CONSEQUENCES OF CEREBRAL WHITE MATTER LESIONS

A longitudinal population-based MRI study

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GEVOLGEN VAN CEREBRALE WITTESTOFAFWIJKINGEN

Een longitudinaal bevolkingsonderzoek

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
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Chapter 2

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Chapter 3

De Leeuw F-E, De Groot JC, Achten E, Oudkerk M, Ramos LMP, Mali WPTM, Van Gijn J, Hofman A and Breteler MMB. Sex differences in the prevalence of cerebral white matter lesions.

Chapter 4

De Groot JC, De Leeuw F-E, Oudkerk M, Van Gijn J, Hofman A, Jolles J and Breteler MMB. Cerebral white matter lesions and subjective cognitive failures. *(Submitted)*

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Chapter 5

De Groot JC, De Leeuw F-E, Oudkerk M, Hofman A, Jolles J and Breteler MMB. Cerebral white matter lesions and depression. *(Submitted)*

Chapter 6

De Groot JC, De Leeuw F-E, Oudkerk M, Van Gijn J, Hofman A, Jolles J and Breteler MMB. Periventricular cerebral white matter lesions predict the rate of cognitive decline. *(Submitted)*

Chapter 7

De Groot JC, De Leeuw F-E, Oudkerk M, Van Gijn J, Hofman A, Jolles J and Breteler MMB. Cardiovascular risk factors, cerebral white matter lesions, and cognitive function.

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— Chapter 1 —

GENERAL INTRODUCTION

Dementia and depression are among the most common mental disorders in the elderly. The prevalence of dementia rises rapidly with age from 0.4% in people aged 55-64 to more than 40% among people aged 90 years or over.[1] The prevalence of depression in the elderly ranges from 1 to 10%, depending on the used definition.[2] In recent years evidence has accumulated that vascular disorders and vascular risk factors play a role in the development of cognitive impairment, dementia and in late-onset depression.[3-5]

Cerebral white matter lesions are frequently seen on magnetic resonance imaging scans of demented patients and patients with a late-onset depressive disorder, but also appear on scans of non demented, non-depressed elderly.[6-9] Apart from age, vascular factors have consistently been associated with the prevalence and severity of these white matter lesions and are thought to play a major role in their development.[3,8,10,11] The white matter of the brain can be distinguished in a periventricular and a subcortical region. Very few studies that investigated white matter lesions distinguished the two different regions.[12-15] This may be important however, as lesions in these different regions may have a different etiology and different clinical consequences.[16]

The aim of this thesis was to report on the frequency distribution of the periventricular and subcortical white matter lesions in non-demented elderly people. Secondly to provide epidemiological evidence for the relation between white matter lesions at the separate regions and neurobehavioral consequences, including cognitive performance and indicators for depression. The studies presented in this thesis are based on the Rotterdam Scan Study; a population based study among 1084 people 60 to 90 years. The study was carried out in 1995 to 1996 and designed to study causes and consequences of age related brain changes.

In chapter 2 previous studies on the relation between white matter lesions and cognitive function are reviewed, with an emphasis on methodological differences and approaches. In chapter 3 the neuroimaging results on white matter lesions as found in the study population are described, with a focus on gender differences in white matter lesions at periventricular and subcortical regions. In chapter 4 the associations between white matter lesions and different measures of cognitive function are reported. Cognitive dysfunction was studied both as subjective failure of cognitive function (chapter 4.1), and as objective cognitive dysfunction (chapter 4.2). The association between white matter lesions and a history of depression and actual depressive symptoms is reported in chapter 5. In addition to these mainly cross-sectional studies, chapter 6 describes a longitudinal study. Within a subsample of the

Rotterdam Scan Study, we investigated the relation between the severity of white matter lesions and rate of cognitive decline as derived from repeated measures of cognitive function over a time span up to 8 years. Finally chapter 7 focuses on the evidence gained in the Rotterdam Scan Study for the mediating role of cerebral white matter lesions in the relation between cardiovascular risk factors and cognitive function. In chapter 8 we look back at the main results of the studies on neurobehavioral consequences of white matter lesions described in this thesis, and discuss some strengths and weaknesses of the studies. This thesis concludes with pointing to the possible clinical implications of the results and giving suggestions for future research on the topic.

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— Chapter 2 —

COGNITIVE CORRELATES OF CEREBRAL WHITE MATTER LESIONS

A REVIEW

The introduction of computer tomography (CT) and magnetic resonance imaging (MRI) has revealed unexpected cerebral findings of unknown consequences. Changes in the white matter of the brain appear in both normal and cognitively impaired elderly individuals and are common in demented patients. White matter lesions are known under a variety of synonyms. On MRI they are also termed white matter lesions, hyperintensities, foci, findings or unidentified bright objects and on CT white matter lucencies or leukoaraiosis.

The pathogenesis and the consequences of these white matter lesions have not been firmly established. The changes themselves do not have a single unique pathological substrate. Clinical, epidemiological and pathological studies indicate a vascular origin for the majority of these changes. It is suggested that these white matter lesions precede the cortical atrophy as seen in Alzheimer's disease and could be important in the pathogenesis of neuropsychiatric changes of the dementias (de la Monte, 1989). Their clinical significance in non-demented subjects remains controversial. Lately the results of a couple of large-scale population based studies have been published concerning the role of white matter lesions (WML) (Liao et al., 1996; Longstreth et al., 1996).

In this paper a review of the literature is given with a focus on the correlation between white matter lesions of unknown origin and cognitive function in the elderly. Emphasis is put on methodological considerations.

A Medline search for white matter lesions on CT or MRI, dementia and cognitive function was used to select papers used for this review. The obtained papers were restricted to age groups older than 45 years. Reference will not be made to other well known causes of white matter disease as stroke, Binswanger's disease, multiple sclerosis, infectious diseases, post-traumatic WML, AIDS, metachromatic leukodystrophia, vitamin B12 deficiency, adult adrenoleukodystrophy and amyloid angiopathy.

Definition of white matter lesions

White matter lesions are discovered by imaging techniques and are defined within that realm. Using computer tomography (CT) these changes appear as lucencies in the white matter of the brain and can be punctate, patchy or diffuse. Hachinski termed them "leukoaraiosis" if there were no changes to the ventricle and sulci locally (Hachinski et al., 1987). On MRI scans the changes appear as hyperintense on

T2 and proton density weighted images, without leaving clear hypointense holes on T1 images. They appear very clearly with the new fast FLAIR techniques (Gawnecain et al., 1997). The plain that is nearly always used because of historical reasons is the axial plane. A consequence of this orientation is that there is an overrepresentation of the frontal and parietal lobes, as compared to the occipital lobes and that flow artifacts may limit the interpretation of the temporal lobes (Scheltens et al., 1992).

The neuropathological substrate of WML is still under discussion. The location of WML is mainly categorized into two regions: deep subcortical and periventricular. This division is based on differences in presumed etiology and pathology. The deep (subcortical) white matter lesions (DWML) could be the result of high blood pressure (Awad et al., 1986; Challa and Moody, 1987) or due to ischemic origins (Baloh and Vinters, 1995). Neuropathologically they correspond to gliosis, demyelinization, small vessel disease, widened Virchov-Robin spaces, atrophy and shrinkage of axons and myelin around blood vessels (Challa and Moody, 1987; Kirkpatrick and Hayman, 1987; Baloh and Vinters, 1995). The periventricular white matter lesions (PVWML) could be the result of prolonged augmented periventricular fluid concentrations, due to breakdown of ventricular ependym. Their pathological substrate is demyelination and reactive gliosis (Sze et al., 1986; Fazekas et al., 1993; Scheltens et al., 1995). These PVWML have not been found to be associated with an ischemic origin unless they are so prominent that they become irregular (Fazekas et al., 1993).

Quantification of white matter lesions

Reported prevalence of WML ranges from 8.6% (Steingart et al., 1987) to 95.6% (Longstreth et al., 1996). This wide range is due to differences in imaging method, technical setting of parameters of the imaging apparatus, scoring-methods of white matter lesions and the selected study-population.

Imaging method, technical settings & imaging parameters

The choice of the imaging apparatus is of influence on the prevalence of WML. CT is a less sensitive technique for detecting WML compared to MRI and therefore studies using CT, not surprisingly, find a lower prevalence of WML (Erkinjuntti et al., 1987; Johnson et al., 1987). The smaller WML that appear as punctate on MRI are often not detected on CT images (Wahlund, 1996).

The image obtained by MRI or CT is influenced by a lot of technical aspects. The strength of the magnetic field of the MRI unit used in the studies varies from 0.02T (Ylikoski et al., 1993) to 1.5T (Schmidt et al., 1993). The use of higher field strengths tends to lead to detection of more WML. However, angulation, slice thickness and interslice gap also influence resolution, signal-to-noise ratios and partial volume effects and thus have to be taken into account. Furthermore, variations in window settings, echo - and repetition times will all give differences in contrast and thus detection. No uniform scanning protocol is used to this day, making the comparison or even pooling of results a compelling task. When using CT equipment the generation of the scanner is of importance as later generation scanners detect WML with more sensitivity (Diaz et al., 1991). Furthermore, in CT studies, as with MRI, the slice thickness, interslice gap, angulation and other technical settings are of importance for the detection of WML and comparability of studies.

The different imaging specifications will affect the sensitivity of the scan for WML but is unlikely to influence the severity distribution of these changes in the population. Therefore, in cross-sectional studies it will mainly affect the power of the various studies to investigate the relation between WML and cognitive function. In prospective studies, however, insensitive scans may hamper the investigation of increase in WML.

Scoring methods of white matter lesions

The wide range in prevalence is for a substantial part due to differences in scoring-methods. Some investigators using MRI do not take into account the punctate deep subcortical changes or the pencilthin lining around the ventricles (Sze et al., 1986; Fazekas et al., 1993). The importance of these kinds of changes has not been established (Sze et al., 1986). Leaving them out of the analyses clearly results in a lower prevalence.

The severity of WML is scored differently in CT and MRI studies. In CT studies the extent of WML is mainly quantified through subjective interpretation. Areas are scored if they have decreased attenuation compared to normal appearing white matter. Severity is scored according to the degree of attenuation (Skoog et al., 1996), the size of the area of low attenuation (Diaz et al., 1991), or both (Rezek et al., 1987; Leys et al., 1990; Blennow et al., 1991; Amar et al., 1995). In MRI studies the number and extent of WML have mostly been graded, instead of using intensity scores. The amount of grades differs between studies. Sometimes grades are given per brain-region and a sum-score is calculated per brain (Junque et al., 1990; Fukui et al., 1994; Baum et al., 1996). Quantitative techniques using MRI have been used to cal-

culate total WML volumes (Almkvist et al., 1992; Boone et al., 1992; Schmidt et al., 1993; DeCarli et al., 1995). Although this technique seems promising it is very time consuming. Automatic quantification programs are too little specific in determining WML, which makes it necessary to trace regions of interest manually.

In the final analyses of WML a dichotomization in absent or present is often used instead of using the grading or quantitative measures (Steingart et al., 1987; Rao et al., 1989; Lopez et al., 1992; Schmidt et al., 1993). Although this dichotomization is often necessary to obtain enough statistical power, it may obscure the relation between WML and cognitive function depending on the cutoff. While the larger extensive confluent lesions might correlate (more) to cognitive function, the smaller lesions might not (or less). Aggregating both grades as 'present' would result in diminished effect estimation.

The regional distribution of WML is mainly categorized into two regions, periventricular and deep (subcortical) white matter. PVWML are often divided in three to four categories with pencilthin lining and small triangular caps as the least severe and large confluent changes that expand far into the periventricular space or finger-like into occipital - or frontal lobes as the most severe. A distinction between regional periventricular areas is sometimes made (Almkvist et al., 1992; Fukui et al., 1994; Baum et al., 1996) although not always used in the analyses. Fazekas and coworkers proposed to aggregate the scores for confluent DWML and irregular PVWML because they possibly share the same neuropathology, and to look separately at other PVWML scores and smaller DWML (Fazekas et al., 1993). A problem with region specific rating scales used for PVWML and DWML is that there is an overlap in the scores between the locations if large periventricular caps are present, which could also be scored as confluent DWML (Scheltens et al., 1992). Other distributions for WML include separate anterior and posterior regions (Leys et al., 1990; van Swieten et al., 1991) or frontal, parietal, temporal and occipital regions (Binetti et al., 1995). Hemispheres have been looked at separately but these revealed no differences (Ylikoski et al., 1993; Skoog et al., 1996).

When studying specific cognitive correlates of WML it is of importance to take into account the affected region, as cognitive functions are not equally distributed over the brain. If regional differences are not taken into account it is possible that an existing relation of WML with cognitive function in one region is diluted by the absence of relation in other brain regions. For the same reason severity scores have to be taken into account. By using visual rating scales a distinction can be made between the amount of punctate, patchy or confluent lesions. Using quantitative measures usually results in a total WML area per region irrespectively of size per hyperintensity. Etiology may differ between differently sized WML and cognitive

function may be differently affected by differently sized WML. Therefore visual-rating scales might be a better choice than quantitative scales. Unfortunately most analyses of the relation between WML and cognitive function thus far used rather unsophisticated and global scales to assess WML.

Selection of study population

Another part of the variation in prevalence and correlates of WML is due to the selection of study subjects. The amount of morbidity and the age-range of the study-population determine to a large extent the prevalence of WML. When selected patient series are used (e.g. van Swieten et al., 1990; van Swieten et al., 1991; Almkvist et al., 1992; Baum et al., 1996), WML will usually be more prevalent than in the community because of the amount of risk factors present in the selected population. Using hospital series the main comparison made is demented versus healthy volunteers. Comparing these groups yields differences in extent of WML and cognitive function but their relation might still be unclear as the impaired cognitive function in the demented group could be due to cerebral cortical involvement. Another problem is that if WML have a subtle effect on cognitive function (Baum et al., 1996), this effect could be overlooked when studying demented subjects because of the overwhelming effect of cortical dysfunction in these patients. Relating cognitive function to WML in demented patients might be possible if within group analyses would be performed.

Although many studies claim to be population-based, many made use of healthy volunteer samples. There are only few studies where subjects were randomly sampled from a clearly defined and known base population. Population samples can be distinguished by the extent of the exclusion criteria used. Extensive exclusion criteria (Matsubayashi et al., 1992; Tupler et al., 1992; Schmidt et al., 1993; DeCarli et al., 1995) as well as minor exclusion criteria (Boone et al., 1992; Ylikoski et al., 1993; Breteler et al., 1994; Longstreth et al., 1996) have been used. The amount of exclusion criteria and response rate of participating subjects determine the selectiveness of the study-population. If a highly selected study-population is chosen, the etiologic contrast will be limited. Comparing results of studies or even pooling the results is complicated by the differences in selection criteria for study-subjects.

Another important issue is sample size. Too small studies will not have enough statistical power to meaningfully investigate any correlate of WML. Furthermore, to be able to adjust for all parameters that might influence the correlation WML - cognitive function a sufficient number of subjects is needed.

Study populations differ in age distribution and age is an important determinant of the amount and severity of WML. Furthermore age correlates with cognitive function. The youngest subject that has been included in studies of WML and cognitive function is 19 years while the eldest is 91 (DeCarli et al., 1995). Most studies use age ranges of 45 to 85 years. Age distribution should be taken into account, not only for its confounding effect, but also because the extent to which selection and survival bias may occur in a study varies with age.

WML and their correlation with cognitive function

In studies on the clinical significance of WML, cognitive function has been measured with a variety of different instruments. In the larger population-based studies limited tests were used on practical grounds (e.g. the Mini Mental State Examination), whereas more extensive neuropsychological test-batteries were used in smaller series of highly selected subjects. The most extensive neuropsychological studies have been conducted in memory clinics thus giving rise to considerable selection bias.

The cognitive domains that have been studied most in respect to WML are global mental functioning, general intelligence, memory, and executive functions like attention, speed of mental processes, planning and strategic reasoning. These domains are most sensitive to early mental deterioration and have discriminatory value for the subtypes of dementia syndromes (Derix, 1994). Many research groups also take a measure for motor skills or reaction time into account (Hunt et al., 1989; Rao et al., 1989; Junque et al., 1990; Schmidt et al., 1991; Almkvist et al., 1992; Matsubayashi et al., 1992; Schmidt et al., 1993; Ylikoski et al., 1993; Baum et al., 1996). Besides, metamemory has been studied as a correlate of WML.

The results for the correlation of WML and cognitive function have been conflicting in outcome. This might be due to differences in scoring methods for WML, assessment of cognitive function and adjustments for confounders and modifiers. Studies addressing the correlation of WML with decline of cognitive function are limited. This due to the fact that most studies have a cross-sectional design or have too little subjects in the follow-up (Fein et al., 1990), or that follow-up time is too short to enable differences in cognitive function to occur or WML to worsen. In the following part the various cognitive domains correlated with WML will be discussed.

Global mental functioning

Global mental functioning has predominantly been investigated with the use of the Mini Mental State Examination (Folstein et al., 1975). Other groups used dementia rating scales like the Extended Scale for Dementia (ESD) (Hersch, 1979; Steingart et al., 1987) the 3MSE (Teng and Chui, 1987; Longstreth et al., 1996) or Blessed test (Blessed et al., 1968; Hunt et al., 1989).

In non-demented subjects, a relation between WML and MMSE score was reported in the H70-study (Skoog et al., 1996) and the study by Matsubayashi and coworkers (Matsubayashi et al., 1992). The H70 study used CT and only looked at moderate or severe WML. Matsubayashi and coworkers used MRI and found a relation only if they neglected the small WML. Taken together these studies have been interpreted as evidence for a threshold effect: a substantial amount of WML needs to be present to have a measurable effect on the MMSE-score. It can be doubted however, that this is truly a threshold effect of WML. It could also result from crude scaling of WML, insensitive outcome measures or small sample sizes. In the Cardiovascular Health Study (Longstreth et al., 1996) a relation was found between WML grade and a modified version of the MMSE, the 3MSE, that is more extensive and more sensitive than the original (Malloy et al., 1997). Although many studies do not find a significant relation between global cognitive tests as the MMSE and WML, the direction of the relation is always such that there is a poorer performance among subjects with more WML. Another problem with the mentioned screening tests is their focus on cortical rather then on subcortical dysfunction (Malloy et al., 1997). These considerations may explain the conflicting results in studies using these global screening instruments in healthy subjects (table 1).

In demented patients the above instruments are also frequently used with conflicting results (see table 2). Only the studies using CT scanners find a robust correlation with the MMSE or ESD outcome (Steingart et al., 1987; Diaz et al., 1991; Skoog et al., 1996). The majority of studies looking at global cognitive decline in demented subjects fail to find a statistically significant relation with WML after adjusting for age. In the Dementia Study from London, Ontario where both CT and MRI were used, a relation was found using CT (Steingart et al., 1987; Diaz et al., 1991) but not using MRI (Mirsen et al., 1991). Leys and coworkers (Leys et al., 1990) also used both imaging techniques but failed to find any relation with MMSE-scores, this could be due to their small sample sizes.

Table 1
White matter lesions and their relation to cognitive function within non-demented subjects

Author	Study population	WML scoring	Separate scores for PVWML/ DWML	Cognitive domains reported to be related with WML[1]	Cognitive domains reported to be unrelated with WML[2]	Confounders considered
Baum '96 (Neurorad)	Hospital, back-pain patients (39% WML, n=41, 45-65 years)	Scaling: - # DWML - # times grade (0-3) PVWML 0.5T MR	Yes	- Global (IQ) - Memory (complex visual position) - CI processing (Trail AB) - Mood (0-6)	- Attention (DS) - Motor function (reaction time)	Age IQ
Boone '92 (Arch Neurol)	Healthy volunteers (54% WML, n=100, 45-83 years)	Scaling: volume of WML (4 strata) 1.5T MR	Only DWML	- Memory (WMS) - Attention (DS)* - CI processing (WCST*, Stroop, ACT*, fluency, SDST)	- Global (MMSE, WAIS-IQ) - Visuospatial abbilities (RO)	Age
Breteler '94 The Rotterdam Study (Stroke)	Population (27% WML, n=90, 65-84 years)	Scaling: 0-1 1.5T MR	No	- Memory (WL-CERAD) - Attention (DS) - CI processing (Stroop, Trail AB*, Fluency*)	- Global (MMSE, CAMCOG, IQ)	Age Gender Education Ventricle/brain ratio
DeCarli '95 (Neurol)	Very healthy volunteers (69% WML, n=51, 19-91 years)	Scaling: volume of WML 0.5T MR	No	- Global (WAIS-IQ) - Visual memory (WMS) - Attention (DS) - CI processing (Trail AB, Fluency, SDST)	- Verbal memory (WMS)	Age Intracranial volume
Fukui '94 (Eur. Neurol)	"Healthy" hospital out-patients (88% WML, n=43, 42-86 years)	Scaling: 0-6 DWML 0-2 PV all per region 0.5T MR & CT	Yes	- Attention (LPOT) for frontal DWML - CI processing (Stroop, WCST) for PVWML - Cortical tasks (Block design) for PVWML	- Global (HDS) - Attention (LPOT) - Cortical tasks (RCPM)	Age Atrophy

Hunt '89 Longit. Aging Process Study, New Mexico (Neurol)	Population sample (74% WML, n=46, 50-90 years)	Scaling: 0-4 1.5T MR	No	-	- Global(Blessed + Jackobs, MMSE, WAIS) - Memory (WMS) - Attention (DS) - CI processing (Fluency) - Cortical tasks (Token test, Block design, RO, BNT) - Motor function (Finger tapping)	Age
Junqué '90 (Arch Neurol)	Selected patients with cerebrovascular risk factors (100% WML, n=41, 51-80 years)	Scaling: 0-4 per region 0-40 total 1.5T MR	No	- Global (Blessed, BMD, MMSE, WAIS-IQ) - Memory (WMS) - CI processing (SMST, Fluency*, Trail B, Stroop*) - Motor function (LMT)* - Mood (HAM-D)	- Motor function (Finger tapping, reaction time)	Age
Longstreth '96 Cardiovascular Health Study (Stroke)	Population (96% WML, n=3301, >65 years)	Scaling: 0-4 1.5T & 0.35T MR	Partly	- Global (3MSE) - CI processing (SDST) - Mood (CESD)	- Memory (other than for names)	Age Gender Education Silent stroke Mood (CESD) Hypertension Test experience
Matsubayashi '92 (Stroke)	Healthy volunteers (82% WML, n=73, 59-83 years)	Scaling: 0-2 PVWML 0.5T MR	Only PVWML	- Global (MMSE, HDS)* - Attention (VCP)* - Motor function (VCP)*	-	Age Atrophy Lacunar infarcts
Rao '89 (Arch Neurol)	Healthy volunteers (20% WML, n=50, 25-60 years)	Scaling: 0/1 1.5T MR	No	- Memory (series of tests) - Attention (DS) - CI processing (Stroop, WCST, Fluency and others) - Motor function (Finger tapping, reaction time and others) - Cortical tasks (series of tests)	- Global (WAIS-IQ, MMSE)	Age Gender Education Hypertension

Table 1 – continued

Author	Study population	WML scoring	Separate scores for PVWML/ DWML	Cognitive domains reported to be related with WML[1]	Cognitive domains reported to be unrelated with WML[2]	Confounders considered
Schmidt '91 (Arch Neurol)	Healthy hypertensive patients (38% WML, n=35, 22-49 years) healthy volunteers (20% WML, n=20, 26-49 years)	Scaling: 0/1 1.5T MR	No	No domain in hypertensive patients No analyses reported within volunteer group.	- Memory (LGT) - Attention (d2 test) - Motor function (reaction time) - Mood (Janke & Debus)	Age Gender Education Treatment Atrophy
Schmidt '93 Austrian Stroke Prev. Study (Neurol)	Healthy volunteers (no neuro-psychiatric disease) (50% WML, n=150, 44-82 years)	Scaling: 0/1 no caps and rims PVWM. 1.5T MR	Only DWML	- Memory (LGT) - Attention (DS) - CI processing (Trail B)* - Motor function (Purdue PB, reaction time)*	- Mood (Janke & Debus)	Age Ventricle/skull ratio Mean arterial pressure
Skoog '96 H70-study (Acta Neurol Scand)	Sample of birth cohort from population (non-dem. 34% WML, n=134, 85 years)	Scaling: 0-1-2/3 CT!	No	- Global (MMSE)* - Memory (TPMT)* - Attention (DS) - CI processing (Identical forms)* - Cortical tasks (Synonym Test, Clock, Block design, Coin test)*	- Memory (MIR, PRT, TWMT) - CI processing (figure classification)	Infarcts Education
Steingart '87 (Arch Neurol)	Volunteers, stroke free, no dementia. (9% WML, n=105, 59-91 years)	Scaling: 0/1 CT!	No	- Global (ESD)	- Motor function (gait) - Mood (subjective depression/cognition)	Age Gender Education Infarcts
Tupler '92 (Arch Neurol)	Healthy volunteers (73% WML, n=66, 45-84 years)	Scaling: 0-3 and 0/1 for DWML 1.5T MR	Only DWML	-	- Memory (BFRT) - CI processing (SDST)	Age Education
Van Swieten '91 (Ann Neurol)	Healthy hypertensive patients (24% WML, n=34, 57-77 years) Healthy volunteers (spouses and/or outpatients) (0% WML, n=18, 57-79 years)	Scaling: 0-2 2 regions 1.5 T MR	No	- Global (MMSE) - Memory (WMS-delayed recall) - CI processing (Trail AB, Stroop)*	- Global (WAIS-IQ) - Memory (15WLT, WMS immediate recall) - Attention (DS) - CI processing (SDST)	Age Gender Education

Ylikoski '93 Helsinki Aging Study (Arch Neurol)	Population cohorts (no WML prevalence reported, n=120, 55-85 years)	Scaling: 0-48 total WML and 0/1 PVWML & DWML 0.02T MR	Yes	- Immediate memory (WMS) - CI processing (Trail A, Stroop)*	- Global (WAIS-IQ) - Memory (Fuld, WMS) - Attention (DS) - CI processing (Fluency) - Motor function (Finger tapping)	Age

* = reported as significant $p < 0.05$; [1] Cognitive domains reported to be related with WML: If the authors report a statistically significant relation with WML or if the presented data show a trend towards a relation; [2] Cognitive domains reported to be unrelated with WML: If the authors report that a relation is not present with WML and/or if the presented data show no trend towards a relation. For abbreviations see table 2

Table 2
White matter lesions and their relation with cognitive function within demented subjects

Author	Study population	WML scoring	Separate scores for PVWML/ DWML	Cognitive domains reported to be related with WML [1]	Cognitive domains reported to be unrelated with WML[2]	Confounders considered
Almkvist '92 (Arch Neurol)	Demented hospital referred patients (46% WML, n=105): 47.6% AD, 28.6% VAD, 7.6% other specific, 16.2% unknown cause)	Scaling: 0/1 per brain region	Yes	- Motor function (object assembly, finger tapping, tactile identification of objects, reaction time)*	- Global (MMSE, WAIS) - Memory (WMS) - Attention (DS) - CI processing (SDST, Fluency)	Age Gender Education
Amar '95 (Age and Ageing)	Referred memory clinic patients: (50% PVWML, n=202, 45-93 years)	Scaling: 0-3 size of PVWML + 0-3 intensity of PVWML = 0-6 lucency score. CT!	No	-Diagnostic groups as a measure of global cognitive function*: 1/ normal 2/ isolated amnesia 3/ possible dementia 4/ dementia (different types)	-	Age
Bennet '92 (J Neurol)	Memory clinic probable AD patients (many exclusion criteria) (27% DWML, 98% PVWML, n=106, 48-84 years)	Scaling: 0/1 DWML 0-3 PVWML 0.5T MRI	Yes	-Motor function (gait disorders)*	-Global (MMSE)	None
Diaz '91 The Dementia Study, Ontario (Arch Neurol)	Probable AD patients (40% WML, n=85, mean age 71 yrs)	Scaling: 0/1 diffuse or focal, CT!	No	-ESD total score* -ESD subscores (23 parts)*	-Digit span from ESD	Age Gender Education Duration of dementia Hypertension

Harrell '91 (Arch Neurol)	Probable and possible AD patients (no prevalence of WML given, n=43) prob/pos AD patients + depression. (no prevalence of WML given, n=18)	Scaling: # DWML 1-6 PVWML 0.5 & 1,5T MRI	Yes	For PVWML: -global (MDRS)	For PVWML: -MMSE in all groups -MDRS in AD/Depr -BPRS in all groups For DWML: -MMSE, MDRS, BPRS in all groups	Age Duration of dementia Hatchinsky score
Lopez '92 (Arch Neurol)	Probable AD patients (50% PVWML, n=44, no age range given, mean 73 yrs)	Scaling: 0/1 per 4 brain regions. CT!	Only PVWML	-Global (MMSE) -Attention (LPOT, DS) -CI processing (Fluency, Trail AB)	- Memory - Cortical tasks (RO, Block design)	Age Education Duration of dementia Activity of daily living (Blessed)
Mirsen '91 The Dementia Study, Ontario (Arch Neurol)	Patients referred for dementia: -AD (64% PVWML, 93% DWML, n=30, mean age 73 yrs) -Mixed (38% PVWML, 88% DWML, n=9, mean age 71 yrs) -VAD (75% PVWML, 100% DWML, n=4, mean age 70 yrs)	Scaling: 0/1 PVWML, 0-4 DWML. 1.5T MRI	Yes	-	-ESD score	Age Gender
Scheltens '92 (Brain)	Alzheimer's disease patients (no cardiac- or cerebrovascular disease) (no overall prevalence of WML given, n=29, age 52-81 yrs)	Scaling: 0/6 in PVWM and 0/24 in DWML. 0.6T MR	Yes	Onset of Alzheimer's disease*		Age
Skoog '96 H70-study (Acta Neurol Scand)	Sample of birth cohort from population (in demented subjects 68% WML, n=98, age 85 yrs)	Scaling: 0-1-2/3 CT!	No	- Global (MMSE)* - Memory (WMS)*	- Attention (digit span)	Age Education Cortical atrophy
Wahlund '94 (Magn Res Imag)	Patients referred for dementia: -Prob AD (30% WML, n=23, 66-84 yrs) -Poss AD (32% WML, n=25, 67-91 yrs) -VAD (77% WML, n=31, 70-89 yrs)	Scaling: relative volume of WML in 6 regions 0.02T MRI	Yes	-	-Global (MMSE)	None

Table 2 – continued

Author	Study population	WML scoring	Separate scores for PVWML/ DWML	Cognitive domains reported to be related with WML [1]	Cognitive domains reported to be unrelated with WML [2]	Confounders considered
Sultzer '95 (Arch Neurol)	VAD inpatients (100% WML, n=11, 59-79 years)	Scaling: in four regions: 0-3 DWML + 0-3 PVWML = 0-6 total WML. 0.35 T MRI	No	NRS score: -total NRS score* -anxiety/depression subscore* -cognition subscore	NRS score: -agitation/disinhibition subscore -behavioral retardation subscore -psychosis subscore	None
Tanabe '97 (Am J Neuro-radiol)	Referred dementia patients (100% WML, 12 prob. AD, 9 pos. AD, 61-78 years)	Scaling: % WML of brain Segmentation technique 1.5T MRI	No	-	-Global (MMSE)	None
Steingart '87 (Arch Neurol)	Referred dementia patients -mixed dementia+ VAD (75% WML, n=8) -prob. AD (32% WML, n=91) -other dementias (29% WML, n=14)	Scaling: 0/1 CT!	No	-ESD in mild and moderate AD	-ESD in advanced & severe AD	Age
Leys '90 (Arch Neurol)	Prob. AD patients: -early onset (n=14) -late onset (n=3)	Scaling: in four regions: 0-3 DWML + 0-3 PVWML = 0-6 total WML. 0.5 T MR! (also CT)	Yes	-	-Global (MMSE)	None

*= reported as significant $p < 0.05$; [1] Cognitive domains reported to be related with WML: If the authors report a statistically significant relation with WML or if the presented data show a trend towards a relation; [2] Cognitive domains reported to be unrelated with WML: If the authors report that a relation is not present with WML and/or if the presented data show no trend towards a relation.

