score smooth caps thicker than 5 mm as 1, caps extending towards the cortex (in which a hint of separate lesions can still be identified) as 2, and the involvement of the entire area from ventricles to cortex as 3. Basal Ganglia lesions are scored according to a different scale: 0 = no leukoaraiosis, 1 = 1 focal lesion, 2 = more than 1 focal lesion, 3 =

confluent lesions. The final score can be used either as separate scores for each region on the two hemispheres, as a sum of the sub-scores (0-30), or as an average of the sub-scores. I have used the sum of the single sub-scores and then classified it into absent (0), mild (1-5), moderate (6-10) and severe (>10).

1.3.1.4 Fazekas' scale (MRI)

This scale, first created to evaluate white matter alterations in Alzheimer's patients, has been largely used to quantify age-related white matter changes, and has been chosen as a tool to recruit patients for large collaborative studies (such as the Leukoaraiosis And DISability study – LADIS[66]), due to its simple applicability and good reproducibility amongst raters. White matter changes are evaluated in two different areas, the periventricular and the deep. The periventricular lesions can be classified into 4 different grades, from absent (0) to "caps or pencil thin lining" (1), "smooth halo" (2) and finally irregular periventricular hyperintensities (3). The deep white matter lesions are similarly graded into 4 severity points, from no lesion (0) to punctuate foci less than 10 mm in diameter or grouped lesions with an overall diameter below 20 mm (1), to beginning confluence of foci seen either as single lesions with a diameter ranging between 10 and 20 mm or grouped lesions with connecting bridges of white matter hyperintensity (2), to finally large confluent areas (3) represented either by single or confluent lesions with a diameter larger than 20 mm. The final score is obtained by summing up the two sub-scores. Some tips have been given by the authors more recently[67]in order to increase the reproducibility of this scale: the lesions are only considered periventricular if they are located within 1 cm from the ventricle, and in direct continuation with the lateral borders of these. Severe periventricular lesions which exceed these limits have to be considered pertaining both to the periventricular and to the deep white matter areas, and therefore scored as both. The purely deep white matter lesions are always separated from the ventricles by a rim of normal signal white matter surrounding the ventricles. The authors

observed, thanks to clinical and pathological correlations, that the periventricular caps and smooth halos are most likely in keeping with normal findings related to ageing. In OXVASC, I used both the periventricular and the deep white matter score, as from the original description of the scale. A total score was calculated summing the two sub-scores (0 to 6), and from this I categorized the patients into “no leukoaraiosis” = 0, “mild ” = 1 or 2, “moderate” = 3 or 4, and “severe” = 5 or 6.

1.3. 2 Evaluation process in OXVASC

In OXVASC all the scans are reviewed weekly at a multi-disciplinary meeting and a neuro-radiologist evaluates all the lesions and quantifies leukoaraiosis and atrophy. This has routinely been ongoing since 2002, and up till now two different radiologists have taken up the task in a consecutive way: the first radiologist evaluated the majority of the scans done up to 2006, and the present has started the evaluation in 2008, evaluating the scans done from 2006 onward. The neuro-radiologist evaluates the scans in a busy semi-clinical setting and the time available only allows the use of one scale (the Oxford scale). All the available scans of patients enrolled over the first 8 years, from 2002 to 2010, have also been reviewed and rated by two clinical research fellows with previous extensive experience in rating leukoaraiosis. The scans were available either as hard copies or as digital imaging on the computerized imaging storing system of the hospital (PACS). One rater (myself) has evaluated all the scans up to 2007-2008, and the second one has mainly looked at the scans from 2008 to 2010. The clinical fellow evaluation has been performed during separate sessions, from a PC located in the research office of the Unit, where the PACS system is available for consultation. Older imaging only available as hard copies have been evaluated on a light board, still in the research offices. These evaluations were performed completely blind from clinical and demographic information, contrary to those of the radiologist, which were usually performed after a brief description of the clinical case and age and sex of the patients were disclosed to start with. The CT

scans were mainly performed on a Toshiba, Aquilion 64, 64-slice scanner, and the MRI on a 1.5 Tesla Philips Achieva scanner. The MRI protocol in use for vascular patients included T2 weighted sequences but only coronal FLAIR images, and T1 sequences were only done sporadically. Leukoaraiosis was assessed on the T2 sequences, using the coronal FLAIR as a helping tool. Wherever T1 sequences were performed, these were used to identify lacunar lesions.

A total of 2124 patients, recruited between years 1 and 8, were considered. CT scan was performed in 1817 of them, and 1803 had evaluation of their scan for leukoaraiosis (in 26 of these patients leukoaraiosis could not be assessed for poor quality of images or for presence of severe oedema secondary to SOL or haemorrhage, leaving a total of 1777 patients with CT evaluation). Overall, 84.8% of the whole total of patients had leukoaraiosis evaluation, corresponding to 99.2% of the patients who had a CT scan. Among the 321 patients who did not have a CT evaluation, 171 did not have any imaging performed (104 were not scanned because considered clinically inappropriate - 37 died before imaging, 27 were not scanned because seen for amaurosis fugax, in 4 cases only in the Eye Hospital, 14 were only seen much later after the event , 26 refused). Among the remaining 150 patients: 129 had only MRI, 7 had imaging taken abroad and 14 were not retrievable from the hospital electronic filing system. MRI was done in 545 patients, and available for evaluation in 529, with 416 patients having both type of imaging.

Figure 1.3 Form used for the evaluation of scans in OXVASC

CT Evaluation

Date Evaluation: _____

Date of scan: _____

OXVASC Number: _____

Van Swieten Scale

3 CT sections are considered for evaluation: choroid plexuses, lateral ventricles and centrum semiovale.
Anterior and posterior regions scored separately, both in the right and the left hemispheres. Anterior region (anterior to central sulcus) evaluated in first and second sections, posterior region evaluated on second and third section. The highest score is chosen, and summed to the highest score of the other section.
0 = no white matter lesion
1 = periventricular hypodensity
2 = white matter lesions extending to the cortex

		Right	Left	Total _____
Choroid plexuses section	Ant.	_____	_____	
Lateral Ventricles section	Ant.	_____	_____	
	Post.	_____	_____	
Centrum Semiovale	Post.	_____	_____	

ARWMC Scale

White matter changes are ill defined and moderately hypointense areas larger than 5 mm.
The right and left hemisphere are evaluated separately and five region are considered in each hemisphere. Frontal area = anterior to central sulcus, parieto-occipital area, temporal area, infratentorial area, basal ganglia region .
White matter lesions: 0 = no lesions, 1= focal lesions, 2 = beginning confluence of lesions, 3 = diffuse involvement of the entire region, with or without involvement of U fibers. Basal ganglia lesions: 0 = no lesions, 1 = 1 focal lesion, 2 = more than 1 focal lesion, 3 = confluent lesions. Scores are considered separately.

	Right	Left
Frontal	_____	_____
Parieto – occipital	_____	_____
Temporal	_____	_____
Basal ganglia	_____	_____
Infratentorial	_____	_____

Oxford Scale

Evaluation of leukoaraiosis extension on a scale from 0 to 3

_____

☐ Confluent
☐ Multifocal lesions
☐ Both

MRI Evaluation

Date Evaluation: _____

Date of scan: _____

OXVASC Number: _____

Fazekas Scale

Periventricular white matter and deep white matter are scored separately and then the scores summed up. Maximum total score = 6. For periventricular lesions: 0 = no change, 1 = CAPS or pencil-thin lining, 2 = smooth halo, 3 = irregular periventricular hyperintensities. For deep white matter lesions: 0 = no lesions, 1 = punctuate foci (single lesion < 10 mm or grouped lesions? 20 mm), 2 = beginning confluence of foci (single lesion 10-20 mm or grouped lesions with connecting bridges only), 3 = large confluent areas (single or confluent lesions > 20 mm).

Periventricular WM _____

Deep white matter _____

Total _____

ARWMC Scale

White matter changes are ill defined and moderately hypointense areas larger than 5 mm.
The right and left hemisphere are evaluated separately and five region are considered in each hemisphere. Frontal area = anterior to central sulcus, parieto-occipital area, temporal area, infratentorial area, basal ganglia region .
White matter lesions: 0 = no lesions, 1= focal lesions, 2 = beginning confluence of lesions, 3 = diffuse involvement of the entire region, with or without involvement of U fibres. Basal ganglia lesions: 0 = no lesions, 1 = 1 focal lesion, 2 = more than 1 focal lesion, 3 = confluent lesions. Scores are considered separately.

	Right	Left
Frontal	_____	_____
Parieto – occipital	_____	_____
Temporal	_____	_____
Basal ganglia	_____	_____
Infratentorial	_____	_____

Oxford Scale

Evaluation of leukoaraiosis extension on a scale from 0 to 3

_____

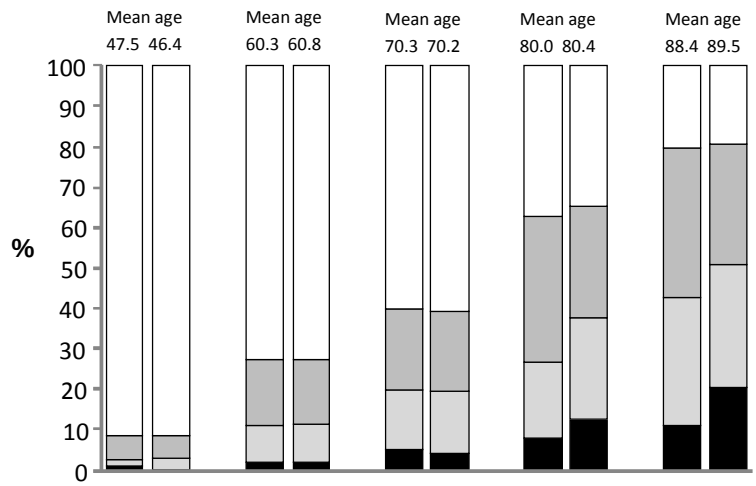
☐ Confluent
☐ Multifocal lesions
☐ Both

1.3.3 Use of the rating scales in statistical analyses

Most of the analyses of associations in this thesis have been done in form of binary logistic regression, using the four categories of leukoaraiosis (0-1-2-3) derived from the final scores of the four scales, and comparing: any degree versus no leukoaraiosis; moderate-severe versus none-mild leukoaraiosis; and severe versus no, mild and moderate leukoaraiosis. All the analyses are adjusted for age as a continuous variable, and often patients have been grouped into age categories, as we know that leukoaraiosis is associated with increasing age. Observing the distribution of leukoaraiosis among different age groups in OXVASC (figure 1.4) has brought the idea of categorising the patients also into a different binary way, integrating the concept of leukoaraiosis in excess for age. So, many of the associations studies have been done with both the types of white matter binary categorisation or, in many instances, I have only used the categorisation into “excess of white matter changes for age”: yes (1) or no (2). This classification consists in considering the presence of leukoaraiosis in excess: at any degree before the age of 55, when at least moderate (>1) in patients between 55 and 75, and when severe (3) in patients over 75 years of age. This classification per se contains an age-adjustment, but I have normally adjusted further for age as continuous variable in my analyses.

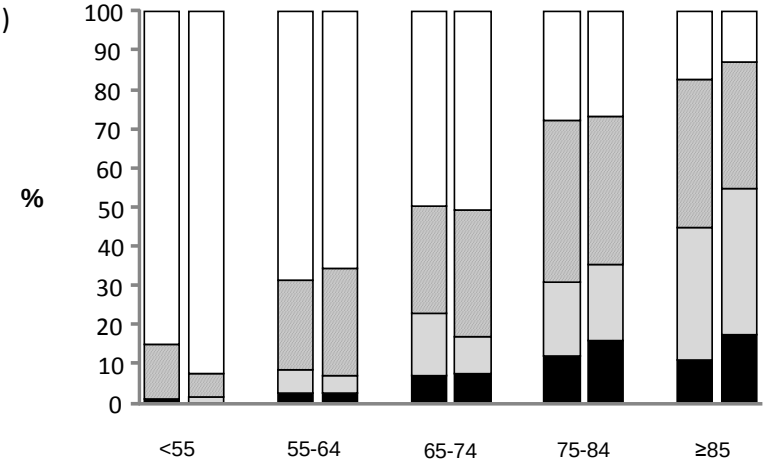
Figure 1.4 Distribution of leukoaraiosis on CT scans, according to different degrees, in different age categories, in men and women, according to the Oxford scale (a) and to the ARWMC scale (b)

(a)



	<55		55 - 64		65 - 74		75 - 84		≥85		
	M	F	M	F	M	F	M	F	M	F	**Total**
Absent	78	66	100	69	131	115	104	119	23	47	852
Mild	5	4	23	15	44	38	101	95	41	72	438
Moderate	1	2	12	9	32	29	53	86	36	74	334
Severe	1	0	3	2	11	8	22	43	12	49	151
Total	85	72	138	95	218	190	280	343	112	242	**1775**

(b)



	M	F	M	F	M	F	M	F	M	F	**Total**
Absent	69	60	87	55	103	86	74	85	19	29	667
Mild	11	4	29	23	56	54	108	121	41	72	519
Moderate	0	1	8	4	33	13	49	51	37	84	293
Severe	1	0	3	2	14	16	32	61	12	39	167
Total	81	65	127	84	206	169	263	318	109	224	**1646**

Leukoaraiosis **Absent** **Mild** **Moderate** **Severe**

1.4 Inter-rater and intra-rater reproducibility of leukoaraiosis grading in OXVASC

I developed the rating tools and performed most of the evaluations in OXVASC. The evaluation started in 2009, seven years after the study had commenced, and after the first radiologist in the study had retired. A second clinical research fellow with some previous experience (Dr. Linxin Li) joined in 2010, in order to continue with the double evaluations of the scans. The second fellow and I trained with a few sessions during which we would apply the scales together and discuss possible problems arising from their application. After these sessions, we evaluated 50 MRI and CT scans jointly: we would give separate evaluations and then discuss the discordant scores. Only in a few cases the evaluations were actually in disagreement, and this was never for more than one point on one scale. The agreement was easily reached in each case by discussion. No formal inter-rater agreement between us was calculated. No inter-rater agreement was calculated between the two radiologists, who evaluated the scans during two different periods. The only way to do this would have been to ask the second radiologist to evaluate scans that had already been graded by the previous colleague, but this would have been too time-consuming in our weekly clinical-radiological meeting.

1.4.1 Inter-rater and intra-rater studies

An inter-rater agreement on the Oxford scale was calculated between mine and the radiologist's evaluations, and this gave a simple kappa value of 0.65. A study of inter-rater agreement between scales was performed between myself and two experienced raters who came to work in the research unit for a short period (Dr. Basil Grueter, Dr. Silvia Lanfranconi). A sample of 140 patients with both CT and MRI scans was selected for the purpose of this sub-study, and a few training sessions over a period of 2 weeks were performed between us 3 evaluators. Operational definitions were discussed and approved (appendix 4), and the evaluations were then performed separately and blinded from any clinical or demographic data. All the evaluators used the same PC to assess the scans.

Table 1.3 summarises the results of this inter-rater study. The values reported are those of the adjusted kappa values, found with the SAS system. According to the Landis and Koch 1977 classification[68], nearly all the agreements were at least substantial (above 0.60). The agreements for the ARWMC scale were calculated for single regions, but the values for the temporal, the infra-tentorial and the basal ganglia regions could not be calculated as the patients with white matter lesions at these levels were too few. I also did an intra-rater study with myself, re-evaluating the same scans after a time interval of 6 months. The agreements, as also reported in table 4, were all above 0.66 and therefore substantial.

Tab. 1.3 Inter- and intra-rater agreement values for CT and MRI scans.

SCALE	Sub-scores	Rater1 vs Rater 2	Rater 3 vs Rater 1	Rater 3 vs. Rater 2	Rater 1 vs Rater1
		K (95% CI)	K (95% CI)	K (95% CI)	K (95% CI)
CT scans					
Van Swieten	**Total**	0.70 (0.63-0.69)	0.63 (0.53-0.74)	0.60 (0.50-0.70)	0.77 (0.70-0.83)
ARWMC	**Frontal right**	0.68 (0.58-0.79)	0.56 (0.43-0.70)	0.55 (0.41-0.67)	0.66 (0.57-0.76)
	Frontal left	0.72 (0.62-0.84)	0.71 (0.61-0.83)	0.55 (0.42-0.68)	0.75 (0.66-0.85)
	Parietal right	0.70 (0.60-0.81)	0.72 (0.62-0.82)	0.65 (0.55-0.76)	0.80 (0.71-0.88)
	Parietal left	0.64 (0.53-0.76)	0.67 (0.56-0.78)	0.56 (0.45-0.67)	0.79 (0.71-0.87)
	Total	0.66 (0.58-0.76)	0.53 (0.42-0.64)	0.43 (0.32-0.55)	0.78 (0.71-0.86)
Oxford	**Total**	0.67 (0.57-0.77)	0.63 (0.54-0.74)	0.55 (0.45-0.66)	0.81 (0.74-0.88)
MRI scans					
Fazekas	**Total**	0.73 (0.65-0.81)	0.68 (0.59-0.76)	0.63 (0.54-0.72)	0.78 (0.73-0.84)
ARWMC	**Frontal right**	0.66 (0.56-0.77)	0.66 (0.57-0.75)	0.69 (0.60-0.79)	0.85 (0.78-0.92)
	Frontal left	0.63 (0.52-0.73)	0.74 (0.65-0.83)	0.76 (0.67-0.86)	0.82 (0.74-0.91)
	Parietal right	0.76 (0.68-0.84)	0.66 (0.56-0.75)	0.78 (0.70-0.86)	0.84 (0.78-0.91)
	Parietal left	0.72 (0.63-0.82)	0.69 (0.60-0.78)	0.71 (0.63-0.80)	0.84 (0.77-0.91)
	Total	0.55 (0.46-0.64)	0.54 (0.45-0.62)	0.60 (0.52-0.69)	0.81 (0.74-0.87)
Oxford	**Total**	0.73 (0.66-0.80)	0.61 (0.53-0.70)	0.65 (0.56-0.74)	0.87 (0.82-0.93)

1.4.2 Reproducibility of the Oxford scale versus the other scales

I also assessed the reproducibility of the Oxford scale compared to the more widespread used and previously assessed ARWMC scale, van Swieten and Fazekas scales for the CT and the MRI scans respectively. Between the Oxford scale and the ARWMC scale (total score), on 1441 CT scans, I found: Kappa 0.92 (SE 0.11, $p<0.0001$) for

presence/absence of leukoaraiosis; Kappa 0.84 (SE 0.015, p<0.0001) for leukoaraiosis moderate-severe versus no-mild leukoaraiosis. Between the Oxford scale and the van Swieten scale (total score), on 1641 CT scans, I found: Kappa 0.92 (95% CI 0.90-0.94 p<0.0001) for presence/absence of leukoaraiosis; Kappa 0.66 (0.63-0.70, p<0.0001) for leukoaraiosis moderate-severe versus no-mild leukoaraiosis. As far as the reproducibility with the MRI scales is concerned, the Kappa value for presence/absence of leukoaraiosis between the Oxford scale and the ARWMC on 494 scans, was 0.89 (0.85-0.93, p<0.0001), and it was 0.82 (0.78-0.87, p<0.0001) for leukoaraiosis moderate-severe versus absent-mild. Between the Oxford scale and the Fazekas scale I found that the kappa value for presence versus absence of leukoaraiosis was 0.85 (0.80-0.90, p<0.0001) and for moderate-severe versus absent or mild leukoaraiosis was 0.87 (0.82-0.92, p<0.0001).

1.4.3 CT versus MRI

On a sample of 416 patients with both CT and MRI, I tested the reliability of leukoaraiosis assessment between CT and MRI, starting from the knowledge that MRI is more sensitive than CT in detecting white matter changes. The Oxford scale was used for the assessment of both CT and MRI, and the reliability was tested for both presence absence and for moderate-severe versus absent or mild leukoaraiosis. As we can see in table 1.4, the cases of leukoaraiosis vs. no leukoaraiosis identified by CT and MRI give an observed agreement of 84.4%, and this increases to 89.7% when considering the cases of no or mild leukoaraiosis versus moderate and severe leukoaraiosis. In table 1.5 I report the kappa values, after the results have been divided according to the age of the population. The kappa values for reproducibility of results either in presence-absence and moderate-severe versus absent or mild leukoaraiosis are all substantial, with slightly more reproducible results in the oldest than in the youngest of the groups.

Tab. 1.4 Cross-tabulation of results of CT and MRI evaluations within the sample of OXVASC patients with both scans

		MRI						
		No LA	**LA**	**Tot.**		**No/Mild**	**Mod/Sev**	**Tot.**
CT	**No LA**	163	56	219	**No/Mild**	277	31	308
	LA	9	188	197	**Mod/Sev**	10	96	106
	Tot.	172	244	416	**Tot.**	287	127	416

Tab. 1.5 CT versus MRI reliability study on 416 patients investigated with both scans

Age (yrs)	**K for Y/N**	**95% CI**	**P**	**K for severity (0-3 scale)**				
				Simple K	**95% CI**	**Weighted K**	**95% CI**	**P**
< 65	0.65	0.53-0.77	<.0001	0.57	0.45-0.69	0.69	0.59-0.79	0.01
> 65	0.63	0.53-0.73	<.0001	0.61	0.53-0.68	0.72	0.66-0.78	<.0001

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Chapter 2

Age and sex-specific rates of leukoaraiosis in TIA and stroke patients: systematic review and population-based study

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2.0 Abstract

Objective: To determine any sex-differences in age-specific prevalence or severity of leukoaraiosis, a marker of white matter ischaemia, in population-based and clinic cohorts of TIA/stroke and in a systematic review of the literature.

Methods: Age-specific sex-differences were calculated for both CT and MRI in the Oxford Vascular Study (OXVASC) and in an MRI-based clinic cohort. I pooled odds ratios for leukoaraiosis in women versus men from published studies by fixed-effect meta-analysis, stratified by patient characteristics (stroke versus non-stroke) and CT versus MRI.

Results: Among 10 stroke studies (all CT-based) leukoaraiosis was most frequent in women (OR=1.42,95%CI 1.27-1.57,p<0.0001), with little heterogeneity between studies (p=0.28). However, no such excess was seen in 10 reports of non-stroke cohorts (0.91,0.67-1.24,p=0.56). Moreover, excess leukoaraiosis in women on CT-imaging in OXVASC (1.38,1.15-1.67,p=0.001) was explained by their older age (age-adjusted OR=1.01,0.82-1.25,p=0.90). Leukoaraiosis was more severe in older (≥75) women (CT-1.50,1.14-1.97,p=0.004 in OXVASC; MRI-1.70,1.17-2.48,p=0.006 in OXVASC and clinic cohort). However, leukoaraiosis was independently associated with early mortality (HR=1.46,1.23-1.73,p<0.0001) suggesting that comparisons in older age groups might be biased by prior premature death of men with leukoaraiosis. Sex-differences in severity of leukoaraiosis were not addressed in previous studies.

Conclusions: Previously reported excess leukoaraiosis in women with TIA/stroke is likely to be confounded by age, and apparently greater severity in older women may be explained by premature death in men with leukoaraiosis.

2.1 Introduction

Onset of coronary artery disease is delayed in women compared to men[1,2], and women have a lower prevalence of peripheral and carotid artery disease, particularly before 75 years of age[3]. However, the overall age-specific incidence of stroke differs much less between the sexes[4], the lifetime risk of stroke is similar in men and women[5,6], and stroke in women appears to be more severe and to lead to more disability than in men[7,8]. This greater relative susceptibility to stroke than to coronary artery disease and the increased severity of stroke in women are unexplained, but could be due to a greater susceptibility to microvascular cerebral ischaemia. Women have been reported to have a higher prevalence and severity of leukoaraiosis than men in some studies[9-12] and a higher progression rate of leukoaraiosis by longitudinal MRI studies,[13,14] although not all studies have confirmed this difference.[15-17] To clarify whether leukoaraiosis is more prevalent and/or more severe in women than in men, or if the previously observed differences might be due to confounding by age, or be secondary to competing risk of earlier vascular death in men, we did a systematic review of the literature on leukoaraiosis and its association with sex, and studied brain imaging in patients in a population based study on stroke and TIA (Oxford Vascular Study - OXVASC) and in an independent TIA-clinic cohort from Stoke-Mandeville Hospital.

2.2 Methods

2.2.1 Systematic review

For my systematic review of the literature I searched two main medical search engines, Medline and Embase (Medline 1950 to present date, Embase 1980 to present date), up to 1/04/2011. I used the terms *leukoaraiosis* or *white matter changes* and matched with the terms *old age/aged*, *hypertension/high blood pressure*, *high cholesterol/hypercholesterolemia*, *cigarette smoking*, *ischaemic heart disease*, *alcohol intake/alcohol consumption*, *diabetes mellitus*, *stroke*, *gender/sex, atrial fibrillation,*

peripheral vascular disease, dementia, carotid artery stenosis/disease. For the purpose of this study I only considered papers reporting the association between sex and leukoaraiosis. There was no restriction by language of publication. I excluded reviews, longitudinal studies (papers reporting on the association between one of these search terms and worsening of leukoaraiosis with time) and research papers based purely on animal models or on laboratory data. I did not set any restriction with regards to the primary objectives of the studies. Inclusion criteria for my meta-analysis were a clear description of gender distribution in the two groups of subjects (leukoaraiosis and leukoaraiosis-free), and a cross-sectional study design. A brief description of the populations and of the objectives of the studies considered in the meta-analysis can be found in Appendix 8, table A2.0. I calculated pooled odds ratios by fixed effect meta-analysis (if heterogeneity between studies was p>0.1 and otherwise by random-effects, and p-values with the Chi-Square test) for presence of leukoaraiosis in women versus men for the studies reporting these data. I grouped the studies according to imaging used (CT or MRI), the mean age of their population, and the study setting (stroke patients versus non-stroke patients).

2.2.2 Population-based study

The OXVASC study is a population-based study of all acute vascular events in a population of 91 000 individuals registered with 63 primary care physicians in 9 general practices in and around Oxford, UK. Methods of OXVASC have been reported previously.[1, 4] In brief, multiple overlapping methods of "hot" pursuit were used to achieve near-complete ascertainment of all individuals with TIA or stroke. These included an urgent neurovascular clinic to which participating general practitioners and the local accident and emergency department send all individuals with suspected TIA or stroke whom they would not normally admit to hospital; daily assessment of admissions to the medical, stroke, neurology, and other relevant hospital wards; and daily searches of the local accident and emergency department attendance register. To not miss patients who

presented late, were referred to other services, or were not referred to secondary care, we also performed monthly computerized searches of family doctor diagnostic coding, hospital discharge codes, and all cranial and carotid imaging studies performed in local hospitals. Patients are followed up for 10-years after the entry event. Follow-up visits include blood pressure check and a questionnaire on general health, recurrent events, medication, and neuropsychological tests at 1 and 6 months and 1, 5 and 10 years. Follow-up is complete for all patients for mortality via centralised death certification records and 5-year follow-up is available in over 95% of patients either by face-to-face follow-up or follow-up via their family doctor.

Consecutive patients with TIA or stroke (ischaemic or haemorrhagic) assessed for OXVASC between 1st April 2002 and 30th April 2010 were included. The only exclusion criterion was lack of availability of adequate brain imaging. Leukoaraiosis was prospectively and independently coded by a neuroradiologist and by an experienced neurologist. Assessments were made blind to clinical data. Large cortico-subcortical strokes, definite subcortical lacunar lesions (well delineated, oval or rounded in shape, measuring 1.5 cm or less, or with the same signal intensity than CSF), and obvious tumours or cysts were excluded from the evaluation by mean of not considering the whole region affected in the scoring of leukoaraiosis. Old, not complete, lacunar infarctions or demyelinating lesions in the context of more diffuse leukoaraiosis could not be excluded by mean of our visual assessment. Leukoaraiosis was graded according to:

1. The ARWMC scale[18] for both CT and MRI, rating 5 different regions in both hemispheres according to a 0-3 score. I used the total score derived from this scale and categorised it into absent (0), mild (1 to 5), moderate (6 to 10) and severe (over 10) leukoaraiosis.

2. A qualitative scale ("Oxford scale") based on the severity score (absent, mild, moderate, or severe) of the Blennow scale[19] for CT scans, and a modified version of the Fazekas scale[20], considering periventricular and deep white matter lesions altogether, for MRI scans.

The neuroradiologist only applied the Oxford scale, while the neurologist applied both the ARWMC scale and the Oxford scale.

MRI scans were performed on a 1.5 Tesla Philips Achieva scanner, and CT scans on a Toshiba, Aquilion 64, 64-slice scanner. The MRI sequences chosen for evaluation were the transverse T2 and the coronal FLAIR. This latter was only available in coronal view, according to the clinical protocol applied in our hospital, and therefore it was mainly used to support and clarify the T2 findings.

2.2.3 Clinic cohort

I also studied MRI scans from a population of 766 consecutive ischaemic strokes or TIA seen in a TIA/Stroke clinic in the Stoke-Mandeville Hospital, near Oxford, who underwent MRI scan (1.5 Tesla Siemens Symphony system) as part of their routine clinical investigation. These scans had been rated by mean of the ARWMC scale by an experienced observer (Basil Gruter). Combination with the 496 scans rated with the same scale from OXVASC gave a total number of 1262 MRI scans, and the same analyses on the association of leukoaraiosis with sex were repeated

2.2.4 Reliabilty studies and statistical analyses

Within the OXVASC cohort, the inter-rater agreement on presence and severity of leukoaraiosis on CT was assessed by kappa-statistics in a subset of 996 consecutive cases and for MRI on 100 cases. I also performed an agreement study between CT and MRI in the 416 patients who had had both modalities of imaging, using the SAS software to calculate both simple and weighted kappa.[21] The inter-rater reproducibility between the Stoke-Mandeville and the OXVASC raters was calculated on a sample of 130 consecutive scans, and the details are also reported in chapter 1.

I calculated age and sex-specific rates of leukoaraiosis, stratified by severity. I also determined sex-differences in presence of leukoaraiosis in three different age strata (<55,

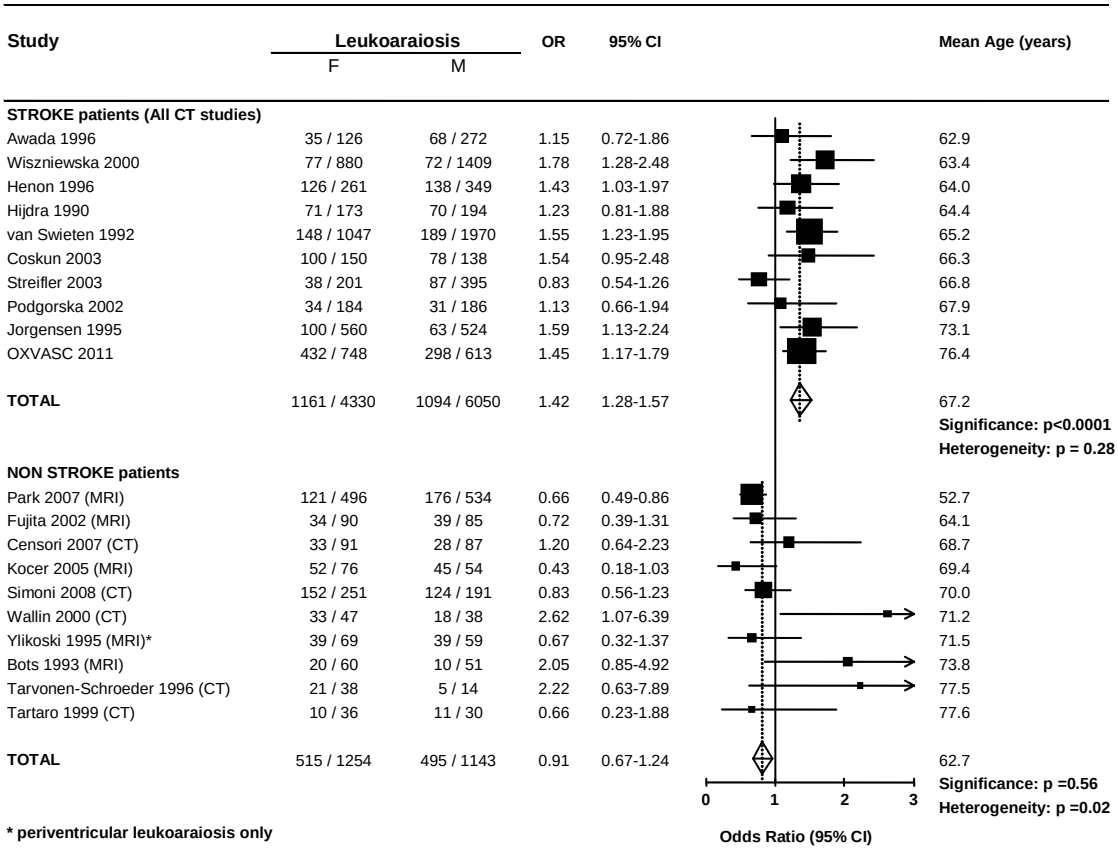
55-74, ≥75) after further adjustment for age as a continuous variable, in logistic regression analyses for: any degree versus no leukoaraiosis; moderate-severe versus none-mild leukoaraiosis; and severe versus no, mild and moderate leukoaraiosis. Multivariate logistic regression analyses were performed with presence of leukoaraiosis as outcome variable and female sex as covariate, inserting as possible confounders age and, in a second model, age and multiple vascular risk factors (h/o hypertension, previous CVA, ischaemic heart disease, diabetes mellitus, atrial fibrillation, peripheral vascular disease, current smoking, hyperlipidaemia, carotid stenosis >50% on either side). I determined the association between CT-detected leukoaraiosis and risk of death in all OXVASC patients and in those aged<75 years in a Cox regression analysis. All analyses were performed using SPSS version 15.

2.3 Results

From my systematic review of the literature, 210 papers on white matter changes reporting on the association with at least one of the search terms were identified on Medline, and 159 on Embase. Many overlaps existed between the two search engines. When specifically looking at papers dealing at some point with gender differences in white matter changes, 36 papers were identified on Medline and 35 on Embase, with an overlap of 24 papers between the 2 search engines, leaving a total of 47 papers. After eliminating reviews on the subject, papers reporting on longitudinal observations (i.e progression of leukoaraiosis in association with sex), laboratory-based or purely radiological experimental papers, I was left with 33 potentially eligible studies. Only 19 of these (14 based on CT and 5 on MRI) reported data on presence of leukoaraiosis stratified by sex. Meta-analysis of data from these 19 studies showed excess leukoaraiosis in women (OR 1.19, 95%CI 1.08-1.33, p=0.03), but there was significant (p<0.0001) heterogeneity between studies. When stratified by type of study population (Fig.2.1), the excess leukoaraiosis in women was only seen in TIA and stroke cohorts (1.42, 1.28-1.57, p<0.0001), with no sex-difference in the non-stroke studies (0.91, 0.67-1.24, p=0.56),

which included healthy subjects, community dwelling people, patients from neurology or general medicine clinics, from dementia clinics and from geriatric or neurology hospital wards. Although the non-stroke studies were generally small, these two estimates were significantly different (p=0.006). Indeed, the frequency of leukoaraiosis was lower in women versus men in those non-stroke studies that used MRI (0.70, 0.56-0.86, p=0.001). All of the studies in TIA/stroke populations were CT-based.

Fig. 2.1 Meta-analysis of studies identified by a systematic review of the published literature on the prevalence of leukoaraiosis stratified by sex. The studies have been stratified according to patient setting (stroke versus non-stroke patients), and according to the type of imaging used (CT or MRI). Pooled odds ratios have been calculated by fixed effect meta-analysis for studies on stroke patients and by random effect meta-analysis in studies on non-stroke patients.



The OXVASC patients comprised 2124 subjects (1127 female) with age ranging from 21.9 to 99.6 years (mean=73.8; sd=13.4). Women were significantly older than men (75.7

vs. 71.5, p<0.001). Patients had been recruited following ischaemic stroke (1069), cerebral or ocular TIA (791), intracerebral haemorrhage (109), subarachnoid haemorrhage (67), and uncertain stroke or retinal artery occlusion (88). Brain imaging was available for review in 1890 (89.0%) of 2124 patients. The most common reasons for non-imaging were death prior to or shortly after arrival at hospital, events occurring abroad, and ocular ischaemia only. Of the 1890 patients studied, 988 (52.3%) were women and the sex-difference in age remained (75.3 vs 71.3, p<0.001).

I reviewed 2306 scans from the 1890 patients (1777 CT and 529 MRI, with 416 patients having both). The inter-rater agreement on presence of leukoaraiosis in 996 consecutive cases imaged by CT and rated by the Oxford scale was moderate to good (k=0.64, 0.59-0.69, for presence of any leukoaraiosis, and 0.58, 0.55-0.62 for severity). The inter-rater agreement on presence of leukoaraiosis in 100 consecutive cases imaged by MRI and rated by the Oxford scale was also good (k=0.78, 0.65-0.90 for presence and 0.66, 0.56-0.76 for severity of leukoaraiosis) (Table 2.1). In the 416 patients who had both CT and MRI, agreement between independent assessments made on the different modalities was not significantly less than the inter-observer reproducibilities of either modality alone (see chapter 1, table 1.5).

Table 2.1 Inter and intra-rater reliability study. Kappa values with 95% confidence interval between the OXVASC neurologist and radiologist and between the OXVASC neurologist and the Stoke-Mandeville neurologist. Intra-rater reliability kappa values have been calculated for the OXVASC neurologist.

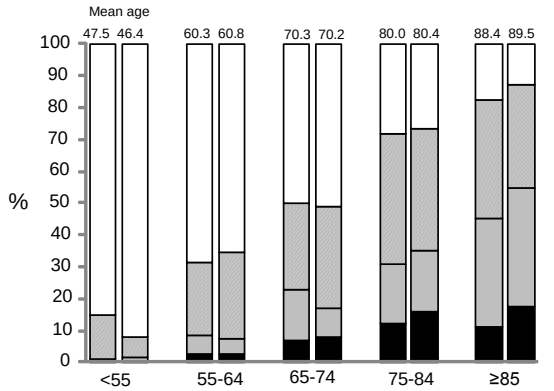
	Number of scans	Scale assessed	K (95% CI)
OXVASC Neurologist versus Radiologist			
	996 CT scans	Oxford scale - severity	0.58 (0.55-0.62)
		Oxford scale - presence	0.64 (0.59-0.69)
	100 MRI scans	Oxford scale - severity	0.66 (0.56-0.76)
		Oxford scale - presence	0.78 (0.65-0.90)
OXVASC Neurologist versus Stoke-Mandeville Neurologist	**130 MRI scans**	ARWMC - categorized 0-3 score	0.54 (0.45-0.62)
OXVASC Neurologist Intra-rater	**130 MRI scans - Oxford scale**	Oxford scale - severity	0.87 (0.82-0.93)
	130 MRI scans - ARWMC	ARWMC categorized 0-3 score	0.81 (0.74-0.87)
	140 CT scans - Oxford scale	Oxford scale - severity	0.81 (0.74-0.88)

Leukoaraiosis appeared to be more frequent in women than in men in those patients imaged by CT in OXVASC (1.38, 1.15-1.67, p=0.001), but women imaged with CT were older than men imaged with CT and when I adjusted the association for age there was no longer any excess leukoaraiosis in women (adjusted OR=1.01, 0.82-1.25, p=0.90) (table2.2). Moreover, in OXVASC patients imaged by MRI, in whom the males and females were of similar age, there was no sex-difference in the frequency of leukoaraiosis (table 2.1). On both CT and MRI, age was the most powerful predictor of presence of leukoaraiosis (OR per 10 years=2.16, 1.96-2.59, p<0.001 for CT; 2.59, 1.96-2.83, p<0.001 for MRI).

I also stratified analyses by age in 10-year bands from age 55 (fig 2.2). Leukoaraiosis was reported more frequently on MRI than on CT, particularly in the younger age groups, but there was little consistent sex-difference in frequency with either modality. However, subcategorisation by severity of leukoaraiosis (ARWMC scale) showed a trend towards more severe leukoaraiosis in women above 75 years of age, both on CT and MRI (fig 2.2, table 3) in OXVASC and on the merged MRI cohort from OXVASC and the clinic cohort from Stoke Mandeville (OR for severe leukoaraiosis in women versus men in the composite MRI cohort: 2.79, 1.63-4.79, p<0.0001,fig 2; table 3).

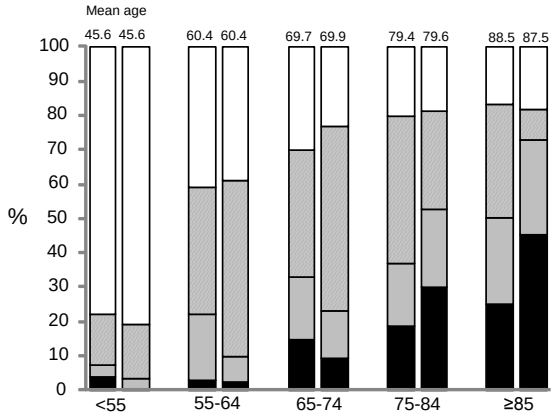
Figure 2.2 Distribution of leukoaraiosis on CT scans of OXVASC patients (A) and MRI scans of OXVASC (B) and Stoke-Mandeville (C) patients, according to sex and age. Leukoaraiosis severity is graded according to the ARWMC scale.

(A)



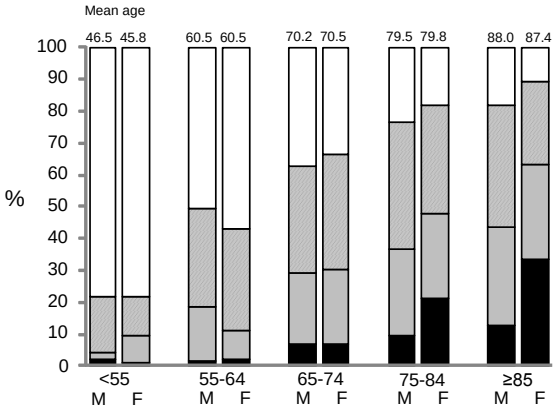
	<55		55-64		65-74		75-84		≥85		
	M	F	M	F	M	F	M	F	M	F	Tot.
Absent	69	60	87	55	103	86	74	85	19	29	667
Mild	11	4	29	23	56	54	108	121	111	72	519
Moderate	0	1	8	4	33	13	49	51	37	84	293
Severe	1	0	3	2	14	16	32	61	12	39	167
Total	81	65	127	84	206	169	263	318	109	224	**1646**

(B)



	<55		55-64		65-74		75-84		≥85		
	M	F	M	F	M	F	M	F	M	F	Tot.
Absent	42	47	30	16	23	10	11	12	2	4	197
Mild	8	9	27	21	28	23	23	18	4	2	163
Moderate	2	2	14	3	14	6	10	14	3	6	74
Severe	2	0	2	1	11	4	10	19	3	10	62
Total	54	58	73	41	76	43	54	63	12	22	**496**

(C)

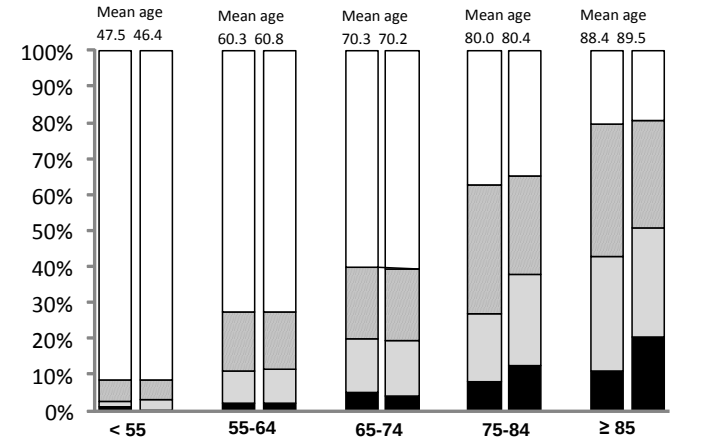


	<55		55-64		65-74		75-84		≥85		
	M	F	M	F	M	F	M	F	M	F	Tot.
Absent	80	76	80	52	79	48	41	35	7	6	504
Mild	18	12	49	29	71	51	69	65	15	15	394
Moderate	2	8	27	8	48	33	47	51	12	17	253
Severe	2	1	2	2	14	10	16	40	5	19	111
Total	102	97	158	91	212	142	173	191	39	57	**1262**

Leukoaraiosis: Absent Mild Moderate Severe

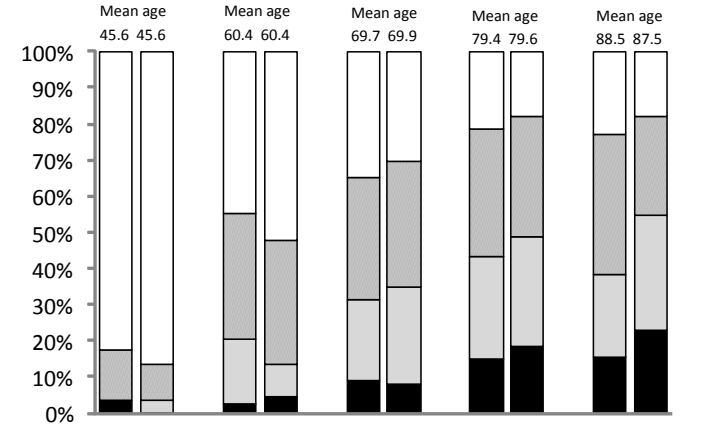
Figure 2.3 Age and sex-specific rates of leukoaraiosis within OXVASC, on CT (a) and MRI scans (b). Leukoaraiosis severity is graded according to the Oxford scale.

(a)



	< 55		55-64		65-74		75-84		≥ 85		
	M	F	M	F	M	F	M	F	M	F	Tot.
Absent	78	66	100	69	131	115	104	119	23	47	852
Mild	5	4	23	15	44	38	101	95	41	72	438
Moderate	1	2	12	9	32	29	53	86	36	74	334
Severe	1	0	3	2	11	8	22	43	12	49	151
Tot.	85	72	138	95	218	190	280	343	112	242	**1775**

(b)



	< 55		55-64		65-74		75-84		≥ 85		
	M	F	M	F	M	F	M	F	M	F	Tot.
Absent	48	51	35	23	28	15	13	12	3	4	232
Mild	8	6	27	15	27	17	21	22	5	6	154
Moderate	0	2	14	4	18	13	17	20	3	7	98
Severe	2	0	2	2	7	4	9	12	2	5	45
Tot.	58	59	78	44	80	49	60	66	13	22	**529**

Leukoaraiosis: Absent Mild Moderate Severe

To determine whether leukoaraiosis might be associated with an increased risk of premature death and hence a competing-risks bias due to earlier death in men compared with women, I determined the association between the presence of leukoaraiosis on CT at entry in OXVASC and time to death in a Cox-regression analysis, also including age, sex, and hypertension as covariates. Leukoaraiosis was a significant independent predictor of death (HR 1.46, 95% CI 1.23-1.73, $p<0.0001$). This association remained when analysis was confined to patients younger than 75 years (1.53, 1.08-2.18, $p=0.02$).

Table 2.2 Differences between sexes in the 1890 patients from the OXVASC study, grouped according to type of scan they have received.
For each group I report presence/absence of leukoaraiosis in women and men and the odds ratios, with and without age-adjustment and adjusted for all the risk factors listed, for presence of leukoaraiosis in women versus men

	CT-Only (1361)			**CT and MRI (416)**			**MRI-only (113)**		
	F (748)	**M** (613)		**F** (194)	**M** (222)		**F** (46)	**M** (67)	
			P			**P**			**P**
Mean Age (SD)	78.16 (11.6)	74.22 (11.6)	**<0.01**	68.30 (13.1)	65.96 (12.7)	0.07	58.79 (16.6)	62.80 (14.6)	0.18
Hypertension	459 (61.4)	332 (54.2)	**<0.01**	98 (50.5)	113 (50.9)	1.00	18 (39.1)	30 (44.8)	0.57
Previous CVA	107 (14.3)	86 (14.0)	0.94	14 (7.2)	15 (6.8)	0.85	4 (8.7)	2 (3.0)	0.22
Ischaemic Heart Disease	132 (17.7)	153 (25.0)	**<0.01**	19 (9.8)	41 (18.5)	**0.02**	6 (13.0)	9 (13.4)	1.00
Diabetes mellitus	91 (12.2)	80 (13.1)	0.62	24 (12.4)	34 (15.3)	0.40	4 (8.7)	8 (11.9)	0.76
Atrial Fibrillation	143 (19.1)	155 (25.3)	**<0.01**	16 (8.2)	22 (9.9)	0.61	1 (2.2)	5 (7.5)	0.40
Peripheral Vascular Disease	38 (5.1)	60 (9.8)	**<0.01**	8 (4.1)	18 (8.1)	0.11	2 (4.3)	2 (3.0)	1.00
Current Smoking	86 (11.5)	83 (13.5)	0.28	33 (17.3)	44 (20.0)	0.53	6 (13.0)	11 (16.4)	0.79
Hyperlipidaemia	184 (24.6)	162 (26.4)	0.53	59 (32.1)	64 (28.8)	0.59	11 (24.4)	20 (29.9)	0.67
> 50% Carotid Stenosis	65 (8.7)	87 (14.2)	**0.02**	12 (8.1)	17(9.8)	0.70	2 (6.9)	7 (12.7)	0.49
Leukoaraiosis on CT									
Presence (%)	386 (66.2)	278 (56.9)		83 (48.5)	89 (44.7)		–	–	
OR (95% CI)	1.49 (1.16-1.91)		**<0.01**	1.17 (0.77-1.76)		0.46	–		
Age-adj OR (95% CI)	1.08 (0.82-1.43)		0.60	0.97 (0.60-1.55)		0.89	–		
Fully adj OR (95% CI)	0.92 (0.65-1.29)		0.61	0.77 (0.44-1.33)		0.34			
Leukoaraiosis on MRI									
Presence (%)	–	–		117 (64.3)	136 (63.8)		20 (46.5)	25 (44.6)	
OR (95% CI)	–			0.93 (0.68-1.54)		0.93	1.08 (0.49-2.40)		0.85
Age-adj OR (95% CI)	–			0.88 (0.55-1.41)		0.60	1.39 (0.58-3.36)		0.46
Fully adj OR (95% CI)	–			0.83 (0.48-1.45)		0.52	1.97 (0.54-7.19)		0.31

Table 2.3 Differences between sexes in baseline clinical characteristics in the OXVASC study and in the Stoke-Mandeville cohort. Mean age is reported in years; standard deviation, while all the other variables are reported as number of patients with the condition (% of total). Fully adjusted means adjusted for age and for all the other vascular risk factors listed in the table.

	OXVASC Cohort						**Stoke-Mandeville Cohort**		
	CT			**MRI**			**MRI**		
	F (942)	**M** (835)		**F** (240)	**M** (289)		**F** (351)	**M** (415)	
			P*			**P***			**P***
Mean Age	78.2; 11.6	74.2; 11.6	**<0.01**	66.5; 15.0	65.2; 13.2	0.31	71.6; 12.3	69.5; 11.8	**0.02**
			P**			**P****			**P****
Hypertension	557 (59.3)	445 (53.4)	**0.01**	116 (48.3)	145 (49.8)	0.79	200 (57.3)	247 (60.4)	0.42
Previous CVA	121 (12.8)	101 (12.1)	0.67	18 (7.5)	17 (5.8)	0.49	35 (10)	46 (11.2)	0.64
Ischaemic Heart Disease	151 (16.3)	194 (23.5)	**<0.01**	25 (10.5)	51 (17.6)	**0.03**	47 (13.6)	87 (21.4)	**<0.01**
Diabetes mellitus	115 (12.2)	114 (13.7)	0.40	28 (11.7)	43 (14.8)	0.31	44 (12.5)	68 (16.4)	0.15
Atrial Fibrillation	159 (16.9)	177 (21.2)	**0.02**	17 (7.1)	28 (9.6)	0.35	35 (10.1)	38 (9.3)	0.71
Peripheral Vascular Disease	46 (4.9)	78 (9.4)	**<0.01**	10 (4.2)	20 (6.9)	0.19	8 (2.3)	24 (6.0)	**0.02**
Current Smoking	119 (12.9)	127 (15.5)	0.13	39 (16.5)	55 (19)	0.49	49 (14.1)	98 (23.9)	**<0.01**
Hyperlipidaemia	243 (26.7)	226 (27.7)	0.67	70 (30.6)	85 (29.6)	0.85	108 (39.3)	132 (38.3)	0.80
> 50% Carotid Stenosis	77 (13.1)	104 (17.7)	**0.04**	14 (7.9)	24 (10.5)	0.40	25 (11.7)	43 (16.2)	0.19
Leukoaraiosis									
Presence	527 (55.9)	400 (47.9)	**<0.01**	135 (56.3)	163 (56.4)	1.00	223 (63.5)	236 (56.9)	0.07
OR (95% CI)	1.38 (1.15-1.67)		**<0.01**	0.99 (0.70-1.40)		0.97	1.32 (0.99-1.77)		0.06
Age-adj OR (95% CI)	1.01 (0.82-1.25)		0.90	0.89 (0.60-1.32)		0.56	1.15 (0.83-1.60)		0.39
Fully adj OR (95% CI)	0.84 (0.65-1.09)		0.18	0.74 (0.46-1.19)		0.22	1.14 (0.68-1.91)		0.62

* T-Test,**Chi-Square

Table 2.4 Odds ratios for prevalence of different degrees of leukoaraiosis in women versus men, according to age, in the OXVASC cohort and in the merged OXVASC and Stoke-Mandeville population. Leukoaraiosis was rated with the ARWMC scale both on CT and MRI. Odds ratios are also adjusted for age as continuous variable in order to minimize the effect due to age within single age stratum.

			OXVASC patients			OXVASC and Stoke-Mandeville (MRI only)		
Age (yrs)	**Leukoaraiosis**	**Imaging**	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**
< 55	**Any**	**CT**	0.52	0.17-1.59	0.250	–	–	–
		MRI	0.83	0.33-2.12	0.700	1.04	0.53-2.06	0.904
	Mod/Sev	**CT**	1.72	0.10-29.5	0.710	–	–	–
		MRI	0.46	0.08-2.73	0.395	3.03	0.87-10.61	0.083
	Severe	**CT**	na	na	na	–	–	–
		MRI	na	na	na	0.58	0.05-6.68	0.666
55-74	**Any**	**CT**	0.97	0.68-1.39	0.880	–	–	–
		MRI	1.25	0.70-2.22	0.546	0.96	0.68-1.35	0.809
	Mod/Sev	**CT**	0.71	0.45-1.14	0.154	–	–	–
		MRI	0.52	0.26-1.03	0.060	0.86	0.58-1.28	0.460
	Severe	**CT**	1.12	0.55-2.30	0.755	–	–	–
		MRI	0.65	0.22-1.92	0.431	1.13	0.52-2.46	0.751
≥75	**Any**	**CT**	1.20	0.85-1.70	0.299	–	–	–
		MRI	1.03	0.46-2.34	0.941	1.44	0.90-2.29	0.130
	Mod/Sev	**CT**	1.28	0.97-1.69	0.087	–	–	–
		MRI	**2.04**	**1.05-3.96**	**0.035**	**1.70**	**1.17-2.48**	**0.006**
	Severe	**CT**	1.43	0.97-2.11	0.076	–	–	–
		MRI	2.06	0.97-4.40	0.062	**2.79**	**1.63-4.79**	**<0.0001**

2.4 Discussion and conclusions

Clinical onset of coronary artery disease and peripheral vascular disease is delayed in women compared with men, but stroke incidence differs much less[1]. One possible explanation is that women are predisposed to cerebral ischaemia, which might be reflected in a greater frequency of leukoaraiosis, as has been reported previously in some studies[9-12]. However, not all studies have found this sex-difference, and given an absence of published data from MRI-based studies in patients with TIA or stroke, I determined sex-differences in frequency and severity of leukoaraiosis using both CT and MRI in a population-based TIA/stroke incidence study, a clinic cohort, and a systematic review of the literature.

I found that the apparent excess of leukoaraiosis in women with TIA/stroke was confounded by age, with no sex-difference on CT or MRI after adjusting or stratifying by age. I also found good inter- and intra-rater reliability of assessment of leukoaraiosis by both imaging modalities.

I did find that leukoaraiosis was more severe in women than men at older ages. This finding was consistent on both CT and MRI and in the population-based cohort and clinic cohort. This sex-difference could in theory reflect an increased susceptibility of white matter to ischaemia in older women, but it is more likely to be an artifact due to sex-differences in premature death i.e. men who survive to their 80s and 90s are a more highly selected group than are women of the same age. In the OXVASC cohort of imaged patients reported here, for example, there were 242 women aged over 85 years, but only 112 men. This could mean that about 130 more men than women born in the same years had already died. Even if the presence or severity of leukoaraiosis were only weakly associated with premature death (e.g. a relative increase in mortality of 10%), it would be enough to account for the sex differences that we have observed in older age groups. In fact, the association that we observed

between leukoaraiosis and risk of subsequent death in the OXVASC cohort was stronger. An objection to this theory might come from the fact that the increased risk of death observed in OXVASC is only applicable to patients who have had a stroke or TIA, while here we are talking about a selection occurred before entering the study, and therefore before the occurrence of stroke or TIA. However, the association between leukoaraiosis and increased mortality has been reported in other studies, either in the general population[38,39] or in stroke patients.[40,41] In patients under the age of 75 years, on the other hand, the numbers of men and women are almost identical (441 men versus 357 women), with much less potential for bias due to premature death, and I found no sex-difference in leukoaraiosis. There was a trend for leukoaraiosis to be more severe in men than women under the age of 65, but the numbers were too small for me to be able to draw any conclusion.

This study has some potential shortcomings. First, I used semi-quantitative methods to assess leukoaraiosis severity and my observations were mainly based on CT scans. However, despite the fact that reproducibility of rating scales is influenced by the nature of the scale itself and by the expertise of the raters,[42, 43] I found good intra- and inter-rater reproducibility for both CT and MRI evaluations. Moreover, although CT scans have a lower sensitivity for detection of white matter lesions when compared with MRI, CT-detected white matter changes might be more relevant clinically,[44] and studies in our centre on the correlation between neuropathology and CT imaging have shown that CT-based assessment of leukoaraiosis is valid.[45,46] It is well recognised that CT scans have a lower sensitivity for white matter changes than MRI, but the concordance of results between different MRI cohorts in this study and then between MRI and CT offers a strong support in favour of the validity of my CT findings.

Second, not all white matter changes represent chronic ischaemia. I might occasionally have included demyelinating or vasculitic lesions or previous focal ischaemic lesions, as these are

not always possible to distinguish from leukoaraiosis by mean of visual evaluation. I believe that this would be unlikely to have resulted in any bias. Third, in the systematic review, I was only able to identify CT-based studies in stroke populations, while the studies in other settings were based both on CT and on MRI. However, I also report the largest single-centre stroke-based MRI cohort so far to address sex-differences in leukoaraiosis.

Overall, therefore, I consider that these findings are unbiased and reliable. The association between presence of leukoaraiosis and female sex can be explained by the strong association of leukoaraiosis to age and by the over-representation of female sex in the older patients with TIA and stroke. The greater severity of leukoaraiosis in older women may represent an artefact due to greater risk of premature death in men with leukoaraiosis. I have found no evidence to support the hypothesis that women have a greater susceptibility to white matter ischaemia than men.

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Chapter 3

Hypertension and white matter changes:
- Systematic review of literature
- Associations with history of hypertension and ten years of BP measures: a population-based study of stroke and TIA patients (OXVASC Study).

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3.0 Abstract

Background: Hypertension is common in the elderly, and is one of the major risk factors for stroke. I explored the association between blood pressure (BP) and WMC with a systematic review of the literature and analysing a ten year period data in a stroke and TIA population-based cohort (OXVASC).

Methods: Systematic review: Medline and Embase were searched for studies on WMC and BP. Studies reporting the number of hypertensive patients with and without WMC were included in a meta-analysis. Population study: in consecutive patients with TIA or stroke, all pre-morbid BPs from primary care records were collected. WMC were rated on baseline CT or MRI with four scales, and age-specific associations with mean systolic and diastolic BP and with most recent and highest BP, calculated based on measurements over 10-years.

Results: Meta-analysis: association between hypertension and WMC was shown, stronger in studies with younger populations. Population study: there was an association between WMC and mean diastolic and systolic BP on CT and/or MRI of 1917 patients with data available. ORs (age and sex adjusted) ranged from 1.09 (0.99-1.20, p=0.064) to 1.31 (1.12-1.53,p<.0001) per 10 mmHg mean systolic BP and from 1.25 (1.04-1.50, p= 0.012) to 1.62 (1.20-2.17, p=0.001) per 10 mmHg mean diastolic BP. All associations with SBP diminished with age and none were significant at age ≥75 years. In contrast, 10-year mean DBP remained positively associated with WMC in the elderly (≥75 years - 1.48, 1.19-1.84, p=0.001), with no evidence of a J-shape.10-year mean BP was more strongly associated than most recent and highest BP.

Conclusions: Both meta-analysis and population study confirmed the association between higher blood pressure and white matter changes, with stronger association in the younger populations. Mean BP better predicted WMC than single BP measures. The associations weakened with age, but higher mean diastolic BP remained more strongly associated than mean systolic BP in the oldest group of the population.

3.1 Introduction

Hypertension affects a large proportion of the population after the age of 60, and is one of the most powerful risk factors for stroke, both ischaemic and haemorrhagic. Hypertension is also considered one of the most important factors leading to damage to small vessels and to blood-brain barrier disruption, and consequently to white matter changes.[1] If hypertension were the sole link between white matter changes and stroke, we would expect a direct relation of the two within each type of stroke considered, and leukoaraiosis could simply represent an epiphenomenon of ageing and high blood pressure. However, several studies have recently advocated the independent effect of white matter changes on stroke incidence and outcome,[2,3] implying that leukoaraiosis is a causal risk factor for stroke.

In this chapter I report the results of a systematic review of the literature on white matter changes and hypertension, with a meta-analysis of all available data. I then report the results of the analyses on history of hypertension and white matter changes within the OXVASC study, exploring the relation between history of hypertension and different subtypes of strokes. I will try to verify whether white matter changes contribute to any type of stroke, independently from hypertension. In a further study, I will look into the association between leukoaraiosis and the mean of blood pressure measures collected from primary care over a period of ten years antedating the entry stroke in the OXVASC study, and will compare this with the associations with both history of hypertension and single blood pressure measurements. The aim is to understand whether a more detailed blood pressure history better predicts the presence and severity of brain white matter changes, independently from age.

3.2 Methods

3.2.1 Systematic review of the literature on blood pressure and leukoaraiosis

I have performed a systematic review of the literature on the subject of leukoaraiosis and blood pressure, and pooled the results of several studies. Two main medical search engines, Medline (1950 to 01/04/2011) and Embase (1980 to 01/04/2011), were searched. The search terms *leukoaraiosis* or *white matter changes* were matched with the terms *hypertension/high blood pressure*. I included in my meta-analysis only studies on humans and with a cross-sectional design. Only papers in English were considered. A few papers were subsequently added, from the retrieved papers references. The association between hypertension and white matter changes was not necessarily the main objective of these studies, but papers were included when they reported the absolute number of hypertensive patients within the leukoaraiosis and the leukoaraiosis-free groups. A brief description of the populations and of the objectives of the studies considered in the meta-analysis can be found in Appendix 8, table A2.0.

3.2.2 History of hypertension and pre-morbid blood pressure measures in OXVASC

I have considered patients recruited in years 1 to 8 (1st April 2002- 30th April 2010) included in the OXVASC study following an ischaemic or haemorrhagic event, excluding subarachnoid haemorrhages and all the secondary causes of intracranial bleed, as well as subdural haematomas. Analyses have been stratified by age. I have considered the variable history of hypertension as from the patient's history collected at the first interview, in terms of binary variable (Y/N). I personally reviewed and cleaned these data.

The definition of ischaemic stroke subtypes was made according to the TOAST[4] classification, agreed upon during regular meetings between the clinical fellows and one of

the neurology consultants. Associations were sought between history of hypertension and subtypes of ischaemic stroke, and between hypertension and presence or severity of leukoaraiosis. Binary logistic regression analyses were used to calculate the odds ratios between exposed and non exposed groups.

All the patients in OXVASC have had their primary care records reviewed by a specialist nurse, who has collected all blood pressure recordings by the general practitioners before the stroke or TIA. A maximum of 5 blood pressure measures per year have been recorded, with the majority of patients having less than 5 measurements per year. Where the number of measurements was higher than 5, these have been randomly selected among the available data, maintaining a chronological order. The measurements up to 10 years prior to the inclusion event have been used to calculate the mean blood pressure. For my analyses I used the mean systolic and the mean diastolic blood pressure, and I also looked at the most recent (closer to the event) systolic and diastolic blood pressure measurements and at the maximum values of systolic and diastolic recorded in the 10 year period. I used regression analyses to calculate the strength of associations, and calculated the odds ratios for 10 mmHg increase in blood pressure.

White matter changes were graded with three different rating scales, as explained in a previous chapter of this thesis. Briefly, I have used the van Swieten scale, the ARWMC scale and an Oxford scale for CT scans, and the Fazekas, the ARWMC and again the Oxford scale for MRIs. Leukoaraiosis was categorized as absent, mild moderate and severe according to each of the scales, and analyses were done in two different ways:

1. With binary logistic regressions, considering as variables, in turn, none versus any; moderate and severe versus none and mild leukoaraiosis; severe versus none, mild, and moderate leukoaraiosis.

