Cerebral small vessel disease in dementia and depression

A prospective population-based MRI study

Acknowledgements

The work presented in this thesis was conducted at the Department of Epidemiology & Biostatistics in close collaboration with the Department of Neurology of the Erasmus Medical Center, Rotterdam.

The Rotterdam Scan Study was supported by grants from the Netherlands Organisation for Scientific Research, and the Netherlands Heart Foundation. Financial support from the study on homocysteine was provided by the EU BIOMED Demonstration Project, which paid for the homocysteine assays.

The author gratefully acknowledges the collaboration with the Department of Radiology, University Hospital Groningen (Prof.dr. M. Oudkerk), the Department of Psychiatry & Neuropsychology, University Maastricht (Prof.dr. J. Jolles), the Clinical Trial Service Unit, University of Oxford, United Kingdom (Prof.dr. R. Clarke), the Department of Neurology, VU Medical Center, Amsterdam (Prof.dr. Ph. Scheltens), the Department of Radiology, VU Medical Center, Amsterdam (Prof.dr. F. Barkhof), the Biomedical Imaging Group Rotterdam, a collaboration between the Department of Radiology and Medical Informatics, Erasmus Medical Center, Rotterdam (Dr. H.A. Vrooman), and the Regional Institute for Ambulatory Mental Health and the general practitioners of Rotterdam and Zoetermeer.

The Department of Epidemiology & Biostatistics and the Department of Neurology of the Erasmus Medical Center, Rotterdam, the Netherlands Organisation for Scientific Research (NWO) and Internationale Stichting Alzheimer Onderzoek contributed in the production costs of this thesis.

Cerebral small vessel disease in dementia and depression. A prospective population-based MRI study. Prins, Niels D. Thesis Erasmus MC, University Medical Center Rotterdam. With summary in English and Dutch.
n.prins@erasmusmc.nl

Interior and cover design by Anna Bosselaar (anna@bonmot.nl).
Printed by Optima Grafische Communicatie, Rotterdam (www.ogc.nl).

ISBN 90-775-95-08-2

Cerebral small vessel disease in dementia and depression

A prospective population-based MRI study

Cerebrale microangiopathie bij dementie en depressie

Een prospectieve MRI studie onder de algemene populatie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
Rector Magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 24 maart 2004 om 11:45 uur
door

Niels Daniël Prins

geboren te Amsterdam

Promotiecommissie

Promotoren	:	Prof.dr. M.M.B. Breteler
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Voor mijn familie

Manuscripts based on the studies described in this thesis

Chapter 2.1
Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Jolles J, Koudstaal PJ, Hofman A, Breteler MMB. Cerebral small vessel disease and decline in information processing speed and memory. Submitted.

Chapter 2.2
Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MMB. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348:1251-22.

Chapter 2.3
Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MMB. Cerebral white matter lesions and the risk of dementia. Arch Neurol 2004. In press.

Chapter 2.4
Prins ND, Den Heijer T, Hofman A, Koudstaal PJ, Jolles J, Clarke R, Breteler MMB. Homocysteine and cognitive function in the elderly: the Rotterdam Scan Study. Neurology 2002;59:1375-80.

Chapter 3
Prins ND, Vermeer SE, Tiemeier H, Hofman A, Koudstaal PJ, Breteler MMB. Brain infarcts, white matter lesions and the risk of depression in the general population. Submitted.

Chapter 4.1
Prins ND, van Straaten ECW, van Dijk EJ, Simoni M, van Schijndel RA, Vrooman HA, Koudstaal PJ, Scheltens Ph, Breteler MMB, Barkhof F. Measuring progression of cerebral white matter lesions on MRI; visual rating and volumetrics. Neurology 2004. In press.

Chapter 4.2
van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Oudkerk M, Koudstaal PJ, Breteler MMB. Progression of cerebral white matter lesions in the population-based Rotterdam Scan Study. Submitted.

Chapter 4.3
Prins ND, van Dijk EJ, Vrooman HA, Oudkerk M, Hofman A, Koudstaal PJ, Breteler MMB. Progression of cerebral white matter lesions and the risk of stroke, dementia, and depression. Submitted.

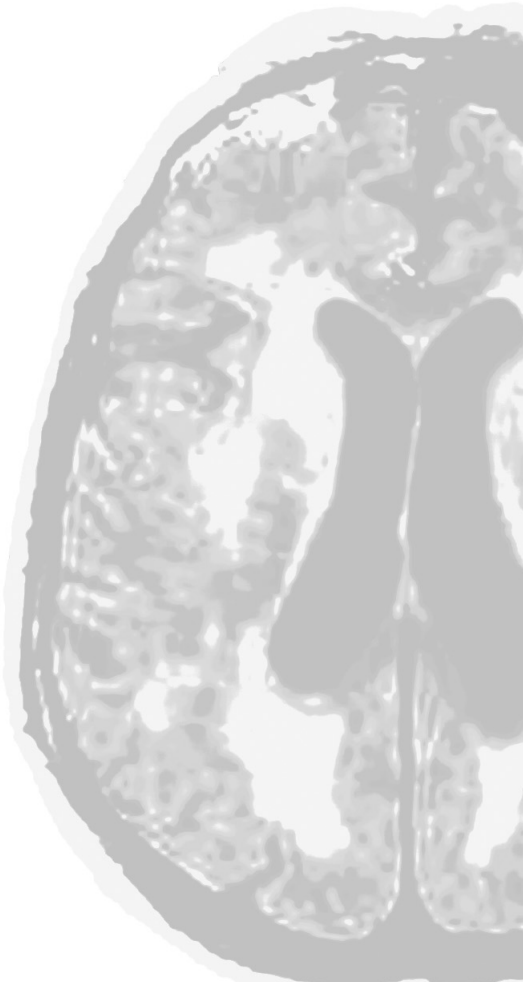
Contents

With all your science can you tell
how it is, and whence it is
that light comes into the soul?