Abbreviations for neuropsychological tests as mentioned in tables 1 and 2

3MSE	= Modified MMSE
ACT	= Auditory Consonant Trigrams
BFRT	= Benton Facial Recognition Test
BMD	= Behavioral Measurement of Disturbance
BNT	= Boston Naming Test
BPRS	= Brief Psychiatric Rating Scale
CAMCOG	= Cognitive test of Cambridge Examination for Mental disorsers of the elderly
CESD	= Centre of Epidemiologic Studies on Depression
CI processing	= Central Information processing
d2 test	= Aufmerksamkeits-belastungstest
DS	= Digit Span
ESD	= Extended Scale of Dementia
Fluency	= Verbal fluency task
Fuld	= Fuld object-memory evaluation
HAM-D	= Hamilton scale for depression
HDS	= Hasegawa Dementia Scale
IQ	= Intelligence quotient
Jancke & Debus	= Jancke's and Debus's Eigenschaftswörterliste
LGT	= Bäumler's Lehrn- und Gedächtnis Test
LMT	= Luria's Motor Test
LPOT	= Letter pick out test; cancellation task
MDRS	= Mattis Dementia Rating Scale
MIR	= MIR memory test
MMSE	= Mini Mental Status Examination
NRS	= Neurobehavioral Rating Scale
PRT	= Prose Recall Test
Purdue PB	= Purdue Pegboard
RCPM	= Raven Colored Progressive Matrices
RO	= Rey-Osterrieth Complex figure
SDST	= Symbol Digit Substitution Test
SMST	= Sternberg Memory Scanning Task
Stroop	= Stroop Coulour-word charts
TPMT	= Thurnstone Picture Memory Test
Trail AB	= Trail making test A & B
TWMT	= Ten word memory test
VCP	= visuospatial cognitive performance test
WAIS	= Wechsler Adult Intelligence Scale
WCST	= Wisconsin Card Sorting test
WL-CERAD	= Word list learning test (Consortium to Establish a Registry for Alzheimer's disease)
WMS	= Wechsler Memory Scale

General intelligence

Several studies used scales to asses global intelligence (Rao et al., 1989; Junque et al., 1990; Boone et al., 1992; Schmidt et al., 1993; Ylikoski et al., 1993; Breteler et al., 1994; DeCarli et al., 1995; Baum et al., 1996) In all studies but one (DeCarli et al., 1995) no relation was found with WML. This was similar for healthy subjects and for dementia patients. DeCarli and coworkers used a composite score of verbal and

performance scaled scores of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955) as a measure of general intelligence. They used this subset instead of the complete WAIS to avoid confounding by age. This might explain the found correlation, as the score on the performance scale is to a large extent dependent on subcortical structure and thus on the amount of intact white matter, whereas a complete WAIS-IQ measurement is more cortically targeted.

Memory

Virtually all studies included the complete or partial Wechsler Memory Scale (WMS) (Wechsler, 1945), wordlist learning tasks (WLT) or other verbal- and visuospatial tasks for explicit memory.

In non-demented subjects, the dependence of memory on WML is controversial. Some groups, including ours, report significant relations (Matsubayashi et al., 1992; Breteler et al., 1994; DeCarli et al., 1995; Baum et al., 1996; Skoog et al., 1996) while others do not (Steingart et al., 1987; Hunt et al., 1989; Rao et al., 1989; Schmidt et al., 1991; Boone et al., 1992; Schmidt et al., 1993; Ylikoski et al., 1993; Fukui et al., 1994; DeCarli et al., 1995; Skoog et al., 1996). Visual memory seems more often related with the presence of WML than verbal memory (DeCarli et al., 1995; Baum et al., 1996; Skoog et al., 1996).

In demented subjects no significant relations between WML and memory functions have been reported, except for the study by Skoog and coworkers (Skoog et al., 1996). In this study verbal memory correlated with WML while visual memory did not.

Executive functions

Executive functions are believed to be controlled by the frontal lobe and the subcortical structures that project to the frontal cortex (Cummings and Benson, 1988). They include mental flexibility, interference coping and conceptual tracking. Tests that are used in this respect are those that measure attention, speed of mental processes, and strategy driven tasks like the verbal fluency task.

Attention and speed of mental processes

Timed tests, which measure speed of mental processes, are believed to be especially sensitive to subcortical disease processes (Cummings, 1986; Cummings and Benson, 1988). The tasks used are cancellation tasks like the Paper & Pencil Memory Scanning Test (Sternberg, 1975; Brand and Jolles, 1987), performance tasks like the Stroop charts 1 & 2 (Stroop, 1935; Houx et al., 1993) and concentration tasks like the Digit-Symbol substitution test (Smith, 1968; Lezak, 1995), the Digit Span back-

wards and forwards (Wechsler, 1955) or the Stroop chart 3. Other often included tests are the Wisconsin Card Sorting Test (Milner, 1964) and the Trail making tests (Reitan, 1958). Attentional tasks are often intermingled with tasks that measure speed of mental processes and difficult to interpret separately. Nearly all studies included some sort of task for measurement of attention and speed of mental processes.

In non-demented subjects most of the timed-tasks that depend on processing speed or sustained attention, relate with WML (Longstreth et al., 1996). The majority of studies found poorer performance on attention tasks among subjects with more WML, albeit not always statistically significant. Some of the conflicting results could be due to methodological problems. Schmidt and coworkers failed to find a relation with most measures of executive functions, but in their analyses they corrected for blood pressure (Schmidt et al., 1993). This may have been overcorrection: as blood pressure is probably in the causal chain of WML correction for it will diminish the relation between WML and cognition. Conflicting results are also reported by Boone and coworkers (Boone et al., 1992). These authors reported significant correlations only for the more complex executive functions, suggesting that the simpler tasks were not sensitive enough to pick up the subtle effect of WML. In healthy subjects Almkvist and coworkers (Almkvist et al., 1992) did not find any correlations with WML. However they used an ultra-low field scanner which detected WML in only 22% of their 23 subjects. Such a low prevalence combined with the small sample size yields little statistical power. Ylikoski and coworkers (Ylikoski et al., 1993) also used an ultra-low field scanner but did find a correlation using 120 subjects.

In demented subjects relations between tests for attention and speed of mental processes and WML are less clear (see table 2) although the amount of neuropsychological tests performed in those studies are less than in studies using the non-demented subjects. It is possible that once dementia is present there is already so much (cortical) brain damage that the subtle influence of WML cannot be detected anymore.

Planning/strategic reasoning

A defect of the semantic memory network should first of all impair verbal fluency tasks (Pollman et al., 1995). In non-demented subjects, verbal fluency tasks correlate with WML (Junque et al., 1990; Almkvist et al., 1992; Boone et al., 1992; Breteler et al., 1994) although limited sample sizes prevent statistical significance. Breteler and coworkers used two types of fluency tasks, a letter B version (naming words beginning with the letter B) and an animal-naming version. The letter-B version corre-

lated with WML while the animal version didn't. As the letter-B version is a more compelling task, this can be interpreted as WML having more impact on more complex tasks. Seemingly, reserve capacity of the semantic network is large enough to maintain a near-to-normal function when not too much demanding tasks are performed.

In demented subjects verbal fluency correlates highly with dementia severity and allows discrimination of most AD patients from controls (Fischer et al., 1988; Pollman et al., 1995). In a CT study Lopez and coworkers (Lopez et al., 1992) reported lower performance on the verbal fluency task in AD patients with PVWML, compared to patients without these changes. Because of limited sample size and little contrast in test-results correlations did not reach significance. Using ultra-low field MRI and more patients Almkvist and coworkers (Almkvist et al., 1992) reported correlations between verbal fluency performance and WML. They used univariate analyses and WML were dichotomized, thus giving ample room for confounding. However, the trend was present within dementia subgroups as well as in healthy controls. There have been no studies with a sufficient amount of demented subjects to control for confounding.

Motor skills & reaction time

It has been hypothesized that WML could give a slowing of reaction time because of demyelinization and affect the motor-skills by influencing the amount of afferent and efferent information necessary for fine motor control. Tests used for this purpose are the Purdue pegboard (Tiffin, 1948), the finger tapping test (Vega, 1969; Almkvist et al., 1992), and self-made reaction-time measurements. In these last tests subjects have to push a button in reaction to a certain stimulus (Almkvist et al., 1992; Schmidt et al., 1993). In non-demented subjects correlations with WML were never reported except for the study by Matsubayashi (Matsubayashi et al., 1992). In demented subjects correlations were reported (Almkvist et al., 1992) though the analyses were not adjusted for age, which was clearly differently distributed in the comparison groups.

Metamemory

Metamemory is defined as knowledge and beliefs about one's own memory functioning (Dixon et al., 1988) and is otherwise known as subjective memory. Metamemory complaints are of importance in the study of WML in two different ways: they can be one of the consequences of WML or they can be a confounding variable in the relation WML - cognitive function. The latter manner will be dis-

cussed under quantification of possible confounders. Subjects with subjective memory complaints and mild cognitive impairment decline faster than cognitively impaired subjects without memory complaints (Schofield et al., 1997), and subjective memory complaints can be a prelude to other cognitive problems. To our knowledge only two studies took into account some measure for subjective memory complaints. Steingart and coworkers reported a trend (no *p*-value given) for the complainers to have more white matter lesions (Steingart et al., 1987). In the Rotterdam Study Breteler and coworkers reported a significant correlation between subjective memory complaints and the severity of WML (Breteler et al., 1994).

Confounding variables

In studying the relation between WML and cognitive function factors should be taken into account that may possibly confound that relation. Age, education, affect status and subjective memory complaints may all suggest or obscure the relation between WML and cognitive function. Imaging findings other than WML can also act as confounders or possibly effect modifiers. These imaging findings include cortical- and subcortical atrophy, brain volume, ischemic zones, and clinical- or silent infarcts. Hypertension, atherosclerosis and other vascular risk factors may contribute to the development of WML but they do not have to be confounders. Adjusting for these factors would be overcorrection and could result in a diminished correlation between WML and cognitive function (Schmidt et al., 1993). The same holds for adjustment for dementia severity score. Dementia severity scores are dependent on cognitive function of the patient and by stratifying or adjusting for this contrast will be lost and correlations with WML diluted.

Practically all of the studies examining WML found these changes to correlate with age. As age is also correlated with cognitive function it is clear that age is a variable that should always be adjusted for in studying the relation between WML and cognitive function. Analyses in age strata provide the possibility of identifying effect modification.

The level of education is associated with some of the known cardiovascular risk factors for WML, like hypercholesterolemia, hypertension, myocardial infarction, and body-mass index. Since the level of education is also is known to influence performance on cognitive test batteries, education can be a confounding variable.

Peoples own believe about their memory, or metamemory, may have a substantial impact in determining how much effort is invested in daily memory tasks (Bandura, 1989; Cavanaugh and Green, 1990; Lovelace and Eugene, 1990; Lovelace,

1990). If memory self-efficacy beliefs are low, less effort than necessary will be invested in memory tasks which leads to low memory performance (Ponds and Jolles, 1996). To the extent that metamemory itself is related to WML, it may confound the relation between WML and cognitive function. No studies thus far have adjusted their analyses for the presence or degree of metamemory problems.

Emotion has been suggested to be altered by subcortical function (Cummings, 1986). Subcortical disorders may affect neurobehavior by interrupting fronto-striatal-thalamic circuits that regulate mood and cognition (Salloway et al., 1996). WML have been reported to be involved in major depression as well as in bipolar disorders (Figiel et al., 1991; McDonald et al., 1991; Aylward et al., 1994; Dupont et al., 1995). Cognitive decline can be the result of a structural brain degeneration but can also be the result of lack of motivation, concentration or interest that are seen in mood disorders (Malloy et al., 1997). The development of depression *and* WML might be the result of an identical underlying disease process such as vascular events in deep subcortical locations (Brown, 1993). Affect status has much the same properties as metamemory; it can be a result of WML but it can also alter cognitive function. Both metamemory and affect-status can be an outcome variable when looking at the consequences of WML, but they can also be a confounder in the relation WML – cognitive function. Moreover, affect status might modify the relation between WML and cognitive function, in that people with affective disorders might be more vulnerable for the effects of WML to cognition. These different mechanisms have to be checked in the analyses by respectively multivariate analyses and stratification. Longstreth and coworkers (Longstreth et al., 1996) reported WML to be related to depression using the Center of Epidemiologic Studies Depression Scale (CES-D (Radloff, 1977)) as an outcome variable. When the CESD score was entered in a multivariate analyses with WML and cognitive function the relation between cognitive function, depression and severity of WML remained significant. This indicates that the relation between WML and cognitive function is not explained by the co-existence of depression.

Future research goals and methodological considerations

It is still not clear whether, and to what extent cognitive decline can be attributed to the progression of WML. Carefully carried out large-scale follow-up studies, uniform rating scales and uniform outcome measures may help to solve this issue.

A joint effort of research groups should be made to develop a method to quantify the extent and localization of WML that is uniformly accepted. This rating scale should be available for CT studies as well as for MRI studies. Scales, whether they are quantitative or qualitative, should provide separate ratings for PVWML, DWML and preferably more detailed localization of these changes within the brain. Automated quantitative methods are promising but need to provide volumes separately for different regions. In follow-up studies quantitative methods are of specific importance as the changes over the years may be small and difficult to trace with visual rating scales. For clinical use a visual rating scale might be more practical than a quantitative scale. There should be consensus about technical settings concerning MRI field strengths, slice thickness, interslice distance and inclination to make studies comparable.

Apart from quantification of WML there should be ratings of cortical- and subcortical atrophy and ventricular size. Ischemic areas, infarcts and other brain appearances should be taken into account.

A major problem in comparing the outcomes of the different studies on the relation between cognitive function and WML is that there is no uniformity in neuropsychological tests used and domains tested. The aggregation of tests per cognitive domain differs among studies and the analyses are sometimes performed using composite scores, sometimes using cutoff points. These scores are inconsistently corrected for possible confounders. The relation between cognitive function and WML should be studied with a clear focus on subcortical function. Analyses should be performed for the different tests separately. Once agreement is reached on which tests belong in which domain, composite scores can be composed per domain. A composite score covering different domains, especially if they cover cortical as well as subcortical domains, can be given as an overall outcome measure but should not be given as the only measure. Using composite scores can dilute the strength of the relations for the separate cognitive domains and diminish the effect estimation of that relation. A generally accepted questionnaire about metamory should be included in the neuropsychological evaluation as a generally accepted depression scale with an emphasis on negative symptoms to determine the role of affective status in the relation of WML with cognitive function.

One of the major drawbacks of many studies in non-demented subjects has been the selection of the study-population. Most studies thus far used healthy volunteers or had a poor response rate. A population-based approach, with a high participation-rate, would be the preferred setting. Another drawback is the use of a cross-sectional design. This design limits the inferences that can be drawn for causal

relationships. A relation that has been found using a study with a cross-sectional design does not provide information for a causal relationship between cognitive function and WML.

In studies using demented subjects, few investigators perform within-group analyses. Subjects are mostly stratified in diagnostic groups or according to severity scales (Steingart et al., 1987; Harrell et al., 1991; Mirsen et al., 1991; Almkvist et al., 1992; Wahlund et al., 1994; Amar et al., 1995). Prevalences of WML are then compared to healthy controls. Because of matching of mental deterioration within groups, there is inherently little spread of cognitive function. To determine the added effect of WML on cognitive function in Alzheimer patients or in other specified forms of dementia, within-group analyses should be performed.

Probably the best design to study the clinical consequences of WML is a longitudinal population-based study in elderly subjects. The time of follow-up is crucial for the conclusions that can be drawn. If the follow-up time is too short changes in severity of WML will be too small to be detected and cognitive decline within the follow-up time could be too subtle to be picked up in the neuropsychological tests. However, if follow-up time becomes too long survival bias may play an increasingly important role.

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– Chapter 3 –

SEX DIFFERENCE IN THE PREVALENCE OF CEREBRAL WHITE MATTER LESIONS

Abstract

White matter lesions are frequently observed on MRI scans of elderly non-demented and demented people. They are attributed to degenerative changes of small vessels and are implicated in the pathogenesis of cognitive decline and dementia. There is evidence that especially periventricular white matter lesions are related to cognitive decline, whereas subcortical white matter lesions may be related to late-onset depression. We report the frequency distribution of subcortical and periventricular white matter lesions, according to age and gender. We randomly sampled 1084 subjects aged between 60-90 years from the general population. All subjects underwent 1.5T MRI-scanning; white matter lesions were rated separately for the subcortical region and the periventricular region. Of all subjects 8 percent were completely free of subcortical white matter lesions, 20 percent had no periventricular white matter lesions and 5 percent had no white matter lesions in either of these locations. The proportion with white matter lesions increased with age, similarly for men and women. Women had more subcortical white matter lesions than men (total volume 1.45 ml versus 1.29 ml; p=0.33), mainly caused by marked differences in the frontal white matter lesion volume (0.89 ml versus 0.70 ml; p=0.08). Periventricular white matter lesions were also more frequent among women than men (mean grade 2.5 versus 2.3; p=0.07). Also severe degrees of subcortical white matter lesions were more common in women than in men (OR 1.1; 95% CI 0.8-1.5) and periventricular white matter lesions (OR 1.2; 95% CI 0.9-1.7), albeit not statistically significant. In conclusion, the prevalence and the degree of cerebral white matter lesions increased with age. Women had a higher degree of white matter lesions than men. This may underlie the observation of a higher incidence of dementia in women than in men, particularly at later age.

White matter lesions are frequently observed on MRI scans of elderly people, they are attributed to degenerative changes of long penetrating arteries.[1-6] Reported prevalence ranges from 5 to 90 percent, depending on study design, study population and rating scales.[1-4,7-9] White matter lesions can be distinguished into those in the subcortical and in the periventricular region. There is evidence that especially periventricular white matter lesions are related to cognitive decline,[10] whereas subcortical white matter lesions may be related with late-onset depression.[11] Only a few studies consider lesions in these regions separately,[12-14] but some based their analysis on a summary score of subcortical and periventricular white matter lesions,[14] as in other studies.[1-3] Although it is well established that the prevalence of white matter lesions increases with age, little is known about site specific frequency, including possible differences between the subcortical and periventricular region, and the lobar location of the lesions. This distinction may be of potential interest since the subcortical and periventricular white matter lesions might have a different pathogenesis and may result in different cognitive or motor consequences. Some studies reported a higher prevalence of white matter lesions among women then men.[1-3] The differences were however not statistically significant, and were only reported for total white matter lesions.

From a population-based sample of subjects over 60 years of age, we report the age and sex specific frequency distribution of either type of white matter lesions by lobar location.

Materials and methods

Study population

The Rotterdam Scan Study was designed to study determinants and cognitive consequences of age related brain abnormalities in the elderly. In 1995-1996, 1904 subjects aged between 60-90 years were randomly selected in strata of age (5 years) and sex from two large ongoing prospective follow-up cohort studies, the Zoetermeer Study and the Rotterdam Study. Both studies have been described in detail elsewhere.[15,16] In short, the Zoetermeer Study is a prospective population based study among 10361 subjects, aged between 5-91 years at baseline, which studies determinants of chronic diseases. The Rotterdam Study is a population based prospective cohort study, among 7983 elderly subjects aged 55 years and over, which studies

determinants of neurological, cardiovascular, locomotor and ophthalmologic diseases in the elderly.

For the Rotterdam Scan Study subjects were invited by a letter, and subsequently contacted by telephone. Upon agreement to participate a list of contraindications was reviewed in order to assess eligibility (dementia; blindness; or presence of MRI contraindications, including prosthetic valves, pacemaker, cerebral aneurysm clips, a history of intra ocular metal fragments, cochlear implants and claustrophobia). From 1904 invited subjects 1724 were eligible. Complete information was obtained, including a cerebral MRI scan, from 1084 persons (response rate 63 percent; 568 from the Rotterdam Study and 516 from the Zoetermeer Study). Each participant signed an informed consent form. The study was approved by the medical ethics committee of Erasmus University Rotterdam, The Netherlands.

MRI Scanning protocol

In all participants an axial T1, T2 and Proton Density (PD) weighted cerebral MRI scan was made on a 1.5T MRI scan. Subjects recruited from the Zoetermeer Study were scanned with a 1.5T MR Gyroscan (Philips, Best, The Netherlands) and participants from the Rotterdam Study were scanned with a 1.5T MR VISION (Siemens, Erlangen, Germany). In order to provide comparability the following pulse sequences were applied: at the Gyroscan T1 (TR 485 ms, TE 14 ms), T2 (TR 2236, TE 90 ms) and PD (TR 2236 ms, TE 20 ms); and at the VISION: T1 (TR 700 ms, TE 14 ms), T2 (TR 2200 ms, TE 80 ms) and PD (TR 2200 ms, TE 20 ms) Slice thickness was 6 mm and 5 mm respectively, with an inter-slice gap of 20 percent. The images were printed on hard copy with a reduction factor of 2.7.

White matter lesions rating scale

White matter lesions were considered present if these were hyper-intense on both PD and T2 weighted images and not hypo-intense on T1 weighted images. White matter lesions were distinguished into those in the subcortical and periventricular region. The number and size of subcortical white matter lesions was rated on hard copy according to their largest diameter in categories of small (<3 mm), medium (3-10 mm) or large lesions (>10 mm). In order to calculate the volume of subcortical white matter lesions on hard copy, they were considered to be spherical with a fixed diameter per size category (range 0-29.5 ml.). Periventricular white matter lesions were rated semi-quantitatively per region: adjacent to the frontal horns (frontal capping); adjacent to the lateral wall of lateral ventricles (bands), and adjacent to the occipital horns (occipital capping), on a scale ranging from 0 to 3. The overall de-

gree of periventricular white matter lesions was calculated by adding up the scores for the three separate categories (range 0-9). All MRI scans were examined by two raters from a pool of four experienced raters. In case of a disagreement of more than one point, a consensus reading was held; in all other cases the readings of both readers were averaged. The inter- and intra-rater studies showed a good to excellent agreement. Weighted kappas for grading the periventricular white matter were between 0.79-0.90. For total subcortical white matter volume the inter- and intra-rater intra-class correlation coefficient was 0.88 and 0.95, respectively.

Statistical analyses

The prevalence of white matter lesions was defined as the presence of any white matter lesion (regardless of size or location) in the brain. The relation between the prevalence of white matter lesions and age was assessed by means of age and sex adjusted linear regression analyses. The frequency distribution of either type of white matter lesions was calculated by 10 years age strata (60-70, 70-80 and 80-90 years). The relation between sex and white matter lesions was assessed by means of age adjusted linear regression with white matter lesions as the dependent variable. Analysis of covariance was performed to obtain sex specific mean volume of subcortical white matter lesions per 10 years age stratum or the mean grade of the periventricular white matter lesions. Sex differences for each category (0,1,2 and 3) of periventricular white matter lesions, per region, were analyzed with the chi-square test. There is increasing evidence that there exists a dose dependent relationship between severity of white matter lesions and cognitive consequences[1,2] and that especially the presence of severe white matter lesions is associated with a reduced cognitive function.[10,17] We therefore separately analyzed severe subcortical and periventricular white matter lesions per sex by means of an age corrected logistic regression model. White matter lesions were dichotomized at the upper quintile of their distribution, which reflects severe white matter lesions. The associations are presented as odds ratios with a 95 percent confidence interval (OR; 95%CI)

Results

The overall response rate was 63 percent; it decreased with age from 73 percent in subjects aged between 60-70 years to 48 percent in participants aged between 80-90 years. Responders were therefore significantly younger than non-responders (mean age 72.4 years versus 75.9 years, $p<0.001$), whereas there was no sex difference.

Figure 1a
Distribution of subcortical white matter lesions by 10-year age category

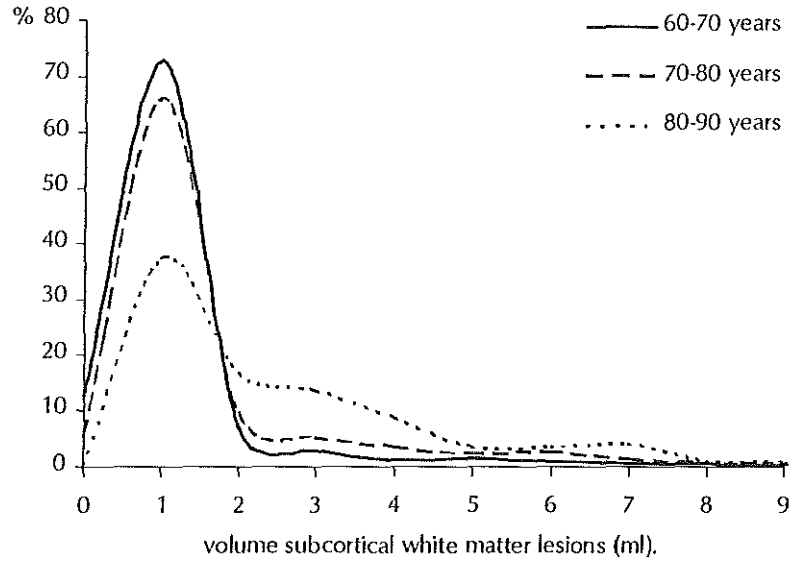
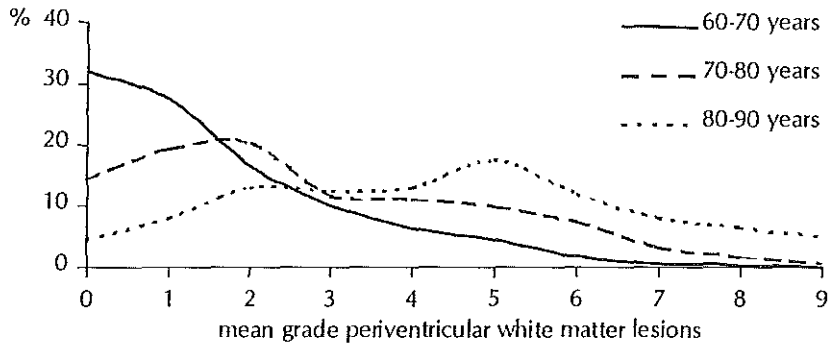


Figure 1b
Distribution of periventricular white matter lesions by 10-year age category



In our study 8 percent of all subjects were completely free of subcortical white matter lesions, 20 percent had no periventricular white matter lesions and 5 percent had no white matter lesions in either of these locations. Frequency of white matter lesions strongly depended on age (figure 1). Of subjects aged between 60-70 years, about 13 percent were completely free of subcortical white matter lesions and 32 percent was free of periventricular matter lesions, whereas for subjects aged between

Table 1
Mean volume of subcortical white matter lesions per lobar location per 10-year age stratum.*

Lobar location	60-70 years (n=466)		70-80 years (n=418)		80-90 years (n=200)		overall (n=1084)	
	men (n=226)	women (n=240)	men (n=204)	women (n=214)	men (n=94)	women (n=106)	men (n=524)	women (n=560)
frontal	0.23 (0.06)	0.43 (0.06)†	0.75 (0.12)	0.90 (0.12)	1.71 (0.31)	1.92 (0.29)	0.70 (0.08)	0.89 (0.07)
parietal	0.25 (0.05)	0.26 (0.05)	0.50 (0.07)	0.45 (0.06)	1.25 (0.17)	1.23 (0.17)	0.53 (0.05)	0.51 (0.04)
occipital	0.01 (0.01)	0.02 (0.01)	0.05 (0.02)	0.02 (0.02)	0.16 (0.05)	0.12 (0.04)	0.05 (0.01)	0.04 (0.01)
temporal	0.00(0.00)	0.00(0.00)	0.01 (0.02)	0.00 (0.00)	0.05 (0.02)	0.02 (0.02)	0.01 (0.00)	0.01 (0.00)
whole brain	0.49 (0.10)	0.72 (0.10)	1.31 (0.18)	1.38 (0.18)	3.18 (0.48)	3.31 (0.44)	1.29 (0.12)	1.45 (0.12)

* Expressed as milliliter white matter lesion volume on hard copy (SE)
† $P < 0.05$

Table 2
Sex specific mean grade of periventricular white matter lesions per region per 10-year age stratum.*

Lobar location	60-70 years (n=466)		70-80 years (n=418)		80-90 years (n=200)		overall (n=1084)	
	men (n=226)	women (n=240)	men (n=204)	women (n=214)	men (n=94)	women (n=106)	men (n=524)	women (n=560)
frontal capping	0.5 (0.0)	0.6 (0.0)†	0.8 (0.1)	1.0 (0.1)‡	1.3 (0.1)	1.5 (0.1)†	0.8 (0.0)	0.9 (0.0)‡
bands	0.6 (0.0)	0.5 (0.0)	0.9 (0.1)	1.0 (0.1)	1.4 (0.1)	1.5 (0.1)	0.8 (0.0)	0.9 (0.0)
occipital capping	0.3 (0.1)	0.3 (0.1)	0.7 (0.1)	0.8 (0.1)	1.4 (0.1)	1.4 (0.1)	0.7 (0.0)	0.7 (0.0)
total periventricular	1.4 (0.1)	1.5 (0.1)	2.4 (0.1)	2.8 (0.1)	4.1 (0.2)	4.4 (0.2)	2.3 (0.1)	2.5 (0.1)

* Expressed as mean grade (SE)
† $P < 0.05$
‡ $P < 0.01$

Table 3
Sex specific frequency distribution of periventricular white matter lesions grades per region per 10-year age stratum.