2. Considering the compound variable “leukoaraiosis in excess of age”. After carefully reviewing the distribution of leukoaraiosis in the OXVASC population (see chapter 1) I drew an age-related threshold of normality for presence of leukoaraiosis according to age, and decided that in patients younger than 55 years, the presence of any leukoaraiosis has to be considered in excess, for patients between 55 and 74 moderate and severe leukoaraiosis can be considered in excess for age, and in patients 75 and older only severe leukoaraiosis can be considered in excess for age.

All the statistical calculations were done using SPSS for Windows, version 15 and 18.

3.3 Results

3.3.1 Blood pressure and leukoaraiosis: a systematic review of the literature and meta-analysis of studies reporting history of hypertension

The systematic review of the literature on leukoaraiosis and blood pressure produced 43 papers mentioning white matter changes and blood pressure: 19 were CT-based and 24 were MRI-based. Among these studies some were longitudinal and some did not report the number of hypertensive patients in the two groups, and therefore they were not included in the meta-analysis. The studies which had as their main objective studying the association between leukoaraiosis and hypertension are summarised in table 3.1. The vast majority of the studies found a positive association between hypertension or some of its components, and white matter changes (Table 3.1). Positive association were found between either presence or severity of white matter changes in cross sectional analyses[5-15] and history of hypertension or higher levels of blood pressure, either systolic or diastolic. Moreover, several other MRI-based longitudinal studies consistently showed worsening of white matter changes or incidence of new white matter lesions associated with higher levels of blood pressure at baseline.[16-22] High diastolic blood pressure has been linked to white matter changes in

several studies,[14,16,19,21] and two studies[5,8] found the variability of diastolic blood pressure to be particularly important to predict the severity of white matter changes. Not many studies on variability of blood pressure and either prevalence or worsening of white matter changes have been made so far, and the populations studied have been too small to be able to draw definitive conclusions on the subject.[23,24]

My meta-analysis only included cross-sectional studies, 19 based on CT imaging[11,25-42] and 9 on MRI studies.[12,10,43-49] Strong associations existed between leukoaraiosis and history of hypertension, both for CT (OR 1.7, 1.5-1.9, P<0.001) and MRI studies (OR 2.3, 2.1-2.6, P<0.001), even though there was a considerable heterogeneity between studies (Figure 3.1). The studies have been ordered according to the age of their population in figure 3.1, and it is clear that, both for CT and for MRI studies, the younger the age of the population, the higher the association between hypertension and white matter changes. When grouping the studies according to age (≤ 65, 65-70, >70) the heterogeneity is reduced and the association becomes weaker with the increasing of the study population age (fig 3.2).

Table 3.1 Summary of Studies on Blood Pressure and White Matter Changes

Study and ref.	Description	Date	Scan Type	WMC scale	BP assessment	FINDINGS
Lille Stroke Registry [11] Henon, Acta Neurol Scand 1996	610 consecutive in-patients with STROKE or TIA. Mean age:64.	1991-1993	CT	Blennow scale: 0-3 for severity and extension. Mean score used	HTN: previously treated, or syst>160 or diast >80 at event or after 1 month	Presence of WMC associated with: htn, age, female sex, diabetes, h/o stroke or TIA. Severity associated with age, female sex, AF, h/o stroke or TIA, brain atrophy , but not with hypertension
Cardiovascular Health Study (CHS) [6] Longstreth, Stroke 1996	Population based,cross-sectional multi-centre study on IHD and stroke. 5888 patients over 65 y-o. 3301 MRI of pts w/o stroke	Baseline 1989-1990	MRI 1.5 T in 3 centres, 0.35 T in one	Liao 0-9 scale. Single rating centre	BP measured at baseline	Association between higher systolic and diastolic BP and presence of WMC
CHS [16] Longstreth Stroke 2005	Population based, longitudinal multi-centre study on IHD and stroke	1919 patients MRI done in 1990-1994 and then at 5 years	MRI 1.5 T	Liao 0-9 scale. Single rating centre	Annual single measurement of BP	Average DBP before initial scan was associated to worsening of WMC
Rotterdam Scan Study [8] de Leeuw, Ann Neurol 1999	Population based, prospective. 1077 subjects 60 to 90 y-o. BP measured between 1975-1978 or between 1990-1993. Aim: to study hypertension in relation to white matter disease	Baseline 1975-1978 and1990-1993	MRI 1.5 T	Subcortical lesions counted and grouped acc to size (< 3 mm, 3-10mm and>10)Volume calculated giving each category a fixed diameter. PV lesions assessed on a 4 point scale. Sum, total of 0-9	BP at baseline and FU. Hypertension defined as SBP >160 or DBP >95. BP values considered in quartiles and linearly. Both Systolic and diastolic blood pressure change cosidered	ORs for presence of severe WMC for 10 mmHg increase of DBP range from 1.2 (1,.0-1.5, PV) to 1.5 (1.2-1.8 SC), for SBP are 1.0 (0.9-1.1 Pv) to 1.1 (1.0-1.3 SC). ORs for change in DBP highly significant for presence of severe WMC, both when DBP reduced and increassed. Less important the effect of SBP variation
Rotterdam Scan Study [9] de Leeuw, Brain 2002	Population based, prospective. 1077 subjects 60 to 90 y-o. BP measured between 1975-1978 or between 1990-1993. Aim: to study hypertension and its duration in relation to white matter disease	Baseline: 1975-1978 or 1990-1993. FU in 1995-1996	MRI 1.5 T	Subcortical lesions counted and grouped acc to size (< 3 mm, 3-10mm and>10)Volume calculated giving each category a fixed diameter. PV lesions assessed on a 4 point scale. Sum, total of 0-9	BP at baseline and FU. Hypertension defined as SBP >160 or DBP >95. Duration of hypertension assessed. Age-stratification	Relationship between duration of hypertension and risk of white matter changes. RRs increase as the duration gets longer
Rotterdam Scan Study [17] van Dijk, Stroke 2008	Population based, prospective. 1077 subjects 60 to 90 y-o. BP measured between 1975-1978 or between 1990-1993. Longitudinal WMC assessment	MRI in 1995-1996 and repeated in 1999-2000	MRI 1.5 T	As above, plus progression of WMC scored as : no progression, minor or marked progression	Extent of progression of WMC related to age, load at baseline, and lacunar infarcts at baseline	WML progression influenced by higher BP at baseline in younger subjects, not in older (over 70) and in pts with lacunar infarcts at baseline
EVA-MRI [7] Dufouil, Neurology 2001	Population-based age 59-71. Longitudinal, 4 years follow up. Aim to study the relation of BP and medications on development of WMC. 830 MRIs. Patients with stroke excluded. Mean age 69.0 years	Recruitment 1991-1993, FU with MRI in 1995-1997	MRI 1.0 T	scale of WMC from A to D. **A**= no lesion, **B**= deep </=3 mm, PV</=5 mm, **C** = one to 10 deep WMH 4 to 10 mmor PVH 6 to 10 mm, **D**= more than 10 deep WMC 4-10mm, or confluent deep WMC or PVWMC >/=11 mm	BP measured at entry, and medications recorded. Hypertension defined as SBP >160 or DBP >95. BP measured again at 4 years (incident, prevalent)	HTN at baseline associated to severe LA at 4 years (OR 2.9) Normotensive treated are at lower risk than hypertensive treated to have severe WMC at 4 years. Incident and prevalent hypertensive more at risk than normotensive of having WMC. Authors suggested that it would be interesting to study the effect of different anti-hypertensive regimes on WMC.
CASCADE [5] **(Clopidogrel After Surgery for Coronary Artery DiseasE)** Launer, Neuroepid. 2000	European multicenter study on vascular risk factors for atrophy and WMC. Population 65-75 already under study for other research. Retrospective. 1810 MRIs.	MRI in 1996-1998. Data from 10 or 5 years earlier	MRI 1T, mobile machine, or 1.5 T	Scheltens scale: number, size and location of subcortical lesions. 0-2 assessment of periventricular lesions. Three independent raters, good K values	BP from 10 years earlier. Analyses for level of BP in increases of 5 mmHg DBP or 10 mmHg SBP, for change in BP per year and for treatment status (untreated, treated successfully, poorly controlled)	Higher levels of BP increase the risk of presence of severe LA (but small ORs and just significant). Change in DBP, both reduction and increase, associated with severe WMC. Less important the effect from SBP. Main effect in PV white matter. Poorly controlled treated hypertensive are the most at risk of LA

Table 3.1, **cont.** Summary of Studies on Blood Pressure and White Matter Changes

Study and ref.	Description	Date	Scan Type	WMC scale	BP assessment	FINDINGS
Atherosclerosis Risk in the Community (ARIC)[10] Liao, Stroke 1996	Cohort of 16000 people 45 to 64 y-o in 1986, followed with yearly visits . Community surveillance on 35 to 74 y-o, with hospital discharge codes and death certificates. 1920 subjects in this study, all over 55 in 1993. Cross sectional study	Clinical baseline in 1986, then every 3 years. MRI 1993-1995,	MRI 1.5 T	0-9 scale with template. Cut point for presence of LA= 3	Three clinical examinations. Hypertension defined as >140/90. Pts classified into Incident and prevalent hypertensive	Association between presence of WMC and hypertensive status. ORs higher between untreated hypertensive and treated but not controlled compared to not hypertensive and treated controlled hypertensive
ARIC[18] Gottesman, Stroke 2010	Longitudinal. Visit 5 in 2004-2006. Over 900 patients of the previously described 1920 repeated MRI. Mean age of participants: 72		MRI 1.5 T	Visual 0-9 scale, Volumetric semi-automated assessment of variation of WMC over time	Mean BP from the previous FUs over about 20 years	Linear association between levels of BP and increasing of WMC volume. No association between baseline values and rate or incidence of progression
Austrian Stroke Prevention Study[19] Schmidt, Neurology 1999	Randomly selected 1998 50-75 y-o healthy volunteers in Graz, Austria. 458 had MRI at baseline, 273 had a second assessment and MRI at 3 years. Mean ager 60+/- 6 years	1991-1994 baseline	MRI 1.5 T, at baseline and 3 years	Only deep white matter lesions. Division into: zero, one to four, five to nine and more than 9 lesions	BP over 160/95 at assessment or in three previous reading, or treatment for hypertension	diastolic high blood pressure is associated to progression of WMC
Framingham Offspring Study[12] Jeerakathil, Stroke 2004	Cross sectional study on 1860 non demented non-stroke patients, children of the original cohort. Mean age:53 years.	MRI between 1999 and 2001	MRI 1 T	Volumetric	History of hypertension, measure of BP at assesment	both values of systolic BP and history of hypertension are associated to higher volumes of WMC
Framingham Offspring Study[20] Debette, Neurology 2011	Longitudinal phase of the above study: MRI repeated between 2005-2007. Clinical data from examination in 1991-95. 1352 subjects, mean age 54+/- 9	MRI in 1999-2001 and 2005-2007	MRI 1 T or 1.5	Volumetric	HTN= bp >140/90 or use of medications	Hypertension and higher SBP in midlife are associated to more rapid increase of WMC
LADIS Study (Leukoaraiosis And DISability)[13] Basile, Cerebrovascular Disease 2006	CROSS SECTIONAL study within this longitudinal study of 639 patients with different degrees of WMC, followed for 3 years	MRI in 2001	MRI 1.5 T from 13 different centres	Fazekas scale	History of hipertension, as per WHO definition >140/90. BP (mmHg) measured at baseline	Hypertension at baseline and higher levels of systolic blood pressure are associated to severity of WMC, in patients with no previous history of stroke
Gothenburg Women Study[14] Guo, Hypertension 2009	539 women followed since 1968, had a CT in 1992/2000. 499 had BP measured both in 1968 and 1992. Cross sectional and longitudinal (only a small sample had 2 CTs)	BP evaluation in 1968, 1975, 1981,1992	CT in 1992 or 2000, both in a small sample	0-3 scale	BP measured with sphygmomanometer	Both presence and severity of LA are associated to higher DBP, MAP and average 24-year DBP and MAP. No relation to SBP and PP. Progression of WMC associated to higher SBP, DBP, MAP (small sub-group).
Three City Dijon MRI Study[21] Godin, Circulation 2011	Prospective population-based cohort of subjects >/= 65. 1319 subjects with mean age 72.4 years	Started 1999-2001. Volunteers followed every 2 years for 4 years	MRI 1.5 T at entry and after 4 years	Volumetric	BP > 140/90 defined as hypertension	Baseline DBP is a significant predictor of WMC progression. Significant association between anti-hypertensive treatment at baseline and WMC progression. The progression of WMC was slowed down in patients who started antihypertensive treatment
PROGRESS[22] Dufouil, Circulation 2005	Patients with h/o stroke or TIA. 192 pts had 2 MRI , 3 years apart. Patients divided into treated (perindopril plus indapamide) and placebo	1995-1997	MRI 1.0 T	Scale A to D use in the EVA-MRI study. Volume calculated according to slice thickness.	All patients had hypertension	Patients who received treatment had lower incidence of new WMC lesions at 3 years FU
GENOA + ARICyoung HTN cohorts[15] Schwartz, Hypertension 2007	Population-based. Hypertensive cohort chosen from the GENOA and the ARIC studies	2001-2006 MRI, 2003-2006 ABP	MRI 1.5 T	Volumetric	Ambulatory BP over 24 hours	higher office SBP associated to higher volume of WMC, especially in black subjects. Nocturnal non-dipping pattern was associated to high WMC volume in white subjects

Table 3.1, **cont.** Summary of Studies on Blood Pressure and White Matter Changes

Smaller studies on selected patients						
Name	**Description**	**Date**	**Scan Type**	**WMC scale**	**BP assessment**	**FINDINGS**
Ambulatory BP and the brain, 5 year FU[24] Goldstein, Neurol 2005	155 healthy subjects, mean age 66.2 investigated. 111 had MRI at 5 years	Not stated	MRI 1.5 T	Volumetric	BP average of ABPM time 1 and 2. Patients grouped in HiLo, HiHi, LoLo, LoHi	the HiHi group has significant higher risk to have severe WMC on MRI compared to the other groups. Relationship between high SBP variability and insular WMC
BP Variability and leukoaraiosis amount in cerebral small vessel disease[23] Marti-Fabregas, Acta Neurol Scand 2001	hypertensive patients grouped in isolated lacunar infarct or Binswanger's disease. Small study: 25 Lacunar infarcts and 38 BD, only 25 in total fulfilled criteria!	Not stated	MRI 1.5 T	Scale 0-48: 0-4 assessment on 6 areas on both hemispheres	24-hour BP variability studied	No association found between BP variability and severity of WMC
Pulse Pressure correlated with Leukoaraiosis in AD[50] Lee, Arch of Gerontology and Geriatrics 2006	119 pts with AD, 117 controls. Only AD patients had MRI	2001-2003	MRI 1.5 T	Fazekas scale	Average of 2 consecutive readings	PP greater in AD than in controls, and in this group there was a significant association between PP and WMC after adjustment for age and sex.

Figure 3.1 Meta-analysis of studies reporting data on blood pressure or on hypertensive status in relation to presence of white matter changes

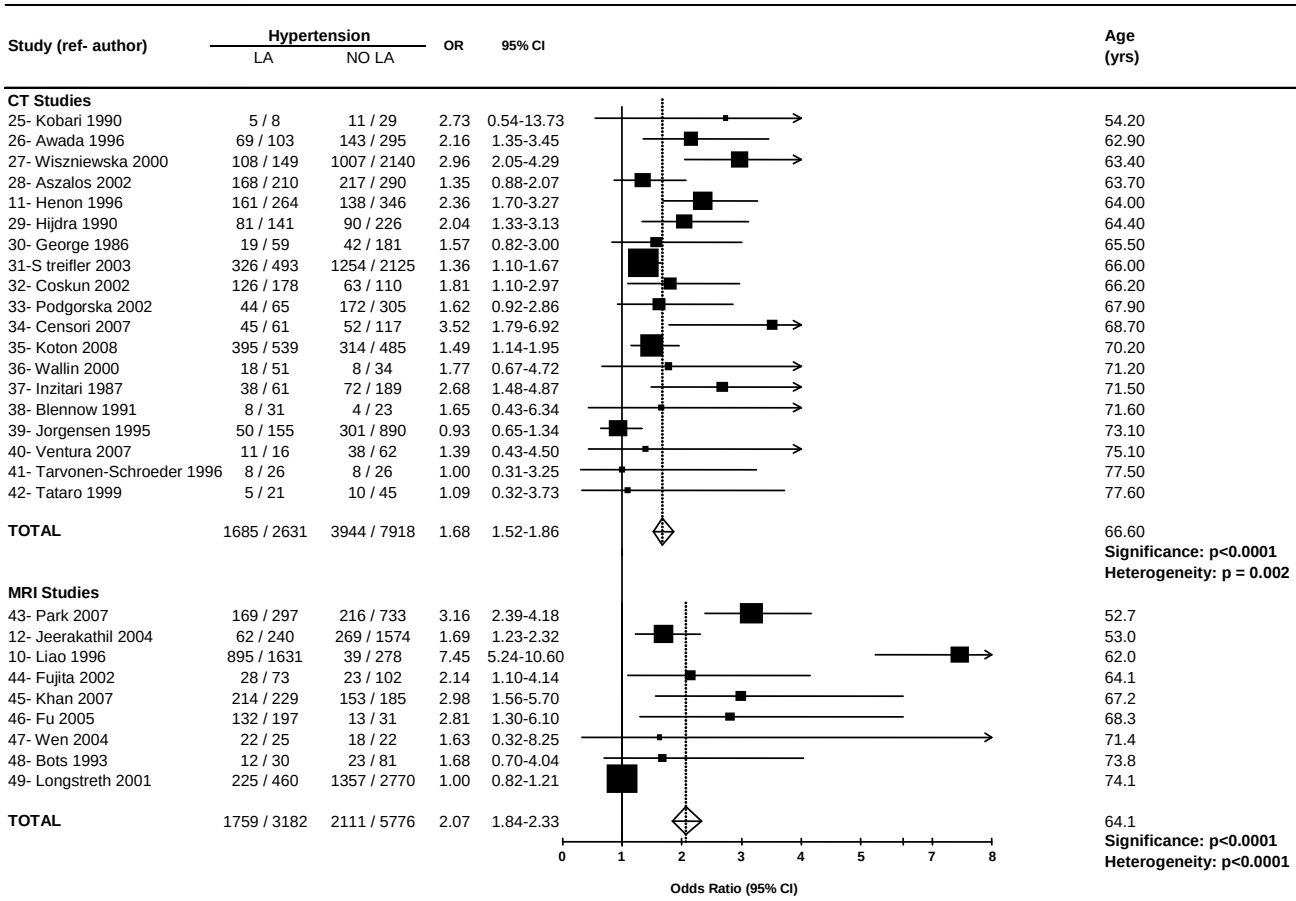
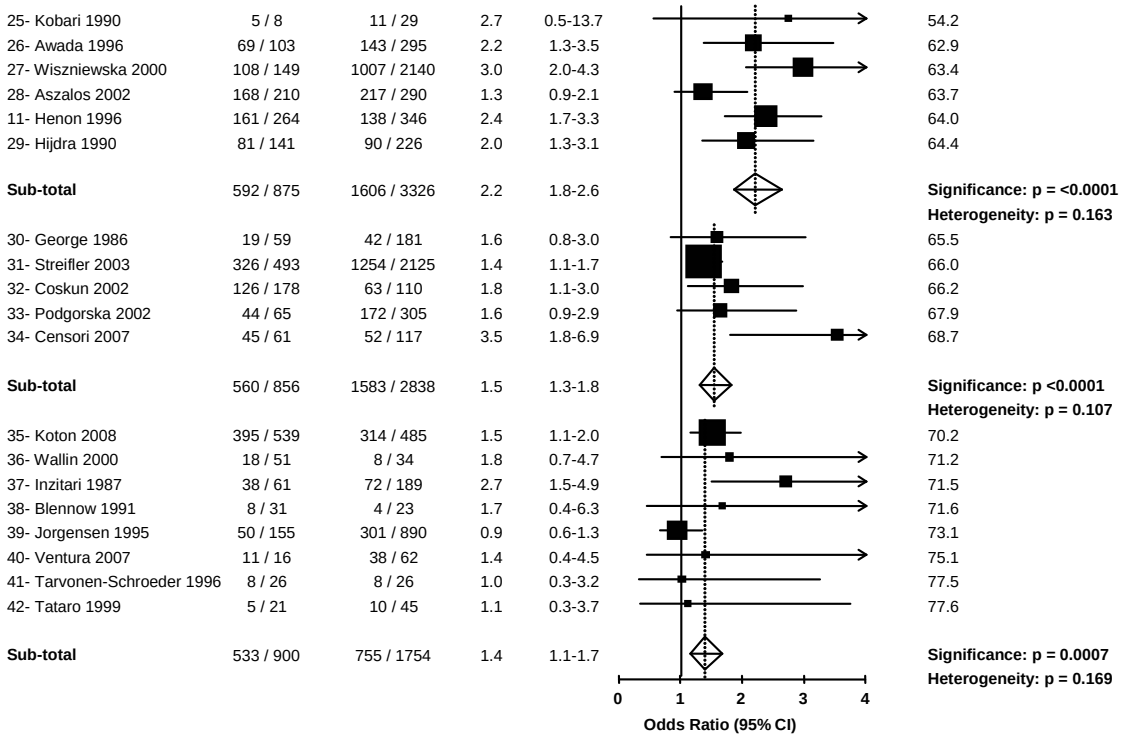
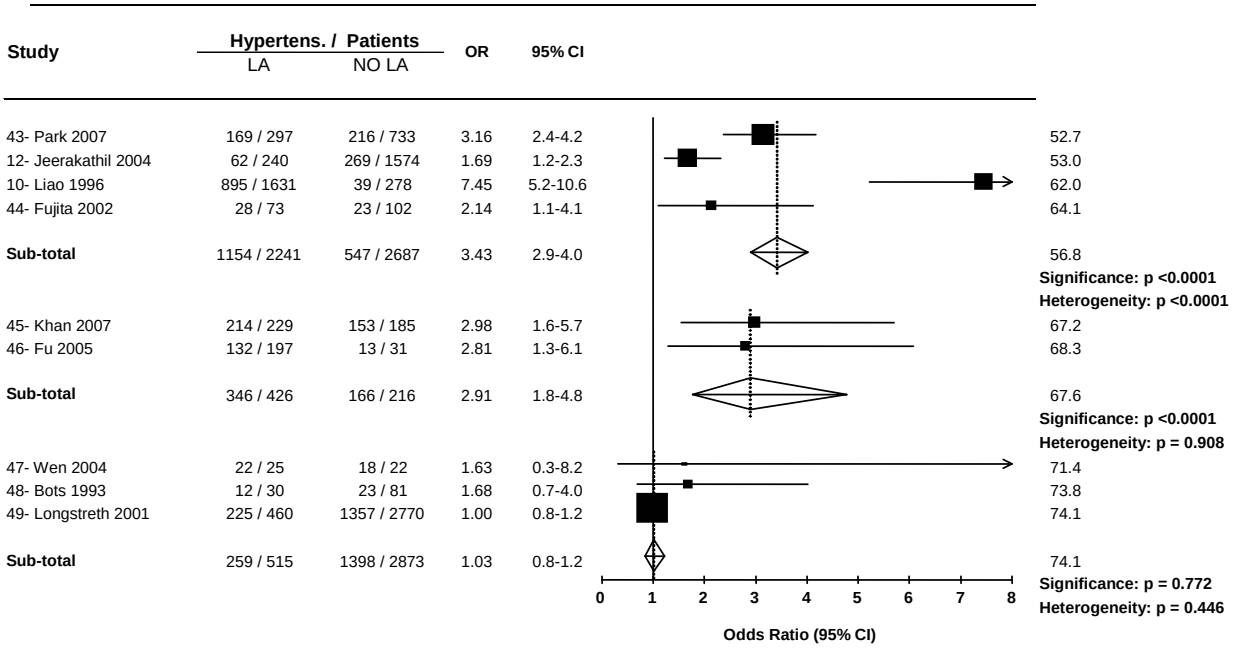


Figure 3.2 Meta-analysis of studies (A-CT, B-MRI) on hypertensive status in relation to presence of white matter changes, grouped according to the age of their population (<65, 65-69, ≥ 70 years).

A)



B)



3.3.2 Pre-morbid diagnosis of hypertension in OXVASC: sex and age-specific distribution

Looking at the distribution of OXVASC patients with known hypertension at the moment of their first event (Figure 3.3), about 60% of the population after the age of 65 is known to be hypertensive, versus 44% in the younger group. More women (637, 60% of total) than men (510, 53% of total) are hypertensive. When adjusting for age, this difference is significant only in the age group of patients between 75 and 84, with women being more likely to be hypertensive (figure 3.3, table 3.2). When analyzing the association between history of hypertension and type of stroke or TIA according to the TOAST classification, hypertension is significantly associated with the large artery subtype (table 3.3). No differences between sexes exist in the distribution of hypertensive patients within each of the stroke subtypes (table 3.4).

Figure 3.3 Hypertensive men and women within age category: absolute percentage of the total number of patients in each group

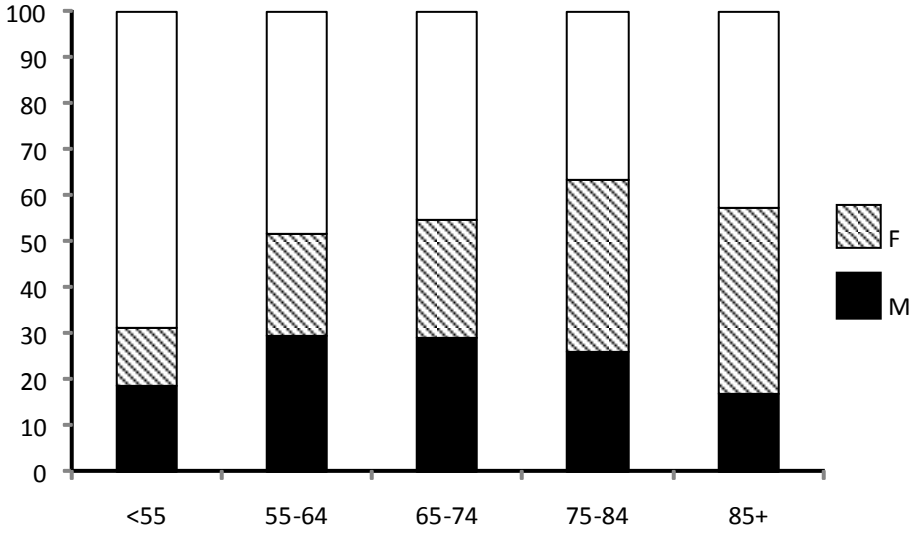


Table 3.2 Prevalence of hypertension, for men and women separately, within each age group. Odds ratios for difference in hypertension prevalence between men and women are reported, with their 95% confidence intervals and significance

	Hypertensive Pts.				
Age (yrs.)	**M/tot.**	**F/tot.**	**OR**	**95% CI**	**P**
<55	39/112	27/99	1.43	0.79-2.57	0.239
55-64	86/172	64/119	0.86	0.54-1.37	0.526
65-74	137/254	122/218	0.92	0.64-1.33	0.659
75-84	189/323	270/399	**0.67**	**0.50-0.91**	**0.011**
≥85	70/133	171/287	0.75	0.50-1.14	0.181

Table 3.3 Presence of hypertension in different TOAST subtypes, after age and sex adjustment.

TOAST	**OR**	**95% CI**	**P**
CE	0.99	0.79-1.25	0.957
LAA	**1.66**	**1.22-2.25**	**0.001**
SMV	1.10	0.84-1.44	0.495
UND	0.85	0.71-1.02	0.087
UNK	0.98	0.74-1.29	0.874
MULT	1.59	0.81-3.11	0.179
OTHER	1.03	0.69-1.53	0.888

Table 3.4 Odds ratios for difference in prevalence of hypertension within each stroke subtype between sexes (male versus female), after age adjustment.

	Hypertensive Pts.				
TOAST	**M/tot.**	**F/Tot.**	**OR**	**95% CI**	**P**
CE	94/177	140/224	0.77	0.51-1.17	0.220
LAA	73/117	69/97	0.81	0.44-1.47	0.479
SMV	80/151	61/101	0.76	0.45-1.28	0.308
UND	156/327	221/404	0.85	0.63-1.15	0.298
UNK	47/92	99/160	0.63	0.37-1.07	0.085
MULT	15/22	13/19	1.00	0.26-3.89	1.000
OTHER	33/58	27/55	1.48	0.69-3.15	0.314

3.3.3 History of hypertension and leukoaraiosis: OXVASC data

History of hypertension is associated with presence and severity of leukoaraiosis both on CT and on MRI scans in our population of strokes and TIA. Table 3.5 reports the results of the binary logistic regression analyses considering any leukoaraiosis versus no leukoaraiosis and moderate/severe versus none/mild leukoaraiosis. The associations range from an OR of 1.99 (1.29-3.08, p=0.002) for moderate/severe leukoaraiosis on MRI scans measured with the Oxford scale, to a minimum of 1.18 (0.94-1.50, p=0.159) for presence of any severity of leukoaraiosis on CT scans according to the van Swieten scale. These associations are stronger in the younger groups, while after the age of 75 they are weak both on CT and MRI scans. On repeating the analyses with the variable of leukoaraiosis in excess for age, the results are similar (table 3.6).

When stratifying the patients on the basis of the TOAST subtype of stroke or TIA at entry to the study, only in patients with TIA or stroke secondary to small vessel disease is leukoaraiosis significantly associated to history of hypertension (table 3.7). Numbers are small for MRI scans and associations are not significant.

Table 3.5 Odds Ratios for history of hypertension as outcome variable, adjusted for age and sex and stratified by age

			Whole Cohort		<65		65-74		≥75	
			OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
CT	**Oxford**	**Any**	**1.29 (1.04-1.61)**	**0.020**	1.48 (0.87-2.53)	0.153	1.31 (0.87-1.99)	0.199	1.25 (0.93-1.67)	0.138
		Mod/Sev	**1.31 (1.04-1.66)**	**0.021**	1.59 (0.71-3.54)	0.261	**1.75 (1.03-2.97)**	**0.039**	1.14 (0.87-1.51)	0.336
	ARWMC	**Any**	**1.26 (1.00-1.59)**	**0.049**	**2.23 (1.31-3.81)**	**0.003**	1.17 (0.77-1.80)	0.461	1.05 (0.76-1.46)	0.768
		Mod/Sev	**1.46 (1.15-1.86)**	**0.002**	2.08 (0.75-5.82)	0.161	**1.81 (1.05-3.13)**	**0.032**	1.30 (0.98-1.72)	0.074
	Van Swieten	**Any**	1.18 (0.94-1.50)	0.159	**1.95 (1.14-3.34)**	**0.015**	1.06 (0.69-1.62)	0.786	1.05 (0.75-1.47)	0.779
		Mod/Sev	**1.44 (1.14-1.82)**	**0.002**	**3.10 (1.16-8.32)**	**0.025**	1.42 (0.85-2.39)	0.182	1.31 (0.99-1.73)	0.060
MRI	**Oxford**	**Any**	1.36 90.90-2.05)	0.140	**2.13 (1.14-3.97)**	**0.018**	1.23 (0.58-2.60)	0.594	0.71 (0.31-1.60)	0.709
		Mod/Sev	**1.99 (1.29-3.08)**	**0.002**	**2.93 (1.16-7.39)**	**0.023**	**3.88 (1.70-8.87)**	**0.001**	0.99 (0.52-1.86)	0.963
	ARWMC	**Any**	1.31 (0.86-2.00)	0.204	1.65 (0.89-3.07)	0.112	1.16 (0.52-2.59)	0.715	1.04 (0.46-2.36)	0.919
		Mod/Sev	1.43 (0.91-2.26)	0.122	1.68 (0.68-4.17)	0.260	1.57 (0.69-3.62)	0.285	1.05 (0.54-2.07)	0.880
	Fazekas	**Any**	**1.60 (1.02-2.51)**	**0.043**	2.02 (1.08-3.79)	0.028	1.58 (0.64-3.89)	0.321	0.94 (0.36-2.47)	0.900
		Mod/Sev	**1.63 (1.05-2.52)**	**0.030**	2.04 (0.87-4.78)	0.102	1.93 (0.89-4.19)	0.098	1.09 (0.57-2.13)	0.781

Table 3.6 ORs for “excess of leukoaraiosis for age” and history of hypertension, adjusted for sex and for age as a continuous variable, stratified by age

	Scale	Whole cohort		< 65		65-74		≥ 75	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
CT	**Oxford**	**1.36 (1.02-1.81)**	**0.034**	1.62 (0.81-3.24)	0.177	**1.75 (1.03-2.97)**	**0.039**	1.10 (0.74-1.64)	0.62
	ARWMC	**1.42 (1.07-1.90)**	**0.017**	**2.60 (1.18-5.74)**	**0.018**	**1.81 (1.05-3.13)**	**0.032**	1.04 (0.71-1.53)	0.834
	van Swieten	1.26 (0.98-1.61)	0.075	**3.41 (1.60-7.27)**	**0.002**	1.42 (0.85-2.39)	0.182	1.004 (0.73-1.38)	0.979
MRI	**Oxford**	**2.27 (1.44-3.57)**	**<.0001**	**2.42 (1.16-5.05)**	**0.019**	**3.88 (1.70-8.87)**	**0.001**	1.09 (0.45-2.49)	0.836
	ARWMC	**1.62 (1.05-2.50)**	**0.030**	1.51 (0.74-3.10)	0.257	1.44 (0.63-3.28)	0.383	1.81 (0.84-3.93)	0.132
	Fazekas	**1.60 (1.05-2.44)**	**0.030**	1.75 (0.88-3.50)	0.113	1.93 (0.89-4.19)	0.098	1.11 (0.52-2.36)	0.797

Table 3.7 Multivariate binary logistic regression analysis. History of hypertension as outcome variable. ORs for presence of any WMC versus no WMC (Mod 1) and for moderate/severe WMC versus no or mild WMC (Mod 2). Adjusted for age and sex and stratified by TOAST subtype of stroke.

			Cardio-embolic		**Large Artery**		**Small Vessel**		**Unknown + Other**	
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
CT	**Oxford**	Mod 1	1.59 (0.99-2.55)	0.055	0.76 (0.36-1.58)	0.455	**1.97 (1.08-3.59)**	**0.027**	1.19 (0.88-1.60)	0.260
		Mod 2	0.94 (0.61-1.70)	0.939	0.97 (0.47-2.00)	0.932	**2.20 (1.20-4.03)**	**0.011**	1.31 (0.94-1.82)	0.127
	ARWMC	Mod 1	1.09 (0.64-1.84)	0.751	1.25 (0.57-2.70)	0.580	**1.87 (1.00-3.49)**	**0.049**	1.20 (0.88-1.66)	0.245
		Mod 2	1.72 (1.01-2.95)	0.046	1.02 (0.47-2.19)	0.961	**2.28 (1.22-4.26)**	**0.010**	1.23 (0.87-1.74)	0.245
	van Swieten	Mod 1	1.12 (0.66-1.90)	0.686	0.83 (0.39-1.81)	0.645	**2.47 (1.29-4.73)**	**0.006**	1.07 (0.77-1.48)	0.686
		Mod 2	1.57 (0.92-2.69)	0.102	1.01 (0.48-2.12)	0.976	**2.25 (1.20-4.21)**	**0.011**	1.32 (0.94-1.85)	0.106
MRI	**Oxford**	Mod 1	1.30 (0.31-5.54)	0.722	0.78 (0.22-2.71)	0.695	1.88 (0.56-6.14)	0.297	1.18 (0.70-1.97)	0.539
		Mod 2	1.21 (0.27-5.54)	0.804	0.90 (0.28-2.96)	0.868	3.10 (0.97-9.93)	0.057	**1.98 (1.10-3.55)**	**0.023**
	ARWMC	Mod 1	0.77 (0.17-3.48)	0.730	0.59 (0.16-2.12)	0.415	1.01 (0.25-4.06)	0.991	1.47 (0.86-2.48)	0.157
		Mod 2	1.57 (0.34-7.34)	0.565	1.41 (0.39-5.02)	0.601	1.48 (0.49-4.51)	0.491	1.27 90.68-2.38)	0.452
	Fazekas	Mod 1	1.22 (0.27-5.54)	0.801	0.83 (0.22-3.06)	0.774	0.91 (0.20-4.15)	0.905	1.77 (0.10-3.13)	0.051
		Mod 2	**8.38 (1.33-52.6)**	**0.023**	0.336 (0.09-1.33)	0.121	1.18 (0.38-3.68)	0.772	1.72 (0.96-3.06)	0.067

3.3.4 Associations between leukoaraiosis and pre-morbid blood pressure measures (10 years before entry in the study): maximum, most recent and mean blood pressure.

A total of 1917 patients had data available on their pre-morbid blood pressure values, 1001 females and 916 males. The women were overall older than the men, with 82.2% of women being 65 or older versus 72.7% of the men. Of these 1917 patients, 1651 patients had CT and 499 had MRI (with 233 patients having both CT and MRI). The mean (SD) number of blood pressure measurements over the 10 years in subjects younger than 65 was 9.7 (8.9), in subjects 65-74 y-o was 14.2 (11.7), and in subjects older than 75 was 16.1 (12).

Higher values of mean blood pressure over the 10 year period preceding the Stroke or TIA were strongly associated with excess of leukoaraiosis for age (table 3.8). This association was evident with all the scales used to evaluate leukoaraiosis, both on CT and MRI, and the associations were stronger for higher mean diastolic than systolic blood pressure, with ORs (adjusted for age and sex) ranging from 1.09 (0.99-1.20, p=0.064) to 1.31 (1.12-1.53,p<.0001) per 10 mmHg mean systolic BP and from 1.25 (1.04-1.50, p= 0.012) to 1.62 (1.20-2.17, p=0.001) per 10 mmHg mean diastolic BP. These associations were strongest in patients younger than 65, especially the systolic blood pressure associations. The associations with the mean diastolic blood pressure remained much stronger than the associations with the systolic BP in the oldest strata of patients. When considering the maximum systolic and diastolic BP recorded over the previous 10 years, the associations with leukoaraiosis were weaker than those found with the mean blood pressure, but higher maximum diastolic BP seemed to better correlate with leukoaraiosis than maximum systolic (table 3.9). Again, the associations became weaker in the older strata of the population, leaving some association only with the higher maximum diastolic blood pressures. The associations between excess of leukoaraiosis and most recent blood pressure

measurements were generally very weak for all ages, but especially for the older strata of the population (table 3.10).

Table 3.8 Associations between 10-year mean systolic and diastolic BP and Excess of WMC for age, according to different scales and scan modality, and stratified by age. All analyses are adjusted for age and sex.

			Whole Cohort		< 65		65-74		≥ 75	
			OR (95%CI)	P	**OR (95%CI)**	**P**	**OR (95%CI)**	**P**	**OR (95%CI)**	**P**
Mean Systolic										
(10 mmHg increase)	CT scales	*Oxford*	1.09 (0.99-1.20)	0.064	**1.28 (1.04-1.56)**	**0.017**	1.15 (0.96-1.37)	0.131	0.99 (0.87-1.14)	0.923
		ARWMC	**1.17 (1.06-1.29)**	**0.001**	**1.37 (1.10-1.70)**	**0.005**	1.18 (0.98 -1.42)	0.084	1.11 (0.97-1.26)	0.128
		van Swieten	**1.12 (1.03-1.21)**	**0.011**	**1.37 (1.12-1.68)**	**0.002**	1.16 (0.97-1.40)	0.100	1.05 (0.94-1.16)	0.417
	MRI scales	*Oxford*	**1.31 (1.12-1.53)**	**<.0001**	**1.37 (1.09-1.73)**	**0.007**	**1.47 (1.10-1.98)**	**0.010**	1.05 (0.76-1.45)	0.754
		ARWMC	**1.21 (1.04-1.41)**	**0.014**	**1.37 (1.10-1.72)**	**0.006**	0.93 (0.69-1.26)	0.650	1.26 (0.93-1.70)	0.133
		Fazekas	**1.16 (1.01-1.35)**	**0.041**	**1.26 (1.02-1.56)**	**0.035**	1.01 (0.77-1.34)	0.916	1.19 (0.88-1.62)	0.265
Mean Diastolic										
(10 mmHg increase)	CT scales	*Oxford*	**1.25 (1.04-1.50)**	**0.012**	1.34 (0.89-2.01)	0.164	1.28 (0.91-1.82)	0.159	1.15 (0.88-1.51)	0.301
		ARWMC	**1.59 (1.31-1.92)**	**<.0001**	**1.82 (1.17-2.83)**	**0.007**	**1.56 (1.08-2.27)**	**0.018**	**1.56 (1.19-2.04)**	**0.001**
		van Swieten	**1.50 (1.26-1.77)**	**<.0001**	**1.65 (1.10-2.49)**	**0.016**	**1.48 (1.03-2.13)**	**0.033**	**1.48 (1.19-1.84)**	**0.001**
	MRI scales	*Oxford*	**1.62 (1.20-2.17)**	**0.001**	1.44 (0.95-2.18)	0.089	**1.96 (1.08-3.56)**	**0.028**	1.51 (0.78-2.93)	0.224
		ARWMC	**1.41 (1.05-1.87)**	**0.020**	**1.69 (1.13-2.53)**	**0.011**	1.11 (0.60-2.03)	0.742	1.23 (0.67-2.26)	0.497
		Fazekas	**1.37 (1.04-1.80)**	**0.027**	1.40 (0.95-2.05)	0.087	1.25 (0.71-2.20)	0.450	1.34 (0.72-2.52)	0.356

Table 3.9 Associations between 10-year maximum systolic and diastolic BP and Excess of WMC for age, according to different scales and scan modality, and stratified by age. All analyses are adjusted for age and sex.

			Whole Cohort		< 65		65-74		≥ 75	
			OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Maximum Systolic BP 1 mmHg increases	CT scales	*Oxford*	1.05 (0.99-1.10)	0.092	**1.15 (1.02-1.30)**	**0.020**	1.09 (0.99-1.20)	0.065	0.99 (0.92-1.06)	0.700
		ARWMC	**1.08 (1.02-1.14)**	**0.005**	**1.16 (1.02-1.33)**	**0.025**	1.07 (0.97-1.18)	0.152	1.06 (0.99-1.14)	0.115
		van Swieten	**1.07 (1.02-1.12)**	**0.006**	**1.19 (1.06-1.35)**	**0.005**	**1.10 (1.01-1.21)**	**0.038**	1.03 (0.97-1.09)	0.319
	MRI scales	*Oxford*	**1.14 (1.05-1.23)**	**0.002**	**1.18 (1.04-1.34)**	**0.011**	1.23 (1.05-1.44)	0.010	1.00 (0.85-1.16)	0.955
		ARWMC	1.08 (0.99-1.17)	0.069	1.13 (0.99-1.28)	0.061	1.05 (0.94-1.16)	0.399	1.09 (0.94-1.25)	0.246
		Fazekas	1.06 (0.98-1.15)	0.120	1.12 (0.99-1.26)	0.075	1.03 (0.89-1.19)	0.708	1.04 (0.90-1.19)	0.626
Maximum Diastolic BP 1 mmHg increases	CT scales	*Oxford*	**1.11 (1.01-1.22)**	**0.031**	1.17 (0.92-1.47)	0.194	1.12 (0.95-1.33)	0.169	1.08 (0.94-1.23)	0.279
		ARWMC	**1.16 (1.06-1.28)**	**0.002**	1.24 (0.97-1.59)	0.086	1.17 (0.98-1.40)	0.090	1.14 (1.00-1.30)	0.057
		van Swieten	**1.14 (1.05-1.25)**	**0.002**	1.27 (1.00-1.60)	0.050	1.13 (0.95-1.35)	0.177	**1.14 (1.02-1.27)**	**0.023**
	MRI scales	*Oxford*	**1.37 (1.15-1.63)**	**0.007**	**1.35 (1.02-1.79)**	**0.037**	**1.64 (1.15-2.33)**	**0.006**	1.17 (0.84-1.62)	0.354
		ARWMC	1.17 (0.99-1.39)	0.063	1.19 (0.92-1.55)	0.188	1.16 (0.93-1.45)	0.187	1.15 (0.86-1.54)	0.335
		Fazekas	**1.23 (1.04-1.45)**	**0.014**	1.18 (0.91-1.53)	0.203	**1.48 (1.04-2.08)**	**0.027**	1.10 (0.81-1.49)	0.536

Table 3.10 Associations between most recent systolic and diastolic BP and Excess of WMC for age, according to different scales and scan modality, and stratified by age. All analyses are adjusted for age and sex.

			Whole Cohort		< 65		65-74		≥ 75	
			OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Most recent Systolic BP 1 mmHg increases	CT scales	*Oxford*	1.02 (0.96-1.10)	0.519	**1.19 (1.02-1.40)**	**0.030**	1.06 (0.94-1.20)	0.334	0.94 (0.85-1.04)	0.204
		ARWMC	1.04 (0.97-1.12)	0.240	1.14 (0.97-1.35)	0.150	1.08 (0.95-1.23)	0.232	0.99 (0.90-1.09)	0.909
		van Swieten	1.06 (1.00-1.13)	0.057	**1.18 (1.00-1.39)**	**0.046**	1.11 (0.98-1.26)	0.108	1.02 (0.94-1.10)	0.626
	MRI scales	*Oxford*	**1.12 (1.01-1.25)**	**0.036**	1.18 (0.99-1.42)	0.066	1.08 (0.91-1.29)	0.382	1.08 (0.86-1.34)	0.518
		ARWMC	1.01 (0.90-1.13)	0.876	1.17 (0.99-1.40)	0.072	**0.79 (0.63-0.99)**	**0.041**	1.05 (0.86-1.28)	0.632
		Fazekas	1.01 (0.91-1.13)	0.81	1.06 (0.89-1.26)	0.514	0.87 (0.72-1.05)	0.158	1.14 (0.92-1.40)	0.225
Most recent Diastolic BP 1 mmHg increases	CT scales	*Oxford*	1.03 (0.91-1.18)	0.603	1.28 (0.94-1.73)	0.111	0.98 (0.78-1.23)	0.854	0.96 (0.81-1.16)	0.695
		ARWMC	**1.20 (1.06-1.36)**	**0.005**	1.29 (0.94-1.78	0.115	1.22 (0.96-1.55)	0.100	1.17 (0.98-1.39)	0.083
		van Swieten	**1.20 (1.07-1.34)**	**0.002**	**1.65 (1.10-2.49)**	**0.016**	1.26 (1.00-1.59)	0.052	1.15 (1.00-1.34)	0.054
	MRI scales	*Oxford*	1.11 (0.90-1.36)	0.351	1.18 (0.83-1.67)	0.349	0.98 (0.68-1.40)	0.896	1.12 (0.74-1.71)	0.582
		ARWMC	1.03 (0.84-1.27)	0.762	1.28 (0.92-1.77)	0.146	0.88 (0.60-1.30)	0.524	0.89 (0.61-1.31)	0.557
		Fazekas	0.99 (0.81-1.21)	0.907	0.99 (0.72-1.37)	0.958	1.05 (0.73-1.50)	0.804	0.88 (0.60-1.31)	0.535

3.4. Discussion and conclusions

Leukoaraiosis is strongly associated with high blood pressure, and this is confirmed by my systematic review of the literature. However, one consistent observation that systematically emerges from the review, from the meta-analysis and from the study of the 10-year mean blood pressure, is that the association decreases with increasing of age. This was noticed in previous studies,[13,17] and the reason behind it is not completely understood. A possible explanation could be in the slow pathogenesis of white matter changes. Leukoaraiosis may be seen as a marker of premature/excessive white matter ageing, and the process that leads to its formation starts probably years before it can be seen on imaging, especially if we consider white matter changes on CT scan, which is less sensitive than MRI. We may hypothesize therefore that in the very elderly the association with hypertension will be weakened by other possible risk factors which contribute to its formation, but also that the patients who have earlier hypertension leading to leukoaraiosis will have had a shorter life expectancy, and this leads to a selection bias. Older patients with leukoaraiosis, who have become symptomatic only late in life (and therefore scanned only at this stage), could be a selected population subgroup presenting some vascular protective factors and, might also have been treated for hypertension since their middle-age. I have not considered in my study the variable treatment, and this constitutes a weakness of my work. The length and type of treatment will be taken into account in future research on this topic.

A second observation arising from this work, is the stronger association of white matter changes with diastolic rather than systolic blood pressure. This has been noticed before[8,14,19] but not really stressed, and the majority of previous studies have limited themselves on talking about “hypertension” in a general way as an association with white matter changes. The association with mean diastolic blood pressure is also particularly relevant when we consider that, as seen in other studies emerging from OXVASC and as

seen in literature already, diastolic blood pressure is also more strongly associated with the lacunar type of stroke, especially in younger subjects. This might be the link that joins lacunar infarcts and white matter changes (and we saw in table 3.7 that white matter changes are associated with hypertension in the lacunar type of stroke more than in the other types), representing a risk factor for the pathogenesis of small vessel disease. This also suggests that patients with small vessel type of stroke might have a higher susceptibility to hypertension in determining ageing of the white matter. I cannot exclude the possibility that the stronger association with diastolic BP might be due to the fact that older patients are more likely to have been on anti-hypertensive treatment for longer, and the diastolic BP is less influenced by this. Also, the 10 mmHg increments chosen for the analyses, might have contributed to a bigger visible effect for diastolic BP, given the smaller range of variation of diastolic compared to systolic BP.

A third observation is that the association between leukoaraiosis and hypertension emerges much stronger when we consider the mean of measured blood pressure over time rather than when we just consider single measurements or simply the history of hypertension.

A few shortcomings must be acknowledged in this study. I have already mentioned the fact that I have not taken into account the effect of medication on the association with the mean blood pressure levels. The mean blood pressure levels in the older patients might have been reduced by the use of medications, and this might have lead to underestimating the association in the oldest strata of the population. A second possible weakness might be seen in the way we have collected the blood pressure measurements, limiting the number to a maximum of five each year. The majority of patients well fitted within this number, but a minority (less than 10%) had more than 5 blood pressure measurements taken in some years. This might have led to an underestimation or to an overestimation of the effect of the association, most likely penalizing the older patients, in

whom blood pressure is normally checked more often. A third possible shortcoming is that our observations on the pre-morbid 10 years are based on blood pressure readings collected by different general practitioners and nurses, and were not standardized. The use of semi-quantitative methods of assessment and the fact that our observations are mainly based on CT findings is another possible weakness of the study. More sophisticated quantitative methods of leukoaraiosis assessments offer the ability to discriminate better between old ischaemic focal lesions and leukoaraiosis, and MRI is more sensitive than CT in detecting white matter changes. Whilst we cannot exclude that some of our scoring might have included previous focal ischaemic lesions or demyelination, we could counter-argue that what we have found is probably more in line with clinical practice, helping clinicians in risk assessing their patients, and this will still most often be done on CT scans with visual assessment.

In conclusion, white matter changes are strongly associated with increasing blood pressure. This association is better seen with multiple blood pressure measurements and might be underestimated using single blood pressure readings or a previous diagnosis of hypertension. The association between hypertension and leukoaraiosis is stronger in younger patients, and this is true for both the association with previous diagnosis of hypertension (as demonstrated both in the meta-analysis and in OXVASC) and for the mean values of blood pressure, as seen in OXVASC. Diastolic blood pressure, more than systolic, is associated with white matter changes. This association remains at all ages of the population, and this might in part be due to the fact that diastolic blood pressure is much less influenced by anti-hypertensive treatments. Further research is needed on the relation between blood pressure, white matter changes and anti-hypertensive medications.

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Chapter 4

Associations between white matter changes and other blood pressure components: visit-to-visit variability and pulse pressure

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4.0 Abstract

Background: Prevalence of white matter changes (WMC) on brain imaging increases steeply with age, and they are thought to reflect chronic subcortical ischaemia. Hypertension is a risk factor for WMC, particularly in younger patients, and variability in blood pressure (BP) is a risk factor for acute stroke. However, the relative contribution of long-term mean BP versus variability in BP to the development of chronic WMC is uncertain. Also, pulse pressure is an index of arterial stiffening, and there have been so far discordant reports on its association with white matter changes. We determined these associations based on all BP measures over a 10-year period in patients with TIA and stroke.

Methods: In consecutive patients with TIA or stroke (Oxford Vascular Study), we collected all pre-morbid BPs from primary care records. WMC were rated on baseline CT or MRI with four scales (ARWMC; van Swieten; Fazekas; Oxford) and age-specific associations with BP average visit-to-visit variability (i.e. the mean difference between successive measures), standard deviation of BP, and pulse pressure, calculated based on measurements over 10-years.

Results: 1840 patients were assessed by MRI (520) and/or CT (1717). Results were similar for each of the WMC scales used and for CT and MRI. Variability in SBP or DBP was not significantly associated with any of the measures of WMC on either CT or MRI at any age, and the same results were found for the associations with pulse pressure.

Conclusions: We found no evidence of any association with variability in BP and with pulse pressure, consistent with the hypothesis that raised long-term mean BP results in chronic subcortical ischaemia whereas variability in BP is associated with an increased risk of acute ischaemic events.

4.1 Introduction

As we have seen previously in this thesis, hypertension is strongly associated with white matter changes, especially in younger patients, and high diastolic blood pressure is particularly important. Variability of blood pressure is a strong risk factor for ischaemic stroke, particularly visit to visit variability.[1,2]

The pathogenesis of leukoaraiosis is most likely related to chronic ischaemia of the white matter. The brain arteriole become stiff and their lumen gets narrower after accumulation of fibro-hyaline material. They also lose their ability to dilate further as a response to reduced blood pressure and therefore allow a reduction of blood flow when this occurs.[3,4] According to this hypothesis, variability of blood pressure should represent a risk factor for severity of white matter changes, but few studies have considered this association. As we have seen in the previous review of studies on white matter changes and blood pressure, only a few studies[5,6,7] have considered this relationship. Moreover, these were based either on selected population settings or on small samples, and their results have been conflicting with regards to association with severity of white matter changes. None of them were based on populations of patients with previous stroke or TIA.

I also considered the association between white matter changes and pulse pressure (PP), a pulsatile component of BP reflecting the stiffness of large arteries, and a risk factor for ischaemic stroke and cardiovascular disease.[8,9,10] Pulse pressure has been little studied in relation to white matter changes, again with conflicting results.[10,11,12] A recent retrospective study on 247 volunteers in the Republic of Korea[11] found a positive association between PP and presence of white matter changes on MRI in men only. However, the study population excluded subjects with stroke or dementia. Another study which considered this association, only looked into a small group (75) of patients with pure Alzheimer's Disease, again excluding subjects with history of stroke or with MRI evidence of previous cerebral infarctions, and found a positive association between both

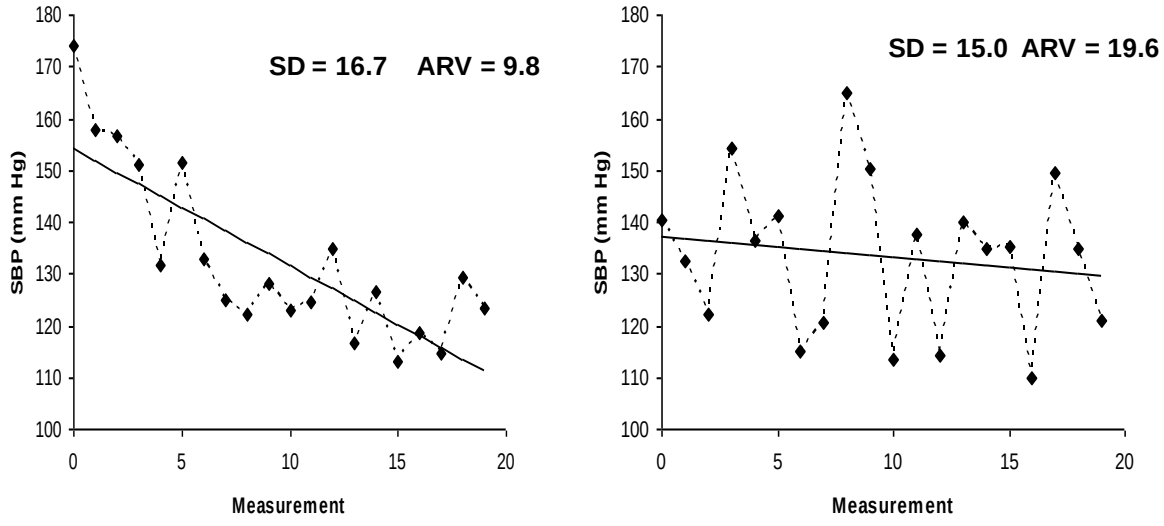
wider and smaller PP and more severe white matter changes. A larger population based study[13] found a positive association between degree of white matter changes and increasing of PP, but again, the study population excluded stroke patients. Moreover, in all these three studies, the pulse pressure was derived from BP readings collected during one single visit, none of them considered the mean of PP derived from a series of BP readings during a prolonged time-frame. The study which most closely resembles the one described in this chapter, is a recent one from Sweden,[10] were a population-based sample of women-only was assessed with CT scan in 2000, and the relation between presence and severity of leukoaraiosis and increase in PP over 4 measurements taken at follow-ups between 1968 and 1992 were assessed. This study failed to find any association between increasing PP and severity of white matter changes.

I attempted to determine the relationship between severity of white matter changes and both variability of blood pressure and pulse pressure, using data from the OXVASC study, based on blood pressure readings from a period of 10 years preceding the vascular event.

4.2 Methods

The OXVASC Study has been described previously in this thesis (see chapter 1). All patients in the study with ischaemic stroke or TIA had their general practitioners records checked for blood pressure readings, dating up to 10 years before the event. For each patient, up to a maximum of 5 blood pressure readings per year were recorded, in a chronological order. As measures of visit to visit variability, we chose two different parameters, the Standard Deviation (SD) of the mean blood pressure and the Average Real Variability (ARV). The standard deviation gives information on the variance of single measurements from the mean BP of the patient, while the average real variability is more indicative of changes between one measurement and the following one and is not influenced by the mean BP (see appendix 5 for formulae). I chose to use both these measures, as they tell us something slightly different. The SD of the mean blood pressure is much more influenced by the change of blood pressure with time (and therefore by treatment or by the physiological changes related to ageing), whilst the ARV is not, as we can see in figure 4.1.

Figure 4.1. Comparison between Standard Deviation and average real Variability of blood pressure readings in two different patients' readings



Pulse pressure is calculated as the difference between the systolic and the diastolic blood pressure, in mmHg. For my analyses I used the average pulse pressure calculated from all 10 year measurements. As previously seen, white matter changes on CT and MRI scans of patients were rated according to different scales (van Swieten scale, ARWMC scale and the Oxford scale for CT scans, and the Fazekas, the ARWMC and again the Oxford scale for MRIs). Leukoaraiosis was categorized as absent, mild, moderate and severe according to each of the scales, and then used as compound variable "leukoaraiosis in excess of age" as binary scale for regression analyses. In order to define this variable, as already seen previously, I drew an age-related threshold of normality for presence of leukoaraiosis according to age (in patients younger than 55 years the presence of any leukoaraiosis is considered in excess, in patients between 55 and 74 moderate and severe leukoaraiosis are considered in excess for age, and in patients 75 and older only severe leukoaraiosis is considered in excess for age).

All the statistical calculations were done using SPSS for Windows, version 15 and 18.

4.3 Results

A total of 1917 patients had information available on their pre-morbid blood pressure values, 1001 females and 916 males. The women were overall older than the men, with 82.2% of women being 65 or older versus 72.7% of the men. Of these 1917 patients, 1651 had CT and 499 had MRI (with 233 patients having both CT and MRI). The mean (SD) number of blood pressure measurements over the 10 years in subjects younger than 65 was 9.7 (8.9), in subjects 65-74 y-o was 14.2 (11.7), and in subjects older than 75 was 16.1 (12).

4.3.1 Blood pressure variability

The only association between severe white matter changes on scan and inter-visit variability of blood pressure was present in the age group between 65 and 74 years, and only when leukoaraiosis was assessed on MRI scans. Overall there was no association between blood pressure visit to visit variability and white matter severity. This was consistent between CT and MRI scans, and there was agreement between the measure of variability with standard deviation and with average real variability (Table 4.1, a-b).

4.3.2 Pulse pressure

Pulse pressure was not associated with severe white matter changes, either on CT or on MRI. When dividing the population according to age, there was a positive association in subjects younger than 65 years of age, both on CT and on MRI, but only if not considering the effect of systolic blood pressure. When using the SBP as a covariate, the association between PP and WMC disappeared also in the younger subgroup of the population (table 4.2).

Table 4.1 Associations between excess of white matter changes for age on both CT and MRI scans and blood pressure visit-to-visit variability. Variability is, measured as standard deviation (SD) in table (a) or average real variability (ARV) in table (b). Odds ratios are adjusted for age (continuous) and sex and are related to increments in mmHg.

(a)

			Whole Population		< 65		65-74		≥75	
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
SD Systolic	**CT**	**Oxford**	1.02 (0.99-1.04)	0.19	1.00 (0.95-1.05)	1.00	1.02 (0.98-1.07)	0.29	1.01 (0.98-1.05)	0.44
		ARWMC	1.01 (0.99-1.04)	0.24	1.01 (0.96-1.07)	0.64	1.03 (0.98-1.07)	0.27	1.01 (0.97-1.04)	0.70
		van Swieten	1.01 (0.99-1.03)	0.22	1.02 (0.97-1.07)	0.54	1.04 (1.00-1.09)	0.07	1.00 (0.97-1.03)	0.99
	MRI	**Oxford**	**1.04 (1.00-1.07)**	**0.04**	1.02 (0.96-1.07)	0.58	**1.10 (1.02-1.17)**	**0.01**	1.00 (0.93-1.07)	0.93
		ARWMC	1.02 (0.99-1.06)	0.20	1.03 (0.97-1.09)	0.40	1.03 (0.96-1.10)	0.47	1.02 (0.96-1.09)	0.55
		Fazekas	1.02 (0.98-1.05)	0.39	1.02 (0.97-1.08)	0.41	1.01 (0.95-1.08)	0.67	1.00 (0.94-1.07)	0.93
SD Diastolic	**CT**	**Oxford**	1.01 (0.97-1.06)	0.59	1.02 (0.92-1.13)	0.70	1.02 (0.94-1.10)	0.71	1.00 (0.94-1.07)	0.88
		ARWMC	0.98 (0.94-1.03)	0.47	1.00 (0.90-1.12)	1.00	1.00 (0.92-1.09)	0.91	0.96 (0.90-1.03)	0.24
		van Swieten	0.99 (0.95-1.03)	0.48	1.02 (0.92-1.12)	0.77	1.00 (0.92-1.09)	0.95	0.97 (0.92-1.02)	0.23
	MRI	**Oxford**	**1.09 (1.01-1.17)**	**0.02**	1.02 (0.91-1.15)	0.69	**1.27 (1.10-1.48)**	**0.001**	0.98 (0.85-1.13)	0.79
		ARWMC	1.04 (0.97-1.12)	0.23	0.96 (0.85-1.08)	0.51	**1.25 (1.07-1.47)**	**0.005**	0.98 (0.87-1.11)	0.77
		Fazekas	1.07 (1.00-1.15)	0.05	1.00 (0.90-1.12)	0.97	**1.25 (1.08-1.46)**	**0.003**	1.00 (0.88-1.14)	0.96

(b)

			Whole Population		< 65		65-74		≥75	
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
ARV Systolic	**CT**	**Oxford**	1.01 (0.99-1.03)	0.16	1.01 (0.97-1.06)	0.61	1.01 (0.97-1.05)	0.61	1.01 (0.98-1.04)	0.42
		ARWMC	1.01 (0.99-1.04)	0.24	1.03 (0.98-1.08)	0.19	1.02 (0.98-1.06)	0.34	1.00 (0.97-1.03)	0.91
		van Swieten	1.02 (1.00-1.03)	0.09	1.02 (0.97-1.07)	0.43	1.03 (0.99-1.07)	0.22	1.01 (0.99-1.03)	0.45
	MRI	**Oxford**	1.02 (0.99-1.05)	0.24	1.00 (0.95-1.05)	0.10	1.06 (0.99-1.13)	0.09	1.01 (0.94-1.08)	0.81
		ARWMC	1.02 (0.98-1.05)	0.38	1.02 (0.97-1.07)	0.46	1.00 (0.93-1.07)	0.93	1.02 (0.96-1.08)	0.53
		Fazekas	1.01 (0.98-1.04)	0.65	1.02 (0.97-1.07)	0.52	0.99 (0.92-1.05)	0.67	1.01 (0.95-1.08)	0.70
ARV Diastolic	**CT**	**Oxford**	1.01 (0.97-1.04)	0.75	1.03 (0.95-1.12)	0.49	0.99 (0.92-1.06)	0.71	1.01 (0.95-1.06)	0.81
		ARWMC	0.98 (0.94-1.03)	0.47	1.04 (0.95-1.14)	0.38	0.99 (0.93-1.07)	0.89	0.98 (0.93-1.03)	0.47
		van Swieten	1.01 (0.97-1.04)	0.73	1.02 (0.94-1.12)	0.63	1.00 (0.94-1.07)	0.97	1.00 (0.95-1.04)	0.89
	MRI	**Oxford**	1.05 (0.99-1.11)	0.10	1.02 (0.93-1.12)	0.72	**1.17 (1.03-1.32)**	**0.01**	0.95 (0.83-1.08)	0.43
		ARWMC	1.02 (0.96-1.08)	0.62	0.99 (0.90-1.09)	0.83	1.11 (0.99-1.25)	0.08	0.94 (0.83-1.06)	0.30
		Fazekas	1.04 (0.98-1.10)	0.21	1.02 (0.93-1.11)	0.70	**1.14 (1.01-1.28)**	**0.04**	0.95 (0.84-1.07)	0.38

Table 4.2 Association between pulse pressure and severe white matter changes. Odds ratios are for each increase of 10 mmHg of pulse pressure. The analyses are adjusted for age and sex (simple adjustment) and for age, sex and systolic blood pressure (SBP Adjustment). The positive significant associations are highlighted in bold.