Henry David Thoreau (1817-1862)

Chapter 1

General introduction



Cerebral white matter lesions and asymptomatic brain infarcts are common in elderly people.[1-3] These brain lesions are thought to result from cerebral small vessel disease, and their presence and severity increase with age and the presence of arterial hypertension.[2-4] There is widespread belief that cerebral small vessel disease plays a role in the aetiology of dementia. Small vessel disease is commonly regarded as the primary pathology in subcortical ischemic vascular dementia, one of the subtypes of vascular dementia.[5-7] Furthermore, vascular factors, including cerebral small vessel disease, are increasingly recognized to be involved in the aetiology of Alzheimer's disease.[8] However, there is hardly any evidence from prospective population-based studies to support these notions.

The vascular depression hypothesis implies that there is a subtype of depression occurring in late-life that is characterized by a distinct clinical presentation and an association with cerebrovascular disease.[9] According to this hypothesis, small vessel disease may also be involved in the aetiology of depression in older people.[10,11] Again, this relationship has hardly been studied prospectively in the general population.

The objective of this thesis was to provide evidence for an aetiologic role of small vessel disease in dementia and depression. For this goal we prospectively investigated the association of both presence, severity and progression of small vessel disease with the development of cognitive decline, dementia and depression in the Rotterdam Scan Study, a large population-based MRI study in elderly people.[2] In chapter 2, we first study the relationship between cerebral small vessel disease on MRI and decline in executive function and memory (chapter 2.1). Second, we assess the association between asymptomatic brain infarcts and the risk of dementia and cognitive decline (chapter 2.2), and the association between cer-

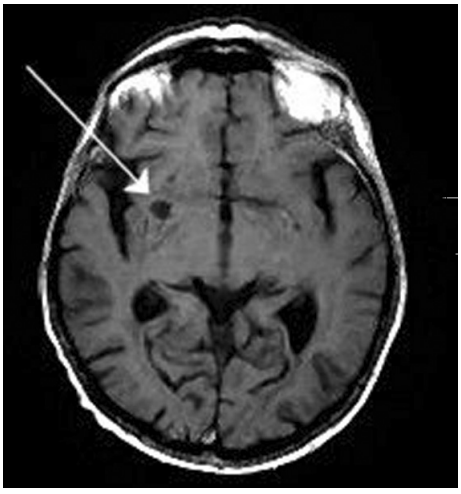


Figure 1. **Lacunar infarct (arrow) in the right putamen.**

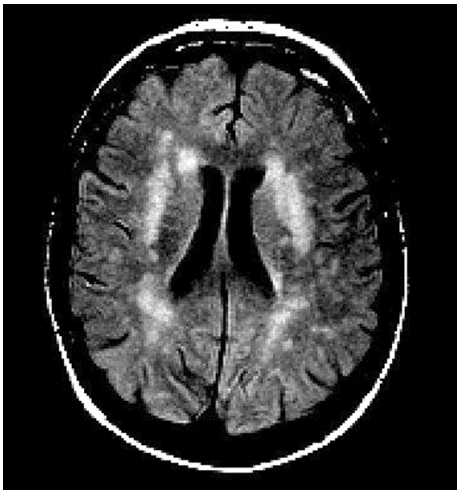


Figure 2. **Cerebral white matter lesions in the periventricular and subcortical region.**

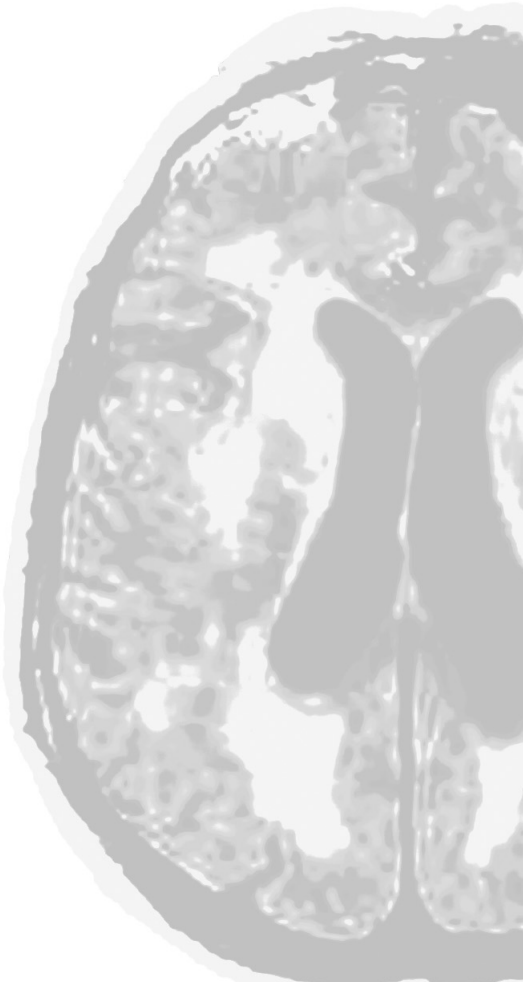
ebral white matter lesions and dementia (chapter 2.3). We also investigate the association between homocysteine, a risk factor for cerebral small vessel disease, and cognitive function (chapter 2.4). Whether brain infarcts and white matter lesions increase the risk of depression is evaluated in chapter 3. Chapter 4 focuses on the assessment and relevance of progression of white matter lesions. We compare different methods for the measurement of progression of white matter lesions (chapter 4.1). Next, we investigate the rate of progression of white matter lesions, and determine risk factors for this progression (chapter 4.2). Finally, we explore whether progression of white matter lesions is related to the risk of stroke, cognitive decline, dementia and depression (chapter 4.3). In chapter 5, we reflect on our main findings and discuss several methodological and conceptual issues related to the topic of this thesis, and speculate on the implications of our results.