Location	Grade	60-70 years		70-80 years		80-90 years		overall	
		men (n=226)	women (n=240)	men (n=204)	women (n=214)	men (n=94)	women (n=106)	men (n=524)	women (n=560)
frontal capping	0	50.0	42.4	29.9	22.9	14.9	8.5	35.9	28.5
	1	40.6	41.7	43.1	42.0	39.4	31.1	41.4	39.8
	2	8.9	14.6	25.5	33.2	40.4	51.9	21.0	28.8
	3	0.5	1.3	1.5	1.9	5.3	8.5	1.7	2.9*
bands	0	43.8	46.2	27.0	25.7	8.5	10.4	30.9	31.6
	1	45.6	43.8	51.0	45.8	43.6	35.8	47.3	43.1
	2	9.7	8.3	18.6	21.0	30.9	34.9	17.0	18.2
	3	0.9	1.7	3.4	7.5	17.0	18.9	4.8	7.1
occipital capping	0	71.7	72.4	48.2	42.5	25.6	23.6	54.2	51.8
	1	20.8	18.8	27.9	32.7	22.3	29.2	23.9	26.1
	2	6.2	7.1	18.1	17.8	34.0	25.5	15.8	14.6
	3	1.3	1.7	5.8	7.0	18.1	21.7	6.1	7.5

Numbers are percentages.
* p=0.005 (Overall chi-square test).

80-90 years these percentages were 0 and 5, respectively. This age effect was similar for men and women. The prevalence of subcortical and periventricular white matter lesions significantly increased with 0.2 percent and 0.4 percent per year, respectively.

Table 1 shows the volume of subcortical white matter lesions per 10 years age stratum by sex. The mean volume of subcortical white matter lesions was highest in the frontal lobe, followed by the parietal, occipital and temporal lobes. This applied to both sexes and all age groups. The mean volume of subcortical white matter lesions increased from 0.6 ml (SE 0.1) for subjects between 60-70 years of age to 3.2 ml. (SE 0.4) for individuals aged between 80-90 years ($p < 0.01$). Women had greater volumes of subcortical white matter lesions than men (total volume 1.45 ml *versus* 1.29 ml; $p=0.33$), mainly caused by differences in the volume of frontal white matter lesions (0.89 ml *versus* 0.70 ml; $p=0.08$).

Table 2 shows sex-specific mean grades of periventricular white matter lesions per 10 years category. The mean grade of periventricular white matter lesions increased from 1.5 (SE 0.1) for subjects between 60-70 years of age to 2.4 (SE 0.1) for individuals aged between 80-90 years ($p < 0.01$). The mean grade of the total periventricular white matter lesions was higher among women than men (2.5 (SE 0.1) *versus* 2.3 (SE 0.1); $p=0.07$), mainly caused by the significant difference in severity of frontal capping between men and women in all age categories.

Table 3 shows the proportion of subjects with different degrees of periventricular white matter lesions for each of the three different locations per 10 years age-stratum. For all age categories and at every location, proportionally more women than men had the most severe periventricular white matter lesions.

Women had more severe periventricular (OR 1.2; 95% CI 0.9-1.7) and subcortical white matter lesions (OR 1.1; 95% CI 0.8-1.5) than men, especially in the frontal region (OR 1.6; 95% CI 1.2-2.1 and OR 1.6; 95% CI 1.2-2.2, for severe frontal periventricular and subcortical white matter lesions, respectively).

Discussion

Our study shows that the severity of subcortical and periventricular white matter lesions is dependent on age and sex. We confirmed the significant association between severity of white matter lesions and age. In addition we showed that women more often had white matter lesions of both kinds, especially in the frontal region.

The strength of this study is its large number of elderly people, including institutionalized persons. Another important feature of our study is the distinction be-

tween white matter lesions in the subcortical and the periventricular region, and according to lobe.

However, some potential methodological shortcomings need to be considered. Our study had a response rate of 73 percent in subjects aged 60-70 years decreasing to 48 percent in participants aged between 80-90 years. This may lead to selection bias, especially in the oldest age category. We consider it likely that if participation in our study were related to the degree of white matter lesions, this would probably have resulted in persons with more severe white matter lesions participating less. Therefore the mean volume of subcortical white matter lesions and the mean grade of periventricular white matter lesions had probably been underestimated. This particularly applies to the oldest participants, among which the response was lowest. However, we consider it unlikely that the sex difference for white matter lesions has been influenced by selection bias, since the response rate was similar for men and women in any age category.

Another point of concern is the validity of the white matter lesions rating scale, since there is potential for measurement error in this procedure. Although we chose anatomical landmarks to separate the lobes we cannot exclude that some misclassification occurred. As it is unlikely that this misclassification would be different for the sexes or age categories, and the resulting bias will be non-differential. When subcortical and periventricular white matter lesions are both abundantly present, it may sometimes be difficult to distinguish between the two. However, our intra -and inter-rater studies showed an excellent to high reliability, suggesting that this was not a major problem in our study.

An important aspect of our rating scale is that it distinguishes between subcortical and periventricular white matter lesions while also their severity was recorded. This will allow us to evaluate whether white matter lesions in these two regions have a different pathogenetic background and different clinical correlates.

Our study showed that subcortical white matter lesion volume was highest in the frontal and parietal lobes, a factor twenty and hundred higher than in the occipital and temporal lobes, respectively. Although the frontal and parietal lobes are larger than the occipital and the temporal lobe, this difference can not explain the vast difference in white matter lesion volume. Scheltens et al. found in a study of 24 'normal' elderly subjects (mean age 68.0 years) that the severity of white matter lesions was highest in the frontal lobe.[18] This observation was even more marked in subjects suffering from Alzheimer's disease. They explained this finding by over-representation of the frontal and parietal lobe compared with the occipital and the temporal lobes axial slices.[18] We cannot exclude that we have relatively overesti-

mated the frontal or parietal lobes, but again the magnitude of the difference in the volume of white matter lesions seems out of proportion to this.

Our study confirms previous findings of a relatively high prevalence and severity of white matter lesions among women. This was also found in the Cardiovascular Health Study and the Atherosclerosis Risk in Communities Study.[2,3] This could be mainly attributed to the significant differences for the subcortical and periventricular white matter lesions in the frontal region. It is unclear how these sex differences must be explained. It is possible that an increased susceptibility for ischemia of the brain secondary to the reduction in estrogen levels after menopause plays a role. The occurrence of hypoxia or ischemia in the cerebral white matter is commonly considered as an intermediate factor in the pathogenesis of white matter lesions.[6] Estrogens have important functions in the brain, including an increase in cerebral blood flow, protection against oxidative stress, stimulation of synaptogenesis and prevention of neuronal atrophy.[19-21] The post-menopausal estrogen reduction might make the female brain more vulnerable by reduction of cerebral blood flow (ischemia) and impairment of neuronal repair mechanisms. This hypothesis is supported by *in vitro* studies that showed protective effects of estrogens on menopause-related cerebral damage by excitotoxicity and the action of free radicals, as occurs during cerebral ischemia.[22-26] As there is a morphological and epidemiological overlap between vascular dementia and Alzheimer's disease, the increased prevalence of cerebral white matter lesions in women could underlie the higher incidence of Alzheimer's disease among women, even after adjustment for prolonged life expectancy, especially at high ages.[27] This hypothesis about the possible role of estrogens is supported by the finding of a significantly increased incidence of Alzheimer's disease among women who did not use estrogen replacement therapy.[28,29]

In conclusion, prevalence of cerebral white matter lesions increased with age. Women had more often severe white matter lesions compared to men. Large prospective population based studies are needed to investigate what underlies these differences and in particular to investigate whether estrogens play a part in the presence and development of white matter lesions and the attendant cognitive decline.

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— Chapter 4.1 —

CEREBRAL WHITE MATTER LESIONS AND SUBJECTIVE COGNITIVE FAILURES

Abstract

Objective: To determine the relation between severity of white matter lesions and subjective cognitive failures and their reported progression.
Design: Population based cross sectional MRI study.
Subjects: Random sample of 1084 elderly subjects from the general population.
Setting: The city of Zoetermeer and a suburb of Rotterdam in the Netherlands, 1995-6.
Main outcome measures: Severity of cerebral white matter lesions, subjective failure of cognitive functioning, and reported progression of these failures over time.
Results: White matter lesions were more severe for individuals reporting progression of subjective failures of cognitive functioning compared to their non failing counterparts, especially within subjects with better than average cognitive performance ($p= 0.008$, for periventricular white matter lesions). We found a linear relationship between the severity of white matter lesions (in quintiles) and the percentage of subjects reporting progression of cognitive failures ($p_{trend}<0.001$, for both regions of white matter lesions). Subjects with severe white matter lesions reported progression of cognitive failures over the last 5 years twice as often, when compared to subjects with only little or no white matter lesions. No significant relations were found between severity of subcortical white matter lesions and subjective cognitive failures when this relation was studied conditional on the severity of periventricular white matter lesion.
Conclusions: The severity of, especially periventricular, white matter lesions was associated with more subjective failures of cognitive function and in particular with reporting progression of these failures.

Complaints about memory correlate poorly with objective memory performance[1,2] but better with depressed mood.[3] However in a longitudinal population-based study of non-demented non-depressed elderly, subjective memory complaints as well as depressive symptoms predicted a dementia syndrome 3 years later, even in subjects without cognitive impairment.[4] Although in cross-sectional studies memory complaints correlated better with depression than with cognitive function, the above findings indicate that subjective cognitive complaints may be a prelude to cognitive impairment or that these complaints are more sensitive than neuropsychological tests to detect slight failures of cognitive function.

Cerebral white matter lesions (WML) have been related to cognitive dysfunction[5,6] and may eventually lead to dementia.[7] A small cross-sectional population-based study previously showed an association between WML and subjective memory complaints among elderly subjects.[8] Based on these findings we hypothesize that when severity of WML is only mild, subjective cognitive failures could occur in the absence of detectable cognitive impairment. Increasing severity of WML would then be accompanied by progression of cognitive failures and by an increased possibility of measurable cognitive impairment.

The aim of this study was to investigate whether periventricular and/or subcortical WML are associated with the number and/or the reported progression of subjective cognitive failures, and whether this association is conditional on the presence of objective cognitive impairment. Because the presence of cognitive complaints could merely reflect the presence of depressive symptoms, we studied whether the association between WML and subjective cognitive failures was conditional on the presence of depressive symptoms.

Methods

Study Population

This study is part of the Rotterdam Scan Study, which was designed to study determinants and cognitive correlates of age related brain changes in the elderly. In 1995-1996, 1904 persons aged between 60 and 90 years were randomly invited in strata of age and gender, from participants of two large ongoing cohort studies; the Rotterdam Study and the Zoetermeer Study. Both studies have been described in detail elsewhere.[9,10]

One hundred and eighty persons had contra-indications for the study (dementia, contraindications for MRI scanning, blindness), so 1,724 were eligible. Complete data were obtained from 1,084 participants (63%). The protocol was approved by the medical ethics committee of the Erasmus University Rotterdam, the Netherlands, and all participants gave written informed consent.

MRI scanning

MRI scanning was performed on 1.5-Tesla scanners (Gyroscan, Philips NT, or Magnetom Vision, Siemens AG). The scanning protocol included a series of axial proton-density (TR 2200ms, TE 20ms), T2-weighted (TR 2200ms, TE 80ms) and T1-weighted (for Gyroscan TR 485ms, for Vision TR 700ms, TE 14ms) images. Sections were 5 or 6 mm thick (scanner dependent) with an interslice gap of 20%. Laser hardcopies were printed with a reduction factor of 2.7.

White matter lesions rating scale

Presence, severity and location of different brain parameters were scored according to a protocol designed for the Rotterdam Scan Study. WML were considered present if visible as hyperintense on both PD and T2 weighted images and not hypointense on T1 weighted images. When the largest diameter of the WML was adjacent to the ventricle it was defined as periventricular, otherwise as subcortical. Periventricular WML were scored semi-quantitatively as 0 (none), 1 (pencilthin lining), 2 (smooth halo), or 3 (large confluent) for three separate regions (adjacent to frontal horns, adjacent to the wall of the lateral ventricles, adjacent to the occipital horns). The total periventricular WML score was calculated by adding the region-specific scores (range 0-9). Subcortical WML were categorized based on their maximum diameter (as appearing on the hardcopy) as small (1-3 mm), medium (3-10 mm) or large (>10 mm). The number of subcortical WML was rated per size-category. In order to calculate a total subcortical WML volume, on hard copy, WML were considered to be spherical with a fixed diameter per size category. Other brain features that were recorded from the MRI images were brain atrophy (cortical and subcortical) and the number of strokes. Cortical atrophy was rated visually on a four-point severity scale. Subcortical atrophy was measured by the ventricle-to-brain ratio (mean of the biventricular width assessed at the frontal horns, body of the caudate nucleus, and at occipital horns of the lateral ventricles divided by the matching brain width).

Two independent readers out of a pool of four experienced physicians examined all scans. In case of disagreement of more than one point for periventricular

WML or cortical atrophy, a consensus reading was held, in other instances scores were averaged. Intra- and inter-rater studies showed good to excellent agreement. Weighted kappas for periventricular WML severity grades were between 0.79-0.90. Interreader and intrareader-intraclass correlation coefficients for total subcortical WML-volume was 0.88 and 0.95 respectively. Spearman's rank test for the correlation between periventricular and subcortical WML was 0.7.

Subjective Cognitive Failures

A semi-structured interview based on the Cognitive Failure Questionnaire[11] was used to obtain information on subjective failures of cognitive function. The interview consisted of 15 questions about cognitive problems (table 1). Responses were

Table 1
Subjective Cognitive Failures Questionnaire

Question	Score range	% with problems*	R (ir)†
Memory problems:			
Do you consider yourself as forgetful?	0-3	41.3%	0.75
Do you experience word-finding problems?	0-3	35.1%	0.67
Do you ever forget names of family members or friends?	0-1	22.7%	0.48
Do people tell you that you tell stories twice?	0-1	23.5%	0.37
Do you ever forget occurrences of the past one or two days?	0-1	7.6%	0.30
Do you worry about forgetfulness?	0-1	17.2%	0.44
Do you experience hinder in everyday-life because of forgetfulness?	0-1	8.9%	0.39
Do you ever misplace items at odd locations, leave the stove burning, or forget how to use everyday appliances?	0-1	5.1%	0.22
Do you ever forget appointments?	0-1	6.6%	0.27
Do you ever lose your way in your neighbourhood or do not recognise a person that is actually well acquainted?	0-1	14.7%	0.15
Related cognitive problems:			
Have you experienced problems with planning of activities?	0-3	4.0%	0.25
Do you have concentration problems?	0-3	12.6%	0.45
Do you think or act more slowly than you used to?	0-3	21.3%	0.52
Do you feel more exhausted than you used to?	0-1	14.7%	0.39
Do you ever feel so depressed that you lose interest in life?	0-1	13.3%	0.32

Scoring of items with 0-3 score range: 0= no problems; 1= doubtful problems; 2= moderate problems; 3= serious problems. Scoring of items with 0-1 score range: 0= no; 1= yes.
* Percentage of the study population reporting problems; indicating at least moderate problems on items having a score range of 0-3, and a score of 1 on dichotomous items.
† Spearman's R(ir): item score-total score correlation coefficient.

added to a sum-score for "subjective cognitive failures" (SCF) with a maximum of 25. Subjective failure in remembering, word finding, planning, concentration, or slowness of thought had a higher weight in the sum-scores.

In addition we assessed whether subjective cognitive failures of remembering, word finding, planning, concentration, or slowness of thought had progressed over the past 5 years. Progression of such failures was defined as present when a subject reported little progression on more than one of these cognitive failures or obvious progression of at least one failure.

Data on both the SCF score and progression of SCF were complete for 1056 subjects. At least some subjective cognitive failures were reported by 762 (72%) subjects, of whom 31% reported progression of cognitive failures over the last 5 years.

Objective cognitive performance

Cognitive performance was assessed by neuropsychological tests, including an abbreviated Stroop test consisting of three subtasks, the Paper-and-Pencil Memory Scanning Task consisting of four subtasks,[12,13] the Letter-Digit Substitution Task which is a modified version of the Symbol Digit Modalities Test,[14] a verbal fluency test and a 15 words verbal learning test based on Rey's auditive recall of words.[15] Performance across tests was made comparable by transforming the raw test scores into standardized *Z*-scores as described elsewhere.[16] As overall measure of cognitive performance we used a compound score, referred to as Cognitive Index, which was calculated as the mean of the *Z*-scores on the 1-letter subtask of the Paper-and-Pencil Memory Scanning Task, the reading subtask of the Stroop test, the Letter-Digit Substitution Task, the added score on the learning trials of 15 words verbal learning test and the delayed recall of this last test. According to tertiles of the Cognitive Index distribution we categorized cognitive performance in poor, average or good.

Other measurements

The following characteristics were considered as possible confounding variables: age, gender, level of education (according to UNESCO)[17] and mood disturbances as determined with the Center of Epidemiologic Studies on Depression Scale (CES-D).[18] Additional neuroimaging findings considered as potential confounding variables in the relation between WML and subjective cognitive failures or cognitive function, were cerebral atrophy and the presence of any strokes.

Statistical analysis

To estimate the influence of each individual item of the SCF-scale to the overall SCF-score we calculated Spearman's correlation coefficients. Differences in SCF-scores between genders and age categories were studied using analysis of covariance (ANCOVA) and linear regression analysis, respectively.

We investigated the relation between WML and subjective cognitive failures in three different ways. First, we determined whether subjects with and without any subjective cognitive failures had different amounts of WML by calculating the adjusted mean severity of WML for both groups, taking the reported progression of subjective cognitive failures into account (ANCOVA). To investigate if the level of objective cognitive performance modified this association we also analyzed this relation in strata of the Cognitive Index.

Next, we investigated if an increased WML severity was associated with a higher SCF-score by performing ANCOVA with WML severity (in quintiles) as the

Table 2
Characteristics of the 1056 participants who completed the Subjective Cognitive Failure Questionnaire

Characteristic	
Mean age in years (SD)	72.2 (7.4)
Number of women (%)	549 (52%)
Number of people with only primary education (%)	359 (34%)
Median score on the CES-D* (interquartile range)	4 (1-9)
Median score on the Mini Mental State Examination (interquartile range)	28 (26-29)
Subjective cognitive failures (SCF)	
Number of people with SCF (%)	760 (72%)
Median of the sum-score on the SCF questionnaire (interquartile range)	2 (0-5)
Number of people with subjective memory failures (%)	697 (66%)
Median sum-score of sub-questionnaire on subjective memory failures (interquartile range)	2 (0-4)
Number of people reporting progression of SCF last 5 years (%)	232 (22%)
Neuroimaging characteristics	
Median volume of subcortical WML (interquartile range)	0.19 (0.03-1.25)
Median grade of periventricular WML (interquartile range)	2.0 (0.5-4.0)
Number of people with any cerebral infarct (%)	137 (13%)
Mean grade of cortical atrophy (SD)	1.1 (0.6)
Mean ventricle-to-brain ratio (SD)	0.32 (0.04)

* Centre of Epidemiological Studies on Depression Scale

independent variable and SCF-score as the dependent variable. For the test for trend over quintiles of WML severity, we used linear regression analysis (adjusting for the same variables as in the ANCOVA).

Finally, we studied whether more severe WML (in quintiles) were associated with a higher percentage of subjects reporting progression of subjective cognitive failures, also by ANCOVA. To investigate whether the level of actual cognitive performance modified the relation between WML severity and reporting progression of subjective cognitive failures, dummy variables were constructed for all 15 combinations of quintiles of WML severity and tertiles of the Cognitive Index. These dummy variables were used as independent variables in the logistic regression model (using subjects with a good cognitive function within the lowest quintile of WML severity as the reference category).

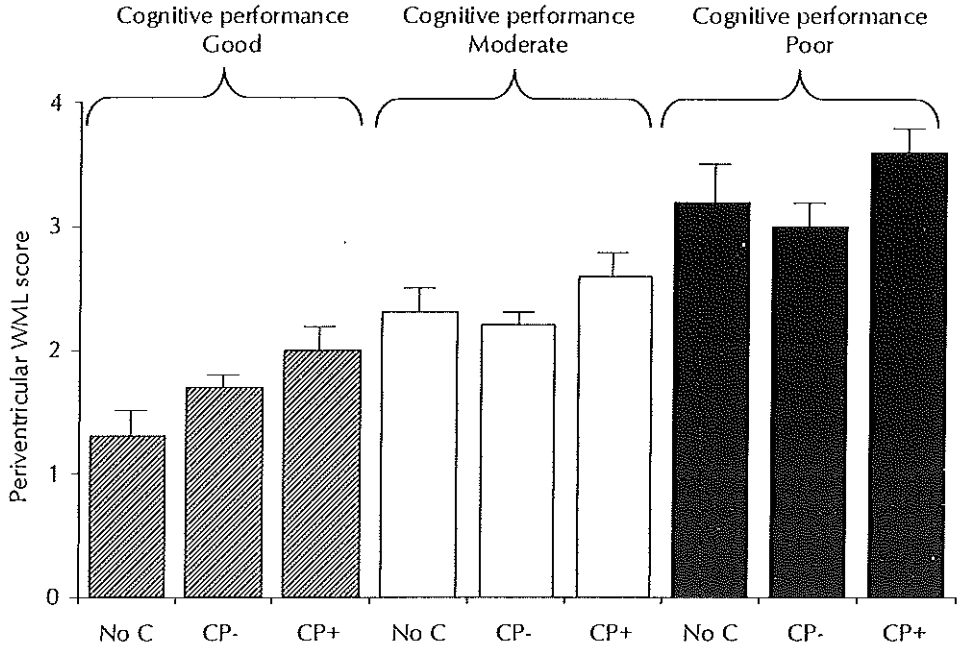
Initially, all analyses were performed for periventricular and subcortical WML separately and adjusted for age and gender with additional adjustments for possible confounding variables. In addition to these analyses, we studied the relation between subcortical WML and subjective cognitive failures independent of periventricular WML and vice versa, by entering both subcortical and periventricular WML simultaneously in the model.

Results

The correlation of the SCF-score with the Cognitive Index was lower (r= -0.19, p< 0.001) than with the CES-D-score (r= 0.35, p< 0.001). The most reported failures on SCF questionnaire (~40%) concerned forgetfulness and word finding problems. The least frequent failures (<7%) concerned forgetting appointments, misplacing items, or failures as forgetting to turn off or how to use appliances (Table 1). The mean correlation of the items to the sum-score was 0.40 (range 0.15-0.75; see table 1). More general characteristics of the study population are shown in table 2. On average, women had more subjective cognitive failures than men (mean SCF-score adjusted for age 3.5 and 2.8, respectively). This gender difference remained when the analyses were corrected for cognitive performance, but disappeared when the score on the CES-D was taken into account. The SCF-score increased 0.4 per 5-year increase in age (p_{trend}<0.001). Adjusting for score on the CES-D and Cognitive Index halved the effect estimate of this relation (the SCF-score increased 0.2 per 5-year increase in age, p_{trend}= 0.14).

Periventricular, but not subcortical WML, tended to be more severe in subjects with subjective cognitive failures compared to subjects without such failures (age

Figure 1
Age and gender adjusted mean severity (SE) of white matter lesions for subjects without subjective cognitive failures (SCF), with SCF but without reporting progression of SCF and subjects who reported progression of SCF, in strata of objective cognitive performance (tertiles of the Cognitive Index).

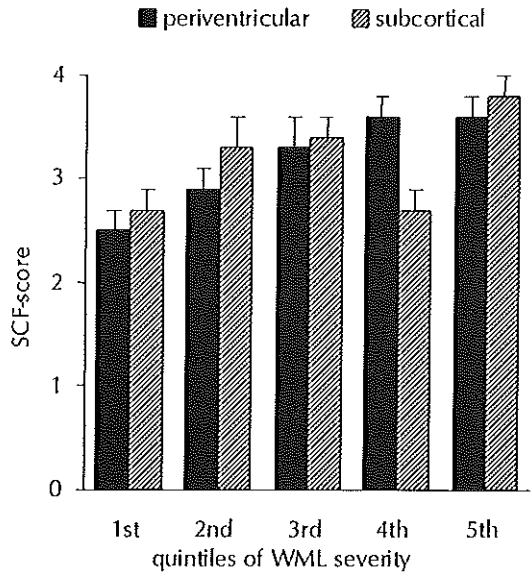


No C : Subjects who reported no SCF (n=115, n=116, n=63 respectively).
CP- : Subjects who reported SCF but denied progression of these failures over the last 5 years (n=175, n=181, n=171 respectively).
CP+ : Subjects who reported SCF and reported progression of these failures over the last 5 years (n=59, n=68, n=108 respectively).
* Significantly different from No C-subjects within this stratum ($p = 0.008$)

and gender adjusted difference in periventricular WML score was 0.2; $p= 0.09$, and in subcortical WML volumes 0.12 ml; $p= 0.52$). In figure 1 the age and gender adjusted severity of periventricular WML is given in strata of actual cognitive performance for subjects with and without subjective cognitive failures, taking the reported progression of such failures over the last 5 years into account. The difference in WML severity between subjects without subjective cognitive failures and subjects reporting progression of such failures over the last 5 years was most outspoken in subjects with a good cognitive performance. The comparison of subcortical WML volumes between subjects with and without any subjective cognitive complaints in strata of cognitive performance never reached statistical significance (all $p> 0.25$).

An additional finding was that both periventricular (figure 1) and subcortical (data not shown) WML severity increased with lower cognitive performance.

Figure 2
Score on the subjective cognitive failure (SCF) questionnaire per quintile of white matter lesion severity adjusted for age and gender (SE)

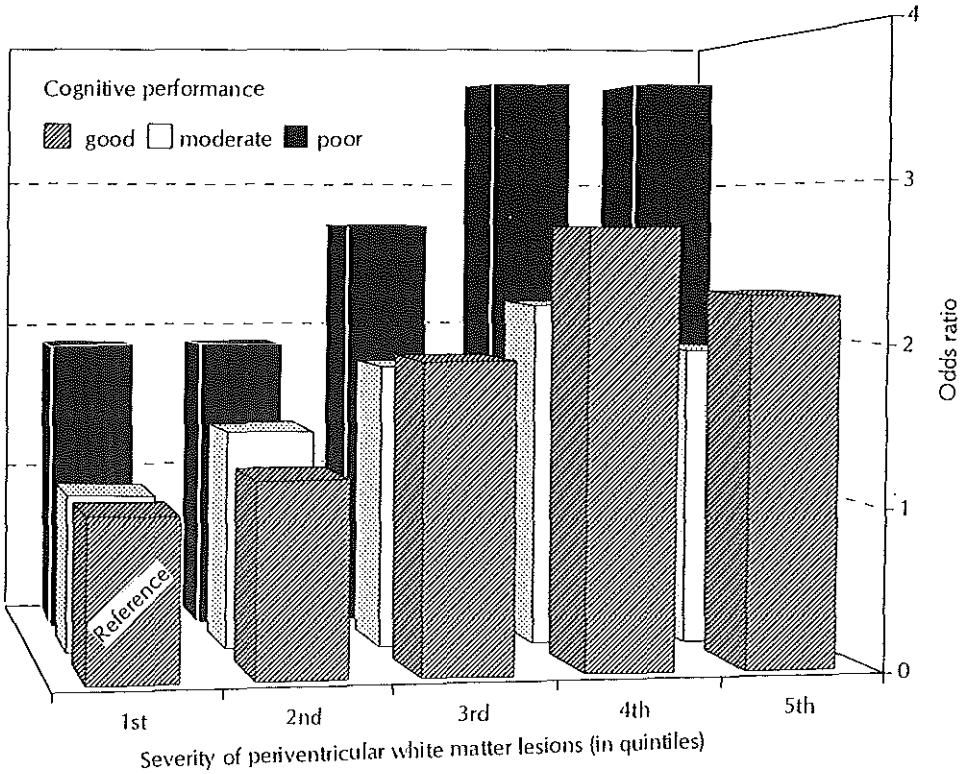


Additional adjustment for level of education, cerebral atrophy and presence of stroke did not change any of the above relations.