				Whole Population		< 65		65-74		≥75	
				OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Pulse Pressure	**CT**	**Oxford**	**Simple**	1.05 (0.93-1.17)	0.45	**1.39 (1.06-1.83)**	**0.02**	1.12 (0.90-1.40)	0.32	0.94 (0.81-1.11)	0.47
			SBP Adj.	0.82 (0.66-1.04)	0.10	1.16 (0.65-2.08)	0.61	0.86 (0.55-1.35)	0.51	0.81 (0.59-1.11)	0.20
		ARWMC	**Simple**	1.06 (0.94-1.19)	0.35	**1.36 (1.01-1.84)**	**0.04**	1.08 (0.85-1.35)	0.53	0.99 (0.85-1.15)	0.88
			SBP Adj.	0.65 (0.51-0.82)	<0.0001	0.75 (0.40-1.41)	0.37	0.66 (0.42-1.05)	0.08	0.62 (0.45-0.86)	0.004
		van Swieten	**Simple**	1.01 (0.91-1.12)	0.84	**1.44 (1.09-1.90)**	**0.01**	1.08 (0.86-1.35)	0.51	0.93 (0.82-1.06)	0.27
			SBP Adj.	0.66 (0.54-0.81)	0.0001	0.93 (0.52-1.66)	0.80	0.70 (0.45-1.11)	0.13	0.62 (0.48-0.81)	0.0004
	MRI	**Oxford**	**Simple**	**1.26 (1.03-1.55)**	**0.02**	**1.54 (1.10-2.15)**	**0.01**	1.43 (1.00-2.06)	0.05	0.94 (0.65-1.35)	0.74
			SBP Adj.	0.78 (0.53-1.14)	0.20	1.17 (0.62-2.18)	0.63	0.74 (0.35-1.59)	0.44	0.63 (0.29-1.33)	0.22
		ARWMC	**Simple**	1.17 (0.96-1.42)	0.12	**1.39 (1.01-1.92)**	**0.05**	0.86 (0.59-1.26)	0.44	1.24 (0.90-1.71)	0.19
			SBP Adj.	0.83 (0.57-1.20)	0.31	0.80 (0.44-1.49)	0.49	0.73 (0.33-1.60)	0.43	0.98 (0.50-1.91)	0.95
		Fazekas	**Simple**	1.12 (0.92-1.35)	0.26	1.32 (0.96-1.80)	0.08	0.94 (0.66-1.34)	0.73	1.13 (0.81-1.58)	0.46
			SBP Adj.	0.81 (0.56-1.16)	0.25	0.97 (0.54-1.74)	0.92	0.71 (0.34-1.49)	0.37	0.84 (0.42-1.66)	0.61

4.4 Discussion and conclusions

Inter-visit intra-patient variability of blood pressure has been demonstrated to be associated with cardiovascular and cerebrovascular morbidity, and also pulse pressure has been associated to ischaemic heart disease and stroke. Studies on the association between white matter changes and blood pressure variability or pulse pressure are scarce and have lead to contrasting results. Also, the settings considered in the previous studies have been quite diverse, and there has been no population study so far analyzing these blood pressure variables, looking at their behavior in different age groups of patients with stroke or TIA.

In my study, visit-to-visit variability of blood pressure in patients with history of stroke or TIA, was not associated with severity of white matter changes, at any age considered. The only other study so far considering this type of blood pressure variability was in the context of the Honolulu-Asia Aging Study (HAAS), which included a selected population sample of men only. The patients were scanned with MRI in old age, at an average age of 82, and the white matter changes were correlated with blood pressure parameters calculated from measures taken in mid-life, over a period of ten years, about 20 years before the scan was attained. This study found an association between variability of systolic BP and white matter changes in old age, but no association with variability of diastolic blood pressure or with pulse pressure. In my study the age range was broader, as the setting was population-based, and the blood pressure measures reflected the 10 years immediately preceding the cerebrovascular event, rather than mid-life exposure to blood pressure variability, as in the HAAS. These might be some of the reasons for the different findings. In the present study I looked at the process of white matter formation as if I were following the process through different ages on different patients, as the study was not strictly longitudinal. I could only make inferences on the meaning of highly variable blood pressure in the 10 years preceding the scan, and I could not say what the meaning of this variability in younger age might have been. There is a plan in OXVASC on expanding the period of observation of the pre-morbid

blood pressure recordings from the GP surgeries, and I do not exclude the future possibility of looking into a more distant type of effect of variability of BP on the formation of white matter changes. From the results of the present study I could exclude any short-medium term effect of blood pressure variability, either systolic or diastolic, on the formation of white matter changes. This lack of association might mean that the effect of blood pressure variability needs longer time to become manifest as white matter changes, but it might also mean that this level of variability of blood pressure is not long enough to determine ischaemia of the white matter, and that the auto-regulatory mechanisms of the brain might be able to overcome this level of variability. The positive associations found in studies of mid-life variability in relation to late life scans would favour the first hypothesis.

When looking at the relationship between pulse pressure and white matter changes, the relation in the younger patients disappeared as soon as we adjusted the analysis for the systolic blood pressure levels, showing that the existing association was mainly mediated by this blood pressure element. As we saw in the previous chapter, systolic blood pressure is unrelated to white matter severity in the older age strata of the population, and from the present study it emerges that pulse pressure follows the behavior of systolic BP, being not much influenced by the fall of diastolic blood pressure typical of the elderly. This lack of relationship, in patients with previous history of stroke or TIA, confirms our previous finding that increase of diastolic BP rather than systolic BP, is associated with more severe white matter changes. We might hypothesize from this, that the physiological fall of diastolic blood pressure in the elderly might even be protective from the worsening of white matter changes, rather than contributing to a worsening of chronic white matter ischaemia, as previously thought.[14]

One of the weaknesses of this study is the lack of consideration of anti-hypertensive medications used by this population, and this is a study that we are planning to do in the near future. Adjustments of our analyses for anti-hypertensive medications might lead to a further change in findings, and could be useful to guide with management of stroke and TIA patients with regards to more or less aggressively lowering blood pressure.

It is also important to consider that the analyses I have presented in this study have been done on a population of stroke and TIA patients, whom, by definition, present a higher than average variability of their blood pressure. A better answer to the initial study question would come from a case-control study, but this has not been possible in the context of OXVASC.

Also, I only considered the peripheral pulse pressure and did not look more in details at the measures of middle cerebral artery stiffness (MCA-Transit Time) and pulsatility (MCA Gosling's pulsatility index) or aortic pulse wave velocity or aortic systolic, diastolic and pulse pressure measured with more sophisticated techniques (i.e. applanation tonometry). A smaller study (100 patients) within OXVASC has recently evaluated the relationship between these indexes and white matter changes on MRI, finding a positive relationship with both their presence and severity (Appendix 6)[15]. This apparent discordance between the studies might lie in the fact that peripheral PP is less sensitive as a tool to measure aortic stiffness, and even less sensitive to measure MCA stiffness and pulsatility. Peripheral pulse pressure is mainly a reflection of higher systolic blood pressure or, in the elderly especially, of a reduction in diastolic blood pressure, and the association of both these components with leukoaraiosis has been reviewed in the previous chapter, showing that the first is importantly associated in the younger group of the population, whilst the second is not associated with white matter changes in any of the age groups considered. Another potential difference from the sub-study on MRI is given by the population setting which is represented by slightly younger patients

and potentially with less severe strokes (as patients who underwent MRI in the acute setting). Strengths of my study are in the population-based setting, in the long pre-morbid period considered, and in the large number of blood pressure readings considered.

4.5 References

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Chapter 5

White matter changes and vascular risk factors other than age and hypertension: systematic review of the literature with meta-analysis and population-based study in patients with stroke or TIA

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5.0 Abstract

Background: The aetiology of white matter changes (WMC) of chronic ischaemic origin (leukoaraiosis) is not completely understood. High blood pressure and increasing age are important associations, but there have been conflicting reports on other vascular risk factors.

Methods: I did a systematic review of the literature and meta-analysis on leukoaraiosis (LA) and its association with vascular risk factors. Medline and Embase and reference lists of all papers identified were searched. I then evaluated white matter changes in the first consequential 1717 CT and 529 MRI scans of a population based cohort of stroke and TIA patients (OXVASC), and explored the associations with vascular risk factors.

Results: Of 1229 papers identified by my search, 74 (50 MR-based and 24 CT-based) reported data on presence of WMC in relation to risk factors. WMC were constantly associated with older age and hypertension, but among the other vascular risk factors only the association with prior stroke reached a positive significance (1.8, 1.5-2.1, P<0.001, 10 studies). There were no significant associations with male sex, hyperlipidaemia, diabetes, smoking, ischaemic heart disease, peripheral vascular disease, or carotid stenosis. Results were consistent for CT and MRI-based studies and there was relatively little heterogeneity between studies. I obtained the same results in the population-based study, where only history of previous stroke was associated with severity of WMC, and only for the MRI evaluations.

Conclusions: The associations of leukoaraiosis with older age and history of hypertension have been confirmed both with the meta-analysis of literature and with the analyses in the OXVASC population. Other major risk factors for atherosclerosis have not been found associated with WMC. However, there is an association with history of previous stroke. This only emerges for MRI-WMC in our population-based cohort of stroke and TIA patients, and might be related to the higher sensitivity of the technique and to the difficulty in separating old ischaemic lesions from more chronic leukoaraiosis.

5.1 Introduction

Cause, pathogenesis and risk factors of white matter changes (WMC) are still under debate. WMC have been found to predict stroke, especially the lacunar type, cognitive decline and dementia,[1] and are an independent contributor to development of disability in the elderly.[2] A better understanding of their aetiology is necessary to determine the extent to which the associations between vascular risk factors and the risks of stroke and dementia may be confounded by WMC. We have seen in previous chapters of this thesis that high blood pressure and increasing age are important risk factors for white matter changes.[3,4,5] There have been conflicting reports of associations with vascular risk factors[4,6-8] other than age and hypertension. White matter changes and lacunar infarcts are often associated and considered as sharing the same vascular risk factors. Recently, a review of 5 stroke registries[9] has tried to clarify the difference in association with vascular risk factors between lacunar and non-lacunar strokes, and this study has reported no major differences between the two categories with regards to hypertension, diabetes and smoking, but clearly a lack of association between lacunar type of strokes and carotid stenosis or ischaemic heart disease. This observation is important as it points to the fact that patients at risk for lacunar stroke must possess some other risk factors responsible for their arteriopathy. The answer to this riddle might lie in the pathology of chronic white matter changes, and might be, at least in part, in the genes. To try and clarify the associations between white matter changes and some of the most important known vascular risk factors apart from age and hypertension, I have done a systematic review of all published studies reporting data on this topic, focusing on ischaemic heart disease, peripheral vascular disease, severe carotid stenosis, smoking status, diabetes, atrial fibrillation, hyperlipidaemia, previous stroke. I have then reviewed the same associations within the OXVASC population, considering the CTs and MRIs of patients recruited in the first 8 years of the study.

5.2 Methods

5.2.1 Systematic review and meta-analysis

Two main medical search engines, Medline 1950 to present date and Embase 1980 to present date, were searched up to 01/04/2011. I used the search terms *leukoaraiosis* or *white matter changes* and matched with the terms *old age/aged*, *hypertension/high blood pressure*, *high cholesterol/hypercholesterolemia*, *cigarette smoking*, *ischemic heart disease*, *alcohol intake/alcohol consumption*, *diabetes mellitus*, *stroke*, *gender/sex, atrial fibrillation, peripheral vascular disease, carotid artery stenosis/disease*. Papers on sub-studies from small group of patients affected by specific conditions were excluded. Papers were included if they had a cross-sectional design and reported on the association between leukoaraiosis and the specific vascular risk factors. More specifically they had to report the number of subjects presenting the risk factor in the group of patients with leukoaraiosis and in the leukoaraiosis-free group. Only papers in English were considered. A few papers were subsequently added, derived from the papers' references. I calculated pooled odds ratios by fixed effect meta-analysis and p-values with the Chi-Square test for presence of each of the vascular risk factor considered, in patients with leukoaraiosis versus patients without. We grouped the studies according to imaging used (CT or MRI), and, for some of the variables, also according to the study setting. A brief description of the populations and of the objectives of the studies considered in the meta-analysis can be found in Appendix 8, table A2.0.

5.2.2. Population-based study

I compared the results of my review with the findings from the consecutive CT and MRI scans of the first 8 years of the population-based OXVASC. The white matter changes on the scans were rated as already seen in the previous chapters. The scores of different scales (van Swieten, ARWMC, Fazekas and Oxford scale) were categorised into a 0 to 3 system and also converted into a binary rating as "excessive for age" or "not". The analyses performed

were all binary logistic regressions, using as independent variables either “Excess of WMC for age” versus not, or “Presence of any degree of WMC” versus no WMC, or “Moderate and Severe WMC” versus “none or mild WMC”. The covariates considered were age and sex and, individually, diabetes, current smoking, previous CVA, previous myocardial infarction or angina, peripheral vascular disease, carotid stenosis >50% on either side, atrial fibrillation (AF), hyperlipidaemia.

5.3 Results

5.3.1. Systematic review

From a first search, 1229 papers were identified: 719 from Embase and 510 from Medline. After two consecutive screenings, eliminating in a first instance duplicate papers in the 2 search engines then papers on languages different from English, papers based only on laboratory or animal data, studies on specific small sub-group of subjects (i.e intravenous drug users), longitudinal studies and studies not reporting the exact prevalence of the vascular risk factor in the 2 groups of interest, only 74 papers were judged suitable. Fifty papers were based on MRI scans, 24 were based on CT assessment of leukoaraiosis. The associations between white matter changes and age, sex and hypertension have been discussed in previous chapters of this thesis.

Age

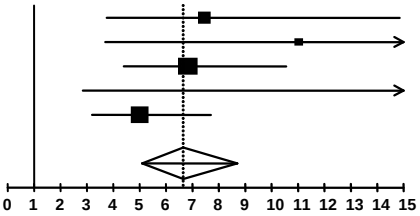
I will only briefly mention here the results of the meta-analysis on the association with age, which was considered by 21 CT-based studies and 33 MRI-based studies. I defined 65 years as a cut off age for the analysis after reviewing all the potential papers and seeing that the majority of them included this type of information about their population or gave enough information to be able to calculate the number of patients older or younger than 65 within the leukoaraiosis or the leukoaraiosis-free groups.The odds ratios were in favour of the

association both for CT (OR 3.8, 95% CI 3.1-4.6, P<0.001, 12 papers[10-21]) and MRI studies (6.6, 5.1-8.7, P<0.001, 5 papers[5,22-25]). The meta-analysis of CT studies yielded significant heterogeneity, which could be accounted for by the different population settings and way of classifying white matter changes, as we can see when splitting the studies into smaller groups (fig.5.1 a-f). Grouping the studies in “unselected patients and healthy volunteers”, “dementia patients” and “stroke patients” explained up to 28.1% of this heterogeneity, and sub-grouping the stroke studies according to the threshold for presence of leukoaraiosis (any level of minimal periventricular disease or a higher level), eliminated up to 85.9% of the heterogeneity. Only one[26] of the CT studies not included in the metanalysis [26-33] did not find a significant association with age, even though it showed a positive trend.

Figure 5.1 (a-f) Systematic review of studies considering age and leukoaraiosis (LA). Patients have been categorized according to a 65 years cut-off.

(a) Age > 65 years and leukoaraiosis (LA) on MRI studies

Study	Age>65 / Patients LA	Age>65 / Patients NO LA	OR	95% CI
Fujita 2002*	56 / 73	32 / 102	7.5	3.7-14.9
Fu 2005** (mild vs.severe)	64 / 69	39 / 69	11.0	3.7-32.7
Park 2007*	73 / 297	33 / 733	6.8	4.4-10.5
Wen 2004**	24 / 25	9 / 22	85.2	2.9-2,543.3
Khan 2007**	184 / 229	83 / 185	5.0	3.2-7.7
TOTAL	404 / 693	200 / 1111	6.6	5.1-8.7

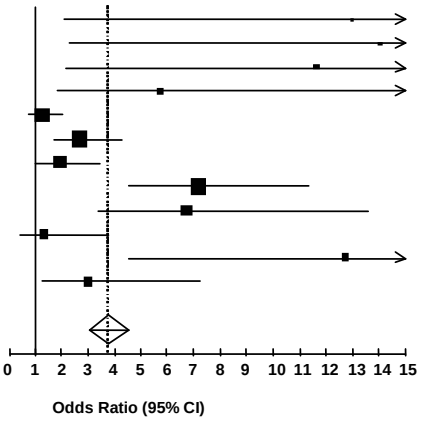


Significance: p<0.001
Heterogeneity: p=0.30

* General population and unselected outpatients, ** Stroke patients

(b) Age > 65 years and leukoaraiosis (LA) on CT studies

Study	Age>65 / Patients LA	Age>65 / Patients NO LA	OR	95% CI
Kobari 1990$	5 / 8	3 / 29	13.0	2.1-80.3
Blennow 1991*	29 / 31	13 / 23	14.1	2.2-88.5
Diaz 1991*	32 / 34	32 / 51	11.6	2.2-62.8
Wallin 2000*	45 / 51	20 / 34	5.7	1.8-18.0
Coskun 2003**	101 / 178	55 / 110	1.3	0.8-2.1
Awada 1996**	64 / 103	114 / 295	2.7	1.7-4.3
Podgorska 2002**	46 / 65	170 / 305	1.9	1.1-3.4
Wiszniewska 2000**	126 / 149	942 / 2140	7.2	4.5-11.4
Jorgensen 1995**	154 / 163	669 / 921	6.7	3.3-13.6
Thein 2007**	13 / 29	12 / 31	1.3	0.5-3.7
Censori 2007$	56 / 61	58 / 117	12.7	4.6-35.5
Karsidag 1995**	30 / 49	13 / 40	3.0	1.3-7.2
TOTAL	706 / 921	2106 / 4096	3.8	3.1-4.6

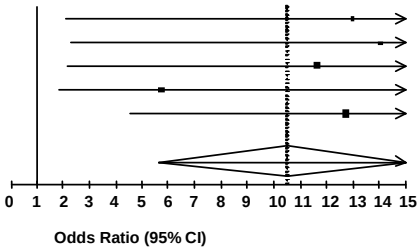


Significance: p<0.001
Heterogeneity: p<0.001

$ Healthy volunteers and unselected geratology patients, * Dementia patients, **Stroke patients

(c) Age > 65 years on CT studies of dementia and unselected patients

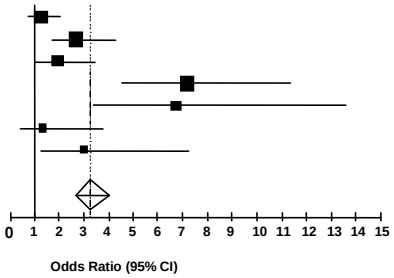
Study	Age>65 / Patients LA	Age>65 / Patients NO LA	OR	95% CI
Kobari 1990	5 / 8	3 / 29	13.0	2.1-80.3
Blennow 1991	29 / 31	13 / 23	14.1	2.2-88.5
Diaz 1991	32 / 34	32 / 51	11.6	2.2-62.8
Wallin 2000	45 / 51	20 / 34	5.7	1.8-18.0
Censori 2007	56 / 61	58 / 117	12.7	4.6-35.5
TOTAL	170 / 185	129 / 254	10.5	5.7-19.4



Significance; p<0.001
Heterogeneity: p=0.84

(d) Age > 65 years on CT studies of Stroke patients

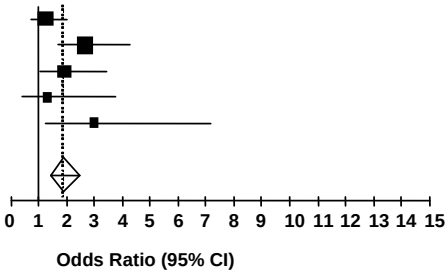
Study	Age>65 / Patients LA	Age>65 / Patients NO LA	OR	95% CI
Coskun 2003	101 / 178	55 / 110	1.3	0.8-2.1
Awada 1996	64 / 103	114 / 295	2.7	1.7-4.3
Podgorska 2002	46 / 65	170 / 305	1.9	1.1-3.4
Wiszniewska 2000	126 / 149	942 / 2140	7.2	4.5-11.4
Jorgensen 1995	154 / 163	669 / 921	6.7	3.3-13.6
Thein 2007	13 / 29	12 / 31	1.3	0.5-3.7
Karsidag 1995	30 / 49	13 / 40	3.0	1.3-7.2
TOTAL	537 / 736	1978 / 3842	3.3	2.7-4.0



Significance: p<0.001
Heterogeneity: p<0.001

(e) Age > 65 years on CT studies of Stroke patients. Periventricular WM considered and mild LA included

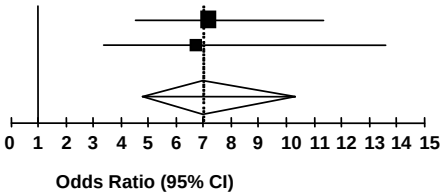
Study	Age>65 / Patients LA	Age>65 / Patients NO LA	OR	95% CI
Coskun 2003	101 / 178	55 / 110	1.3	0.8-2.1
Awada 1996	64 / 103	114 / 295	2.7	1.7-4.3
Podgorska 2002	46 / 65	170 / 305	1.9	1.1-3.4
Thein 2007	13 / 29	12 / 31	1.3	0.5-3.7
Karsidag 1995	30 / 49	13 / 40	3.0	1.3-7.2
TOTAL	256 / 424	366 / 781	1.9	1.5-2.5



Significance: p<0.001
Heterogeneity: p= 0.17

(f) Age > 65 years on CT studies of Stroke patients. Only severe LA considered.

Study	Age>65 / Patients LA	NO LA	OR	95% CI
Wiszniewska 2000	126 / 149	942 / 2140	7.2	4.5-11.4
Jorgensen 1995	154 / 163	669 / 921	6.7	3.3-13.6
TOTAL	281 / 312	1612 / 3061	7.0	4.8-10.3



Significance: p<0.001
Heterogeneity: p = 0.88

Diabetes

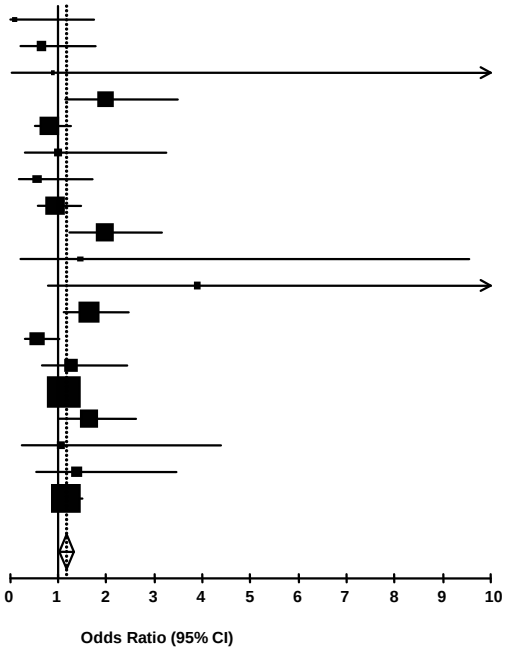
The association with diabetes was considered in 19 CT-papers, and 2 found this to be positive.[13,17] Amongst the MRI studies, 16 considered the association and 5 found this to be positive.[5,24,34-36] For the purpose of my meta-analysis I found 19 CT[10,13-18,20-21,26-33,37-38] and 7 MRI-based[5,23,25,34,39-41] suitable studies. There was a very weak association only in the CT-based studies (OR for CT studies 1.2, 1.0-1.3, P=0.008; OR for MRI studies 1.2, 0.9-1.5, P=0.233). I critically reviewed some of the studies showing a positive association. In the sample studied by Ylikoski,[34] diabetes was associated with presence of white matter lesions in the youngest group only. The more recent study by Khan[5] on risk factors profile differences between large vessel disease (LVD) and small vessel disease (SVD) stroke patients, found significant association between diabetes and SVD, but the association was stronger with patients presenting with isolated lacunar infarcts rather than with isolated leukoaraiosis, both considered part of the same SVD group. Moreover, analysing in detail the CT studies in the metanalysis, the main contributors[28,29] did a multivariate analysis and they both found diabetes not being significantly associated with leukoaraiosis. Among the studies not entered in the metanalysis, three found a positive association between leukoaraiosis and diabetes. Two of them were actually focused on metabolic syndrome, and found an association between Impaired Fasting Glucose, rather than diabetes, respectively with presence of

leukoaraiosis[24] and with periventricular white matter lesions[35]. The third paper was from the SMART Study,[36] and found leukoaraiosis significantly more represented amongst subjects with diabetes mellitus.

Figure 5.2 (a-b) Meta-analysis of CT (a) and MRI (b) studies on the association between white matter changes and diabetes mellitus

(a) Meta-analysis of CT Studies

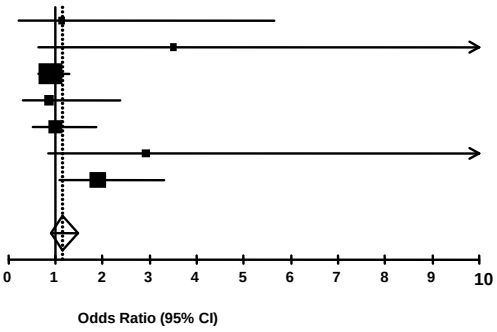
Study	Diabetes / Patients LA	Diabetes / Patients NO LA	OR	95% CI
George 1986	0 / 59	14 / 181	0.1	0.0-1.7
Inzitari 1987	5 / 61	23 / 189	0.6	0.2-1.8
Kobari 1990	0 / 8	2 / 29	0.9	0.0-22.1
Hijdra 1990	31 / 141	28 / 226	2.0	1.1-3.5
Jorgensen 1995	26 / 155	177 / 890	0.8	0.5-1.3
Tarvonen-Schroeder 1996	8 / 26	8 / 26	1.0	0.3-3.2
Karsidag 1995	7 / 49	9 / 40	0.6	0.2-1.7
Awada 1996	44 / 103	131 / 295	0.9	0.6-1.5
Henon 1996	48 / 264	35 / 346	2.0	1.2-3.2
Tataro 1999	2 / 21	3 / 45	1.5	0.2-9.6
Wallin 2000	10 / 51	2 / 34	3.9	0.8-19.1
Wiszniewska 2000	34 / 149	324 / 2140	1.7	1.1-2.5
Coskun 2002	29 / 178	28 / 110	0.6	0.3-1.0
Podgorska 2002	15 / 65	58 / 305	1.3	0.7-2.4
Streifler 2002	113 / 493	448 / 2125	1.1	0.9-1.4
Streifler 2003	31 / 125	79 / 471	1.6	1.0-2.6
Ventura 2007	3 / 16	11 / 62	1.1	0.3-4.4
Censori 2007	9 / 61	13 / 117	1.4	0.6-3.4
Koton 2008	180 / 539	146 / 485	1.2	0.9-1.5
TOTAL	596 / 2564	1539 / 8116	1.2	1.0-1.3



Significance: p = 0.008
Heterogeneity: p = 0.03

(b) Meta-analysis of MRI Studies

Study	Diabetes / Patients LA	Diabetes / Patients NO LA	OR	95% CI
Ylikoski 1995	8 / 100	2 / 28	1.1	0.2-5.7
Marti-Fabregas 2001	7 / 13	3 / 12	3.5	0.6-19.2
Longstreth 2001	47 / 460	110 / 981	0.9	0.6-1.3
Wen 2004	24 / 72	8 / 22	0.9	0.3-2.4
Jeerakathil 2004	12 / 240	79 / 1574	1.0	0.5-1.9
Fu 2005	47 / 197	3 / 31	2.9	0.9-10.1
Khan 2007	21 / 229	37 / 734	1.9	1.1-3.3
TOTAL	166 / 1311	242 / 3382	1.2	0.9-1.5



Significance: p = 0.23
Heterogeneity: p = 0.16

Smoking

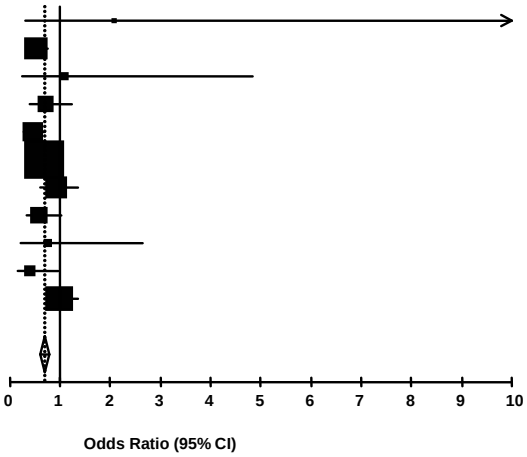
No CT study[14,17-20,26,30,32-33] found a positive association with smoking (either current or previous, according to study), while three[17-18,33] found an inverse association. Four MRI studies[5,42-44] found a positive association. My meta-analysis included 11 CT[10,14,16-18,20,26-27,30,32-33] and 7 MRI[5,23-24,39-40,43,45] studies. No positive association emerged (OR for CT studies 0.7, 0.6-0.8, P<0.001; OR for MRI studies 1.0, 0.8-1.2, P=0.826), despite some heterogeneity.

Figure 5.3 (a-b) Meta-analysis of CT (a) and MRI (b) studies on smoking and leukoaraiosis

(a) Meta-analysis of CT Studies (all current smoking)

Study	Smoke / Patients LA	Smoke / Patients NO LA	OR	95% CI
Kobari 1990	2 / 8	4 / 29	2.1	0.3-14.2
Jorgensen 1995	46 / 163	397 / 921	0.5	0.4-0.7
Tartaro 1999	3 / 21	6 / 45	1.1	0.2-4.8
Podgorska 2002	23 / 65	133 / 305	0.7	0.4-1.2
Wiszniewska 2002	24 / 149	636 / 2140	0.5	0.3-0.7
Streifler 2002	176 / 493	952 / 2125	0.7	0.6-0.8
Streifler 2003	52 / 125	206 / 471	0.9	0.6-1.4
Coskun 2003	33 / 178	31 / 110	0.6	0.3-1.0
Ventura 2007	4 / 16	19 / 62	0.8	0.2-2.6
Censori 2007	7 / 61	29 / 117	0.4	0.2-1.0
Koton 2008	106 / 539	96 / 485	1.0	0.7-1.4
TOTAL	476 / 1818	2509 / 6810	0.7	0.6-0.8

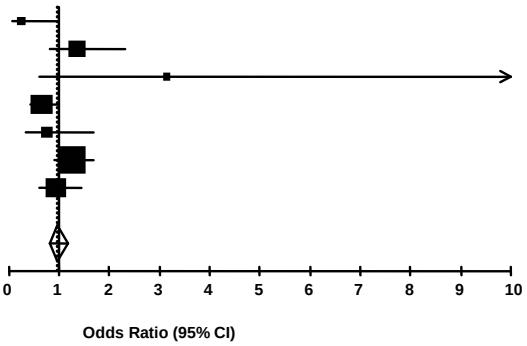
Significance: p <0.0001
Heterogeneity: p = 0.09



(b) Meta-analysis of MRI Studies *current smoking, **either current or previous smoking

Study	Smoke / Patients LA	Smoke / Patients NO LA	OR	95% CI
Bots 1993**	3 / 30	24 / 81	0.3	0.1-1.0
Dufouil 2001*	47 / 511	22 / 319	1.4	0.8-2.3
Marti-Fabregas 2001*	9 / 13	5 / 12	3.2	0.6-16.3
Longstreth 2001**	33 / 460	103 / 981	0.7	0.4-1.0
Fu 2005*	52 / 197	10 / 31	0.8	0.3-1.7
Park 2007*	83 / 297	174 / 733	1.2	0.9-1.7
Khan 2007**	162 / 229	133 / 185	0.9	0.6-1.5
TOTAL	389 / 1737	471 / 2342	1.0	0.8-1.2

Significance: p = 0.83
Heterogeneity: p = 0.03



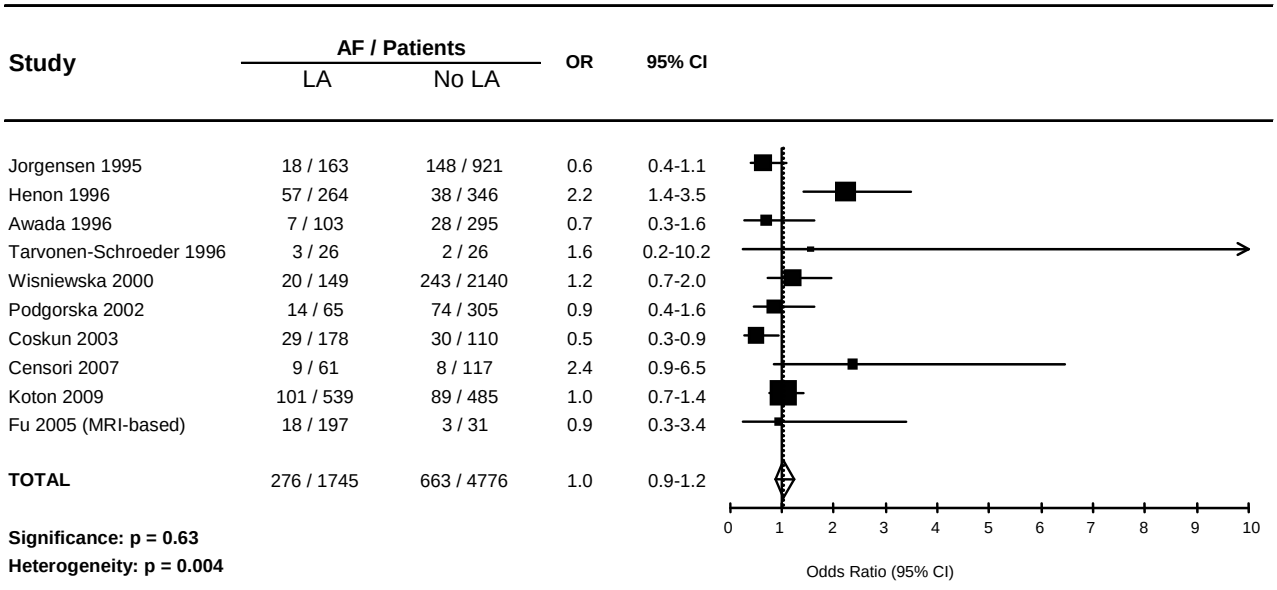
Hyperlipidaemia

Nine CT-based studies[13,15,17-19,28,32-33,48] considered the relationship between leukoaraiosis and hyperlipidaemia, and the meta-analysis showed an overall inverse association (OR 0.7, 0.6-0.8, P<0.001). Ten MRI papers[3,5,16,20-21,24,34,39,46-47] considered the association, but only two studies were suitable for consideration in the meta-analysis (OR 1.2, 0.9-1.5, P=0.164).

Atrial Fibrillation (AF)

The association between AF and leukoaraiosis was considered by ten studies[14-18,20,23,27-28,38] among those reviewed, and nine were CT-based. Only one study[28] found a positive association between presence and severity of leukoaraiosis and AF. The authors hypothesised that AF could contribute to a reduced brain perfusion leading to worsening of white matter changes. The meta-analysis of these studies shows no association between white matter changes and AF (combined OR for CT and MRI studies 1, 0.9-1.2, P = 0.632). Again, there was significant heterogeneity among studies.

Figure 5.4 Meta-analysis of CT and MRI-based studies on the association between Atrial Fibrillation (AF) and leukoaraiosis (LA)



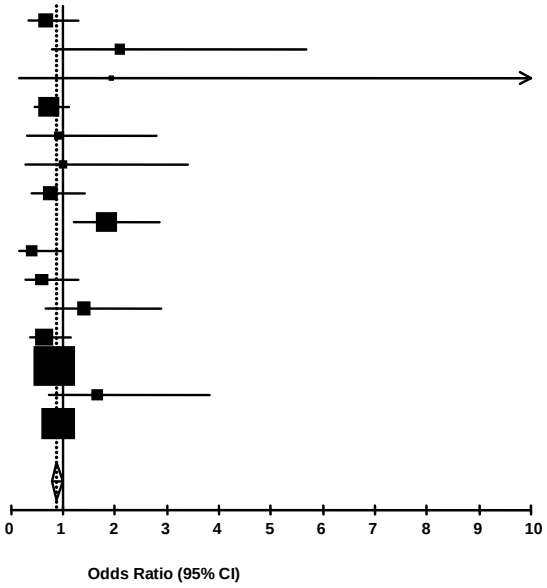
Ischaemic heart disease (IHD)

No association with ischaemic heart disease (IHD) was found in my meta-analysis of fifteen suitable CT studies[10,13-18,20-21,27-28,31,33,37-38] and six MRI studies[5,23-24,34,39,45] (OR for CT studies 0.9, 0.8-1.1, P=0.074; OR for MRI studies 1.0, 0.7-1.6, P=0.907).

Figure 5.5 (a-b) Meta-analysis of CT (a) and MRI (b) studies on the association between Ischaemic heart disease (IHD) and leukoaraiosis (LA)

(a) Meta-analysis of CT Studies

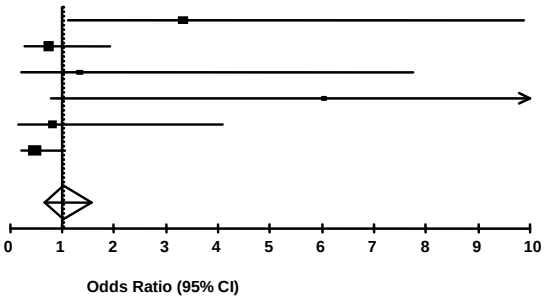
Study	IHD / Patients LA	IHD / Patients NO LA	OR	95% CI
George 1986	14 / 59	58 / 181	0.7	0.3-1.3
Inzitari 1987	7 / 61	11 / 189	2.1	0.8-5.7
Kobari 1990	1 / 8	2 / 29	1.9	0.2-24.5
Jorgensen 1995	28 / 163	206 / 921	0.7	0.5-1.1
Karsidag 1995	8 / 49	7 / 40	0.9	0.3-2.8
Tarvonen-Schroeder 1996	7 / 26	7 / 26	1.0	0.3-3.4
Awada 1996	14 / 103	51 / 295	0.8	0.4-1.4
Henon 1996	56 / 264	44 / 346	1.8	1.2-2.8
Wallin 2000	25 / 51	24 / 34	0.4	0.2-1.0
Wiszniewska 2002	7 / 149	162 / 2140	0.6	0.3-1.3
Coskun 2002	26 / 178	12 / 110	1.4	0.7-2.9
Podgorska 2002	20 / 65	125 / 305	0.6	0.4-1.1
Streifler 2002	165 / 493	801 / 2125	0.8	0.7-1.0
Censori 2007	12 / 61	15 / 117	1.7	0.7-3.8
Koton 2008	189 / 539	180 / 485	0.9	0.7-1.2
TOTAL	579 / 2269	1705 / 7343	0.9	0.8-1.0



Significance: p = 0.07
Heterogeneity: p = 0.03

(b) Meta-analysis of MRI Studies

Study	IHD / Patients LA	IHD / Patients NO LA	OR	95% CI
Bots 1993	8 / 30	8 / 81	3.3	1.1-9.9
Ylikoski 1995	23 / 100	8 / 28	0.7	0.3-1.9
Marti-Fabregas 2001	4 / 13	3 / 12	1.3	0.2-7.7
Fu 2005	33 / 197	1 / 31	6.0	0.8-45.8
Park 2007	2 / 297	6 / 733	0.8	0.2-4.1
Khan 2007	7 / 229	46 / 734	0.5	0.2-1.1
TOTAL	77 / 866	72 / 1619	1.0	0.7-1.6



Significance: p = 0.91
Heterogeneity: p = 0.04

Peripheral vascular disease (PVD)

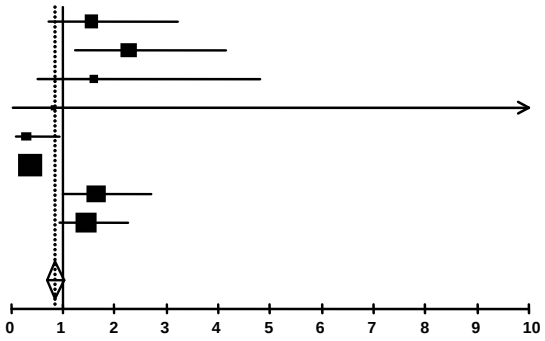
Ten studies, eight with CT[17-18,21,27,30-31,33,38] and two with MRI,[39,45] considered the association between leukoaraiosis and PVD. Only one of them[45] found a significant association. The result of the meta-analysis performed on their results shows an overall not significant association between leukoaraiosis and PVD (combined OR 0.9, 0.7-1.1, P=0.324).

Figure 5.6 (a-b) Meta-analysis of CT (a) and MRI (b) studies on the association between peripheral vascular diasease (PVD) and leukoaraiosis (LA)

(a) PVD on CT studies

Study	PVD / Patients LA	PVD / Patients No LA	OR	95% CI
George 1986	13 / 59	28 / 181	1.5	0.7-3.2
Jorgensen 1995	16 / 163	42 / 921	2.3	1.2-4.2
Tarvonen-Schroeder 1996	16 / 26	13 / 26	1.6	0.5-4.8
Karsidag 1995	1 / 49	1 / 40	0.8	0.0-13.4
Wisniewska 2000	3 / 149	137 / 2140	0.3	0.1-1.0
Streifler 2002	31 / 493	323 / 2125	0.4	0.3-0.5
Streifler 2003	26 / 125	65 / 471	1.6	1.0-2.7
Koton 2009	55 / 539	35 / 485	1.5	0.9-2.3
TOTAL	161 / 1603	644 / 6389	0.9	0.7-1.0

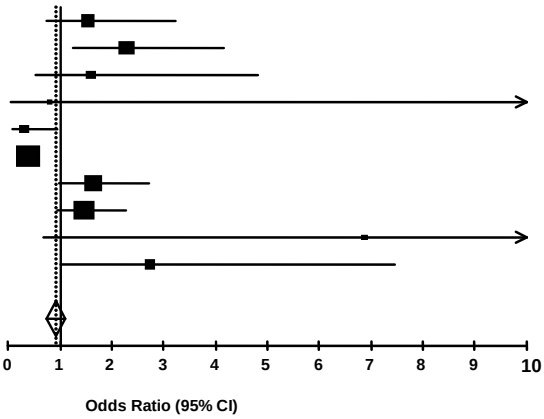
Significance: p = 0.12
Heterogeneity: p <0.0001



(b) PVD on CT and MRI* studies

Study	PVD / Patients LA	PVD / Patients No LA	OR	95% CI
George 1986	13 / 59	28 / 181	1.5	0.7-3.2
Jorgensen 1995	16 / 163	42 / 921	2.3	1.2-4.2
Tarvonen-Schroeder 1996	16 / 26	13 / 26	1.6	0.5-4.8
Karsidag 1995	1 / 49	1 / 40	0.8	0.0-13.4
Wisniewska 2000	3 / 149	137 / 2140	0.3	0.1-1.0
Streifler 2002	31 / 493	323 / 2125	0.4	0.3-0.5
Streifler 2003	26 / 125	65 / 471	1.6	1.0-2.7
Koton 2009	55 / 539	35 / 485	1.5	0.9-2.3
Marti-Fabregas 2001*	5 / 13	1 / 12	6.9	0.7-70.8
Bots 1993*	9 / 30	11 / 81	2.7	1.0-7.5
TOTAL	175 / 1646	656 / 6482	0.9	0.7-1.1

Significance: p = 0.32
Heterogeneity: p <0.0001



Internal Carotid Artery (ICA) stenosis

The association between white matter changes and Internal Carotid Artery (ICA) stenosis was considered in 12 papers. Eight papers found no association,[28,30,33,45,48-51] three found positive associations between degree of stenosis and severity of leukoaraiosis[7,52,53] and one[17] found a positive association between presence of leukoaraiosis and only the mild degree (<50%) of ICA Stenosis (OR 2.23, 95% CI 1.32-3.76, P 0.003), while severe carotid stenosis was not associated with white matter changes. I also looked into the association between white matter changes and intima-media thickness, and found 8 studies[7,8,45,52,54,55,56,57] among which only one[57] did not find a positive association. No meta-analysis could be performed for lack of suitable data from all these studies.

Previous ischaemic stroke

Among the studies reviewed, the relationship between leukoaraiosis and ischaemic stroke was examined under several different perspectives: stroke as a risk factor for presence or severity of leukoaraiosis (which is what I was interested in my meta-analysis), leukoaraiosis as a risk factor for stroke and stroke recurrence, and leukoaraiosis as a possible marker of small vessel disease associated to the lacunar type of stroke. Seventeen CT-based studies out of twenty-six reviewed considered the relation between stroke and leukoaraiosis addressing one of the above issues, and ten of these[13-17,20,27-28,37-38] were suitable to enter in the metanalysis, three of which were performed on acute stroke patients. No MRI studies amongst those considered in this review were suitable for the metanalysis. The association between history of previous stroke and presence of white matter changes was strongly significant (OR 1.8, 1.5-2.1, P<0.001, with no large heterogeneity between studies). Eleven MRI-based studies took into account the association between leukoaraiosis and stroke, but they were not suitable to be entered in our metanalysis. Among these, longitudinal observations from the Cardiovascular Health Study[44] and form the Rotterdam Scan Study[42]

showed that the progression of leukoaraiosis over time is more evident and severe in patients with stroke on their initial scans, confirming what had already been seen in association with a past medical history of stroke.[5,36,48]

Figure 5.7 Meta-analysis of studies (all CT-based) on the association between history of previous stroke and leukoaraiosis (LA)

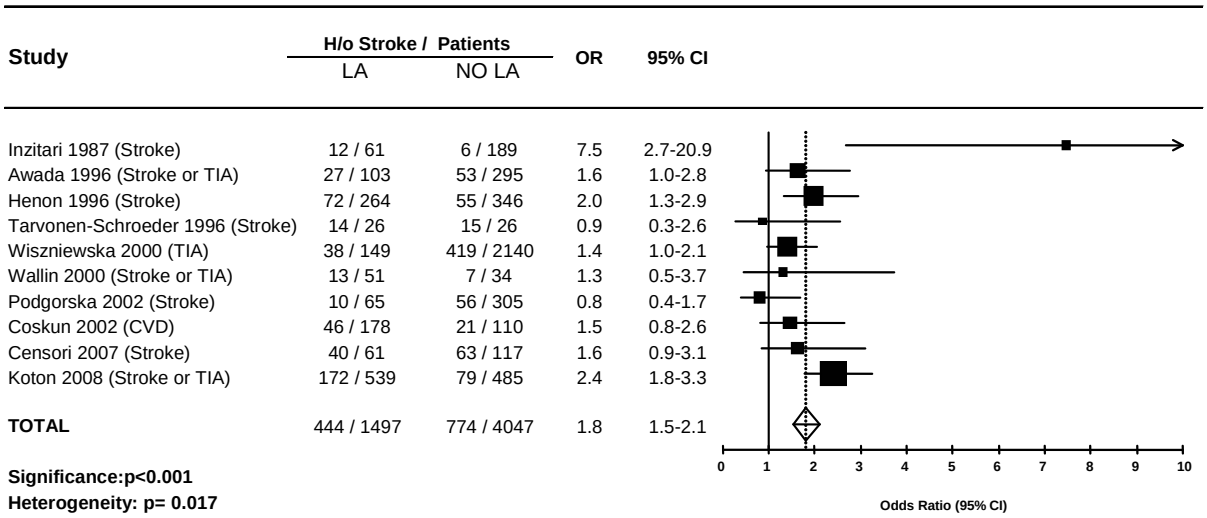


Table 5.1 Summary of the findings from meta-analysis of studies on vascular risk factors and white matter changes

	MRI Studies					CT Studies				
	N studies	OR	95% CI	Ps	Phet.	N studies	OR	95% CI	Ps	Phet.
Age										
Age >65 yrs. (all patients)	**5**	**6.6**	**5.1-8.7**	**<0.001**	**0.3**	**12**	**3.8**	**3.1-4.6**	**<0.001**	**<0.001**
Age >65 yrs. (neurol. pts)	**na**	**na**	**na**	**na**	**na**	**5**	**10.5**	**5.7-19.4**	**<0.001**	**0.84**
Age >65 yrs. (stroke pts-only severe LA)	**na**	**na**	**na**	**na**	**na**	**2**	**7**	**4.8-10.3**	**<0.001**	**0.88**
Age >65 yrs. (stroke pts-also mild LA)	**na**	**na**	**na**		**na**	**5**	**1.9**	**1.5-2.5**	**<0.001**	**0.17**
Vascular Risk Factors										
Hypertension	**9**	**2.1**	**1.8-2.3**	**<0.001**	**<0.001**	**19**	**1.7**	**1.5-1.9**	**<0.001**	**0.002**
Dyslipidaemia	**2**	1.2	0.9-1.5	0.16	<0.001	9	**0.7**	**0.6-0.8**	**<0.001**	**0.54**
Diabetes	7	1.2	0.9-1.5	0.23	0.16	19	1.2	1.0-1.3	0.008	0.02
Smoking	**7**	1	0.8-1.2	0.82	0.03	11	**0.7**	**0.6-0.8**	**<0.001**	**0.08**
Atrial Fibrillation	1	0.9	0.4-2.3	1.07	na	9	1	0.9-1.2	0.61	0.002
Peripheral Vascular Disease	**2**	**3.3**	**1.3-8.1**	**0.01**	**0.47**	8	0.9	0.7-1.0	0.12	<0.001
Carotid Stenosis >50%	1	0.9	0.1-9.0	1.07	na	4	0.8	0.7-1.0	0.61	0.002
Ischemic Heart Disease	**6**	1	0.7-1.6	0.9	0.04	17	0.9	0.8-1.0	0.07	0.03
Previous Stroke	**n.a**	n.a	n.a	n.a	n.a	10	**1.8**	**1.5-2.1**	**<0.001**	0.017

5.3.2 Population-based study

Among the 1717 patients whose CT scan was evaluated with the Oxford scale, 1710 had data on previous stroke, IHD, AF, Diabetes, PVD, hypertension, smoking, and 1564 had data on the degree of carotid stenosis. Among the 1584 patients whose CT were also evaluated with the ARWMC and with the van Swieten scales, respectively 1584 and 1580 patients had data on previous stroke, IHD, AF, Diabetes, PVD, hypertension, smoking, and 1089 had data on carotid stenosis. Among the 520 patients whose MRI was rated with the Oxford scale, 517 had data on previous stroke, IHD, AF, Diabetes, PVD, hypertension, smoking, and 412 had data on carotid stenosis, while among the 489 patients whose MRI were also evaluated with the ARWMC and the Fazekas scale, all of them had data on previous stroke, IHD, AF, Diabetes, PVD, hypertension, smoking, and 390 had also data on the degree of carotid stenosis.

I performed the analysis considering initially each single risk factor in association with the presence of excessive white matter changes for age, also adjusting for age and sex (table 5.2). Doing so, I only found an association with previous stroke, and this was only present for the MRI evaluations, when leukoaraiosis was rated with the Oxford scale. No other association was significant, except for a significant inverse association between white matter changes and carotid stenosis. Repeating the analysis inserting all the vascular risk factors in a multivariate model, and this time also using age and sex as variables, only hypertension, age and history of previous stroke resulted positively associated with white matter changes, with history of previous stroke only for white matter changes on MRI. Atrial fibrillation, carotid stenosis and diabetes were found inversely associated (table 5.3).

Table 5.2 Associations between LA and vascular risk factors in OXVASC. Adjusted for age and sex.

			Excess of WMC for age		Any WMC degree		Moderate+Severe WMC	
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Diabetes	**CT**	**Oxford**	1.12 (0.76-1.67)	0.57	**1.39 (1.01-1.90)**	**0.04**	1.22 (0.87-1.70)	0.24
		ARWMC	1.08 (0.72-1.63)	0.70	1.23 (0.88-1.73)	0.23	1.15 (0.81-1.64)	0.44
		van Swieten	1.27 (0.89-1.81)	0.18	1.39 (0.98-1.96)	0.06	1.25 (0.89-1.77)	0.20
	MRI	**Oxford**	0.64 (0.32-1.27)	0.20	0.54 (0.31-0.96)	0.04	0.79 (0.42-1.45)	0.44
		ARWMC	0.86 (0.46-1.61)	0.64	0.92 (0.51-1.64)	0.77	0.77 (0.40-1.47)	0.42
		Fazekas	0.87 (0.47-1.59)	0.65	0.77 (0.41-1.42)	0.40	0.66 (0.35-1.25)	0.20
AF	**CT**	**Oxford**	0.73 (0.50-1.06)	0.10	0.84 (0.64-1.10)	0.20	0.83 (0.63-1.10)	0.20
		ARWMC	0.80 (0.56-1.16)	0.24	0.99 (0.73-1.33)	0.92	1.00 (0.75-1.33)	0.98
		van Swieten	0.89 (0.65-1.21)	0.45	0.94 (0.70-1.27)	0.70	0.90 (0.68-1.19)	0.46
	MRI	**Oxford**	1.14 (0.55-2.37)	0.72	0.93 (0.45-1.94)	0.85	1.30 (0.65-2.59)	0.46
		ARWMC	1.27 (0.63-2.58)	0.51	0.75 (0.36-1.59)	0.46	1.20 (0.58-2.47)	0.63
		Fazekas	1.06 (0.51-2.16)	0.88	0.79 (0.35-1.79)	0.57	1.26 (0.62-2.59)	0.52
PVD	**CT**	**Oxford**	0.79 (0.44-1.41)	0.42	1.52 (1.00-2.31)	0.05	0.92 (0.60-1.41)	0.69
		ARWMC	0.69 (0.38-1.26)	0.23	1.08 (0.70-1.68)	0.73	0.81 (0.52-1.27)	0.36
		van Swieten	1.10 (0.70-1.73)	0.69	1.15 (0.74-1.81)	0.53	1.20 (0.79-1.83)	0.40
	MRI	**Oxford**	0.59 (0.22-1.58)	0.29	0.53 (0.24-1.21)	0.13	0.84 (0.37-1.88)	0.66
		ARWMC	0.36 (0.12-1.06)	0.06	0.66 (0.28-1.54)	0.33	0.57 (0.24-1.35)	0.20
		Fazekas	0.72 (0.30-1.73)	0.46	0.63 (0.25-1.58)	0.32	0.69 (0.31-1.58)	0.38
IHD	**CT**	**Oxford**	0.96 (0.68-1.36)	0.83	1.05 (0.80-1.36)	0.74	0.97 (0.74-1.28)	0.82
		ARWMC	1.03 (0.73-1.46)	0.87	0.93 (0.70-1.24)	0.61	0.83 (0.62-1.11)	0.21
		van Swieten	1.13 (0.84-1.52)	0.44	0.98 (0.73-1.30)	0.87	0.94 (0.71-1.25)	0.68
	MRI	**Oxford**	1.15 (0.64-2.05)	0.64	0.95 (0.54-1.68)	0.86	1.01 (0.58-1.77)	0.97
		ARWMC	0.87 (0.48-1.57)	0.65	0.77 (0.43-1.36)	0.36	0.81 (0.45-1.46)	0.49
		Fazekas	0.98 (0.56-1.74)	0.95	0.95 (0.51-1.79)	0.88	0.78 (0.44-1.39)	0.40
Smoking	**CT**	**Oxford**	0.92 (0.60-1.42)	0.70	**1.48 (1.06-2.05)**	**0.02**	1.13 (0.78-1.64)	0.51
		ARWMC	1.33 (0.89-1.99)	0.17	1.40 (0.99-1.96)	0.06	**1.60 (1.10-2.34)**	**0.01**
		van Swieten	1.31 (0.90-1.91)	0.15	1.36 (0.96-1.92)	0.08	1.35 (0.92-1.96)	0.12
	MRI	**Oxford**	0.89 (0.48-1.65)	0.71	1.20 (0.70-2.07)	0.51	0.91 (0.48-1.75)	0.78
		ARWMC	0.73 (0.39-1.36)	0.33	1.26 (0.73-2.16)	0.41	1.00 (0.51-1.94)	1.00
		Fazekas	1.14 (0.65-2.00)	0.64	1.75 (0.98-3.12)	0.06	0.96 (0.51-1.81)	0.91
Hyperlipidaemia	**CT**	**Oxford**	1.12 (0.83-1.52)	0.45	1.06 (0.83-1.34)	0.66	1.12 (0.87-1.44)	0.37
		ARWMC	1.20 (0.86-1.62)	0.24	0.89 (0.69-1.14)	0.36	1.03 (0.79-1.33)	0.86
		van Swieten	1.02 (0.77-1.34)	0.90	0.95 (0.73-1.22)	0.66	1.25 (0.97-1.62)	0.09
	MRI	**Oxford**	1.01 (0.64-1.60)	0.96	1.25 (0.81-1.92)	0.31	1.20 (0.77-1.87)	0.42
		ARWMC	1.31 (0.84-2.04)	0.23	1.31 (0.84-2.03)	0.24	1.27 (0.80-2.02)	0.31
		Fazekas	1.14 (0.73-1.76)	0.57	1.10 (0.69-1.76)	0.70	1.30 (0.83-2.03)	0.26
Carotid stenosis	**CT**	**Oxford**	0.61 (0.35-1.07)	0.09	1.12 (0.80-1.58)	0.51	0.93 (0.63-1.37)	0.71
		ARWMC	0.90 (0.56-1.43)	0.65	1.22 (0.84-1.76)	0.30	1.03 (0.70-1.52)	0.89
		van Swieten	1.12 (0.74-1.67)	0.60	1.24 (0.85-1.79)	0.26	1.14 (0.78-1.66)	0.49
	MRI	**Oxford**	0.38 (0.13-1.10)	0.07	0.84 (0.39-1.80)	0.65	0.71 (0.32-1.55)	0.39
		ARWMC	0.44 (0.17-1.17)	0.10	0.75 (0.36-1.60)	0.46	0.31 (0.13-0.78)	0.01
		Fazekas	0.28 (0.09-0.80)	0.02	0.76 (0.33-1.74)	0.51	0.52 (0.24-1.14)	0.10
Previous Stroke	**CT**	**Oxford**	1.19 (0.80-1.75)	0.39	1.21 (0.88-1.67)	0.24	1.08 (0.78-1.48)	0.65
		ARWMC	1.44 (0.99-2.11)	0.06	1.04 (0.74-1.46)	0.84	1.06 (0.76-1.48)	0.73
		van Swieten	1.21 (0.86-1.70)	0.29	1.15 (0.81-1.64)	0.44	1.32 (0.96-1.83)	0.09
	MRI	**Oxford**	**2.98 (1.49-5.97)**	**0.002**	1.86 (0.80-4.31)	0.15	**2.12 (1.03-4.37)**	**0.04**
		ARWMC	1.00 (0.45-2.22)	1.00	0.59 (0.27-1.29)	0.19	0.87 (0.39-1.95)	0.73
		Fazekas	1.93 (0.94-3.96)	0.08	1.14 (0.46-2.81)	0.78	1.18 (0.55-2.56)	0.67

Table 5.3 Multivariate regression analysis: stepwise backward LR. The variable excess of WMC for age, according to different scales, has been entered as outcome. Variables entered as covariates in step 1: age, male sex, hypertension, hyperlipidaemia, diabetes, previous stroke, ischaemic heart disease, atrial fibrillation (AF), carotid stenosis > 50%, peripheral vascular disease, current smoking

		Significant Associations	OR (95% CI)	P
Oxford Scale	**CT**	**Hypertension**	1.80 (1.24-2.62)	0.002
		***AF **	*0.55 (0.31-0.99)*	0.04
		***Carotid stenosis**	*0.54 (0.31-0.95)*	0.03
	MRI	**Previous Stroke**	2.93 (1.26-6.78)	0.01
		Hypertension	2.63 (1.57-4.40)	<.0001
		***Diabetes**	0.25 (0.10-0.65)	0.004
		***Carotid stenosis**	0.31 (0.10-0.93)	0.037
ARWMC Scale	**CT**	**Hypertension**	1.55 (1.09-2.21)	0.01
	MRI	***nil***		
van Swieten scale	**CT**	**Age**	1.03 (1.01-1.04)	0.001
		Hypertension	1.60 (1.16-2.20)	0.005
Fazekas scale	**MRI**	**Hypertension**	1.71 (1.06-2.77)	0.03
		Previous stroke	2.34 (1.01-5.42)	0.05
		***Diabetes**	0.46 (0.21-0.99)	0.05
		***Carotid stenosis**	0.25 (0.09-0.75)	0.013

*** Inverse associations**

5.4 Discussion and conclusions

In the previous two decades many studies have been performed on the possible risk factors for white matter changes, to better understand their nature and their possible prognostic meaning. In order to define a risk factor, this has to be present before the condition arises, and the difficulty with white matter changes is that we do not know exactly when they originate. The majority of studies on scans are made on subjects who are somewhat symptomatic, and generally in their old age. From the few population-based studies that have considered this subject, we have realized that most certainly white matter changes are age-related, but it is still impossible to say when they start forming and when external factors may start contributing towards their formation. With this in mind, I have tried to review exhaustively the studies performed so far about possible factors contributing to leukoaraiosis.

My review has considered all the studies on the well known vascular risk factors, as the pathogenesis of white matter changes has so far been linked to chronic ischaemia secondary to degeneration of the penetrating small arteriolae. It is quite interesting to see that the conclusion of my review is not strikingly in favour of any of these associations, contrary to what we are accostumed to think and to what in many instances we communicate to our patients. The only convincing association I have found, beside age, is with hypertension and with previous ischaemic stroke. The link with diabetes and smoking, which are often mentioned as risk factors for both small and large vessel type of arteriopathy, has resulted as being weak. In particular, the association with smoking could be interpreted as “protective” from my meta-analysis of CT studies. However, this is most likely the effect of a survival selection created by the strong association between smoking and early mortality. This is more evident in the meta-analysis of CT studies because MRI studies usually encompass younger populations. With regards to the association with previous stroke, unfortunately I could only include in the meta-analysis CT-based studies. This association is quite difficult to

study when based upon visual-only evaluation of white matter changes, as it can be not straightforward to distinguish between chronic white matter changes and old white matter lesions residual from previous strokes. The studies considered in my review were all based on visual evaluation of leukoaraiosis, as opposed to quantitative volumetric measurements, as the former represented the vast majority of the research performed on this specific topic up to 2011.

Another interesting observation arising from my review is the possibility of an association between the degree of intima-media thickness (IMT) and the severity of white matter changes. Not many studies have taken this relationship into account, and none gave enough information to be inserted in a meta-analysis, but the majority found a positive association. There is still debate as to whether IMT should be considered as a marker of large vessel atherosclerosis or as a more general marker of hypertensive disease, and it is interesting to observe an opposite behavior towards white matter changes, when compared with carotid stenosis, of which this entity is considered a precursor. More research on this regard needs to be done, and it is not excluded the possibility of this within the OXVASC study in the future.

One possible weakness of my review was given by the inter-studies difference in the evaluation of presence of white matter changes. Some of the studies simply used the definition of leukoaraiosis given by Hachinski, and other studies adopted semi-quantitative rating scales and used different cut-offs to define presence or absence of leukoaraiosis. The relatively small number of studies entered in the meta-analyses illustrates the difficulties in performing a systematic review on a subject still studied in such a heterogeneous way. My review included several papers considering leukoaraiosis but not having as primary objective the study of the association between leukoaraiosis and vascular risk factors, and therefore not giving enough information in order to be inserted in a meta-analysis. However, to my

knowledge, this is the first attempt to perform a systematic review with meta-analysis on leukoaraiosis and its association with vascular risk factors.

The conclusions of my population-based study reflected what had already been seen in the systematic review. Beside age and hypertension, only history of previous stroke was associated with white matter changes. In this case, the association was stronger for MRI-detected white matter changes. With regard to this, we must consider two things: first, the number of MRI scans was much smaller than the number of CT scans considered (517 versus 1710), and second, MRI are more sensitive than CT in detecting white matter changes, and in the context of a blinded visual evaluation it might be quite difficult to distinguish between a residual change from a previous infarction and chronic white matter changes.

The fact that the same results were found in the population-based study and in the systematic review, points to the robustness of the findings. Nevertheless, one must consider that the results of the population-based study are only applicable to patients presenting with stroke or TIA, while the systematic review included different types of population, as this was not one of our inclusion/exclusion criteria.