References

1. Longstreth WT, Jr., Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke 1996; 27:1274-82.
2. de Leeuw FE, de Groot JC, Achten E, et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001; 70:9-14.
3. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population- based rotterdam scan study. Stroke 2002; 33:21-5.
4. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke 1997; 28:652-9.
5. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993; 43:250-60.
6. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. The Lancet Neurology 2002; 1:426-36.
7. Erkinjuntti T, Inzitari D, Pantoni L, et al. Research criteria for subcortical vascular dementia in clinical trials. J Neural Transm Suppl 2000; 59:23-30.
8. Kalaria RN. Small vessel disease and Alzheimer's dementia: pathological considerations. Cerebrovasc Dis 2002; 13 Suppl 2: 48-52.
9. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. Arch Gen Psychiatry 1997; 54:915-22.
10. Baldwin RC, O'Brien J. Vascular basis of late-onset depressive disorder. Br J Psychiatry 2002; 180:157-60.
11. O'Brien JT, Ames D. White matter changes in depression and Alzheimer's disease: a review of Magnetic Resonance Imaging studies. International Journal of Geriatric Psychiatry 1996; 11.

Chapter 2

Cerebral small vessel disease and dementia



2.1

Cererebral small vessel disease and decline in information processing speed and memory

Abstract

Cerebral small vessel disease is common in elderly people and may contribute to the development of dementia. The objective of the present study was to evaluate the relationship between measures of cerebral small vessel disease on MRI and rate of decline in specific cognitive domains in 832 participants from the prospective, population-based Rotterdam Scan Study. Participants were 60 to 90 years of age and free from dementia at baseline in 1995 to 1996. White matter lesions (WML), cerebral infarcts and generalized brain atrophy were assessed on baseline MRI. We performed neuropsychological testing at baseline and repeatedly in 1999 to 2000, and in 2001 to 2003. We used random-effects models for repeated measures to examine the association between quantitative MRI measures and rate of decline in global cognitive function, information processing speed, and memory. There were a total of 2266 assessments for the 832 participants in the study, with an average time from the initial to last assessment of 5.2 years. Periventricular WML, brain infarcts, and generalized brain atrophy on MRI were associated with the rate of decline in cognitive function. These structural brain changes were specifically associated with decline in information processing speed. The associations between MRI measures of cerebral small vessel disease and cognitive decline did not change after additional adjustment for vascular risk factors or depression. After exclusion of participants with an incident stroke, the associations of periventricular WML and brain infarcts with information processing speed were no longer significant, which may indicate that stroke plays an intermediate role in the relationship between cerebral small vessel disease and cognitive decline. Our results suggest that in elderly people cerebral small vessel disease may contribute to the development of dementia by affecting information processing speed.

Introduction

There is increasing evidence that cerebral small vessel disease contributes to the development of cognitive decline and dementia.[1,2] Cerebral small vessel disease can be visualized on MRI as white matter lesions (WML) and lacunar infarcts.[3,4] Generalized brain atrophy on MRI is a characteristic finding in AD,[5,6] but is also associated with vascular risk factors and small vessel disease.[7] Both the presence of brain infarcts, and severity of WML and generalized brain atrophy on MRI, are associated with an increased risk of dementia.[8,9] A diagnosis of dementia is often preceded by a preclinical phase of many years.[10] During this phase, people already perform less well on psychometric tests.[11,12] A sharp decline in psychometric performance is observed at the time that the first clinical changes in cognitive functioning and behavior start to interfere with activities of daily living.[13]

Establishing the temporal relationship between cerebral small vessel disease and cognitive decline in the general population may provide evidence for a causal role of cerebral small vessel disease in the etiology of dementia. It will also help answering the question whether small vessel disease differentially affects information processing speed, since the typical cross-sectional findings in individuals with WML and lacunar infarcts are suggestive of disconnection of fronto-subcortical structures.[14,15] The objective of the present study was to evaluate the relationship between measures of cerebral small vessel disease on MRI and rate of decline in specific cognitive domains in a large sample of community-dwelling elderly.

Methods

Participants

The Rotterdam Scan Study is a prospective, population-based cohort study, designed to study causes and consequences of age-related brain changes on MRI in the elderly. The characteristics of the 1077 participants have been described previously.[15] All participants were free of dementia at baseline. Baseline examination in 1995 to 1996 comprised a structured interview, neuropsychological tests, physical examination, blood sampling, and all participants underwent an MRI scan of the brain. Each participant gave informed consent to protocol, which was approved by the medical ethics committee of the Erasmus Medical Center Rotterdam.

In 1999 and 2000, we reinvited 973 participants for a second examination with a protocol similar to that of the baseline examination; of those invited 787 participated (81%). The remaining 104 participants were not reinvited for the following reasons: 82 had died, 17 had been institutionalized, 4 had moved abroad, and 1 could not be reached. In 2001 and 2003, we reinvited 844 participants for a third examination that comprised an interview, physical examination, and neuropsychological tests; of those invited 653 participated (response 79%).

The remaining 233 participants were not reinvited for the following reasons: 187 had died, 29 had been institutionalized, 11 had moved and could not be reached, and for 6 participants the invitation was postponed for logistical reasons. The present study is based on 832 participants who had at least one follow-up neuropsychological assessment.