As shown in figure 2, subjects with more severe WML had higher SCF-scores (p_{trend}< 0.001 for quintiles of periventricular WML; p_{trend}= 0.02 for quintiles of subcortical WML) although differences were small. After additional adjustment for possible confounding variables (including level of cognitive performance and score on the CES-D), the differences in SCF-score between the lowest and highest quintile of periventricular or subcortical WML decreased to 0.6 or 0.9, respectively (p_{trend}= 0.02 for quintiles of periventricular WML; p_{trend}= 0.08 for quintiles of subcortical WML). When the relation between periventricular WML and SCF-scores was analyzed conditional on the severity of subcortical WML and vice versa, no significant trends were found for either quintiles of periventricular or subcortical WML (p_{trend}= 0.13 and p_{trend}= 0.75, respectively).

The percentage of people reporting progression of subjective cognitive failures over time increased linearly with the severity of both periventricular and subcortical WML. When adjusted for age and gender, only 15% of subjects with none to mild WML (lowest quintile) reported progression of subjective cognitive failures, which percentage increased up to 30% for subjects with severe WML (highest quintile) (p_{trend}< 0.001 for both regions of WML). These relations remained when additionally adjusted for possible confounders (including the level of cognitive performance and the CES-D score). However, when the association between periventricular WML and progression of subjective cognitive failures was studied conditional on the se-

Figure 3
The risk for reporting progression of subjective cognitive failures over the last 5 years per severity of periventricular white matter lesions in strata of objective cognitive performance, expressed as age and gender adjusted odds ratios.



verity of subcortical WML and vice versa, the associations with periventricular WML remained (p_{trend}= 0.10), whereas for subcortical WML the association disappeared (p_{trend}= 0.42). This motivated us to focus on periventricular WML for the stratified analyses.

When we stratified people on the level of cognitive performance (tertiles of the Cognitive Index), an increased severity of periventricular WML was related to an increased risk of reporting progression of subjective cognitive failures over time in all three strata (figure 3). Among subjects with a good cognitive performance, subjects within the highest quintile of the periventricular WML severity had an approximately 2.5-fold increased risk (OR= 2.3, 95%CI: 0.9-5.9) for reporting progression of subjective cognitive failures compared to subjects in the lowest quintile of periventricular WML. Subjects who had a poor cognitive performance had higher risks for reporting progression of subjective cognitive failures compared to subjects

with an average or good cognitive performance, irrespective of the severity of WML (figure 3).

Discussion

In this study, the severity of white matter lesions was associated with subjective cognitive failures and to reporting progression of such failures. The relation was found for periventricular as well as for subcortical WML but more consistently for periventricular WML. To our knowledge this is the first large-scale population based study on the relationship between cerebral white matter lesions and subjective cognitive failures.

Before we interpret these results we have to discuss the nature of subjective cognitive failures. Subjective cognitive failures are not identical to subjective cognitive complaints. Failures are everyday mishaps in cognitive tasks, only reported when actively asked for, and differ from complaints in that the latter are reported spontaneously or have been the reason for seeking medical advice. The cognitive problems on which we report in this study represent at least subjective cognitive failures but could include cognitive complaints.

In a study by Breteler and coworkers an association was reported between white matter lesions and memory complaints or failures, although no inferences could be made to the location of WML and no stratification was performed on objective cognitive performance.[8] We found more severe WML in subjects reporting subjective cognitive failures compared to subjects without such failures, especially in subjects with a better than average cognitive performance. This finding is of importance as complaints about cognitive function may precede measurable cognitive dysfunction[19] or even dementia.[4] Additionally we observed more severe WML in subjects who reported progression of subjective cognitive failures compared to subjects who denied progression. This is in line with an earlier report by Schofield and coworkers, who reported that memory complaints per se did not relate to memory impairment, but subjects who reported new memory complaints after 1 year of follow up were 5 times more likely to have measurable cognitive impairment compared to subjects who still denied having memory problems.[20]

The association between subjective cognitive failures and indicators for depression (CES-D score) was stronger than with cognitive function. It could therefore be argued that subjective cognitive failures are a proxy for depression rather than for cognitive dysfunction. This however does not exclude the possibility that subjective cognitive failures could be a prelude to cognitive dysfunction. The results are com-

patible with this hypothesis as, firstly, we found a more robust association between subjective cognitive failures and periventricular than with subcortical WML, while periventricular WML are reported to have an association with cognitive dysfunction[21,22] whereas subcortical WML have been related to depression.[3,23] A second indication for subjective cognitive failures being a prelude to cognitive dysfunction is seen in figure 1, where a stepwise increase of the periventricular WML severity is observed when we compare 1) people without subjective cognitive failures and with a better than average cognitive performance, 2) people with subjective cognitive failures and reported progression of subjective cognitive failures, and 3) people with cognitive dysfunction with or without subjective cognitive failures.

Taken together, the relationship between WML severity and subjective cognitive failures followed a kind of dose-dependent pattern. On the lower end of the WML severity distribution are subjects without subjective cognitive failures and with a good cognitive performance, followed by subjects with subjective cognitive failures but still without measurable dysfunction. At the high end are subjects who report subjective cognitive failures that had progressed over the last five years, and who, upon measurement of cognitive function, are found to perform worse on cognitive tests than average. Our data suggest that reporting progression of subjective cognitive failures might be an early warning sign related to progression of WML and imminent cognitive decline.

Although in this study we asked for progression of subjective cognitive failures, the study is not longitudinal. Prospective studies are needed to confirm that progression of WML severity is indeed accompanied by progression of subjective cognitive failures and eventually to measurable cognitive impairment.

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— Chapter 4.2 —

CEREBRAL WHITE MATTER LESIONS AND COGNITIVE FUNCTION

Abstract

Cerebral white matter lesions (WML) have been associated with cognitive dysfunction. Whether periventricular or subcortical WML relate differently to cognitive function is still uncertain. In addition, it is unclear whether WML are related to specific cognitive domains, such as memory or psychomotor speed. We determined the relation of periventricular and subcortical WML with cognitive function in 1084 elderly subjects randomly sampled from the general population. Quantification of WML was assessed by means of an extensive rating scale on 1.5T MRI scan images. Cognitive function was assessed using multiple neuropsychological tests from which we constructed compound scores for psychomotor speed, memory performance and global cognitive function. When analyzed separately, both periventricular and subcortical WML were related to all measures of the neuropsychological tests. When periventricular WML were analyzed conditional on subcortical WML and vice versa, the relation between periventricular WML and global cognitive function remained unaltered (p_{trend} for quintiles = 0.001) whereas this relation with subcortical WML disappeared (p_{trend} for quintiles = 0.97). Subjects with most severe periventricular WML performed nearly one standard deviation below average on tasks involving psychomotor speed (-0.85 SD, $p = 0.001$), and more than half a standard deviation below average for global cognitive function (-0.61 SD, $p < 0.001$). Tasks that involve speed of cognitive processes appear to be more affected by WML than memory tasks

Cerebral white matter lesions (WML) have been associated with cognitive impairment in demented and non-demented elderly subjects.[1-3] There have been a number of reports associating WML to speed of cognitive processes.[4-6] The subcortical structures of the brain are thought to be especially important for the speed of cognitive processes and memory function.[7-9] The white matter of the subcortical structures can be distinguished into the area just under the cortex and the area surrounding the ventricles. The subcortical region has a high density of short looped U-fibers, which connect adjacent cortical areas, whereas the periventricular region contains many long association fibers that connect the cortex with subcortical nuclei like the striatum and more distant cortical areas.[10] White matter lesions in these separate regions might affect cognition in different ways. In most of the research performed to date, the different locations of WML have been rated and combined in a single score,[1,11] or only one of the two regions has been considered.[6,12-14] Studies that analyzed periventricular and subcortical WML separately are limited and inconclusive about their distinctive relationship with cognition.[5,15-17]

The aim of the present study was to determine whether the location and severity of white matter lesions are reflected in different aspects of cognitive function in an elderly population. The study was conducted in 1084 non-demented Dutch subjects aged 60-90 years.

Subjects and Methods

Study Population

The Rotterdam Scan Study was designed to study determinants and cognitive correlates of age related brain changes in the elderly. In 1995-1996, a random sample of 1,904 subjects aged between 60 and 90 years was invited by strata of age and gender, from participants of two large ongoing cohort studies, the Rotterdam Study and the Zoetermeer Study. The Rotterdam Study is a prospective population-based study among 7,983 elderly subjects aged 55 years and over, designed to study determinants of chronic diseases in the elderly.[18] The Zoetermeer Study, also a population-based study, is concerned with prevalence of various chronic diseases.[19] Both studies have been described in detail elsewhere.[18,19]

Since 180 of the invited 1,904 subjects had contra indications for the study (dementia, contra indications for MRI scanning, blindness), 1,724 were eligible. Complete data were obtained in 1,084 participants (response 63%). The study was

approved by the Medical Ethics Committee of the Erasmus University and written consent was obtained from each participant. Compared with non-participants, the participants of the study were younger (mean age difference 3.8 years, $p < 0.001$) and more educated (5% more subjects with university level education, $p = 0.05$). Baseline systolic blood pressures measurements for subjects originally invited from the Zoetermeer Study, were significant lower in participants compared to non-participants (age and gender adjusted difference; 2.4 mm Hg, $p = 0.03$), whereas this was not significant for subjects originally invited from the Rotterdam Study. Baseline Mini Mental State Examination scores were available for subjects originally invited from the Rotterdam Study and were higher in participants compared with non-participants (age and gender adjusted mean difference 0.4 points, $p < 0.001$).

MRI scanning

MRI scanning was performed on 1.5-Tesla scanners (Gyroscan, Philips NT, or Magnetom Vision, Siemens AG). The scanning protocol included a series of axial proton-density {TR 2200, TE 20, NEX 1, matrix 192x256, flip angle 80°}, T2-weighted {TR 2200, TE 80, NEX 1, matrix 192x256, flip angle 80°} and T1-weighted {for Gyroscan TR 485, for Vision TR 700, TE 14, NEX 1, matrix 192x256, flip angle 70°} images. Sections were 5 or 6 mm thick (scanner dependent) with an interslice gap of 20%. After optimization of the images on the scanner screen, data was archived on magnetic optical disk and laser hardcopies were printed with a reduction factor of 2.7.

White matter lesions rating scale

Presence, severity and location of morphological brain characteristics were rated according to a protocol designed for the Rotterdam Scan Study. WML were considered present in case of hyperintense lesions on both proton density and T2 weighted images, not hypointense on T1 weighted images. When the largest diameter of the WML was adjacent to the ventricle it was defined as periventricular, otherwise as subcortical. Periventricular WML were rated semi-quantitatively as 0 (none), 1 (pencilthin lining), 2 (smooth halo), or 3 (large confluent) for three separate regions, adjacent to frontal horns (frontal caps), adjacent to the wall of the lateral ventricles (bands) and adjacent to the occipital horns (occipital caps). The total periventricular WML score was calculated by adding the region specific scores (range 0-9). Subcortical WML were categorized according to their maximum diameter (as appearing on the hardcopy) as small (1-3 mm), medium (3-10 mm) or large (>10 mm). The number of subcortical WML was rated per size-category for the frontal, parietal, occipital

and temporal lobes. Distinction between lobes was according to anatomical landmarks. We approximated a total subcortical WML volume (in ml on hardcopy) by assuming subcortical WML spherical with diameters of 2 mm, 6 mm or 12 mm (according to their size-category) and adding these volumes. Other features recorded from the MRI images were brain atrophy (cortical and subcortical) and the presence and number of strokes. Cortical atrophy was rated visually on a four-point severity scale. Subcortical atrophy was measured by the ventricle-to-brain ratio (mean of the biventricular width at the level of the frontal, and occipital horns and at the level of the body of the caudate nuclei divided by the corresponding brain width at those levels).

Two independent readers from a pool of four experienced physicians examined all scans. In case of disagreement of more than one point a consensus reading was held, in other instances scores were averaged. Intra- and inter-rater studies showed good to excellent agreement. Weighted kappas for periventricular WML severity grades were between 0.79 and 0.90. Interreader and intrareader-intraclass correlation coefficients for total subcortical WML volume were 0.88 and 0.95, respectively. Of all subjects only 5% had no WML at all, whereas 20% were free of periventricular WML and 7% had no signs of subcortical WML. 73% of all subjects had both periventricular and subcortical WML. Pearson's correlation coefficient between periventricular and subcortical WML was 0.6.

Measurement of cognitive function

Cognitive function was assessed with neuropsychological tests that were considered to be sensitive and suitable for use in this study population. These tests took no longer than 30 minutes to complete. The tests were aimed to assess the speed of cognitive processes, memory function and global cognitive function and were chosen because of their robustness in detecting age-related impairment and sensitivity to subcortical dysfunction.[20] To evaluate speed of mental processes four tests were used: an abbreviated Stroop test consisting of three subtasks, the Paper-and-Pencil Memory Scanning Task consisting of four subtasks,[21,22] the Letter-Digit Substitution Task which is a modified version of the Symbol Digit Modalities Test,[23] and a verbal fluency test in which as many animals as possible had to be named within 60 seconds. Memory function was evaluated by a 15 words verbal learning test; a test used to evaluate the ability to acquire and retain new verbal information based on Rey's auditive recall of words.[24] As measures for global cognitive function we used a combination of above-mentioned tests[25] as well as the widely used Mini Mental State Examination (MMSE).[26] Most of these tests have been used in other large-scale

studies of cognition.[27,28] The tests were carried out in quiet rooms and administered by trained investigators; a stopwatch was used in timed tests.

Performance across tests was made comparable by transforming the raw test scores into Z-scores as described elsewhere.[25] We calculated compound scores for psychomotor speed, memory performance and global cognitive function from these Z-scores. The compound score for psychomotor speed was calculated as the mean Z-scores for the 1-letter subtask of the Paper-and-Pencil Memory Scanning Task, the reading subtask of the Stroop test and the Letter-Digit Substitution Task. The sign of the speed score was inverted to make it reflect above average performance when positive and below average performance when negative. A compound score for memory function was calculated by taking the mean of two Z-scores from the 15 words verbal learning test; one for the added scores on three learning trials of this test, and one for the delayed recall of this test. As overall measure of cognitive function a compound score was used, referred to as Cognitive Index. It was calculated as the mean of the Z-scores on the 1-letter subtask of the Paper-and-Pencil Memory Scanning Task, the reading subtask of the Stroop test, the Letter-Digit Substitution Task, the added score on the learning trials of 15 words verbal learning test and the delayed recall of this last test. If, during testing, the test assistant encountered problems, a code was given for test status, reflecting reliability of the test result. Separate codes were given for lack of motivation, presence of a cognitive or physical handicap, or deviation from the instructions. For 99% of all subjects a score for psychomotor speed and memory performance could be calculated of which 91% completed all tests without any recording of test problems. Lack of motivation possibly interfered with testing in 2.7% of subjects, deviation from the test-instructions in 0.7%, technical difficulties in 0.4% (like a broken pencil or stopwatch failure) and 5.7% had combinations of these possible problems.

Other Measurements

The following characteristics were considered as possible confounding variables: age, gender, level of education (according to UNESCO)[29] and mood disturbances (determined with the Center of Epidemiologic Studies Depression Scale (CES-D)).[30] These data were obtained during a two-hour visit of each participant to the local research facilities. Additional neuroimaging findings considered as confounding variables in the relation between WML and cognitive function were cortical and subcortical atrophy and the presence and number of any strokes.

Table 1
Characteristics of the Rotterdam Scan Study participants by age-category and gender (mean (SD)).

Characteristics	Age-category (years)			Gender	
	60-69	70-79	80-89	Male	Female
Number of subjects	466	418	200	524	560
Age	65.2 (2.6)	74.6 (2.8)	83.7 (2.8)	72.2 (7.2)	72.4 (7.7)
% only primary education	30.0 %	33.8 %	49.0 %	27.3 %	42.3 %
Total subcortical WML volume	0.6 (1.6)	1.4 (2.6)	3.3 (4.5)	1.3 (2.9)	1.5 (2.9)
Number of large WML	0.4 (1.4)	1.0 (2.5)	2.8 (4.6)	1.0 (2.8)	1.1 (2.8)
Number of medium WML	1.6 (3.0)	2.9 (4.3)	5.0 (4.9)	2.4 (3.7)	3.0 (4.4)
Number of small WML	15.5 (17.3)	22.8 (22.1)	26.4 (18.8)	18.2 (18.3)	22.3 (20.3)
Total periventricular WML score	1.4 (1.6)	2.6 (2.1)	4.2 (2.4)	2.3 (2.1)	2.5 (2.3)
Score frontal 'caps'	0.6 (0.6)	0.9 (0.8)	1.4 (0.8)	0.8 (0.7)	0.9 (0.8)
Score 'bands'	0.6 (0.6)	0.7 (0.9)	1.5 (0.9)	0.8 (0.8)	0.9 (0.8)
Score occipital 'caps'	0.3 (0.6)	0.9 (0.8)	1.4 (1.0)	0.7 (0.9)	0.7 (0.9)
% with previous stroke on MRI	6.9 %	16.8 %	18.0 %	14.3 %	11.3 %
Cortical atrophy score	0.8 (0.4)	1.2 (0.5)	1.7 (0.6)	1.2 (0.6)	1.0 (0.6)
Ventricle-to-brain ratio	0.30 (0.03)	0.32 (0.03)	0.34 (0.04)	0.32 (0.04)	0.31 (0.04)

Statistical analysis

The relationships of periventricular and subcortical WML with cognitive performance were assessed by means of multivariate regression with adjustment for age, gender and educational level. WML were analyzed in quintiles of severity to allow for a non-linear relationship with cognitive function. Analyses of covariance (ANCOVA) were performed to obtain adjusted mean cognitive performance by quintiles of WML severity. Additional adjustments were made for the presence of depressive symptoms, severity of brain atrophy and number of strokes. For the test of trend of the ANCOVA results, quintiles of WML severity were considered as a continuous variable in a multiple linear regression model, with adjustment for the same variables

Table 2
The relation between WML severity and neuropsychological-test outcome (regression coefficients and 95% CI, controlling for age, gender, educational level and test status).

Neuropsychological test	Difference in test-result per unit increase of WML	
	Subcortical WML in ml (95% CI) (range 0-29.5)	Periventricular WML in grades (95% CI) (range 0-9)
Mini Mental State Examination (score)	-0.05 (0.00 ; -0.10)	-0.08 (-0.02 ; -0.15)
Stroop test		
Reading (part 1 in sec)	0.14 (0.03 ; 0.26)	0.27 (0.12 ; 0.43)
Naming (part 2 in sec)	0.29 (0.15 ; 0.44)	0.48 (0.29 ; 0.68)
Interference (part 3 in sec)	0.43 (-0.08 ; 0.94)	1.07 (0.40 ; 1.74)
Paper & Pencil Memory Scanning Task		
1 letter (sec)	0.30 (0.09 ; 0.51)	0.50 (0.22 ; 0.79)
2 letters (sec)	0.61 (0.27 ; 0.96)	1.05 (0.59 ; 1.52)
3 letters (sec)	0.62 (0.21 ; 1.01)	0.94 (0.40 ; 1.48)
Letter Digit Substitution Task		
(number of letters/min)	-0.20 (-0.33 ; -0.06)	-0.42 (-0.61 ; -0.24)
Verbal fluency		
(number of animals/min.)	-0.15 (-0.26 ; -0.04)	-0.27 (-0.41 ; -0.11)
15 words verbal learning test		
Total in 3 trials (number of words)	-0.09 (-0.21 ; 0.02)	-0.23 (-0.38 ; -0.08)
Delayed recall (number of words)	-0.05 (-0.11 ; 0.01)	-0.14 (-0.21 ; -0.06)
Recognition (number of words)	-0.06 (-0.11 ; -0.01)	-0.11 (-0.18 ; -0.04)
Cognitive Index (Z-score)	-0.02 (-0.04 ; -0.01)	-0.05 (-0.07 ; -0.03)
Simple psychomotor speed (Z-score)	-0.03 (-0.04 ; -0.01)	-0.05 (-0.08 ; -0.03)
Memory performance (Z-score)	-0.02 (-0.04 ; 0.00)	-0.05 (-0.07 ; -0.02)

as in the ANCOVA. To study the relation between cognitive function and subcortical WML conditional on the severity of periventricular WML and vice versa, periventricular and subcortical WML were entered simultaneously in the multivariate model.

Results

Characteristics of the 1084 participants of the study are given in Table 1. As expected, age was related to the severity of both periventricular and subcortical WML. After adjustment for age, women tended to have more WML than men (difference in mean periventricular WML score is 0.2, $p = 0.07$ and in mean subcortical WML volume 0.16, $p = 0.34$).

Increasing severity of both periventricular WML and subcortical WML correlated consistently with worse performance across all tests of cognitive function (Table 2). Additional adjustments for score on the CES-D, degree of cerebral atrophy and number of cerebral infarcts did not alter these results.

The relation between WML in quintiles of severity and global cognitive function is shown in Figure 1. The Cognitive Index was related with severity of both subcortical WML ($p_{trend} < 0.001$) and periventricular WML ($p_{trend} < 0.001$) (Figure 1, upper panel). Because subcortical and periventricular WML were highly correlated we assessed the relation between cognitive function and subcortical WML conditional on the presence of periventricular WML and vice versa (Figure 1, lower panel). The relations with the Cognitive Index remained the same for periventricular WML ($p_{trend} = 0.001$) but largely disappeared for subcortical WML ($p_{trend} = 0.75$). The analyses of psychomotor speed and memory showed similar results. For subjects with the most severe periventricular WML (score 9) performance for psychomotor speed was -0.85 SD (95% CI: -1.31 to -0.39) below average, while for the less severe periventricular WML (score 0-6) this difference was only -0.15 SD (95% CI: -0.35 to 0.05). For memory these scores were -0.45 SD (95% CI: -0.99 to 0.09) and -0.19 SD (95% CI: -0.34 to -0.04), respectively.

When periventricular WML were analyzed (conditional on subcortical WML severity) for frontal, occipital and lateral regions separately (Figure 2), mainly the lateral bands showed a clear relationship with the cognitive compound scores (Cognitive Index $p_{trend} = 0.006$, psychomotor speed $p_{trend} = 0.003$, memory $p_{trend} = 0.22$). For the other periventricular regions the relationships were not significant ($p_{trend} > 0.40$). For subcortical WML we separately analyzed total lesion volume per lobe and the number of subcortical WML per size category. When analyzed conditional on

Figure 1
The relation between WML severity and cognitive function (expressed as mean Z-scores (+SEM) for Cognitive Index adjusted for age, gender, educational level and test status.

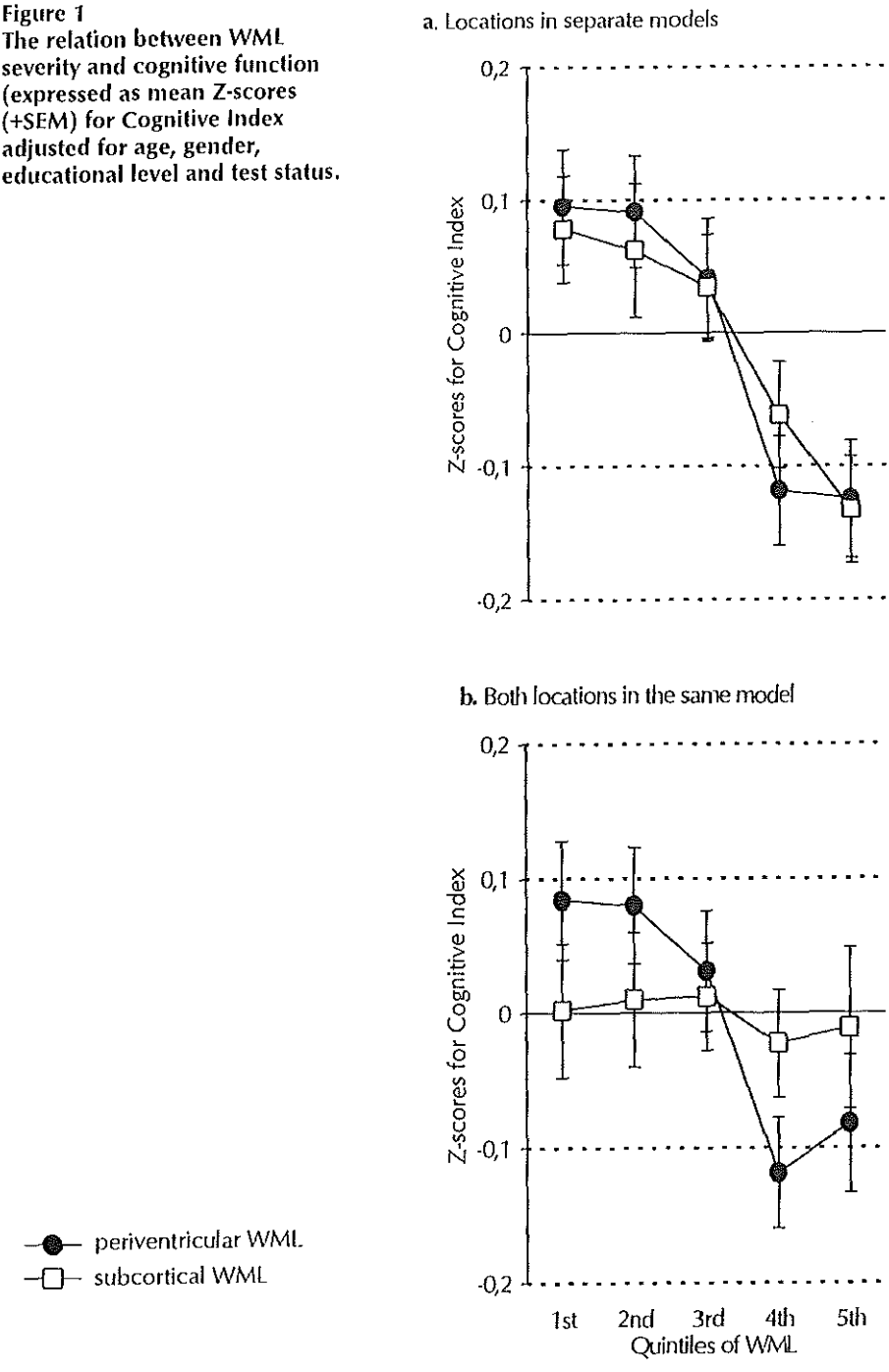
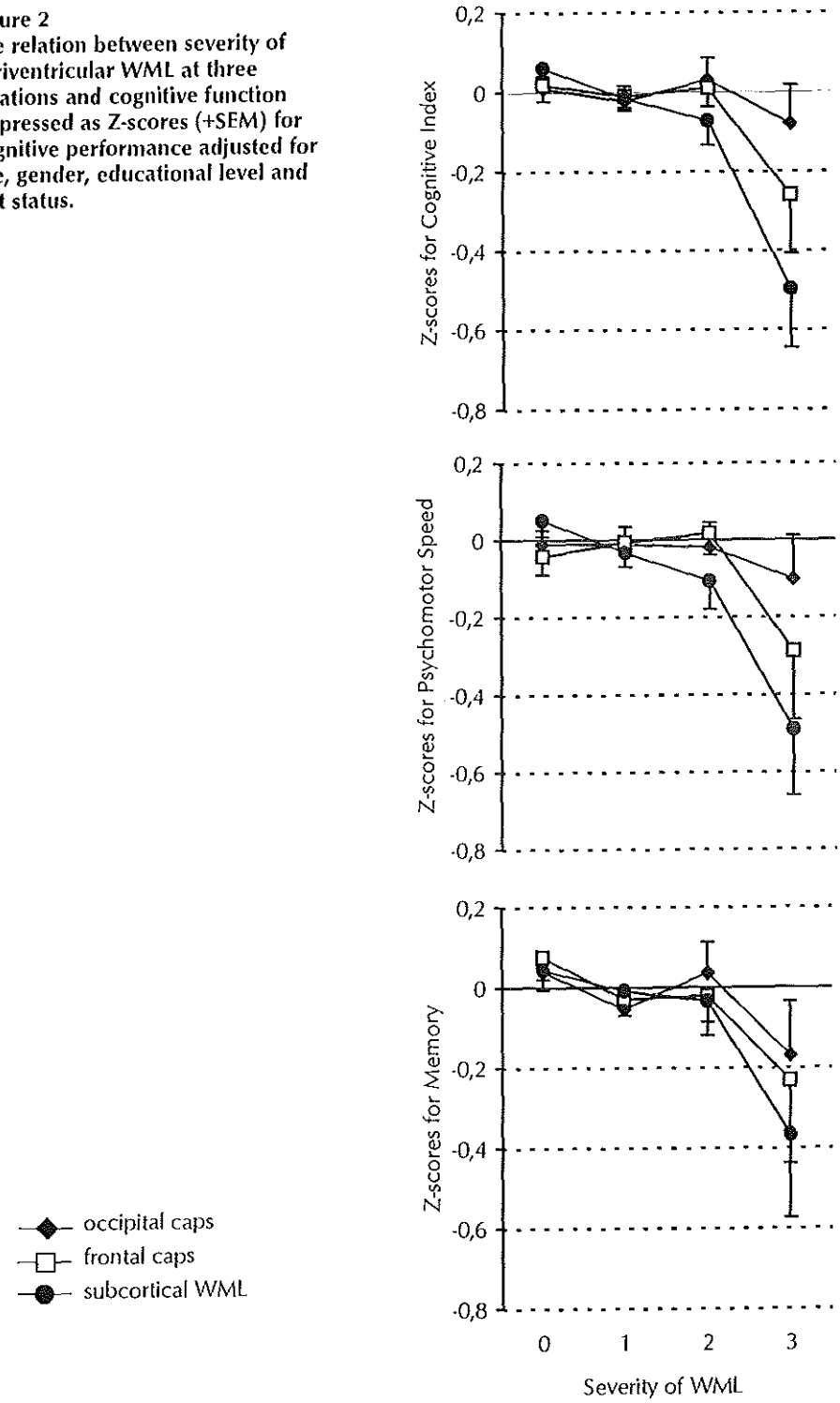


Figure 2
The relation between severity of periventricular WML at three locations and cognitive function (expressed as Z-scores (+SEM) for cognitive performance adjusted for age, gender, educational level and test status.



periventricular WML severity, no relation was found between subcortical WML and any of the three cognitive compound scores.