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Chapter 6

Age-specific differences of subtypes of strokes (TOAST) in association with CT-detected white matter changes: the OXVASC study, years 1-8

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6.0 Abstract

Background: Various studies have researched on the spectrum of risk factors associated with different types of strokes, with conflicting results. I aimed to look into the associations between vascular risk factors, white matter changes (WMC) and stroke subtypes in a population-based cohort of strokes and TIA.

Methods: All the CT brain scans of patients recruited in years 1 to 8 in the OXVASC study were evaluated for WMC. Strokes were grouped in 5 subtypes on the basis of their pathogenesis, according to the "Trial of Org 10172 in Acute Stroke Treatment" (TOAST) classification: large artery atherosclerosis (LAA), cardioembolic (CE), small vessel occlusion (SMV), other determined etiology, and undetermined etiology. Age-specific associations between different types of ischaemic stroke and WMC, adjusted for presence of vascular risk factors, were researched by mean of logistic regression analyses.

Results: 1921 patients with TIA or stroke were considered, and 36.5% fell in the "Undetermined" category. The CE was the most represented (20.1%) of the three main categories and their mean age (78.8 years +/- 12.03) was the highest. SMV strokes/TIA represented a younger group of mainly male patients (mean age 71.5 yrs +/- 12.3, 60.4% male). Significant carotid stenosis was strongly associated with the LAA, ischaemic heart disease and AF were strongly associated with the CE, and diabetes and current smoke were associated with the SMV type of stroke. WMC, rated with any of the scales, were significantly associated with the small vessel type of stroke in patients over 65 years of age, independently from other vascular risk factors.

Conclusions: SMV stroke is strongly associated with current smoking and diabetes, and is the only type of stroke to be independently associated with excess of white matter changes on CT scans, especially after the age of 65. SMV type of stroke and WMC may represent two different results of genetic-environmental interactions within the same spectrum of pathology.

6.1. Introduction

Small vessel brain pathology traditionally includes white matter changes, microbleeds and lacunar stroke.[1,2,3] The relationship between these pathologies is recognized, and it is often reported to be secondary to the common risk factor of hypertension. As we have seen in previous chapters, though, hypertension is not predominantly present in the small vessel type of stroke. In this study I have explored the association between white matter changes and lacunar stroke in the OXVASC population, grouping my patients according to their pathogenesis with the "Trial of Org 10172 in Acute Stroke Treatment" (TOAST) classification.[4] I have only considered CT scan-detected leukoaraiosis, and therefore I have not looked into the association between white matter changes and microbleeds. Microbleeds are in fact detected only on MRI, using the gradient-echo sequence, and not enough patients recruited in years 1 to 8 have been studied with this.

I have looked at the distribution of different types of ischaemic stroke/TIA in relation to age, sex and vascular risk factors, researching possible associations between them and white matter changes, again in relation to vascular and demographic risk factors.

6.2 Methods

Within years 1 to 8 of the population-based OXVASC Study, I selected the patients recruited with ischaemic stroke and TIA and assessed the pathogenesis of their event with the TOAST classification. This classification was created for a double blind placebo controlled trial on the use of a heparinoid after acute stroke (Trial of Org 10172 in Acute Stroke Treatment). The classes of strokes described were originally five: large artery atherosclerosis, cardioembolism, small artery occlusion, stroke of other determined etiology, and stroke of undetermined etiology, which encompasses cases where two or more causes could be

responsible or case in which only incomplete investigations have been performed (unknown), or cases in which no cause has been found despite a complete set of investigations has been made.[4] As part of the OXVASC study routine, each individual case is discussed at specific TOAST meetings, where one of the consultants is present to help with the grouping decision on the basis of the tests performed, and to guide on whether more tests should be performed. This classification presents some limitations. As highlighted in the original paper by Adams in 1993, this method needs the availability of many diagnostic tests, and therefore is expensive and time-consuming. We are able to allocate only a minority of patients to a group within the first week from an event, and the majority requires about a month, when the results of the investigations become available. The small vessel stroke group is often difficult to diagnose, and this is mainly on the base of the clinical characteristics of the event, according to the original Fisher's syndromes.[5] Presence of hypertension as risk factor is not taken into account for this decision. The unknown group, where not enough tests have been performed, tends to be composed by the most severe and old cases, who are often admitted to hospital in terminal condition and die before any test could be performed. Ultimately, a large number of patients end up being classified as undetermined, despite the complete set of investigations performed. Routine tests in OXVASC include a blood sample (electrolytes and renal function, lipids, liver function tests, CRP, full blood count, thyroid function tests) an ECG and brain plus vascular imaging (either CT head and carotids Doppler or MRI with MRA) on the day of the clinic assessment. In the following weeks prolonged 5-day ECG and trans-thoracic or bubble contrast echocardiogram are performed if indicated. On particular instances, pro-coagulative state blood tests, trans-oesophageal echocardiogram, EEG, or cerebral angiogram may be requested, if they are thought to help with the diagnosis.

All the CT scans available from patients recruited with ischaemic stroke or TIA in years 1-8 of OXVASC were evaluated for presence of white matter changes with 3 different rating scales

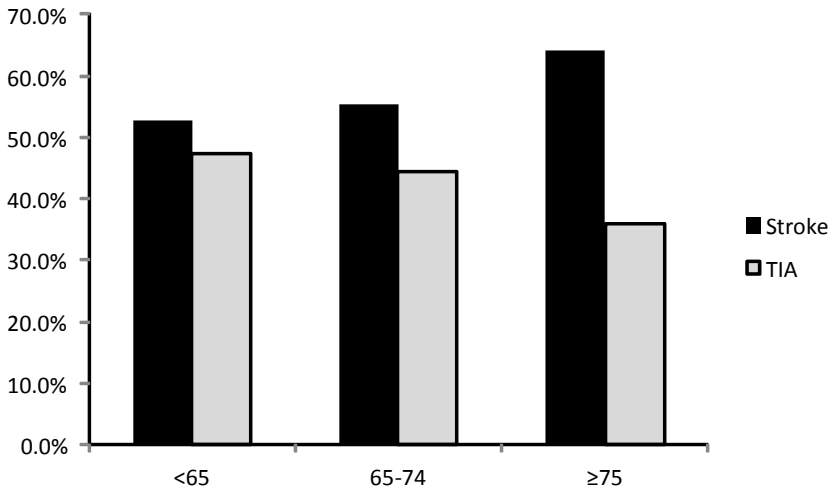
(Oxford, ARWMC and van Swieten scales), as described previously in this thesis (chapter 1). The ratings were categorized as “excess of WMC for age”, and used in binary logistic regression analyses. The analyses were all done with SPSS 20 for Windows.

6.3 Results

6.3.1 TOAST subtypes in the OXVASC population

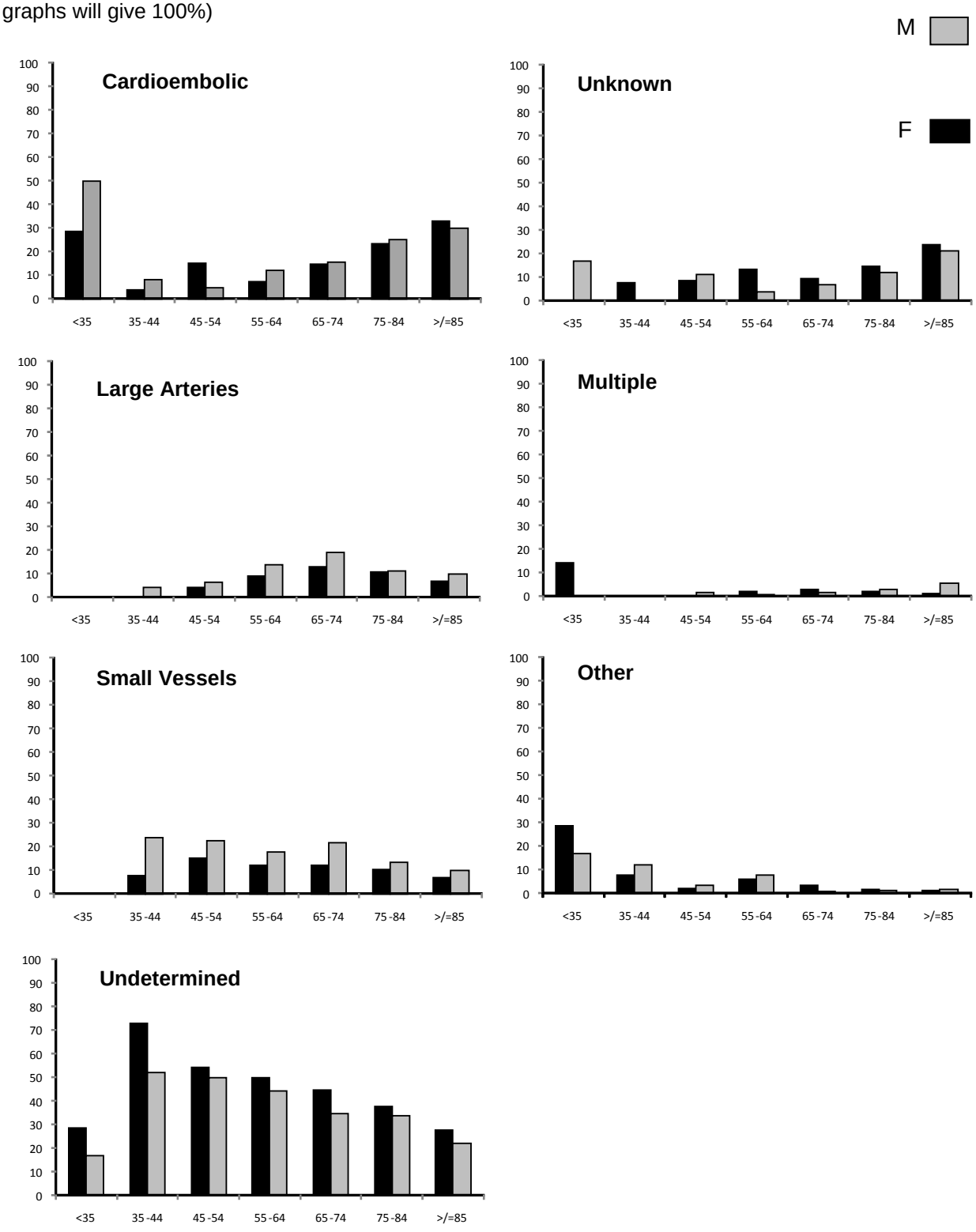
From a total of 2052 patients with cerebrovascular events seen in the first 8 years of OXVASC (2002-2010), 1929 had definite, probable or possible and treated ischaemic stroke or TIA, and 1921 of these were classified according to the TOAST criteria. The mean age of the whole population was 74.13 yrs +/- 13.03, ranging from 24.7 to 99.6. In the stroke group, 596 patients (51.9%) were women, and 552 (48.1%) men. In the TIA group 423 were women (54.1%) and 358 (45.9%) were men. The women were older compared to the men in both groups, with a mean age of 77.6 years +/- 12.5 versus 73.1 years +/- 12.3 (P<0.001) in the stroke patients, and a mean age of 74.7 years +/- 13.2 versus 70.0 +/- 12.8 (P<0.001) in the TIA patients. When dividing the patients in age categories (<65, 65-74, and ≥75), the number of TIAs reduced in favor of the number of strokes with increasing age (Fig. 6.1).

Fig. 6.1 Prevalence of stroke and TIA within age categories.



Out of 1921 events, 396 (20.5%) were cardio-embolic, 212 (11.0%) were due to large arteries thrombosis, 250 (13%) were due to small vessel disease, and the other 1063 (55.3%) were undetermined (of which 721, 37.5% of total, were really undetermined despite appropriate investigations, 248, 12.9%, were unknown because not investigated properly, 41, 2.1%, had multiple possible causes identified, and 53, 2.8% had other causes for their stroke). The majority of patients fell into the group of undetermined strokes/TIA, in which, despite extensive investigations, no cause was found for the vascular event. The mean age of patients in this group was 71.5 years, and the patients above the age of 75 in this group were mainly represented by women. The patients who did not receive complete set of investigations (Unknown type of stroke/TIA) were much older than the others, with a mean age of 79.21 years+/- 12.2, and also in this group the older patients were mainly women. Cardioembolic strokes and TIA constituted the majority of strokes among very young patients (<35 y-o), but overall represented the oldest group among the three, with a mean age of 78.8 years +/- 12.03. The majority of patients above 85 years of age in this group was represented by women ($P < 0.001$). The large artery type of stroke was mainly represented by men in the age strata between 55 and 75 years of age, and the small vessel type encompassed a slightly younger age group (Figure 6.2).

Figure 6.2 Proportion (%) of TOAST types of stroke and TIA among women and men within each 10 year age group in OXVASC (Summing the same-colour columns from the same age group from all the graphs will give 100%)



6.3.2 Prevalence of risk factors and of excess of CT-detected white matter changes, according to TOAST subtype

Small vessel type of strokes/TIA occurs mainly among men of slightly younger age compared to the cardioembolic and the large artery types. Looking at the distribution of the most common vascular risk factors across TOAST subtypes, as expected, atrial fibrillation and history of ischaemic heart disease were most common in the cardioembolic type of stroke, and carotid stenosis in the large artery type. Hypertension was a common risk factor for all types of strokes, and ultimately slightly more prevalent in the large artery type. Current smoking (OR independent from other RFs 1.76, 95% CI 1.13-2.76, p=0.013) and diabetes (1.75, 1.07-2.86, p= 0.030) were most common among small vessel type of strokes (tables 6.1 and 6.2).

Looking at the distribution of white matter changes across different types of stroke and TIA, the small vessel type was the one with the highest burden. This association remained significant also after adjusting for all the other vascular risk factors, was constant across different scales used to evaluate WMC, and remained also when TIA patients were eliminated from the analysis (table 6.2 and 6.4).

The distribution of white matter changes within three different age strata (<65, 65-74 and ≥75) in each type of stroke/TIA was also studied, entering in turn WMC excess assessed with each of the scales, into a step-wise multivariate model including age (continuous), male sex, hypertension, ischaemic heart disease, previous stroke, previous TIA, hyperlipidaemia, diabetes, PVD, AF, carotid stenosis >50% on either side, and current smoking. This analysis (table 6.3) showed again that white matter changes were independently associated only with the small vessel type of stroke, but only in patients older than 65. Repeating a multivariate

analysis, also subdividing the age groups according to sex, I found no significant differences between men and women (i.e. OR for WMC according to ARWMC scale in SMV stroke in men 65-74 was 3.24, 95% CI 1.33-7.91, p=0.010, and in women of same age group 4.13, 1.21-14.11, p=0.024).

Table 6.1. Mean age, prevalence of the most common vascular risk factors and of white matter changes in the OXVASC population, according to stroke subtype

	Total Pop.	**CE**	**LAA**	**SMV**	**UND**	**UNK**	**MULT**	**OTHER**
N	1929	396	212	250	721	248	41	53
Age *yrs(St.Dev)*	74.2 (13.0)	78.7 (12.1)	74.4 (9.8)	71.5 (12.3)	71.5 (13.1)	79.3 (12.2)	77.1 (13.2)	64.1 (15.5)
Vascular RFs (categorical)								
Male Sex (%)	47.1	44.2	55.2	60.4	45.1	36.7	53.7	49.1
Hypertension (%)	56.4	58.1	66.5	56.4	51.7	58.1	68.3	52.8
Diabetes (%)	12.9	8.6	17.0	18.0	11.7	15.3	19.5	5.7
AF (%)	18.2	65.2	6.1	3.6	3.9	6.9	56.1	5.7
Hyperlipidaemia (%)	27.7	20.8	35.1	29.2	30.0	24.3	31.7	22.6
Current Smoking (%)	13.7	7.1	17.9	21.6	14.6	9.3	12.2	15.1
IHD (%)	20.5	29.3	25.0	14.0	17.1	19.0	31.7	11.3
Carotid stenosis (%)	15.5	7.6	70.2	4.3	5.1	13.7	61.5	n.a
Previous stroke (%)	12.8	16.9	10.4	10.4	10.4	17.7	14.6	13.2
Previous TIA (%)	12.7	13.9	16.0	12.0	13.2	8.5	12.2	7.5
PVD (%)	7.0	7.8	14.6	4.8	5.1	7.3	9.8	1.9
Excess of WMC for age								
LA Oxford (%)	13.8	11.0	16.3	20.4	11.9	14.2	12.8	11.8
LA ARWMC (%)	15.1	11.0	17.6	26.5	11.9	14.0	13.5	25.9
LA v Swieten (%)	21.2	19.3	28.5	31.4	16.0	20.1	21.6	25.9

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Table 6.2. Distribution of age, male sex and vascular risk factors within different types of stroke and TIA. Binary logistic regression analyses are presented adjusted for age and sex (A+S Adj) and adjusted for all the other vascular risk factors listed in the table (multiv).

		CE		LAA		SMV		UND		Unk+Mult.+Other	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age (10 *yrs)*	Univ.	**1.48 (1.34-1.63)**	**<0.0001**	1.00 (0.90-1.10)	0.87	0.84 (0.74-0.90)	<0.0001	0.77 (0.71-0.83)	<0.0001	**1.22 (1.10-1.34)**	**<0.0001**
	Multiv.	**1.34 (1.00-1.62)**	**0.023**	1.10 (0.90-1.34)	0.42	1.00 (0.90-1.22)	0.81	0.90 (0.82-1.10)	0.32	0.82 (0.66-0.90)	0.044
Vascular RFs (categorical)											
Male Sex	A. Adj	1.02 (0.81-1.29)	0.84	**1.45 (1.09-1.95)**	**0.012**	**1.73 (1.32-2.28)**	**<0.0001**	0.77 (0.63-0.93)	0.006	0.78 (0.61-0.99)	0.045
	Multiv.	0.85 (0.54-1.32)	0.46	1.24 (0.77-1.98)	0.38	**1.98 (1.39-2.81)**	**<0.0001**	0.72 (0.55-0.94)	0.017	0.77 (0.47-1.26)	0.30
Hypertension	A+S Adj.	0.96 (0.77-1.21)	0.76	**1.66 (1.22-2.25)**	**0.001**	1.11 (0.84-1.46)	0.45	0.80 (0.66-0.97)	0.020	1.02 (0.80-1.30)	0.87
	Multiv.	0.83 (0.53-1.31)	0.43	1.18 (0.71-1.96)	0.51	1.33 (0.92-1.92)	0.13	0.88 (0.66-1.18)	0.40	0.97 (0.58-1.64)	0.92
Diabetes	A+S Adj.	0.62 (0.42-0.91)	0.014	1.44 (0.98-2.12)	0.07	**1.54 (1.08-2.20)**	**0.018**	0.80 (0.60-1.06)	0.12	1.21 (0.86-1.70)	0.27
	Multiv.	0.51 (0.25-1.05)	0.07	1.52 (0.79-2.91)	0.21	**1.75 (1.07-2.86)**	**0.030**	0.85 (0.56-1.29)	0.44	0.68 (0.31-1.50)	0.34
AF	A+S Adj.	**27.3 (20.2-37.0)**	**<0.0001**	0.24 (0.14-0.43)	<0.0001	0.15 (0.08-0.29)	<0.0001	0.12 (0.08-1.19)	<0.0001	0.52 (0.37-0.74)	<0.0001
	Multiv.	**38.4 (23.8-62.0)**	**<0.0001**	0.22 (0.10-0.51)	<0.0001	0.07 (0.02-0.23)	<0.0001	0.08 (0.05-0.14)	<0.0001	**1.93 (1.06-3.50)**	**0.032**
Hyperlipidaemia	A+S Adj.	0.67 (0.51-0.88)	0.003	**1.48 (1.09-2.01)**	**0.011**	1.06 (0.79-1.43)	0.68	1.17 (0.95-1.44)	0.13	0.87 (0.67-1.14)	0.32
	Multiv.	0.72 (0.44-1.19)	0.20	1.03 (0.61-1.73)	0.93	0.91 (0.60-1.37)	0.64	1.12 (0.81-1.53)	0.50	1.27 (0.75-2.17)	0.37
Current Smoking	A+S Adj.	0.61 (0.40-0.93)	0.021	**1.52 (1.02-2.27)**	**0.039**	**1.67 (1.17-2.39)**	**0.005**	0.85 (0.64-1.13)	0.26	0.86 (0.58-1.26)	0.44
	Multiv.	0.52 (0.24-1.14)	0.10	1.45 (0.76-2.74)	0.26	**1.76 (1.13-2.76)**	**0.013**	0.70 (0.48-1.03)	0.07	0.95 (0.48-1.88)	0.89
IHD	A+S Adj.	**1.66 (1.29-2.16)**	**<0.0001**	1.29 (0.92-1.81)	0.14	0.60 (0.41-0.88)	0.008	0.81 (0.64-1.03)	0.09	0.87 (0.65-1.17)	0.36
	Multiv.	**2.02 (1.18-3.45)**	**0.010**	0.98 (0.54-1.78)	0.96	0.61 (0.36-1.04)	0.07	0.96 (0.65-1.41)	0.83	1.02 (0.54-1.91)	0.96
Carotid stenosis	A+S Adj.	0.34 (0.20-0.58)	<0.0001	**31.0 (21.0-46.2)**	**<0.0001**	0.21 (0.10-0.41)	<0.0001	0.18 (0.12-0.26)	<0.0001	**1.81 (1.10-2.97)**	**0.020**
	Multiv.	0.27 (0.13-0.55)	<0.0001	**32.0 (19.8-51.6)**	**<0.0001**	0.20 (0.10-0.41)	<0.0001	0.15 (0.10-0.24)	<0.0001	**2.46 (1.40-4.32)**	**0.002**
Previous stroke	A+S Adj.	1.28 (0.94-1.74)	0.12	0.75 (0.47-1.20)	0.23	0.84 (0.54-1.30)	0.44	0.80 (0.60-1.08)	0.14	1.34 (0.97-1.86)	0.08
	Multiv.	1.47 (0.80-2.69)	0.22	0.58 (0.27-1.25)	0.17	0.75 (0.41-1.37)	0.35	1.04 (0.67-1.62)	0.85	1.50 (0.76-2.98)	0.25
Previous TIA	A+S Adj.	1.05 (0.76-1.46)	0.78	1.37 (0.92-2.03)	1.37	0.97 (0.65-1.47)	0.90	1.15 (0.87-1.52)	0.33	0.58 (0.39-0.87)	0.009
	Multiv.	0.83 (0.45-1.55)	0.56	0.76 (0.39-1.50)	0.44	1.03 (0.62-1.71)	0.91	1.31 (0.88-1.95)	0.18	0.73 (0.35-1.53)	0.41
PVD	A+S Adj.	1.05 (0.69-1.61)	0.82	**2.53 (1.63-3.91)**	**<0.0001**	0.61 (0.33-1.13)	0.12	0.71 (0.48-1.05)	0.09	0.94 (0.59-1.51)	0.80
	Multiv.	0.65 (0.26-1.58)	0.34	1.55 (0.74-3.27)	0.25	0.75 (0.33-1.70)	0.49	1.00 (0.55-1.79)	0.99	1.14 (0.47-2.71)	0.78
Excess of WMC for age											
Oxford	A+S Adj.	0.70 (0.48-1.02)	0.07	1.29 (0.84-1.98)	0.24	**1.93 (1.35-2.77)**	**<0.0001**	0.78 (0.57-1.05)	0.10	0.96 (0.64-1.45)	0.86
	Multiv.	0.59 (0.29-1.20)	0.15	1.43 (0.73-2.79)	0.30	**2.32 (1.51-3.56)**	**<0.0001**	0.48 (0.32-0.71)	<0.0001	1.62 (0.87-3.01)	0.13
ARWMC	A+S Adj.	0.60 (0.41-0.89)	0.010	1.24 (0.81-1.91)	0.32	**2.60 (1.81-3.61)**	**<0.0001**	0.69 (0.50-0.93)	0.017	1.01 (0.68-1.51)	0.96
	Multiv.	0.47 (0.24-0.93)	0.030	1.11 (0.59-2.08)	0.76	**3.09 (2.06-4.65)**	**<0.0001**	0.50 (0.34-0.73)	<0.0001	1.16 (0.60-2.24)	0.65
van Swieten	A+S Adj.	0.72 (0.53-0.99)	0.043	**1.60 (1.10-2.31)**	**0.013**	**2.21 (1.60-3.07)**	**<0.0001**	0.65 (0.49-0.85)	0.002	0.92 (0.64-1.31)	0.63
	Multiv.	0.46 (0.25-0.84)	0.012	1.40 (0.80-2.44)	0.24	**2.54 (1.72-3.76)**	**<0.0001**	0.58 (0.41-0.82)	0.002	1.04 (0.56-1.93)	0.90

Table 6.3. White matter changes in each type of stroke, according to age groups. Multivariate stepwise backwards logistic regression. Variables entered with leukoaraiosis assessed with each scale at a time were: age (continuous), male sex, hypertension, ischaemic heart disease, previous stroke, previous TIA, hyperlipidaemia, diabetes, PVD, AF, carotid stenosis >50% on either side, current smoking.

		CE		LAA		SMV		UND	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
<65	Oxford	1.15 (0.20-6.59)	0.87	1.63 (0.29-8.89)	0.57	1.46 (0.56-3.75)	0.44	0.71 (0.32-1.59)	0.41
	ARWMC	1.07 (0.12-9.71)	0.96	0.79 (0.09-7.32)	0.83	1.34 (0.49-3.64)	0.57	0.72 (0.30-1.74)	0.47
	v Swieten	0.67 (0.07-6.40)	0.73	0.97 (0.15-6.42)	0.98	0.74 (0.26-2.12)	0.57	1.15 (0.49-2.70)	0.75
65-74	Oxford	0.31 (0.07-1.28)	0.11	1.67 (0.63-4.47)	0.31	**2.51 (1.25-5.03)**	**0.010**	0.56 (0.30-1.07)	0.08
	ARWMC	0.44 (0.11-1.82)	0.26	1.68 (0.65-4.38)	0.28	**3.40 (1.70-6.80)**	**0.001**	0.43 (0.22-0.82)	0.010
	v Swieten	0.31 (0.07-1.33)	0.12	1.67 (0.66-4.23)	0.28	**3.72 (1.87-7.38)**	**<0.0001**	0.40 (0.21-0.76)	0.005
≥75	Oxford	0.75 (0.29-1.91)	0.54	1.15 (0.36-3.66)	0.81	**2.36 (1.19-4.70)**	**0.015**	0.38 (0.20-0.71)	0.003
	ARWMC	0.50 (0.23-1.12)	0.09	0.89 (0.33-2.40)	0.82	**3.78 (2.08-6.88)**	**<0.0001**	0.53 (0.30-0.93)	0.027
	v Swieten	0.55 (0.27-1.06)	0.07	1.47 (0.66-3.27)	0.35	**2.67 (1.54-4.63)**	**<0.0001**	0.58 (0.36-0.94)	0.027

Table 6.4 Distribution of age, male sex and vascular risk factors within different types of stroke (TIA excluded). Binary logistic regression analyses are presented adjusted for age and sex (A+S Adj) and adjusted for all the other vascular risk factors listed in the table (multiv).

		CE		LAA		SMV		UND	
		OR (95% CI)	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Age (10 *yrs)*	Univ.	**1.48 (1.22-1.63)**	**<0.0001**	0.90 (0.82-1.10)	0.90	0.82 (0.73-0.90)	0.001	0.82 (0.74-0.90)	<0.0001
	Multiv.	1.22 (0.90-1.62)	0.11	1.22 (0.90-1.80)	0.14	1.01 (0.82-1.22)	0.88	0.90 (0.82-1.10)	0.41
Vascular RFs (categorical)									
Male Sex	A. Adj	0.91 (0.68-1.20)	0.49	**1.52 (1.02-2.26)**	**0.038**	**1.75 (1.26-2.44)**	**0.001**	0.81 (0.62-1.05)	0.11
	Multiv.	0.75 (0.43-1.32)	0.32	1.52 (0.80-2.89)	0.20	**1.71 (1.11-2.64)**	**0.014**	0.69 (0.48-0.10)	0.05
Hypertension	A+S Adj.	0.95 (0.72-1.26)	0.72	1.23 (0.82-1.83)	0.32	1.08 (0.77-1.50)	0.67	0.93 (0.72-1.22)	0.61
	Multiv.	0.90 (0.51-1.60)	0.72	0.95 (0.49-1.85)	0.89	1.09 (0.70-1.71)	0.69	0.97 (0.66-1.43)	0.87
Diabetes	A+S Adj.	0.62 (0.39-0.98)	0.041	1.35 (0.79-2.28)	0.27	1.54 (1.00-2.37)	0.050	0.89 (0.60-1.31)	0.54
	Multiv.	0.68 (0.28-1.65)	0.40	1.61 (0.69-3.77)	0.27	1.68 (0.93-3.06)	0.09	0.74 (0.43-1.29)	0.44
AF	A+S Adj.	**23.2 (16.01-33.6)**	**<0.0001**	0.18 (0.08-0.42)	<0.0001	0.10 (0.04-0.24)	<0.0001	0.13 (0.07-0.23)	<0.0001
	Multiv.	**29.4 (15.82-54.6)**	**<0.0001**	0.30 (0.10-0.90)	0.032	0.06 (0.02-0.27)	<0.0001	0.07 (0.03-0.16)	<0.0001
Hyperlipidaemia	A+S Adj.	0.56 (0.39-0.80)	0.001	1.02 (0.65-1.59)	0.95	1.31 (0.92-1.88)	0.13	1.42 (1.07-1.90)	0.017
	Multiv.	0.56 (0.28-1.10)	0.09	1.11 (0.53-2.33)	0.78	1.15 (0.69-1.91)	0.59	0.94 (0.60-1.45)	0.76
Current Smoking	A+S Adj.	0.64 (0.39-1.03)	0.07	1.30 (0.75-2.25)	0.35	1.44 (0.93-2.23)	0.10	1.15 (0.79-1.67)	0.46
	Multiv.	0.61 (0.24-1.51)	0.28	1.32 (0.57-3.05)	0.51	1.31 (0.75-2.29)	0.340	0.91 (0.55-1.51)	0.72
IHD	A+S Adj.	**1.61 (1.17-2.22)**	**0.003**	0.84 (0.51-1.38)	0.49	0.65 (0.42-1.01)	0.05	1.04 (0.75-1.43)	0.83
	Multiv.	2.0 (0.99-4.05)	0.055	0.78 (0.34-1.80)	0.56	0.52 (0.27-1.00)	0.05	1.52 (0.91-2.57)	0.11
Carotid stenosis	A+S Adj.	0.37 (0.19-0.74)	0.005	**22.9 (13.3-39.2)**	**<0.0001**	0.25 (0.12-0.54)	<0.0001	0.26 (0.15-0.44)	<0.0001
	Multiv.	0.31 (0.13-0.77)	0.011	**26.1 (13.9-49.1)**	**<0.0001**	0.23 (0.11-0.51)	<0.0001	0.21 (0.12-0.38)	<0.0001
Previous stroke	A+S Adj.	1.10 (0.76-1.58)	0.63	0.61 (0.33-1.15)	0.13	0.74 (0.45-1.22)	0.24	1.13 (0.79-1.62)	0.51
	Multiv.	1.27 (0.60-2.68)	0.54	0.67 (0.26-1.77)	0.42	0.69 (0.34-1.40)	0.31	1.14 (0.66-1.96)	0.64
Previous TIA	A+S Adj.	1.02 (0.65-1.60)	0.94	**1.89 (1.09-3.28)**	**0.02**	1.05 (0.60-1.81)	0.87	1.03 (0.66-1.60)	0.90
	Multiv.	1.00 (0.41-2.44)	0.99	1.21 (0.48-3.09)	0.69	1.15 (0.57-2.32)	0.69	1.14 (0.62-2.10)	0.67
PVD	A+S Adj.	1.19 (0.73-1.95)	0.49	1.54 (0.82-2.89)	0.18	0.66 (0.33-1.32)	0.24	0.80 (0.47-1.35)	0.40
	Multiv.	0.56 (0.18-1.72)	0.31	0.95 (0.33-2.72)	0.92	0.95 (0.37-2.43)	0.91	1.05 (0.49-2.27)	0.90
Excess of WMC for age									
Oxford	A+S Adj.	0.62 (0.40-0.95)	0.03	1.19 (0.69-2.05)	0.53	**1.59 (1.04-2.42)**	**0.031**	0.95 (0.66-1.39)	0.80
	Multiv.	0.63 (0.27-1.46)	0.28	1.60 (0.67-3.79)	0.29	**1.71 (1.02-2.87)**	**0.042**	0.52 (0.31-0.86)	0.010
ARWMC	A+S Adj.	0.46 (0.28-0.73)	0.001	1.17 (0.68-2.01)	0.58	**2.38 (1.59-3.54)**	**<0.0001**	0.84 (0.57-1.24)	0.38
	Multiv.	0.38 (0.16-0.89)	0.026	1.23 (0.56-2.72)	0.61	**2.57 (1.59-4.17)**	**<0.0001**	0.56 (0.34-0.90)	0.016
van Swieten	A+S Adj.	0.69 (0.47-0.99)	0.046	1.45 (0.91-2.33)	0.12	**1.77 (1.21-2.59)**	**0.003**	0.80 (0.57-1.13)	0.21
	Multiv.	0.42 (0.20-0.88)	0.023	1.60 (0.79-3.23)	0.2	**1.92 (1.21-3.06)**	**0.006**	0.68 (0.44-1.05)	0.08

6.4 Discussion and conclusions

The association between strokes subtypes and different vascular risk factors is still under study, in the attempt to identify specific targets of primary and secondary prevention.[6-11] Beyond the obvious associations of carotid stenosis with large artery type of stroke and of atrial fibrillation and ischaemic heart disease with the cardio-embolic one, the distribution of the other vascular risk factors among different subtypes has often been discordant in different population settings and studies. In particular, small vessel type of strokes have been inconsistently associated with hypertension, smoking and diabetes, [7,10] and the lack of a distinctive presence of specific classic vascular risk factors has raised the possibility of their existence as a distinctive arteriopathy, secondary to risk factors yet to be completely identified.[10] On the other hand, the association between small vessel type of stroke (lacunes) and white matter changes has been recently stressed, and again, this has been reported to be independent from the presence of shared vascular risk factors.[12] The OXVASC study offered the opportunity to study these associations in a large population-based study of all strokes and TIA.

The use of CT scans instead of MRI, and the TOAST classification could be seen by someone as possible weaknesses of my study. With regards to the first point, I agree that MRI is more sensitive than CT for white matter changes, and that the diffusion-weighted imaging offers help in characterizing stroke sub-types, but I did not have a large enough number of MRI scans for this kind of analyses in patients from the first 8 years of the study. The number of MRI scans in the OXVASC population has increased since 2010, as patients receive routine MRI brain since then. As far as the TOAST classification is concerned, I do not think that this represents a major shortcoming, as TOAST is a well recognized way to classify stroke according to their pathogenesis, and it has been widely used in large studies. Nevertheless, there have been numerous criticisms to the way different types of strokes are

grouped in TOAST, and, especially, to the criteria it is based upon. In particular, the majority of strokes fall into the undetermined category, which in some studies includes patients who have not been investigated enough to have a more specific diagnosis but in OXVASC includes only patients whom, despite all the relevant investigations, have not been diagnosed with a specific type of stroke. Another criticism is to the fact that no clear indication is given with regards to how much we should pursue investigating patients before deciding that we cannot establish a pathogenesis for the stroke. Different studies have used different criteria. TOAST was created for a large therapeutic trial, which needed an easy and clear classification of strokes, and still remains the most straightforward classification, once parameters are set within a certain population in study. Recently new classifications of stroke pathogenesis have been created, like the Causative Classification System (CCS)[13] and the ASCO (Atherosclerosis, Small vessel, Cardio-embolic, Other)[14], and studies have been made to compare these different methods.[15] The CSS in particular, being a refined version of TOAST, reduces the proportion of undetermined strokes, increasing the number of strokes in each of the other 4 categories. It has been suggested that a single classification based on the combination between TOAST, CCS and ASCO would be the most complete way to classify strokes pathogenetically.[15] The OXVASC study has now been going on for over 10 years, and the TOAST classification has been adopted since its beginning. Therefore, despite the large number of patients falling into the undetermined category, I have used this method.

According to the TOAST classification, the majority of patients in this study were classified as undetermined stroke type, and among the three major types of strokes the most represented was the cardio-embolic one. Cardio-embolic strokes and TIA were significantly older than small vessel and large artery ones, despite representing the majority of strokes among young patients. This was in keeping with the well known fact that the risk of atrial fibrillation increases with age.[16] On the other hand, small vessel strokes and TIA were more

represented among the relatively younger group of population, before the age of 55. This was particularly interesting when considering that small vessel type of strokes were the only type independently associated with white matter changes, after the age of 65. This association, as already hypothesized before in literature[10] raises the possibility of a distinctive arteriopathy based on pathogenetic mechanisms possibly partly independent from the classically recognized vascular risk factors, calling for more research on different environmental and/or genetic risk factors. Lacunes and white matter changes may represent two different epiphenomena of this distinctive pathology, in association with other clinic-radiological entities that I have not considered in this study: microbleeds and enlarged perivascular spaces.[17] One possible explanation could be the linear progression of small vessel disease through different stages, with the initial burden of this microvascular pathology more likely to manifest itself earlier on in life as symptomatic lacunar stroke, in subjects presenting other additional vascular risk factors, and therefore most frequently in males. In relatively healthier subjects, this pathology might remain silent for a long period, and possibly never clinically manifest itself in an obvious way. If these subjects though were to have a brain scan, they would probably show at this point (over 65 years of age) radiological signs of small vessel pathology, like white matter changes. This would be in keeping with what observed in large population-based studies.[18,19,20,21] Moreover, if the behavioral and cognitive state of these patients were studied with sensitive enough tools, they would probably show signs of decline compared to the WMC-free population.[22] This progression pretty much resembles what is globally recognized as a natural evolution related to ageing, and therefore the term Age-related WMC has been considered appropriate.[23] However, this should not lead us to believe this association necessarily unavoidable. A step forward could be made by studying the small vessel pathology starting from the consideration of the existence of a distinctive type of “small vessel disease-prone” subjects, who possibly show increased susceptibility to the effect of some common vascular risk factors on their brain small vessels, rather than focusing the

search on these known vascular risk factors. This short chapter on the association between stroke subtypes, white matter changes and common vascular risk factors encourages this view.

Recently, I have participated in a case-control study[24] performed between patients from OXVASC and healthy controls from the OPTIMA Study,[25] where the presence of vascular risk factors and white matter changes have been compared between stroke and stroke-free patients (Appendix 7). Interestingly, once again, the presence of leukoaraiosis, after adjusting for age, did not differ greatly between cases and control apart from the clear increase, independent from other vascular risk factors, in the group of small vessel type of strokes. This finding fits perfectly with the hypothesis of a distinctive and large group of subjects in the general population, carriers of increased susceptibility to pathological effects of common vascular risk factors and possibly exposed to risk factors still to be identified.

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Chapter 7

Prognostic value of white matter changes for risk of stroke recurrence and outcome in terms of disability

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7.0 Abstract

Background: Various studies have highlighted the importance of white matter changes detected by CT and MRI in predicting incident and recurrent strokes and long term loss of autonomy. No study on this topic so far has been done on a large population-based setting of patients with stroke and TIA.

Methods: I evaluated white matter changes, applying 4 different rating scales, in consecutive CT and MRI scans of patients recruited in years 1 to 8 in the OXVASC study. Severe white matter changes on scans were studied (with logistic regression models) in relation to the risk of recurrent stroke, to the severity of the presenting event (NIH Stroke Scale), and to the risk of worsening level of disability at one year from the event (modified Rankin Score). Analyses were done using SPSS for Windows, version 18 and 20.

Results: Out of a population of 2052 patients, 1578 out of 1729 CT scans were evaluated with 3 different scales (Oxford, ARWMC, van Swieten), and the remaining only with the Oxford scale. 489 MRI scans out of a total of 520 were evaluated with three scales (Oxford, ARWMC, Fazekas), and the remaining 31 only with the Oxford scale. I found no association between severity of white matter changes on CT or MRI and risk of recurrent stroke (HR 1.36,0.94-1.98, p=0,11 for WMC with Oxford scale). There was a positive trend for risk of haemorrhagic recurrence, and for ischaemic recurrence in young patients presenting with cardioembolic stroke or for older patients with lacunar stroke. There was no association between leukoaraiosis and severity of the presenting event, but there was an association with pre-morbid mRS>2 (2.04,1.48-2.80 p<.0001 for Oxford scale) and also with worsening of mRS at one year, especially in patients with lacunar stroke as presenting event (3.57, 1.55-8.18, p=0.003).

Conclusions: Severe white matter changes on CT and MRI are associated with a higher level of premorbid disability and predict worse outcome at one year from a stroke or TIA. No association emerges between leukoaraiosis and risk of stroke recurrence in this population.

7.1 Introduction

Clinical meaning and prognostic relevance of white matter changes on CT and MRI have been investigated over the past 30 years, in different clinical settings. MRI has become gradually more accessible in the majority of centres, and most of the studies on white matter changes nowadays use this technique, which is more sensitive than CT in exploring white matter. This development has introduced the dilemma related to what should be considered as an abnormal finding and what, on the other side, should be merely considered a normal variant of ageing. Recent studies on the subject support a prognostic role of white matter changes detected on MRI in determining a higher risk of stroke occurrence, dementia and mortality[1]. However, studies on pathology associated to post-mortem MRI[2] have shown that some of the white matter lesions identified by MRI, in particular focal isolated deep white matter lesions and periventricular caps, do not correspond to any ischemic changes, but display aspecific spongiotic changes. It is difficult to know whether these changes may represent the initial stage of a pathological feature or whether they are completely different and innocuous lesions, and should therefore not be considered in studies concerning clinical meanings of white matter changes.

MRI-detected white matter changes have been associated with risk of incident stroke in large population-based cohorts with exclusion of patients with previous stroke[3-5] or not,[6,7] in cohorts of high risk patients like in the SMART study,[8] which investigated patients with symptomatic large artery disease, and in cohorts of patients admitted to hospital for a stroke.[9] The association with recurrent stroke has also been found in studies with CT scans in patients with TIA or stroke in the Dutch-TIA trial, in the Lille stroke/dementia study cohort, in the NASCET study cohort,[10,11,12] and in selected patients with severe leukoaraiosis and motor deficits.[13,14] White matter changes have also been associated with a risk of poor outcome after stroke in terms of disability.[15,16,17] Recently the LADIS study, a multicentre prospective

study on the development of disability in a population of non-disabled subjects with leukoaraiosis, has shown an increase risk of progression to disability in patients with more severe degrees of leukoaraiosis,[18,19] demonstrating a dose-effect of white matter lesions on progression to disability.

In this chapter, I will investigate the prognostic value of severe white matter changes on the initial CT or MRI of patients presenting with TIA or Stroke in the OXVASC study. In particular, I will be looking at their value for stroke recurrence and stroke severity and outcome at one year in terms of disability. Although many studies have already been performed on this subject, there is no large population-based study on stroke and TIA patients reported in literature, and therefore the strength of my conclusions lie mostly in the size and the setting of my population.

7.2 Methods

The OXVASC Study[20,21] has already been described in detail in chapter 1 and in Appendix 1. Briefly, all acute incident and recurrent vascular events (cardiovascular, cerebrovascular and peripheral) are ascertained by means of hot and cold pursuit methods, to reach a near-complete ascertainment. The hot pursuit methods comprise a daily TIA/minor stroke clinic with direct referral from the GPs and hospital search through the A&E, the medical wards, the stroke unit, through the daily admissions lists, and search in the bereavement office. Cold pursuit is performed by specialist nurses who search through the coroner office registries and general practices archives once monthly. Patients who agree to be followed by us do so by signing an informed consent. Blood is collected for research at the first ascertainment visit, and patients receive a full set of investigations comprising structural brain imaging, vascular imaging and cardiac investigations (ECG, echocardiogram and prolonged ECG trace). OXVASC has been approved by the local ethical committee.

For the purpose of this study I have considered the patients recruited during the first eight years of OXVASC, from the 1st of April 2002 to the 31st of March 2010. Only patients with a reasonable diagnosis of TIA or stroke (definite, probable, and possible and treated) have been considered, and subarachnoid hemorrhages have been excluded. The CT scans have been performed in the majority of cases in the scanner in the John Radcliffe Hospital (Toshiba, Aquilion 64, 64-slice scanner). The MRI scans have been acquired by the 1.5 T scanner in the John Radcliffe Hospital (Philips Achieva). The scans were reviewed by a neuroradiologist, who applied a semi-quantitative scale to grade leukoaraiosis from 0 to 3 (Oxford scale). Where the radiologist evaluation was missing, I have used my own evaluations. With help from a colleague (Dr. Linxin Li), after a period of training and then evaluation of 50 CT and of 50 MRI scans together, we evaluated the scans from year 1 to 8 and applied different rating scales beside the Oxford scale. In particular, as already described in chapter 1, we applied the van Swieten and the ARWMC scale to the CT scans and the Fazekas and the ARWMC scale to the MRI scans. Inter-rater and intra-rater agreements have already been reported in chapter 1. Regression analyses were performed using white matter changes as variable dichotomized in different ways. In particular, I considered no white matter changes versus any degree of white matter changes and none or mild versus moderate-severe white matter changes for each of the rating scales applied. Also, the variable white matter changes was adjusted for age into a binary variable considering the excess of white matter changes for age, as previously described, for each of the scales considered. Many of the analyses in this and the following chapter have been performed stratifying patients in age groups. Most frequently I have used 75 years as cut-off of to distinguish between older and younger patients. This age was chosen because leukoaraiosis appears to step up in severity after this point, and also in view of the reasonably balanced number of patients available in the two groups, which allows good analyses results (see figure 2.2).

Stroke recurrence:

This has been analysed separately for any type of stroke, ischaemic or primary intracerebral haemorrhages.

Stroke severity:

NIH Stroke Scale[22] was performed by a clinician at the moment of the first assessment. The regression analysis to research association between white matter changes at entry and severity of both incident and recurrent event was done on the whole cohort and then grouping the patients according to the TOAST classification. The NIHSS was categorized into score equal or lower than 3 and higher than 3. This cut-off was chosen because used previously in OXVASC, and also because literature on the subject[23] validates its use.

Stroke outcome and disability:

As a measure of stroke outcome and residual disability at one year I used the modified version of the Rankin Scale (mRS).[24,25] I considered as binary outcome a Rankin score > 2, with patients with mRS of 3 or more considered disabled. To evaluate the strength and the independence of this association, I inserted as dependent variable in a binary logistic regression the baseline Rankin score > 2 and as cofactors presence of leukoaraiosis on CT as excess of white matter changes for age in the different scales, male sex, previous cerebro-vascular accidents, previous transient ischaemic attacks, history of angina or myocardial infarction, diabetes, atrial fibrillation, peripheral vascular disease, hypertension and current smoking. I also did a subsequent analysis with the Barthel score at baseline, to try and identify which were the areas mainly affected by the presence of white matter changes. The Barthel score[26] includes 10 separate items (feeding, bathing, grooming, dressing, bowels, bladder, toilet, transfers, mobility, stairs), and I considered them in a binary way as normal/impaired, looking for the ORs of having each of them abnormal in presence of severe

white matter changes. To see whether any association between leukoaraiosis on entry scan (CT) and worse outcome at one year existed, I calculated the difference between the one year score of the Rankin scale and the score at baseline, and considered any positive difference as a sign of worsening. I performed multiple binary logistic analyses on the whole cohort and stratifying by TOAST type of first event, adjusting for age, sex, NIH of first event.

All the statistic analyses were performed on SPSS for Windows, version 18 and version 20.

7.3 Results

7.3.1 Population in study

The total population comprised 2052 patients, of which 1076 were female (52.4%). The age of the population ranged from 22 to 100 years, with a mean of 74.2 years (±13), and there was a significant ($p<0.0001$) difference in age between men (71.9, sd 12.6) and women (76.3, sd 13.1). From the whole population, 1750 patients had CT scan and 546 patients had MRI. A total of 1885 patients had at least CT or MRI at entry in the study (91.9%, see chapter 1), 131 patients had only MRI and 1332 patients only had CT scan. Among the 1750 patient who had CT scans, 1729 were evaluated with the Oxford scale by either the radiologist or by me, and 1578 patients also were assessed with the other rating scales. In 151 CT scans I could not apply the other scales because the images were not available for evaluation anymore (either lost or archived and not retrievable). Of the 546 MRI scans, 520 had evaluation by either the radiologist or by me, and of these 489 also received the evaluation with the Fazekas and the ARWMC scale, with 57 scans not available for evaluation. My analyses have also included the patients who had both scans in each group, CT and MRI, and therefore my results will concern 1729 CT scans with the Oxford scale and 1578 CT

scans with the other scales, and 520 MRI scans with the Oxford scale and 489 MRI scans for the Fazekas and ARWMC scales.

7.3.2 Prognostic value of white matter changes for risk of stroke recurrence

There were 312 recurrent ischaemic strokes during the study period, and 23 recurrent primary haemorrhages. Within the patients who were classified according to the TOAST criteria, 93 recurrences happened in the cardioembolic group, 31 in the large artery stroke type, 50 in the small vessel type, 158 in the remaining group (undetermined, unknown, multiple, other strokes). With regards to primary intracerebral haemorrhages, 5 happened in the cardio-embolic group, 5 were secondary to previous haemorrhages and the remaining 13 happened in the composite group of undetermined, unknown, multiple aetiology and other types of stroke. In total, 13 out of 23 patients presenting with recurrent haemorrhagic stroke were on Aspirin, 2 were on Warfarin and 8 were not on any antiplatelet or anticoagulant treatment (5 of these had had a previous primary intracerebral haemorrhage as presenting event in OXVASC). Univariate analyses showed a strong association between white matter changes and risk of recurrent stroke, in particular the risk of ischaemic stroke was increased in the patients over 75 years of age. The associations became weaker after adjusting for age and sex (mod. 1 table 7.1) and lost significance after inserting in the model also hypertension, diabetes, smoking, atrial fibrillation, and significant carotid stenosis (mod. 2). The results were consistent among the three different rating scales adopted. With regards to risk of haemorrhagic recurrences, there was a positive trend of association in the oldest cohort, with more severe degrees of white matter changes. Correcting by age, sex and other risk factors for haemorrhage (mod.1 and 2 table 7.1) made the associations stronger, even though they only reached statistical significance when white matter changes were assessed with the Oxford scale. Considering white matter changes as “excess for age” in the different scales

(table 7.2a and 7.2b) I found no association between white matter changes and risk of recurrences of any type (the numbers were too small to be able to say anything certain about the risk of recurrent haemorrhagic stroke). Stratifying the patients according to the type of stroke at entry, in particular considering only patients with the three major types of strokes (cardioembolic, large artery and small vessels), did not show any strong and consistent association between severe white matter changes on CT at entry and risk of recurrent ischaemic event (table 7.3). The analyses could not be performed with the MRI, as the cases were too few.

Table 7.1 Leukoaraiosis on CT scan and risk of recurrent stroke. The recurrent events have been grouped in ischaemic, haemorrhagic or either. Patients have been stratified according to their age, and leukoaraiosis has been considered either as present vs. absent (any) or moderate/severe vs. none or mild. Univariate analysis (unadj.). Mod 1: adjusted for age and sex. Mod 2 for Any CVA and Ischaemic CVA : age, sex, hypertension, diabetes, smoking, atrial fibrillation and significant carotid stenosis. Mod 2 for Haemorrhagic CVA (primary intracerebral haemorrhages only): age, sex, hypertension, diabetes, smoking

			Whole Cohort				<75 y-o				≥75 y-o			
Type of recurrence	Scale		Any Leukoaraiosis		Moderate/Severe		Any Leukoaraiosis		Moderate/Severe		Any Leukoaraiosis		Moderate/Severe	
			HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Any CVA (328)	**Oxford**	**Unadj.**	**1.40 (1.12-1.75)**	**0.003**	**1.43 (1.12-1.82)**	**0.004**	1.09 (0.74-1.61)	0.66	0.95 (0.56-1.64)	0.86	1.33 (0.97-1.83)	0.07	**1.43 (1.07-1.92)**	**0.016**
		Mod.1	1.12 (0.88-1.43)	0.35	1.21 (0.94-1.55)	0.14	0.95 (0.63-1.41)	0.79	0.82(0.47-1.42)	0.47	1.23 (0.90-1.70)	0.20	1.33 (0.99-1.79)	0.06
		Mod.2	1.06 (0.80-1.41)	0.67	1.10 (0.81-1.50)	0.53	0.86 (0.55-1.33)	0.49	0.83 (0.46-1.50)	0.54	1.33 (0.91-1.96)	0.14	1.31 (0.90-1.90)	1.16
	ARWMC	**Unadj.**	**1.77 (1.35-2.32)**	**<.0001**	**1.41 (1.10-1.79)**	**0.006**	1.44 (0.98-2.13)	0.06	1.00 (0.58-1.71)	0.99	**2.09 (1.32-3.33)**	**0.002**	**1.39 (1.04-1.87)**	**0.028**
		Mod.1	1.47 (1.09-1.98)	0.01	1.16 (0.90-1.50)	0.27	1.23 (0.81-1.84)	0.33	0.81 (0.46-1.41)	0.45	**1.89 (1.18-3.02)**	**0.008**	1.28 (0.95-1.73)	0.10
		Mod.2	1.33 (0.96-1.84)	0.08	1.07 (0.78-1.46)	0.68	1.09 (0.71-1.69)	0.69	0.72 (0.38-1.34)	0.29	**1.91 (1.10-3.32)**	**0.020**	1.26 (0.86-1.83)	0.23
	van Swieten	**Unadj.**	**1.66 (1.29-2.12)**	**<.0001**	**1.52 (1.20-1.92)**	**0.001**	1.39 (0.97-2.01)	0.08	0.74 (0.41-1.31)	0.30	**1.67 (1.13-2.48)**	**0.010**	**1.73 (1.28-2.33)**	**<.0001**
		Mod.1	**1.34 (1.02-1.76)**	**0.036**	1.26 (0.98-1.62)	0.08	1.20 (0.81-1.76)	0.37	0.61 (0.34-1.10)	0.10	**1.52 (1.02-2.26)**	**0.042**	**1.60 (1.18-2.17)**	**0.002**
		Mod.2	1.32 (0.97-1.78)	0.08	1.09 (0.82-1.46)	0.54	1.24 (0.82-1.87)	0.31	0.80 (0.49-1.28)	0.35	1.50 (0.94-2.41)	0.09	1.41 (0.95-2.09)	0.09
Ischaemic (303)	**Oxford**	**Unadj.**	**1.35 (1.07-1.71)**	**0.011**	**1.35 (0.05-1.74)**	**0.021**	0.99 (0.65-1.50)	0.96	0.88 (0.50-1.58)	0.68	1.33 (0.96-1.84)	0.09	1.35 (0.99-1.83)	0.06
		Mod.1	1.08 (0.84-1.39)	0.56	1.13 (0.87-1.47)	0.37	0.87 (0.57-1.33)	0.51	0.77 (0.43-1.39)	0.38	1.21 (0.86-1.68)	0.27	1.23 (0.90-1.68)	0.20
		Mod.2	1.00 (0.75-1.33)	0.99	1.05 (0.76-1.44)	0.78	0.79 (0.50-1.25)	0.32	0.81 (0.44-1.50)	0.50	1.26 (0.85-1.86)	0.26	1.23 (0.84-1.81)	0.29
	ARWMC	**Unadj.**	**1.78 (1.35-2.36)**	**<.0001**	**1.37 (1.06-1.78)**	**0.016**	1.37 (0.91-2.05)	0.14	1.01 (0.57-1.77)	0.99	**2.29 (1.39-3.76)**	**0.001**	1.34 (0.99-1.82)	0.06
		Mod.1	**1.47 (1.08-2.01)**	**0.015**	1.12 (0.86-1.47)	0.41	1.18 (0.78-1.81)	0.46	0.84 (0.47-1.49)	0.54	**2.02 (1.22-3.35)**	**0.006**	1.21 (0.89-1.65)	0.23
		Mod.2	1.26 (0.90-1.75)	0.18	1.04 (0.75-1.44)	0.81	1.03 (0.66-1.62)	0.88	0.70 (0.36-1.34)	0.28	**1.74 (0.99-3.03)**	**0.050**	1.23 (0.83-1.81)	0.30
	van Swieten	**Unadj.**	**1.72 (1.33-2.22)**	**<.0001**	**1.50 (1.18-1.92)**	**0.001**	1.39 (0.95-2.03)	0.09	0.74 (0.40-1.34)	0.32	**1.83 (1.20-2.78)**	**0.005**	**1.71 (1.25-2.32)**	**0.001**
		Mod.1	**1.39 (1.05-1.85)**	**0.023**	1.24 (0.95-1.61)	0.11	1.22 (0.81-1.83)	0.34	0.62 (0.34-1.15)	0.13	**1.63 (1.06-2.50)**	**0.025**	**1.55 (1.13-2.13)**	**0.006**
		Mod.2	1.33 (0.97-1.81)	0.08	1.08 (0.81-1.46)	0.60	1.27 (0.83-1.93)	0.27	0.82 (0.50-1.33)	0.42	1.48 (0.91-2.40)	0.11	1.36 (0.91-2.03)	0.14
Haemorrhagic (23)	**Oxford**	**Unadj.**	1.75 (0.75-4.06)	0.20	**2.94 (1.29-6.71)**	**0.011**	1.61 (0.38-6.78)	0.52	2.41 (0.48-12.0)	0.28	1.38 (0.44-4.36)	0.58	2.76 (0.97-7.80)	0.06
		Mod.1	1.36 (0.55-3.40)	0.51	**2.59 (1.08-6.20)**	**0.033**	1.12 (0.26-4.77)	0.88	1.62 (0.32-8.25)	0.56	1.58 (0.49-5.05)	0.44	**3.31 (1.15-9.51)**	**0.026**
		Mod.2	1.48 (0.59-3.72)	0.41	**2.83 (1.17-6.85)**	**0.020**	1.32 (0.30-5.71)	0.71	2.13 (0.40-11.3)	0.38	1.78 (0.55-5.72)	0.34	**3.41 (1.19-9.78)**	**0.020**
	ARWMC	**Unadj.**	2.60 (0.85-7.97)	0.10	2.20 (0.92-5.23)	0.08	**8.79 (1.03-75.3)**	**0.047**	1.14 (0.14-9.46)	0.91	0.87 (0.23-3.28)	0.84	2.19 (0.76-6.33)	0.15
		Mod.1	1.98 (0.59-6.67)	0.27	1.75 (0.70-4.40)	0.23	5.17 (0.59-45.5)	0.14	0.61 (0.07-5.21)	0.65	0.98 (0.26-3.76)	0.98	2.56 (0.87-7.48)	0.09
		Mod.2	2.13 (0.62-7.27)	0.23	1.97 (0.78-4.98)	0.15	6.21 (0.70-55.2)	0.10	0.78 (0.09-6.71)	0.82	1.07 (0.28-4.11)	0.93	2.96 (1.00-8.76)	0.05
	van Swieten	**Unadj.**	1.73 (0.66-4.51)	0.26	1.96 (0.81-4.75)	0.14	4.08 (0.79-21.0)	0.09	1.01 (0.12-8.36)	1.00	0.70 (0.22-2.28)	0.55	2.01 (0.66-6.15)	0.22
		Mod.1	1.25 (0.44-3.57)	0.68	1.56 (0.61-4.03)	0.36	2.34 (0.44-12.5)	0.32	0.57 (0.07-4.79)	0.60	0.79 (0.24-2.65)	0.71	2.34 (0.75-7.23)	0.14
		Mod.2	1.31 (0.46-3.76)	0.62	1.70 (0.65-4.43)	0.28	2.56 (0.49-13.5)	0.27	0.70 (0.08-5.99)	0.74	0.87 (0.26-2.92)	0.82	2.50 (0.80-7.81)	0.12

Table 7.2 Risk of recurrent stroke (any type, ischaemic or haemorrhagic) in presence of excess of white matter changes for age on CT scans (a) and on MRI scans (b). Variables entered in the multivariate analysis are: age, sex, history of stroke or TIA preceding the event, history of angina or myocardial infarction, diabetes mellitus, peripheral vascular disease, hypertension, current smoking, significant carotid stenosis on either side.

(a)

		Any Recurrence		Ischaemic		Haemorrhagic	
		HR (95%CI)	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
Oxford	Univariate	1.40 (1.04-1.89)	0.03	1.33 (0.97-1.83)	0.07	2.46 (0.97-6.26)	0.06
	Multivariate	1.36 (0.94-1.98)	0.11	1.31 (0.89-1.94)	0.18	3.14 (0.80-12.3)	0.10
ARWMC	Univariate	1.24 (0.92-1.67)	0.17	1.21 (0.88-1.66)	0.25	1.82 (0.67-4.97)	0.24
	Multivariate	1.17 (0.82-1.66)	0.39	1.14 (0.79-1.65)	0.49	2.52 (0.63-10.2)	0.19
van Swieten	Univariate	**1.33 (1.02-1.73)**	**0.040**	1.29 (0.97-1.70)	0.08	2.18 (0.87-5.46)	0.10
	Multivariate	1.18 (0.86-1.63)	0.31	1.14 (0.82-1.59)	0.44	2.72 (0.73-10.1)	0.14

(b)

		Any Recurrence		Ischaemic		Haemorrhagic	
		HR (95%CI)	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
Oxford	Univariate	1.24 (0.75-2.05)	0.41	1.38 (0.83-2.31)	0.22	n.a	n.a
	Multivariate	0.93 (0.50-1.75)	0.82	1.10 (0.59-2.07)	0.76	n.a	n.a
ARWMC	Univariate	1.02 (0.60-1.74)	0.93	1.15 (0.67-1.96)	0.62	n.a	n.a
	Multivariate	1.20 (0.64-2.24)	0.57	1.36 (0.73-2.56)	0.33	n.a	n.a
Fazekas	Univariate	1.04 (0.62-1.72)	0.89	1.17 (0.70-1.96)	0.56	n.a	n.a
	Multivariate	1.04 (0.58-1.88)	0.90	1.20 (0.66-2.18)	0.55	n.a	n.a

Table 7.3. Risk of recurrent ischaemic stroke in patients entered in the study with a first event perteining to the three major categories of the TOAST classification. Variables entered in the multivariate analysis: age, sex, hypertension, previous stroke, previous TIA, atrial fibrillation, ischaemic heart disease, peripheral vascular disease, hyperlipidaemia, significant carotid stenosis on either side.

Type of Stroke/TIA			All		<75		≥75	
			HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Cardioembolic	**Oxford**	**Univ.**	**2.77 (1.55-4.97)**	**0.001**	2.86 (0.94-8.65)	0.06	**2.75 (1.38-5.48)**	**0.004**
		Multiv.	**2.91 (1.22-6.94)**	**0.016**	**5.61 (1.60-19.7)**	**0.007**	1.56 (0.42-5.79)	0.50
	ARWMC	**Univ.**	1.29 (0.67-2.51)	0.45	2.80 (0.94-8.28)	0.06	0.93 (0.40-2.16)	0.86
		Multiv.	1.41 (0.61-3.24)	0.42	3.00 (0.87-10.3)	0.08	0.76 (0.22-2.66)	0.67
	vanSwieten	**Univ.**	1.70 (1.00-2.88)	0.05	2.14 (0.63-7.22)	0.22	1.65 (0.90-3.00)	0.10
		Multiv.	1.58 (0.76-3.30)	0.22	2.16 (0.57-8.22)	0.26	1.50 (0.60-3.74)	0.39
Large artery	**Oxford**	**Univ.**	0.60 (0.18-1.97)	0.40	0.33 (0.04-2.51)	0.28	1.07 (0.24-4.73)	0.93
		Multiv.	1.52 (0.41-5.68)	0.54	0.358 (0.03-4.18)	0.41	3.46 (0.57-21.0)	0.18
	ARWMC	**Univ.**	0.75 (0.26-2.16)	0.60	0.31 (0.04-2.42)	0.27	1.49 (0.42-5.24)	0.54
		Multiv.	1.08 (0.36-3.25)	0.89	0.13 (0.01-2.60)	0.18	2.99 (0.55-16.3)	0.21
	vanSwieten	**Univ.**	0.66 (0.27-1.62)	0.33	0.25 (0.03-1.91)	0.18	1.02 (0.35-2.94)	0.97
		Multiv.	0.76 (0.30-1.93)	0.56	0.10 (0.01-1.18)	0.07	0.88 (0.24-3.26)	0.85
Small vessel	**Oxford**	**Univ.**	1.32 (0.67-2.60)	0.43	0.74 (0.25-2.21)	0.59	**2.73 (1.11-6.71)**	**0.029**
		Multiv.	1.06 (0.50-2.26)	0.87	0.60 (0.18-1.99)	0.41	2.34 (0.78-7.14)	0.14
	ARWMC	**Univ.**	1.20 (0.63-2.28)	0.59	0.62 (0.21-1.84)	0.39	2.11 (0.91-4.88)	0.08
		Multiv.	0.87 (0.42-1.78)	0.70	0.56 (0.17-1.83)	0.34	1.36 (0.48-3.88)	0.56
	vanSwieten	**Univ.**	1.34 (0.72-2.46)	0.36	0.63 (0.21-1.85)	0.40	2.21 (0.98-5.00)	0.06
		Multiv.	0.91 (0.45-1.83)	0.79	0.54 (0.16-1.79)	0.31	1.44 (0.53-3.95)	0.48

7.3.3 White matter changes and severity (NIHSS) of stroke

7.3.3.1 Incident events

Considering the first events separately as ischaemic stroke, TIA or primary intracerebral haemorrhage, I found that the mean NIHSS did not increase with the severity of leukoaraiosis on CT (fig.7.1). White matter changes on CT did not appear to be a significant predictor of NIHSS greater than 3 in patients with TIA or with intracerebral haemorrhage (age and sex adjusted OR for moderate/severe leukoaraiosis in TIA 1.32 95% CI 0.51-3.38, p= 0.57, age and sex adjusted OR for moderate/severe leukoaraiosis in PICH 0.84, 0.30-2.36, p=0.75) and in patients with ischaemic stroke (univariate OR for any LA 1.41, 95% CI 1.09-1.93, p=0.008, and OR for LA moderate/severe 1.39, 1.06-1.83, p=0.017, age and sex adjusted OR for any LA 1.01, 0.76-1.35, p=0.929, for LA moderate/severe 1.06, 0.79-1.41, p=0.718). When considering only the white matter changes in excess for age (table 7.4), again, no association emerged between severity of the event and excess of white matter changes either on CT or on MRI scan at entry.