Magnetic Resonance Imaging procedure

We made axial T1-, T2-, and proton density weighted scans on 1.5-Tesla MRI scanners (MR Gyroscan, Philips, Best, the Netherlands and MR VISION, Siemens, Erlangen, Germany). The slice thickness was 5 or 6 mm (scanner dependent) with an interslice gap of 20%.[16] WML severity was graded for periventricular and subcortical areas separately. Periventricular WML were scored semiquantitatively (range: 0 to 9). For subcortical WML, a total volume was approximated, based on number and size (range: 0 to 29.5 ml).[17] Cerebral infarcts were defined as focal hyperintensities on T2-weighted images, 3 mm in size or larger, and with a corresponding prominent hypointensity on T1-weighted images.[8] Generalized brain atrophy was scored on T1-weighted images. Cortical atrophy was rated on a semiquantitative scale (range 0 to 15) using reference scans. Subcortical atrophy was measured by the ventricle-to-brain ratio (range: 0.21 to 0.45).[18]

Cognitive decline

Participants underwent the following neuropsychological tests at the baseline and follow-up examinations: the Mini-Mental State Examination,[19] the Stroop test,[20,21] the Letter-Digit Substitution Task,[22,23] a verbal fluency test (animal categories),[24] and a 15-word verbal learning test (based on Rey's recall of words).[25] We used parallel versions of the same tests at the follow-up examinations. For each participant, we calculated z scores (individual test score minus mean test score divided by the standard deviation) for the tests at baseline and follow-up using the mean and standard deviation of the baseline tests. We constructed compound scores for global cognitive function (Cognitive Index), information processing speed, and memory. The compound score for global cognitive function was the average of the z scores of the Stroop test (sum of the reading, color naming and interference subtask), the Letter-Digit Substitution Task (number of correct digits in one minute), the verbal fluency test (number of animals in one minute), and the immediate and delayed recall of the 15-word verbal learning test. The compound score for information processing speed was the average of the z scores for the Stroop test (sum of the reading, color naming and interference subtask) and the Letter-Digit Substitution Task (number of correct digits in one minute). The compound score for memory was the average of the z scores for the immediate and delayed recall of the 15-word verbal learning test.

Ascertainment of dementia

All participants were free of dementia at baseline. We screened all participants for dementia at follow-up with the Mini-Mental State Examination (MMSE)[19] and the Geriatric

Mental State Schedule.[26] Screenpositive subjects were evaluated using the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) diagnostic interview.[27] Participants who were suspected of having dementia based on their CAMDEX performance were examined by a neurologist, and underwent additional neuropsychological testing. In addition, we continuously monitored the medical records of all participants at the general practitioners office, and at the Regional Institute for Outpatient Mental Health Care (RIAGG) to obtain information on interval cases of dementia until April 1st 2002.[8]

Other baseline measurements

The following baseline variables were used as possible confounders: age (continuously per year); sex; educational status,[28] disturbances of mood (defined as a Center of Epidemiologic studies Depression Scale (CES-D) score of 16 or higher),[29] Apolipoprotein E (APOE) genotype,[30] (dichotomized into carriers and non-carriers of the APOE ε4 allele). Incident stroke during follow-up was assessed through self-report and checking of medical records, and verified by a neurologist.[8]

Data analysis

To examine the association between quantitative MRI measures and rate of cognitive decline we used random-effects models for repeated measures (PROC MIXED with residual maximum likelihood method; SAS Systems for Windows release 6.12; SAS Institute, Cary, NC). Random-effects modeling of longitudinal data can be conceptualized as a method in which regression coefficients to account for within-subject change of scores across time are simultaneously estimated for all individuals in the sample, and in the same analysis, between subject predictors of these within-subject change indices are evaluated.[31] This approach utilizes all available data and accounts for within-person correlation across time, which results in increased statistical power for estimating effects.[32,33] We included random-effect terms to account for differences between participants in cognitive performance at baseline and in rate of cognitive decline. To account for effects on baseline cognitive performance we included terms for age, sex, and education. Age was the only demographic variable that was related to cognitive decline in preliminary analyses, so we included a term to account for the effect of age on rate of cognitive decline.

First, we evaluated the association between MRI measures and cognitive performance at baseline and rate of cognitive decline, by adding terms individually to the models. We analyzed periventricular and subcortical WML, and subcortical and cortical brain atrophy in quintiles of their distributions to study the shape of the associations, and continuously per standard deviation. Brain infarcts were analyzed as present versus absent. Second, we adjusted for incident stroke, vascular risk factors and depressive symptoms. Third, we studied the association of the MRI measures with cognitive decline, conditional on other MRI measures, by entering all MRI measures jointly in the same model. Fourth, we examined possible interaction of MRI measures with APOE in relation to cognitive decline, by in-

cluding effects for the interaction of the MRI measures with presence versus absence of the APOE ε4 allele in the models. Finally, we repeated the analyses on the association between MRI measures and cognitive decline after exclusion of participants with incident dementia during follow-up.