We also studied WML severity in relation to the MMSE score, as another test for global cognitive function. Only periventricular WML in the occipital region showed significant associations with the MMSE score ($p_{trend} = 0.015$) conditional on other locations of WML. This relationship did not change after additional adjustment for score on the CES-D, degree of cerebral atrophy and number of strokes.

Discussion

This population-based study in a large sample of elderly subjects is the first to find that separate regions of WML relate to different cognitive domains. We observed, on the basis of multiple neuropsychological tests, that mainly periventricular WML, rather than subcortical WML, were associated with cognitive impairment.

It could be argued that, although the response rate in this study was reasonable, response bias might have affected our results. Participants from this study were younger and had lower blood pressures than non-participants. As old age and high blood pressure are established risk factors for the presence and severity of WML, the group with the most severe WML is probably underrepresented in our study. Baseline MMSE scores (1990-1993) could only be compared between participants to non-participants of the Rotterdam Study, but it is likely that the comparisons would be the same if we had been able to include the Zoetermeer Study. Participants had higher baseline MMSE scores than non-participants. Most likely the selection can only have impeded the detection of the association between WML and cognitive function. Our findings thus would constitute a conservative estimation of the relation between WML severity and cognitive function.

Why periventricular and subcortical WML have a different relation with cognitive function is as yet not clear. Subcortical WML probably disrupt mainly short cortico-cortical connections consisting of arcuate U-fibers which have a high density in the areas just underlying the gray matter, whereas the periventricular WML affect areas with a high density of long associating tracts that connect more distant cortical areas with each other.[10,31] The performance on the multiple neuropsychological tests that we used depends on the connections between many cortical areas, not necessarily adjacent, and thus depends upon the long associating tracts. This might explain why cognitive function is especially impaired in individuals with periventricular WML.

The cognitive function most affected by WML was psychomotor speed, in agreement with previous studies.[4,5,32] Our findings are in line with the notion that mainly the speed of cognitive processes is diminished in subcortical dementia.[7,33] Schmidt et al suggested that only complex mental processes were affected by WML, leaving simple tasks unaltered.[6] In contrast, we found that the affected speed components also involved simple timed psychomotor tasks.

There have been only three studies in volunteers on the neuropsychological correlates of WML with separate analyses for subcortical and periventricular WML.[5,15,16] Only one of these studies was population-based.[5] The studies by Ylikoski et al[15] and Fukui et al[16] showed speed of cognitive function to be related with periventricular WML, but not with subcortical WML. Baum et al[15] have reported the contrary. The relation between cognition and subcortical WML has never been reported conditional on the presence or severity of periventricular WML and vice versa. In order to have an idea about the relation of a distinct brain characteristic with cognitive function, it is important to control for other features. Our study suggests that subcortical WML have only a marginal independent relation with cognitive function as opposed to periventricular WML.

In conclusion, this study suggests that WML are related to impairment of cognitive functions, in particular those that involve a speed component. By means of the compound scores for cognition we were able to relate more robust measures of cognition to WML than with separate tests. The reported relations remained stable when relations were studied with periventricular WML conditional on subcortical WML, even when we adjusted for other brain abnormalities (atrophy and stroke) and for other characteristics that could influence cognitive outcome measures such as educational level and the presence of depressive symptoms. Although our findings are biologically plausible and very robust, they need further confirmation in prospective studies.

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— Chapter 5 —

CEREBRAL WHITE MATTER LESIONS AND DEPRESSION

Abstract

Background: There is evidence for a vascular etiology in late-life depression. Cerebral white matter lesions are thought to represent vascular pathology. In psychiatric patients white matter lesions have been related to affective disorders and to a history of late onset depression. The relation between white matter lesions and mood disturbances in the general population is not known. We determined whether depressive symptoms are more frequent in people with cerebral white matter lesions and whether a history of depression and age of onset of depression are related to the presence and severity of white matter lesions.

Methods: In a population based study of 1,084 persons between 60 and 90 years we scored the presence and severity of subcortical and periventricular white matter lesions using magnetic resonance imaging. The presence of depressive symptoms was assessed using the Center for Epidemiological Studies Depression Scale. A standardized questionnaire was used to obtain data on history of depression. We examined the relation between white matter lesions and depressive symptoms and history of depression using multiple logistic regression analysis.

Results: Persons with severe white matter lesions (upper quintile) had 3 to 6 times as often depressive symptoms as compared to persons with only mild or no white matter lesions (lowest quintile) (subcortical OR=5.8; 95%CI 2.1 to 16.3 and periventricular OR=2.9; 95%CI 1.7 to 7.6). In addition, individuals with severe subcortical, but not periventricular, white matter lesions (upper quintile) compared to persons with only mild or no white matter lesions (lowest quintile) had 4 times more often a history of late onset depression (OR=3.9; 95%CI 0.9 to 16.1).

Conclusions: The severity of subcortical white matter lesions is related to the presence of depressive symptoms as well as to a history of late onset depression.

For the majority of persons with a depression syndrome the age of onset is in the late twenties, but it is also common to have an onset after age forty.[1,2] Between 1% and 2% of elderly persons suffer from a major depression.[3] When a first depressive episode occurs in late life, a different etiology is suggested as compared to a younger age of onset.[4] It has been suggested that a cerebro-vascular component is probably more important in the etiology of late-life depression than genetic or psychological factors.[5-8] Interest in cerebrovascular disease as a risk factor for depression has grown in the past five years, and associations between factors as hypertension and transient ischaemic attacks with depression have been reported.[9] Cerebral white matter lesions (WML) are thought to result from cerebrovascular brain damage.[10] Studies on the relation between WML and depression have been performed only within psychiatric patients or contrasting psychiatric patients to volunteers. Within the clinical setting, severity of WML has been related to the presence of depression[11-13] and with poor outcome of depression.[14] Furthermore, when studying persons with a late-life depression, an increased severity of WML has been associated with a later age of onset.[5,11,15] Although these clinical studies provide clues to the relation between WML and depression they have limitations because of the highly selected study population. No large-scale epidemiological studies have been published concerning the role of WML as determinants of late-life depressive symptoms in the community.

The aim of the present study was to investigate whether cerebral white matter lesions are associated with the presence of depressive symptoms in elderly persons. Furthermore we studied whether a history of depression is associated to severity of WML and whether this is the same for depressive episodes that started early in life and those that started in late-life. The study was conducted among 1084 Dutch persons aged 60-90 years.

Subjects and methods

Subjects

The Rotterdam Scan Study was designed to study determinants and cognitive correlates of age related brain changes in the elderly. In 1995-1996, 1904 persons aged between 60 and 90 years were randomly invited by strata of age and gender, from participants of two large ongoing cohort studies; the Rotterdam Study and the Zoetermeer Study. The Rotterdam Study is a population based prospective cohort

study among 7983 elderly persons aged 55 years and over, which is designed to study determinants of neurologic, cardiovascular, endocrinal and ophthalmologic diseases in the elderly. The Zoetermeer study is a population based prospective cohort study that was originally concerned with prevalence of various chronic diseases. Both studies have been described in detail elsewhere.[16,17]

Of the 1,904 invited subjects 180 persons had contra-indications for the study (dementia, contra-indications for MRI scanning, blindness), and therefore 1,724 were eligible. Complete data were obtained from 1,084 participants (response rate 63%). The protocol was approved by the medical ethics committee of the Erasmus University Rotterdam, the Netherlands, and all participants gave written informed consent. Among the invited subjects, participants in the study were younger (mean age difference 3.8 years, $p < 0.001$) and more educated (5% more subjects with university level education, $p = 0.05$) when compared to non-participants. Baseline blood pressures measurements for subjects originating from the Zoetermeer Study, were lower in participants compared to non-participants (age and gender adjusted difference in diastolic blood pressure 0.8 mm Hg, $p = 0.25$, systolic blood pressure 2.4 mm Hg, $p = 0.03$), whereas this was not significant for subjects originating from the Rotterdam Study. Baseline Mini Mental State Examination scores were available for subjects originally invited from the Rotterdam Study and were higher in participants compared with non-participants (age and gender adjusted mean difference 0.4 points, $p < 0.001$).

Magnetic resonance imaging

MRI scanning was performed on 1.5-Tesla scanners (Gyroscan, Philips NT, or Magnetom Vision, Siemens AG). The scanning protocol included a series of axial proton-density (PD) {TR 2200, TE 20, NEX 1, matrix 192x256, flip angle 75°}, T2-weighted {TR 2200, TE 80, NEX 1, matrix 192x256, flip angle 80°} and T1-weighted {TR 700, TE 17, NEX 1, matrix 192x256, flip angle 90°} images. To cover the whole brain, sections were 5 or 6 mm thick (scanner dependent) with an interslice gap of 20%. After optimization of the images on the scanner screen data were archived on magnetic optical disk and laser hardcopies were printed (using a reduction factor of 2.7).

White matter lesions rating scale

Presence, severity and location of different brain parameters were scored according to a protocol designed for the Rotterdam Scan Study. WML were considered present if visible as hyperintense on both PD and T2 weighted images and not

hypointense on T1 weighted images. Periventricular WML were scored semi-quantitatively as 0 (none), 1 (pencilthin lining), 2 (smooth halo), or 3 (large confluent) for three separate regions (adjacent to frontal horns, adjacent to the wall of the lateral ventricles, adjacent to the occipital horns). The total periventricular WML score was calculated by adding the region-specific scores (range 0-9). Subcortical WML were categorized based on their maximum diameter (as appearing on the hardcopy) as small (1-3 mm), medium (3-10 mm) or large (>10 mm) and counted for the frontal, parietal, occipital and temporal lobes. Separation of lobes was according to anatomical landmarks. We approximated a total subcortical WML-volume by considering the subcortical WML to be spheres with diameters of respectively 2 mm, 6 mm or 12 mm (for the different size categories) and adding these volumes. Other brain features that were recorded from the MRI images were cerebral atrophy (cortical and subcortical) and the presence and number of strokes. Cortical atrophy was rated visually on a four-point severity scale. Subcortical atrophy was measured by the ventricle-to-brain ratio (mean of the bi-ventricular width assessed at the frontal horns, body of the caudate nucleus, and at occipital horns of the lateral ventricles divided by the corresponding brain width).

All scans were examined by two independent readers from a pool of four experienced physicians. In case of disagreement of more than 1 point for periventricular WML or cortical atrophy scores a consensus reading was held, in other instances the mean of two scores were averaged. Intra- and inter-reader studies showed a good to excellent agreement. Weighted kappas for periventricular WML severity grades were between 0.79-0.90. Interreader and intrareader-intraclass correlation coefficients for subcortical WML-volume were 0.88 and 0.95, respectively.

Of all persons only 5.0% had no WML at both periventricular and subcortical locations, 217 (20%) were without any sign of periventricular WML, while 81 (7.5%) were without any subcortical WML.

Depressive symptoms and history of depression

During a two-hour visit at the local research facility all participants underwent an extensive evaluation. A semi-structured interview by a trained physician (JCdG, FEdL) included questionnaires about physical and mental health and a recording of all concurrently used medication. For the presence of actual depressive symptoms the Center of Epidemiologic Studies Depression Scale (CES-D) was used as a self-report questionnaire.[18] Depressive symptoms were defined as present when the subject scored at or above 16 points on the CES-D.[18] Persons who used

antidepressive medication were defined as having depressive symptoms irrespective of their actual CES-D score, because we considered that depressive symptoms probably had been the indication for the medication prescription.[19]

All participants were asked for their history of depressive episodes. To obtain more specificity, we carefully excluded normal reactions to stressful events or normal grief. If depressive episodes had occurred, the persons were asked for the age of onset and whether the episodes had prompted to ask medical advice. We defined depression as those depressive episodes that had required attention of a general practitioner, psychologist, or psychiatrist. This definition includes minor depression as defined by the Research Diagnostic Criteria,[20,21] and also includes more severe depression syndromes as major depression or bipolar depression. We used the age of 60 years as cut-off point to define late onset and early onset depression.[4,15]

The CES-D questionnaire was completed by 1074 persons of whom 79 persons scored at or above the cut-off point of 16. Antidepressive medication was used by 20 persons of whom 12 scored below the cut-off point of the CES-D. Therefore, 91 persons fulfilled our definition for the presence of depressive symptoms. Eight hundred and twenty two persons reported never having had depressive episodes. Of the 262 persons who reported previous depressive episodes 193 met our criteria for depression, and of these 185 remembered the age of onset. Onset before the age of 60 years was reported by 132 persons versus a late onset in 53. As expected, at the time of the interview, persons who reported a late onset were older (mean 75.5, range 61.6-89.7) than persons who reported an early onset (mean 68.5, range 59.0-87.1).

Other measurements

The following variables were considered as possible confounding variables: age, gender, level of education (United Nations Educational, Scientific and Cultural Organization, UNESCO), [22] and cognitive function as measured by the Mini Mental State Examination (MMSE).[23] Additional neuroimaging findings considered as potential confounders in the relation between WML and depression were presence of any stroke,[24] and cerebral atrophy.[25]

Statistical analysis

All analyses were adjusted for age and gender. Demographic characteristics and depression variables were compared between persons without (n=54) and with (n=1030) any WML at subcortical or periventricular location using analysis of

covariance (ANCOVA). Because 95% of subjects had at least some WML we subsequently studied the relation between severity of WML and depression variables. To allow for a non-linear relation between WML severity and CES-D score or presence of depressive symptoms we analyzed these relations in quintiles of the WML-severity distribution using analyses of covariance (ANCOVA). In addition, logistic regression analysis was used to calculate odds ratios (OR) for the association between severity of WML (in quintiles) and the presence of depressive symptoms using the lowest quintile of WML severity as the reference category.

The relation between severity of WML and age of onset of a reported history of depression (in years) was analyzed using multiple linear regression, additionally adjusting for age-square. We used logistic regression to calculate odds ratios (OR)

Table 1
Characteristics of participants without any white matter lesions and of participants with periventricular and/or subcortical white matter lesions.

Characteristics	White matter lesions		$p^{\#}$
	Absent (n=54)	Present (n=1030)	
Mean age in years (SD)	66.8 (4.9)	72.5 (7.4)	<0.001
Gender (men/women)	22/32	502/528	0.15
No of subjects with primary education only (%)	13 (24.1%)	352 (34.2%)	0.41
Median score on the Mini Mental State Examination (range)	29 (24-30)	28 (13-30)	0.51
No of subjects with stroke on MRI (%)	4 (7.4%)	134 (13.0%)	0.73
Median grade of cortical atrophy (range 0.0-3.0)	0.8	1.0	0.20
Mean ventricle-to-brain ratio (SD) (range 0.21-0.45)	0.30 (0.03)	0.32 (0.04)	0.08
Depression variables:			
No of subjects with depressive symptoms (%) [a]	1 (1.9%)	90 (8.9%)	0.06
No of subjects using anti-depressive medication (%)	1 (1.9%)	19 (1.8%)	0.84
No of subjects with a history of minor depression (%)[b]	13 (24.1%)	179 (17.4%)	0.71
No of subjects with early-onset (%)[c]	13 (24.1%)	119 (11.6%)	0.21
No of subjects with late-onset (%)[d]	0 (0.0%)	53 (5.1%)	0.19

[#] Analyses of covariance adjusted for age, gender and educational level, where appropriate.
[a] Defined as CES-D scores ≥16 or the use of anti-depressive medication
[b] Defined as depressive feelings which prompted medical attention
[c] Early onset defined as depressive feelings starting <60 years which prompted medical attention
[d] Late onset defined as depressive feelings starting ≥60 years which prompted medical attention

for the association between severity of WML (in quintiles) and history of depression (with the people that never reported depressive episodes as the control-group and the lowest quintile of WML severity as the reference group). For all above analyses additional adjustments were made for score on the MMSE, severity of cerebral atrophy and the presence of any stroke.

As periventricular WML and subcortical WML severity correlated considerably (Spearman's ρ =0.7, $p< 0.01$), we additionally analyzed the relations between depression variables and the severity of periventricular WML conditional on the severity of subcortical WML and vice versa by entering both variables simultaneously in the multivariate model.

Results

Depressive symptoms and white matter lesions

Characteristics of the 1084 participants of the Rotterdam Scan Study are given in Table 1. In the group without any white matter lesions (n=54) there were no subjects with a score higher than 16 on the CES-D while in the group with WML this level was reached in 7%. There was a significant difference (p= 0.01; analysis adjusted for age, gender and educational level) in mean score on the CES-D between the group without any WML (CES-D score=3.9 (SE 0.8)) compared to those with any WML (CES-D score=6.0 (SE 0.2)). This difference remained when the analysis was additionally adjusted for score on the MMSE, cerebral atrophy or presence of stroke. Mean CES-D scores per quintile of WML severity revealed a trend (periventricular WML p_{trend}= 0.02; subcortical WML p_{trend} = 0.21) for higher scores in more severe WML, when adjusted for possible confounding by age, gender, educational level, score on the MMSE, cerebral atrophy and presence of stroke. The mean CES-D scores of the upper four quintiles were higher than in the lowest quintile (difference in CES-D score = 1.6 ($p< 0.001$) for periventricular WML and 1.3 (p= 0.007) for subcortical WML). Depressive symptoms were more often present in higher WML quintiles (Figure 1). In the lowest quintile of WML only 2 to 3% of all persons met the criteria for depressive symptoms, while in the other quintiles this varied between 6 and 13%. Table 2 shows odds ratios per quintile of WML severity for the presence of depressive symptoms when additionally adjusted for score on the MMSE, cerebral atrophy and the presence of stroke. Persons in the higher quintiles of the WML severity distribution had odds for the presence of depressive symptoms that were up to 6 times those in the

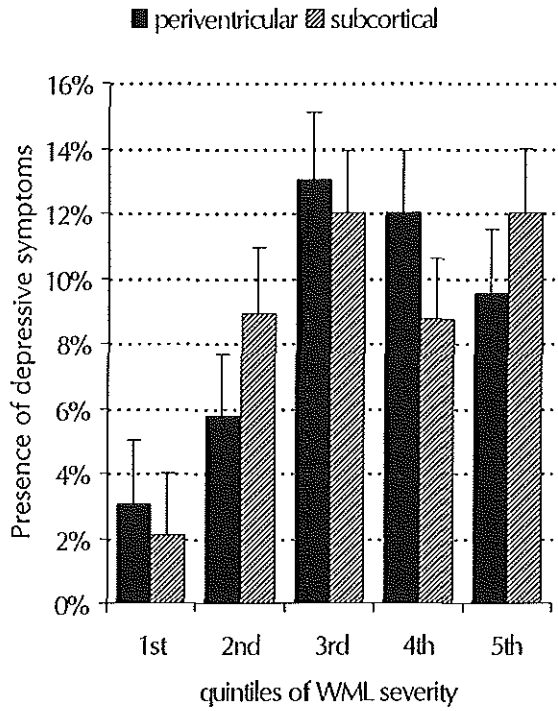


Figure 1
Presence of depressive symptoms* per WML severity quintile (adjusted for age, gender and educational level (+SE)).

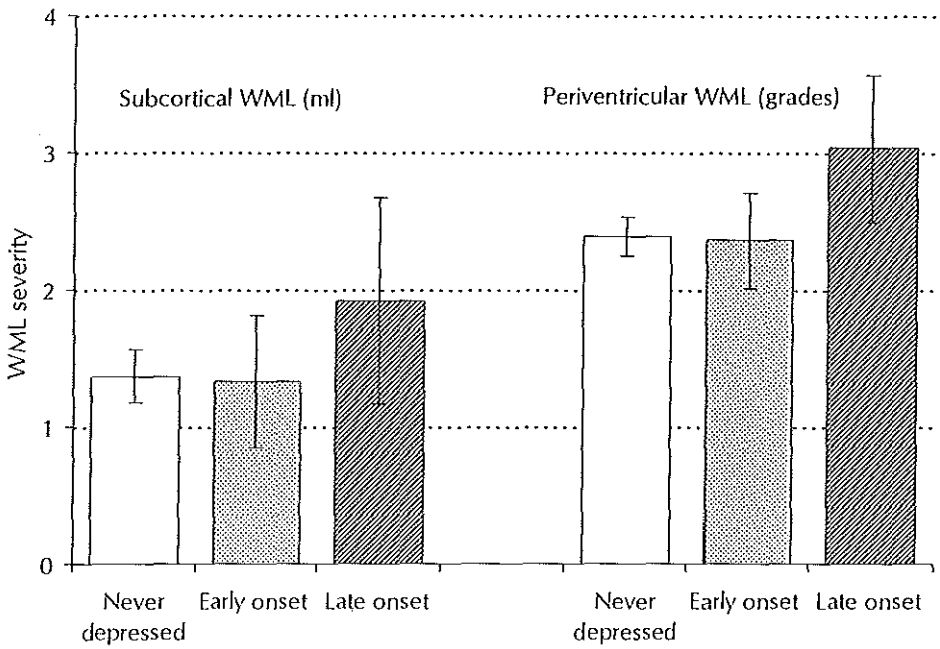
*Defined as CES-D score ≥16 or the use of anti-depressive medication.

Table 2
The relation between severity of white matter lesions (WML) and the presence of depressive symptoms (CESD ≥ 16 or the use of anti-depressive medication) expressed as odds ratios.

Severity of WML in quintiles	Model 1 [a]		Model 2 [b]	
	OR	(95% CI)	OR	(95% CI)
Subcortical WML (range in ml)				
1st (0.00-0.02)	1.0	Ref.	1.0	Ref.
2nd (0.03-0.10)	4.5	(1.6;12.5)	3.8	(1.3;10.8)
3rd (0.11-0.38)	5.9	(2.2;16.0)	4.3	(1.5;12.1)
4th (0.39-1.87)	4.2	(1.5;11.7)	2.9	(1.0;8.9)
5th (1.88-29.52)	5.8	(2.1;16.3)	4.7	(1.5;15.0)
Periventricular WML (range in scores)				
1st (0.0-0.0)	1.0	Ref.	1.0	Ref.
2nd (0.5-1.0)	1.9	(0.7;4.9)	1.5	(0.6;3.9)
3rd (1.5-2.0)	4.7	(1.9;11.3)	3.2	(1.2;8.1)
4th (2.5-4.0)	4.0	(1.6;9.8)	2.5	(0.9;6.8)
5th (4.5-9.0)	2.9	(1.1;7.6)	1.6	(0.5;4.8)

[a] Adjusted for age, gender, level of education, presence of stroke, cerebral atrophy, and score on the Mini Mental State Examination.
[b] As model 1, but the relation between periventricular WML and the presence of depressive symptoms conditional on the severity of subcortical WML, and vice versa.

Figure 2
Severity of white matter lesions in subjects without depressive episodes and in subjects with early-onset and late-onset depression (means adjusted for age, age², gender and educational level (+95% CI)).



reference category. Although the strength of the associations slightly diminished when subcortical WML were studied conditional on severity of periventricular WML and vice versa, the pattern of more depressive symptoms among persons with more severe WML did not change.

History of depressive episodes and white matter lesions

Among people who reported a previous depression, an increase in WML severity was associated with a later age of onset (per grade periventricular WML severity, age of onset was 1.3 years later (p=0.14) and per volume unit subcortical WML age of onset was 1.1 years later (p=0.01)). When we dichotomized age of onset of depression in early and late onset, we found that persons who had had a late onset of depression have more severe periventricular and subcortical WML than persons who had had an early onset of depression. People who had had an early onset depression did not differ in WML severity from those people who never had depressive episodes (Figure 2).

When the association between severity of WML (in quintiles) and history of depression was expressed in odds ratios (Table 3), no increased odds ratios were found for reporting a previous depression in higher quintiles of the WML severity distribution. However, when we analyzed this relation in strata of age of onset of depression, severity of WML was associated with a history of late onset (p_{trend} = 0.03 for subcortical WML, p_{trend} = 0.13 for periventricular WML) but not for an early onset of depression (p_{trend} > 0.9 for both subcortical and periventricular WML). Additional adjustments for the presence of stroke, cerebral atrophy and score on the MMSE did not change these results. When the association between subcortical WML severity and late onset of depression was studied conditional on periventricular WML severity and vice versa, the association with subcortical WML severity became stronger and remained marginally significant (p_{trend} = 0.09 for subcortical WML), whereas this disappeared for periventricular WML (p_{trend} = 0.79 for periventricular WML).

Table 3
Severity of white matter lesions and the relation with a reported history of depression and with its age of onset (odds ratios and 95% CI; adjusted for age, gender and educational level).

	History of depression [a]			
Severity of WML in quintiles	Yes [b] (n=193)	Early onset (n=132)	Late onset (n=53)	Late onset [c] (n=53)
Subcortical WML				
1st	1.0 Ref.	1.0 Ref.	1.0 Ref.	1.0 Ref.
2nd	1.3 (0.8;2.2)	1.4 (0.8;2.5)	2.0 (0.5;7.2)	2.1 (0.6;8.0)
3rd	1.2 (0.7;1.9)	1.1 (0.6;1.9)	3.4 (1.1;10.8)	3.6 (1.1;12.6)
4th	1.1 (0.6;1.9)	1.0 (0.5;1.8)	2.9 (0.9;9.3)	3.3 (0.8;12.7)
5th	1.3 (0.8;2.3)	1.1 (0.6;2.2)	3.6 (1.1;11.3)	3.9 (0.9;16.1)
Periventricular WML				
1st	1.0 Ref.	1.0 Ref.	1.0 Ref.	1.0 Ref.
2nd	0.7 (0.4;1.2)	0.8 (0.4;1.3)	0.5 (0.1;1.7)	0.4 (0.1;1.4)
3rd	1.1 (0.7;1.9)	1.0 (0.6;1.8)	1.7 (0.6;4.5)	1.0 (0.3;3.1)
4th	1.2 (0.7;2.0)	1.2 (0.7;2.1)	1.5 (0.5;3.9)	0.7 (0.2;2.4)
5th	1.0 (0.5;1.7)	0.7 (0.4;1.5)	1.5 (0.6;4.2)	0.6 (0.2;2.4)

[a] The group without a history of depressive episodes (n=822) was used as the control group.
[b] Of the 193 people who reported a history of depression, 8 did not remember the age of onset.
[c] Additionally adjusted for presence of stroke, cerebral atrophy, MMSE-score and conditional on the severity of either periventricular or subcortical WML, as applicable.

Discussion

This study relates structural brain alterations of the white matter to indicators of current and former depression. This study is unique in that it is population-based and includes a large sample of elderly persons to assess the relation between WML and depression. We report a significant association between severity of WML and the presence of depressive symptoms and history of late onset depression.

There are some methodological issues that need to be discussed. A first point that needs attention is the possibility of selection-bias in our sample. Participants of our study were younger and had lower blood pressures than non-participants. As old age and high bloodpressure are established risk factors for the presence and severity of WML, people with the most severe WML were probably underrepresented in our study. Likewise, persons with current mood disturbance may have been underrepresented.[26] In our sample, the mean score on the CES-D and the percentage of persons who scored at or above the cut-off was lower than that found by others.[27,28] Although we cannot exclude that the relation between WML and depression was different among non-participants, we consider this unlikely. The probable under representation of both people with the most severely affected brains and depressed individuals may have resulted in underestimating the strength of the association between WML and depressive symptoms.

A second issue to consider is our case finding. We used the cut-off of 16 points on the CES-D[29] to define the presence of depressive symptoms. A previous study in an elderly Dutch population that used the same cut-off point, reported a sensitivity of 100%, and a specificity of 88% for major depression and a positive predictive value of 13.2% for diagnosis of DSM-III affective disorder.[28] DSM diagnosed affective disorders are frequent in the elderly, although they comprise only the top of the iceberg of all people with depressed mood.[7] For the definition of a history of depression we used answers on a standardized questionnaire. We ascertained the severity of the reported depressive episodes by carefully attempting to rule out normal reactions to stressful events and by adding the item of having consulted a physician to the definition. The used definition includes the criteria of a minor depression as defined by the Research Diagnostic Criteria,[21] and may include more severe depression. Because the questionnaire is retrospective it is possible that recall bias has occurred. It may be that subjects with the most severe WML more easily forget depressive episodes because of coexisting cognitive problems. This bias however would lead to underreporting of depressive episodes especially in people with the more severe WML and as such an underestimation of the relation between

WML and depressive episodes. Another problem with retrospective questionnaires is that people are more likely to remember the more severe depressive episodes. This would only aid in differentiating between clinically relevant depressive episodes and adequate reactions to grief or anxiety.