Figure 7.1 Mean NIHSS of the first event in study across different levels of leukoaraiosis on the first CT scan. Patients are divided into primary intracerebral haemorrhage (top line), ischaemic stroke (middle line) and TIA (bottom line).

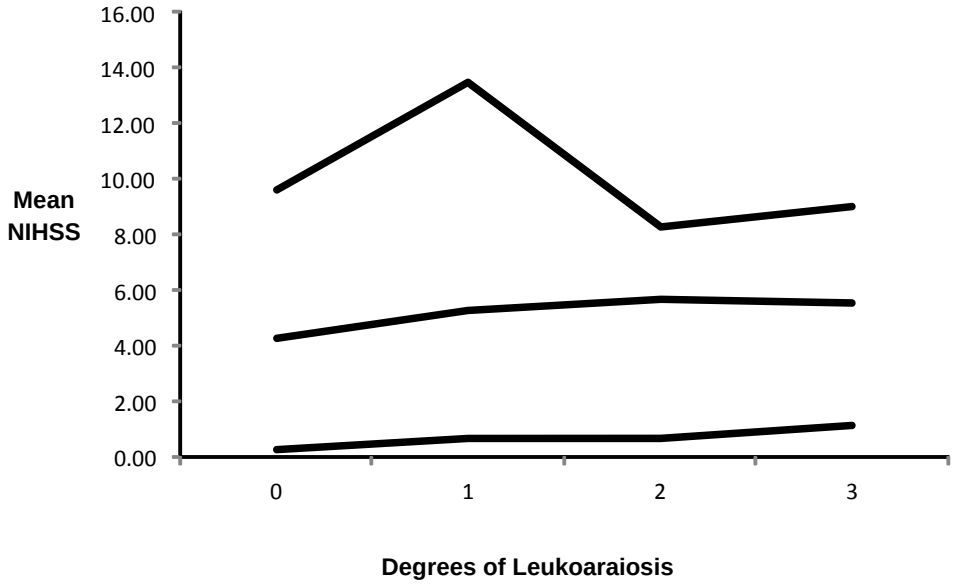

Table 7.4. Risk of NIHSS>3 at first event in the study, according to presence of excess of white matter changes, in the whole population (a), in ischaemic stroke (b) and TIA (c). Variables entered in the multivariate analysis, apart from excess of white matter changes: age, sex, hypertension, smoking, peripheral vascular disease, diabetes mellitus, previous stroke.

(a)

CT scans				**MRI scans**			
		OR (95% CI)	P			OR (95% CI)	P
Oxford	Univ.	**1.39 (1.04-1.86)**	**0.02**	Oxford	Univ.	**1.91 (1.03-3.55)**	**0.04**
	Multiv.	1.33 (0.99-1.79)	0.06		Multiv.	**2.19 (1.13-4.26)**	**0.02**
ARWMC	Univ.	0.97 (0.71-1.32)	0.85	ARWMC	Univ.	1.40 (0.75-2.62)	0.30
	Multiv.	0.91 (0.66-1.24)	0.54		Multiv.	1.56 (0.81-3.00)	0.18
van Swieten	Univ.	1.36 (1.05-1.76)	0.02	Fazekas	Univ.	1.38 (0.75-2.56)	0.30
	Multiv.	1.19 (0.91-1.55)	0.21		Multiv.	1.37 (0.72-2.59)	0.33

(b)

CT scans				**MRI scans**			
		OR (95% CI)	P			OR (95% CI)	P
Oxford	Univ.	1.08 (0.77-1.52)	0.65	Oxford	Univ.	1.82 (0.90-3.65)	0.09
	Multiv.	1.05 (0.74-1.49)	0.79		Multiv.	2.07 90.98-4.36)	0.06
ARWMC	Univ.	0.81 (0.56-1.15)	0.23	ARWMC	Univ.	1.16 (0.57-2.37)	0.69
	Multiv.	0.80 (0.55-1.15)	0.22		Multiv.	1.29 90.61-2.73)	0.51
van Swieten	Univ.	1.12 (0.83-1.52)	0.46	Fazekas	Univ.	1.32 (0.66-2.63)	0.43
	Multiv.	1.00 (0.73-1.37)	0.10		Multiv.	1.33 (0.65-2.74)	0.44

(c)

CT scans				**MRI scans**			
		OR (95% CI)	P			OR (95% CI)	P
Oxford	Univ.	1.43 (0.41-4.99)	0.57	Oxford	Univ.	2.16 (0.19-24.3)	0.53
	Multiv.	0.97 (0.26-3.63)	0.97		Multiv.	14.3 (0.13-1542)	0.27
ARWMC	Univ.	1.24 (0.36-4.34)	0.73	ARWMC	Univ.	1.79 (0.16-20.1)	0.64
	Multiv.	0.71 (0.19-2.74)	0.62		Multiv.	8.82 (0.24-328.7)	0.24
van Swieten	Univ.	0.86 (0.25-2.99)	0.81	Fazekas	Univ.	1.61 (0.14-18.1)	0.70
	Multiv.	0.56 (0.15-2.08)	0.38		Multiv.	2.06 (0.13-31.7)	0.60

When considering different types of stroke according to the TOAST classification, the association between excess of white matter changes for age on CT or MRI at entry and severity of first stroke (NIHSS >3) was only present for large vessel type of stroke, but only when assessed with the Oxford scale, and therefore unconvincing to be meaningful (table A7.2, appendix 8).

7.3.3.2 Severity of recurrent events

Considering the whole cohort, 297 (88.7%) patients had an available NIHSS of their recurrent event. Moderate-severe leukoaraiosis assessed with the Oxford scale showed a significant association with severity of NIHSS before and after adjustment for age, sex, NIHSS of first event and TOAST type of recurrent event (unadjusted OR 2.10, 95% CI 1.20-3.66, p=0.009 adjusted 2.57, 1.26-5.27, p=0.01). This association was not significant when white matter changes were assessed with the van Swieten scale (adjusted OR 1.91, 0.93-3.94, p=0.08) and with the ARWMC scale (1.66, 0.79-3.49, p=0.18), even though there was a positive trend.

When looking only into the group of strokes following an initial TIA, a total of 105 patients, I could not find any significant association between NIHSS and either presence or severity of white matter changes on CT scan at entry in the study. Considering only the patients with ischaemic stroke as both first and recurrent event, a total of 188 patients had a NIHSS of the recurrent stroke available for analysis. White matter changes moderate/severe assessed with the Oxford scale were associated with severity of recurrent stroke (unadjusted OR 2.39, 95% CI 1.16-4.90, p=0.018 adjusted 3.727, 1.41-9.82, p=0.008), while this association did not emerge with the other two scales, despite a positive trend. Presence of any degree of leukoaraiosis assessed with the ARWMC scale, rather than the moderate/severe degree, was associated to worse NIHSS (unadjusted OR 2.34, 95% CI 1.11-4.95, p=0.026 adjusted

3.84, 1.24-11.9, p=0.02) (table 7.5). The association was stronger when using the values of white matter changes on CT scans adjusted for age, referred to as “excess of white matter changes for age” (table 7.6). The results for the MRI scans did not reach significance, most likely due to the smaller number of observations. When grouping the patients according to the TOAST type of the initial event, despite the small number of patients, a positive association emerged between severity of recurrent stroke and presence of severe white matter changes on the entry scan, especially for patients presenting with a lacunar type of first event (table 7.7).

I also repeated the analyses considering only ischaemic recurrent strokes, and the associations remained (table7.8). The haemorrhagic recurrent events were too few (only 16 cases available) to allow any association study.

Table 7.5 Associations between leukoaraiosis on the CT scan at entry and the severity of the recurrent event, considered as a binary outcome of NIHSS≥3. Odds ratios are reported for the univariate analysis (unadjusted) and for the multivariate analysis (adjusted) considering as covariates in step 1 age, sex, NIHSS of first event, and TOAST types of recurrent event.

			Any LA		Moderate-Severe LA	
			OR (95% CI)	P	OR (95% CI)	P
Any first event	**Oxford scale**	**Unadj.**	1.39 (0.86-2.24)	0.178	**2.09 (1.20-3.66)**	**0.009**
		Adj.	1.35 (0.68-2.67)	0.388	**2.57 (1.25-5.27)**	**0.010**
	ARWMC	**Unadj.**	**1.92 (1.08-3.43)**	**0.027**	1.23 (0.73-2.09)	0.438
		Adj.	2.25 (0.99-5.15)	0.054	1.66 (0.79-3.49)	0.181
	van Swieten	**Unadj.**	1.35 (0.80-2.28)	0.266	**1.69 (1.01-2.81)**	**0.045**
		Adj.	1.41 (0.65-3.05)	0.385	1.91 (0.93-3.94)	0.079
Ischaemic stroke as first event	**Oxford scale**	**Unadj.**	1.42 (0.78-2.63)	0.253	**2.39 (1.16-4.90)**	**0.018**
		Adj.	2.00 (0.81-4.90)	0.132	**3.72 (1.41-9.82)**	**0.008**
	ARWMC	**Unadj.**	**2.34 (1.11-4.95)**	**0.026**	0.87 (0.45-1.68)	0.671
		Adj.	**3.84 (1.24-11.9)**	**0.020**	1.15 (0.44-3.03)	0.773
	van Swieten	**Unadj.**	1.58 (0.80-3.10)	0.187	1.44 (0.75-2.76)	0.273
		Adj.	2.04 (0.75-5.54)	0.161	1.95 (0.76-5.05)	0.492
TIA as first event	**Oxford scale**	**Unadj.**	1.51 (0.66-3.43)	0.326	1.39 (0.53-3.60)	0.502
		Adj.	0.78 (0.24-2.54)	0.676	1.42 (0.40-5.03)	0.585
	ARWMC	**Unadj.**	1.41 (0.54-3.67)	0.485	2.06 (0.81-5.21)	0.128
		Adj.	1.34 (0.31-5.76)	0.697	2.04 (0.55-7.53)	0.287
	van Swieten	**Unadj.**	1.10 (0.45-2.68)	0.831	2.06 (0.86-4.94)	0.106
		Adj.	0.58 (0.14-2.36)	0.446	2.16 (0.62-7.48)	0.226

Table 7.6 Association between excess of white matter changes for age on the initial scan and NIHSS>3 at recurrent event. Variables entered in the multivariate analysis are: age, sex, hypertension, previous stroke, peripheral vascular disease, NIHSS >3 at first event, TOAST type of first event

	CT scans				**MRI scans**			
			OR (95% CI)	P			OR (95% CI)	P
All patients	Oxford	Univ.	**3.13 (1.53-6.41)**	**0.002**	Oxford	Univ.	1.86 (0.65-5.38)	0.249
		Multiv.	**3.45 (1.57-7.60)**	**0.002**		Multiv.	1.32 (0.33-5.31)	0.697
	ARWMC	Univ.	**2.32 (1.19-4.52)**	**0.014**	ARWMC	Univ.	2.44 (0.84-7.10)	0.102
		Multiv.	**2.48 (1.20-5.14)**	**0.015**		Multiv.	1.75 (0.43-7.08)	0.431
	van Swieten	Univ.	**2.51 (1.40-4.49)**	**0.002**	Fazekas	Univ.	2.44 (0.87-6.86)	0.089
		Multiv.	**2.62 (1.37-5.01)**	**0.004**		Multiv.	1.73 (0.45-6.72)	0.426
Stroke as first event	Oxford	Univ.	2.17 (0.92-5.12)	0.076	Oxford	Univ.	1.79 (0.49-6.48)	0.380
		Multiv.	**2.74 (1.04-7.23)**	**0.041**		Multiv.	0.87 (0.11-6.85)	0.896
	ARWMC	Univ.	1.81 (0.84-3.92)	0.130	ARWMC	Univ.	2.65 (0.72-9.74)	0.142
		Multiv.	2.08 (0.89-4.86)	0.091		Multiv.	2.29 (0.27-19.2)	0.444
	van Swieten	Univ.	**2.53 (1.21-5.26)**	**0.013**	Fazekas	Univ.	2.74 (0.78-9.61)	0.115
		Multiv.	**2.59 (1.14-5.88)**	**0.023**		Multiv.	3.11 (0.33-29.3)	0.321
TIA as first event	Oxford	Univ.	**4.97 (1.26-19.6)**	**0.022**	Oxford	Univ.	4.00 (0.53-30.1)	0.179
		Multiv.	4.26 (0.87-20.9)	0.074		Multiv.	0.94 (0.017-51.4)	0.975
	ARWMC	Univ.	3.73 (0.91-15.4)	0.068	ARWMC	Univ.	4.00 (0.53-30.1)	0.179
		Multiv.	2.55 (0.49-13.3)	0.266		Multiv.	0.94 (0.017-51.4)	0.975
	van Swieten	Univ.	2.64 (0.93-7.51)	0.070	Fazekas	Univ.	4.00 (0.53-30.1)	0.179
		Multiv.	2.23 (0.64-7.75)	0.208		Multiv.	0.94 (0.017-51.4)	0.975

Table 7.7 Risk of NIHSS>3 at recurrent event (any type of stroke), given excess of white matter changes for age on the initial scan. Patients subdivided according to type of stroke at entry in the study. Only CT scan results reported (MRI numbers were too small). Variables entered in the multivariate analysis are: age, sex, hypertension, previous stroke, peripheral vascular disease, NIHSS >3 at first event, TOAST type of first event

Subtype of initial Stroke/TIA			OR (95% CI)	P
Cardioembolic (88 cases)	Oxford	Univ.	4.57 (0.96-21.9)	0.06
		Multiv.	**5.91 (1.12-31.1)**	**0.036**
	ARWMC	Univ.	7.56 (0.092-62.2)	0.06
		Multiv.	**13.6 (1.34-137)**	**0.027**
	van Swieten	Univ.	2.10 (0.67-6.54)	0.20
		Multiv.	2.87 (0.79-10.5)	0.11
Large artery (32 cases)	Oxford	Univ.	1.50 (0.12-18.5)	0.75
		Multiv.	0.19 (0.00-71.5)	0.58
	ARWMC	Univ.	2.57 (0.24-28.1)	0.44
		Multiv.	n.a	
	van Swieten	Univ.	1.69 (0.26-11.1)	0.58
		Multiv.	**55.2 (4.6-665)**	**0.002**
Small vessel (52 cases)	Oxford	Univ.	3.07 (0.78-12.01)	0.11
		Multiv.	5.88 (0.88-39.5)	0.07
	ARWMC	Univ.	**8.00 (1.85-34.5)**	**0.005**
		Multiv.	**9.04 (1.46-56.0)**	**0.018**
	van Swieten	Univ.	**14.0 (3.18-61.6)**	**<.0001**
		Multiv.	**55.2 (4.6-665)**	**0.002**

Table 7.8 Association between excess of white matter changes for age on the initial scan and NIHSS>3 at recurrent event. Only ischaemic recurrent strokes considered. Variables entered in the multivariate analysis: age, sex, hypertension, previous stroke, peripheral vascular disease, NIHSS >3 at first event, TOAST type of first event

CT- WMC scale		OR (95% CI)	P
Oxford	Univ.	**2.34 (1.12-4.89)**	**0.024**
	Multiv.	**2.76 (1.22-6.23)**	**0.015**
ARWMC	Univ.	1.91 (0.97-3.80)	0.06
	Multiv.	2.11 (1.00-4.46)	0.05
van Swieten	Univ.	**1.92 (1.05-3.50)**	**0.033**
	Multiv.	**2.10 (1.07-4.12)**	**0.031**

7.3.4 Prognostic value of white matter changes for stroke outcome and disability at one year

7.3.4.1 Premorbid modified Rankin score and Barthel scale

In OXVASC, a premorbid modified Rankin score greater than 2 is strongly associated with age and also with presence and severity of white matter changes on the CT scan at entry in the study (figures 7.2 and 7.3). These associations remain after adjustment for other possible co-factors responsible of a worse modified premorbid Rankin score. After entering in a multivariate model age, sex, previous strokes, previous transient ischaemic attacks, history of angina or myocardial infarction, diabetes, atrial fibrillation, peripheral vascular disease, hypertension and current smoking, both presence of any level of leukoaraiosis and leukoaraiosis moderate/severe were strongly associated to Rankin greater than 2. White matter changes (both presence versus absence and moderate-severe versus no or mild leukoaraiosis), previous CVA, diabetes, female sex and age remained associated to worse Rankin score when inserted in a multivariate step-wise analysis. These associations were equally strong for any scale used to evaluate white matter changes (Tables 7.9 and 7.10). Same results were found when considering white matter changes in excess for age, and when grouping patients according to age (table 7.11). After adjusting for age, for cardiac disease and for other possible causes of disability, leukoaraiosis influenced the pre-morbid Rankin score only in patients who went on having cardio-embolic stroke (table 7.12).

To identify what kind of disability is associated to excess of white matter changes, I analysed the associations with the single items of the Barthel scale. A wide range of associations emerged, but those between white matter changes and impaired bladder, bowels control and mobility were the strongest (table A7.3 appendix).

Figure 7.2. Prevalence (%) of patients with mRS >2 within leukoaraiosis severity groups on the CT scan at entry in the study, in different age strata.

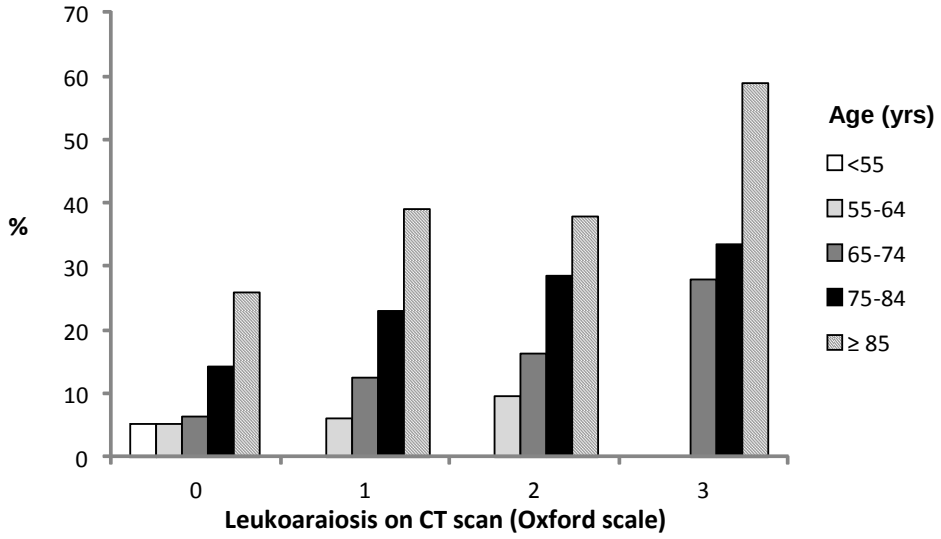

Figure 7.3 Prevalence of different degrees of WMC within patients with premorbid mRS >2. Patients are grouped according to age

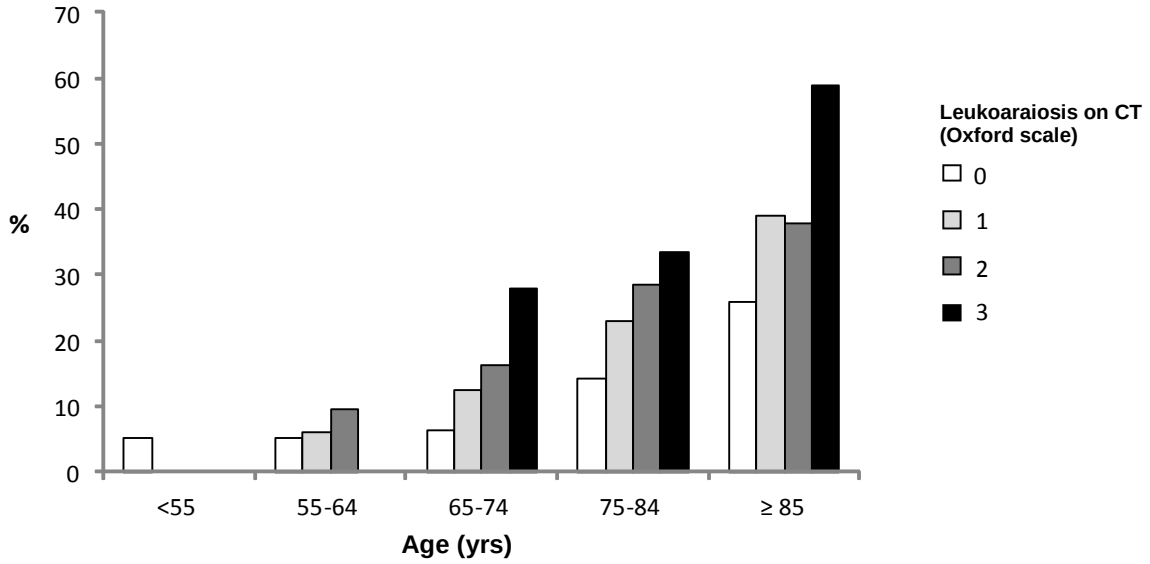

Table 7.9 Prediction of premorbid Rankin score >2 with a multiple binary logistic regression. Variables entered in model 1, besides CT-detected leukoaraiosis: age, male sex. Variables entered in model 2: age, male sex, previous strokes, previous transient ischaemic attacks, diabetes, ischaemic heart disease, atrial fibrillation, peripheral vascular disease, hypertension and current smoking.

		Any LA		Moderate/Severe LA	
		OR (95% CI)	P	OR (95% CI)	P
Oxford	Mod.1	**1.98 (1.46-2.69)**	**<.0001**	**1.74 (1.32-2.29)**	**<.0001**
	Mod.2	**1.90 (1.39-2.60)**	**<.0001**	**1.77 (1.33-2.35)**	**<.0001**
ARWMC	Mod.1	**1.80 (1.22-2.65)**	**0.003**	**1.76 (1.32-2.34)**	**<.0001**
	Mod.2	**1.92 (.29-2.87)**	**0.001**	**1.82 (1.35-2.45)**	**<.0001**
van Swieten	Mod.1	**2.28 (1.58-3.28)**	**<.0001**	**1.84 (1.38-2.45)**	**<.0001**
	Mod.2	**2.27 (1.56-3.31)**	**<.0001**	**1.83 (1.36-2.46)**	**<.0001**

Table 7.10 Associations with premorbid Rankin score >2. Multivariate stepwise analysis. Variable entered in step 1, with each of the CT-detected leukoaraiosis variables separately: history of CVA, history of TIA, diabetes, age, sex.

	Any LA		Moderate/Severe LA	
Scale	OR (95% CI)	P	OR (95% CI)	P
Oxford	**1.92 (1.41-2.62)**	**<.0001**	**1.73 (1.31-2.29)**	**<.0001**
ARWMC	**1.87 (1.26-2.78)**	**0.002**	**1.76 (1.31-2.36)**	**<.0001**
van Swieten	**2.27 (1.57-3.30)**	**<.0001**	**1.79 (1.33-2.40)**	**<.0001**

Table 7.11 Excess of white matter changes for age on initial CT scan and ORs of premorbid modified Rankin >2. Age, male sex, previous strokes, previous transient ischaemic attacks, diabetes, ischaemic heart disease, atrial fibrillation, peripheral vascular disease, hypertension and current smoking were entered in the multivariate analysis.

		All patients		< 75		≥75	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Oxford	Univariate	**2.04 (1.48-2.80)**	**<0.0001**	**2.49 (1.34-4.62)**	**0.004**	**2.37 (1.58-3.55)**	**<0.0001**
	Multivariate	**2.07 (1.45-2.97)**	**<0.0001**	**2.14 (1.06-4.30)**	**0.033**	**2.14 (1.38-3.32)**	**0.001**
ARWMC	Univariate	**1.52 (1.09-2.12)**	**0.013**	**2.33 (1.23-4.42)**	**0.009**	1.40 (0.93-2.10)	0.11
	Multivariate	1.41 (0.98-2.03)	0.07	**2.36 (1.14-4.89)**	**0.021**	1.30 (0.85-2.01)	0.23
van Swieten	Univariate	**2.24 (1.68-2.98)**	**<0.0001**	**3.05 (1.67-5.58)**	**<0.0001**	**1.82 (1.31-2.55)**	**<0.0001**
	Multivariate	1.74 (1.28-2.38)	**<0.0001**	**2.60 (1.31-5.14)**	**0.006**	**1.58 (1.11-2.26)**	**0.011**

Table 7.12 Excess of white matter changes for age on initial CT scan and ORs of premorbid modified Rankin >2 in patients grouped according to the 3 major sub-types of ischaemic stroke. Age, male sex, previous strokes, previous transient ischaemic attacks, diabetes, ischaemic heart disease, atrial fibrillation, peripheral vascular disease, hypertension and current smoking were entered in the multivariate analysis.

		Cardio-embolic		Large Artery		Small Vessel	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Oxford	Univariate	**3.72 (1.84-7.54)**	**<0.0001**	2.08 (0.78-5.53)	0.14	0.62 (0.21-1.88)	0.40
	Multivariate	**4.06 (1.75-9.41)**	**0.001**	2.82 (0.90-8.86)	0.08	0.70 (0.21-2.37)	0.57
ARWMC	Univariate	1.93 (0.94-3.95)	0.07	1.77 (0.67-4.68)	0.25	1.07 (0.42-2.69)	0.89
	Multivariate	2.05 (0.90-4.65)	0.09	1.87 (0.60-5.86)	0.28	1.06 (0.39-2.89)	0.91
van Swieten	Univariate	**2.60 (1.44-4.70)**	**0.002**	2.08 (0.88-4.94)	0.10	1.507 (0.64-3.52)	0.34
	Multivariate	**2.19 (1.11-4.31)**	**0.023**	1.90 (0.69-5.22)	0.21	1.33 (0.53-3.35)	0.54

7.3.4.2 Worsened modified Rankin score at one year from the event

To seek a possible association between presence of white matter changes and worse stroke outcome at one year, the differential score between the 1 year mRS and the baseline was considered. Patients displaying a positive difference between the two scores were labeled as worsened. A total of 1590 patients had an available premorbid Rankin score and at 1 year follow up. Of these, 117 improved (2 patients by 3 points, 12 patients by 2 points and 103 patients by one point) and 910 worsened, while the others remained at the same level.

There was a trend of positive association between leukoaraiosis on baseline CT and worsening of the mRS at one year from the event, especially in patients younger than 75 (figure 7.4). When white matter changes were assessed with the Oxford and the ARWMC scale the association was significant, especially for the most severe degrees, and this remained independently of other cofactors: age, sex, previous history of angina or myocardial infarction, previous cerebrovascular accidents, previous transient ischaemic attacks, atrial fibrillation, current smoking, hypertension, NIH score of the index event and recurrence of any

type of stroke. When white matter changes were assessed with the van Swieten scale the association did not reach statistical significance (table 7.13). When further adjusting the white matter changes for age, and considering the "excess of white matter changes for age", the associations became stronger and constant through different scales adopted (table 7.14), although no significance was reached with the MRI scans.

Figure 7.4 Prevalence of worsened 1-year mRS among patients with different degrees of leukoaraiosis, stratified by age.

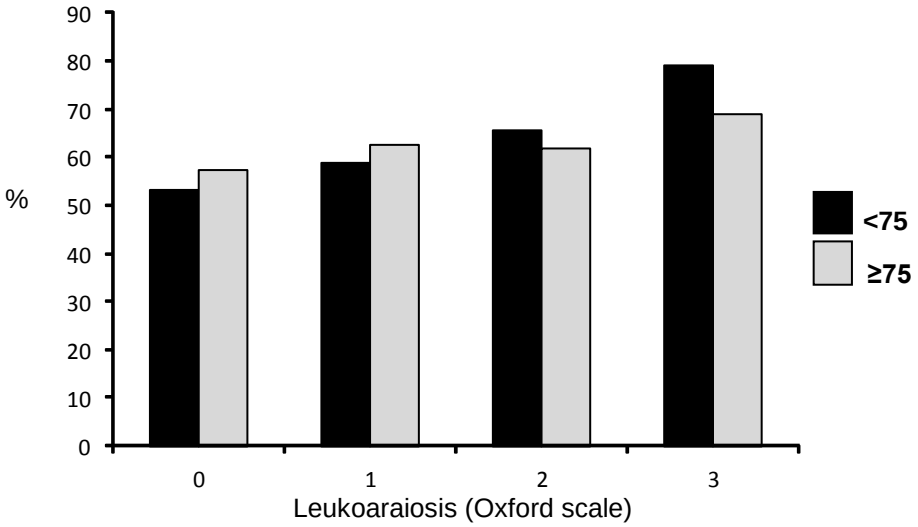

Table 7.13 Associations between white matter changes on CT at baseline and worsening of the modified Rankin Score at 1 year from the event. Variables entered with leukoaraiosis in model 1: age, sex. Variables entered with leukoaraiosis in model 2: age, sex, NIHSS of first event, any recurrent events, history of CVA or of TIA at baseline, ischaemic heart disease, diabetes, hypertension, atrial fibrillation, peripheral artery disease, current smoking.

		Any LA		Moderate/Severe LA	
Scale		**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Oxford	Mod.1	**1.34 (1.06-1.70)**	**0.02**	**1.36 (1.04-1.78)**	**0.02**
	Mod.2	**1.34 (1.04-1.73)**	**0.03**	**1.37 (1.03-1.83)**	**0.03**
ARWMC	Mod.1	**1.37 (1.05-1.78)**	**0.02**	**1.45 (1.10-1.90)**	**0.01**
	Mod.2	1.25 (0.94-1.66)	0.12	**1.36 (1.02-1.83)**	**0.04**
van Swieten	Mod.1	1.22 (0.95-1.57)	0.13	1.25 (0.96-1.62)	0.10
	Mod.2	1.16 (0.88-1.53)	0.29	1.25 (0.94-1.66)	0.12

Table 7.14. ORs of worsening of mRS at one year according to presence of excess of white matter changes on the presenting CT (a) or MRI (b). Age, sex, NIH score of first event, any recurrent events, history of CVA or of TIA at baseline, ischaemic heart disease, diabetes, hypertension, atrial fibrillation, peripheral artery disease, current smoking were entered in the multivariate analysis in addition to white matter changes.

(a)

Scale		OR (95% CI)	P
Oxford	Univariate	**1.69 (1.20-2.34)**	**0.003**
	Multivariate	**1.79 (1.26-2.54)**	**0.001**
ARWMC	Univariate	**1.37 (1.00-1.88)**	**0.050**
	Multivariate	1.36 (0.99-1.89)	0.060
van Swieten	Univariate	**1.47 (1.11-1.96)**	**0.007**
	Multivariate	**1.44 (1.07-1.93)**	**0.015**

(b)

Scale		OR (95% CI)	P
Oxford	Univariate	1.37 (0.88-2.16)	0.168
	Multivariate	1.27 (0.78-2.07)	0.345
ARWMC	Univariate	1.14 (0.73-1.78)	0.554
	Multivariate	1.11 (0.69-1.79)	0.671
Fazekas	Univariate	1.22 (0.79-1.87)	0.367
	Multivariate	1.12 (0.71-1.77)	0.635

When grouping the patients according to the TOAST type of their first event, association with white matter changes on the entry scan was evident only in the older patients (over 75) with small vessel type of first stroke (table 7.15), and this was independent once again of the scale used to evaluate white matter changes. This association emerged again, even though not as strong and not reaching significance, when I considered leukoaraiosis as “excess of white matter changes on the CT scan at entry” (the numbers were not sufficient to repeat the

analysis on the MRI scans) in relation to worsening of mRS at one year (table 7.16). To see whether this association might have been biased by the fact that many small vessel events present actually as TIA at entry and then go on developing a stroke, I repeated the analysis selecting only those patients with stroke at entry, and the associations remained largely unchanged (table 7.17).

Table 7.15 One year worsening of mRS according to presence of leukoaraiosis on CT. Patients stratified according to type of stroke/TIA and age, and data reported for presence of any leukoaraiosis and leukoaraiosis moderate/severe evaluated with the three different rating scales. Analyses adjusted for age, sex, previous CVA/TIA, IHD, diabetes, AF, PVD, hypertension, current smoking, NIH of first event, any recurrent event.

			Oxford Scale		ARWMC scale		van Swieten scale	
			OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
CE stroke at entry	**Whole cohort**	**Any LA**	**2.11 (1.11-4.02)**	**0.02**	1.69 (0.79-3.60)	0.18	1.95 (0.96-3.96)	0.07
		Mod/Sev LA	**2.35 (1.03-5.37)**	**0.04**	1.51 (0.71-3.20)	0.28	1.37 (0.66-2.84)	0.41
	Under 75	**Any LA**	3.69 (0.65-20.8)	0.14	3.73 90.54-25.7)	0.18	**20.79 (1.92-224)**	**0.01**
		Mod/Sev LA	na		na		na	
	Over 75	**Any LA**	**2.31 (1.09-4.91)**	**0.03**	1.74 (0.70-4.32)	0.23	1.50 (0.64-3.50)	0.35
		Mod/Sev LA	1.87 (0.77-4.56)	0.17	1.45 (0.65-3.23)	0.37	1.32 (0.60-2.90)	0.50
LAA stroke at entry	**Whole cohort**	**Any LA**	1.55 (0.63-3.78)	0.34	0.96 (0.36-2.54)	0.93	0.62 (0.24-1.63)	0.33
		Mod/Sev LA	0.82 (0.32-2.13)	0.69	1.33 (0.54-3.28)	0.54	1.10 (0.46-2.61)	0.84
	Under 75	**Any LA**	1.37 (0.37-5.08)	0.64	**0.86 (0.22-3.38)**	0.82	0.64 (0.17-2.48)	0.52
		Mod/Sev LA	0.80 (0.17-3.91)	0.79	1.36 (0.29-6.40)	0.70	0.85 (0.19-3.74)	0.83
	Over 75	**Any LA**	2.51 (0.46-13.6)	0.29	1.34 (0.20-9.08)	0.77	1.1 (0.16-7.57)	0.93
		Mod/Sev LA	1.18 (0.27-5.18)	0.83	1.42 (0.33-6.13)	0.64	0.89 (0.20-3.96)	0.88
SMV stroke at entry	**Whole cohort**	**Any LA**	1.98 (1.00-3.92)	0.05	1.68 (0.79-3.59)	0.18	1.02 (0.47-2.20)	0.96
		Mod/Sev LA	**3.55 (1.73-7.31)**	**0.001**	**2.54 (1.23-5.27)**	**0.01**	1.94 (0.95-3.97)	0.07
	Under 75	**Any LA**	1.19 (0.45-3.17)	0.72	0.87 (0.31-2.44)	0.79	0.80 (0.30-2.11)	0.65
		Mod/Sev LA	2.10 (0.68-6.48)	0.20	1.68 (0.53-5.31)	0.38	1.22 (0.40-3.73)	0.72
	Over 75	**Any LA**	**3.82 (1.17-12.5)**	**0.03**	4.22 (0.96-18.6)	0.06	1.18 (0.28-4.99)	0.82
		Mod/Sev LA	**5.69 (1.97-16.4)**	**0.001**	**3.55 (1.26-9.98)**	**0.02**	**2.92 (1.02-8.37)**	**0.05**
Undetermined or Other type of stroke at entry	**Whole cohort**	**Any LA**	1.07 (0.75-1.52)	0.71	1.15 (0.79-1.69)	0.46	1.21 (0.83-1.76)	0.32
		Mod/Sev LA	1.09 (0.72-1.65)	0.70	1.18 (0.76-1.82)	0.47	1.21 (0.80-1.82)	0.37
	Under 75	**Any LA**	1.60 (0.92-2.78)	0.09	1.67 (0.95-2.96)	0.08	**2.19 (1.24-3.88)**	**0.01**
		Mod/Sev LA	1.92 (0.86-4.28)	0.11	1.03 (0.44-2.38)	0.96	1.34 (0.60-2.97)	0.48
	Over 75	**Any LA**	0.72 (0.44-1.18)	0.19	0.74 (0.43-1.28)	0.28	0.71 (0.41-1.23)	0.22
		Mod/Sev LA	0.85 (0.51-1.41)	0.52	1.12 (0.66-1.91)	0.68	1.07 90.65-1.76)	0.78

Table 7.16 Worsened mRS at one year in relation to presence of excess of white matter changes for age on CT scan at entry, after subdivision of patients according to the three major categories in TOAST (first event). Variables entered in the multivariate analysis are: age, sex, hypertension, atrial fibrillation, peripheral vascular disease, ischaemic heart disease, previous stroke, previous TIA, diabetes, current smoking, significant carotid stenosis on either side, NIHSS of first event

Age			All		< 75		≥ 75	
			OR (95% CI)	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Cardioembolic strokes/TIA	Oxford	Univ.	2.61 (0.87-7.85)	0.09	n.a	-	1.66 (0.52-5.28)	0.39
		Multiv.	4.93 (0.92-25.6)	0.06	n.a	-	1.92 (0.29-13.0)	0.50
	ARWMC	Univ.	1.06 (0.46-2.43)	0.90	n.a	-	0.81 (0.33-1.95)	0.63
		Multiv.	1.72 (0.53-5.55)	0.37	n.a	-	1.21 (0.31-4.67)	0.78
	van Swieten	Univ.	1.89 (0.86-4.16)	0.12	n.a	-	1.76 (0.77-3.99)	0.18
		Multiv.	2.52 (0.83-7.67)	0.10	n.a	-	2.15 (0.65-7.15)	0.21
Large artery strokes/TIA	Oxford	Univ.	1.13 (0.47-2.73)	0.79	1.03 (0.30-3.48)	0.96	1.24 (0.34-4.50)	0.74
		Multiv.	1.04 (0.29-3.78)	0.96	1.02 (0.17-6.26)	0.99	0.45 (0.05-4.19)	0.48
	ARWMC	Univ.	1.23 (0.53-2.86)	0.63	1.45 (0.44-4.71)	0.54	0.97 (0.28-3.35)	0.96
		Multiv.	1.26 (0.39-4.03)	0.70	3.23 (0.44-23.8)	0.25	0.32 (0.04-2.54)	0.28
	van Swieten	Univ.	1.12 (0.54-2.32)	0.77	0.94 (0.32-2.81)	0.92	1.42 (0.52-3.88)	0.50
		Multiv.	1.40 (0.53-3.71)	0.50	1.47 (0.26-8.30)	0.66	0.97 (0.22-4.39)	0.97
Small vessels strokes/TIA	Oxford	Univ.	**2.19 (1.04-4.63)**	**0.039**	2.03 (0.81-5.08)	0.13	2.95 (0.76-11.5)	0.12
		Multiv.	2.24 (0.96-5.25)	0.06	1.82 (0.55-5.97)	0.33	3.86 (0.78-19.05)	0.10
	ARWMC	Univ.	1.86 (0.96-3.59)	0.07	1.71 (0.71-4.10)	0.23	2.09 (0.76-5.73)	0.15
		Multiv.	1.91 (0.88-4.16)	0.10	1.04 (0.32-3.34)	0.95	**3.89 (1.04-14.6)**	**0.044**
	van Swieten	Univ.	1.64 (0.88-3.06)	0.12	1.15 (0.49-2.73)	0.75	2.33 (0.92-5.92)	0.07
		Multiv.	1.44 (0.68-3.08)	0.34	0.60 (0.18-1.99)	0.41	3.02 (0.89-10.2)	0.08

Table 7.17 Worsened mRS at one year in relation to presence of excess of white matter changes for age on CT scan at entry, considering patients in the three major TOAST categories (first event). Only ischaemic strokes at entry considered (TIA excluded). Variables entered in the multivariate analysis are: age, sex, hypertension, atrial fibrillation, peripheral vascular disease, ischaemic heart disease, previous stroke, previous TIA, diabetes, current smoking, significant carotid stenosis on either side, NIHSS of first event

		Cardio-embolic		Large Artery		Small Vessel	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Oxford	Univariate	4.46 (0.57-34.8)	0.15	0.88 (0.27-2.92)	0.84	2.26 (0.96-5.34)	0.06
	Multivariate	2.82 (0.28-28.3)	0.38	0.23 (0.02-2.41)	0.22	2.83 (0.99-8.06)	0.05
ARWMC	Univariate	2.06 (0.45-9.48)	0.36	0.80 (0.27-2.36)	0.69	**2.28 (1.07-4.85)**	**0.033**
	Multivariate	3.21 (0.33-31.3)	0.32	0.60 (0.09-3.77)	0.58	2.25 (0.92-5.53)	0.08
van Swieten	Univariate	2.57 (0.73-9.10)	0.14	0.73 (0.28-1.93)	0.53	**2.44 (1.16-5.10)**	**0.018**
	Multivariate	2.70 (0.47-15.4)	0.26	0.94 (0.21-4.16)	0.93	2.11 (0.85-5.24)	0.11

7.4 Discussion and conclusions

Some considerations emerge from the analyses on this population-based cohort of patients with stroke and TIA. First, white matter changes on CT or MRI are not a strong independent predictor of recurrent stroke, in particular of ischaemic strokes. There is a trend of association with recurrent haemorrhagic events, even though our cases are too few (only 18 in patients with ischaemic stroke at entry) to lead us to conclusive evidence. Also, no clear association exists between any of the subtypes of ischaemic stroke (TOAST) and risk of recurrences according to presence of severe white matter changes, even though a possible trend emerges with cardioembolic type of stroke (especially in the youngest group), and with the small vessels type (especially in the oldest group). We could speculate this to be secondary to the strict secondary prevention carried on in OXVASC, where every patient receives antiplatelet, anti-hypertensive and lipid-lowering treatment from the moment they are seen in clinic. If this were the case, this would mean that the risk of recurrences in the general population is mainly secondary to other vascular risk factors, and the association between

white matter changes and recurrent events found in other studies might simply be due to a higher susceptibility to the damaging consequences of these risk factors in patients with white matter changes. The trend to have more recurrent events in young cardioembolic strokes might be just apparent, reflecting the fact that young patients with a cardioembolic source might have had previous silent embolic events, which are identified on imaging as residual white matter changes. The white matter changes would not constitute a risk of recurrence in this case, but would identify patients at higher risk secondary to a more active source of emboli. The trend in older patients with lacunar type of strokes is slightly more difficult to find an explanation for, but it might be due to the fact that patients with leukoaraiosis and lacunar type of strokes are both more susceptible than other type of patients to the effect of vascular risk factors, both the classically known ones and those which have yet to be identified (see chapter 5).

A second key finding is that severe white matter changes on CT or MRI at entry do not influence the severity of the first stroke, but they are associated with more severe recurrent stroke, and this is mainly led by the small vessel type of strokes. We might hypothesize that, given the long time it takes to accumulate white matter changes, mechanisms of compensation arise in the remaining of the white matter. When the first stroke occurs, the damage secondary to the presence of white matter changes might be partly compensated by these mechanisms. At this point though, the fine equilibrium present the first time around is lost, and the worst severity of a subsequent stroke in patients with higher initial load of white matter changes reflects the presence of a larger quantity of damaged white matter, which equals to a larger damage in cerebral networks, ultimately responsible for disability.

A third observation is that severe white matter changes on scan at entry are associated with a higher pre-morbid disability level, represented by a higher modified Rankin Score. This is in keeping with what has already been found in the European LADIS cohort, where, in subjects with no disability to start with, white matter changes on the initial scan have been associated with a higher risk of developing disability in the following few years. The LADIS study found strong association between severity of white matter changes and urinary incontinence[26] and gait abnormalities,[27] and our sub-analysis of the Barthel single items reflects this, as we found stronger associations with urinary and bowels problems and with mobility. I also found that this was particularly true for patients presenting with cardio-embolic type of stroke, and this was independent of age and of the obvious presence of pre-morbid cardiovascular disease and major risk factors. One possible explanation to this could be that patients with embolic type of stroke might have had previous clinically silent strokes. Their appearance on CT scan would be that of leukoaraiosis, but the white matter damage might have been more severe than that occurring with chronic white matter changes, the former happening in a step-wise fashion leaving less time to compensatory mechanisms.

Finally, white matter changes on CT scans are associated to a higher risk of poor outcome in terms of worsening of modified Rankin Score at one year from the stroke. This is particularly evident in patients older than 75 and presenting with small vessel type of stroke at entry in the study, and it might be secondary to the fact that the majority of patients with lacunar type of stroke might exhibit a loss of cortical-subcortical networks in presence of severe white matter changes, much more relevant than the one in patients suffering from cortical type of strokes. This will be reflected by a progressive deterioration in time in terms of autonomy, rather than by improvement secondary to network plasticity. Also, it might be that secondary prevention strategies slow down the formation of white matter changes secondary to cardio-

embolism and large artery damage, but do not arrest the progression of small vessel disease, even though one year is a relatively short period.

One shortcoming of this study lies in the small number of MRI scans. This does not allow us to draw conclusions regarding specific patient settings, for example when dividing into different age groups or when looking into different subtypes of ischaemic strokes. Therefore our observations need to be taken cautiously, and the findings from the CT scans are definitely more robust.

In conclusion, in patients with TIA and stroke, white matter changes on CT scan are associated with a worse outcome in terms of disability at one year and with a higher severity of future recurrent cerebro-vascular events. There is no evidence that white matter changes influence the risk of recurrent ischaemic events. Despite many studies have already been performed on this subject, as mentioned in the introduction, the strength of my conclusions is mainly given by the size and the unique setting (population-based) of the study cohort.

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Chapter 8

Prognostic value of white matter changes for risk of mortality, myocardial infarction, and dementia in a population of patients with TIA and stroke

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8.0 Abstract

Background: Several studies have reported on the association between presence of severe white matter changes on brain imaging and increased risk of death, and recently also on the association with depressive and cognitive symptoms. My aim was to investigate the risk of death in stroke patients presenting severe white matter changes on their acute brain imaging and, if increased, explore possible reasons behind this. I then looked into the association between severe white matter changes and risk of ischaemic heart disease, and also explored possible cognitive decline at one year from the stroke.

Methods: I scored the severity of white matter changes on CT and MRI of patient recruited in the first 8 years of the Oxford Vascular Study (OXVASC) with 4 different rating scales. Hazard ratios for myocardial infarction and death from vascular or non vascular cause were calculated on a follow-up period of 10 years in total. Odds ratios for worsening of Mini Mental State Examination (MMSE) at one year from stroke were also calculated.

Results: severe white matter changes on CT and MRI at entry were associated with a higher risk of death in the 10 year follow-up period. There was no increased risk of myocardial infarction and no association with development of clinical depression. I found association with worsening of MMSE at one year from the event, especially in younger patients (OR 2.12, 95%CI 1.15-3.92, p=0.017 when WMC assessed with ARWMC scale).

Conclusions: In patients with TIA and stroke, severe white matter changes on the initial scan represent a negative prognostic marker for early death. No specific cause has been found for this. Specifically, I found no increased risk of myocardial infarction and of vascular death. Moreover, after a stroke, patients with severe white matter changes have a faster cognitive deterioration compared with patients with no or mild white matter changes. The increased risk of death could be associated with increased frailty and predisposition to develop health issues of any kind.

8.1 Introduction

After analyzing the prognostic value of white matter changes on CT or MRI of patients with stroke and TIA with regards to stroke recurrence and outcome, in this chapter I shall report on their prognostic value for the risks of myocardial infarction, all-cause mortality and dementia.

Severe white matter changes on MRI have been longitudinally associated with development of depressive symptoms[1,2] and have also been found prognostically associated with development of dementia in stroke patients[3,4], or in unselected subjects[5,6,7], even though some studies have not confirmed this association[8]. Various studies have found the association between white matter changes and risk of premature death in patients with stroke,[3,9,10] in patients with other vascular risk factors,[11,12,13] or in unselected population-based cohorts.[14,15,6] Are patients with stroke and severe white matter changes really at risk of an earlier death? And if so, is this secondary to vascular events or to some other causes? These are the questions I will address in this chapter.

8.2 Methods

I have considered patients enrolled in the first 8 years of the OXVASC study, followed up for a total period of nearly 10 years. What follows is a list of the variables considered in this chapter, with the description of the methods used and a definition of the variables within the OXVASC study.

Myocardial infarction: Both non-ST elevation myocardial infarction and ST-elevation myocardial infarction have been considered. The time (in days) to myocardial infarction has been introduced in a Cox regression model as dependent variable, using as covariates either any degree of leukoaraiosis or leukoaraiosis moderate/severe, or the variable “excess of white matter changes for age”, and age, sex, diabetes, hypertension, current smoking,

previous history of angina or MI, peripheral vascular disease, and hyperlipidaemia. The analyses were performed in the whole cohort and then stratifying by age with 75 years or more as cut-off, and then also in each individual group of patients stratified by TOAST type of stroke/TIA at entry in the study.

Deaths: I considered as cause of death the underlying cause as per decision by the Information Centre for Health and Social Care, (formerly the Office of National Statistics), on the basis of the International Classification of Diseases codes (currently ICD-10) of the causes of death stated on death certificates. I then grouped the causes into four categories: cardiac, stroke-related, peripheral vascular disease-related, and non vascular. The analyses were performed using Cox regression models with time to death or to follow up as end point and death as the outcome event. I adjusted the analyses for age as a continuous variable (model 1), and also inserted as cofactors possible risk factors for earlier death in stroke patients (age, sex, history of ischaemic heart disease, diabetes, history of atrial fibrillation, peripheral vascular disease, hypertension, current smoking and NIHSS of the first event in model 2).

Anxiety and depression: In OXVASC no formal scales are administered to patients to measure their possible level of depression, and the data we have are limited to use of antidepressant medications and the history of a clinically manifest depression from the patient or from the GP. At baseline patients are asked to describe their mood, in particular they are asked whether they are often feeling sad or depressed. At follow up, besides taking any history of treated depression, the researchers gather information about the patient mood with the Euro-QOL self-administered 5 points questionnaire,[16] where the patient has to choose between “I am not anxious or depressed”, “I am moderately anxious or depressed” and “I am extremely anxious or depressed”. I looked into the association between presence and severity of CT detected leukoaraiosis with self-reported anxiety-depression at one month

and at one year, and also at the association with the number of patients treated for depression at one month and at one year. I also looked at any association between white matter changes and new occurrence of anxiety depression or starting of anti-depressive medication.

Dementia: Patients in OXVASC are administered MMSE[17] at their first follow up, one month after the event, and again at the 3, 6, 12 and 60 months follow up. Since 2007 the Montreal Cognitive Assessment (MOCA)[18] has been introduced at months 6, 12 and 60. I have considered the first month FU MMSE as the baseline test, and looked for possible associations between the MMSE scores and white matter changes on baseline CT or MRI. I have also researched possible associations between baseline white matter changes and MMSE at one year, and with worsening of MMSE at one year. The MMSE scores have been analysed as a binary variable, with cut-offs at 24 and at 27. I chose these two cut offs because, despite some debate in literature, they are the most commonly used to detect, respectively, subjects with dementia and with mild cognitive impairment.[19,20] Worsening has been considered as any negative change in score and as change of category from either 27-30 to under 27 or from 24-30 to under 24, and of at least 2 points in difference.

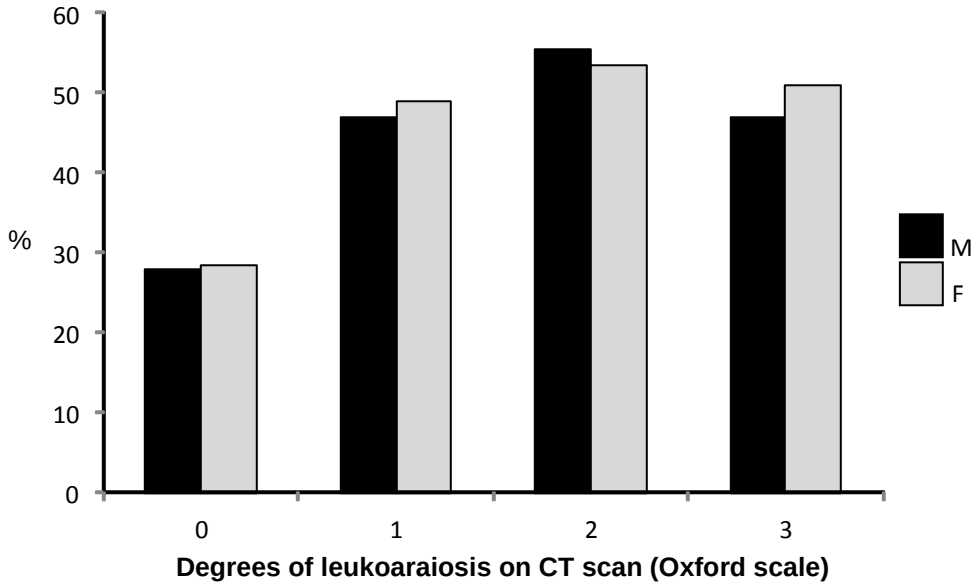
8.3 Results

8.3.1 White matter changes and risk of death

A total of 830 patients out of the 2052 patients (40.4%) with stroke/TIA included in the first 8 years of study had died by their follow up at 25th October 2011 (9 years and 6 months). The time to death varied from 0 to 9.5 years after the stroke/TIA, with a mean of 3.8 years ± 2.71. The deaths occurring within the first 30 days after stroke were considered “early deaths” secondary to the event itself. Looking at the deaths within patients with different degrees of white matter changes on their initial CT scan, there was a clear difference between patients

with and without white matter changes, those with no white matter changes having lower mortality. There were no sex differences (figure 8.1).

Figure 8.1 Number of deaths (%) within different degrees of white matter changes on CT scan at entry in OXVASC, for men and women over the period April 2002-October 2011. All deaths (early and late) have been considered.



When looking at the cumulative risk of death during the follow up period up to October 2011, patients with presence of leukoaraiosis on their CT scans at entry in the study had a significantly higher risk than patients with no leukoaraiosis at entry, and this was true for both younger and older patients in the study, considering as cut-off 75 years of age, and after entering in the model age, sex, history of ischaemic heart disease, diabetes, history of atrial fibrillation, peripheral vascular disease, hypertension, current smoking and NIHSS of the first event as covariates (table 8.1). Similar results are found when considering white matter changes as binary variable “excess of white matter changes for age” (table 8.2). The results for the MRI were all non significant, but there were very few events in the MRI groups, and this needs considering. Kaplan-Meier curves for mortality in patients with moderate-severe WMC versus no-mild WMC on CT or MRI, considering or not the deaths in the first 30 days

after the stroke (which are considered early death, secondary to the acute event itself), are reported (figure 8.2). When dividing the cause of death in vascular (acute or chronic cerebrovascular disease, acute or chronic cardiovascular disease and death for peripheral vascular disease) versus non vascular, both types of death remained associated to excess of white matter changes on CT scans, but the association was stronger for the non vascular deaths, especially in subjects younger than 75 (tables 8.3 and 8.4).

In order to find a possible trend of mortality among the non vascular causes of death, I looked at the individual causes in patients younger than 75. There were 15 patients younger than 75 with excess of white matter changes for age, who died for non vascular causes. Among these, 6 died of malignancy, 3 of pneumonia, and then there were single cases of sarcoidosis, Parkinson's disease, renal failure, urinary tract infection, dementia, and ischaemic bowel disease. I had the cause of death in 43 of the 56 cases of patients under 75 and with no white matter changes who died of a non vascular cause. Among these, 13 died of malignancy, 12 of chest infections, 3 of pulmonary embolism, 2 of diabetes mellitus, 2 of gastro-intestinal haemorrhage, and then single cases of alcoholic liver disease, renal failure, urinary tract infection, cardiomyopathy, neutropenic sepsis, pancreatitis, asthma, COPD, motor neuron disease, skull fracture, osteomyelitis. Overall there was a slightly higher incidence of deaths secondary to malignancies in the group of patients with white matter changes (40% versus 30.3%), but the numbers were too small to identify a statistically significant trend in a cause of death.

Depression and anxiety have been previously reported as associated to severe white matter changes in unselected patients,[1,2] and they are associated with an increased risk of death.[21] I looked into their association with severe white matter changes in our population, in order to explore another possible explanation for the increased mortality among these patients. No

association was found between leukoaraiosis on CT scan and both self-reported depression/anxiety at one month and at one year, and treated depression at one month and at one year. Moreover, no association was present between leukoaraiosis and new occurrence of anxiety-depression or starting of treatment for depression (Appendix 8, Table A8.4).

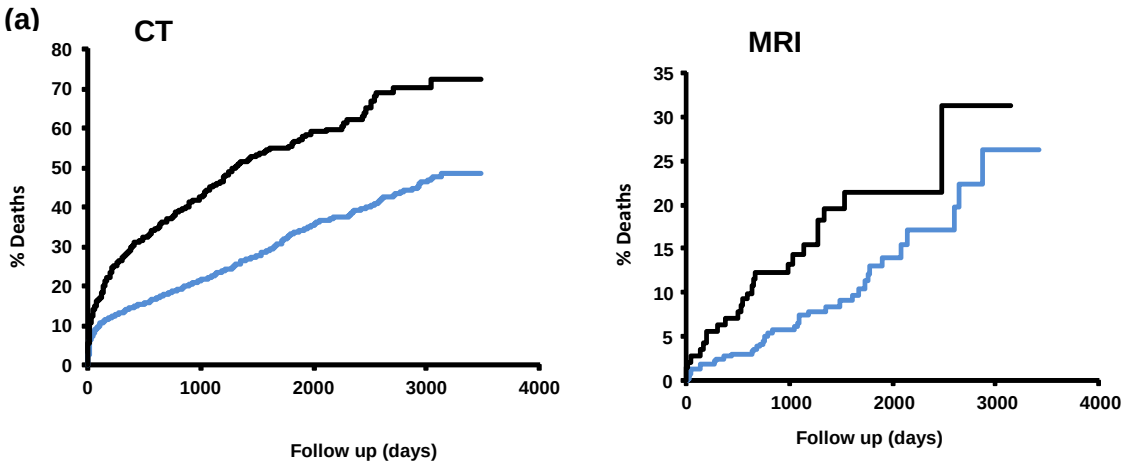
Table 8.1 Risk of death from any cause, according to presence of leukoaraiosis on CT scan at entry in the study, and stratifying by age. Cofactors entered in the model besides leukoaraiosis were age and sex (Model 1) and age, sex, history of ischaemic heart disease, diabetes, history of atrial fibrillation, peripheral vascular disease, hypertension, current smoking and NIHSS of the first event (Model 2)

Patients	Leukoaraiosis (LA)		Oxford Scale		ARWMC scale		van Swieten scale	
			HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Whole cohort	**Any LA**	Mod1	**1.47 (1.24 -1.74)**	**<.0001**	**1.38 (1.11-1.71)**	**0.004**	**1.30 (1.07-1.58)**	**0.010**
		Mod2	**1.45 (1.22-1.73)**	**<.0001**	**1.36 (1.09-1.69)**	**0.007**	**1.24 (1.02-1.51)**	**0.029**
	Mod/Sev LA	Mod1	**1.43 (1.21-1.68)**	**<.0001**	**1.36 (1.15-1.61)**	**<.0001**	**1.37 (1.16-1.61)**	**<.0001**
		Mod2	**1.48 (1.26-1.75)**	**<.0001**	**1.34- (1.13-1.58)**	**0.001**	**1.36 (1.15-1.61)**	**<.0001**
Under 75	**Any LA**	Mod1	**1.63 (1.15-2.31)**	**0.006**	**1.59 (1.03-2.44)**	**0.036**	**1.47 (1.01-2.14)**	**0.042**
		Mod2	**1.60 (1.12-2.28)**	**0.009**	**1.78 (1.15-2.76)**	**0.010**	1.46 (1.00-2.12)	0.05
	Mod/Sev LA	Mod1	**1.74 (1.15-2.63)**	**0.009**	**1.62 (1.04-2.51)**	**0.033**	**1.61 (1.05-2.47)**	**0.028**
		Mod2	**1.85 (1.21-2.83)**	**0.005**	**1.70 (1.08-2.67)**	**0.022**	**1.69 (0.10-2.61)**	**0.019**
75 and over	**Any LA**	Mod1	**1.43 (1.17-1.73)**	**<.0001**	**1.31 (1.02-1.69)**	**0.035**	1.24 (0.99-1.56)	0.66
		Mod2	**1.39 (1.14-1.69)**	**0.001**	1.28 (0.99-1.66)	0.06	1.20 (0.95-1.51)	0.12
	Mod/Sev LA	Mod1	**1.40 (1.18-1.67)**	**<.0001**	**1.33 (1.11-1.59)**	**0.002**	**1.33 (1.11-1.59)**	**0.002**
		Mod2	**1.43 (1.19-1.70)**	**<.0001**	**1.29 (0.07-1.55)**	**0.007**	**1.31 (0.10-1.58)**	**0.003**

Table 8.2. Cox regression analyses for HRs of death from any cause in presence of excess of WMC for age (univariate) and in presence of excess of WMC for age, adjusted for age, sex, and all the vascular risk factors listed above in figure 3 (multivariate).

			Whole population		< 75		≥ 75	
			HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
CT	**Oxford**	Univ.	**1.29 (2.04-1.60)**	**0.019**	**1.92 (1.27-2.88)**	**0.002**	**1.32 (1.03-1.71)**	**0.029**
		Multiv.	**1.37 (1.11-1.71)**	**0.004**	**1.72 (1.12-2.63)**	**0.013**	**1.31 (1.01-1.70)**	**0.039**
	ARWMC	Univ.	**1.41 (1.15-1.72)**	**0.001**	**1.87 (1.23-2.86)**	**0.004**	**1.33 (1.06-1.67)**	**0.016**
		Multiv.	**1.34 (1.10-1.64)**	**0.005**	**1.60 (1.02-2.51)**	**0.039**	**1.34 (1.06-1.69)**	**0.013**
	van Swieten	Univ.	**1.80 (1.52-2.14)**	**<0.0001**	**2.02 (1.35-3.01)**	**0.001**	**1.54 (1.27-1.86)**	**<0.0001**
		Multiv.	**1.41 (1.18-1.68)**	**<0.0001**	**1.75 (1.14-2.68)**	**0.010**	**1.37 (1.13-1.67)**	**0.002**
MRI	**Oxford**	Univ.	0.95 (0.52-1.74)	0.86	1.31 (0.51-3.32)	0.58	0.87 (0.39-1.97)	0.75
		Multiv.	0.84 (0.44-1.61)	0.60	0.77 (0.27-2.24)	0.64	0.90 (0.38-2.11)	0.81
	ARWMC	Univ.	1.41 (0.80-2.47)	0.23	1.49 (0.58-3.85)	0.41	1.20 (0.59-2.41)	0.62
		Multiv.	1.32 (0.73-2.38)	0.35	1.59 (0.56-4.52)	0.38	1.21 (0.57-2.56)	0.61
	Fazekas	Univ.	1.56 (0.91-2.67)	0.11	1.53 (0.62-3.80)	0.36	1.62 (0.83-3.16)	0.16
		Multiv.	1.35 (0.77-2.36)	0.30	1.07 (0.40-2.86)	0.90	1.60 (0.79-3.28)	0.20

Figure 8.2 Kaplan-Meier curves (1-survival) of death (any cause) at follow up, respectively for CT-detected leukoaraiosis (left) and MRI-detected leukoaraiosis (right), including deaths in the first 30 days (a) or excluding them (b). The blue line represents patients with no or mild leukoaraiosis, the black line represents patients with moderate-severe leukoaraiosis.