RESULTS

Table 1 gives the baseline characteristics of the study population. People without a follow-up examination were older, less educated, performed worse on the Mini-Mental State Examination, and had more severe periventricular WML and cortical atrophy at baseline, compared to people with a follow-up examination (table 1). Two hundred thirty participants (28%) had two neuropsychological assessments, and 602 (72%) had three assessments, contributing to a total of 2266 assessments. Average time from the initial to last assessment was 5.3 years (SD 1.2; range 2.8 - 7.9). The mean annual decline on the Cognitive Index was 0.022 points (95% confidence interval 0.029 to 0.014), on the MMSE 0.031 points (95% confidence interval 0.057 to 0.005), in information processing speed 0.053 points (95% confidence

Table 1. **Characteristics of the study population**

Characteristic	People with a follow-up examination n = 832	People without a follow-up examination n = 245	P-value for difference*
Age, yr	71	76	<0.01
Women, %	53	48	0.12
Primary education only, %	32	44	0.03
Systolic blood pressure, mmHg	146 (21)	150 (23)	0.46
Diastolic blood pressure, mmHg	79 (12)	78 (12)	0.91
Hypertension, %	48	62	0.07
Diabetes, %	6	11	0.07
Depression, no CES-D positive, %	7	9	0.44
MMSE score	28 (2)	27 (3)	<0.01
APOE ε4 carriers, %†	27	26	0.74
Periventricular WML, score	2.2 (2.1)	3.2 (2.4)	0.02
Subcortical WML, ml	1.2 (2.5)	2.1 (4.0)	0.16
Subcortical atrophy, VBR	0.31 (0.035)	0.33 (0.036)	0.53
Cortical atrophy, score	5.2 (2.7)	6.8 (3.0)	0.01
Cerebral infarcts, %	23	29	0.92

Values are unadjusted means (SD) or percentages; *age and sex adjusted difference in mean or percentage; †APOE genotype was not determined in 79 of the 832 people with a follow-up examination and in 27 of the 245 people with a follow-up examination.

Table 2. **Association of age and MRI measures with decline in information processing speed and memory.**

Variable	Information processing speed		Memory	
	Estimate	95% CI	Estimate	95% CI
Age (per year increase)	-0.006	(-0.007; -0.004)	-0.002	(-0.004; -0.000)
Periventricular WML (per SD increase)	-0.015	(-0.024; -0.006)	-0.003	(-0.018; 0.012)
Subcortical WML (per SD increase)	-0.008	(-0.018; 0.003)	-0.003	(-0.019; 0.013)
Brain infarcts (yes vs. no)	-0.020	(-0.040; 0.000)	0.009	(-0.022; 0.040)
Subcortical atrophy (per SD increase)	-0.014	(-0.023; -0.005)	0.000	(-0.013; 0.014)
Cortical atrophy (per SD increase)	-0.030	(-0.040; -0.020)	0.007	(-0.009; 0.022)

Estimates are regression coefficients (95% confidence interval) for annual decline in z score. All models are controlled for age, sex, education, and the interaction of age with time.

interval 0.062 to 0.045), and in memory 0.024 points (95% confidence interval 0.012 to 0.037). Higher age was associated with a higher rate of cognitive decline. For each year increase in age, the annual rate of decline on the Cognitive Index increased with 0.004 points (95% confidence interval 0.003 to 0.005), and decline on the MMSE increased with 0.012 points (95% confidence interval 0.009 to 0.016). Age was also associated with decline in information processing speed and memory (table 2). Increasing severity of WML and generalized brain atrophy, and the presence of brain infarcts were associated with decline on the Cognitive Index (figure). Per standard deviation increase in periventricular WML severity the annual rate of decline on the MMSE increased with 0.035 points (95% confidence interval 0.003 to 0.066). Annual decline on the MMSE for people with brain infarcts was 0.085 points (95% confidence interval 0.02 to 0.15) larger than for people without brain infarcts on MRI. Other MRI measures were not associated with decline on the MMSE (data not shown). Periventricular WML, brain infarcts, and subcortical and cortical atrophy were associated with annual decline in information processing speed, but not with decline in memory (table 2). Additional adjustment for vascular risk factors or depressive symptoms did not change the estimates (data not shown). During follow-up 42 participants developed a stroke. After exclusion of participants with an incident stroke, the associations of periventricular WML and brain infarcts with change in information processing speed were no longer significant (regression coefficient per standard deviation increase in periventricular WML -0.007 (95% confidence interval -0.016 to 0.002), for presence of brain infarcts -0.006 (95% confidence interval -0.025 to 0.014)), whereas the associations of generalized brain atrophy with change in information processing speed remained (regression coefficient per standard deviation