We found presence as well as severity of WML related to the presence of depressive symptoms. This relation was found for subcortical as well as for periventricular WML, although the odds ratios for subcortical WML were higher and more robust. In this general population WML were related with a history of late onset, but not with early onset of depression, as has been reported from patient series.[30] When we made the distinction between subcortical and periventricular WML we found only subcortical WML related to history of late onset depression, which is also in line with reports from patient series.[4,15,25,31,32]

How should we interpret our results? It is possible that the depressive symptoms are a psychological reaction to declining cognitive function because of WML. However, we found the relation to be independent of cognitive status as the relation between WML and depressive symptoms remained when we controlled for the score on the MMSE. Another possible explanation could be that other cerebral characteristics, correlated to the presence of WML, are responsible for the observed association between WML and depression. Ventricular enlargement, presence of stroke and cortical atrophy has all been related to mood disturbances.[25] However, the found relation between WML severity and depressive symptoms did not change when we controlled for these possible confounders. We found especially subcortical WML related with indicators of depression. Subcortical pathways, in particular intact corticostriatal connections, are important for the expression of normal mood and motivation,[33,34] making it biologically plausible that subcortical WML that interrupt these connections can cause mood alterations. An alternative hypothesis for the association between WML and depression would be that it is not the cerebrovascular pathology that leads to the depression, but rather that those subjects who are prone to depression have an increased risk of vascular disease.[35] If this would be the case, we would have expected a more prominent association with early onset minor-depression than with late onset, making this explanation less likely.[11]

In summary, this population-based study of a random sample of elderly demonstrated an increasing risk for depressive symptomatology with increasing severity of WML. In addition we found a relation between a history of late onset depression and severity of mainly subcortical WML. These findings can have implications for clinical practice. Presence of depressive symptoms in an elderly individual should prompt physical examination and possibly ECG-monitoring and neuroimaging in search for cerebrovascular risk factors as possible causes for these

symptoms. Another implication regards the possible prevention of late-life major depression. Since WML are thought to have a mainly cerebrovascular etiology[36,37] recognizing this high risk group may provide an opportunity to prevent depressive symptoms from evolving into a major depressive disorder.[1,27,38]

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— Chapter 6 —

PERIVENTRICULAR CEREBRAL WHITE MATTER LESIONS PREDICT THE RATE OF COGNITIVE DECLINE

Abstract

Background: The prospect of declining cognitive functions is a major fear for many elderly. It is important to identify risk factors that influence the rate of cognitive decline. Cerebral white matter lesions have been associated with cognitive dysfunction in cross sectional studies, but longitudinal studies are scarce. We examined whether the rate of decline in cognitive performance as measured by the Mini Mental State Examination over a period up to eight years, was related to the severity of cerebral white matter lesions at two distinct locations as assessed by magnetic resonance imaging.

Methods: From 1990 to 1998, repeated Mini Mental State Examination scores were obtained for a sample of 568 elderly, aged 55 to 85 at baseline, from a population based longitudinal study. For each individual a decline in cognitive performance per year was calculated. In 1995-96 cerebral magnetic resonance imaging was done and the severity of white matter lesions was rated for periventricular and subcortical regions separately.

Findings: More severe white matter lesions were associated with a greater decline in Mini Mental State Examination scores over a mean of follow up period of 5.5 years (SD 1.5). For subjects with the most severe periventricular white matter lesions, the rate of cognitive decline was 2.5 times faster than average (95% confidence interval 1.4 to 3.3). There was no relation between severity of subcortical white matter lesions and rate of cognitive decline.

Interpretation: The severity of periventricular, but not subcortical, white matter lesions is associated with an increased rate of cognitive decline.

Lesions in the cerebral white matter have been associated with cognitive impairment in demented and non-demented elderly subjects.[1-3] Most studies to date were cross-sectional. The few longitudinal studies that have been performed either had small sample sizes or did not distinguish different regions of white matter lesions (WML) and were inconclusive.[4-8]

The white matter of the brain can be distinguished into the area just under the cortex (subcortical) and the area adjoining the ventricles (periventricular). White matter lesions in these two regions may affect cognition in different ways.[3] In most of the research performed to date, WML have been rated and combined in a single score,[1,9,10] or only one of the two regions has been taken into account.[11-14] The few studies that analyzed periventricular and subcortical WML separately in relation to cognition were cross-sectional and did not allow firm conclusions.[15-18]

The aim of the present study was to investigate whether severity of white matter lesions is associated with the rate of cognitive decline and whether this is different for periventricular and subcortical WML. We based our study on a random sample of 568 non-demented Dutch elderly aged 60-90 years who have been followed for a period of up to eight years.

Methods

Study Population

The Rotterdam Scan Study was designed to study determinants and cognitive correlates of age-related brain changes in the elderly. In 1995-1996, a random sample of elderly persons aged between 60 and 90 years was invited by strata of age and gender, from participants of two large ongoing cohort studies; the Rotterdam Study and the Zoetermeer Study. Only for the Rotterdam Study data on cognitive measures were obtained on multiple occasions; therefore the present study is based on the subjects invited from the Rotterdam Study. The Rotterdam Study is a prospective population-based study among 7,983 elderly subjects aged 55 years and over, designed to study determinants of selected chronic diseases in the elderly.[19] The Rotterdam Study had its baseline assessment in 1990-93 and has regular follow up examinations; the first in 1993-94 and the second started in 1997.

For the Rotterdam Scan Study, in 1995-1996, 965 subjects were selected from the cohort of the Rotterdam Study. Since 125 of them had contra indications against

participation (overt dementia, contra indications for MRI scanning, blindness), 837 were eligible. MRI images were obtained in 568 participants (68%).

The study was approved by the Medical Ethics Committee of the Erasmus University and written consent was obtained from each participant. Among the 965 invited subjects, the 568 participants, compared to non-participants of the Rotterdam Scan Study were younger (mean age difference 4.9 years, $p < 0.001$), more educated (2.4% more subjects with university level education, $p = 0.05$), had lower blood pressures at baseline examination (age and gender adjusted difference in systolic blood pressure 2.5 mm Hg, $p < 0.05$) and higher baseline Mini Mental State Examination scores (age and gender adjusted mean difference 0.5 points, $p < 0.001$).

MRI scanning protocol

MRI scanning was performed in 1995-1996 on a 1.5-Tesla scanner (Magnetom Vision, Siemens AG). The scanning protocol included a series of axial proton-density (TR 2200ms, TE 20ms), T2-weighted (TR 2200ms, TE 80ms) and T1-weighted (TR 700ms, TE 14ms) images. Sections were 5 mm thick with an interslice gap of 20%. Laser hardcopies were printed with a reduction factor of 2.7.

White matter lesions rating scale

Presence, severity and location of morphological brain characteristics were rated according to a protocol designed for the Rotterdam Scan Study. WML were considered present if lesions were hyperintense on both proton density and T2 weighted images, and not hypointense on T1 weighted images. When the largest diameter of the WML was adjacent to the ventricle it was defined as periventricular, otherwise as subcortical. Periventricular WML were rated semi-quantitatively as 0 (none), 1 (pencil-thin lining), 2 (smooth halo), or 3 (large confluent) for three separate regions; adjacent to the frontal horns (frontal caps), adjacent to the wall of the lateral ventricles (bands) and adjacent to the occipital horns (occipital caps). The total periventricular WML score was calculated by adding the region specific scores (range 0-9). Subcortical WML were categorized according to their maximum diameter (as appearing on the hardcopy) as small (1-3 mm), medium (3-10 mm) or large (>10 mm). The number of subcortical WML was rated per size-category for the frontal, parietal, occipital and temporal lobes. Distinction between lobes was according to anatomical landmarks. We approximated a total subcortical WML volume (in ml on hardcopy) by assuming that subcortical WML were spherical with diameters of 2 mm, 6 mm or 12 mm (according to their size category) and by adding these vol-

umes. Other features recorded from the MRI images were brain atrophy (cortical and subcortical) and the presence and number of infarcts. Cortical atrophy was rated on a four-point severity scale. Subcortical atrophy was measured by means of the ventricle-to-brain ratio (mean of the biventricular width at the level of the frontal and occipital horns, and at the level of the body of the caudate nuclei, divided by the corresponding brain width at those levels).

Two independent readers from a pool of four experienced physicians examined all scans. In case of disagreement of more than one point for severity of periventricular WML or cortical atrophy a consensus reading was held, in other instances scores were averaged. Intra- and inter-rater studies showed good to excellent agreement. Weighted kappas for periventricular WML severity grades were between 0.79 and 0.90. Interreader and intrareader-intraclass correlation coefficients for total subcortical WML volume were 0.88 and 0.95, respectively. Of all 568 subjects only 5% had no WML at all, whereas 16% were free of periventricular WML and 8% had no signs of subcortical WML. 87% of all subjects had at least some degree of both periventricular and subcortical WML. Pearson's correlation coefficient between periventricular and subcortical WML was 0.6.

Measurement of cognitive decline

In the regular surveys of the Rotterdam Study the Mini Mental State Examination (MMSE)[20] is administered to all participants as part of the screening for dementia.[21] Although this test was originally developed as a screening instrument for dementia, it has proven to be a reliable measure of global cognitive function, at least on the population level.[22-24] We also included the MMSE in the neuropsychological tests of the Rotterdam Scan Study. Until November 1998, 26 of the 568 participants in the Rotterdam Scan Study had died, one had moved out of the study area, and 376 had already been invited for the next follow up in the Rotterdam Study. Since 42 refused, 334 participants were examined a fourth time with MMSE. Mean total follow up time was 5.5 years (SD= 1.5, range 2.5-8.1). On the basis of the three or four MMSE-assessments, and assuming a linear decline over time in the follow-up period, we calculated individual slopes of decline in MMSE score for all 568 participants.

Other measurements

The following characteristics were considered as possible confounding variables: age, gender, level of education (according to UNESCO criteria)[25] and affective status (determined with the Center of Epidemiologic Studies Depression Scale

(CES-D)).[26] These data were obtained during a two-hour visit of each participant to the local research facilities at the time of MRI assessment. Additional neuroimaging characteristics considered as confounding variables in the relation between WML and cognitive function were cortical and subcortical atrophy, and the presence and number of any infarcts.

Statistical analysis

We calculated individual slopes for decline in MMSE scores, with the use of a random effect model (PROC MIXED) from SAS Systems for Windows (release 6.12). We used all available MMSE measurements as outcome variable and time of measurement as independent variable, with time at baseline examination as t=0. As random effects we used the intercept and time of MMSE measurement. To compute the estimated slopes and intercepts of the individual MMSE scores we added the estimated fixed effect and the individual random effect.

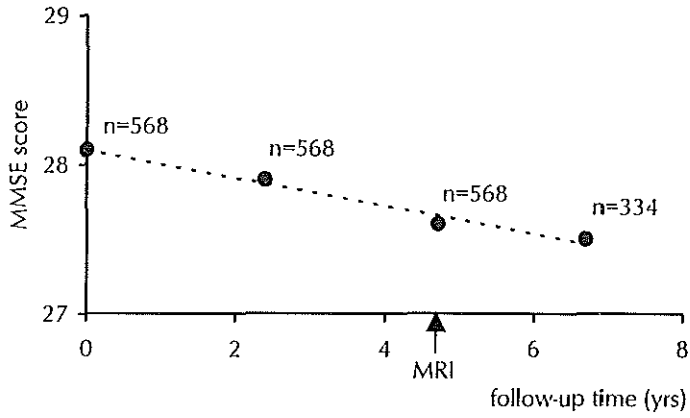
The relation between age at the time of MRI scanning and rate of cognitive decline was assessed by gender adjusted analyses of variance with age in 10 year strata. The difference in rate of cognitive decline between genders was analyzed by age adjusted analyses of variance. The relations between the severity of periventricular and subcortical WML and the rate of cognitive decline were assessed by

Table 1
General characteristics of the 568 participants at the time of neuroimaging

Characteristics	
Mean age in years (SD)	73.6 (8.0)
No of women (%)	284 (50%)
No of subjects with only primary education (%)	177 (31%)
Median score on the CES-D* (interquartile range)	4 (1-9)
No of subjects with depressive symptoms‡ (%)	32 (6%)
Median score on the Mini Mental State Examination (interquartile range)	28 (27-29)
Neuroimaging characteristics	
Median volume of subcortical WML (interquartile range)	0.38 (0.04-2.14)
Median total periventricular WML score (interquartile range)	2.5 (1-4)
No of subjects with old infarcts on MRI (%)	79 (14%)
Mean grade of cortical atrophy (SD)	1.2 (0.6)
Mean ventricle-to-brain ratio (SD)	0.31 (0.04)

* CES-D = Center for Epidemiological Studies on Depression Scale
‡ Depressive symptoms defined as present when CES-D score ≥ 16.

Figure 1
Mean MMSE scores at four measurements at mean follow up time with indication of the time of MRI



means of multivariate regression with adjustment for age (at the time of MRI scanning) and gender. Additional adjustments were made for educational level, presence of depressive symptoms, severity of brain atrophy and number of infarcts. WML were first analyzed in quintiles of severity to allow for a non-linear relationship with cognitive decline. Quintiles were chosen to allow similar severity distributions for periventricular WML, which were rated on a semi-quantitative rating scale, and subcortical WML, which were rated continuously. As a next step we analyzed the relation between finer subdivisions of WML severity and cognitive decline, by categorizing the severity of periventricular WML in the original 10 severity categories, and subcortical WML in deciles of the distribution for the ANCOVA analyses. For the test of trend, the same 5 or 10 categories of WML severity were considered a continuous variable in a multiple linear regression model, with adjustment for the same variables as in the ANCOVA.

To study the relation between cognitive function and subcortical WML conditional on the severity of periventricular WML and vice versa, periventricular and subcortical WML were entered simultaneously in the multivariate model.

Results

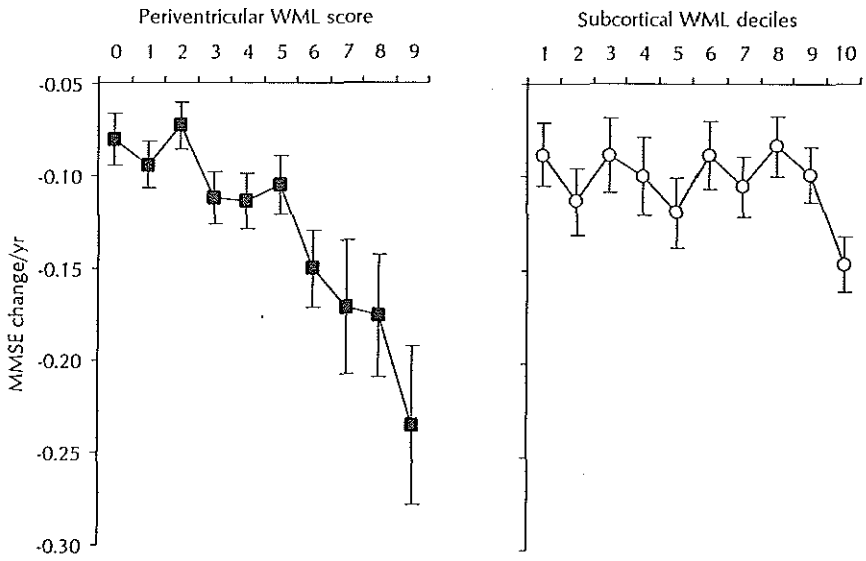
Characteristics of the study population at the time of MRI assessment are given in table 1. At baseline examination (1990-93) the mean MMSE score was 28.1 (SD= 1.6), at first follow up (1993-94) the mean was 27.9 (SD= 1.6), at the time of MRI

Table 2
The Relation Between Severity of White Matter Lesions and Rate of Decline on the Mini Mental State Examination (MMSE) Score Expressed in Score per Year (SE).

Quintiles of WML Severity	Periventricular WML			Subcortical WML		
	Mean rate of decline on the MMSE score			Mean rate of decline on the MMSE score		
	Model 1*	Model 2†	Model 3‡	Model 1*	Model 2†	Model 3‡
1st	-0.08 (0.01)	-0.09 (0.01)	-0.08 (0.02)	-0.10 (0.01)	-0.10 (0.01)	-0.12 (0.01)
2nd	-0.10 (0.02)	-0.09 (0.02)	-0.09 (0.01)	-0.10 (0.02)	-0.08 (0.02)	-0.10 (0.02)
3rd	-0.07 (0.01)	-0.08 (0.01)	-0.07 (0.01)	-0.10 (0.01)	-0.10 (0.01)	-0.10 (0.01)
4th	-0.11 (0.01)	-0.11 (0.01)	-0.11 (0.01)	-0.10 (0.01)	-0.10 (0.01)	-0.09 (0.01)
5th	-0.14 (0.01)	-0.13 (0.01)	-0.14 (0.01)	-0.12 (0.01)	-0.12 (0.01)	-0.09 (0.01)
Test for trend	$p = 0.001$	$p = 0.007$	$p = 0.02$	$p = 0.17$	$p = 0.21$	$p = 0.57$

* Model 1: Adjusted for age and gender.
† Model 2: As model 1 but with additional adjustment for level of education, presence of depressive symptoms, cerebral atrophy, and presence of old infarct(s).
‡ Model 3: As model 2, but for periventricular WML conditional on severity of subcortical WML, and vice versa.

Figure 2
The relation between severity of white matter lesions (WML) and cognitive decline expressed as (age and gender adjusted) rate of decline in MMSE score per year (SE).



scanning (1995-96) it was 27.6 (SD= 2.2) and at the last follow up in 1998 it was 27.5 (SD= 2.1). The average slope of the decline on the MMSE score was -0.10 (SD= 0.13) per year (figure 1).

The rate of cognitive decline depended on the age of the participants and was more than double in subjects over 80 years compared with subjects in the age-range 60-69. Mean gender-adjusted rate of decline in MMSE scores per year for the 10 years age categories were -0.07 (SE = 0.01), -0.09 (SE = 0.01) and -0.17 (SE = 0.01) for age ranges 60-69, 70-79 and 80 years and over, respectively (all $p< 0.05$). No gender differences in age-adjusted rates of cognitive decline were found.

When individuals were categorized in quintiles of WML severity, steeper slopes of decline in MMSE scores were found in higher quintiles of WML severity (table 2). The difference between the lowest and highest quintile of severity was statistically significant for periventricular WML ($p= 0.002$) but not for subcortical WML ($p= 0.46$). Similarly, the test for trend over quintiles of WML severity was statistically significant for periventricular WML only. The association between severity of periventricular WML and rate of decline of MMSE scores remained after adjustment for possible confounders as educational level, CES-D score, cerebral atrophy and presence of stroke on MRI ($p_{trend}= 0.007$) and when analyzed conditional on severity of subcortical WML ($p_{trend}= 0.02$).

When severity of WML was studied with finer subdivisions as shown in figure 2, more severe periventricular WML were associated with a steeper slope of decline in MMSE scores (adjusted for age and gender, $p_{trend} < 0.001$). Individuals with the most severe periventricular WML (n= 9) had a decline in MMSE score per year that was nearly 2.5 times greater than average (mean slope = -0.24; 95% CI: -0.33 to -0.14). The association with periventricular WML remained after addition adjustment for possible confounders as educational level, CES-D score, cerebral atrophy and presence of stroke on MRI ($p_{trend} < 0.001$). When the analyses were performed conditionally on severity of subcortical WML, individuals with the most severe periventricular WML had a decline in MMSE score per year that was still more than twice as steep (mean decline = -0.22; 95% CI: -0.32 to -0.12) than the average decline. Subcortical WML were not associated (figure 2) with cognitive decline. There were no significant differences in the slopes between deciles of subcortical WML (p=0.16); the test for trend over these deciles of subcortical WML was not significant (p_{trend}= 0.12). Adjustment for possible confounders did not change these associations.

Discussion

We investigated the relation between decline in cognitive function over a period of up to 8 years and the severity of cerebral white matter lesions, in a large sample of non-demented elderly people. The rate of decline over this time period as measured by the MMSE was related with the severity of periventricular but not with subcortical WML.

In the selection of our study population some bias has occurred, as participants of our study were younger, and more educated and had lower blood pressures than those who did not participate. As all these factors are associated with WML as well as with cognitive performance, there probably is an under-representation of subjects with the most severe WML and the highest degree of cognitive decline. It is unlikely that the relation between severity of WML and cognitive decline would be different in non-participants, and therefore the selection bias will only have weakened the relation between severity of WML and rate of cognitive decline.

There are important methodological differences that distinguish our study from previous investigations. Most previous studies found relations between cognitive function and WML only in a cross-sectional design.[1,10,11,17] Three longitudinal studies investigated the relation between WML and cognitive decline, but two were underpowered because of small sample size or short time intervals, used only de-

mented patients, or had different scanning protocols at baseline and follow up.[4,6] Although in the study by Swan and co-workers a relation between WML volume and decline of MMSE measurements was found, this was based on only two MMSE measurements and WML were not distinguished in periventricular or subcortical regions.[8] We addressed the issue with multiple measurements of cognitive performance over a long time interval, in relation to severity of periventricular or subcortical WML.

Although the MMSE is a rough measure of global cognitive function, the rate of its decline nevertheless correlated with the severity of WML. The mean overall decline was 0.1 points per year and is in accordance with previous studies.[22,27] The rate of decline as found for individuals with the highest WML severity was in between that found for normal aging and for individuals with Binswanger's disease,[28] which attests to the clinical relevance of these results. Because we made only a single MRI scan, we cannot be sure that the decline in cognitive performance can be attributed to progression of WML, despite our adjustment in the analyses for cerebral atrophy and presence of infarcts. Serial MRI assessments, are needed to confirm that periventricular lesions of the white matter are an important factor in the development of cognitive decline in the elderly.

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– Chapter 7 –

CARDIOVASCULAR RISK FACTORS FOR CEREBRAL WHITE MATTER LESIONS AND COGNITIVE FUNCTION

Abstract

Objective: To determine to what extent cerebral white matter lesions mediate the relation between cardiovascular risk factors and cognitive function.
Design: Population based cross sectional MRI study.
Subjects: Random sample of 1084 elderly subjects, aged 60-90 years, from the general population.
Setting: The city of Zoetermeer and a suburb of Rotterdam in the Netherlands, 1995-1996.
Main outcome measures: Severity of periventricular and subcortical white matter lesions and global cognitive function as assessed with multiple neuropsychological tests.
Results: Hypertension, atrial fibrillation, measures of atherosclerosis, and myocardial infarction were all associated with in particular more severe periventricular white matter lesions and worse scores for global cognitive functions. The severity of periventricular white matter lesions, but not subcortical white matter lesions was related to lower scores for cognitive function. Seventeen to sixty-seven percent of the association between cardiovascular risk factors and cognitive function could be explained by white matter lesions.
Conclusions: Results of this study are compatible with the hypothesis that white matter lesions mediate the association between cardiovascular risk factors and cognitive function.

Magnetic resonance images of demented and non-demented elderly people often show cerebral white matter lesions (WML).[1-3] Many studies have related these WML on the one hand to vascular risk factors[1,3-6] including hypertension,[1-3] atherosclerosis,[7] and cardiac disease,[8-10] and on the other hand to cognitive dysfunction and dementia.[11] Vascular disorders are thought to play a role in the development of cognitive impairment and dementia,[12-17] and it has been hypothesized that this might occur through white matter lesions.[1,3,18-21] We assessed in a population-based study whether cardiovascular risk factors are associated with cognitive function and, if so, to what extent cerebral white matter lesions are an intermediate in this relation.

Methods

Study Population

This study is part of the Rotterdam Scan Study, a prospective population based study which was designed to study determinants and cognitive correlates of age related brain changes in the elderly. In 1995-1996, 1904 persons aged between 60 and 90 years were randomly invited in strata of age and gender, from participants of two large ongoing cohort studies; the Rotterdam Study and the Zoetermeer Study. Both studies have been described in detail elsewhere.[22,23]

One hundred and eighty persons had contra-indications for the study (dementia, contraindications for MRI scanning, blindness), so 1,724 were eligible. Complete data were obtained from 1,084 participants (63%). Compared with non-participants, the participants of the study were younger (mean age difference 3.8 years, $p < 0.001$) and more educated (5% more subjects with university level education, $p = 0.05$). Baseline systolic blood pressure measurements for subjects invited from the original Zoetermeer Study were significant lower in participants compared with non-participants (age and gender adjusted difference; 2.4 mm Hg, $p = 0.03$), whereas this was not significant for subjects invited from the original Rotterdam Study. The protocol of the study was approved by the medical ethics committee of the Erasmus University Rotterdam, the Netherlands, and all participants gave written informed consent.

Measurement of cardiovascular risk factors

We evaluated cardiovascular risk factors that had been associated with white matter lesions as well as with cognitive function in previous studies. These risk factors were

hypertension,[2,14,15,18,24] atrial fibrillation,[16,25,26] measures for atherosclerosis (plaques in the carotid arteries and the ankle-to-brachial index[12,7]) and myocardial infarction.[1,12] Information on these risk factors was obtained as part of the physical examination in the Rotterdam Scan Study.

Blood pressure was measured two times on the right arm with a random zero sphygmomanometer in sitting position. The average of these two measurements was used. Hypertension was defined as a diastolic blood pressure ≥95 mm Hg and/or a systolic blood pressure ≥160 mm Hg and/or the self reported use of blood pressure lowering medication.

As a measure for atherosclerosis in the cerebral arteries we assessed the presence of plaques in the carotid arteries ultrasonographically using a 7.5 MHz sector transducer (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, USA). Plaques were defined as a focal widening relative to adjacent segments, with protrusion into the lumen of only calcified deposits or a combination of calcifications and non-calcified material. They were scored as present or absent on the anterior and posterior wall of the left and right-sided common carotid artery, bifurcation and internal carotid artery, leading to a total plaque severity score ranging from 0-12. Data were available for 974 subjects (90%). In a random 110 subjects data were not obtained because we lacked the technical assistance to perform these measurements.

The ankle-to-brachial index was used as an indicator of peripheral atherosclerosis and was assessed by taking the ratio of the systolic blood pressure measured at the tibial artery to the systolic blood pressure measured at the right arm with a random zero sphygmomanometer, in sitting position. Blood pressure in the tibial artery was measured with a 8 Mhz continuous wave Doppler probe and a random zero sphygmomanometer, in supine position (Huntleigh 500D, Huntleigh Technology, Bedfordshire, UK). Subjects with an ankle-to-brachial index less than 0.9 were considered to suffer from peripheral arterial disease.[27,29] Measurements were available for 1048 subjects (97%). Because the tibial artery was sometimes closed completely or the Doppler-sounds were too weak to assess the blood pressure properly we could not obtain data from 3% of participants.

The presence of atrial fibrillation and myocardial infarction was assessed as indicators of cardiovascular disease. A 12-lead ECG could be recorded from 960 subjects (89%) by means of an ACTA electrocardiograph (ESAOTE, Firenze, Italy) and was stored digitally. For the detection of rhythm disturbances we used a 10 seconds resting ECG. For 124 subjects ECGs could not be evaluated because of technical problems with the ECG recorder. All ECGs were processed by the Modular ECG Analysis System (MEANS).[29] The program provides a rhythm and contour

interpretation, and has been extensively evaluated.[29-31] For atrial fibrillation, and myocardial infarction the MEANS interpretation was used.

Measurement of white matter lesions

MRI scanning was performed on 1.5-Tesla scanners (Gyroscan, Philips NT, or Magnetom Vision, Siemens AG). The scanning protocol included a series of axial proton-density (TR 2200ms, TE 20ms), T2-weighted (TR 2200ms, TE 80ms) and T1-weighted (for Gyroscan TR 485ms, for Vision TR 700ms, TE 14ms) images. Sections were 5 or 6 mm thick (scanner dependent) with an interslice gap of 20%. Laser hardcopies were printed with a reduction factor of 2.7.

Presence, severity and location of cerebral white matter lesions were scored according to a protocol designed for the Rotterdam Scan Study. WML were considered present if visible as hyperintense on both PD and T2 weighted images and not hypointense on T1 weighted images. When the largest diameter of the WML was adjacent to the ventricle it was defined as periventricular, otherwise as subcortical. Periventricular WML were scored semi-quantitatively as 0 (none), 1 (pencilthin lining), 2 (smooth halo), or 3 (large confluent) for three separate regions (adjacent to the frontal horns, adjacent to the wall of the lateral ventricles, adjacent to the occipital horns). The total periventricular WML score was calculated by adding the region-specific scores (range 0-9). Subcortical WML were categorized based on their maximum diameter (as appearing on the hardcopy) as small (0-3 mm), medium (3-10 mm) or large (>10 mm). The number of subcortical WML was rated per size-category. In order to calculate a total subcortical WML volume, on hard copy, WML were considered to be spherical with a fixed diameter per size category.

Two independent readers out of a pool of four experienced physicians examined all scans. In case of disagreement of more than one point for periventricular WML, a consensus reading was held, in other instances scores were averaged. Intra- and inter-rater studies showed good to excellent agreement. Weighted kappas for periventricular WML severity grades were between 0.79-0.90. Interreader and intra-reader-intraclass correlation coefficients for total subcortical WML-volume were 0.88 and 0.95, respectively. Spearman's rank test for the correlation between periventricular and subcortical WML was 0.6.

Cognitive function

Cognitive function was assessed by neuropsychological tests, including an abbreviated Stroop test consisting of three subtasks, the Paper-and-Pencil Memory Scanning Task consisting of four subtasks,[32-34] the Letter-Digit Substitution Task which

is a modified version of the Symbol Digit Modalities Test,[35] a verbal fluency test and a 15 words verbal learning test based on Rey's auditive recall of words.[36] Performance across tests was made comparable by transforming the raw test scores into Z-scores as described elsewhere.[37] As a measure for global cognitive function we used a compound score, referred to as Cognitive Index. It was calculated as the mean of the Z-scores on the one letter subtask of the Paper-and-Pencil Memory Scanning Task, the reading subtask of the Stroop test, the Letter-Digit Substitution Task, the added score on the learning trials of the 15 words verbal learning test and the delayed recall of this last test.

Statistical analysis

The analysis took a four-step approach. We documented: 1) the relation between cardiovascular risk factors and severity of white matter lesions, 2) the relation between white matter lesions and cognitive function, 3) the relation between cardiovascular risk factors and cognitive function, and 4) the relation between cardiovascular risk factors and cognitive function, conditional on the severity of white matter lesions.