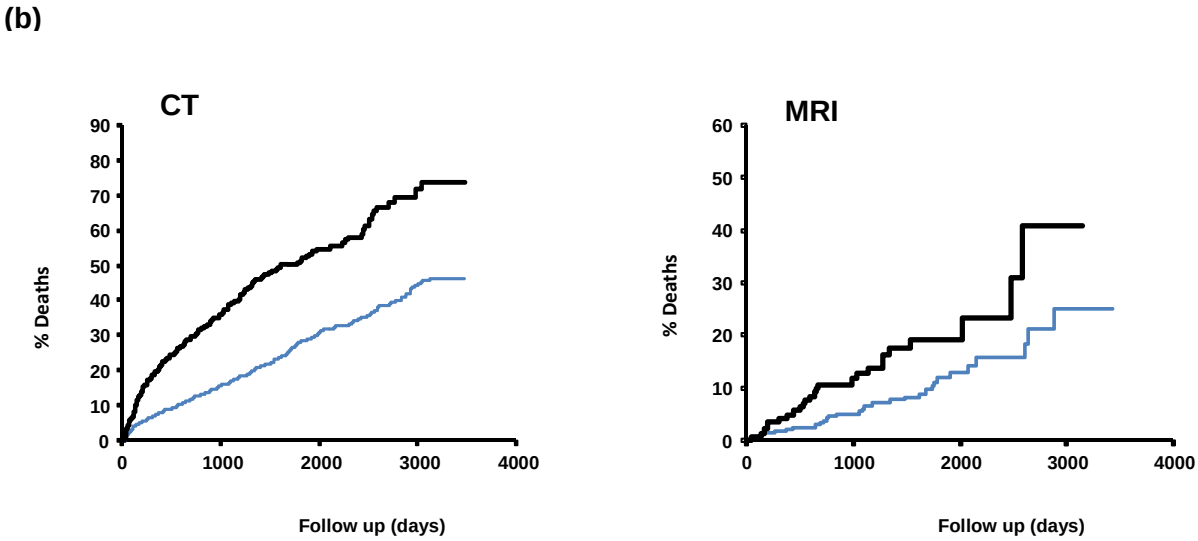


Table 8.3 Risk of death stratified as Vascular (cardiac, stroke, PVD) and Non Vascular death (all other causes) according to presence of leukoaraiosis on CT scan at entry in the study, and stratifying by age. Cofactors entered in the model besides leukoaraiosis were age and sex (Model 1) and age, sex, history of ischaemic heart disease, diabetes, history of atrial fibrillation, peripheral vascular disease, hypertension, current smoking and NIHSS of the first event (Model 2)

	Patients	Leukoaraiosis (LA)		Oxford Scale		ARWMC scale		van Swieten scale	
				HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Vascular	**Whole cohort**	**Any LA**	Mod1	**1.29 (1.01-1.65)**	**0.040**	**0.70 (0.51-0.97)**	**0.032**	0.83 (0.63-1.09)	0.17
			Mod2	1.28 (1.00-1.65)	0.05	0.75 (0.54-1.05)	0.09	0.92 (0.69-1.22)	0.56
		Mod/Sev LA	Mod1	**1.30 (1.04-1.62)**	**0.023**	1.07 (0.85-1.34)	0.59	1.18 (0.94-1.49)	1.18
			Mod2	**1.27 (1.01-1.60)**	**0.041**	1.08 (0.85-1.37)	0.51	1.13 (0.89-1.43)	0.33
	Under 75	**Any LA**	Mod1	1.28 (0.73-2.25)	0.40	0.48 (0.21-1.08)	0.08	0.59 (0.32-1.09)	0.09
			Mod2	1.67 (0.92-3.01)	0.09	0.52 (0.21-1.29)	0.16	0.81 (0.41-1.59)	0.53
		Mod/Sev LA	Mod1	1.03 (0.52-2.05)	0.93	0.71 (0.33-1.53)	0.38	0.90 (0.42-1.90)	0.78
			Mod2	1.15 (0.56-2.36)	0.70	0.90 (0.39-2.04)	0.79	1.26 (0.56-2.84)	0.58
	Over 75	**Any LA**	Mod1	**1.35 (1.02-1.77)**	**0.038**	0.79 (0.55-1.14)	0.21	0.91 (0.66-1.26)	0.58
			Mod2	1.20 (0.90-1.60)	0.23	0.80 (0.55-1.17)	0.25	0.88 (0.63-1.21)	0.43
		Mod/Sev LA	Mod1	**1.42 (1.11-1.82)**	**0.005**	1.15 (0.90-1.48)	0.28	1.28 (0.99-1.64)	0.06
			Mod2	**1.32 (1.03-1.70)**	**0.029**	1.11 (0.86-1.44)	0.42	1.11 (0.86-1.44)	0.43
Non Vascular	**Whole cohort**	**Any LA**	Mod1	1.30 (1.00-1.68)	0.05	0.86 (0.62-1.20)	0.38	**1.40 (1.09-1.80)**	**0.006**
			Mod2	**1.40 (1.07-1.84)**	**0.014**	0.89 (0.64-1.24)	0.49	1.05 (0.77-1.44)	0.74
		Mod/Sev LA	Mod1	**1.59 (1.23-2.05)**	**<.0001**	1.17 (0.90-1.51)	0.24	1.07 (0.83-1.38)	0.62
			Mod2	**1.66 (1.28-2.16)**	**<.0001**	1.21 (0.93-1.58)	0.16	1.09 (0.84-1.41)	0.53
	Under 75	**Any LA**	Mod1	1.49 (0.88-2.53)	0.14	0.90 (0.46-1.74)	0.75	0.97 (0.53-1.77)	0.93
			Mod2	**1.76 (1.00-3.08)**	**0.048**	1.25 (0.60-2.58)	0.55	1.06 (0.63-2.66)	0.49
		Mod/Sev LA	Mod1	0.90 (0.48-1.70)	0.74	0.87 (0.45-1.69)	0.69	0.94 (0.48-1.85)	0.86
			Mod2	0.98 (0.50-1.91)	0.95	0.98 (0.46-2.08)	0.96	1.10 (0.51-2.34)	0.81
	Over 75	**Any LA**	Mod1	1.30 (0.96-1.77)	0.10	0.85 (0.58-1.27)	0.43	0.97 (0.67-1.40)	0.88
			Mod2	1.34 (0.97-1.84)	0.08	0.86 (0.57-1.29)	0.46	0.98 (0.67-1.43)	0.98
		Mod/Sev LA	Mod1	**1.89 (1.41-2.54)**	**<.0001**	1.25 (0.94-1.67)	0.13	1.11 (0.84-1.48)	0.46
			Mod2	**1.93 (1.42-2.61)**	**<.0001**	1.28 (0.95-1.73)	0.11	1.10 (0.82-1.47)	0.53

Table 8.4. Cox regression analysis for HRs of dying from a vascular or a non vascular death in presence of excess of white matter changes for age (univariate) and also after adjustment for age, sex, vascular risk factors and NIHSS of the first event

			Whole population		< 75		≥ 75	
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Vascular	**Oxford**	Univ.	**1.41 (1.08-1.85)**	**0.013**	**2.02 (1.15-3.56)**	**0.015**	**1.48 (1.08-2.02)**	**0.015**
		Multiv.	1.25 (0.95-1.64)	0.12	**2.00 (1.10-3.63)**	**0.024**	1.18 (0.86-1.68)	0.32
	ARWMC	Univ.	1.30 (0.99-1.71)	0.06	1.52 (0.80-2.86)	0.20	**1.28 (0.94-1.73)**	**0.115**
		Multiv.	1.24 (0.94-1.64)	0.13	1.30 (0.72-2.72)	0.33	1.30 (0.95-1.78)	0.10
	van Swieten	Univ.	**1.74 (1.38-2.19)**	**<0.0001**	1.60 (0.88-2.92)	0.12	**1.54 (1.20-1.97)**	**0.001**
		Multiv.	1.21 (0.95-1.53)	0.12	1.41 (0.74-2.67)	0.29	1.23 (0.95-1.59)	0.12
Non Vascular	**Oxford**	Univ.	1.22 (0.88-1.70)	0.24	**2.10 (1.20-3.68)**	**0.009**	1.16 (0.76-1.77)	0.51
		Multiv.	1.26 (0.90-1.78)	0.18	**2.00(1.11-3.59)**	**0.021**	1.05 (0.68-1.65)	0.80
	ARWMC	Univ.	**1.58 (1.18-2.11)**	**0.002**	**2.39 (1.37-4.18)**	**0.002**	**1.41 (1.00-1.99)**	**0.050**
		Multiv.	**1.52 (1.13 -2.04)**	**0.005**	**2.03 (1.13-3.65)**	**0.018**	**1.46 (1.03-2.07)**	**0.033**
	van Swieten	Univ.	**1.87 (1.45-2.42)**	**<0.0001**	**2.57 (1.51-4.37)**	**<0.0001**	**1.52 (1.14-2.03)**	**0.005**
		Multiv.	**1.49 (1.15-1.93)**	**0.003**	**2.20 (1.25-3.88)**	**0.006**	**1.37 (1.02-1.85)**	**0.040**

8.3.2 White matter changes and risk of myocardial infarction

Patients in years of study 1-8 suffered a total of 86 myocardial infarctions during the study period up to 25th October 2011 (58 among patients older than 75 and 28 in patients younger than 75). When considering the type of stroke at entry, myocardial infarction happened in 4.8% of all the cardioembolic and 4.8% of all the small vessel disease type of stroke at entry, in 7.9% of the large arteries type of stroke at entry, and in 3.3% of the patients entered in the study for an undetermined type of stroke or with multiple possible etiologies, or with other type of strokes. Presence of white matter changes on CT seemed to be an independent risk factor for occurrence of myocardial infarction in the younger patients when all the types of stroke were considered, even though the associations were not reproducible with more severe degrees of white matter changes. The association was significant when white matter changes were measured with the ARWMC scale (HR 2.57, 95% CI 1.05-6.30, p=0.04) and with the van Swieten scale (3.64, 1.46-9.05, p=0.006), but there was only a positive trend with the Oxford scale (1.96, 0.87-4.42, p=0.11) (table 8.5). When adjusting further for age, repeating the analysis with the value of white matter changes in excess for age, no significant association between white matter changes and risk of myocardial infarction emerged, even though there was a positive trend (table 8.6). When subdividing the patients according to the type of stroke at entry in the study the number of patients in each group fell considerably and made the statistical meaning of the analyses difficult to interpret, and therefore I have omitted this analysis from the thesis.

Table 8.5 Risk of myocardial infarction in patients presenting with leukoaraiosis on their initial CT scan in the study

		Oxford Scale		ARWMC scale		van Swieten scale	
		HR (95%CI)	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
Whole cohort	**Any LA**	0.89 (0.54-1.45)	0.63	1.36 (0.77-2.41)	0.29	1.56 (0.89-2.74)	0.13
	Mod/Sev LA	1.12 (0.67-1.89)	0.66	1.18 (0.70-2.00)	0.54	1.02 (0.61-1.70)	0.94
Under 75	**Any LA**	1.96 (0.87-4.42)	0.11	**2.57 (1.05-6.30)**	**0.04**	**3.64 (1.46-9.05)**	**0.01**
(28 pts)	**Mod/Sev LA**	1.85 (0.72-4.85)	0.21	1.65 (0.63-4.32)	0.31	1.01 (0.36-2.83)	0.98
Over 75	**Any LA**	0.58 (0.32-1.05)	0.07	0.88 (0.44-1.78)	0.73	0.82 (0.42-1.61)	0.57
(58 pts)	**Mod/Sev LA**	0.95 (0.51-1.75)	0.87	0.99 (0.53-1.83)	0.97	0.97 (0.53-1.76)	0.92

Table 8.6 Multivariate Cox regression analysis. Risk of myocardial infarction in patients with excess of white matter changes for age on CT or MRI scan at entry. Variables entered, besides white matter changes, are: age, sex, hypertension, history of myocardial infarction or angina at entry in the study, hyperlipidaemia, peripheral vascular disease, current smoking.

		Whole population		< 75		≥ 75	
		HR (95% CI)	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
CT	**Oxford**	1.17 (0.60-2.30)	0.64	2.23 (0.89-5.57)	0.09	0.57 (0.17-1.86)	0.35
	ARWMC	1.55 (0.87-2.75)	0.14	1.76 (0.71-4.37)	0.23	1.41 (0.65-3.05)	0.39
	van Swieten	1.38 (0.82-2.33)	0.23	1.40 (0.56-3.52)	0.47	1.28 (0.66-2.46)	0.47
MRI	**Oxford**	0.78 (0.21-2.96)	0.72	0.18 (0.02-1.76)	0.14	2.21 (0.39-12.7)	0.37
	ARWMC	0.74 (0.20-2.74)	0.65	0.20 (0.02-1.97)	0.17	1.96 (0.30-12.7)	0.48
	Fazekas	1.23 (0.41-3.72)	0.71	0.17 (0.02-1.53)	0.11	2.28 (0.37-14.0)	0.38

8.3.3 White matter changes and dementia in OXVASC

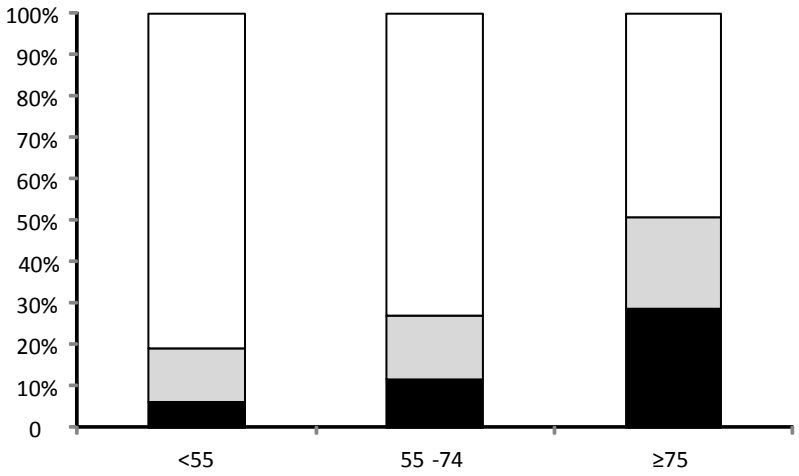
8.3.3.1 MMSE – age and WMC-specific distribution of scores in OXVASC

In our population 1313 patients had an available Mini Mental State Examination (MMSE) at one month from their event, and 1009 at one year. Among the patients with CT scan evaluated with the Oxford scale, a total of 1168 patients had MMSE at one month, and 896 at one year. Among the patients with CT evaluation according to the van Swieten and the ARWMC scale, 1089 patients had MMSE at one month and 841 had also the one year follow up. Among patients with MRI evaluated with the Oxford scale, 413 patients

had MMSE at one month and 329 also at one year, while among patients with MRI evaluated with the ARWMC and the Fazekas scale, 388 had MMSE at one month and 309 had also MMSE at one year. The MMSE score was strongly influenced by the age of patients, with the majority of the scores lower than 27 in patients older than 75. The age-specific distribution was similar at baseline and at one year, with a higher proportion of patients under the score of 27 in the age group over 75 at the one year follow-up (fig.8.3). Looking at the distribution of the MMSE scores within different degrees of leukoaraiosis, a lower score on the MMSE was more likely to be found among patients with higher degrees of leukoaraiosis. The difference was mainly between presence and absence of any degree of leukoaraiosis when this was assessed with CT scan, and between severe and anything below severe when this was assessed with MRI (Fig. 8.4). This distribution was likely to reflect the sensitivity of the tests, with MRI being more sensitive and therefore showing some effect only with higher degrees of white matter changes.

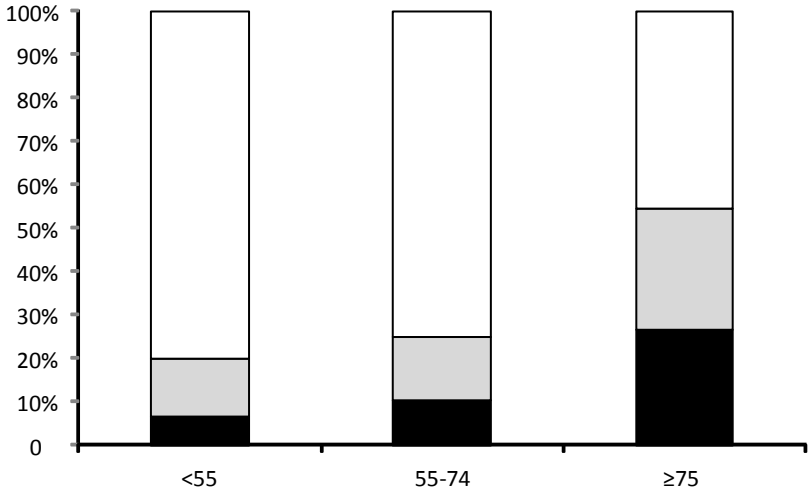
Fig 8.3 Age-specific distribution of MMSE scores at (a) the 1 month FU, in the OXVASC population (1313 cases) and (b) the 1 year FU (1009 cases). Scores are grouped into 0-23 (black), 24-26 (grey) and 27-30 (white area)

(a)



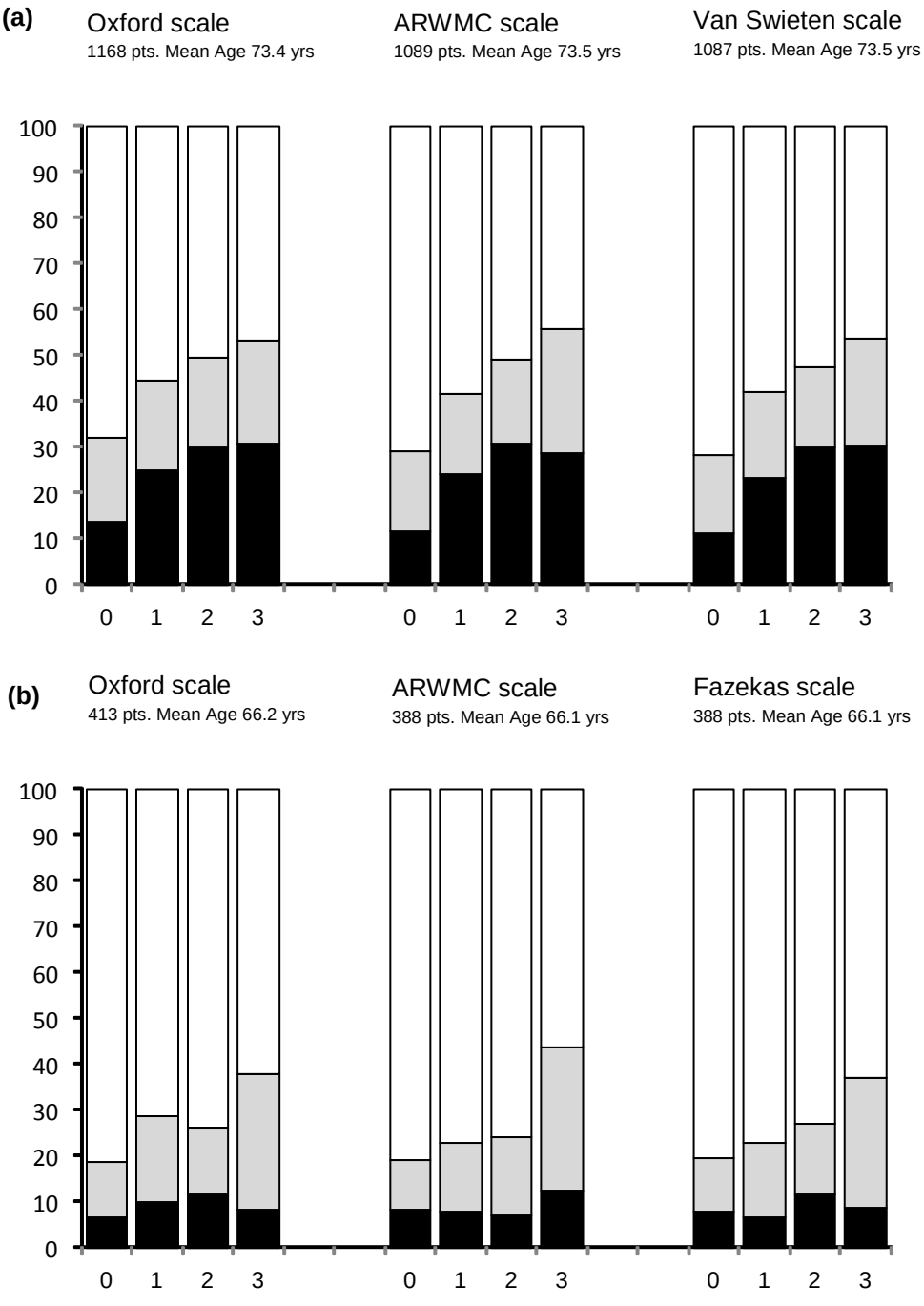
	<55	55 -74	≥75
< 27	25 (18.9%)	144 (26.8%)	327 (50.8%)
<24	8	62	184

(b)



	<55	55-74	≥75
< 27	22 (19.8%)	106 (24.8%)	255 (54.3%)
<24	5	44	124

Fig 8.4 White matter changes-specific distribution of MMSE scores at the 1 month FU, in the OXVASC population (1313 cases). Severity of leukoaraiosis on CT (a) and on MRI (b) is rated as “none = 0”, “mild =1”, “moderate =2” and “severe =3” in each of the scales used. MMSE scores are grouped into 0-23 (black), 24-26 (grey) and 27-30 (white area)



8.3.3.2 Associations between MMSE scores and severity of WMC

Looking at the association between low MMSE scores and white matter changes, a weak association is found between scores lower than 24 at one month and at one year from the event, and severe white matter changes. This is mainly accounted for by patients under 75 years of age (tables 8.7-8.10).

Table 8.7 Odds Ratios for MMSE <24 at one month from the event. For each rating scale leukoaraiosis is considered as present versus absent (any) or moderate and severe versus none or mild. Data adjusted for age (continuous) and sex.

		Whole cohort		Under 75		75 and older	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
CT scans							
Oxford	**Any**	**1.44 (1.04-2.00)**	**0.027**	1.53 (0.88-2.65)	0.130	1.39 (0.93-2.10)	0.11
	Mod/Sev	**1.39 (1.00-1.93)**	**0.047**	1.79 (0.92-3.47)	0.09	1.29 (0.89-1.88)	0.18
ARWMC	**Any**	**1.71 (1.19-2.47)**	**0.004**	**2.00 (1.13-3.55)**	**0.018**	1.57 (0.97-2.54)	0.07
	Mod/Sev	1.36 (0.98-1.91)	0.07	1.34 (0.64-2.78)	0.44	1.35 (0.92-1.99)	0.12
van Swieten	**Any**	**1.80 (1.24-2.61)**	**0.002**	**1.94 (1.09-3.46)**	**0.024**	1.74 (1.06-2.84)	0.03
	Mod/Sev	**1.42 (1.02-1.97)**	**0.039**	1.44 (0.72-2.87)	0.30	1.39 (0.95-2.04)	0.09
MRI scans							
Oxford	**Any**	1.06 (0.47-2.36)	0.89	1.31 (0.47-3.66)	0.61	0.70 (0.20-2.47)	0.58
	Mod/Sev	0.95 (0.43-2.06)	0.89	0.87 (0.26-2.88)	0.82	1.07 (0.36-3.15)	0.91
ARWMC	**Any**	0.65 (0.29-1.45)	0.30	0.49 (0.17-1.43)	0.19	1.10 (0.27-4.39)	0.90
	Mod/Sev	0.72 (0.31-1.70)	0.46	1.29 (0.38-4.42)	0.68	0.43 (0.13-1.38)	0.16
Fazekas	**Any**	0.57 (0.24-1.35)	0.20	0.60 (0.20-1.80)	0.37	0.49 (0.11-2.12)	0.34
	Mod/Sev	0.95 (0.42-2.12)	0.89	1.74 (0.57-5.34)	0.33	0.57 (0.19-1.76)	0.33

Table 8.8 Odds Ratios for MMSE <24 at one month from the event, using the values of excess of white matter changes by age according to the 4 scales. Data are adjusted for age and sex.

		All Ages		< 75		≥ 75	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
CT	**Oxford**	1.40 (0.93-2.13)	0.11	1.64 (0.85-3.16)	0.14	1.30 (0.75-2.24)	0.35
	ARWMC	1.15 (0.76-1.72)	0.51	1.41 (0.70-2.84)	0.34	1.06 (0.64-1.75)	0.84
	van Swieten	1.30 (0.91-1.85)	0.16	1.49 (0.77-2.88)	0.24	1.22 (0.80-1.87)	0.36
MRI	**Oxford**	0.89 (0.37-2.12)	0.79	0.77 (0.24-2.47)	0.66	0.97 (0.25-3.81)	0.96
	ARWMC	0.77 (0.32-1.88)	0.57	1.04 (0.32-3.39)	0.95	0.49 (0.12-1.93)	0.31
	Fazekas	0.99 (0.44-2.25)	0.98	1.38 (0.48-3.98)	0.56	0.57 (0.14-2.26)	0.42

Table 8.9 Odds Ratios for MMSE <24 at one year from the event. For each rating scale, white matter changes are considered as present versus absent (any) or moderate and severe versus none or mild. Data adjusted for age and sex.

		Whole cohort		Under 75		75 and older	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
CT scans							
Oxford	**Any**	**1.61 (1.09-2.38)**	**0.016**	1.57 (0.79-3.11)	0.20	1.63 (1.00-2.64)	0.05
	Mod/Sev	1.43 (0.96-2.11)	0.08	1.43 (0.62-3.33)	0.41	1.44 (0.91-2.26)	0.12
ARWMC	**Any**	1.27 (0.84-1.94)	0.26	1.29 (0.65-2.55)	0.47	1.28 (0.74-2.20)	0.38
	Mod/Sev	**1.49 (1.00-2.22)**	**0.049**	2.12 (0.97-4.66)	0.06	1.33 (0.84-2.10)	0.23
van Swieten	**Any**	1.48 (0.96-2.28)	0.07	1.40 (0.70-2.80)	0.34	1.57 (0.89-2.79)	0.12
	Mod/Sev	1.46 (0.99-2.16)	0.06	1.91 (0.87-4.20)	0.11	1.35 (0.86-2.11)	0.20
MRI scans							
Oxford	**Any**	2.18 (0.92-5.18)	0.08	1.67 (0.54-5.13)	0.38	3.67 (0.76-17.8)	0.11
	Mod/Sev	1.56 (0.75-3.27)	0.24	1.03 (0.30-3.57)	0.97	2.18 (0.79-5.99)	0.13
ARWMC	**Any**	1.33 (0.55-3.22)	0.52	1.02 (0.32-3.26)	0.97	2.62 (0.53-13.0)	0.24
	Mod/Sev	1.76 (0.81-3.86)	0.16	1.39 (0.39-4.93)	0.61	1.88 (0.65-5.41)	0.25
Fazekas	**Any**	1.18 (0.46-3.01)	0.74	1.22 (0.37-4.06)	0.75	1.22 (0.23-6.45)	0.82
	Mod/Sev	1.43 (0.66-3.08)	0.36	1.53 (0.46-5.14)	0.49	1.48 (0.52-4.17)	0.46

Table 8.10 Odds Ratios for MMSE <24 at one year from the event, using the values of excess of leukoaraiosis by age according to the six scales. Data are adjusted for age and sex.

		All Ages		< 75		≥ 75	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
CT	**Oxford**	1.44 (0.87-2.38)	0.15	1.37 (0.59-3.16)	0.46	1.61 (0.84-3.08)	0.15
	ARWMC	1.27 (0.80-2.04)	0.31	1.97 (0.91-4.27)	0.08	1.06 (0.58-1.95)	0.85
	van Swieten	1.49 (0.98-2.26)	0.07	2.02 (0.95-4.30)	0.07	1.34 (0.80-2.25)	0.27
MRI	**Oxford**	1.48 (0.68-3.24)	0.33	0.89 (0.27-2.98)	0.85	3.03 (0.93-9.84)	0.07
	ARWMC	1.69 (0.80-3.59)	0.17	1.12 (0.33-3.77)	0.86	1.85 (0.63-5.46)	0.27
	Fazekas	1.50 (0.68-3.27)	0.31	1.24 (0.39-3.94)	0.71	2.45 (0.84-7.15)	0.10

When considering the worsening of MMSE scores between one month and one year from the event (at least 2 points), the associations with white matter changes became stronger. These are reported in table 8.11, and again, they are mainly seen in the younger patients.

Table 8.11 Worsening of MMSE of at least 2 points between one month and one year from the event. Age and sex have also been entered in the model

		All Ages		< 75		≥ 75	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
CT	**Oxford**	**1.75 (1.13-2.70)**	**0.012**	**2.00 (1.07-3.73)**	**0.030**	1.58 (0.99-1.08)	0.14
	ARWMC	1.35 (0.89-2.05)	0.16	**2.12 (1.15-3.92)**	**0.017**	0.95 (0.53-1.69)	0.85
	van Swieten	1.23 (0.83-1.83)	0.30	**1.95 (1.07-3.56)**	**0.029**	0.91 (0.55-1.51)	0.91
MRI	**Oxford**	**1.91 (1.03-3.57)**	**0.04**	2.02 (0.88-4.61)	0.10	2.38 (0.84-6.78)	0.10
	ARWMC	1.55 (0.82-2.91)	0.18	1.35 (0.56-3.25)	0.50	1.88 (0.72-4.93)	0.20
	Fazekas	1.58 (0.86-2.92)	1.14	1.55 (0.67-3.57)	0.31	1.93 (0.73-5.07)	0.19

8.4 Discussion and conclusions

This is the first large population-based study on the prognostic value of white matter changes on CT or MRI in patients with stroke or TIA.

After correcting for age and for the most common vascular risk factors, I did not find any associations between white matter changes and risk of myocardial infarction. This is in keeping with what mainly found previously in literature, and with the fact that patients with leukoaraiosis are more likely to show the effects of vascular risk factors on small vessels, and seem therefore less susceptible to large artery type of events.

Severe white matter changes on scan at entry were strongly associated with a higher risk of death from any cause following a stroke or TIA. When the causes of death were analysed separately, white matter changes appeared more often associated with non vascular type of deaths, especially in the younger patients (under 75). It was impossible to establish a relation between severe white matter changes and a particular cause of death, and when considering the possibility of an association between white matter changes and depression or anxiety, I could not find any. This finding, in association with the fact that white matter changes appear to increase the burden of disability both before and after a

stroke, induces to think that the increase in mortality risk could be secondary to an increased general frailty and susceptibility to any kind of death. It has been previously shown that severe leukoaraiosis is mainly found in patients with lacunar infarction at entry. Beyond the associations with other vascular risk factors, which are similar to those of the other types of stroke at entry, the lacunar-type patients seem less prone to develop large vessel type of cardio and cerebro-vascular conditions, which are mainly responsible for sudden vascular death.

A lower MMSE at baseline was not associated with higher degrees of white matter changes, but I found a strong association with worsening of MMSE score at one year from the vascular event, in patients younger than 75. This is again in keeping with the finding of a higher risk of worsening disability score at one year from the event in this group of patients, as the decline in cognition is obviously related to a decline in level of autonomy. The availability of MMSE only, as a tool for evaluating the cognitive decline at one year, is a limitation of my study. It is well established that MMSE is not appropriate to detect fine deficits of planning and executive functions, which are mainly affected in patients with severe white matter changes.[22] The Montreal Cognitive Assessment is a better tool on this respect, and is currently administered to OXVASC patients in conjunction with MMSE. Future studies within OXVASC will be able to use this scale to explore more subtle cognitive changes in association with white matter changes. The emerging of an association even with the use of a less sensitive tool makes the finding more meaningful.

Another consideration needs to be made with regards to the assessment of depression and anxiety in our population. I looked into these associations mainly to identify a possible explanation for the increased risk of non-vascular death in our subjects affected by severe white matter changes. Again, the tools used to identify any depressive symptoms were limited to self-assessment questionnaires or to previous clinical diagnosis or treatment. The lack of a more sensitive assessment scale limits the value of this study to the

association with obvious clinical depression, which is often not the case in patients with subcortical type of ischaemic changes.

As a last limitation, already mentioned in other chapters of this thesis, is the fact that my results are mainly limited to CT-detected white matter changes. Data concerning patients evaluated with MRI were only partial, and therefore not providing robust enough associations.

Despite a few limitations, my study is the first to explore in detail the prognostic value of white matter changes with regards to the risk of myocardial infarction, mortality, and cognitive decline in a large population-based cohort of patients with stroke or TIA. The finding of an increased risk of non-vascular mortality and of cognitive decline, especially in the youngest group affected by severe white matter changes, is particularly important for future research on prevention and also for possible approaches to rehabilitation after different types of strokes. At present, patients presenting a lower degree of physical disability immediately after a stroke are those more neglected from a rehabilitation point of view. It might well be the case that in the medium-long term they are those who indeed need more attentions, in terms of cognitive and behavioral type of rehabilitation.

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Chapter 9

Conclusions and future research

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9.0 Summary

I have started this thesis with a few questions in mind: can leukoaraiosis be definitely said to be a risk factor for stroke, or is it merely a marker of brain ageing? Are there any differences between genders in the prevalence of white matter changes? Is leukoaraiosis important in influencing the severity of stroke and the disability following this? Is leukoaraiosis involved in the risk of premature death, development of cardiovascular disease, dementia? I tried to answer these questions by reviewing the existing literature and by studying a large population-based cohort of stroke and TIA patients from the OXVASC Study.[1]

In the first chapter, after a brief introduction on the definition and pathogenesis of white matter changes, I reviewed the existing literature on prevalence of leukoaraiosis. A considerable heterogeneity was evident, with prevalence rates ranging from 5.3 to 98.6% according to different population settings.[2,3] I grouped the studies according to their use of CT or MRI and, within each of these groups, according to population settings. Despite this, heterogeneity remained within groups. Studies on healthy subjects or on the general population were carried out with MRI, and the prevalence reported ranged between 27% (Rotterdam Study, 1994)[4] and 98.6% (EVA-MRI Study, 2001)[3], with the largest studies (those with a population of at least 1000 subjects),[4,5,6] reporting an average prevalence of 92% in patients over the age of 60. I went through the single studies and, beside the different age and settings of the populations in study, I explained the heterogeneity on the basis of: 1.The evaluation technique (i.e. volumetric versus visual), 2. Different scales, and therefore different thresholds, in considering white matter changes being of significance, 3. Different machine generations and, for MRI only, 4. Different magnetic field strengths. I then introduced the OXVASC Study as my research setting, and described the CT and MRI evaluation process and the scales chosen to perform this (van Swieten, ARWMC and Oxford scale for CT scans, Fazekas, ARWMC and Oxford for

MRI). I explained the adjustment by age that I used to study correlations with white matter changes within each of the scales used, as a very strong correlation exists between age and white matter changes and therefore the same level of significance cannot be used for young and elderly patients. In the end, I looked into inter and intra-rater and inter-scales reliability, finding substantial-to-good kappa values. I also assessed the reliability of CT versus MRI in 416 patients, using the same scale (Oxford scale), and found this to be good (weighted kappa 0.69 to 0.72, according to the age of patients).

In chapter 2, I examined the question regarding possible gender differences in prevalence and severity of leukoaraiosis. I did a systematic review of the literature on the subject, and then assessed age-specific prevalence of white matter changes in women and men separately in OXVASC. The systematic review showed higher rates of leukoaraiosis in women, only when stroke patients were considered. In OXVASC, I found that leukoaraiosis was equally prevalent between genders when adjusting for age. Leukoaraiosis was more severe in older women (over 75), but was also associated with earlier mortality, which suggested that this finding could be biased by a stronger female representation in that age group. I also studied the age and sex-specific distribution of leukoaraiosis in a comparison stroke and TIA clinic cohort investigated with MRI, and the results were comparable with our population-based cohort. I therefore showed that there was no evidence of a greater susceptibility of women to white matter ischemia, coming from our population-based cohort of stroke and TIA patients.

Chapter 3 and 4 focused on the relationship between hypertension and leukoaraiosis. Hypertension has long been recognised to be strongly associated with leukoaraiosis, and is also the main risk factor for stroke, after ageing. I reviewed the literature on the subject doing a systematic review and meta-analysis, and then I studied the age and sex-specific association between leukoaraiosis and hypertension in the stroke and TIA patients within OXVASC. I looked into the associations of severity of leukoaraiosis with the history of

hypertension and also with blood pressure variables (mean systolic and diastolic, maximum systolic and diastolic and most recent systolic and diastolic blood pressure) recorded during a 10 years period prior to the entry in the study. General practitioner records had been searched to collect these data. The association with history of hypertension emerged both from the systematic review and from the OXVASC study. Interestingly, this association was stronger in the younger patients and tended to reduce with age, and this was also confirmed by the meta-analysis of previous studies. When looking at the association with specific blood pressure components, mean systolic and diastolic blood pressure were more strongly associated than the maximum and the most recent values. Diastolic blood pressure emerged to be the strongest association, persisting also in the eldest cohorts, while the association with systolic blood pressure tended to diminish in the oldest patients. From the ten year pre-morbid data, I also derived information regarding blood pressure variability, and studied the age-specific association between white matter changes and blood pressure variability (both standard deviation and average real variability) and pulse pressure. My analyses did not show any association between leukoaraiosis and these blood pressure measures.

In the following chapter (5), I examined the relationship between white matter changes and other vascular risk factors, namely: hyperlipidaemia, diabetes, smoking, atrial fibrillation, peripheral vascular disease, significant carotid stenosis, ischaemic heart disease, previous stroke. I first did a systematic review of the literature, and then analysed these relationships within the first 8 years of OXVASC. Both from the review of literature and from the OXVASC analysis, history of previous stroke was the strongest association with leukoaraiosis, while no strong and consistent associations were found with the other risk factors.

In chapter 6, I explored more in detail the age-specific relation between leukoaraiosis, vascular risk factors and different stroke subtypes, according to the TOAST classification.[7]

Leukoaraiosis was strongly associated with the small vessel type of stroke, independently from all the other vascular risk factors. The association was age-dependent, and emerged in subjects over 65 years of age.

Chapter 7 and 8, finally, dealt with the prognostic relevance of leukoaraiosis in patients with stroke. I found that leukoaraiosis was not associated with risk of recurrent ischaemic stroke, but there was a positive trend with increased risk of recurrent haemorrhagic stroke. From my analyses leukoaraiosis was not associated with the severity of the first stroke, assessed by the NIHSS,[8] but it was associated with both the pre-morbid and the one year post stroke level of disability assessed by the mRS.[9,10] I found that white matter changes were strongly associated with risk of early death in patients with stroke and TIA, but I could not identify any specific cause of this. The risk of death was not associated with cardiovascular cause, which was also in keeping with the lack of any association between severity of white matter changes and history of ischaemic heart disease in my population. There was an association between worsening of cognition (determined as worsened MMSE[11]) at one year from the stroke and severity of white matter changes and in younger patients, which seemed to reflect the overall increased frailty of stroke patients with severe white matter changes.

9.1 Conclusions

My research has helped consolidating the existing knowledge on the meaning of leukoaraiosis in patients with stroke, and has also brought some new views, which need some further work. As I have stressed in the conclusions of each chapter, there are weaknesses, and the most obvious is perhaps having based my observations mainly on Computed Tomography data, as I did not have as many MRI evaluations available. There is a plan to repeat the analysis in a near future on MRI data, as, since 2010, MRI are performed routinely in OXVASC, and the scans are still being evaluated according to my

criteria. Another criticism to my thesis could come from the fact that I used multiple scales in all my analyses, creating perhaps some difficulties in the interpretation of the results. I did this to test the inter-scale reliability, and to see whether I could observe any systematic differences among the scales. I thought that it could be useful to show all these analysis in my results, as a way to consolidate the strength of the different scales. In fact, I think that the overall message coming across is that there are differences among the various scales, but they are minimal. All the scales, in the end, point to the same direction of associations. The Oxford scale was, especially for the CT scans, the one with the largest number of observations, even though mixed between the radiologist's and mine. I could have used this scale only, but I wanted to consolidate my findings also using scales that had previously been validated in other large studies. Having found good reliability between these scales, I am now confident to use any of them for future publications.

I have confirmed that leukoaraiosis is strongly associated with ageing, and I have shown that, differently from the common perception, white matter changes have not got a strong association with the classic vascular risk factors, apart from hypertension. Also, I have found that the association with high blood pressure is likely to be driven by higher diastolic blood pressure levels especially in young age, and the association with high systolic blood pressure tends to disappear in the older strata of the population. I have approached the question related to difference of leukoaraiosis prevalence between sexes, which had so far not been systematically studied considering age-specific associations.

It is important, though, to bear in mind that my conclusions are only applicable to patients with history of stroke or TIA, and I cannot generalize these results to the rest of the population.

I believe that more research needs to be done on the prognostic meaning of leukoaraiosis in stroke patients. This is a subject that has been long debated and has been in recent years reviewed systematically.[12] The strength of my findings lies in the size of the cohort in study and in its population-based setting. I have found that white matter changes increase the risk of death from any cause during a ten-year follow-up, and are associated with a worse outcome at one year from the event in terms of disability, but are not associated with recurrence of ischaemic stroke. The fact that our population receives an excellent secondary prevention after the first event needs to be considered when transferring these findings to different cohorts. I have not identified a specific reason behind the increased risk of death, but I have seen that patients with severe white matter changes have a worse functional and cognitive outcome at one year from the stroke. Stroke patients with leukoaraiosis appear frailer than subjects with no white matter changes, and the reasons are still not completely clear.

9.2 Future research

While working on white matter changes in the OXVASC population, I started looking into several different subjects of possible research, which have not been unfolded within my thesis for either lack of time or resources. I do not exclude the possibility of looking into these in the future, either personally or with the help of colleagues.

Cortical atrophy has not been considered in this research, and this is an important factor to take into account when we study the effect of white matter changes on brain ageing. Atrophy can be primary in degenerative disorders, or secondary to clinically manifest or silent strokes. Recent studies on the subject have advocated the complexity of measuring both cortical atrophy and white matter changes in presence of previous stroke lesions.[13] I have not considered the effect of cortical atrophy, as the OXVASC data on this are still incomplete, and are limited to a simple and not age-blinded 0-3 score. A future study

should include the automatic evaluation of brain volumes on MRI scans and use it as cofactor in the analyses on clinical associations and, especially, on cognitive decline and disability outcome after stroke.

An association study between white matter changes and microbleeds has also not been mentioned in my thesis, and needs to be done in the future. I looked into the data on microbleeds in OXVASC, but at the time of my research the MRI scans were still too few to give large enough numbers for any study on the subject, and microbleeds had not been systematically evaluated by the neuro-radiologist. Since 2010 this has been done routinely, as MRI scans with T2 Star sequences (to identify bleeds) are performed in all OXVASC patients.

The study on the association between white matter changes and post-stroke cognitive decline, which I have started and discussed in chapter 8 of this thesis, needs further work. Patients in OXVASC have been recently studied more extensively from a cognitive point of view. Data on their MOCA (Montreal Cognitive Assessment)[14] at various follow ups post stroke, in association with more extensive information collected from general practitioners and proxies regarding their pre-morbid cognitive state, will help to determine the role of white matter changes in post-stroke cognitive decline. As already mentioned, this research should be completed by the study of association with brain atrophy, in order to try and determine the role played independently by white matter changes and atrophy in post-stroke decline.[15,16]

One other possible future research is on the association between white matter changes and pro-thrombotic factors or inflammatory and neuronal damage markers in the serum of stroke and TIA patients. Possible associations could be studied in relation to different stroke outcomes, in order to try and identify possible reasons behind the worse outcome of patients with severe leukoaraiosis, which could help finding specific secondary

prevention tools for these patients. In OXVASC, blood is collected on the day of the first evaluation, usually within 5 days from the event, and various biomarkers have been routinely dosed in the serum (table 9.1). I preliminary looked at these associations within the first 1000 patients assessed with CT, and did not find any evidence of strong associations. Data from the laboratory analyses were only partial at the time I did this preliminary check. More laboratory and imaging data, with also MRI evaluations, would help clarifying possible associations.

Finally, several studies have now considered brain small vessel disease in association with other systemic signs of microvascular disease, specifically in the retina and in the kidneys,[17] and there is evidence of association between reduced glomerular filtration rate (eGFR) and white matter changes in young patients with first ever stroke.[18] The association between degrees of white matter changes and renal function (estimated GFR) still needs to be assessed in the OXVASC population, and this will be another future research.

Table 9.1 Biomarkers dosed in OXVASC patients

OXVASC Biomarkers	Brief Description
D-Dimer	Marker of active fibrinolysis
Tumour Necrosis Factor (TNF)	Inflammatory cytokine, associated with atherosclerosis
Neuron Specific Enolase (NSE)	Glycolytic enzime released by damaged neuronal cells in blood and CSF. Correlates with the volume of brain infarction in acute stroke.
Protein Z	Vit.K-dependent glycoprotein. Low levels are associated with arterial thrombosis
Fibrinogen	Glycoprotein converted into fibrin by thrombosis. Acute phase protein
ADAMTS-13	Metalloproteinase enzyme that cleaves vWF molecules. When low causes TTP
Von Willebrand Factor (vWF)	Bridging adhesion molecule that binds platelets to the sites of endothelial damage
Poly aCL	Antiphospholipid antibodies - anticardiolipin and Beta2Glycoprotein. High titres are associated with antiphodpholipid syndrome and stroke.
Fatty Acid Binding Protein (FABP)	Expressed by heart and neuronal cells
C-reactive protein (CRP)	Inflammation marker
Interleukin 6 (IL6)	Cytokine promoting the production of acute phase proteins. Also produced by smooth muscles in blood vessel walls
Prothrombin Time (PT)	Time needed by the blood to clot
Activated Partial Thromboplastin Time (APTT)	Measures the activity of the intrinsic and common pathways of coagulation
P Selectin (PSel)	Cell adhesion molecule released on activation of platelet/endothelium
CVDefSer	Antiphosphorilcoline antibodies
Brain Derived Neurotrophic Factor (BDN F)	Helps in neuroregeneration. Present also in platelets.
Glial Fibrillary Acidic Protein (GFAP)	Found in neurones
Neutrophil Gelatinase associated Lipocalin (N GaL)	Released by neutrophils as part of the inflammatory response
Thrombomodulin (TM)	Found on the endothelium. Binds thrombin and activats the protein C anticoagulant pathway
GLN/GLU	Glutamine and Glutamate. Associated with chronic fatigue post stroke

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Appendix 1

OXFORD VASCULAR STUDY (OXVASC)

Summary Protocol

Version 7: 03/03/2011

Aims

The Oxford Vascular Study has three unique aims. First, we will determine the incidence and case-fatality of stroke and acute coronary syndromes (ACS) in the same population at the same time. Second, since we are uniquely fortunate to have previous Oxford populations-based incidence studies of stroke (OCSP)[1] and acute MI (OXMIS),[2] we will be able to determine time trends in incidence and case-fatality. By comparison with follow-up data from these studies follow-up will also allow time trends in disability rates and risk of recurrent vascular events. Third, we will study differences between clinical and molecular risk factors for stroke and ACS, and identify those particularly associated with specific subtypes of ischaemic stroke. The study will also establish a core of detailed clinical and imaging data, with stored blood, that will be a valuable resource for future research into the causes of vascular disease.

Background

Why study stroke, ACS and other acute vascular events in a single population?

ACS is the leading cause of death in the developed world, causing more than twice as many deaths as stroke.[3] However, mortality data underestimate the burden of stroke. Stroke is the main cause of neurological disability in the developed world,[4] and a common cause of dementia, depression, epilepsy, falls and fractures. The incidence, case-fatality, longer-term sequelae of stroke and ACS have never been measured in the same

population at the same time. Comparison of OCSP and OXMIS suggests that mortality due to stroke is lower than that due to ACS, but overall incidence is similar, and the total clinical burden of stroke may be greater. A formal comparison would provide a firm basis on which local and national policy decisions about allocation of limited NHS funding for clinical services and limited governmental funding for medical research could be made. Dr Rothwell has highlighted the considerable imbalance in research funding between stroke and ACS.[5] NHS clinical initiatives also tend to give a higher priority to MI than to stroke.

Why measure time trends in incidence and sequelae of stroke and ACS?

Mortality due to stroke and ACS has fallen in most countries over the past four decades. However, the relative contributions of changes in incidence and case-fatality are uncertain.[6] There are no data from the UK on recent time trends in age and sex specific incidence or disability rates for stroke and ACS. However, there have been major changes over the last 20 years in life-style, primary and secondary prevention treatments, and particularly in population demographics. Reliable data on the current and projected future burdens of stroke and ACS will allow future clinical and research funds to be targeted appropriately.

Why compare risk factors for stroke and MI?

Little is known about the differences between risk factors for stroke and ACS. There are some differences in the effects of blood pressure and cholesterol, and Rothwell and colleagues have identified differences in haematological risk factors,[7,8] and similarities in markers of stability of atherosclerotic plaques.[9,10] However, more data are required. A better understanding of differences in risk factors would allow preventive strategies to be targeted effectively depending on the predominant pathology, would help to refine individual risk prediction models, and would help develop joint prevention strategies. Professor Mant has performed several studies of the feasibility of delivering primary and secondary vascular prevention services in the community.[11-14]

Risk of stroke after TIA or minor stroke

Rothwell and colleagues have recently shown that the risk of stroke after TIA or minor stroke is very high during the first few days[15], and that absolute benefits from preventative treatments fall rapidly with time after the initial event[16]. Clinical characteristics and risk factors associated with the highest risk of early stroke and reasons for delays in presentation to medical services, assessment and investigation need to be determined.

Methods

The detailed methods of the study are set out in the Case Definition and Ascertainment Protocol. However, some of the main methodological issues are also summarised below.

Approximately 2400 patients have been recruited so far. However, we propose to continue to recruit patients until 31/3/2010 in order to be able to achieve the large sample sizes necessary for many of the substudies.

Sample size calculations: The sample size required varies for the different sub-studies. Some representative calculations are given below:

1) In the studies of predictors of early recurrent stroke after TIA or minor stroke, we expect a risk of stroke of approximately 10% at 7 days and 15% at 30 days on the basis of our year 1-2 data. By April 2007, we will have data on 1000 probable or definite TIAs and minor ischaemic strokes in OXVASC with approximately 100 recurrent strokes at 7 days follow-up (or 150 if further events within 24 hours are included) and 200 events at 3 months. Potentially important characteristics, such as vertebrobasilar territory, previous evidence of large artery disease (angina, MI or PVD) or ocular events have a prevalence of about 25%. To detect a doubling in the 7-day risk of stroke associated with a characteristic with a prevalence of 25%, a total sample of 635 patients would be required for 80% power at the 95% level of confidence. For characteristics with a prevalence of

nearer 50% (e.g. male sex, known hypertension etc), a sample of 750 will give us 80% power to detect a difference in the 30-day absolute risk of stroke of 60% (e.g. 11.5% vs 18.5% - i.e. 15% overall). Thus, we will have power to begin to detect clinically important risk factors by April 2007. Given the need for 20 outcome events per variable included in subsequent multivariate modeling, we will have the power to study the interactions of multiple different characteristics by April 2008.

2) Thrombosis is a key pathological process in ischaemic stroke. Several coagulation proteins are risk factors for development of atherosclerosis and/or acute arterial thrombotic events, particularly in the young, and are of prognostic value in patients with coronary heart disease, but there have been no large prospective studies in unselected (predominantly elderly) patients with TIA and stroke. Whether routine measurement of markers of haemostatic activation and thrombosis is worthwhile in clinical practice is uncertain. We have completed a two-year pilot study and propose to continue to measure a panel of markers of platelet / endothelial cell activation (VWF, P-selectin), haemostatic turnover (Prothrombin fragment F1+2, D-dimer), natural anticoagulants (Protein C, Protein S, antithrombin), as well as fibrinogen, Protein Z (antigen and antibodies), and antiphospholipid antibodies (aPL) in consecutive patients with TIA or ischaemic stroke in OXVASC. Measurements will be related to clinical characteristics, aetiological subtype of the TIA or stroke, and to the risk of vascular events during follow-up. Based on OXVASC years 1 and 2, we expect to recruit 1000 patients aged ≥50 yrs with TIA or ischaemic stroke by April 2007). After a further year, mean follow-up will be 3.0 years. Based on our own studies, we expect 20% of patients to have a recurrent ischaemic stroke (30% for stroke, MI or vascular death). Power will be lowest for abnormalities with a low prevalence, such as aPL. Assuming a prevalence of 8% (as in pilot study) and a 10% rate of non-vascular death during follow-up, a sample of 585 patients would give 80% power to detect a doubling in the rate of recurrent stroke associated with aPL at the 95% level of confidence. With 1000 patients (April 2007) we will be powered to detect a relative risk of

1.7. However, most of the other risk factors are continuous variables and will provide greater statistical power. For example, based on the measurements obtained in the pilot study for PZ, using the parameters outlined above, and assuming a linear relationship with stroke risk, we would have 90% power at the 95% level of confidence to detect a doubling in the risk of recurrent ischaemic stroke from the lowest to highest quintile with 800 patients. Power will be greatest in patients with large artery atherosclerosis in whom the risk of recurrent stroke is highest, but we have not powered this study to determine whether predictive power of risk factors differs between subtypes. We will, however, be powered to detect differences in case-case comparisons of levels of haemostatic markers between subtypes.

3) Clinicians have major difficulties in diagnosing TIA reliably because of a lack of data on the nature of several well-recognised clinical syndromes. In years 1-2 of OXVASC, the most common such syndromes (usually in elderly patients with vascular risk factors) were transient speech arrest, isolated slurred speech, isolated double vision, isolated non-recurrent vertigo, and late-onset non-recurrent migraine-like syndromes. In routine practice, some such patients get a non-vascular diagnosis, whereas others are treated as TIAs – depending on the view that the GP or specialist takes on the nature of the syndromes. However, there are virtually no useful data on which to base judgements about their aetiology in the elderly. If these events are TIAs and are associated with a high risk of subsequent stroke, then misdiagnosis is a missed opportunity for prevention. If they are not TIAs, then risky or costly preventive treatments are not indicted. OXVASC is therefore performing prospective cohort studies of the prognosis of these syndromes. Such studies have been highly informative in the past for similar “TIA-like” syndromes, such as transient global amnesia, atypical transient monocular blindness and lone bilateral blindness. Among patients referred to the OXVASC clinic during years 1-2, 20% (180 cases, including approx 25 of each of the five most common syndromes) had other “TIA -like” syndromes of uncertain aetiology. We propose to continue to recruit and follow-

up such cases until April 2010, by which time we will have approx 100 patients with of each of the specific syndromes with an average follow-up of 4 years, and approx 900 patients with "TIA -like" syndromes of uncertain aetiology in total. A sample of 100 patients will allow us to differentiate reasonably reliable between the age-sex adjusted normal population expected risk of stroke over 4 years (about 5%) and the risk that we would expect if these events were associated with the same risk as definite TIAs (about 30% over 4 years).

Study Population: The study is confined to 9 GP practices that were involved in the OCSP and OXMIS. The population is based on general practices within the catchment of the JRH, is predominantly Caucasian (5% Asian, 1% Afro-Carribean), and includes a full range of social deprivation. Exact population characteristics are determined using the computerised general practice age and sex registers. These provide accurate and up-to-date estimates of the denominator allowing easy identification of cross boundary flow and turnover within the population.

Definition of cases: The definition of stroke and TIA is the same as in the OCSP. Definitions of ACS has however changed substantially since OXMIS. Where new diagnostic techniques have been introduced (e.g. MRI scanning for stroke, and troponin levels for ACS) cases will be categorised as incident using the original OCSP/OXMIS definitions as well as on the basis of new definitions and techniques.[18] All events will be categorised as "first-ever-in-a-lifetime" or recurrent. Stroke will be defined according to the standard criteria used in the OCSP.[1] An OXMIS compatible definition of myocardial infarction (MI) will be defined by WHO MONICA criteria (history, ECG, enzymes, and autopsy reports).[2]

Case-ascertainment: The pilot and post-pilot phases of the study (1 April 2002 – 31 March 2005) have allowed us to:

1) Refine the design of the study, make any necessary changes to the study forms and databases, and identify the most efficient methods of communication with the general practices and relevant hospital staff.

2) Ensure that case-ascertainment was reliable and complete.

3) Make a provisional comparison of the overall incidence of stroke and ACS in the same population at the same time.

4) Estimate of time trends in incidence. All of the GP practices included in the pilot study were also in the OCSP and OXMIS. All the data collected will therefore contribute to the main study of temporal trends in incidence of stroke and ACS.

Continuing case ascertainment will be as similar as possible to the initial phase of the study. The same multiple overlapping sources will be used. Participating GPs will notify us of any patient with a possible TIA, stroke or ACS, whether or not the patient was admitted to hospital. TIA patients will be reviewed because a significant proportion fulfils the criteria for stroke. Patients who have an event whilst temporarily away from Oxford will be included, but visitors to Oxford who are not normally resident and registered with a GP will not be included. A pager will be carried by a research registrar between 8am and 6pm from Monday to Friday. At other times contact with the study office will be via an answer-phone or fax.

Each practice has a liaison GP, and the study nurse visiting weekly. All participating GPs receive a three monthly newsletter. Patients with possible TIA or stroke who do not require hospital admission will be seen in a daily clinic. Patients for whom hospital assessment is not possible will be assessed in the community by the clinical research registrar.

Computerised admission and discharge registers, and casualty attendance registers will be reviewed daily at the JRH, the Radcliffe Infirmary (RI), and at the Oxford Eye Hospital

(to identify acute ocular ischaemic events). All requests for brain imaging, carotid Doppler Ultrasound studies, and cardiac enzymes will be reviewed. All sudden deaths outside hospital will be identified via the Coroner's Office and the Departments of Pathology and Neuropathology. All cause of deaths of individuals in the practices will be reviewed. Consent will be obtained from study patients for their record to be 'flagged' with the Office of National Statistics (ONS), which will provide information on the date, place and cause of death. This will allow long term mortality data to be collected for study patients, especially those who move out of Oxfordshire.

Assessment of cases: All patients with possible TIA, stroke, ACS, or other acute vascular event will be assessed by a study researcher as soon as possible after notification. Data will be extracted from medical records for cases first identified only after death or after a prolonged delay (e.g. if their stroke occurred whilst temporarily out of Oxford). In stroke patients, we will collect data on standard blood tests (haematology, biochemistry), an ECG, brain imaging (Magnetic Resonance Imaging [MRI] where possible, and/or CT-brain if MRI contraindicated or delayed), vascular imaging (MR-angiography [MRA] where possible, Doppler ultrasound or CT-angiography if MRA contraindicated) and echocardiography where relevant. In ACS patients, we will collect data on standard blood tests, serial cardiac enzymes (including troponin) and ECGs. We will record any autopsy information in patients who die prior to investigation. We will ascertain from the patient and their and medical records (including review of all GP records) any past history of strokes, TIAs or coronary events, other vascular diseases, medications, and risk factors (including blood pressure and cholesterol, if available).

Details of all potential TIAs and strokes will be reviewed at a weekly meeting with Prof Rothwell (Neurologist), Dr Schulz (Neurologist) and Dr Küker (Neuroradiologist) and classified according to the OCSP and TOAST criteria. Clinical history, serial ECGs and cardiac enzymes of all potential MIs will be reviewed with Dr Adrian Banning (Cardiologist).

Patients attending the daily TIA and minor stroke clinic for assessment will be issued with an automated blood pressure machine with a Bluetooth capability, and will be asked to measure their blood pressure three times a day. The system automatically transmits the blood pressure back to the relevant OXVASC clinician, who will monitor the blood pressure and prescribe medication if required. The patients' own GP will be notified of any proposed changes in medication. At the routine OXVASC one month follow-up visit patients will also be fitted with a 24-hour blood pressure monitor, which will be collected from them the following day. Those patients with a TIA or stroke who are admitted to hospital, but are well enough to go home within 1 month, will be offered monitors and training at their 1 month follow up home visit. Those who are still in hospital at 1 month will be offered monitors and training upon discharge home.

Blood sampling: A sample of blood (no more than 20ml) will be taken for later analysis. Where possible, this will be done at the same time as blood is being taken for routine clinical tests. The blood sample will be distributed between several tubes (sodium EDTA, clotted, heparin & coagulation) to provide material for future analyses in line with current MRC guidelines. Samples will be used to measures markers of haemostatic activation and thrombosis. DNA will be extracted to study polymorphisms that might be risk factors for thrombotic stroke. The consent form states the blood will be used for genetic research aimed at understanding genetic influences on vascular disease but these are unlikely to have any personal implications for the participant.

Consent: The protocol for consent is based on those used in the OCSP and OXMIS. The study physician or research nurse will give a brief verbal explanation of the study to all potential participants. The patient will then be given a written information sheet. In patients who have problems reading due to stroke (visual field defect), or for other reasons, the information sheet will be read to the patient. If the patient is happy to make a decision about participation in the study, then written consent will be obtained. If the patient requires a period of time to consider the decision then this will be respected.

Consent will be more complicated in certain circumstances. Firstly, there will be problems obtaining a normal signature from some patients with dominant hemisphere strokes. In such cases we will try to obtain a signature with the patient's non-dominant hand, and have this signature witnessed by a member of the nursing staff. Secondly, some potential participants will be unable to give informed consent due to their neurological deficit, or other acute complication. In this situation, we will attempt to contact the next-of-kin to obtain surrogate consent. If the next-of-kin is not available we will assume consent for the purposes of recording basic clinical information from the medical records, but not for clinical examination or any venepuncture in excess of what is clinically indicated.

Approximately 15-20% of stroke patients have some degree of either dysphasia or cognitive impairment. Surrogate consent is not legally well defined, but since our study is purely observational we think that consent from next-of-kin is reasonable. This is standard practice in acute stroke research. Where consent from neither the patient or the next-of-kin is available, the Declaration of Helsinki[19] allows for research in this area if the specific reasons for not obtaining consent are reviewed by an independent ethics committee. Doyal[20] has argued that, where informed consent is not possible, then it should be clear there are important potential benefits from the research, and the risks of involvement should not exceed those associated with everyday life. If the research is epidemiological

and medical records are to be used but consent cannot be obtained then this would be acceptable in light of potential benefits for patient or in the public interest provided confidentiality is maintained.

If assent is given by the legal guardian for the participant to take part in the study at the outset, assent will be gained again at each follow up. In circumstances where assent is gained at the outset but the participant recovers sufficiently to be able to give informed consent this will be obtained at the next scheduled contact.

Deaths outside hospital: Some acute vascular events result in death outside hospital. We will identify these cases from records of the Coroner's Office, the Department of Pathology, and from notification by participating general practices.

Controls: Controls will be recruited from spouses or friends of study participants in order to identify individuals with stable vascular disease who have never had an acute event ("disease controls") and individuals without known vascular disease ("healthy controls"). OXVASC already collects data on some "disease-controls" i.e. patients undergoing investigation or treatment for stable angina, asymptomatic carotid stenosis or peripheral vascular disease. Our reasons for wanting to extend our collection of controls:

1) To perform case-control studies looking at potential risk factors for the development vascular disease.

2) To allow us to determine the population attributable fraction (PAF) for existing vascular risk factors and hence determine the potential PAF for any as yet undiscovered risk factors.

As well as understanding the strength of a relationship between risk factor and risk, it is important to know the proportion of cases in the population that are attributable to the risk factor (PAF) so that the potential population impact of risk factor modification can be

estimated and the relative contribution of risk factors to different subtypes of stroke can be determined. There would be little point, for example in trying to identify novel risk factors for a particular subtype of stroke if existing modifiable risk factors were sufficient to account for the vast majority of such strokes in the population. There are no previous large population-based studies of PAFs for stroke and no published data on the different subtypes.

The controls will be asked for the same background medical information as patients with acute vascular events who are enrolled in the study. This includes data on past medical history, family history, details of medications taken, and questions on relevant lifestyle factors such as diet and exercise. This will be followed by measurement of pulse, blood pressure, height, weight, and waist, hip and neck circumference. Twenty millilitres of blood will be taken for storage and later analysis. There will be no requirements for follow-up assessments. Only individuals aged over 35 years will be included (over 99% of cases are aged >35 years). Potential controls will be given an information sheet and asked for consent to inclusion in the study. The interview and blood collection will take place at the place of the participant's choice.

Sample size required will vary depending on the prevalence of the particular risk factor in cases and controls. To have 80% power at the 95% level of confidence to detect a risk ratio of 1.5 between cases and controls for a risk factor with a 20% prevalence in controls would require 310 of each. 480 cases and controls would be required to detect a risk ratio of 2.0 for a risk factor with a prevalence of 5%. For certain analyses we would wish to closely match cases and controls for factors, such as age, sex, and deprivation. We therefore propose to recruit a pool of 1000 controls in order to allow us to perform appropriately powered and matched analysis. By April 2008, we will have recruited a sufficient number of cases with specific acute vascular events (e.g. approximately 500 lacunar strokes, 400 large artery strokes, and about 600 cardioembolic strokes and strokes of undetermined aetiology) to allow adequately powered case-control

comparisons. We will use logistic regression to estimate the PAF for sets of risk factors with adjustment for other confounding factors, Confidence intervals will be estimated using a delta-method variance formula.