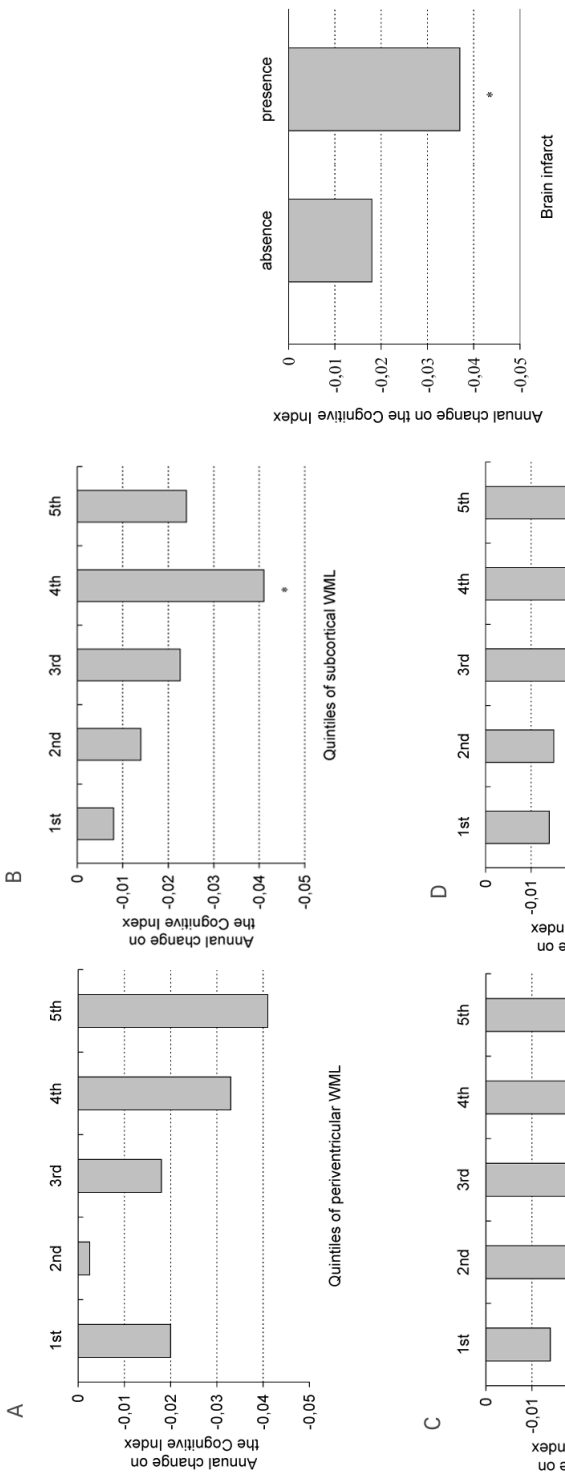


Figure. Relation between periventricular WML (A), subcortical WML (B), subcortical atrophy (C), and cortical atrophy (D) in quintiles, and rate of cognitive decline, expressed as mean change per year on the Cognitive Index, adjusted for age, sex, and level of education. Bars are standard errors.
* Significantly different from first quintile.

increase in subcortical atrophy -0.010 (95% confidence interval -0.019 to -0.002), and per standard deviation increase in cortical atrophy -0.023 (95% confidence interval -0.032 to -0.014)). When MRI measures were analyzed conditional on each other, the association with information processing speed remained significant for periventricular WML, subcortical atrophy, and cortical atrophy. The associations of periventricular WML, brain infarcts, subcortical and cortical atrophy with information processing speed attenuated, but remained significant after exclusion of participants who developed dementia (n=23) during follow-up. No statistically significant interactions were present between MRI measures and presence of the APOE ε4 allele, in relation to cognitive decline (data not shown).

Discussion

In this large population-based study, we found that periventricular WML, brain infarcts, and generalized brain atrophy on MRI, were associated with the rate of decline in cognitive function. These structural brain changes on MRI, which are thought to be caused by small vessel disease, were specifically associated with decline in information processing speed.

Several methodological issues should be addressed. This study was performed in a large number of elderly participants from the general population, who were nondemented at baseline, and followed for five years on average. The use of random-effects models in combination with the large sample size has lead to precise estimates. However, people who participated in this study were younger, more educated, had a higher MMSE score at baseline, and had less severe periventricular WML and cortical atrophy, compared to people who did not undergo a follow-up examination. This attrition is likely to have resulted in an underestimation of the association between structural brain changes on MRI and rate of cognitive decline. This should be taken into account when generalizing our results to the general population at large.

Previously, other population-based studies reported on the relationship between indicators of cerebral small vessel disease on MRI and cognitive decline. Garde and colleagues reported on the relationship between WML severity and decline in intelligence.[34] We previously reported on the association between WML and decline on the Mini-Mental State Examination,[35] and between silent brain infarcts and decline in cognitive function.[8] The Cardiovascular Health Study reported that subcortical brain atrophy was associated with cognitive decline, whereas brain infarcts, high WML grade, and high sulci width, were not.[36] They defined cognitive decline as a decline of five points or more on the Modified Mini-Mental State examination in three years, and used this as a dichotomous variable in the analyses. This will have reduced statistical power, and may explain the absence of a statistically significant relation with cerebral infarcts, WML, and sulci width. Furthermore, WML were analyzed as severe versus non severe, and no distinction was made between WML severity in the periventricular and subcortical region. Our observation that WML and

infarcts in particular affect speed of information processing is in line with previous findings from studies in nondemented older people relating WML and infarcts to cognitive function and decline.[15,37-39]

None of the structural MRI measures were associated with rate of decline in memory. Memory decline is a pivotal symptom in dementia, and is particularly related to medial temporal atrophy.[40] We previously reported that (silent) brain infarcts, periventricular WML, and subcortical brain atrophy increase the risk of dementia.[8] The present results suggest that WML, infarcts, and generalized brain atrophy contribute to dementia mainly by affecting non-memory related cognitive function. However, selective drop out of participants with memory decline should also be taken into account. Of the 832 people who participated in the present study, 23 (3%) developed dementia during follow-up, compared to 25 (10%) of the 245 people who did not participate.

Different pathophysiological mechanisms may underlie the associations of periventricular WML, cerebral infarcts, and generalized brain atrophy with cognitive decline, and more specific, decline in information processing speed. In our study, the vast majority (89%) of brain infarcts was lacunar, and were located in the basal ganglia and subcortical region.[41] Both lacunar infarcts and WML are thought to result from arteriolosclerosis. Occlusion of the arteriolar lumen leads to lacunar infarcts, while critical stenosis of multiple medullary arterioles leads to hypoperfusion and widespread incomplete infarction of the cerebral white matter.[3,42] Lacunar infarcts and WML are thought to interrupt prefrontal subcortical loops, which leads to impaired prefrontal lobe functioning, including impaired information processing speed.[42-44] We observed that adjustment for incident stroke attenuated the association of WML and brain infarcts on MRI with cognitive decline, which suggests that new infarcts play an intermediate role.[8] Furthermore, progression of WML may mediate the association between WML and cognitive decline, since WML severity is a strong predictor of WML progression.[45] Apart from having a direct effect on cognitive function, lacunes and WML may also be an indicator of AD encephalopathy. WML and lacunes are frequently found in patients with AD, and evidence suggests that these lesions interact with typical AD pathology, such as amyloid plaques and neurofibrillary tangles.[2] Generalized brain atrophy may result from both AD and cerebrovascular disease.[5,31] Neuronal loss in cortical associative areas, as well as cerebrovascular damage to white matter fiber tracts connecting these areas, may explain cognitive decline associated with generalized atrophy.