For all analyses we used multivariate linear regression models in which we adjusted for age and gender. In addition the level of education (according to UNESCO[38]) was considered as a possible confounding variable in all studied relations with cognitive function. Missing values were handled in the multivariate models by the missing variable indicator method.[39] The relation between the severity of WML in both the periventricular and subcortical region and cognitive function was studied, with and without adjustment for the severity of WML in the other region. The relation between cardiovascular risk factors and cognitive function was studied in separate models for each of the cardiovascular risk factors, and with the score on the Cognitive Index as the dependent variable. Next, by adding the severity of WML (both subcortical and periventricular) to these models, we studied to what extent the relation between cardiovascular risk factors and cognitive function was mediated by WML. The mediating effect of WML was estimated by the percent of change in the effect estimates as calculated for the relation between cardiovascular risk factors and cognitive function with and without adding WML to the model.

Results

In table 1 the characteristics of the study population are given per age category. On average, older subjects had less education and performed worse on cognitive tests

Table 1
Characteristics of the study population by age category

Characteristic	Total population (n= 1084)	Age 60-69 (n= 466)	Age 70-79 (n= 418)	Age 80-90 (n= 200)
Mean age (SD)	72.3 (7.4)	65.2 (2.6)	74.6 (2.8)	83.7 (2.8)
% women	52	51	51	53
% with only primary education	34	30	34	49
Mean score on the Cognitive Index	0.00 (0.74)	0.34 (0.59)	-0.10 (0.68)	-0.62 (0.71)
Cardiovascular risk factors				
% with hypertension†	51	43	52	68
Mean systolic blood pressure (SD)	147.4 (21.6)	143.0 (21.14)	149.7 (21.1)	152.7 (21.7)
Mean diastolic blood pressure (SD)	78.7 (11.7)	79.7 (11.2)	78.6 (12.0)	76.4 (12.1)
% with atrial fibrillation	3	2	3	7
% with carotid plaques	62	50	70	75
Median severity of carotid plaques*	2 (0 - 4)	1 (0 - 1)	2 (0 - 4)	3 (0 - 5)
% with peripheral atherosclerosis‡	17	10	18	33
% with myocardial infarction	10	9	12	10
Severity of white matter lesions (WML)				
Median periventricular WML score*	2.0 (0.5 - 4.0)	1.0 (0.0 - 2.0)	2.0 (1.0 - 4.0)	4.0 (2.0 - 6.0)
Median subcortical WML volume*	0.20 (0.03 - 1.28)	0.08 (0.07 - 0.37)	0.25 (0.04 - 1.31)	1.52 (0.28 - 3.80)

* = interquartile range; † = defined as a diastolic blood pressure ≥95 mm Hg and/or a systolic blood pressure ≥160 mm Hg and/or the use of blood pressure lowering drugs; ‡= defined as ankle-to-brachial index below 0.9.

than younger subjects. They had also more cardiovascular risk factors and more severe white matter lesions. Of all subjects only 5% had no WML at all, whereas 20% were free of periventricular WML and 7% had no signs of subcortical WML. 73% of all subjects had both periventricular and subcortical WML. The severity of periventricular WML ranged from 0 to 9 and for subcortical WML from 0 to 29.5 ml.

Subjects with cardiovascular risk factors had more severe WML than subjects without cardiovascular risk factors (table 2). This was observed for all five cardiovascular risk factors for especially periventricular WML. When we studied the relation between the severity of periventricular or subcortical WML and cognitive function for the two regions of WML separately, we found that the severity of lesions in both regions correlated strongly with cognitive function. The change in Cognitive Index per increase in periventricular WML score was -0.05 (95% CI: -0.07 to -0.03). The change in Cognitive Index per increase in subcortical WML volume (ml) was -0.02 (95% CI: -0.04 to -0.01). Because periventricular and subcortical WML are highly correlated, we assessed the relation between cognitive function and subcortical WML conditional on the severity of periventricular WML, and vice versa. The relations between periventricular WML and cognitive function did not change for these analyses (change in Cognitive Index per increase in periventricular WML score was -0.05 (95% CI: -0.07 to -0.03). Subcortical WML were not related to cognitive function when we investigated the relation conditional on the severity of periventricular WML (change in the Cognitive Index per increase in subcortical WML volume (ml) was 0.00 (95%CI: -0.02 to 0.02)).

Table 2
The increase in white matter lesion severity at periventricular and subcortical regions in relation to the presence of cardiovascular risk factors

	Difference in white matter lesions severity according to the presence of cardiovascular risk factors	
Risk factor	Periventricular (score)	Subcortical (volume-ml)
Hypertension (n= 556)	0.5 (0.2 to 0.7)*	0.62 (0.29 to 0.95)*
Atrial fibrillation (n= 31)	0.7 (0.0 to 1.4)*	0.32 (-0.67 to 1.31)
Plaques in the carotid arteries, per point (range 0-12)	0.1 (0.0 to 0.1)*	0.06 (-0.01 to 0.13)†
Peripheral atherosclerosis (n= 177)	0.3 (0.0 to 0.7)*	0.21 (-0.24 to 0.67)
Myocardial infarction (n= 99)	0.3 (-0.1 to 0.7)	0.09 (-0.48 to 0.67)

*= $p \leq 0.05$; † = $p < 0.10$; All values are means (95% CI) adjusted for missing values, age and gender.

Table 3
The decrease in cognitive performance in relation to the presence of cardiovascular risk factors with and without taking severity of white matter lesions into account

Risk factor	Difference in score on the Cognitive Index according to the presence of cardiovascular risk factors		%MRC
	Unconditional on WML severity	Conditional on WML severity	
Hypertension (n= 556)	-0.09 (-0.16 to -0.01)*	-0.06 (-0.14 to 0.02)	33
Atrial fibrillation (n= 31)	-0.18 (-0.42 to 0.06)	-0.15 (-0.37 to 0.09)	17
Plaques in the carotid arteries, per point (range 0-12)	-0.02 (-0.03 to -0.00)*	-0.01 (-0.03 to 0.00)	50
Peripheral atherosclerosis (n= 177)	-0.03 (-0.13 to 0.08)	-0.01 (-0.11 to 0.10)	33
Myocardial infarction (n= 99)	-0.03 (-0.16 to 0.10)	-0.01 (-0.14 to 0.12)	67

*= $p \leq 0.05$; All values are means (95% CI) adjusted for missing values, age, gender, and educational level.; %MRC = percent mediator (white matter lesions) related change, calculated as the percent decrease in difference in score on the Cognitive Index, when comparing the unconditional to the conditional model.

Subjects with cardiovascular risk factors had consistently lower scores on the Cognitive Index than subjects without cardiovascular risk factors (table 3, first column). When these relations were studied conditional on the severity of both periventricular and subcortical WML, the difference in score on the Cognitive Index between subjects with or without cardiovascular risk factors decreased 17 to 67 percent (table 3, second column).

Discussion

In this population based study among 1084 non-demented elderly between the ages 60 and 90 years we found that cardiovascular factors, including, hypertension, atrial fibrillation, plaques in the carotid arteries, peripheral atherosclerosis and myocardial infarction were associated with lower cognitive function. Also, we found that cardiovascular risk factors were related to especially more severe periventricular white matter lesions, while the severity of mainly these periventricular white matter lesions was associated with lower cognitive function. Finally, we found that 17 to 67 percent of the association between the cardiovascular risk factors and cognitive function could be mediated via white matter lesions.

One of the strengths of this study is its large number of elderly people from a general population. Other strengths are the availability of several cardiovascular risk factors, the separate ratings of periventricular and subcortical WML, and the detailed neuropsychological testing.

Before we interpret our findings, we have to consider whether they are valid. The overall response rate was 63%, which raises the question of selection bias. Since participants were younger and had lower blood pressures than non-participants, it is likely that non-responders had a higher prevalence of the cardiovascular risk factors, as well as higher degrees of white matter lesions and worse cognitive function. We could think of no reason why the association between cardiovascular risk factors, white matter lesions and cognitive function would be different in non-participants. Missing data for the ECG or duplex assessments occurred mostly at random and will not have introduced bias. However, missing data on measures for peripheral atherosclerosis probably occurred specifically among subjects with severe atherosclerosis. However, only 36 subjects had missing data on this measure. With respect to cognitive function, these 36 subjects did not differ from subjects whose data were complete. Therefore, if anything, these missing data would only have impeded on the detection of a relation between the cardiovascular risk factors and cognitive function. Misclassification can also cause biased effect estimates. We probably mis-

classified some subjects with paroxysmal atrial fibrillation as having no atrial fibrillation due to our short ECG recording time.[40] We may also have missed some myocardial infarctions, in particular if there were no typical ECG characteristics,[30,41] non Q-wave infarctions[41,42] or typical ECG characteristics had disappeared with time.[30,41] Both possibilities for misclassification were probably unrelated to the severity of white matter lesions and cognitive function, and will have therefore only diminished the contrast between the classified risk groups.

We found that within our study cardiovascular risk factors were consistently associated with cognitive function, which is in line with reports by others.[2,14,15,18,24,26] The effect estimates for the associations between the cardiovascular risk factors and cognitive function were rather small and not all were statistical significant. However, there are several reasons why we may have underestimated these associations. These include the misclassifications of the determinants as referred to above; the fact that we restricted the study-population to non-demented elderly, leading to little variation in cognitive function; and also because the cross-sectionally obtained measures for cardiovascular risk factors may not be a good reflection of someone's lifetime exposure to these risk factors.

It has been suggested that the relation between cardiovascular risk factors and cognitive function is mediated through white matter lesions, although this has never been formally evaluated.[1,3,18-21] Our results indicate that white matter lesions could indeed be intermediate in this relation because, when we studied the association between cardiovascular risk factors and cognitive function conditional on the severity of white matter lesions, effect estimates for this association decreased consistently. There are at least two possible explanations why the associations did not disappear entirely. It could mean that the relation between cardiovascular risk factors and cognitive function is only partly mediated through white matter lesions, and that there are other mediators in this relation, like other structural brain features, metabolic, or genetic factors.[43-49] An alternative explanation is that this is largely a statistical phenomenon due to the large variation in all used measures, and the fact that the used measures are only proxies for the actual measures under study.

To our knowledge, we are the first to report results compatible with a mediating role of white matter lesions in the relation between cardiovascular risk factors and cognitive function. However, this study does not provide evidence for causality of this relationship because of the cross-sectional design of the study. To clarify the cascade leading to cognitive decline, serial assessments of risk factors, neuroimaging characteristics and cognitive measures are needed. When, in longitudinal studies, the mediating role of white matter lesions can be confirmed, it may add to our understanding and prospects for prevention of cognitive decline.

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— Chapter 8 —

GENERAL DISCUSSION

The overall and unifying aim of the studies described in this thesis was to provide epidemiological knowledge on the possible deleterious consequences of cerebral white matter lesions. The studies were conducted as part of the Rotterdam Scan Study, a population-based MRI study on determinants and consequences of age-related brain changes among 1084 subjects aged 60 to 90 years.

In the previous chapters each individual study has been discussed as to its merits and limitations. This chapter first provides some background on cerebral white matter lesions. Then the main findings of these studies will be reviewed. Next, methodological issues that came up during these studies will be discussed. Finally, some clinical implications and suggestions for further research are given.

Background

With the advent of radiological techniques like computer tomography scanning followed by the more sensitive magnetic resonance imaging, it became possible to visualize the inside of the living brain. It was noted that the white matter was frequently affected, especially in the elderly.[1] As this finding was even more frequent in patients who suffered from dementia[2] and in patients with a late-onset depression[3] the question arose whether white matter lesions in healthy elderly could be involved in the etiology of the above conditions.

The pathogenesis of white matter lesions remains unclear. Age, high blood pressure and indicators for atherosclerosis have consistently been reported as risk factors for white matter lesions.[4-7] The same risk factors are established as risk factors for the development of vascular dementia, but may also be involved in the development of other forms of dementia,[8-10] and in the development of late-onset depression.[11,12]

The white matter of the brain can be distinguished into the periventricular region and the subcortical region. The periventricular region surrounds the fluid-filled ventricles at the core of the brain, and the subcortical region is the layer directly underneath the cortical gray matter. The periventricular and subcortical white matter differ in respect to anatomy and function. Long associating nerve fibers, connecting distant cortical areas with each other and connecting subcortical with cortical structures are found in the periventricular region, whereas short looped U-fibers, connecting adjacent cortical areas are found in the subcortical region.[13] In addition to these structural differences, different risk factors may underlie white matter lesions at the distinct locations[14,15] and consequences of lesions in these separate re-

gions may differ.[16] Despite these dissimilarities, only a few studies distinguished between the two separate regions. We considered it of importance to study these periventricular and subcortical regions separately and independently from each other.

Main findings

In the Rotterdam Scan Study, information on subjective cognitive failures, cognitive function and indicators for depression was obtained from 1084 non-demented people, aged 60-90 years, who all underwent magnetic resonance imaging of the brain.

Frequency distribution of white matter lesions

Most people had some degree of white matter lesions (84%). Of all participants 20 percent were free of periventricular white matter lesions and 8 percent was free of subcortical white matter lesions. This is in line with the figures given in other studies although actual reported prevalence figures highly differ depending on the study design, study population, imaging technique and rating scale.[4-6,17-19] We considered it more useful to describe the severity distribution of white matter lesions rather than merely the prevalence. Severe periventricular white matter lesions (grade 3) were found in 10 percent and large subcortical white matter lesions (>10 mm) were found in 19 percent of the participants. The correlation between periventricular and subcortical white matter lesions was considerable (Spearman's Rho was 0.6 between severity of both regions). Severity of both periventricular and subcortical white matter lesions increased with age. Subcortical white matter lesions were predominantly located in the frontal and parietal regions. Gender differences were small, though the prevalence and severity of both periventricular and subcortical white matter lesions was significantly higher among women. These gender differences were mainly due to white matter lesions in the frontal region.

Correlates and consequences

All our studies on the clinical correlates of white matter lesions led to one unifying conclusion, namely: these lesions are not benign or trivial. Consequences of white matter lesions differ according to their location. Periventricular white matter lesions lead to cognitive decline, whereas subcortical white matter lesions increase the risk for mood disturbances. These conclusions are based on the following evidence:

1/ Subjective cognitive failures

People of all ages report subjective cognitive failures, but the number of reported failures increases with age (chapter 4.1), as do complaints about cognitive function.[20,21] There are reports that people who have cognitive complaints indeed have an increased risk for developing dementia even if no cognitive impairment can be detected at that instance,[22] although this has been questioned by others.[23] We found that among people with a better than average cognitive performance, those who reported cognitive failures had more severe white matter lesions than those who did not report cognitive failures. When these people additionally reported that these failures had progressed over the past few years, white mater lesions were found to be even more severe. For people with a lower than average cognitive performance more severe white matter lesions were found, but for these people the reporting of cognitive failures had no relation to the severity of white matter lesions. People with severe white matter lesions were twice as likely to report progression of cognitive failures compared to people with no to moderate white matter lesions. These findings are suggestive for a causal link between white matter lesions and advancing stages of cognitive problems. In our study we found that the correlation between subjective cognitive failures and depressive symptoms was higher than the correlation with cognitive function. It could therefore be argued that subjective cognitive failures represent depressed mood rather than cognitive problems.[24,25] However, subjective cognitive failures in our study were particularly related to periventricular white matter lesions, as was objective cognitive function (chapter 4.2 and chapter 6), whereas subcortical white matter lesions were particularly involved in depression (chapter 5). These distinctive associations have also been described for Alzheimer's disease versus major depression.[16] Taken together, this suggest that subjective cognitive failures may be a prelude to cognitive dysfunction.

2/ Cognitive dysfunction

Although white matter lesions have been associated with cognitive dysfunction in previous studies,[6,26,27] only a few studies distinguished between periventricular and subcortical regions of white matter lesions.[28-31] The results of these latter studies were inconclusive. As can be concluded from the review of all studies on the relation between cerebral white matter lesions and cognitive functions (chapter 2), one should distinguish the different regions of white matter lesions in studying the relation with cognitive function. Data from the Rotterdam Scan Study provide evidence that only periventricular white matter lesions have an independent relation with cognitive function (see figure 1b, chapter 4.2). When the different cognitive domains were addressed, the strongest relations were found with psychomotor

speed. (p_{trend} = 0.003 over quintiles of white matter lesions severity). People with the most severe white matter lesions performed nearly one standard deviation below average on the measure for psychomotor speed. This finding is of importance as a decreased mental speed is an established core element of subcortical dysfunction.[32,33]

3/ Depression

There is increasing evidence for a relation between small vessel disease and depression.[11] The late onset form of depression relates poorly with psychological and social stressors.[11] Structural brain alterations with a vascular origin have been attributed to, in particular, late-onset depression and have led to the new term of vascular depression.[12] Results from chapter 5 indicate that when severe white matter lesions are present, people were five times as likely to have depressive symptoms compared to people with no to moderate white matter lesions. Furthermore, they four times more often reported a history of depression with a late onset. These associations were found for subcortical white matter lesions, but not for periventricular lesions.

4/ Cognitive decline

Very few studies investigated whether the severity of white matter lesions is related to decline of cognitive performance over time.[34-37] Results from these studies are conflicting and inconclusive mainly because of small and highly selected samples. In the study described in chapter 6 we tackled this question with nearly 600 participants who had three to four measures for global cognitive function spaced 2 years apart and a MRI assessment within this time. We found that the severity of periventricular white matter lesions predicted the rate of cognitive decline. The rate of decline for people with severe periventricular white matter lesions was 2.5 times faster than average (95% CI 1.1-3.3). There was no independent relation with the severity of subcortical white matter lesions. There are similarities and controversies with the findings of the study by Swan and coworkers who studied the association between a 10-year decline in cognitive function and white matter lesions in 317 elderly twins[38]. Although these investigators found no relation between severity of white matter lesions and change in global cognitive function, associations were reported with decline in psychomotor tasks. They however had only two measurements for cognitive function over a 10-year period and they did not distinguish between periventricular and subcortical regions of white matter lesions. Both these limitations may have contributed to a false negative association between severity of white matter lesions and global cognitive function. Taken together, both our study and the study by Swan et al. provide evidence for an association between severity of white matter lesions and rate of cognitive decline.

Cardiovascular factors, white matter lesions and cognitive function

No studies have quantified the role of white matter lesions in the relation between cardiovascular risk factors and cognitive function, whereas this pathway has been suggested by several authors.[4,6,39-42] We investigated the role of white matter lesions in the relation between hypertension, atrial fibrillation, plaques in the carotid arteries, peripheral atherosclerosis and myocardial infarction and global cognitive function. We found that all the above cardiovascular risk factors were associated with lower cognitive function. Also, we found that cardiovascular risk factors were related to especially more severe periventricular white matter lesions, while the severity of mainly these periventricular white matter lesions was associated with lower cognitive function (see also chapter 4.2). When we studied the association between cardiovascular risk factors and cognitive function conditional on the severity of white matter lesions, effect estimates for this association decreased 17 to 67 percent. This suggests that white matter lesions are indeed an intermediate in the relation between cardiovascular risk factors and cognitive dysfunction.

Methodological considerations

Study design

The observational studies presented in this thesis were based on cross-sectional and longitudinal data. Although cross sectional studies are limited in the interpretation regarding causality, they are very useful in generating hypotheses, which then can be tested in, preferably, longitudinal studies. In chapter 4.1 observational relations of a cross-sectional nature are reported, however a semi-longitudinal component (i.e. reporting previous progression of cognitive failures) made some causal interpretations possible. Causality of the cross-sectional relations as described in chapter 4.2 gained plausibility by confirmation in the longitudinal study as presented in chapter 6. Similarly, in chapter 5 both cross-sectional and semi-longitudinal evidence is presented gaining plausibility for a causal association.

Choice of the study population

When selecting a study population for a given research question we have to think of the population we want to attribute our results to. In the Rotterdam Scan Study we wanted to test the hypothesis that white matter lesions are associated with decreased cognitive function, and eventually to an increased incidence of dementia. As this is a

unifying hypothesis we had no apparent exclusion criteria other than prevalent dementia and contraindications for MRI scanning. Two study populations were chosen reflecting the average Dutch elderly.

For participation in the Rotterdam Scan Study, we invited people from two population-based studies, the Rotterdam Study and the Zoetermeer Study. These two populations were chosen because information was available from earlier examinations.[43,44] For people originating from the Zoetermeer study, data were available from as early as 1975, for the Rotterdam Study from 1990. These baseline data included risk factors for cerebrovascular damage and, for people originating from the Rotterdam Study, data on cognitive function. The availability of these historical data was of major importance for the possibility of relating cardiovascular risk factors to white matter lesions, and for relating white matter lesions to decline in cognitive function. The selected age range of 60 to 90 years was chosen because prevalence of both the determinant (white matter lesions and cerebrovascular risk factors) and the outcome (subjective cognitive failures, cognitive impairment) is high in this age range.

Validity

An important issue in any research is the validity of the results. Validity refers to the amount of bias or systematic error, which is often distinguished in selection bias, information bias and confounding.

Selection bias

Selection bias occurs when the relation between the determinant (white matter lesions) and outcome (cognitive function or depression) would be different for participants compared to eligible non-participants of the study. Whenever the response rate of an invitation to a study is not equal to a 100%, this form of bias can play a role. In the Rotterdam Scan Study 63% of all eligible subjects agreed to participate. Participants, compared to non-participants, were younger, had lower blood pressures, higher educational levels and a better cognitive function. Although the differences were small, more risk factors for white matter lesions were present in the non-participant group. As cognitive function was also lower in the non-participants, it is likely that the relation between determinant and outcome is not different between non-participants and participants. In addition, by missing information of non-participants, we most likely missed the extremes of the white matter lesion and cognitive function distribution. Therefore, missing these subjects probably only limited the statistical power to detect a modest relation between white matter lesions and cognitive function.

Information bias

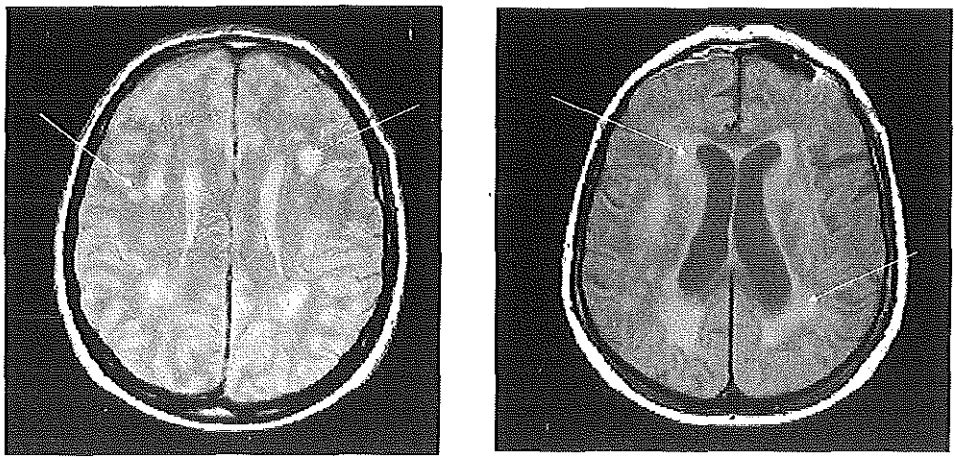
Incorrect information on the determinant, outcome or confounders will lead to misclassification. If information on the determinant is not dependent on the outcome, misclassification of the determinant will be non-differential. Non-differential misclassification tends to bias the results towards the null, which makes it more difficult to detect a relation between determinant and outcome. If information on the determinant depends on the outcome, than differential misclassification could occur. Differential misclassification of the relation under study can lead to over- or underestimation of the strength, limiting the validity of the results.

In an attempt to minimize misclassification of the determinant, two investigators independently rated all measures for white matter lesions without knowledge of the outcome variable. Another advantage of dual rating was the enhanced precision of the measurement. We assigned white matter lesions to either the periventricular or the subcortical region by careful examining if the largest diameter of a white matter lesion was adjacent to the ventricles or not. If the largest diameter of a white matter lesions was adjacent to the ventricle it was considered as having originated from this ventricular lining, if not, it was considered as having evolved from the subcortical white matter (see figure).

This definition could have resulted in some degree of misclassification. Subcortical white matter lesions could be misclassified as periventricular white matter lesions, if large subcortical white matter lesions would progress to such an extent that they became attached to the ventricular lining. Also, severe periventricular white matter lesions could progress far into the subcortical region thereby incorporating subcortical white matter lesions. Although we cannot exclude that misclassification of white matter lesions occurred in some instances, we do not believe that this has played a major role. This is supported by our findings that in particular periventricular white matter lesions were associated with cognitive dysfunction, whereas in particular subcortical white matter lesions were associated with depression. If differential misclassification had played a substantial role, these distinctive relations would not be expected.

Measures of subjective cognitive failures, cognitive function and mood status in our studies were assessed before MRI scanning and therefore independently from knowledge about the determinant. Therefore the assessment of the outcome could only suffer from random error. This error can have its implications for precision but not for validity. Reducing measurement error, enlarging the size of study, and having multiple questions for measuring one outcome can enhance precision (as discussed in chapter 4.1). In addition, we used a structured interview to state these questions

Figure
Example of an MRI image, illustrating subcortical and periventricular white matter lesions.



instead of a written questionnaire, thereby obtaining a better estimate of the true value of the individual answers and ensuring that all questions were answered. Precision in measurement of cognitive function was greatly enhanced by performing multiple neuropsychological tests, and by constructing compound scores for cognitive function from these. The tests within one compound score assess the same cognitive domain and act therefore as multiple measurement of the same variable, thereby reducing intra-individual variability and giving a better estimate of the true value per domain. Precision in the measurement of depression variables was enhanced by the use of a valid and reliable questionnaire, and by having a structured interview for gathering information on psychiatric history. The use of antidepressive medication was noted after visual inspection of the used medication itself. This method minimizes recall bias and adds to precision of the recorded data. We are well aware that the definition we used is not as specific as a formal psychiatric diagnosis. This limitation however does not need to compromise the validity of the data.

Confounding

Except for ensuring validity and precision of a determinant and an outcome variable we have to consider confounding variables. When we describe a relation between the determinant and the outcome, a third variable might account for an observed relation between determinant and outcome. Because in etiologic research we are interested in a causal relation between determinant and outcome, we have to avoid

confounding.[45] The most important confounder in the relation between white matter lesions and cognitive function or depression is age, and potentially, gender, level of education and other neuroimaging characteristics. Because of the large number of subjects and the age-and gender stratified invitation to the Rotterdam Scan Study we were able to control for these confounding variables without losing too much statistical power. Because white matter lesions are thought to cause both depression and cognitive dysfunction it is not immediately evident that controlling for cognitive function when evaluating depression, or vice versa is necessary or wishful.[46] We therefore reported results with and without adjusting for either cognitive function or depression. We did not adjust for the presence of cardiovascular risk factors in the relation between white matter lesions and cognitive function as cardiovascular risk factors are thought to cause white matter lesions. If we would adjust for these risk factors an existent association between white matter lesions and cognitive function and/or depression might disappear due to over-adjustment.

Assessment of cognitive function

As the cerebral white matter is a subcortical structure, lesions in this area are thought to result in subcortical dysfunction. Core features of subcortical dysfunction include cognitive slowing, memory disturbances and mood disturbances.[32] Age-related cognitive impairment is also thought to result mainly of decline in processing speed.[47] We therefore focused our outcome measures to the above aspects by constructing compound scores for psychomotor speed, memory and global cognitive function (Cognitive Index). The compound scores consisted of the mean of three, four, and seven cognitive tests, respectively, that were individually standardized to Z-scores. The neuropsychological tests used in the compound scores were chosen because of their robustness in detecting age-related impairment and sensitivity to subcortical dysfunction.[48-51] The measure for psychomotor speed was limited to only the most basic elements of psychomotor function as this enabled us to make a strict classification of test parameters based on the cognitive domain that was intended to be measured. For example, the Stroop test consists of three subtasks of which we used only the simplest (reading) task in most analyses. The more complex subtasks of the Stroop test (interference) measure psychomotor tasks, but also sensorimotor processes as stimulus encoding and response selection, which cannot be unraveled into its components and are therefore more difficult to interpret. For the memory compound score we used the free recall capabilities, which are affected by cortical as well as subcortical dysfunction.[32] As measures for global cognitive function we used

a combination of above-mentioned tests[51] as well as the widely used Mini Mental State Examination (MMSE).[52] We chose our tests and summary scores after careful consideration, but other methods of data-reduction are clearly possible. Other combinations of tests could very well provide valuable answers in research on cognitive aging.

Clinical relevance

On a cross-sectional level we found one standard deviation decrease in cognitive performance and a 2.5 times increased rate of cognitive decline when severe white matter lesions were present. One might question the clinical significance of such differences. However these studies were performed within non-demented subjects and as such we did not have a lot of contrast in cognitive function. Although a decrease of one standard deviation or a decline of 0.25 MMSE points per year may be of little importance on an individual level, it is of importance on the population level.[8,53] Above results suggest that reducing the severity of white matter lesions might result in an upward shift of the population distribution of cognitive performance, reducing the proportion of people at risk for dementia. Reducing the number of people with cognitive impairment will result in a better quality of life for the individual and less costs for healthcare.

In addition to the possible beneficial effects on cognitive function, reducing the severity of white matter lesions might have a beneficial effect on the number of people suffering from depressive symptoms, and on the occurrence of late-onset depression. If true, than reducing the severity of white matter lesions would be of enormous health benefit and certainly certifies further research in the cascade leading to the development and progression of white matter lesions.