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Appendix 2

OXFORD VASCULAR STUDY 09Aug10

TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 Year 7-9

SUBJECT ID NO:

Patient identification label
(check address is current)

Was patient interviewed	**Y**	**N**	**U**

If NO why not?	Please tick
1	Refused interview
2	Aphasic and relatives could not be contacted
3	Too unwell/ multiple medical problems
4	Dementia (need to record MMSE or AMTS) and relatives could not be contacted
5	Late ascertainment and no reply to invitation to join study
6	Ascertainment after death
7	Diagnosis uncertain
9	Unknown

Patient contact details	
Telephone (day)	
Telephone (evening)	
Mobile	
Fax number	
Email address 1	
Email address 2	

Next of kin details	
Relationship to patient	
First name	
Surname	
Address 1st line	
Address 2nd line	
City/town	
County	
Postcode	
Country	
Telephone (day)	
Telephone (evening)	
Mobile phone no	
Fax number	
Email addres	

OXVASC db: Name

OXFORD VASCULAR STUDY 09Aug10

TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 **Year 7-9**

11 digit OXCODE for notification event											

Consultant	

1 Physician
2 Physician with stroke interest
3 Neurologist
4 General surgeon
5 Vascular surgeon
6 Cardiologist
7 Neurosurgeon
9 Other

Name Examiner

GP DETAILS					
Surname					
Location		01 Beaumont Street 03 East Oxford 04 Berinsfield	05 Malthouse 06 Kidlington (Exeter) 07 Wantage	08 Marcham Road 09 Stert Street 10 Kidlington (KYMG) 99 Other (please provide)	Other:
First name or Initials					

Summary Diagnosis		Specify:

S= Stroke
T= TIA
A= Amaurosis fugax
R= Retinal artery Occlusion
M= MI
B= Burden
Z= Other (specify)

Is this the first ever in a lifetime (incident) stroke? *	**Y**	**N**	**U**
Is this the first ever in a lifetime (incident) TIA? *	**Y**	**N**	**U**

* Please tick as appropriate

Date of notification event (DD-MM-YY)	

Location of interview	1 JRH inpatient 2 RI in patient 3 Community hosp 4 Outpatients 5 Home 6 Other (specify)		Specify:
Follow-up plan at 1 month	1 OXVASC TIA clinic 3 Refused follow-up 4 Other (specify) 6 No follow-up 7 Home visits		Specify:
Info on form obtained from	1 Patient 2 Relative 3 GP 4 hospital records 5 Death certificate 6 Other (specify)		Specify:
Source of 1st notification	1 GP 2 JRH admission 3 Other Hospital (specify) 4 Other referrals (specify) 5 Health authority search 6 Death 7 Troponin 9 Other (specify)		Specify:

Other sources of notification (select all appropriate)	1	2	3	4
	Specify:	Specify:	Specify:	Specify:

If one had not identified the patient via the route of 1st notification would patient have been identified by other source of ascertainment? (please circle)	Y	N	U

OXVASC db: 1

HISTORY OF NOTIFICATION EVENT	Please tick if:	All fields unknown on page 3+4

Narrative history & examination

Did patient have PRANS events?	Y	N	U	Date most recent	OXCODE for PRANS event:
				U	

Details:

OXVASC db: 2

OXFORD VASCULAR STUDY 09Aug10
TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 **Year 7-9**

Notification event*		**What did you think was wrong?**
Date DD-MM-YY	**Time** 24 hr clock	
U	: U	

* The event that led to first seeking medical attention

Did notification event occur during hospital stay (while admitted for other reason)?	**Y**	**N**	**U**
Were you alone?	**Y**	**N**	**U**
If you were with someone who was it?	U		
Who called for help?	U		
If you did not call for help at time of event, why not?	U		

Who did you 1st call for help?	1= Medical 2=Non-Medical 9= Unknown		**Date** DD-MM-YY	**Time** 24 hr clock
1st call for ANY help non-medical or medical			Please give date/time for any 1st call *	
				: U
1st call for MEDICAL help GP/ A&E / 999/ NHS direct			Please give date/time for 1st medical call	
				: U

* This could be the same date and time as the first call for medical help (please provide anyway)

Calls for medical attention		**Date** DD-MM-YY	**Time** 24 hr clock
GP by telephone	**Y / N**		:
GP in person	**Y / N**		:
Telephoned 999	**Y / N**		:
Went to A&E in person	**Y / N**		:
Telephoned NHS direct	**Y / N**		:
Went to OEH	**Y / N**		:
Other (Specify)	**Y / N**		:

Outcome of first call for medical assistance

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				Date DD-MM-YY	Time 24 hr clock
Seen by GP / A&E in person?	**Y**	**N**	**U**		: U
If GP referred subject to OXVASC clinic: **Notification by GP to OXVASC**					: U
If subject was not referred to OXVASC: **Admitted to hospital?**	**Y**	**N**	**U**		: U
If admitted to hospital but not referred to OXVASC: **Ascertainment** by OXVASC staff					: U
Assessment by OXVASC staff					: U

HISTORY OF NOTIFICATION EVENT	**Please tick if:**	**All fields unknown on page 5+6**

Duration of symptoms Please leave blank for stroke	Hrs:		Mins:	
Onset on wakening from sleep?	**Y**	**N**	**U**	
Time awake (ignore if onset not on wakening from sleep) 24 hr clock	: U			
Activity at onset (within 2 hrs of onset)		1= Asleep 2= Sedentary 3= Mild-moderate 6= Strenuous 9= Unknown		
What were you doing in the same 2 hrs on the day prior to the event?				
Drugs within previous hour	**Y**	**N**	**U**	
Meal within previous hour	**Y**	**N**	**U**	
Record exact activity	U			
Location of event	1 Home 2 Work 3 Leisure (non-sport) 4 Sport 8 Other (specify) 9 Unknown		Specify:	

OXVASC db: 3

ONSET ANGER SCALE		**Anger level**
Onset NOT on wakening from sleep	In the **two hours prior to the event** what best describes your emotional state from the list provided?	
	In the **exact same two hours on the day prior to your event** which best describes your mood?	
OR:		
Onset ON wakening from sleep	If you had your event on wakening how were you in the **two hours before you went to bed**?	

1 = **Calm**
2 = **Busy** (but not hassled)
3 = **Mildly angry** (irritated and hassled, but does not show)
4 = **Moderately angry** (so hassled it shows in your face)
5 = **Very angry** (body tense, clenching fists or teeth)
6 = **Furious** (almost out of control, very angry, pound table, slam door)
7 = **Enraged** (lost control, throwing objects, hurting yourself or others)
9= **Unknown**

Was there a further event between notification event and assessment?	Y	N	U

If yes to above please indicate number of events between any of the following:	
	No. events
Between notification event and seeing GP/ other medical opinion (including notification event)	# U
Between seeing GP and notification by GP to OXVASC	# U
Between notification by GP and OXVASC assessment	# U

Were there any events in the month preceding the notification event?	Y	N	U
How many events were there in the month before notification event?	# U		

Has this patient had a recurrent event between notification event and OXVASC assessment?	Y	N	U

This question is identical to the one at the top, answers should be the same.

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HISTORY OF NOTIFICATION EVENT

Event	History of events between notification event and assessment		
1	**Notification event itself**		
2		**Event date*:** U	**Time** : U
3		**Event date*:** U	**Time** : U
4		**Event date*:** U	**Time** : U
5		**Event date*:** U	**Time** : U

Use extra piece of paper for event 6 onwards. * DD-MM-YY 24 Hr clock

If admitted as a result of the notification event (use ambulance sheet)

Was subject admitted to hospital? as a direct result of the notification event	Y	N	U

If YES then please answer:

Was subject admitted by ambulance?	Y	N	U

If admitted by ambulance:	**Date** DD-MM-YY	**Time** 24 hr clock
Arrival of emergency service with patient	U	: U
Arrival of emergency service in Hospital *	U	: U

* If not on ambulance sheet use blue admissions

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	ACS						**Cerebral**						**Peripheral**		
	NSTEMI			**STEMI**			**TIA**			**CVA**					
Prior acute events?	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
	Possible*			Possible*			Possible*			Possible*					
# of events	U			U			U			U			U		
Date of most recent	U			U			U			U			U		

* Please circle if it is unclear what type of event it was

OXVASC db: 4

BACKGROUND MEDICAL HISTORY

PRIOR TO NOTIFICATION EVENT ONLY

	Y/N/U	Age at diagnosis		
Please tick if:	**All No**	**All U**	**Tick if:**	**All age U**
Angina				U
Hypertension				U
Myocardial infarction				U
Diabetes Mellitus				U
Valvular heart disease				U
Intermittent Claudication				U
Peripheral vascular intervention			Age at 1st intervention:	U
Atrial fibrillation				U
Hyper lipidaemia				U
Cardiac failure				U

Diabetes Mellitus — Treatment

Diet			Tablets			Insulin		
Y	N	U	Y	N	U	Y	N	U

Valvular heart disease — Nature: U

Peripheral vascular intervention

Site: (1 Arm, 2 Leg, 3 Bowel, 4 Carotid, 5 Abdo aneurysm, 6 Thoracic aneurysm, 7 Other, 8 Uncertain)

Type:	Angiogram			Angioplasty			Bypass			Amputation		
	Y	N	U	Y	N	U	Y	N	U	Y	N	U

Result: U

Atrial fibrillation

1 Current, 2 Previous, 9 Unknown	TREATMENT: 1=Cardioversion, 2=Paroxysmal, 3=Persistent, 4=Permanent, 9=Unknown	Pace maker			Type pacemaker
Choose from above:	Choose from above:	Y	N	U	U

Hyper lipidaemia — Treatment

Diet			Statin			Other		
Y	N	U	Y	N	U	Y	N	U

Cardiac failure — **Treated** (loop diuretic)? Y N U

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CONTINUING BACKGROUND MEDICAL HISTORY

PRIOR TO NOTIFICATION EVENT ONLY

	Y/N/U choose	Age at:	
Please tick if:	**All No** / **All U**	**Tick if:**	**All age U**

Migraine			**With Aura?**						**Prolonged aura (>1hr)**								
			Y		**N**		**U**		**Y**		**N**		**U**				
Epilepsy		**Age @ Diagnosis**															
		U															
Cardiac intervention		**Age @ 1st Intervention**		**Number**		**Angiogram**			**Angioplasty**			**Stent**			**Bypass**		
		U				**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
		Results of angiogram:				U											
Carotid: Endarterectomy		**Age @ 1st operation**		**Side**													
		U		**Left**				**Right**				**Both**					
Carotid: Stent		**Age @ 1st operation**		**Side**													
		U		**Left**				**Right**				**Both**					
Asthma																	
Liver disease																	
COAD																	
Peptic ulcer disease																	
Previous venous thromboses			**Number**		**Details:** Please enter U if not known												
Any other past medical history		**Details:** Please enter U if not known															
SLE Look in notes		**Age @ Diagnosis**		**Anticardiolipin antibodies (aCL)**					**Lupus anticoagulant (LA)**								
		U		**Y**		**N**		**U**	**Y**		**N**		**U**				

OXVASC db: 7

CONTINUING BACKGROUND MEDICAL HISTORY			
PRIOR TO NOTIFICATION EVENT ONLY			
	Y/N/U choose		
Please tick if:	**All No**	**All U**	
Autoimmune disease		**Diagnosis**	U
Allergies	Please list all. If no allergies or unknown please enter No or Unknown.		
Nosebleeds			
Bleeding after dental extraction			
Any cancer			
End stage renal failure/ dialysis			

LIST OF MEDICATION BEFORE ONSET OF NOTIFICATION EVENT					
Aspirin	Y	N	U	**Dose** mg/day	U
Dipyridamole	Y	N	U		
Clopidogrel	Y	N	U		
Warfarin	Y	N	U	**INR**	U

Do you currently take any vitamin supplements?		Y	N	U
Vitamin B	**B6?**	Y	N	U
	Folate?	Y	N	U
	B12?	Y	N	U

Names of (other) current vitamin supplements	Please list all. If no other vitamin supplements were taken at time of notification event please enter "No other".

OXVASC db: 8

Was your BP measured at any time prior to the notification event?	**Y**	**N**	**U**
Date of most recent BP measurement prior to notification Event DD-MM-YY			U
How many times have you had your BP measured in the last year?			U

Have you ever been on OCP?	**Y**	**N**	**U**
Have you ever been on HRT?	**Y**	**N**	**U**
No of years in lifetime on HRT and/or OCP			U

		1	2	3	4	5	
Previous stroke or TIA? Y N U		**Date most recent event** DD-MM-YYYY Prior to notification event	**Any other previous?** Y N	**No. of previous events** ALL events prior to notif. Event	**Date 1st event** DD-MM-YY Provide date even if same as most recent (number previous events = 1)	**Duration** (mins) **recent**	**longest**
Hemi-spheric stroke carotid	**R**		Y N	#			
	L		Y N				
Hemi-spheric TIA carotid	**R**		Y N			Mins: U	Mins: U
	L		Y N			Mins: U	Mins: U
Vertebro-basilar stroke			Y N				
Vertebro-basilar TIA			Y N			Mins: U	Mins: U
Stroke unknown territory			Y N				
TIA unknown territory			Y N			Mins: U	Mins: U
Amau-rosis fugax	**R**		Y N			Mins: U	Mins: U
	L		Y N			Mins: U	Mins: U
Retinal infarc-tion	**R**		Y N				
	L		Y N				

Comments:

OXVASC db: 9

MEDICATION

Was subject taking medication <u>at the time of</u> the notification event? If YES provide names below	Y	N	U

	NAME DRUG	Y	N	U	Dose mg/day	Other unit? Please specify
1	**Aspirin**				U	U
2					U	U
3					U	U
4					U	U
5					U	U
6					U	U
7					U	U
8					U	U
9					U	U
10					U	U
11					U	U
12					U	U
13					U	U
14					U	U
15					U	U
16					U	U

Other additional medication + dose/unit	If all lines above have been used and subject is not taking other medication please enter "No other" here.

OXVASC db: 9

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BACKGROUND FAMILY HISTORY

Patient is adopted	**Y**	**N**	**U**	**Twin**	**Y**	**N**	**U**
Total number of siblings (inc)				**Any vascular history**	**Y**	**N**	**U**

Oldest → Youngest

		Dad	Mum	Sib 1	Sib 2	Sib 3	Sib 4	Sib 5	Sib 6	Sib 7	Sib 8	Sib 9	Sib 10	Sib 11	Sib 12
Stroke	**Y/N/U**														
	Age 1st*														
MI	**Y/N/U**														
	Age 1st*														
PVD	**Y/N/U**														
	Age 1st*														
BrainHaem	**Y/N/U**														
	Age 1st*														
Diabetes	**Y/N/U**														
	Age 1st*														
Hyperlip aedemia	**Y/N/U**														
	Age 1st*														
Hyper tension	**Y/N/U**														
	Age 1st*														
	Sibling* is:														

T = Twin **M** = Half-sibling mother's side **S** = Sibling **F** = Half-sibling father's side

Age/Sibling: please fill in "U" if unknown

	Alive/ Dead			Sex		Age at death	Cause of death
Mother	**A**	**D**	**U**			U	U
Father	**A**	**D**	**U**			U	U
Sib1 oldest	**A**	**D**	**U**	**M**	**F**	U	U
Sib 2	**A**	**D**	**U**	**M**	**F**	U	U
Sib 3	**A**	**D**	**U**	**M**	**F**	U	U
Sib 4	**A**	**D**	**U**	**M**	**F**	U	U
Sib 5	**A**	**D**	**U**	**M**	**F**	U	U
Sib 6	**A**	**D**	**U**	**M**	**F**	U	U
Sib 7	**A**	**D**	**U**	**M**	**F**	U	U
Sib 8	**A**	**D**	**U**	**M**	**F**	U	U
Sib 9	**A**	**D**	**U**	**M**	**F**	U	U
Sib 10	**A**	**D**	**U**	**M**	**F**	U	U
Sib 11	**A**	**D**	**U**	**M**	**F**	U	U
Sib 12	**A**	**D**	**U**	**M**	**F**	U	U

Total number of *subject's children* **# Male** **# Female**

please fill in "U" if unknown **OXVASC db: 10**

AUTOIMMUNE HISTORY- Personal			
Do you have an autoimmune disease?	*Y*	*N*	*U*
Thyroid	*Y*	*N*	*U*
Early onset diabetes	*Y*	*N*	*U*
Pernicious anaemia	*Y*	*N*	*U*
Rheumatoid arthritis	*Y*	*N*	*U*

SMOKING			
Have you ever smoked?	*Y*	*N*	*U*
Are you a lifetime non-smoker?	*Y*	*N*	*U*
Smoking oddities ***(pipes etc)***			*U*
Are you an ex-smoker?	*Y*	*N*	*U*
If so at what age did you stop?	***Age:***		*U*
<u>If you have stopped</u>: *How many years did you smoke?*	***# Years:***		*U*
Do you currently smoke?	*Y*	*N*	*U*
How many do you smoke per day?	***Number:***		*U*
<u>If you are still smoking</u>: *How many years have you smoked?*	***# Years:***		*U*

OXVASC db: 11

Premorbid modified Rankin

Do you have any symptoms?	*Y*	*N*	*U*
Are you able to look after yourself and carry out normal activities?	*Y*	*N*	*U*
Does anyone else help pay the bills, do the shopping, cleaning etc?	*Y*	*N*	*U*
Do you need someone to help you walk?	*Y*	*N*	*U*
Do you need help to wash yourself?	*Y*	*N*	*U*
Do you need to be lifted in and out of bed?	*Y*	*N*	*U*

0 = no symptoms at all
1 = no significant disability despite symptoms: able to carry out all usual duties and activities
2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3 = moderate disability: requiring some help, but able to walk without assistance
4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6 = death

Score

Rose PVD: IHD questionnaire

NOTE: ALL QUESTIONS RELATE TO SYMPTOMS PRIOR TO THE NOTIFICATION EVENT

PART A

a) Have you ever had any pain or discomfort in your chest?	*Y*	*N*	*U*	n: **go to part C**
b) Do you get the pain or discomfort when you walk up hill or hurry?	*Y*	*N*	*U*	n: **go to part B**
c) Do you get it when you walk at an ordinary pace on the level?	*Y*	*N*	*U*	
d) When you get any pain or discomfort in your chest what do you do? (1=stop, 2=slow down, 3= continue at same pace, 9= unknown)				
e) Does it go away when you stand still?	*Y*	*N*	*U*	
f) How soon? (**1**=10 minutes or less **2**= > 10 minutes **9**= unknown)				

PART B

Have you ever had severe pain across the front of your chest lasting half an hour or more?	*Y*	*N*	*U*

PART C

a) Do you get pain in either leg when you are walking?	*Y*	*N*	*U*
b) Does this pain ever begin when you are standing still or sitting?	*Y*	*N*	*U*
c) Do you get this pain in your calf (or calves)	*Y*	*N*	*U*
d) Do you get it when you walk up hill or hurry?	*Y*	*N*	*U*
e) Do you get it when you walk at an ordinary pace on the level?	*Y*	*N*	*U*
f) Does the pain ever disappear while you are still walking?	*Y*	*N*	*U*
g) What do you do if you get it when you are walking? (**1**=stop, **2**=slow down, **3**=continue at same pace, 9= ***unknown***)			
h) What happens if you stand still? (1=usually continues for more than 10 minutes, **2**= usually disappears in 10 minutes or less, **9**= unknown)			

OXVASC db: 12

Premorbid Barthel

	Score	Key
Feeding		0 = unable 1 = needs help cutting, spreading butter, etc, or requires modified diet 2 = independent
Bathing		0 = dependent 1 = independent (or in shower)
Grooming		0 = needs help with personal care 1 = independent face/hair/teeth/shaving (implements provided)
Dressing		0 = dependent 1 = needs help but can do about half unaided 2 = independent (including buttons, zips, laces, etc.)
Bowels		0 = incontinent (or needs to be given enemas) 1 = occasional accident 2 = continent
Bladder		0 = incontinent, or catheterised and unable to manage alone 1 = occasional accident 2 = continent
Toilet use		0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping)
Transfers (bed to chair and back)		0 = unable, no sitting balance 1 = major help (one or two people, physical), can sit 2 = minor help (verbal or physical) 3 = independent
Mobility (on level surfaces)		0 = immobile 1 = wheelchair independent, including corners, > 50 metres 2 = walks with help of one person (verbal or physical) > 50 metres 3 = independent (but may use any aid; for example, stick) > 50 metres
Stairs		0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent

BARTHEL SCORE	

OXVASC db: 13-16

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FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

Interviewer's perception of patient personality		1 Very relaxed 2 Fairly relaxed 3 Average	4 Prone to stress 5 Highly stressed 9 Unknown	
In terms of stress what kind of person are you?				
Place of residence		1 Home 2 Home of relative 3 Home of friend 4 Warden housing	5 Care home 8 Other (specify) 9 Not known	**8-Specify:**
Do you live alone? Y/N/U		**If NO with whom?**	**SPOUSE or:**	
Are you a carer*? Y/N/U		*Physical assistance to wash/dress/mobility		
Does anyone assist you at home?		1 Spouse 2 Relative 3 Private carer	4 Community services (specify) 5 No assistance needed 9 Not known	**4-Specify:**
Marital status		1 Married 2 Widow	3 Single 4 Separated	5 Partner 9 Not known
Employment status		1 Working FT 2 Working PT 3 Caring for home	4 Unemployed 5 Unable to work	6 Retired 7 Student 9 Not known
Most recent occupation (spouse's occupation if not employed)				U
Socioeconomic class		1 **Professional** (Doctors, accountants, engineers) **2 Managerial/technical** (Marketing, sales managers, teachers, journalists 3N **Skilled non-manual** (Clerks, cashiers, retail staff) 3M **Skilled manual** (Carpenters, van/lorry drivers, Joiner)	4 **Partly skilled** (Warehousemen, security guards, machine/tool operators) 5 **Unskilled** (Building/civil engineering labourers, other labourers, cleaners) 6 **Armed forces** 9 **Unknown**	
Ethnic origin		1 White 2 Black Carribean 3 Black African	4 Indian 5 Pakistani 6 Bangladeshi	7 Chinese 8 Other 9 Not known
Exercise (Clinician judgement on amount of physical activity –age corrected- per week)		1 None 2 Below average	3 Normal 4 Above average 9 Not known	
Alcohol units per week*		* *Please use guidelines provided below*		
Age left school	U			
Education		1 Basic 2 Further	3 Higher 9 Not known	
Age left full-time education	U			

(Sparkling) wine and Champagne					
	ml	**10%- units**		**14% -units**	
M glass	175		1.75		2.5
L glass	250		2.5		3.5
Bottle			7.5		10.5

Lager, Beer and Cider					
	ml	**4% - units**		**9%- units**	
Bottle	330		1.3		3
Can	440		1.8		4
Pint	568		2.3		5.1

Shots (Gin, Rum, Vodka, Whisky, Tequila, Sambuca)			
	ml		**Units**
Small		25	1
Large		35	1.3
Double		50	2
L double		70	2.8

275 ml bottle alcopops: 1.4 units

50 ml glass Sherry/ Port: 1 Unit

OXVASC db: 17

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

SLEEP		
What is the likelihood of you dozing in the following <u>three</u> situations:		
1) Sitting and reading		0= No chance of dozing 1= Slight chance of dozing 2= Moderate chance of dozing 3= High chance of dozing 9= Unknown
2) Lying down to rest in the afternoon		
3) Sitting and talking to someone		
On average, how many hours of sleep do you get per night?	U	
Do you snore?	Y N U	
Have you been told that you stop breathing at night?	Y N U	
Do you take medications for high blood pressure?	Y N U	
People tell me that I snore		1= Never 2= Rarely (1-2x / year) 3= Occasionally (4-8x /year) 4= Sometimes (1-2x /month) 5= Often (1-2x /week) 6= Usually (3-5x /week) 7= Always (every night) 8= I don't know 9= Unknown
People tell me that I gasp, choke or snort while I am sleeping		

NUTRITION		
How is your appetite?		1= Good 2= Normal 3= Poor 4= Uncertain
Do you have a healthy diet?	Y N U	
On average, how many portions of fish do you eat per week? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= 2 /week 4= ≥ 3/week 9= Unkown
Do you add salt to your food?	Y N U	
Do you drink full fat or low fat dairy milk (cow/goat)?		1= Full fat 2= Low fat (skimmed/ semi-skimmed) 3= No milk consumed 4= No dairy consumed 9= Uncertain
On average, how many portions of fresh fruit and vegetables? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= several/ week 4= 1 /day 5= 2-4 /day 6= > 4 /day 9= Unknown

OXVASC db: 18

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TIA & STROKE

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FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

MOOD	Do you often feel sad or depressed?	**Y**	**N**	**U**	
DRIVING	Do you drive?	**Y**	**N**	**U**	
Handedness	Left/Right/Both/Unknown				R= Right L= Left B= Both U= Unknown
Clinical impression of frailty (corrected for age)					1= Frail 2= Normal 9= Unknown

LIFE EVENTS

ave any of these events happened to you over the last year*?	**Y**	**N**	**U**	**How upset were you by these events?**
Death or serious illness of close friend or relative	**Y**	**N**	**U**	
Financial difficulty	**Y**	**N**	**U**	
Divorce or break up of close friend or relatives	**Y**	**N**	**U**	
Major conflict with children or grandchildren	**Y**	**N**	**U**	
Muggings, robberies, accidents	**Y**	**N**	**U**	

1= Very much
2= Moderately
3= Not too much
9= Unknown

OTHER	

*Data entry instructions: N should be changed to Y if any of the answers below are answered as Y or if OTHER has been filled in.

AMTS

Age	**0**	**1**
Time (nearest hour)	**0**	**1**
Year	**0**	**1**
Name or place	**0**	**1**
Recognition of 2 persons	**0**	**1**
Date and month of birth	**0**	**1**
Date of 1st World War	**0**	**1**
Queen's name	**0**	**1**
Count 20-1 backwards	**0**	**1**
5 mins recall full street address	**0**	**1**

0= Fail
1= Pass

If AMTS not done explain why not

OXVASC db: 19

GENERAL EXAMINATION					
	cm*			**inches***	
Collar size					U
Waist measurement					U
Hip measurement					U
Height					U
	kg*			**stone***	
Weight					U
Arcus	Y	N	U		
Xanthelasma	Y	N	U		
Nicotine staining	Y	N	U		
Ear crease	Y	N	U		
Own teeth/ denture	O	D	U	O= own teeth D= denture U= unknown	

*Data entry instructions: If it is obvious that "cm" measurements have been placed in the "inches" column and vice versa please ensure data is entered on the db in the correct field. A note with initials is required on this form to make a note of this data change. The same is valid for

For all patients: **1st HEART RATE and BLOOD PRESSURE post event**				
		Date DD-MM-YY	**Time** 24 hr clock	
		U	: U	
Blood pressure 1st BP post event		**Sys**	**Dias**	U
Heart rate 1st HR post event				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Recorded by	P Paramedic G GP A A&E C Clinic O Other N Not recorded U Unknown			

OXVASC db: 20

For admitted patients only: **TEMP, HEART RATE and BLOOD PRESSURE at admission**				
Temp on admission		°C		U
Admission Heart rate				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
BP on admission		Sys	Dias	U
Sats/air		**%**		U
BM				U

For all subjects: **HEART RATE and BLOOD PRESSURE at assessment**				
BP on assessment		Sys	Dias	U
Heart rate on assessment				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
Cardiac murmur?		Y	N	U
Cardiac failure?		Y	N	U
Any pre-existing neurological disability?		Y	N	U

OXVASC db: 20

OXFORD VASCULAR STUDY 09Aug10

TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 Year 7-9

STROKE	Normal exam		All Unknown	

Prestroke disability	U	Predicted 30 day Rankin	U

SYMPTOMS AT ONSET

	Weakness		Sensory			Eyes/vision		Other	
	Right	Left	Right	Left		Right	Left		
	Please fill in: Y / N / U					Y / N / U			Y / N / U
Face					**Hemianopia**			**Dysphasia**	
Arm					**Monocular**			**Dysarthria**	
Hand								**Vertigo**	
Leg					**Diplopia**			**Headache**	

FINDINGS ON EXAMINATION:

Glasgow Coma Scale			
Eyes	**/4**	1 – No eye opening 2 – Eye opening in response to pain	3- Eye opening in response to speech 4- Spontaneous eye opening
Motor	**/6**	1 – No response to pain 2 – Extensor posturing to pain 3 - Flexor response to pain	4 – Withdrawal to pain 5 - Localizing response to pain 6 – Obeys commands
verbal	**/5**	1 – No speech 2 – Incomprehensible speech 3 – Inappropriate speech	4 – Confused conversation 5 – Oriented

	Weakness		Sensory			Eyes/ vision		Other	
	Right	Left	Right	Left		Right	Left		
	Please fill in: Y / N / U					Y / N / U			Y / N / U
Face					**Hemianopia**			**Dysphasia**	
Arm					**Gaze palsy**			**Dysarthria**	
Hand					**Nystagmus**			**Ataxia**	
Leg								**Neglect**	

NIH STROKE SCALE For instructions see separate sheet						Tick if: NOT DONE	
LOC		LOC questions		LOC commands		Best gaze	
Best visual		Facial Palsy		Right arm		Left arm	
Right leg		Left leg		Limb ataxia		Sensory	
Language		Dysarthria		Neglect		**TOTAL**	

OXVASC db: 21

STROKE PROGNOSIS	
Date of prognostic markers DD-MM-YY	U

Please tick:	**All fields normal**	**All fields unknown**
Hemianopia	1= No deficit 2= Mild 3= Moderate 4= Severe 9= Unknown	
Inattention		
Dysarthria		
Swallowing		
Dysphasia		

Limb deficit (able to lift both arms to horizontal MRC≥3)	**Y**	**N**	**U**
Unable to sit independently	**Y**	**N**	**U**
Unable to stand independently	**Y**	**N**	**U**
Unable to walk independently (Cannot walk without help of another or aid)	**Y**	**N**	**U**
Urinary incontinence	**Y**	**N**	**U**
Catheterised	**Y**	**N**	**U**

ABCD^2 score

A (Age); 1 point for age ≥60 years ☐

B (Blood pressure) ≥ 140/90 mmHg); 1 point for hypertension at the acute evaluation ☐

C (Clinical features); 2 points for unilateral weakness, 1 for speech disturbance without weakness ☐

D (Symptom duration); 1 point for 10-59 minutes, 2 points for ≥60 minutes ☐

D (Diabetes); 1 point ☐

Total ☐

MANAGEMENT - DISCHARGE

MANAGEMENT			
Did you discuss the need to change diet with subject?	**Y**	**N**	**U**
Did you discuss the need to reduce weight with subject?	**Y**	**N**	**U**
Did you discuss the need to quit smoking with subject?	**Y**	**N**	**U**

DRUG MANAGEMENT												
	New				**Continued**				**Contra-indicated**			
Aspirin	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
Dipyridamole	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
Clopidrogel	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
Warfarin	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
Low molecular weight heparin	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
GPIIIa/IIb	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
Unfractionated heparin	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
Lipid lowering	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
Ace inhibitors	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
Thiazide diuretics	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
Loop diuretics	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
Beta blockers	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
Other antihypertensive	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
Antiarrythmics	**Y**	**N**	**U**		**Y**	**N**	**U**		**Y**	**N**	**U**	
Other (Please specify new Y/N/U, continued Y/N/U, contra-indicated Y/N/U)												

OXVASC db: M, D

Appendix 3

Oxford Radcliffe Hospitals NHS Trust

Department of Primary Health Care
Institute of Health Sciences
Old Road
Headington
Oxford OX3 7LF

The Stroke Prevention Research Unit
Department of Clinical Neurology
Level 6, West Wing
John Radcliffe Hospital
Oxford
OX3 9DU

OREC A: 05/Q1604/70

1st June 2005

Study title: The Oxford Vascular Study (OXVASC)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The purpose of this study is to find out how common vascular disease (e.g. heart attacks, strokes, transient ischaemic attacks and other circulatory problems) is in Oxfordshire and how it affects people's lives. This has never been done before for different types of vascular disease at the same time and in the same population. We hope the study will provide us with useful information on the best way of providing a service for those who suffer from these common problems. We hope we can build up a detailed picture of the way that people recover and the subsequent changes in health over several years.

Why have I been chosen?

You have been chosen because you are registered with one of the nine GP practices in Oxfordshire which are collaborating in the study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to read and be asked to sign a consent form. You will be given a copy of the information sheet and signed consent form to keep. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

If you decide to take part you would agree to an interview and a clinical examination by the researcher. It would also involve taking an extra sample of blood in the hospital or clinic. We

would also like to gather some information on risk factors for vascular disease from both your hospital and GP notes. The study would also involve being followed up by telephone or at home by a researcher in thirty days time, in six months, at one year, two years and five years. All the information collected will be completely confidential.

What do I have to do?

This is an observational study and taking part in the study will not affect your current or future care. No investigations, new drugs or other treatments will be tested.

What are the possible disadvantages and risks to taking part?

You will be required to give a blood sample which will cause mild discomfort. Where possible this will be taken at the same time as those collected in the course of your normal medical care. There are no additional risks involved.

What are the possible benefits of taking part?

We hope the information we get from this study may help us to treat future patients with vascular disease better.

What if something goes wrong?

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

It is likely that the results of this study will be published in medical journals after completion of the research. If you decide to take part in the study you will not be identified in any report.

Who is organising and funding the research?

This research is being organised by Professor Rothwell at The Stroke Prevention Research Unit, University of Oxford in collaboration with the Department of Primary Health Care, the Department of Cardiology and your participating General Practice. The study is funded by the Stroke Association and the Medical Research Council.

Who has reviewed the study?

The Oxfordshire Research Ethics Committee has approved the study.

Contact for Further Information

If you would like any further information please ask the researcher who is discussing this information sheet with you or by contacting the Oxford Vascular Study Office on 01865 231601.

Thank you for reading this.

The Stroke Prevention Research Unit

Department of Clinical Neurology

Level 6, West Wing

John Radcliffe Hospital

Oxford

Department of Primary Health Care

Institute of Health Sciences

Old Road

Headington

Oxford OX3 7LF

28th December 2006

CONSENT FORM

Title of Project: **OXFORD VASCULAR STUDY (OXVASC)**

Name of Researchers: Professor Peter Rothwell, Dr Ami Banerjee, Dr Lucy Binney, Dr Arvind Chandratheva, Dr Olivia Geraghty, Dr Lars Marquardt, Dr Nicola Paul, Dr Michela Simoni, Louise Silver, Linda Bull, Sarah Welch, Fiona Cuthbertson

	Please tick the relevant box	Yes	No
1.	I confirm that I have read and understand the information sheet dated 1st June 2005 for the above study and have had the opportunity to ask questions.	☐	☐
2.	I agree to take part in the above study.	☐	☐
3.	I understand that sections of any of my medical notes may be looked at by responsible individuals where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I understand that information held by the NHS and records maintained by the General Register Office may be used to keep in touch with me and follow up my health status.	☐	☐
4.	I understand future research using the blood sample I give may include genetic research aimed at understanding the genetic influences on vascular disease, but that the results of these investigations are unlikely to have any implications for me personally.	☐	☐
5.	I agree to take part in the follow up study that involves being interviewed at home or a place of my choice, by telephone or in person at 1, 6 , 12 , 24 and 60 months.	☐	☐
6.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	☐	☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Witness	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Stroke Prevention Research Unit

Department of Clinical Neurology

Level 6, West Wing

John Radcliffe Hospital

Oxford

OX3 9DU

Copies: 1 for patient; 1 for researcher; 1

to be kept with hospital notes

Department of Primary Health Care

Institute of Health Sciences

Old Road

Headington

Oxford OX3 7LF

ASSENT FORM

21st March 2005

Title of Project: **OXFORD VASCULAR STUDY (OXVASC)**

Name of Researchers: Professor Peter Rothwell, Dr Ami Banerjee, Dr Lucy Binney, Dr Arvind Chandratheva, Dr Olivia Geraghty, Dr Lars Marquardt, Dr Nicola Paul, Dr Michela Simoni, Louise Silver, Linda Bull, Sarah Welch, Fiona Cuthbertson.

Please initial box	**Yes**	**No**
1. I confirm that I have read and understand the information sheet dated 1st June 2005 for the above study and have had an opportunity to ask questions.	☐	☐
2. I understand that the participation of my relative is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected.	☐	☐
3. I understand that sections of any of my relative's medical notes may be looked at by responsible individuals where it is relevant to taking part in research. I give assent for these individuals to have access to these records.	☐	☐
4. I understand future research using the blood sample my relative gives may include genetic research aimed at understanding the genetic influences on vascular disease, but that the results of these investigations are unlikely to have any implications for my relative personally.	☐	☐
5. I agree for my relative to take part in the above study.	☐	☐

_____	_____	_____
Name of Next of Kin	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Copies: 1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 4

Oxford, 19-20-21/01/2010

Michela Simoni

INTER-RATER RELIABILITY STUDY OF VISUAL RATING SCALES FOR LEUKOARAIOSIS ON CT AND ON MRI SCANS

INITIAL SESSION: CONSENSUS RATING AND AGREEMENT ON DEFINITIONS

RATERS: MICHELA SIMONI, SILVIA LANFRANCONI, BASIL E. GRÜTER

1. GENERAL CONSIDERATIONS

A. What are we evaluating?

This is a study on visual evaluation scales for **LEUKOARAIOSIS** (LA), and that is what we all should look at. Hachinski in 1987 defined LA as a "diminution of the density of representation of white matter", and as "symmetric patchy or diffuse areas of low density in the hemispheric white matter". LA is represented by hypodense areas (darker than the normal white matter, with density between the normal WM and the CSF) on CT scans and as hyperintense areas (whiter than the normal white matter) on T2 weighted MRI sequences (those preferred for the evaluation of white matter). LA is often not detected or only partly visible in T1 sequences, as hypointense areas.

B. Lacunes

They are expression of small vessel disease but differ from LA in their pathogenesis. LA is probably due to pathology of smaller vessels (arteriole of 100-200 microns of diameter) arising from the sub-arachnoid and from the sub-ependymal arterial networks.

Fischer's definition of lacune implies a lesion which is

- round or oval in shape,
- measuring between 2 mm and 1.5 cm in diameter
- located in the typical territory supplied by deep or superficial small perforating arteries
- not in cortical territories
- without the morphologic and topographic distribution consistent with internal watershed infarcts

Lacunes may be the only expression of WM changes in a patient and may be associated to LA in a different patient.

On CT scans, lacunes are usually seen as the same density of CSF. Their density may be lower than the CSF (i.e they may appear not as black), depending on the distance of the CT slice from the lesion. It is sometimes impossible to distinguish a lacune from an area of LA, especially in cases with severe LA.

On MRI scans, lacunes show, again, the same density as the CSF. They can be distinguished from LA by looking at the T1 sequences, where they appear as well defined black lesions.

Lacunes, isolated (not in the context of a severe pattern of white matter changes) rounded or oval well defined lesions, with CSF signal density/intensity, **are not considered in the grading of leukoaraiosis**.

C. Perivascular spaces (Wirchow-Robin)

They are recognised to be expression of small vessel disease in older people. Sometimes are difficult to differentiate from lacunes. They usually appear as lesions with same signal as CSF, well demarcated, of variable size, typically located in the posterior commissure area. They are not considered in LA grading.

D. Large lesions (infarcts, haemorrhages, cysts, etc..)

They make it impossible to evaluate the extent of white matter disease. In our evaluation we will not consider the area(s) of the brain interested by these lesions.

2. VISUAL SCALES

1. Van Swieten (CT)

We start with choosing three sections to consider for the evaluation: 1 slice at the level of the choroid plexus, 1 at level of the cella media of the lateral ventricles, 1 at the level of the centrum semiovale. The third slice is chosen as the second above the last slice showing the ventricles, provided this one shows enough white matter for the evaluation (in which case we consider the slice immediately above the ventricles).

We evaluate separately the 2 hemispheres. On slice 1 we only evaluate the region anterior to the central sulcus, on slice 2 we evaluate both the anterior and the posterior regions, on slice 3 we only evaluate the posterior region.

We grade each area on each hemisphere with a score from 0 to 2, where 0 is absence of LA, 1 is presence of pure periventricular LA, 2 is LA extending towards the cortex.

By consensus: when LA is only at subcortical level with complete sparing of the peri-ventricular areas we rate it as 0. We grade 2 on this scale only when there is a complete extension of LA from the ventricles to the cortex.

We choose the highest score for each of the 2 regions (either on right or left hemisphere) and we sum them to obtain a total score (ranging from 0 to 4).

2. ARWMC scale - Wahlund's scale (CT and MRI)

Lesions are considered only if ill-defined and with diameter >/= 5 mm. Five regions to consider, separately for each hemisphere: Frontal, parieto-occipital, temporal, infra-tentorial, basal ganglia.

Frontal, parieto-occipital, temporal, infra-tentorial regions are rated according to the following scale:

0 = no LA

1 = focal lesions

2 = beginning confluence of lesions

3 = diffuse involvement of the entire region, with or without involvement of U fibers

By consensus: In case of periventricular disease only:

- thin caps are considered as 0
- thicker caps *(>/=5 mm)* seen as well defined continuous areas are scored as 1
- caps extending towards the cortex (in which a hint of separate lesions can still be identified) are scored as 2
- entire involvement of the area from ventricles to cortex is scored as 3

Basal Ganglia lesions are scored differently:

0 = no LA

1 = 1 focal lesion (>/= 5 mm)

2 = > 1 focal lesion

3 = confluent lesions

It is difficult to score the infra-tentorial area on CT scans, where artefact images are often present.

3. Oxford scale (CT and MRI)

0 = no LA

1 = mild LA

2 = moderate LA

3 = severe LA

Scale taking into account the **extension of LA** in a global way, at the level of the whole brain. The "whole picture" needs to be considered rather than the quality of single lesions.

When the degree of LA is 2 or 3, a distinction is made according to pattern of LA:

- Multi-focal lesions

- Confluent

- Both

4. Fazekas scale (MRI)

Periventricular and deep white matter are rated separately. The scores are summed up to give a total score (0-6).

PV lesions

0 = no lesion

1 = caps or pencil-thin lining

2 = smooth halo

3 = irregular periventricular hyper-intensities

Deep white matter lesions

0 = no lesion

1= punctuate foci (single lesion </= 10 mm or grouped lesions </= 20 mm)

2 = beginning confluence of foci (single lesion between 10 and 20 mm, grouped lesions with connecting bridges only)

3 = large confluent areas (single or confluent lesions > 20 mm).

3. MEASUREMENTS ON CT FILMS

We use as a comparison the ruler represented next to each image, which on our films is 5 cm long.

SECOND SESSION (28/01/2010):

CONSENSUS RATING AND AGREEMENT ON DEFINITIONS on MRI SCANS.

RATERS: MICHELA SIMONI, SILVIA LANFRANCONI, BASIL E. GRÜTER

All our patients have T2 sequences, none or a few have T1. Only a small proportion of the MRI we are going to evaluate have FLAIR sequences, and, even in these cases, it will be a coronal study rather than an axial one (which is the preferred view for the application of visual scales). A large proportion of patients have diffusion sequences.

We are going to evaluate T2 sequences, using the FLAIR coronal and the T1 (when available) to help distinguish lesions and lacunes when in doubt.

Rating MRI with the Fazekas scale:

About the difference between a score of 1 and a score of 2 in the deep white matter: we have agreed to consider as a single lesion lesions connected by "bridges" of LA and having a diameter of 10 mm or less. So, these lesions will be scored as 1.

So, it will be:

Deep white matter lesions

0 = no lesion

1= punctuate foci (single lesion </= 10 mm or grouped lesions </= 20 mm or **grouped lesions with connecting bridges only, and measuring </= 10 mm**)

2 = beginning confluence of foci (single lesion between 10 and 20 mm, grouped lesions with connecting bridges only, and measuring **>/= 10 mm**)

3 = large confluent areas (single or confluent lesions > 20 mm).

Appendix 5

SD	Standard deviation	$\sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{(n-1)}}$
ARV	Average real variability	$\frac{1}{n-1}\sum_{i=1}^{n-1}\lvert x_{i+1} - x_i \rvert$

Appendix 6

Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility

Alastair JS Webb[†] BMBCh MSc, Michela Simoni[†] MD MRCP, Sara Mazzucco[†,X] MD PhD, Wilhelm Kuker[†] FRCR, Ursula Schulz[†] PhD, *Peter M Rothwell[†] FMedSci

Affiliations: [†] Stroke Prevention Research Unit, University of Oxford, UK

[X] Department of Neurological, Neuropsychological, Morphological and Movement Sciences, Section of Clinical Neurology, University of Verona, Italy

Abstract

Background and Purpose Arterial stiffening reduces damping of the arterial waveform and hence increases pulsatility of cerebral blood flow, potentially damaging small vessels. In the absence of previous studies in patients with recent TIA or stroke, we determined the associations between leukoaraiosis and aortic and middle cerebral artery stiffness and pulsatility.

Methods Patients were recruited from the Oxford Vascular Study within 6 weeks of a TIA or minor stroke. Leukoaraiosis was categorised on MRI by two independent observers with the Fazekas and ARWMC scales. MCA stiffness (transit time: MCA-TT) and pulsatility (Gosling's index: MCA-PI) were measured with transcranial ultrasound, and aortic pulse wave velocity (ao-PWV) and aortic systolic, diastolic and pulse pressure (SBP, DBP, PP) with applanation tonometry (Sphygmocor).

Results In 100 patients, MCA-PI was significantly greater in patients with leukoaraiosis (0.91 vs 0.73, $p<0.0001$). Severity of leukoaraiosis was associated with MCA-PI and aortic PWV (Fazekas: $\chi^2=0.39$, MCA-PI $p=0.01$, ao-PWV $p=0.06$; ARWMC: $\chi^2=0.38$, MCA-PI $p=0.015$; ao-PWV $p=0.026$) for periventricular and deep white matter lesions, independent of aortic SBP, DBP and PP and MCA-TT, with MCA-PI independent of age. In a multivariate model ($r^2=0.68$, $p<0.0001$), MCA-PI was independently associated with aortic-PWV ($p=0.016$) and aortic-PP ($p<0.0001$) and inversely associated with aortic-DBP ($p<0.0001$) and MCA-TT ($p=0.001$).

Conclusions MCA pulsatility was the strongest physiological correlate of leukoaraiosis, independent of age, and was dependent upon aortic-DBP and PP and aortic and MCA stiffness, supporting the hypothesis that large artery stiffening results in increased arterial pulsatility, with transmission to the cerebral small vessels resulting in leukoaraiosis.

Introduction

Prevention of premature leukoaraiosis by treating the underlying causes in middle age may reduce the risk of stroke[1] and dementia,[2] and other consequences of cerebral small vessel disease,[3, 4] but the aetiology is not yet fully understood. The relative importance of haemodynamic factors as opposed to a primary microangiopathy[5] in the development of leukoaraiosis is unclear and associations with age, hypertension and diabetes are consistent with both processes.[6] Previous studies have suggested a relationship between increased middle cerebral artery (MCA) pulsatility measured by transcranial Doppler ultrasound (TCD) and leukoaraiosis or lacunar infarction in patients with hypertension[7] and diabetes,[8] although not necessarily independent of age. However, increased cerebral pulsatility has often been interpreted as a consequence of small vessel disease due to changes in downstream resistance,[9] rather than as a causal factor related to increased central arterial stiffness and reduced damping of the cerebral arterial waveform.[10] Yet the cerebral circulation appears to be specifically adapted to dampen the arterial waveform[11] and increased aortic stiffness has been associated with leukoaraiosis,[12] lacunar stroke,[13] and cerebral pulsatility.[10] However, these relationships all strongly covary with age and are susceptible to residual confounding. Previous studies have not measured leukoaraiosis, aortic pulse wave velocity (PWV) and middle cerebral pulsatility optimally in the same patient group and no study has also measured aortic pulsatility and middle cerebral artery stiffness,

key components of the hypothesised mechanism in which increased aortic pulsatility is transmitted via stiff large vessels to the cerebral microvasculature.

Therefore we performed the first study assessing the dependence of leukoaraiosis on arterial stiffness and pulsatility in both the aorta and middle cerebral artery in patients with recent TIA or minor stroke, to assess the degree to which leukoaraiosis depends independently on each of these measures, after adjustment for significant clinical features, particularly age.

Methods

Consecutive consenting and eligible participants within 6 weeks of a TIA or minor stroke (NIHSS<5) were recruited to a physiological substudy of the Oxford Vascular Study (OXVASC)[14] between January and December 2011 from the acute TIA and stroke clinic associated with the study. Participants were excluded if they were under 18 years, unable to have an MRI scan, cognitively impaired (MMSE<23), pregnant or had had a recent myocardial infarction (<1 month), unstable angina, heart failure (NYHA 3-4 or ejection fraction <40%) or untreated severe bilateral carotid stenosis (>70%) or occlusion. The study was approved by the Oxfordshire Research Ethics Committee.

MRI scans were performed during the acute clinical assessment on a 3T MRI system (Siemens Magnetom Verio) according to a standardised protocol using vendor-designed sequences. The protocol comprised T2-weighted TSE and FLAIR sequences, diffusion and susceptibility-weighted

images, a T1-weighted spin-echo 2D sequence post contrast application as well as a time-of-flight MRA of the intracranial vessels and a contrast enhanced MRA of the large neck arteries.

All axial T2 scans were scored according to a modified version of the Fazekas[15] scale by an experienced observer (MS) blinded to clinical and physiological data, as this score is the simplest, most commonly used and well-validated semi-quantitative score for leukoaraiosis. MS also graded scans by the ARWMC[16] score to demonstrate the consistency of the results. Finally, leukoaraiosis was also independently scored by MS and a consultant neuroradiologist (WK), who was not blinded to the patient's clinical details, on a simple 4 point scale: 'None', 'Mild,' 'Moderate' or 'Severe' relative to the patient's age (Oxford scale). For comparison, the Fazekas and ARWMC scores were also categorised into four approximately equally sized groups (Fazekas: none 0, mild 1, moderate 2, severe ≥3; ARWMC: none 0, mild 1-3, moderate 4-9, severe ≥10).

Physiological tests were performed at rest in a quiet, dimly-lit, temperature-controlled room (21-23^{0}C). Applanation tonometry (Sphygmocor, AtCor Medical, Sydney, Australia) was used to measure carotid-femoral pulse wave velocity (aortic-PWV), aortic augmentation index and central aortic systolic, diastolic and pulse pressure (ao-SBP, ao-DBP, ao-PP),[17] calibrated to the average of 3 brachial blood pressures measured supine after at least 10 minutes rest. TCD (Doppler Box, Compumedics DWL, Singen, Germany) was performed with a handheld 2MHz probe at the temporal bone window on the

same side as carotid applanation. The waveform envelope was acquired at 100Hz simultaneously with ECG and blood pressure at 200Hz (Finometer, Finapres Medical Systems, The Netherlands), via a Powerlab 8/30 with LabChart Pro software (ADInstruments, USA). The MCA was insonated at 50mm, or if this was not adequate, at the depth giving the optimal waveform. Data were exported to Matlab R2010a for calculation of mean MCA transit time (MCA-TT) measured from the QRS complex to the foot of at least 7 beats as identified by intersecting tangents.[18] All waveforms were visually inspected and beats corrupted by artefact were excluded. MCA-PWV was calculated as the distance between the sternal notch and the temporal bone window divided by MCA-TT.[19] MCA pulsatility was calculated as Gosling's pulsatility index (MCA-PI= (systolic CBFV-diastolic CBFV) / mean CBFV).

Kappa statistics were derived to asses inter-rater agreement for assessment of leukoaraiosis with the Oxford score, and agreement of severity of leukaraiosis between the Fazekas and ARWMC scales. Differences between patient groups in continuous variables were assessed by t-tests or ANOVA, with tests for linear trend for severity of leukoaraiosis, whilst differences in frequencies were compared by chi-squared tests. Univariate relationships between continuous variables were assessed by linear regression. Multivariate predictors of continuous physiological outcome variables were determined by general linear models but due to the non-normal, positively skewed distribution of the semi-quantitative scores for leukoaraiosis, relationships between leukoaraiosis severity and either clinical or

physiological measures were assessed with ordinal regression. Relationships were assessed with and without adjustment for age and gender and then adjusted for additional cardiovascular risk factors including: history of hypertension, stroke, hypercholesterolaemia, current smoking, family history of stroke, diabetes, height, and brachial systolic and diastolic BP.

All analyses were performed in Matlab R2010a, SPSS 17.0 and Microsoft Excel 2010.

Results

Of 110 patients recruited, 10 (9%) had inadequate temporal bone windows for TCD. 30 patients had no leukoaraiosis on the Fazekas scale (38 had no periventricular leukoaraiosis and 42 had no deep white matter lesions), compared to 39 on the ARWMC and Oxford scales. The inter-rater agreement for leukoaraiosis in 100 consecutive cases imaged by MRI and rated by the Oxford scale was good (k=0.78, 95% CI 0.65-0.90 for presence of leukoaraiosis and weighted k=0.66, 0.56-0.76 for severity of leukoaraiosis). Agreement in assessment of the severity of leukoaraiosis between the ARWMC and Fazekas scales was also good (weighted k=0.60, 0.48-0.72).

In univariate comparisons, age, frequency of hypertension and a lower diastolic blood pressure were associated with increasing severity of leukoaraiosis (table 1). MCA-PI increased with age, female sex, diabetes, creatinine and a lower DBP (supplemental table S1, http://stroke.ahajournals.org), whereas

aortic pulse pressure was associated with elevated SBP, age and female gender. Aortic PWV was similarly associated with age, SBP, hypertension and creatinine but MCA-TT was only associated with age. There was no relationship between event type (stroke vs TIA), aetiology or territory and either leukoaraiosis or physiological measures. Patients with leukoaraiosis had significantly greater MCA-pulsatility (0.91 vs 0.73, $p<0.0001$), aortic PWV (10.5 vs 8.1 m/s, $p<0.0001$), aortic pulse pressure (47.3 vs 35.8 mmHg, $p<0.0001$) and MCA stiffness, whether measured as mean transit time (153 vs 164 ms, $p<0.0001$) or MCA-PWV (1.38 vs 1.31 m/s, $p=0.016$), on all scales. Furthermore, these relationships showed a dose-response relationship with increasing severity of leukoaraiosis (see figure 1). MCA-PI and aortic-PWV were independent predictors of total score on the Fazekas and ARWMC scales (Ordinal regression: Fazekas $\chi^2=0.39$, MCA-PI $p=0.01$, ao-PWV $p=0.06$; ARWMC $\chi^2=0.38$, MCA-PI $p=0.015$; ao-PWV $p=0.026$) in models including MCA-PI, MCA-TT, ao-PWV, ao-PP, ao-SBP and ao-DBP. In models adjusting for age, gender and major cardiovascular risk factors, only MCA-PI and age remained as independent predictors (table 2). The same associations with total Fazekas score were also found for periventricular ($\chi^2=0.31$, MCA-PI $p=0.029$, ao-PWV $p=0.044$) and deep white matter scores ($\chi^2=0.34$, MCA-PI $p=0.03$, ao-PWV $p=0.08$) except that aortic-PWV was not independently associated with deep lesions. Models including aortic pulsatility index instead of aortic PP and MCA-PWV instead of MCA-TT were not significantly different, and the same results were found with adjusted logistic regression comparing patients with leukoaraisos versus no leukoaraiosis.

MCA-PI was dependent upon both pulsatility and arterial stiffness in both the aorta and the MCA with strong associations with ao-PP, ao-PWV and MCA-TT and, whilst there was no association with SBP, there was a strong negative association with DBP (figure 2). In addition, there was a relationship between aortic and middle cerebral artery stiffness but only when the analysis was limited to patients with less variable ao-PWV (SD for repeated measures <2): ao-PWV vs MCA-TT r^2=0.075, p=0.013; ao-PWV vs MCA-PWV r^2=0.063, p=0.023. In multivariate comparisons, MCA-PI was independently associated with aortic-DBP, aortic-PP, aortic-PWV and MCA-TT (r^2=0.680, ao-PP p<0.0001, ao-DBP p<0.0001, MCA-TT p=0.001, ao-PWV p=0.016), all of which were independent of age and cardiovascular risk factors except for aortic-PWV (see table 2).

Discussion

This study demonstrates a significant relationship between MCA pulsatility and the presence and severity of leukoaraiosis in a cohort of patients with recent TIA and minor stroke, with similar results for both periventricular and deep white matter disease. This relationship was independent of age and other physiological measures, and was significantly stronger than the association between leukoaraiosis and aortic stiffness or aortic pulsatility. The very strong association (r^2>0.6) of MCA-PI with aortic pulsatility, diastolic BP, aortic stiffness and MCA stiffness, further suggests that MCA-PI is mainly dependent upon these measures, rather than on distal small vessel resistance.

Leukoaraiosis is strongly associated with cognitive impairment,[1, 2] an increased risk of stroke,[1] increased morbidity as a result of stroke[20, 21] and increased mortality.[1] However, it is unclear whether leukoaraiosis has a predominantly ischaemic aetiology due to either chronic ischaemia[22, 23] or incomplete episodic infarction, or whether it represents a primary microangiopathy that directly causes both leukoaraiosis and the associated physiological changes.[5, 24] Whilst both hypotheses could explain the clinical associations, the former hypothesis is supported by studies showing a relationship between the anatomical distribution of leukoaraiosis and lower cerebral blood flow[22] or cerebrovascular reactivity,[25] whilst the latter hypothesis is supported by independent genetic associations with leukoaraiosis,[26] superficially similar white matter disease in CADASIL[27] and COL4A1 mutations[28] and the demonstration of increased blood-brain barrier permeability in patients with leukoaraiosis, both in lesions and in normal appearing white matter.[5, 24] However, ultimately it is likely that these two mechanisms are not mutually exclusive. Ours is the first study to assess the association of leukoaraiosis with stiffness and pulsatility in both the aorta and cerebral arteries in one cohort. We demonstrated a significantly stronger association of leukoaraiosis with MCA-PI than with any other physiological measure, despite similar associations with age, suggesting a more direct pathophysiological relationship. In addition, this means that it is unlikely that differences in leukoaraiosis and cerebral pulsatility are solely due to independent effects of age on the brain. The very strong correlation of MCA-PI with aortic pulsatility and large artery stiffness also suggests a

causative pathophysiological relationship. Together these findings imply that increased arterial stiffening causes increased transmission of enhanced aortic pulsatility to the cerebral circulation, causing leukoaraiosis either due to alterations in perfusion during diastole, due to increased endothelial shear stress or due to impaired cerebral autoregulation of fluctuations in blood pressure. Previous studies demonstrating a relationship between leukoaraiosis and either cerebral pulsatility[7] or aortic stiffness[12] have only assessed one component of this mechanism and could not determine whether increased cerebral pulsatility results from leukoaraiosis or whether arterial stiffening and leukoaraiosis are only independent markers of age.

Our study has some limitations. First, it was a cross-sectional, observational study and therefore it is possible that the physiological associations with leukoaraiosis are confounded by a systemic primary microangiopathy, but this is unlikely given the strength of the relationship between the physiological variables and MCA-PI. Nonetheless, larger longitudinal studies will be required to confirm these findings. Second, the patients were heterogeneous in both age and stroke aetiology. This resulted in an increased range of leukoaraiosis, increasing the sensitivity of the study, but there were insufficient patients to identify whether these associations differed by specific subgroups, particularly whether the same associations applied to patients with lacunar and non-lacunar stroke. Third, we did not assess whether the relationships between leukoaraiosis and the vascular indices were confounded by other haemodynamic measures such as longer-term blood pressure variability over beat-to-beat, 24 hour or

day-to-day timeframes.[29] Finally, we did not address whether there were coexistent changes in blood brain barrier permeability in this patient group.

Assessing the potential contribution of haemodynamic factors to the aetiology of leukoaraiosis is important for guiding the development of interventions, especially as no direct interventions exist to treat a primary microangiopathy. Current antihypertensive medications may reduce cerebral arterial pulsatility, and this could potentially be part of the explanation for differences between antihypertensive medications in the resultant risk of stroke[30] and cognitive impairment,[31] possibly by effects on blood-pressure variability or associated mechanisms. In addition, therapies directed at reducing aortic stiffness in middle-age could delay the development of leukoaraiosis. Further research needs to assess the longitudinal relationship between cerebral pulsatility and the development of leukoaraiosis, and ideally test whether interventions which reduce cerebral pulsatility or aortic stiffness also prevented development of leukoaraiosis.

Conclusions

Leukoaraiosis is closely associated with cerebral arterial pulsatility, which is strongly dependent upon aortic pulsatility and large artery stiffness. This is consistent with the hypothesis that arterial stiffening results in increased aortic pulsatility and its transmission to the cerebral circulation and may play a pathophysiological role in the development of leukoaraiosis and its clinical sequelae. Ultimately,

treatment aimed at reducing arterial stiffness in middle age might be most effective in preventing stroke, dementia and other consequences of cerebral small vessel disease.

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	Fazekas Scale Score				
	0 (n=30)	1 (n=21)	2 (n=24)	≥3 (n=25)	p-value
Age	53 (15)	66.5 (12)	68.5 (11)	74.9 (7.9)	<0.0001
Male	22 (73)	13 (62)	14 (58)	17 (68)	0.58
Event type:					
Stroke	11 (37)	9 (43)	9 (38)	9 (36)	0.76
TIA	19 (63)	12 (57)	15 (63)	16 (64)	
Hypertensive	9 (30)	7 (33)	12 (50)	17 (68)	0.03
Diabetes	2 (6.7)	3 (14)	2 (8.3)	6 (24)	0.10
Family History*	5 (17)	5 (24)	5 (21)	10 (40)	0.08
Hyperlipidaemia	9 (30)	8 (38)	7 (29)	12 (48)	0.27
Atrial Fibrillation	0 (0)	1 (4.8)	3 (13)	3 (12)	0.05
Current smoker	7 (23)	2 (9.5)	4 (17)	5 (20)	0.82
Blood Pressure:					
Systolic	124.1 (16.4)	132.9 (14.9)	131.6 (18.8)	129.6 (19.9)	0.28
Diastolic	78.7 (11.8)	77.6 (11.1)	74.4 (12.7)	70.7 (12.3)	0.01
Creatinine	79.8 (15.4)	75.3 (16)	77.5 (17.9)	89.6 (25.7)	0.08
BMI	28.1 (5.9)	27.5 (5.3)	27.5 (5.5)	26.9 (3.8)	0.44

Table 1. Demographic characteristics of patients according to severity of leukoaraiosis. Severity of leukoaraiosis is measured according to the total score on the Fazekas scale. Continuous variables are presented as mean (sd) with p-values for trend across levels of leukoaraiosis. Frequencies are presented as number (%), with p-values for trend. *Family History refers to a reported history of stroke in either parent.

Outcome	Global model			Independent Associations		
	Model design	r^2 / χ^2	p-value	Variable	β	p-value
Fazekas Scale (adj physiology)	Ordinal Regression*	39.44	<0.001	MCA-PI Aortic PWV	4.79 0.15	0.01 0.06
Fazekas Scale (adj age+gender)	Ordinal Regression†	48.07	<0.001	MCA-PI Age	4.75 0.074	0.011 0.003
Fazekas Scale (adj all variables)	Ordinal Regression‡	48.98	<0.001	MCA-PI Age	4.33 0.089	0.037 0.002
MCA – PI (adj physiology)	GLM *	0.680	<0.001	Aortic PP Aortic DBP Aortic PWV MCA-TT	0.006 -0.009 0.011 -0.002	<0.0001 <0.0001 0.016 0.001
MCA – PI (adj age+gender)	GLM †	0.686	<0.001	Aortic PP Aortic DBP Aortic PWV MCA-TT	0.005 -0.008 0.009 -0.002	<0.001 <0.001 0.079 0.004
MCA – PI (adj all variables)	GLM ‡	0.744	<0.001	Aortic PP Aortic DBP MCA-TT Diabetes	0.006 -0.006 -0.002 0.101	0.004 0.007 0.006 0.005

Table 2. Associations of severity of leukoaraiosis and middle cerebral artery pulsatility in multivariate models including demographic and physiological variables. Severity of leukoaraiosis is measured according to the total score on the Fazekas scale. Ordinal regressions are presented for severity of leukoaraiosis due to the non-Normal distribution of leukoaraiosis severity, whilst physiological determinants of MCA-PI are assessed by general linear models (GLM), with and without adjustment for clinical features. *Physiological variables include aortic SBP and DBP and pulse pressure, aortic stiffness (PWV), MCA stiffness (transit time) and MCA pulsatility (MCA-PI). †Additionally adjusted for age and gender; ‡ additionally adjusted for history of hypertension, stroke,

hypercholesterolaemia, current smoking, family history of stroke, diabetes, height, and brachial systolic and diastolic BP.

Appendix 7

Population-based case-control study of white matter changes on brain imaging in ischaemic stroke subtypes

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Key words: White Matter Changes, Small Vessel Disease, stroke, aetiology, stroke subtype

Abstract

Background: White matter changes (WMC) are a common finding on brain imaging and are associated with an increased risk of ischaemic stroke. They are most frequent in small vessel stroke, but in the absence of comparisons with normal controls the exact nature of association is unclear and it is uncertain whether WMC are associated to a lesser extent with other stroke subtypes. We therefore compared the frequency and severity of WMC in different aetiological subtypes of ischaemic stroke versus normal controls in a population-based study.

Methods: We evaluated presence and severity of WMC on CT brain imaging and on MRI brain imaging using modified Blennow/Fazekas scale and ARWMC scale respectively in a population-based study of patients with incident TIA or ischaemic stroke (Oxford Vascular Study - OXVASC) and a study of local healthy controls (Oxford Project to Investigate Memory and Ageing – OPTIMA), with stratification by stroke aetiology (TOAST classification) and age.

Findings: Among 1601 consecutive eligible patients with first-ever ischaemic events (998 stroke; 603 TIA), 1453 had CT brain imaging, 562 had MR imaging and 414 had both. Compared with 313 healthy controls (all with CT and 131 with MRI) and after adjustment for age, sex, diabetes and hypertension, moderate-to-severe WMC (ARWMC scale) were more frequent in patients with small vessel events (OR=3·51, 95%CI 2·13-5·76, p<0·0001) but not in large artery (1·03, 0·64-1·67, p=0·89), cardioembolic (0·87, 0·56-1·34, p=0·52), or undetermined (0·90, 0·62-1·30, p=0·57) subtypes. The association of WMC with small vessel events decreased with age (<75 years - 5·24, 2·21-12·38; 75-84 - 3·51, 2·13-5·76; ≥85 -1·31, 0·36-4·72). Results were consistent for other WMC scales and for MRI and CT separately.

Interpretation: In contrast to small vessel TIA and stroke, WMC were not independently associated with other aetiologies, suggesting that the association between small vessel events and WMC must be explained by risk factors and mechanisms that are not involved in the aetiology of other subtypes of TIA and stroke.