In conclusion, we showed that measures of cerebral small vessel disease on MRI in nondemented elderly people are associated with decline in cognitive function, and particularly affect information processing speed. Our results contribute to increasing evidence for an etiologic role of cerebral small vessel disease in cognitive dysfunction and dementia.

References

1. Roman GC. Stroke, cognitive decline and vascular dementia: the silent epidemic of the 21st century. Neuroepidemiology 2003; 22: 161-4.
2. Kalaria RN. Small vessel disease and Alzheimer's dementia: pathological considerations. Cerebrovasc Dis 2002; 13 Suppl 2:48-52.
3. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke 1997; 28:652-9.
4. Lammie GA. Pathology of small vessel stroke. Br Med Bull 2000; 56:296-306.
5. Fox NC, Scahill RI, Crum WR, Rossor MN. Correlation between rates of brain atrophy and cognitive decline in AD. Neurology 1999; 52:1687-9.
6. Scahill RI, Schott JM, Stevens JM, Rossor MN, Fox NC. Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. Proc Natl Acad Sci U S A 2002; 99:4703-7.
7. Walters RJ, Fox NC, Schott JM, et al. Transient ischaemic attacks are associated with increased rates of global cerebral atrophy. J Neurol Neurosurg Psychiatry 2003; 74:213-6.
8. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003; 348: 1215-22.
9. Kuller LH, Lopez OL, Newman A, et al. Risk factors for dementia in the cardiovascular Health Cognition Study. Neuroepidemiology 2003; 22:13-22.
10. Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB. The preclinical phase of alzheimer disease: A 22-year prospective study of the Framingham Cohort. Arch Neurol 2000; 57:808-13.
11. Masur DM, Sliwinski M, Lipton RB, Blau AD, Crystal HA. Neuropsychological prediction of dementia and the absence of dementia in healthy elderly persons. Neurology 1994; 44: 1427-32.
12. Fabrigoule C, Rouch I, Taberly A, et al. Cognitive process in preclinical phase of dementia. Brain 1998; 121 (Pt 1):135-41.
13. Rubin EH, Storandt M, Miller JP, et al. A prospective study of cognitive function and onset of dementia in cognitively healthy elders. Arch Neurol 1998; 55:395-401.
14. Wolfe N, Linn R, Babikian VL, Knoefel JE, Albert ML. Frontal systems impairment following multiple lacunar infarcts. Arch Neurol 1990; 47:129-32.
15. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. Ann Neurol 2000; 47:145-51.
16. de Leeuw FE, de Groot JC, Achten E, et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001; 70:9-14.
17. de Groot JC, de Leeuw FE, Oudkerk M, Hofman A, Jolles J, Breteler MM. Cerebral white matter lesions and subjective cognitive dysfunction: the Rotterdam Scan Study. Neurology 2001; 56:1539-45.
18. den Heijer T, Oudkerk M, Launer LJ, Van Duijn CM, Hofman A, Breteler MM. Hippocampal, amygdalar, and global brain atrophy in different apolipoprotein E genotypes. Neurology 2002; 59:746-8.
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189-98.
20. Golden CJ. Identification of brain disorders by the Stroop Color and Word Test. J Clin Psychol 1976; 32:654-8.
21. Houx PJ, Jolles J, Vreeling FW. Stroop interference: aging effects assessed with the Stroop Color-Word Test. Exp Aging Res 1993; 19:209-24.
22. Lezak MD. Neuropsychological assessment. New York: Oxford University Press, 1995: xviii, 1026.
23. Jolles J, Houx PJ, van Boxtel MPJ, Ponds

RWHM. The Maastricht Aging Study: Determinants of cognitive aging. Maastricht: Neuropsych Publishers, 1995.