Future research

Dementia and depression impose a major burden on individuals, caregivers and on society. Within our aging society, it is an obligation and a necessity to study possible modifiable risk factors for the development of these conditions. Vascular risk factors might be among these factors and, during the last decade, gained interest of researchers worldwide.[8,10,54] In this thesis we reported on the mediating role of white matter lesions in the relation between cardiovascular risk factors and cognitive function, and on the relation between the severity of white matter lesions and cog-

nitive impairment, cognitive decline and depressed mood. However, many questions remain unanswered, and confirmation in prospective studies is needed. Preferably, to overcome biased study results, these questions need to be answered in a community setting. Within such a setting, nested case control studies can be employed for specific research questions if these are thought to be more feasible. In studies on causes and consequences of white matter lesions, periventricular and subcortical regions need to be distinguished, as results from our studies clearly illustrated the importance of this distinction.

When we address directions for future research it is perhaps best to begin at the start of the proposed cascade leading to dementia. In chapter 7 we discussed the limitations of using cardiovascular risk factors as proxies for cerebral abnormal haemodynamics and hypoperfusion. More direct non-invasive measures for cerebral circulation are to be preferred in these studies. In addition to the plaques in the carotid arteries the wall thickness of these arteries has to be studied prospectively as a measure for developing atherosclerosis. If thickening of the carotid wall would go accompanied by increasing severity of white matter lesions this would be an indication for a causal relation. One of these methods could be the use of CO^2 enhanced transcranial Doppler to measure actual vasomotor reactivity and blood flow at the level of the cerebral vessels. This method has been adopted as a pilot study in the Rotterdam Scan Study and relations between vasomotor reactivity and white matter lesions have been reported.[55,56] To unravel causes and consequences using this technique, prospective studies are essential. The same holds for studies using MR Spectroscopy. This technique enables us to study the metabolism of the brain at specified sites. In a hypoperfused area it is expected that metabolism is altered, which could precede white matter lesions. This technique has also been employed in a pilot study within the Rotterdam Scan Study, but remains to be evaluated.[57]

In future studies on the consequences of white matter lesions prospective studies are also of major importance. Serial neuroimaging assessments will be of utmost importance in these prospective studies. If a change in white matter lesion severity can be related to a change in outcome measures it would greatly enhance evidence for a causal relation. A major question remaining to be answered is whether white matter lesions are associated with a higher incidence of dementia. Also, these studies could clarify whether subjects who report progression of subjective cognitive failures are a high-risk group for the development of cognitive dysfunction, and if this transition coincides with increasing severity of white matter lesions. Assumptions as derived from our cross-sectional studies can be verified by relating progression of white matter lesions to a decrease in cognitive performance or the development of depression.

Developing methods to evaluate progression of white mater lesions will be a challenge for future research. Although several semi-automated quantitative techniques have been developed for this purpose, they are still elaborate and time consuming and seemingly not suitable for the use in large population based studies. There is very little knowledge about how white matter lesions progress. Whether small lesions gradually develop into large lesions or that these lesions have a completely different pathophysiology is not known. Serial assessment of other structural brain changes could also provide insight in causes and consequences for neurobehavioral functioning of (sub)cortical atrophy and other MRI findings, like silent cerebral infarcts, tortuosity of lenticostriatal vessels and widened Virchov-Robin spaces.

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— Chapter 9 —

SUMMARY

This thesis describes the neurobehavioral correlates and consequences of cerebral white matter lesions as seen on MRI scans of elderly people. The focus is on cognitive dysfunction and on indicators of depression. Cognitive dysfunction is often a prelude to dementia, and depression often coincides with cognitive dysfunction. Both cognitive dysfunction and depression highly diminish the quality of life.

The prevalence and severity of white matter lesions in the brain seems related to the aging process. Moreover white matter lesions are seen more often within demented and elderly depressed patients than in healthy aged matched controls. It is suggested that cardiovascular risk factors are causally related to these cerebral white matter lesions (see thesis F.-E. de Leeuw, 1999) and that these white matter lesions in turn play a role in the etiology of dementia and late-life depression. If this proposed cascade is true, this might open possibilities for intervention in this cascade and thereby prevent cognitive impairment to progress.

Chapter 2 provides a review of the studies on white matter lesions and cognitive function from a methodological point of view. Merits and limitations of previous studies are discussed and the prevailing evidence for a relation between the two is summarized. Several methodological issues are stressed in this review. Firstly, when choosing a study population it is of importance not to exclude people with prevalent cardiovascular disease, as people with these conditions form a high-risk group for developing white matter lesions. Secondly, the relevance of distinguishing periventricular and subcortical regions and maximizing the precision of the severity measurement of white matter lesions is pointed out. Finally, it is underscored that in the assessment of cognitive function, the emphasis should be on subcortical brain functions, measured with neuropsychological tests sensitive enough to detect even slight alterations in brain function.

In **chapter 3** we report on the sex differences in the frequency distributions of white matter lesions in the participants from the Rotterdam Scan Study. In total 1084 randomly selected elderly persons, aged between 60 to 90 years, participated in this population based longitudinal MRI study (response 63%). Periventricular white matter lesions were rated on a visual scale in four severity categories for three separate locations (range of the total 0-9). White matter lesions at subcortical regions were counted per size category and per lobe. We calculated a volume for the total subcortical white matter lesions from these frequencies by assuming every lesion had a fixed diameter per size category. Both the severities of periventricular and subcortical white matter lesions had a distribution that was skewed to the left. Most people had some degree of white matter lesions (84%). Very little people were found to have no white matter lesions at all. Severe periventricular white matter le-

sions (grade 3) were found in 10 percent, while large subcortical white matter lesions were found in 18.6 percent of participants. The correlation between periventricular and subcortical white matter lesions was considerable (Spearman's Rho was 0.6 between severity of both regions). An age-related increase in severity of both periventricular and subcortical white matter lesions was confirmed. In the distribution of subcortical white matter lesions a predominant frontal and parietal pattern was observed. Gender differences were small but women had slightly more, and more severe, white matter lesions than men.

Chapter 4.1 describes the relation between the severity of white matter lesions and subjective cognitive failures. These subjective cognitive failures are everyday mishaps that are reported when asked for. Information on these subjective cognitive failures was obtained by a standardized interview about forgetfulness, concentration problems, planning problems etc. These failures correlate better with depressive symptoms ($R= 0.35$, $p<0.001$) than with cognitive function ($R= -0.19$, $p<0.001$) cross-sectionally, but nevertheless may precede cognitive impairment. People with more severe white matter lesions more often reported subjective cognitive failures than people with less severe white matter lesions. Moreover people with more severe white matter lesions more often reported that these failures had become worse over the last five years. These associations were more marked for periventricular than for subcortical white matter lesions.

In **chapter 4.2** the relation between severity of white matter lesions and cognitive function was assessed using multiple neuropsychological tests from which we constructed compound scores for psychomotor speed, memory performance and global cognitive function. When analyzed separately, both periventricular and subcortical white matter lesions were related to all measures of the neuropsychological tests. When periventricular white matter lesions were analyzed conditional on subcortical WML and vice versa, the relation between periventricular white matter lesions and global cognitive function remained unaltered (p_{trend} for quintiles = 0.001) whereas this relation with subcortical WML disappeared (p_{trend} for quintiles = 0.97). Subjects with most severe periventricular WML performed nearly one standard deviation below average on tasks involving psychomotor speed (-0.85 SD, $p = 0.001$), and more than half a standard deviation below average for global cognitive function (-0.61 SD, $p < 0.001$). Tasks that involve speed of cognitive processes appear to be more affected by WML than memory tasks.

In **Chapter 5** we investigated the relation between white matter lesions and indicators of depression. Cerebral white matter lesions are thought to represent vascular pathology. In psychiatric patients white matter lesions have been related to affective disorders and to a history of late onset depression. We found that persons

with severe white matter lesions (upper quintile) had 3 to 6 times as often depressive symptoms as compared to persons with only mild or no white matter lesions (lowest quintile) (subcortical OR=5.8; 95%CI 2.1 to 16.3 and periventricular OR=2.9; 95%CI 1.7 to 7.6). In addition, individuals with severe subcortical, but not periventricular, white matter lesions (upper quintile) compared to persons with only mild or no white matter lesions (lowest quintile) had 4 times more often a history of late onset depression (OR=3.9; 95%CI 0.9 to 16.1). We conclude that the severity of subcortical white matter lesions is related to the presence of depressive symptoms as well as to a history of late onset depression.

We described the relation between severity of white matter lesions and rate of decline of cognitive function over time in **chapter 6**. More severe white matter lesions were associated with a greater decline in global cognitive function as measured by the Mini Mental State Examination scores over a mean follow up period of 5.5 years (SD 1.5). For subjects with the most severe periventricular white matter lesions, cognitive function declined 2.5 times faster than average (95% confidence interval 1.4 to 3.3). There was no relation between severity of subcortical white matter lesions and rate of cognitive decline. From these findings we conclude that the severity of periventricular rather than subcortical white matter lesions is associated with decline of cognitive function.

Finally in **chapter 7** we examined whether cerebral white matter lesions mediate the relation between cardiovascular risk factors and cognitive function. The relation between cardiovascular risk factors and cognitive dysfunction has been described several times. However, to what extent the relation between cardiovascular factors and cognitive function is mediated through white matter lesions is not known. Our data suggested, that the relation between several cardiovascular risk factors (atherosclerosis, hypertension, atrial fibrillation and myocardial infarction) and cognitive function is at least partially mediated by cerebral white matter lesions.

In **chapter 8** we discuss the results of the studies presented in this thesis. We conclude that cerebral white matter lesions are not benign. They probably represent vascular damage to the brain and they have measurable effects on both cognitive function and mood status. We conclude that cognitive problems, from subjective cognitive failures to overt cognitive impairment, are related to the severity of periventricular white matter lesions, whereas depressive symptoms and minor depression are associated with the severity of subcortical white matter lesions. Some of these studies were longitudinal, others cross-sectional and further studies are still needed to elucidate the cascade leading from vascular risk factors to dementia. A key element in these future studies will be the availability of serial MRI scans.

– Hoofdstuk 10 –

SAMENVATTING

Dit proefschrift beschrijft de gedragsneurologische correlaten en gevolgen van wittestofafwijkingen zoals deze voorkomen op MRI-beeldvorming van de hersenen van oudere personen. Het accent ligt op cognitieve dysfunctietekenen van depressie. Cognitieve dysfunctie is het voornaamste symptoom van dementie; depressie gaat vaak samen met cognitieve dysfunctie. Ons cognitief functioneren en onze gemoedstoestand bepalen een groot deel van onze kwaliteit van leven.

Het vóórkomen en de ernst van wittestofafwijkingen in de hersenen zijn gerelateerd aan het verouderingsproces. Bovendien worden wittestofafwijkingen vaker gezien bij dementen en oudere depressieve personen dan bij gezonde controlepersonen van dezelfde leeftijd. Cardiovasculaire risicofactoren zijn waarschijnlijk causaal gerelateerd aan wittestofafwijkingen (zie proefschrift F.-E. de Leeuw, 1999) en deze wittestofafwijkingen spelen op hun beurt een rol in de etiologie van dementie en depressie ontstaan op latere leeftijd. Als de voorgestelde cascade waar is, dan opent dit mogelijkheden voor interventie zodat voortschrijdende cognitieve achteruitgang wellicht kan worden voorkomen.

De studies beschreven in dit proefschrift onderzoeken of de bovengenoemde cascade een rol kan spelen in de ontwikkeling van cognitieve achteruitgang en depressie ontstaan op latere leeftijd.

In **hoofdstuk 2** wordt een overzicht van studies betreffende wittestofafwijkingen en cognitief functioneren gegeven vanuit een methodologisch standpunt. Een discussie met betrekking tot de sterke en zwakke punten van voorafgaande studies en een samenvatting betreffende het bestaan van een relatie tussen de twee wordt beschreven. Diverse aspecten van onderzoeksopzet worden behandeld. Ten eerste, bij het kiezen van een onderzoekspopulatie is het van belang om ook personen met reeds bestaande cardiovasculaire ziekten te includeren, daar zij een groep vormen met een verhoogd risico op het ontwikkelen van wittestofafwijkingen. Ten tweede wordt het belang van het maken van een regionaal onderscheid van wittestofafwijkingen in periventriculaire en subcorticale gebieden en het maximaliseren van de precisie van het meten van de ernst van wittestofafwijkingen benadrukt. Ten slotte wordt benadrukt dat de bepaling van het cognitief functioneren moet gebeuren door middel van neuropsychologische testen die gevoelig genoeg zijn om zelfs kleine veranderingen van met name subcorticale hersenfuncties te detecteren.

In **hoofdstuk 3** rapporteren wij de geslachtsverschillen in de frequentieverdeling van deelnemers aan de Rotterdam Scan Studie. In totaal 1084 personen namen deel aan deze longitudinale MRI-populatiestudie (respons 63%). De leeftijd van de participanten varieerde van 60 tot 90 jaar. In dit hoofdstuk wordt ook de

ontwikkelde scoringsschaal voor wittestofafwijkingen beschreven en rapporteren wij de prevalentie, frequentie en verdeling van de wittestofafwijkingen per regio zoals gevonden in de Rotterdam Scan Studie. Periventriculaire wittestofafwijkingen werden gescoord op een visuele schaal in vier categorieën van ernst voor drie aparte locaties (totaalbereik van 0-9). Wittestofafwijkingen in subcorticale gebieden werden geteld in drie categorieën van grootte en per hersenkwab. Een volume voor de totale hoeveelheid subcorticale wittestofafwijkingen werd berekend met de aanname dat elke laesie een bolvorm heeft met een vaste diameter per grootte-categorie. Zowel de ernst van periventriculaire als die van subcorticale wittestofafwijkingen hadden een verdeling die ten opzichte van de normale verdeling verschoven was naar links. De meeste deelnemers hadden wel enige wittestofafwijkingen (84%). Zeer weinig deelnemers hadden totaal geen wittestofafwijkingen. Tien procent van de deelnemers had ernstige (graad 3) periventriculaire wittestofafwijkingen en 18.6% had grote (diameter groter dan 10 mm) subcorticale wittestofafwijkingen. Er bestond een aanzienlijke correlatie tussen periventriculaire en subcorticale wittestofafwijkingen (Spearman's Rho=0.6 tussen de ernst van beide gebieden). Een aan leeftijd gerelateerde toename in ernst van zowel periventriculaire als subcorticale wittestofafwijkingen werd bevestigd. In de verdeling van subcorticale wittestofafwijkingen werd een voornamelijk pariëtaal en frontaal patroon waargenomen. Ofschoon de verschillen in wittestofafwijkingen tussen mannen en vrouwen klein bleken, kwamen wittestofafwijkingen bij vrouwen vaker voor en waren ernstiger dan bij mannen.

Hoofdstuk 4.1 beschrijft de relatie tussen de ernst van wittestofafwijkingen en subjectief cognitief falen. Dit subjectief cognitief falen bestaat uit dagelijkse foutjes van het cognitief functioneren die gerapporteerd worden wanneer er specifiek naar gevraagd wordt. Informatie betreffende dit subjectief cognitief falen werd verkregen door middel van een gestandaardiseerd en gestructureerd interview betreffende vergeetachtigheid, concentratieproblemen, planningsproblemen etc. Mensen met ernstigere wittestofafwijkingen rapporteerden vaker subjectief cognitief falen dan mensen met minder ernstige wittestofafwijkingen. Bovendien rapporteerden mensen met ernstigere wittestofafwijkingen vaker dat dit falen erger was geworden gedurende de laatste vijf jaar. Deze associaties waren overtuigender voor periventriculaire dan voor subcorticale wittestofafwijkingen. Dit patroon doet vermoeden dat, hoewel dit soort falen cross-sectioneel beter correleert met depressieve symptomen ($R=0.35$, $p<0.001$) dan met cognitief functioneren ($R= -0.19$, $p<0.001$), het desalniettemin een voorloper zou kunnen zijn van cognitieve achteruitgang. Dit gezien de gelijkenis met de bevindingen in **hoofdstuk 4.2,** waarin de relatie tussen ernst van wittestofafwijkingen en het objectief cognitief functioneren werd geëvalueerd, gebruik-

makend van verschillende neuropsychologische testen. Uit de scores op deze testen construeerden wij samengestelde scores voor psychomotorische snelheid, geheugenprestatie en globaal cognitief functioneren. Indien periventriculaire en subcorticale wittestofafwijkingen apart werden geanalyseerd, was de ernst van de wittestofafwijkingen in beide regio's gerelateerd aan het cognitief functioneren. Wanneer in deze relaties periventriculaire wittestofafwijkingen conditioneel op subcorticale wittestofafwijkingen werden geanalyseerd (en vise versa), bleef de relatie tussen periventriculaire wittestofafwijkingen en globaal cognitief functioneren bestaan, terwijl de relatie met subcorticale wittestofafwijkingen verdween. Personen met ernstige periventriculaire wittestofafwijkingen presteerden op taken betreffende psychomotore snelheid bijna één standaarddeviatie onder gemiddeld (-0.85 SD, p = 0.001) en op taken betreffende globaal functioneren meer dan een halve standaarddeviatie onder gemiddeld (-0.61 SD, $p < 0.001$). De ernst van de wittestofafwijkingen bleek meer gerelateerd aan de snelheid van het cognitief functioneren dan aan geheugenfuncties.

In **hoofdstuk 5** wordt de relatie tussen wittestofafwijkingen en indicatoren voor depressie beschreven. Van cerebrale wittestofafwijkingen wordt gedacht dat ze vasculaire pathologie vertegenwoordigen. Binnen patiëntenpopulaties is beschreven dat wittestofafwijkingen gerelateerd zijn aan zowel affectieve stoornissen als aan een voorgeschiedenis van depressie ontstaan op late leeftijd. Wij vonden dat ook in de bevolking personen met ernstige wittestofafwijkingen (hoogste quintiel) vergeleken met personen met milde of helemaal geen wittestofafwijkingen (laagste quintiel) 3 tot 6 keer (periventriculair: OR=2.9; 95%CI 1.7 tot 7.6; subcorticaal: OR=5.8; 95%CI 2.1 tot 16.3) zo vaak depressieve symptomen hadden. Bovendien hadden personen met ernstige subcorticale wittestofafwijkingen vergeleken met personen met milde of helemaal geen wittestofafwijkingen vier keer (OR=3.9; 95%CI 0.9 tot 16.1) zo vaak een voorgeschiedenis van depressie ontstaan op latere leeftijd. Dit laatste werd niet gevonden voor periventriculaire wittestofafwijkingen. Wij concludeerden dat de ernst van subcorticale wittestofafwijkingen gerelateerd is aan zowel de aanwezigheid van depressieve klachten als aan een voorgeschiedenis van depressie ontstaan op latere leeftijd.

De relatie tussen de ernst van wittestofafwijkingen en de snelheid van cognitieve achteruitgang over de tijd wordt beschreven in **hoofdstuk 6**. Meer ernstige wittestofafwijkingen waren geassocieerd met een groter verval in globaal cognitief functioneren. Voor het verval in cognitief functioneren werd het verval in Mini-Mental-State-Examination-scores gebruikt zoals herhaaldelijk gemeten over een periode van gemiddeld 5.5 jaar (SD 1.5). Voor personen met de meeste ernstige periventriculaire wittestofafwijkingen was de snelheid van cognitieve achteruitgang

2.5 keer (95%CI 1.4 tot 3.3) sneller dan gemiddeld. Wij vonden geen relatie tussen de ernst van subcorticale wittestofafwijkingen en de snelheid van cognitieve achteruitgang. Uit deze bevindingen concluderen wij dat met name de ernst van periventriculaire wittestofafwijkingen gerelateerd is aan de snelheid van cognitieve achteruitgang.

Tenslotte wordt in **hoofdstuk 7** de mediërende rol van cerebrale wittestofafwijkingen in de relatie tussen cardiovasculaire risicofactoren en het cognitief functioneren beschreven. Dat cognitieve dysfunctie geassocieerd is met de aanwezigheid van cardiovasculaire risicofactoren is verschillende keren beschreven. Echter, in hoeverre deze relatie gemedieerd wordt via wittestofafwijkingen is tot op heden niet bekend, ondanks de resultaten van sommige studies die laten zien dat deze cascade aannemelijk is. De relatie tussen verschillende cardiovasculaire risicofactoren (atherosclerose, hypertensie, atriumfibrilleren en myocardinfarct) en cognitieve functie zoals gevonden binnen ons onderzoek, kon gedeeltelijk verklaard worden door de ernst van wittestofafwijkingen.

In **hoofdstuk 8** worden de belangrijkste resultaten van de onderzoeken die in dit proefschrift zijn beschreven geëvalueerd, rekening houdend met de restricties van deze onderzoeken. Wij concluderen dat wittestofafwijkingen geen onschuldig fenomeen zijn. Zij zijn waarschijnlijk het gevolg van vasculaire schade aan de hersenen, hetgeen gevolgen heeft voor het cognitief functioneren en de stemming. Wij concluderen dat cognitieve problemen, van subjectief cognitief falen tot een meetbare versnelde cognitieve achteruitgang, gerelateerd zijn aan de ernst van periventriculaire wittestofafwijkingen, terwijl depressieve symptomen en depressie ontstaan op oudere leeftijd geassocieerd zijn met de ernst van subcorticale wittestofafwijkingen. Enkele van deze studies waren longitudinaal, andere cross-sectioneel, maar toekomstig onderzoek blijft nodig om uit te zoeken hoe de cascade is die vasculaire risicofactoren verbindt aan dementie. Een sleutelelement in toekomstige studies zal de beschikbaarheid van opeenvolgende MRI-scans zijn.

Epiloog

Een bevolkingsonderzoek van deze omvang in geenszins mogelijk zonder de hulp van vele mensen. Veel dank gaat uit naar de meer dan duizend ouderen die hebben deelgenomen aan dit onderzoek. Na twee uur onderzoek op het onderzoekscentrum waren zij daarnaast bereid om in de avonduren of de weekenden nog meer uren te geven om de MRI-scan te ondergaan. Het is hartverwarmend dat mensen ondanks hun soms matige conditie tot veel bereid zijn om de wetenschap te dienen.

Behalve de mensen op wie dit proefschrift gebaseerd is, zijn er nog vele mensen van groot belang geweest voor het slagen van deze missie. Als eerste wil ik hierin bedanken mijn promotor professor Jolles. Waarde Jelle, jij hebt mij attent gemaakt op deze unieke neuro-psychiatrische studie. Ik ben blij dat onze initiële samenwerking in Maastricht op deze wijze een vervolg heeft kunnen krijgen. Je niet aflatende neuropsychiatrische interesse heeft mij altijd geïnspireerd. Je detaillistische kennis van neurocognitieve processen is goed voor vele boeiende discussies met deze inmiddels epidemiologisch gedoctrineerde promovendus. Ten tweede wil ik professor Hofman bedanken. Beste Bert, epidemiologische kennis is een zo belangrijk deel geworden van elk wetenschappelijk onderzoek, dat ik erg blij ben dat je me hierin hebt kunnen vormen. Ik ben er trots op in 'jouw' instituut gewerkt te hebben. Je grote wetenschappelijke interesses in neurodegeneratieve processen is een grote stimulans voor mij geweest. Je bijna obsessieve geloof in een goede afloop was een mooi contrast ten opzichte van mijn vaak wat sombere instelling. Natuurlijk gaat erg veel dank uit naar mijn co-promotor dr Breteler. Monique, als een heus co-enzym heb je het tempo van het onderzoeksproces gekataliseerd. Je inzet voor dit onderzoek was altijd intens zelfs toen je 'noodgedwongen' enkele maanden je aandacht op maturatie richtte in plaats van op degeneratie. Ik hoop dat Frans het me vergeeft dat ik zoveel van je geëist heb. Ik hoop dat onze samenwerking ook in het vervolgonderzoek van 'onze' Rotterdam Scan Study voortgang vindt. Dr Launer, beste Lenore, jou inzet is voor mij van grote waarde geweest in de opstartfase van de studie. Je rol als interim co-promotor vervulde je uitstekend en het is dankzij jou dat de start van het onderzoek nauwelijks enige vertraging op heeft gelopen. Good luck and happiness in your homeland.

Onder de radiologische leiding van professor Mali, Matthijs Oudkerk en Lino Ramos bleek het mogelijk om in de avonduren en in de weekenden MRI-scans te kunnen maken. De dagelijkse gang van zaken werd in uitstekende banen geleid door Deni Kraus, Bart Schraa en Willeke Rouw. De vele goed belegde broodjes van het AZU bleken te zorgen voor een uitstekende sfeer in de wachtruimte van het MRI

complex. Ik dank Eric Achten, Philip Scheltens en John van Swieten voor hun onderricht in het lezen van MRI-scans en met name voor het ontwikkelen van de scoringsschalen voor wittestofafwijkingen. De radiologische ondersteuning bij het scoren van de 65.040 afzonderlijke MRI-sneden werd verzorgd door Eric Achten en Roel Heijboer. Zonder hun hulp was het niet mogelijk geweest om zoveel MRI's te beoordelen in zo'n korte tijd. Rik, de Gents-Vlaamse gastvrijheid die ik hierbij genoot was zeker bourgondisch te noemen. Roel, onze gemeenschappelijke 'gemotoriseerde' hobby leidt wellicht nog tot meerdere ontmoetingen.

Een aparte positie neemt de Maastrichtse groep in. Bij Peter Houx kon ik altijd terecht met neuropsychologische vragen, Astrid Quist heeft mij prima ingewerkt in de finesses van het afnemen van dergelijke onderzoeken en Martin van Boxtel was altijd thuis voor data-reducerende analysetechnieken. 'My man in Maastricht,' Pieter-Jelle Visser, was altijd bereid onderdak te verschaffen (en een Mestrichts biertje) ten behoeve van cursussen of afspraken in het verre zuiden. De openhartigheid van de Maastrichtse groep zorgt ervoor dat de fysieke afstand tot de randstad drastisch gereduceerd wordt.

Om de meer dan 2500 onderzoeksuren op de onderzoekscentra goed te laten verlopen was de hulp van Agnes van de Voorn, Ria Rijneveldshoek, Micheline de Haas, Anneke Korving, Joke Jansen, Inge Haumersen, Hanneke van Meurs, Dick Slof, alsmede van de vele 'stand-ins' onontbeerlijk. Dankzij hun enorme inzet was het enthousiasme van de deelnemers groot en de sfeer goed. Eén alinea in deze tekst doet hun hulp zeker te weinig eer aan.

Een niet te miskennen groep werd gevormd door de informatiserings-experts. Veel heb ik te danken aan Marcel Eijgermans en René Vermeeren. Zonder hen was geen deelnemer uitgenodigd, geen getal ingevoerd en geen computercrash opgelost. Bij de opzet en uitvoer van een grootschalig onderzoek kan hun hulp niet vroeg genoeg worden ingezet.

Eén iemand die eigenlijk goed als eerste genoemd had kunnen worden is Frank-Erik de Leeuw. Frank-Erik, elke scan is door ons samen beoordeeld, het merendeel van de deelnemers door ons samen gezien en elk artikel betreffende 'ons' onderzoek hebben we samen geschreven. Dat we nu elkaar kunnen steunen in de verdediging van het proefschrift is een mooie kroon op onze hopelijk nog langdurige band. Arjen Slooter en Casper Bijkerk, al na de eerste dag was duidelijk dat onze gemeenschappelijke zoölogische interesse voor een erg gezellige tijd zou zorgen. Arjen, onze Haagse tijd zal voor altijd een bijzondere plaats in mijn hippocampus hebben. Jammer dat we het uitzicht op de Dom niet kunnen delen.

Vier jaar op de 21ste verdieping is aangenaam vertoeven, mede dankzij het contact met de vele mede promovendi. Het is helaas niet mogelijk iedereen te

bedanken aan wie ik warme herinneringen bewaar, maar Sanjay Harhangi en Tom den Heijer kunnen niet onvernoemd blijven. Jullie komst op *de* Maatschaps-kamer heeft tot heerlijke koffie en goede neuroepidemiologische discussies geleid. Tom en Sarah, veel succes bij het vervolg van het mooie MRI project. De eindstrijd van dit proefschrift werd met name veraangenaamd door het groepje 'nablijvers'; Iris Westendorp, Caroline van Rossum en Raan Ramrattan. Dankzij hen bleven zelfs zeventig-urige werkweken haalbaar en gezellig. Mijn paranimf Sandra Kalmijn neemt een bijzondere plaats in. Sandra, niet alleen mijn wetenschappelijke problemen kon ik altijd bij jou kwijt. Het feit dat jij nu bij de verdediging aan mijn zijde staat past bij je rol die je vervulde tijdens andere life events.

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About the author

Jan Cees de Groot was born in Groningen, the Netherlands, on December 25th, 1965, where he lived until he attended secondary school at the "Montessori Lyceum" in Rotterdam. Subsequently, he studied architecture for a year at the Technical University in Delft.

He did his medical studies at the University of Utrecht, from which he graduated in 1993. During his studies, he performed six months of neurobehavioral research within the laboratory of Neuropsychoendocrinology (head: Prof A. Etgen.) at the department of Psychiatry of the Albert Einstein College of Medicine in the Bronx, New York, USA (head: Prof. H.M. van Praag), and worked with Prof. J. Jolles during the summer of 1993, when he performed neurobiologic research at the Neuropsychology and Psychobiology section of the University of Maastricht. After his military service for the Netherlands Royal Navy, he briefly was a resident in neurosurgery at the St. Elisabeth Hospital in Tilburg.

In 1995 he started the work described in this thesis at the Department of Epidemiology & Biostatistics (head: Prof. A. Hofman) of the Erasmus Medical Center Rotterdam in collaboration with the department of Psychiatry and Neuropsychology of the University of Maastricht (Prof. H.M. van Praag and Prof. J. Jolles). During this work he received his training in epidemiology at the Netherlands Institute for Health Sciences in Rotterdam (MSc in Clinical Epidemiology, 1998).

From Januari 1999 he will be a resident in neurology at the department of Neurology (head: Prof. RAC Roos) of the Leiden University Medical Center.