Introduction

White matter changes (WMC) are frequently reported on brain imaging, predominantly in older individuals, but their aetiology remains unclear. WMC are independently associated with an increased risk of incident stroke after adjustment for age, sex and vascular risk factors in population-based cohort studies[1-6] and in high risk populations,[7-10] and also with an increased risk of recurrent stroke.[11-14] However, previous cohort studies did not report the risk association stratified by subtype of ischaemic stroke or by age, and although most cross-sectional studies report a higher prevalence and severity of WMC in lacunar stroke versus other aetiologies,[15-22] some studies were non-blinded, with stroke aetiology assessed only on brain imaging,[15, 16, 21, 22] one study showed more WMC in large vessel stroke,[23] no study stratified analyses by age or sex, and there have been no adequately powered studies comparing imaging in different stroke subtypes with imaging in healthy controls. It is uncertain, therefore, whether WMC are associated purely with lacunar stroke or with ischaemic stroke more generally. Moreover, it is unclear in some studies whether associations might have been explained by confounding by shared associations with vascular risk factors, particularly hypertension.[17, 19, 20, 22]

More reliable data on the association between WMC and ischaemic stroke subtypes would be helpful in understanding the role of WMC in the aetiology of stroke, in determining shared vascular risk factors and genetics, and potentially in informing investigation of individuals found to have WMC on brain

imaging done for other reasons. A large prospective cohort study with baseline brain imaging and detailed stroke subtyping on follow-up could provide such data, but would need to be very large in order to have sufficient stroke outcomes of each aetiological subtype to reliably distinguish between their risk associations. Foreknowledge of findings on baseline imaging might also influence preventive treatment and thereby bias associations. We therefore carried out the first population-based case-control study of the associations of WMC and aetiological subtype of TIA or ischaemic stroke, comparing brain imaging in patients with incident ischaemic events with imaging in age-matched population controls.

Methods

Consecutive patients with first-in-a-life-time incident TIA or ischaemic stroke who underwent brain imaging at assessment in the Oxford Vascular (OXVASC) study between 1st April 2002 and 31st March 2011 were studied. OXVASC is a population-based study of all acute vascular events in a population of 91 000 individuals registered with 101 primary care physicians in nine general practices in and around Oxford, UK. Methods of OXVASC have been reported previously.[24] Briefly, multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke. These include: 1) a daily, rapid access "TIA clinic" to which participating general practitioners and the local accident and emergency department refer all

individuals with suspected, but not hospitalized TIA or stroke; 2) daily searches of admissions to the medical, stroke, neurology , and other relevant wards; 3) daily searches of the local accident and emergency department attendance register; 4) daily searches of in-hospital death records via the Bereavement Office; 5) monthly searches of all death certificates and coroner's reports for out of hospital deaths; 6) monthly searches of primary care diagnostic coding and hospital discharge codes; 7) monthly searches of all brain and vascular imaging referrals.

Detailed clinical history was recorded in all patients. Patients routinely had CT or MR brain imaging depending on the period of recruitment. In the first four years, CT brain was the first line imaging modality and MRI was only done if clinically indicated. From 1st April 2006 onwards MRI was done routinely in all patients with posterior circulation TIA or stroke and MRI also became routine in all other study patients from 1st April 2010 onwards. A small proportion of OXVASC patients do not undergo brain imaging, most commonly due to death prior to or shortly after arrival at hospital, events occurring abroad, and ocular ischaemia only. Patients also underwent vascular imaging (carotid Doppler or CTA /MRA or DSA) and 12-lead electrocardiography (ECG). Echocardiography and 24-hour ECG (HOLTER) monitoring were done when clinically indicated. All cases were reviewed by a senior neurologist and classified according to the Oxfordshire Community Stroke Project (OCSP) classification[25] as well as the modified Trial of Org10172 in Acute Stroke Treatment (TOAST) criteria.[266,27]

Controls were healthy individuals who had no history of TIA or stroke who were recruited as elderly volunteers without symptoms of memory impairment for two control groups related to the Oxford Project to Investigate Memory and Ageing (OPTIMA) study. In the first group (OPTIMA controls), all had CT brain imaging. In the second group (CHALLENGE Study), all had CT and MR brain imaging. In both control groups, all subjects underwent a detailed clinical history and physical examination. CT and MR brain imaging in both groups was performed in the same hospital as patients in the OXVASC cohort. CT scans were performed on a Toshiba, Aquilion 64, 64-slice scanner. MRI scans were performed on a 1·5T Philips Achieva scanner.

Written informed consent was obtained in all participants and both OXVASC and OPTIMA studies were approved by the local ethics committee.

Assessment of WMC: Details of imaging protocols and assessment of WMC in the OXVASC study have been published previously.[28] Briefly, WMC was prospectively coded by a neuroradiologist and by an experienced neurologist, independently and blind to clinical data, using two scales:

1) Modified Blennow and Fazekas scale: a simple qualitative scale (absent, mild, moderate, or severe) based on the severity score of the Blennow scale for CT, [29] and a modified version of the Fazekas scale,[30] considering periventricular and deep white matter lesions altogether, for the MRI.

2) ARWMC scale[31] for both CT and MRI, rating five different regions in both hemispheres according to a 0-3 score. Total score was categorised as: absent (0), mild (1-5), moderate (6 -10) and severe (>10) WMC.

CT-based visual rating of WMC in the OPTIMA Study has been shown to validate well with subcortical vascular disease found at post-mortem. [32, 33] In OXVASC, inter-rater agreement on presence and severity of WMC was moderate to good on CT (kappa=0·64, 95%CI 0·59-0·69, for presence of any WMC, and 0·58, 0·55-0·62 for severity; modified Blennow scale) and on MRI (k=0·78, 0·65-0·90 for presence and 0·66, 0·56-0·76 for severity of WMC; modified Fazekas scale). Agreement between independent assessments made on CT versus MRI in the same patients was not significantly less than the inter-observer reproducibilities of either modality alone.[34] To ensure comparable assessment of WMC on MRI in both OXVASC cases and OPTIMA controls, assessments were limited to transvere T2 sequences· Large cortico-subcortical strokes, definite lacunar lesions (well delineated, oval or rounded in shape, measuring 1·5 cm or less, or with the same signal intensity than cerebrospinal fluid), perivascular spaces and obvious tumours or cysts were not categorised as WMC.

Statistical analysis: We analysed the differences in presence and severity of WMC between cases and controls separately in those who had CT imaging and those who had MR imaging. We compared

the prevalence of any WMC and moderate-to-severe WMC between each TIA/stroke subtype (OCSP/TOAST) and the control group using $\chi 2$ test and logistic regression analysis with adjustment for age, sex, diabetes and hypertension. In the absence of any significant heterogeneity in associations we then obtained pooled estimates of the CT-based and MRI-based associations (MRI evaluation was used in those who had both CT and MR imaging) with Mantel-Haenzel-Peto meta-analysis. Analyses were also stratified into age groups. All analyses were performed using SPSS version 20.

Results

Of 1601 eligible OXVASC patients with first-ever ischaemic events (998 stroke; 603 TIA), 1453 had CT brain imaging, 562 had MR imaging and 414 had both. TOAST subtype was cardioembolic in 367 (22·9%), large artery in 175 (10·9%), small vessel in 216 (13·5%), multiple in 44 (2·7%), other determined cause in 30 (1·9%), undetermined (despite full investigation) in 598 (37·4%) and unknown (incomplete investigation) in 171 (10·7%). OCSP subtype was lacunar in 319 (19·9%) and non-lacunar in1282 (80·1%).

Of the 313 healthy controls from OPTIMA, all had CT brain imaging and 131 had MR brain imaging. Apart from history of TIA or stroke, the baseline characteristics of the OXVASC cases and OPTIMA

controls were broadly similar. Among those imaged with CT, cases and controls had similar mean/SD age (cases - 74·1/12·6; controls - 75·3/8·7), gender distribution (female 51·4% vs. 54·0%) and history of myocardial infarction (10·5% vs. 8·3%), although, as expected, more cases had a history of hypertension (55·5% vs. 34·5%, p<0·0001) and diabetes (13·1% vs. 3·5%, p<0·0001). Among those imaged with MR, cases were younger than controls (66·8/14·3 vs. 77·4/6·1, p<0·0001) and were again more likely to have hypertension (51·6% vs. 37·4%, p=0·003) and diabetes (13·2% vs.3·8%, p=0·002). All analyses below are therefore adjusted for age, sex, diabetes and hypertension. Differences between aetiological subtypes of TIA and stroke in baseline characteristics are shown in table 1.

In OXVASC cases, the prevalence and severity of WMC did not differ significantly between the scales used (moderate-to-severe WMC - CT: ARWMC - 26·6%, modified Blennow - 27·3%, kappa=0·65, 95%CI 0·60-0·70, p<0·0001; MRI: ARWMC - 28·1%, modified Fazekas - 27·6%, kappa=0·75, 0·69-0·81, p<0·0001). As expected, prevalence of any WMC was higher on MRI than on CT (patients with both modalities - ARWMC: CT - 47·9%, MRI - 64·7%; modified scales: CT - 47·1%, MRI - 58·7%) resulting in only moderate agreement between the two modalities (ARWMC – kappa=0·61, 95%CI 0·55-0·67, p<0·0001; modified scales – kappa=0·70, 0·63-0·77, p<0·0001). However, agreement was good for moderate or severe WMC (ARWMC – kappa=0·68, 0·61-0·75, p<0·0001; modified scales –

kappa=0·77, 0·71-0·83, p<0·0001). Moreover, the associations between vascular risk factors and WMC were highly consistent between CT and MRI and between the different scales (table 2).

In multivariate analyses including all patients, only older age and small vessel subtype were consistently associated with WMC overall (table 2), although history of hypertension was also of borderline significance. Compared with other aetiological subtypes, patients with small vessel TIA or stroke were significantly more likely to have any WMC (ARWMC: CT-OR=1·81, 95%CI 1·17-2·81, p=0·01; MRI - 2·83, 1·48-5·40, p=0·002; pooled - 2·09, 1·45-3·00, p=0·0001) and to have moderate or severe WMC (ARWMC: CT-2·68, 1·72-4·18, p<0·0001; MRI - 4·56, 2·50-8·32, p<0·0001; pooled - 3·23, 2·26-4·62, p<0·0001). Moreover, there was no independent association between WMC and atrial fibrillation (table 2) or with the presence of unilateral or bilateral ≥50% carotid stenosis (any WMC – ARWMC: unilateral - adjusted OR=0·98, 95%CI 0·68-1·42, bilateral - 0·83, 0·39-1·74; modified scale: unilateral - 1·04, 0·73-1·49, bilateral - 1·02, 0·51-2·04).

The strong association between small vessel events and WMC was also evident in the comparison of cases and population controls (table 3; web appendix 1-2) before and after adjustment for age, sex, diabetes and hypertension (Modified Blennow - OR=1·85, 95%CI 1·15-2·99, p=0·01, ARWMC- 2·68,

1·63-4·41 p=0·0001) and for moderate-to-severe WMC only (2·62, 1·60-4·28, p=0·0001, 3·51, 2·13-5·76, p<0·0001).

In contrast, there were no significant differences in the prevalence of any or moderate-to-severe WMC between any of the other subtypes of TIA and stroke and controls after adjustment for age, sex, diabetes and hypertension (ARWMC- any WMC: cardioembolic – OR=1·06, 95%CI 0·71-1·57, large artery -1·31, 0·82-2·11, undetermined - 1·22,0·88-1·71; moderate-to-severe WMC: cardioembolic - 1·03, 0·64-1·67, large artery - 1·03, 0·64-1·67, undetermined – 0·90, 0·62-1·30, table 3). The results were very similar for the other scales (table 3, web appendix 1-2). Results were similar for separate analysis of TIA vs. controls and stroke vs. controls (table 4) and for male vs. female (small vessel events vs. control in male: ARWMC –adjusted OR=4·21, 95%CI 2·04-8·66, p=0·0001, female: 2·98, 1·38-1·79, p=0·01; non-small vessel events in male: 0·97, 0·59-1·60, female: 1·12, 0·70-1·79).

The associations of moderate-to-severe WMC and small vessel events were strongest at younger ages (figure 1 and web appendix 3; <75 years- Modified Blennow OR=4·07, 95%CI 1·70-9·72, p=0·002; ARWMC - 5·24, 2·21-12·38, p=0·0002; 75-84 years- Modified Blennow - 2·62, 1·60-4·28, p=0·0001; ARWMC – 3·51, 2·13-5·76, p<0·0001; ≥85 years- Modified Blennow - 1·40, 0·43-4·54, p=0·57; ARWMC - 1·31, 0·36-4·72, p=0·68). The trend was similar for any WMC (web appendix 3).

In the analyses stratified by the OCSP classification (clinical lacunar vs. non-lacunar subtypes), there was some heterogeneity between CT-based and MRI-based comparisons, but results were broadly similar (web appendix 4), the association with lacunar subtype being similar to that with small vessel subtype based on TOAST classification.

Discussion

In this population-based study, we showed that WMC were strongly and independently associated with small vessel TIA and stroke, but not with other aetiological subtypes. Our results were consistent in CT-based and MRI-based comparisons, for any WMC and moderate-to-severe WMC, and also for the purely clinical lacunar subtype (LACI). In each case, these associations were strongest at younger ages.

The association between lacunar infarcts and WMC has been documented by cross-sectional clinical, radiological (CT and MRI) as well as pathological studies.[15,16,35] Moreover, progression of WMC on follow-up has also been shown to be associated with prior lacunar infarction,[36, 37] accepting that up to one third of lacunar infarcts diagnosed may be due to large vessel disease.[38] However, only a few conflicting studies[17–20] have compared the relationship between WMC and different aetiological stroke subtypes and there have been no previous case-control studies with sufficient power to stratify

analyses by subtype. The only previous case-control study of WMC was a well-designed MRI-based study in the early 1990s,[39] but had only 27 patients in the subset of cases with lacunar infarction and did not find any greater prevalence of WMC in these cases than in controls. Although this finding conflicts with our case-control findings (based on 78 small vessel cases imaged with MRI and 200 with CT) and with most previous case: case comparisons of stroke subtypes, [15–22] the earlier case-control study was consistent with our findings with regard to the absence of any association between WMC and non-small vessel infarcts.[39] Previous cross-sectional studies of stroke cases provide conflicting evidence about the association of WMC and non-small vessel stroke. Some studies showed that WMC were less frequent in territorial infarcts compared to lacunar infarcts, [15, 38]whereas another found that large vessel stroke had more WMC than other subtypes, [23]and a study in young stroke patients reported that WMC was more often present with small vessel disease or large vessel disease than with undetermined or other determined aetiology stroke. [20] However, none of these studies adjusted for confounding by age and other risk factors.

Our finding that after adjustment of age, sex and history of hypertension, there was no association between WMC and non-small vessel TIA/stroke is consistent with other evidence. Firstly, in the case:case comparison within OXVASC, we did not find any independent association between WMC and unilateral or bilateral carotid stenosis (≥50%) or atrial fibrillation (table 2). Secondly, previous

studies have also shown that there appears to be no association between WMC and side or severity of atherosclerotic carotid stenosis[40-43] or atrial fibrillation.[35]

WMC are clearly related strongly to age, irrespective of any major role of vascular risk factors.[28] However, the independent association of WMC with small vessel events but not with other aetiologies of TIA or stroke suggests that WMC and small vessel events do share some additional genetic or environmental risk factors. The association between these two pathologies could reflect a shared increase in susceptibility to a traditional risk factor, such as hypertension, or be due to as yet undetermined novel risk factors, but it does not necessarily indicate any association between WMC and the vascular pathology of small vessel events. In patients with similar underlying small vessel pathology, the increased occurrence of lacunar-type events in patients with WMC could simply reflect an increased susceptibility to ischaemia in the white matter.

Although we consider our findings to be valid, our study does have several limitations. First, our observations were partly based on CT scans. However, although MRI is more sensitive than CT in the detection of mild early WMC, more severe changes are detected more equally.[31] Moreover, we found good agreement for moderate or severe WMC on CT versus MRI, and CT-based visual rating of WMC in the OPTIMA Study validated well with subcortical vascular disease found at post-mortem.[32, 33] Most

importantly, however, our main findings in analyses based on CT were highly consistent with our analyses confined to MRI only. Second, we used semi-quantitative scales rather than lesion volume methods in our MRI-based analysis. Although possibly less sensitive, visual scores are closely related to volumes,[44] and may be more specific as they are less prone to artefacts due to accidental inclusion of areas of cerebral infarction. Third, as our controls were recruited from volunteers without memory complaint, there could be a healthy volunteer bias. However, any such bias would tend to overestimate the association between WMC and non-small vessel events, which we did not find anyway. Fourth, we used only history of hypertension to reflect the role of blood pressure in our analyses, which perhaps explains the relatively weak association between hypertension and WMC. However, the same definition was used in cases and controls and the lack of association between WMC and non-small vessel events could not be explained by any failure to account for blood pressure effects. Finally, we used the TOAST criteria to classify TIA and stroke subtypes. Although TOAST is the most widely accepted stroke classification, it does have some shortcomings.[27] However, we also used the OCSP clinical classification and found similar results. Moreover, we found no association between WMC and non-small vessel events despite the possibility that some might have been misclassified small vessel events.

Our finding that WMC were independently associated with small vessel TIA and ischaemic stroke, particularly in the younger patients, but not with non-small vessel events has a number of implications.

First, the association between small vessel events and WMC must be explained by mechanisms that are not involved in the aetiology of other subtypes of TIA and stroke. Further research is needed to determine the shared mechanism(s) that underlie this association between acute and chronic white matter ischaemia. Second, as WMC are not independently associated with carotid stenosis or atrial fibrillation or with large vessel or cardioembolic TIA and stroke, screening for carotid stenosis or cardiac causes in patients with incidental WMC on brain imaging done for non-vascular reasons may not be necessary. Rather, such individuals should have their blood pressure closely monitored. Third, also with relevance to the counselling and investigating patients with incidental WMC, our finding that the independent association between WMC and even small vessel TIA and stroke is lost at older ages suggests that WMC may be of little prognostic significance, at least for stroke, at older ages. Future prospective cohort studies should stratify prognostic analyses by age.

Research in Context panel

Systematic review

We searched Medline (1950-2012) and Embase (1988-2012) and also hand-searched relevant journals and the reference lists of included papers. We used the search terms "white matter changes", "white matter hyperintensities", " leukoaraisosis", "white matter disease", "small vessel disease", "lacunar", "stroke", "subtype" and "aetiology". Searches were restricted to human studies. All reviews,

cohort studies, cross sectional studies were included. No previous case-control studies of the association of WMC with ischaemic stroke subtypes were found.

Interpretation

Our study shows that in contrast to small vessel TIA and stroke, WMC are not independently associated with other ischaemic stroke subtypes, suggesting that the association between small vessel events and WMC must be explained by risk factors and mechanisms that are not involved in the aetiology of other subtypes of TIA and stroke.

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Table 1 Baseline characteristics among aetiological subtypes

CT	Cardioembolic (n=357)		Large vessel (n=155)		Small vessel (n=200)		Undetermined (n=514)		Unknown (n=162)		Multiple (n=43)		Other cause (n=22)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Mean age (SD)	78·0 (11·9)		74·0 (10·4)		71·5 (12·2)		70·7 (12·7)		80·2 (11·1)		80·0 (8·0)		56·8 (12·5)	
Female	195	54·6%	65	41·9%	81	40·5%	271	52·7%	106	65·4%	18	41·9%	11	50·0%
History of hypertension	208	58·3%	100	64·5%	116	58·0%	260	50·6%	80	49·4%	33	76·7%	10	45·5%
History of diabetes	38	10·6%	25	16·1%	40	20·0%	57	11·1%	23	14·2%	7	16·3%	1	4·5%
History of smoking	176	49·3%	97	62·6%	118	59·0%	275	53·5%	62	38·3%	27	62·8%	12	54·5%
Peripheral vascular disease	25	7·0%	24	15·5%	10	5·0%	19	3·7%	11	6·8%	5	11·6%	0	-
History of hyperlipidaemia	81	22·7%	60	38·7%	59	29·5%	150	29·2%	32	19·8%	15	34·9%	3	13·6%
History of myocardial infarction	55	15·4%	24	15·5%	9	4·5%	39	7·6%	16	9·9%	8	18·6%	1	4·5%
MRI	Cardioembolic (n=66)		Large vessel (n=86)		Small vessel (n=78)		Undetermined (n=285)		Unknown (n=13)		Multiple (n=12)		Other cause (n=22)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Mean age (SD)	69·2 (15·9)		72·2 (10·1)		66·1 (13·8)		65·4 (14·4)		66·2 (16·4)		78·9 (7·0)		54·4 (14·2)	
Female	38	57·6%	26	30·2%	29	37·2%	132	46·3%	9	69·2%	3	25·0%	10	45·5%
History of hypertension	37	56·1%	54	62·8%	41	52·6%	131	46·0%	9	69·2%	9	75·0%	9	40·9%
History of diabetes	10	15·2%	12	14·0%	9	11·5%	34	11·9%	6	46·2%	1	8·3%	2	9·1%
History of smoking	31	47·7%	57	66·3%	40	51·3%	164	58·0%	6	46·2%	10	83·3%	13	61·9%
Peripheral vascular disease	3	4·5%	12	14·0%	2	2·6%	11	3·9%	0	-	3	25·0%	0	-
History of hyperlipidaemia	19	28·8%	31	36·0%	27	34·6%	91	31·9%	1	7·7%	6	50·0%	2	9·1%
History of myocardial infarction	5	7·6%	10	11·6%	2	2·6%	16	5·6%	0	-	1	8·3%	0	-

Table 2 Associations of risk factors and presence or severity of white matter changes (WMC) in OXVASC 2002-2011 (Multivariate Logistic Regression analysis)

	CT			MRI			Pooled results		
Risk factors in multivariate analysis	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
ARWMC									
Any WMC vs· no WMC									
Age (per year)	1·11	1·09-1·13	<0·0001	1·09	1·07-1·10	<0·0001	1·10	1·08-1·11	<0·0001
Sex	0·83	0·60-1·16	0·27	0·80	0·52-1·22	0·30	0·82	0·63-1·06	0·13
History of hypertension	1·18	0·86-1·63	0··30	1·50	0·97-2·32	0·07	1·28	0·99-1·66	0·06
History of diabetes	1·29	0·79-2·11	0·31	0·62	0·33-1·17	0·14	0·98	0·67-1·44	0·92
History of smoking	1·56	1·12-2·17	0·01	1·19	0·78-1·83	0·42	1·41	1·09-1·83	0·01
History of hyperlipidaemia	0·72	0·50-1·05	0·09	1·42	0·89-2·26	0·14	0·94	0·70-1·26	0·67
Atrial fibrillation	0·81	0·56-1·17	0·26	1·09	0·55-2·16	0·81	0·86	0·63-1·19	0·38
History of myocardial infarction	1·16	0·69-1·94	0·57	0·59	0·26-1·37	0·22	0·97	0·62-1·50	0·88
Small vessel vs· non-small vessel	1·70	1·08-2·67	0·02	2·85	1·49-5·46	0·002	2·01	1·39-2·92	0·0002
Moderate-to-severe WMC vs· no-mild WMC									
Age (per year)	1·11	1·09-1·14	<0·0001	1·09	1·07-1·12	<0·0001	1·10	1·09-1·12	<0·0001
Sex	0·88	0·62-1·25	0·47	1·05	0·65-1·68	0·85	0·94	0·70-1·24	0·65
History of hypertension	1·49	1·05-2·11	0·03	1·45	0·90-2·33	0·13	1·47	1·11-1·95	0·01
History of diabetes	1·44	0·87-2·39	0·16	0·90	0·46-1·75	0·75	1·21	0·81-1·82	0·35
History of smoking	1·09	0·82-1·45	0·56	0·84	0·53-1·34	0·47	1·02	0·80-1·30	0·9
History of hyperlipidaemia	0·94	0·62-1·40	0·75	1·14	0·69-1·86	0·62	1·01	0·74-1·38	0·95
Atrial fibrillation	0·94	0·64-1·38	0·75	1·66	0·88-3·12	0·12	1·09	0·79-1·51	0·59
History of myocardial infarction	0·83	0·49-1·40	0·48	1·08	0·45-2·57	0·87	0·89	0·57-1·39	0·60
Small vessel vs· non-small vessel	2·62	1·64-4·17	<0·0001	4·87	2·65-8·95	<0·0001	3·30	2·28-4·77	<0·0001
Modified scales									
Any WMC vs· no WMC									
Age (per year)	1·10	1·08-1·12	<0·0001	1·09	1·07-1·11	<0·0001	1·09	1·08-1·11	<0·0001
Sex	0·93	0·67-1·28	0·64	1·01	0·67-1·52	0·98	0·96	0·74-1·23	0·72
History of hypertension	1·34	0·98-1·83	0·07	1·43	0·94-2·18	0·10	1·37	1·06-1·76	0·01
History of diabetes	1·54	0·96-2·49	0·07	0·43	0·23-0·78	0·01	0·95	0·65-1·38	0·79
History of smoking	1·31	0·96-1·79	0·09	1·13	0·75-1·72	0·55	1·24	0·97-1·59	0·08
History of hyperlipidaemia	0·81	0·56-1·16	0·24	1·39	0·89-2·18	0·15	1·00	0·75-1·33	1·00
Atrial fibrillation	1·02	0·72-1·44	0·93	1·47	0·75-2·89	0·26	1·10	0·81-1·50	0·55
History of myocardial infarction	1·34	0·82-2·18	0·24	0·78	0·35-1·77	0·56	1·16	0·77-1·77	0·48
Small vessel vs· non-small vessel	1·74	1·12-2·70	0·01	2·65	1·46-4·81	0·001	2·01	1·41-2·87	0·0001
Moderate-to-severe WMC vs· no-mild WMC									
Age (per year)	1·08	1·06-1·10	<0·0001	1·09	1·06-1·11	<0·0001	1·08	1·07-1·10	<0·0001
Sex	0·8	0·58-	0·28	1·1	0·69-	0·68	0·9	0·69-	0·55

	3	1·17			1·75		2	1·21	
History of hypertension	1·14	0·81-1·60	0·46	1·25	0·78-1·99	0·35	1·18	0·89-1·55	0·25
History of diabetes	1·18	0·71-1·94	0·53	0·77	0·39-1·51	0·44	1·01	0·67-1·51	0·96
History of smoking	0·87	0·64-1·20	0·40	0·84	0·53-1·32	0·45	0·86	0·67-1·12	0·26
History of hyperlipidaemia	1·03	0·70-1·54	0·87	1·18	0·73-1·92	0·51	1·09	0·80-1·48	0·59
Atrial fibrillation	1·20	0·83-1·74	0·33	1·58	0·84-2·96	0·16	1·29	0·94-1·77	0·12
History of myocardial infarction	1·58	0·97-2·57	0·06	0·53	0·20-1·39	0·20	1·27	0·82-1·96	0·28
Small vessel vs· non-small vessel	1·93	1·22-3·07	0·01	4·77	2·66-8·54	<0·0001	2·74	1·91-3·94	<0·0001

Table 3 Pooled odds ratio for prevalence of any and moderate-to-severe WMC in TIA/stroke patients vs. controls

		Adjusted OR* (95%CI)	p	Adjusted OR* (95%CI)	p
		Any		**Moderate-to-severe**	
ARWMC	ALL	1·43 (1·08-1·90)	0·01	1·23 (0·91-1·68)	0·18
	Small vessel	2·68 (1·63-4·41)	0·0001	3·51 (2·13-5·76)	<0·0001
	Large artery	1·31 (0·82-2·11)	0·26	1·03 (0·64-1·67)	0·89
	Cardioembolic	1·06 (0·71-1·57)	0·79	0·87 (0·56-1·34)	0·52
	Undetermined	1·22 (0·88-1·71)	0·24	0·90 (0·62-1·30)	0·57
Modified scales	ALL	1·08 (0·81-1·43)	0·61	1·25 (0·93-1·70)	0·15
	Small vessel	1·85 (1·15-2·99)	0·01	2·62 (1·60-4·28)	0·0001
	Large artery	0·98 (0·61-1·57)	0·93	1·03 (0·63-1·68)	0·91
	Cardioembolic	0·86 (0·58-1·29)	0·48	1·17 (0·78-1·76)	0·45
	Undetermined	0·79 (0·57-1·10)	0·16	0·77 (0·53-1·11)	0·16

*Adjusted for age, sex, diabetes and hypertension. WMC=White matter changes. TIA=Transient ischaemic attack.

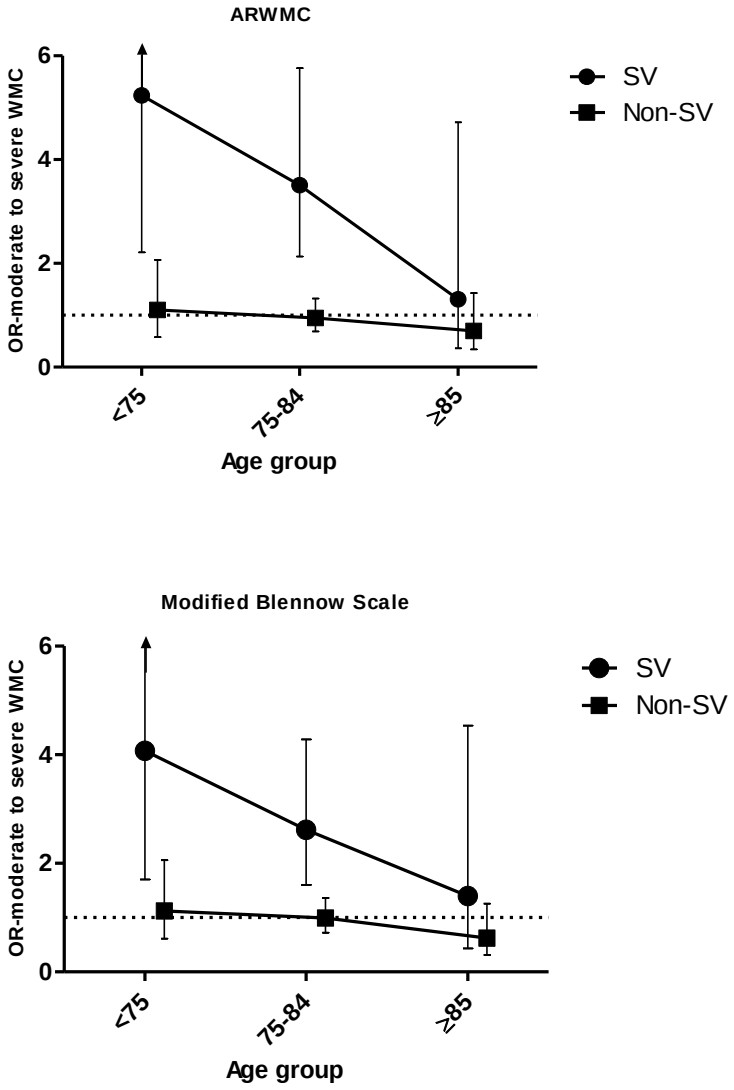
Table 4 Pooled odds ratio for prevalence and severity of WMC in stroke cases vs. controls and TIA cases vs. controls

			Any WMC		Moderate-to-severe WMC	
			Adjusted OR* (95%CI)	p	Adjusted OR* (95%CI)	p
ARWMC						
	All	SV	2·68 (1·63-4·41)	0·0001	3·51 (2·13-5·76)	<0·0001
		Non-SV	1·24 (0·92-1·67)	0·15	0·95 (0·69-1·32)	0·78
	Stroke	SV	2·71 (1·58-4·67)	0·0003	3·52 (2·05-6·04)	<0·0001
		Non-SV	1·41 (1·02-1·97)	0·04	1·08 (0·76-1·54)	0·67
	TIA	SV	2·55 (1·06-6·14)	0·04	3·07 (1·34-7·05)	0·01
		Non-SV	0·99 (0·69-1·40)	0·94	0·74 (0·50-1·10)	0·13
Modified scales						
	All	SV	1·85 (1·15-2·99)	0·01	2·62 (1·60-4·28)	0·0001
		Non-SV	0·90 (0·67-1·20)	0·46	0·99 (0·72-1·36)	0·94
	Stroke	SV	1·74 (1·04-2·92)	0·04	2·27 (1·31-3·91)	0·003
		Non-SV	0·95 (0·68-1·31)	0·75	1·17 (0·83-1·66)	0·37
	TIA	SV	1·98 (0·84-4·65)	0·12	3·47 (1·56-7·73)	0·002
		Non-SV	0·76 (0·54-1·08)	0·12	0·70 (0·48-1·03)	0·07

*Adjusted for age, sex, diabetes and hypertension. WMC=White matter changes. TIA=Transient ischaemic attack. SV=Small vessel, non-SV=non-small vessel (large vessel+cardioembolic+undetermined+other aetiology).

Figure 1 Age-, sex- , diabetes- and hypertension- adjusted odds of the prevalence of moderate-to-severe WMC in TIA/stroke patients vs. controls stratified by age

WMC=White matter changes· SV=small vessel, non-SV=non-small vessel (large vessel+cardioembolic+undetermined+other aetiology).



Appendix 8

Additional tables and figures

Table A2.0. Description of the studies considered in the meta-analyses of various risk factors in chapters 2, 3, 5. Studies are ordered alphabetically according to the first author's name.

First author	Year	Population Setting	Size (n.)	Imaging	Primary Objective of Study	Risk Factors Considered
Agartz	1992	Healthy volunteers	76	MRI	Association between white matter changes and the size of CSF spaces?	Sex, Age, BP, Hyperlipidaemia, Diabetes, Smoking,IHD
Aszalos	2002	Stroke	500	CT	To determine the frequency of hypertension in the Hungarian stroke population and analyse differences of risk factors associations in the 2 groups of hypertensives and not	BP
Awada	1996	Stroke in-patients	398	CT	Different associations of vascular risk factors in patients with stroke according to presence of LA?	Sex, Age, BP, Diabetes, IHD, Stroke, AF
Basile	2006	Out-patients with LA and no disability	639	MRI	Which are the main determinant of LA severity?	Sex, Age, BP, Diabetes, Smoking, Hyperlipidaemia, IHD, Stroke
Benedetti	2006	Healthy Subjects	89	MRI	Study on ageing and brain changes	Age, Sex
Biessels	2006	Dementia	431	MRI	does diabetes predispose to a particular type of dementia?	Diabetes
Bokura	2008	Healthy Subjects	1151	MRI	Association with metabolic syndrome	Sex, BP, Age, Diabetes, Hyperlipidaemia, Smoking
Bots	1993	Population-based (Rotterdam)	111	MRI	Association between WMC and atherosclerosis	Sex, Age, BP, Hyperlipidaemia,Smoking, IHD, PVD, Carotid stenosis
Breteler	1994	Population-based, demented excluded (Rotterdam)	96	MRI	Prevalence and clinical correlates of WMC, and their role in cognitive decline in the elderly	Sex, Age
Censori	2007	Neurology in-patients	178	CT	Are high levels of homocisteine a risk factor for severe LA?	Sex, Age, BP, Hyperlipidaemia, Diabetes, Smoking, IHD, Stroke, AF
Coskun	2003	Stroke	288	CT	Any association between LA and vascular risk factors?	Sex, Age, BP, Diabetes, Hyperlipidaemia, Smoking, Stroke, AF, IHD
De Leeuw	2001	Population-based (Rotterdam)	1077	MRI	What is the prevalence of white matter lesions, according to different brain regions, and in association to gender and age?	Sex, Age,
Fu	2005	First ever stroke	228	MRI	Is LA an independent RF for stroke?	Age, Diabetes, Stroke, Smoking, AF, IHD
Fujita	2002	Out-patients	175	MRI	Association between LA and platelet hyperaggregability?	Sex, Age, BP
George	1986	Healthy subjects and demented patients	275 pts (151 demented and 124	CT	Prevalence of WMC and definition of their clinical and pathological meaning	Sex, Age, BP, Diabetes, IHD, PVD
Goldstein	2005	Healthy Subjects	121	MRI	Association with ambulatory BP	BP
Henon	1996	Stroke/TIA in-patients	610	CT	Is LA associated with vascular risk factors and demographic characteristics?	Sex, Age, BP, Hyperlipidaemia, Diabetes, AF, Carotid Stenosis, Stroke
Henon	2003	Stroke in-patients	202	CT	What is the influence of pre-stroke and post-stroke dementia on the risk of stroke recurrence?	Stroke, IHD
Hijdra	1990	Stroke (ischaemic and haemorrhagic)	367	CT	Clinical associations of WMC	Sex, Age, BP, Diabetes, IHD, Stroke
Hofman	1999	Post-Concussional Disorder and controls	13 pts and 13 controls	MRI/MTR	To determine whether MTR can ber reliable in assessing white matter changes	Sex, Age
Hopkins	2006	Healthy Subjects	243	MRI	Prevalence of LA?	Sex, Age
Hsu	2008	Healthy Subjects	145	MRI	Gender differences in LA?	Sex, Age
Inzitari	1987	Demented patients (140) and controls (110)	250	CT	Risk factors for LA? Link between LA and dementia?	BP, Diabetes,IHD, Stroke
Inzitari	1990	ICH and controls	116 ICH, 155 controls	CT	Is LA a risk factor for ICH?	Stroke
Jeerakathil	2004	Healthy Subjects	1814	MRI	Are WMC related to a cumulative factor of stroke risk predictor?	Sex, Age, BP, Diabetes, Hyperlipidaemia, Smoking, IHD, Stroke
Jorgensen	1995	Stroke and TIAs	1084	CT	To determine factors imp[ortant in the development of LA and to study the influence of LA on stroke outcome.	Sex, Age, BP, Diabetes,Smoking, Stroke, PVD, AF, IHD
Karsidag	1995	Stroke	89	CT	What are the RFs that correlate to LA? What is the relation between LA and different types of strokes?	Sex, Age, BP, Diabetes, IHD, Stroke, PVD
Khan	2007	Stroke and Controls	885 and 734	MRI/CT	Associations between vascular risk factors and SVD	Sex, Age, BP, Diabetes, Hyperlipidaemia, Smoking, IHD
Kobari	1990	Normal volunteers	37	CT	Pathogenetic characteristics of LA in normal volunteers	Age, BP, Diabetes, Smoking, IHD
Kocer	2005	Heart failure or AF and controls with atherosclerosis risk factors	50 patients and 80 controls	MRI	Is there any association between leukoaraiosis and low output heart failure or AF?	Sex, BP, Diabetes, Hyperlipidaemia, IHD, Stroke
Koton	2008	Stroke/TIA in-patients	1024	CT	Is LA correlated to poor outcome at one month and at one year after a stroke or TIA in hospitalised patients?	Age, Hyperlipidaemia, Diabetes, Stroke, PVD, Smoking, AF, IHD

Table A2.0, continue

First author	Year	Population Setting	Size (n.)	Imaging	Primary Objective of Study	Risk Factors Considered
Lee	2006	Dementia (AD) and controls	75 and 117	MRI	Relation between LA and BP	BP
Longstreth	2005	Population-based (CHS)	1119	MRI	Incidence, manifestations and predictors of worsening white matter grade over a five year period	Sex, Age, BP,Hyperlipidaemia, Smoking, IHD, Stroke
Longstreth	1998	Population-based (CHS)	5888	MRI	Are WMC associated to vascular risk factors in the elderly population?	Sex, Age, BP, Stroke
Longstreth	2001	Population-based (CHS)	3230	MRI	Association between vascular risk factors and different MRI clusters (normal, simple infarct,	Sex, Age, Diabetes, BP, Smoking
Marti-Fabregas	2001	Binswanger's disease (13), Lacunar infarcts (12)	25	MRI	Existence of relation between the presence of LA and BP variability measured by 24 hour tape	Sex, Age, BP, Diabetes, hyperlipidaemia, Smoking, IHD, PVD
Minn	2005	First-ever ischaemic stroke	50	CT	What is the incidence of silent infarcts and the relationship between silent infarcts and other stroke risk factors in very elderly patients with first ever acurte ischemic stroke?	Stroke
Padovani	1997	Stroke and controls	50 stroke and 50	MRI	Are LA and venttricular enlargment correlated to vascular risk factors?	Sex, Age, BP, Diabetes, IHD, Stroke
Pantoni	2005	Neurology clinics, independent on IADL	639	MRI	Are LA severity and its progression related to progression to disability in the elderly patients?	Sex, Age
Park	2007	Healthy volunteers	1030	MRI	Relationship between LA and metabolic syndrome	Sex, Age, BP, Hyperlipidaemia, Diabetes, IHD, Smoking
Podgorska	2002	Stroke	370	MRI	Is LA affecting stroke outcome and cognitive	Sex, Age, Diabetes, Stroke, Hyperlipidaemia,
Puisieux F	2001	In-patients	79	CT	Association between LA and BP variability?	Age, BP, Stroke
Schmidt	2003	Stroke	273	MRI	Any association between vascular risk factors and progression of LA?	Age, BP
Schwartz	2007	Population-based (ARIC)	610	MRI	Race-specific association with vascular risk factors	Sex, Age, BP, Diabetes, Hyperlipidaemia, Smoking
Streifler	2002	Symptomatic carotid disease	2618	CT	To determine: 1. the risk of stroke in patient with symptoms secondary to carotid disease and LA; 2. frequency of death or major complications after CEA in pts with LA	Age, BP, Diabetes,Hyperlipidaemia, Smoking, Stroke, PVD, IHD, Carotid stenosis
Streifler	2003	Symptomatic carotid disease	685	CT	To determine the progression of LA in patients with symptomatic ICA stenosis	Sex, Age, BP,Diabetes, Hyperlipidaemia, Smoking, IHD, Stroke, PVD, Carotid stenosis
Sullivan	1990	Elderly with depression	60 patients, 40 healthy	MRI	Any significant association with vascular risk factors in old depressed patients WMC?	Sex, Age, BP, Hyperlipidaemia, Diabetes, IHD, Stroke
Tartaro	1999	Neurologically healthy	66	CT	Association between LA and ambulatory BP monitoring?	BP, Diabetes, Smoking, Hyperlipidaemia
Tarvonen-Schroeder	1996	Neurology patients	52	CT	Association between LA and cause of death	Age, Sex, BP, Diabetes, IHD, Stroke, PVD, AF
Thein	2007	Stroke	60	CT	Vascular risk factors and prognostic meaning of leukoaraiosis	Age, BP, Hyperlipidaemia, diabetes, smoking, IHD
Tiehuis	2008	Symptomatic arterial disease	1043	MRI	Association with diabetes	Diabetes
Turner	2004	Sibships of patients of the GENOA study	483	MRI	Any heritability of LA?	Age, BP
van Den Heuvel	2004	Nested MRI substudy of the PROSPER study	554	MRI	Any different progression of LA according to gender?	Sex
van Dijk	2008	Population-based (Rotterdam)	668	MRI	Relation between risk factors and progression of LA	Sex, Age, BP, Smoking, Stroke
Ventura	2007	Healthy Subjects	73	CT	Prevalence and risk factors of leukoaraiosis	Age, Diabetes, Smoking, Hyperlipidaemia
Viana-Batista	2008	Neurology clinics, independent on IADL	29	MRI	Is severity of LA (measured with DWI ADC and lesion load) correlated to high BP, age and worse performance in cognitive tests?	Age, BP
Wallin	2000	Demented patients (AD and vascular dementia)	85	CT	Relation between LA on CT and clinical symptomatology, vascular factors, BBB function and other CT changes	Sex, Age, BP, Diabetes, IHD, Stroke
Wen	2004	Lacunar infarcts	94	MRI	Is LA a determinant of cognitive decline amongst patients with lacunar infarcts?	Sex, Age, BP, Diabetes, IHD, Stroke
Wisniewska	2000	Stroke/TIA	155	CT	Any difference in association of vascular risk factors	Sex, Age, BP, Diabetes, Hyperlipidaemia,
Ylikoski	1995	Neurologically healthy	128	MRI	Frequency and risk factors of LA	Sex, Age, BP, Diabetes, Stroke, IHD
Yue	1997	Healthy(1488), abnormal MRI (688), TIA and minor stroke (328), cognitive impairment (144), other neurology or cancer (1178)	3660	MRI	Is there any association between brain atrophy and/or white matter changes **and** age, sex, racial differences?	Sex, Age

Table A6. 1. Distribution of TOAST types of strokes and TIA among women and men of different age groups

		<35	P	35-44	P	45-54	P	55-64	P	65-74	P	75-84	P	>/=85	P	Tot.
CE	M	3		2		3		19		37		73		37		174
	F	2	0.65	1	0.56	7	0.21	7	**0.02**	30	0.39	86	0.3	89	**<0.001**	224
LAA	M	0		1		4		22		45		32		12		116
	F	0	na	0	na	2	0.41	9	**0.02**	26	**0.02**	40	0.35	18	0.27	96
SMV	M	0		6		14		28		51		39		12		150
	F	0	na	2	0.16	7	0.13	12	**0.01**	24	**0.002**	38	0.91	18	0.27	102
UND	M	1		13		31		70		83		98		27		323
	F	2	0.56	19	0.29	25	0.42	49	**0.05**	90	0.6	140	**0.006**	75	**<0.001**	402
UNK	M	1		0		7		6		16		35		26		91
	F	0	na	2	na	4	0.37	13	0.11	19	0.61	54	**0.04**	64	**<0.001**	157
MULT	M	0		0		1		1		4		8		7		21
	F	1	na	0	na	0	na	2	0.56	6	0.53	7	0.8	3	0.21	21
OTH	M	1		3		2		12		2		4		2		26
	F	2	0.56	2	0.66	1	0.56	6	0.16	7	0.1	6	0.53	3	0.66	30
Tot.		13		51		108		256		440		660		393		1921

Table A7.2 ORs of NIHSS>3 at first event (ischaemic strokes only) in the study, according to presence of excess of white matter changes on the entry scan. Strokes have been divided according to the three main pathogenetic types, following the TOAST classification

	CT scans				**MRI scans**			
			OR (95% CI)	P			OR (95% CI)	P
Cardioembolic strokes	Oxford	Univ.	1.28 (0.57-2.87)	0.544	Oxford	Univ.	n.a	n.a
		Multiv.	1.14 (0.49-2.65)	0.763		Multiv.	n.a	n.a
	ARWMC	Univ.	0.68 (0.29-1.61)	0.380	ARWMC	Univ.	n.a	n.a
		Multiv.	0.67 (0.27-1.67)	0.387		Multiv.	n.a	n.a
	van Swieten	Univ.	1.16 (0.60-2.23)	0.658	Fazekas	Univ.	0.48 (0.05-4.74)	0.526
		Multiv.	0.94 (0.47-1.88)	0.855		Multiv.	n.a	n.a
Large artery strokes	Oxford	Univ.	**1.28 91.14-9.34)**	**0.028**	Oxford	Univ.	**8.33 (1.49-46.7)**	**0.016**
		Multiv.	**3.69 (1.19-11.43)**	**0.024**		Multiv.	**12.63 (1.58-101)**	**0.017**
	ARWMC	Univ.	1.57 90.55-4.45)	0.397	ARWMC	Univ.	1.57 (0.55-4.45)	0.397
		Multiv.	2.08 90.67-6.48)	0.205		Multiv.	4.01 (0.40-40.2)	0.237
	van Swieten	Univ.	1.41 (0.58-3.47)	0.452	Fazekas	Univ.	1.23 (0.23-6.55)	0.811
		Multiv.	1.67 (0.62-4.50)	0.308		Multiv.	1.23 (0.16-9.52)	0.840
Small vessels strokes	Oxford	Univ.	1.10 (0.47-2.59)	0.820	Oxford	Univ.	2.60 (0.54-12.45)	0.232
		Multiv.	0.93 (0.37-2.32)	0.872		Multiv.	8.65 (0.44-169)	0.156
	ARWMC	Univ.	1.24 (0.57-2.72)	0.593	ARWMC	Univ.	2.19 (0.49-9.74)	0.304
		Multiv.	0.89 (0.38-2.07)	0.781		Multiv.	3.07 (0.43-21.7)	0.261
	van Swieten	Univ.	1.40 (0.65-2.99)	0.389	Fazekas	Univ.	4.0 (0.84-19.1)	0.082
		Multiv.	1.00 (0.44-2.26)	0.999		Multiv.	5.69 (0.75-43.4)	0.093

Table A7.3 ORs of abnormal baseline individual Barthel items according to presence of excess of white matter changes on CT or MRI scans.Analyses are adjusted for age, sex and history of previous stroke.

		Whole		Under 75		Over 75				Whole		Under 75		Over 75
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
Feeding	**Oxford Scale**	**2.44 (1.21-4.93)**	**0.013**	1.43 (0.36-5.71)	0.614	**2.68 (1.16-6.16)**	**0.021**	**Bladder control**	**Oxford Scale**	**1.74 (1.04-2.90)**	**0.034**	2.66 (0.98-7.21)	0.054	1.66 (0.90-3.07)
	ARWMC	2.03 (0.98-4.21)	0.058	2.43 (0.63-9.3)	0.195	1.84 (0.75-4.54)	0.185		**ARWMC**	1.15 (0.66-2.00)	0.627	1.62 (0.53-4.95)	0.397	1.12 (0.58-2.15)
	van Swieten	1.53 (0.76-3.06)	0.235	2.00 (0.53-7.59)	0.309	1.29 (0.56-2.96)	0.551		**van Swieten**	**1.61 (1.01-2.55)**	**0.044**	2.07 (0.74-5.76)	0.165	1.58 (0.94-2.67)
	Oxford scale	6.18 (0.98-39.1)	0.053	2.25 (0.13-37.6)	0.574	11.97 (0.86-166)	0.065		**Oxford scale**	**4.72 (1.40-15.87)**	**0.012**	4.98 (0.73-34.13)	0.102	**7.89 (1.40-44.4)**
	ARWMC	3.91 (0.62-24.6)	0.147	2.29 (0.14-38.2)	0.564	3.17 (0.25-40.4)	0.375		**ARWMC**	**5.68 (1.53-21.04)**	**0.009**	**32.25 (1.83-566)**	**0.017**	5.03 (0.92-27.56)
	Fazekas	4.34 (0.69-27.2)	0.118	2.20 (0.13-36.6)	0.584	5.47 (0.43-69.8)	0.191		**Fazekas**	**4.09 (1.14-14.73)**	**0.031**	7.80 (0.74-82.7)	0.088	3.93 (0.77-20.15)
Bathing	**Oxford Scale**	**1.79 (1.09-2.94)**	**0.021**	1.15 (0.40-3.29)	0.790	**1.99 (1.11-3.56)**	**0.020**	**Toilet**	**Oxford Scale**	**2.79 (1.48-5.28)**	**0.002**	1.53 (0.38-6.17)	0.550	**3.21 (1.54-6.66)**
	ARWMC	1.48 (0.89-2.47)	0.136	1.57 (0.57-4.37)	0.384	1.50 (0.82-2.76)	0.193		**ARWMC**	1.06 (0.49-2.27)	0.883	1.53 (0.37-6.44)	0.560	0.94 (0.37-2.38)
	van Swieten	1.43 (0.91-2.25)	0.122	2.00 (0.77-5.14)	0.153	1.25 (0.74-2.12)	0.409		**van Swieten**	1.35 (0.72-2.54)	0.351	1.83 (0.48-6.91)	0.375	1.19 (0.57-2.47)
	Oxford scale	**4.43 (1.38-14.22)**	**0.012**	2.69 (0.49-14.7)	0.254	**7.56 (1.33-42.9)**	**0.022**		**Oxford scale**	n.a	n.a	n.a	n.a	n.a
	ARWMC	**5.20 (1.57-17.2)**	**0.007**	4.24 (0.75-23.9)	0.102	5.61 (0.92-34.1)	0.061		**ARWMC**	10.0 (0.94-106)	0.056	6.96 (0.24-201)	0.258	n.a
	Fazekas	2.89 (0.91-9.16)	0.071	2.29 (0.43-12.13)	0.330	3.56 (0.67-18.9)	0.136		**Fazekas**	n.a	n.a	n.a	n.a	n.a
Grooming	**Oxford Scale**	**3.09 (1.66-5.74)**	**≤0.001**	2.66 (0.82-8.63)	0.103	**3.12 (1.48-6.56)**	**0.003**	**Transfers**	**Oxford Scale**	**2.07 (1.12-3.85)**	**0.021**	0.98 (0.26-3.62)	0.969	**2.68 (1.30-5.52)**
	ARWMC	1.83 (0.94-3.58)	0.076	2.03 (0.55-7.49)	0.289	1.81 (0.81-4.05)	0.146		**ARWMC**	0.93 (0.44-1.95)	0.844	0.53 (0.11-2.47)	0.414	1.12 (0.47-2.64)
	van Swieten	1.70 (0.92-3.14)	0.090	2.23 (0.65-7.71)	0.205	1.48 (0.72-3.05)	0.282		**van Swieten**	1.09 (0.58-2.02)	0.794	0.70 (0.19-2.65)	0.600	1.20 (0.59-2.44)
	Oxford scale	n.a	n.a	n.a	n.a	n.a	n.a		**Oxford scale**	**9.55 (1.76-51.9)**	**0.009**	3.66 (0.55-24.3)	0.179	n.a
	ARWMC	**14.73 (1.49-145)**	**0.021**	15.6 (0.83-295)	0.067	n.a	n.a		**ARWMC**	4.46 (0.93-21.4)	0.062	2.75 (0.39-19.2)	0.308	n.a
	Fazekas	n.a	n.a	n.a	n.a	n.a	n.a		**Fazekas**	**6.55 (1.22-35.1)**	**0.028**	3.02 (0.47-19.5)	0.245	n.a
Dressing	**Oxford Scale**	**1.84 (1.08-3.15)**	**0.026**	1.21 (0.41-3.60)	0.728	**2.00 (1.06-3.77)**	**0.033**	**Mobility**	**Oxford Scale**	**1.91 (1.15-3.19)**	**0.013**	1.30 (-.45-3.75)	0.633	**2.22 (1.22-4.04)**
	ARWMC	1.43 (0.82-2.50)	0.208	1.45 (0.45-4.67)	0.534	1.49 (0.77-2.86)	0.233		**ARWMC**	1.40 (0.81-2.41)	0.218	1.44 (0.48-4.31)	0.518	1.47 (0.78-2.75)
	van Swieten	1.25 (0.76-2.07)	0.376	2.07 (0.71-6.07)	0.186	1.05 (0.59-1.89)	0.858		**van Swieten**	**1.81 (1.14-2.88)**	**0.012**	1.88 (0.69-5.14)	0.217	**1.80 (1.06-3.06)**
	Oxford scale	**9.86 (2.48-39.2)**	**0.001**	**6.06 (1.07-34.2)**	**0.041**	**22.18 (1.73-284)**	**0.017**		**Oxford scale**	**3.29 (1.05-10.4)**	**0.042**	3.84 (0.78-18.9)	0.098	3.78 (0.55-26.2)
	ARWMC	**7.56 (1.84-31.0)**	**0.005**	**10.1 (1.37-75.0)**	**0.024**	5.38 (0.49-59.6)	0.170		**ARWMC**	2.19 (0.66-7.31)	0.202	4.24 (0.75-23.9)	0.102	1.78 (0.26-12.4)
	Fazekas	**5.84 (1.45-23.5)**	**0.013**	4.44 (0.74-26.8)	0.104	9.40 (0.84-105)	0.069		**Fazekas**	2.64 (0.82-8.56)	0.105	2.29 (0.43-12.1)	0.330	4.04 (0.71-23.2)
Bowels	**Oxford Scale**	**1.97 (1.04-3.74)**	**0.038**	1.28 (0.32-5.11)	0.725	**2.41 (1.115-5.04)**	**0.020**	**Stairs**	**Oxford Scale**	1.37 (0.88-2.14)	0.163	1.07 (0.43-2.63)	0.889	1.50 (0.89-2.54)
	ARWMC	1.31 (0.65-2.65)	0.445	1.34 (0.32-5.64)	0.691	1.39 (0.61-3.16)	0.427		**ARWMC**	1.27 (0.81-1.99)	0.298	1.85 (0.77-4.43)	0.167	1.16 (0.68-1.98)
	van Swieten	1.61 (0.88-2.94)	0.123	1.60 (0.42-6.05)	0.492	1.68 (0.84-3.33)	0.142		**van Swieten**	**1.53 (1.04-2.24)**	**0.029**	**2.33 (1.03-5.27)**	**0.042**	1.35 (0.87-2.10)
	Oxford scale	**9.46 (1.78-50.3)**	**0.008**	n.a	n.a	**8.78 (1.43-53.8)**	**0.019**		**Oxford scale**	1.94 (0.79-4.77)	0.147	1.81 (0.47-6.98)	0.386	2.40 (0.66-8.66)
	ARWMC	**4.57 (1.02-20.6)**	**0.048**	6.99 (0.24-201)	0.257	5.96 (0.96-36.9)	0.055		**ARWMC**	1.46 (0.57-3.73)	0.427	2.13 (0.47-9.67)	0.328	1.16 (0.34-4.04)
	Fazekas	**6.84 (1.30-36.1)**	**0.024**	n.a	n.a	5.63 (0.91-34.9)	0.063		**Fazekas**	1.51 (0.61-3.74)	0.379	1.42 (0.32-6.28)	0.647	1.78 (0.53-5.92)

Table A8.4 Association between leukoaraiosis and anxiety-depression. Variables entered in Model 1, besides leukoaraiosis: age and male sex; variables entered in Model 2: age, sex, history of cerebrovascular disease at entry in the study, history of angina or MI, diabetes, current smoking, ischaemic stroke as event at entry.

		Leukoaraiosis (LA)		Oxford Scale OR (95%CI)	P	ARWMC scale HR (95%CI)	P	van Swieten scale HR (95%CI)	P
Self-reported Anxiety-Depression	**At one month from the event**	**Any LA**	Mod1	1.04 (0.77-1.41)	0.810	1.07 (0.76-1.51)	0.709	1.13 (0.81-1.58)	0.467
			Mod2	1.02 (075-1.39)	0.893	1.06 (0.74-1.49)	0.765	1.12 (0.80-1.56)	0.519
		Mod/Sev LA	Mod1	0.96 (0.68-1.34)	0.789	0.97 (0.68-1.38)	0.861	0.98 (0.70-1.39)	0.929
			Mod2	0.93 (0.66-1.304)	0.658	0.95 (0.67-1.37)	0.794	0.98 (0.69-1.38)	0.888
	At one year from the event	**Any LA**	Mod1	1.24 (0.89-1.73)	0.206	1.21 (0.84-1.74)	0.308	1.17 (0.82-1.67)	0.392
			Mod2	1.20 (0.86-1.68)	0.285	1.15 (0.80-1.67)	0.457	1.12 (0.78-1.61)	0.539
		Mod/Sev LA	Mod1	1.09 (0.76-1.58)	0.631	1.25 (0.86-1.81)	0.245	1.00 (0.69-1.46)	0.980
			Mod2	1.06 (0.73-1.53)	0.777	1.19 (0.81-1.73)	0.375	0.97 (0.66-1.41)	0.855
	New depressed at one year	**Any LA**	Mod1	1.14 (0.69-1.87)	0.617	1.28 (0.74-2.21)	0.385	1.13 (0.67-1.93)	0.642
			Mod2	1.12 (0.68-1.85)	0.657	1.19 (0.68-2.07)	0.543	1.09 (0.64-1.86)	0.760
		Mod/Sev LA	Mod1	1.19 (0.70-2.03)	0.514	1.11 (0.64-1.92)	0.703	0.95 (0.55-1.65)	0.865
			Mod2	1.20 (0.70-2.04)	0.514	1.05 (0.61-1.83)	0.855	0.92 (0.53-1.60)	0.768
Treated Depression	**At one month from the event**	**Any LA**	Mod1	0.93 (0.63-1.38)	0.721	0.74 (0.47-1.17)	0.195	0.89 (0.59-1.36)	0.596
			Mod2	0.84 (0.56-1.26)	0.397	0.69 (0.43-1.09)	0.108	0.82 (0.54-1.26)	0.366
		Mod/Sev LA	Mod1	0.90 (0.59-1.38)	0.619	0.90 (0.58-1.42)	0.655	0.71 (0.45-1.11)	0.136
			Mod2	0.82 (0.53-1.27)	0.383	0.87 (0.55-1.37)	0.542	0.68 (0.43-1.07)	0.091
	At one year from the event	**Any LA**	Mod1	1.04 (0.72-1.52)	0.827	1.11 (0.73-1.68)	0.635	1.12 (0.75-1.68)	0.584
			Mod2	0.94 (0.64-1.38)	0.746	1.00 (0.65-1.54)	0.992	1.02 (0.68-1.54)	0.928
		Mod/Sev LA	Mod1	1.01 (0.67-1.53)	0.967	0.97 (0.63-1.49)	0.878	1.05 (0.69-1.60)	0.827
			Mod2	0.99 (0.65-1.52)	0.965	0.89 (0.57-1.39)	0.609	0.98 (0.64-1.51)	0.925
	New depressed at one year	**Any LA**	Mod1	0.97 (0.56-1.69)	0.914	1.42 (0.75-2.67)	0.280	1.39 (0.76-2.54)	0.284
			Mod2	0.91 (0.51-1.61)	0.746	1.20 (0.62-2.29)	0.529	1.21 (0.66-2.23)	0.543
		Mod/Sev LA	Mod1	0.97 (0.52-1.82)	0.930	0.83 (0.43-1.62)	0.586	1.16 (0.62-2.16)	0.643
			Mod2	0.99 (0.52-1.88)	0.973	0.73 (0.37-1.45)	0.365	1.09 (0.57-2.07)	0.793

Table A8.5 History of hypertension as cofactor (with age and sex) for presence of any WMC versus no WMC (Mod 1) or moderate/severe versus no/mild WMc (Mod2), for each of the scale used, in CT (a) and MRI (b)

(a)		Whole cohort		<55		55-64		65-74		75-84		≥85	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Oxford	Mod 1	**1.29 (1.04-1.61)**	**0.020**	1.49 90.44-5.07)	0.521	1.47 (0.80-2.67)	0.210	1.31 (0.87-1.99)	0.199	1.20 (0.84-1.70)	0.320	1.36 (0.80-2.31)	0.263
	Mod 2	**1.31 (1.04-1.66)**	**0.021**	na		1.72 (0.73-4.09)	0.220	**1.75 (1.03-2.97)**	**0.039**	1.13 (0.79-1.62)	0.490	1.18 (0.77-1.81)	0.455
ARWMC	Mod 1	**1.26 (1.00-1.59)**	**0.049**	**3.32 (1.05-10.5)**	**0.040**	**1.94 (1.06-3.56)**	**0.032**	1.17 (0.77-1.80)	0.461	1.22 (0.83-1.79)	0.315	0.71 (0.37-1.34)	0.290
	Mod 2	**1.46 (1.15-1.86)**	**0.002**	na		2.42 (0.81-7.20)	0.110	**1.81 (1.05-3.13)**	**0.032**	**1.48 (1.02-2.16)**	**0.040**	1.09 (0.70-1.69)	0.706
van Swieten	Mod 1	1.18 (0.94-1.50)	0.159	**4.71 (1.45-15.3)**	**0.010**	1.50 (0.82-2.75)	0.190	1.06 (0.69-1.62)	0.786	1.24 (0.84-1.82)	0.283	0.64 (0.32-1.28)	0.205
	Mod 2	**1.44 (1.14-1.82)**	**0.002**	na		2.96 (1.11-7.94)	0.031	1.42 (0.85-2.39)	0.182	1.42 (0.99-2.04)	0.055	1.15 (0.74-1.81)	0.532

(b)		Whole cohort		<55		55-64		65-74		75-84		≥85	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Oxford	Mod 1	1.36 90.90-2.05)	0.140	2.27 (0.73-7.10)	0.156	2.05 (0.95-4.41)	0.067	1.25 (0.58-2.71)	0.567	0.44 (0.16-1.22)	0.115	1.65 (0.30-9.23)	0.569
	Mod 2	**1.99 (1.29-3.08)**	**0.002**	4.62 (0.38-56.7)	0.232	2.66 (0.97-7.29)	0.058	**4.86 (2.01-11.7)**	**<.0001**	0.93 (0.45-1.93)	0.841	0.85 (0.19-3.81)	0.834
ARWMC	Mod 1	1.31 (0.86-2.00)	0.204	2.04 (0.72-5.79)	0.181	1.56 (0.70-3.46)	0.276	1.20 (0.52-2.76)	0.663	0.69 (0.25-1.90)	0.475	2.83 (0.36-22.5)	0.325
	Mod 2	1.43 (0.91-2.26)	0.122	6.13 90.58-65.1)	0.133	1.21 (0.44-3.35)	0.712	1.84 (0.77-4.39)	0.169	1.01 (0.46-2.21)	0.975	1.25 (0.26-6.06)	0.782
Fazekas	Mod 1	**1.60 (1.02-2.51)**	**0.043**	1.81 (0.64-5.10)	0.262	**2.33 (1.01-5.35)**	**0.047**	1.74 (0.68-4.45)	0.246	0.80 (0.24-2.65)	0.716	0.76 (0.06-9.32)	0.830
	Mod 2	**1.63 (1.05-2.52)**	**0.030**	2.77 (0.41-18.6)	0.294	1.82 (0.69-4.77)	0.225	2.21 (0.98-4.95)	0.055	0.95 (0.44-2.05)	0.887	2.20 (0.45-10.7)	0.327