24. Welsh KA, Butters N, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. Neurology 1994; 44:609-14.
25. Brand N, Jolles J. Learning and retrieval rate of words presented auditorily and visually. J Gen Psychol 1985; 112:201-10.
26. Copeland JR, Kelleher MJ, Kellett JM, et al. A semi-structured clinical interview for the assessment of diagnosis and mental state in the elderly: the Geriatric Mental State Schedule. I. Development and reliability. Psychol Med 1976; 6:439-49.
27. Roth M, Tym E, Mountjoy CQ, et al. CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. Br J Psychiatry 1986; 149:698-709.
28. UNESCO. International Standard Classification of Education (ISCED). Paris: UNESCO, 1976.
29. Radloff L. The CES-D Scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977; 1:385-401.
30. Wenham PR, Price WH, Blandell G. Apolipoprotein E genotyping by one-stage PCR. Lancet 1991; 337:1158-9.
31. Mungas D, Reed BR, Jagust WJ, et al. Volumetric MRI predicts rate of cognitive decline related to AD and cerebrovascular disease. Neurology 2002; 59:867-73.
32. Beckett L. Analysis of longitudinal data. In: Gorelick PB, Attes M, eds. Handbook of neuroepidemiology. New York: Marcel Dekker, Inc, 1994:31-62.
33. Diggle PJ, K-Y L, Zeger SL. Analysis of longitudinal data. Oxford: Clarendon Press, 1994.
34. Garde E, Mortensen EL, Krabbe K, Rostrup E, Larsson HB. Relation between age-related decline in intelligence and cerebral white-matter hyperintensities in healthy octogenarians: a longitudinal study. Lancet 2000; 356:628-34.
35. De Groot JC, De Leeuw FE, Oudkerk M, et al. Periventricular cerebral white matter lesions predict rate of cognitive decline. Ann Neurol 2002; 52:335-41.
36. Kuller LH, Shemanski L, Manolio T, et al. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. Stroke 1998; 29:388-98.
37. Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Carmelli D. Biobehavioral characteristics of nondemented older adults with subclinical brain atrophy. Neurology 2000; 54:2108-14.
38. O'Brien JT, Wiseman R, Burton EJ, et al. Cognitive associations of subcortical white matter lesions in older people. Ann N Y Acad Sci 2002; 977:436-44.
39. Vataja R, Pohjasvaara T, Mantyla R, et al. MRI correlates of executive dysfunction in patients with ischaemic stroke. Eur J Neurol 2003; 10:625-31.
40. Mungas D, Jagust WJ, Reed BR, et al. MRI predictors of cognition in subcortical ischemic vascular disease and Alzheimer's disease. Neurology 2001; 57:2229-35.
41. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population- based rotterdam scan study. Stroke 2002; 33:21-5.
42. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. Lancet Neurol 2002; 1:426-36.
43. Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. J Psychosom Res 2002; 53: 647-54.
44. Cummings JL. Frontal-subcortical circuits and human behavior. J Psychosom Res 1998; 44:627-8.
45. Schmidt R, Enzinger C, Ropele S, Schmidt H, Fazekas F. Progression of cerebral white matter lesions: 6-year results of the Austrian Stroke Prevention Study. Lancet 2003; 361: 2046-8.

2.2

Silent brain infarcts and the risk of dementia and cognitive decline

Abstract

Background – Silent brain infarcts are frequently seen on magnetic resonance imaging (MRI) in healthy elderly people and may be associated with dementia and cognitive decline.

Methods – We studied the association between silent brain infarcts and the risk of dementia and cognitive decline in 1015 participants of the prospective, population-based Rotterdam Scan Study, who were 60 to 90 years of age and free of dementia and stroke at baseline. Participants underwent neuropsychological testing and cerebral MRI at baseline in 1995 to 1996 and again in 1999 to 2000 and were monitored for dementia throughout the study period. We performed Cox proportional-hazards and multiple linear-regression analyses, adjusted for age, sex, and level of education and for the presence or absence of subcortical atrophy and white matter lesions.

Results – During 3697 person-years of follow-up (mean per person, 3.6 years), dementia developed in 30 of the 1015 participants. The presence of silent brain infarcts at baseline more than doubled the risk of dementia (hazard ratio, 2.26; 95 percent confidence interval, 1.09 to 4.70). The presence of silent brain infarcts on the baseline MRI was associated with worse performance on neuropsychological tests and a steeper decline in global cognitive function. Silent thalamic infarcts were associated with a decline in memory performance, and nonthalamic infarcts with a decline in psychomotor speed. When participants with silent brain infarcts at baseline were subdivided into those with and those without additional infarcts at follow-up, the decline in cognitive function was restricted to those with additional silent infarcts.

Conclusions – Elderly people with silent brain infarcts have an increased risk of dementia and a steeper decline in cognitive function than those without such lesions.

Introduction

Dementia is a major health problem in Western countries. Dementia will develop in one in four 55-year-olds,[1] and the number of patients with dementia will rise as life expectancy increases. Evidence has accumulated that vascular abnormalities have a role in the development of dementia. Patients with stroke are at increased risk for both vascular dementia and Alzheimer's disease.[2-4] People who were found at autopsy to have lacunar cerebral infarcts were more likely to have had dementia than those without infarcts, and fewer pathological findings of Alzheimer's disease were needed in persons with such infarcts for clinical symptoms of dementia to be present.[5,6] Patients with Alzheimer's disease more frequently have asymptomatic (i.e., silent) brain infarcts on magnetic resonance imaging (MRI) than do control subjects without dementia.[7,8] The prevalence of silent brain infarcts is also high in elderly populations without dementia,[9-11] but little is known about their prognostic relevance. We therefore examined the relation between silent brain infarcts and the risk of dementia and cognitive decline in the general population.

Methods

Participants

The Rotterdam Scan Study is a prospective, population-based cohort study designed to study the causes and consequences of brain changes in the elderly.[12] In 1995 to 1996, we randomly selected 1717 participants 60 to 90 years of age, with stratification according to age (in five-year groups) and sex, from two ongoing population-based studies.[13,14] A total of 1077 elderly people without dementia participated (63 percent). Participants were significantly younger and more highly educated and performed better on the Mini–Mental State Examination than nonparticipants.[15] The medical ethics committee of the Erasmus Medical Center approved the study, and each participant gave written informed consent.

The baseline examination in 1995 to 1996 comprised a structured interview, physical examination, blood sampling, and neuropsychological tests at the research center, as well as a cerebral MRI scan. For the present study we excluded 62 participants with a history of stroke before the baseline evaluation (Fig. 1).[16] We monitored all 1015 participants throughout the study by reviewing medical records from their general practitioners after baseline for death and major complications, including cognitive problems, dementia, stroke, and transient ischemic attack. In 1999 to 2000, we reinvited 914 of the 1015 participants for a second examination, of whom 739 participated (81 percent) (Fig. 1). The remaining 101 participants were not reinvited, for the following reasons: 75 had died, 15 had been institutionalized for dementia, 7 had already been examined in 1999 as part of the regular examination for the Rotterdam Study,[14] 3 had moved abroad, and 1 could not be reached.

People who were ineligible or who declined to undergo the second examination were

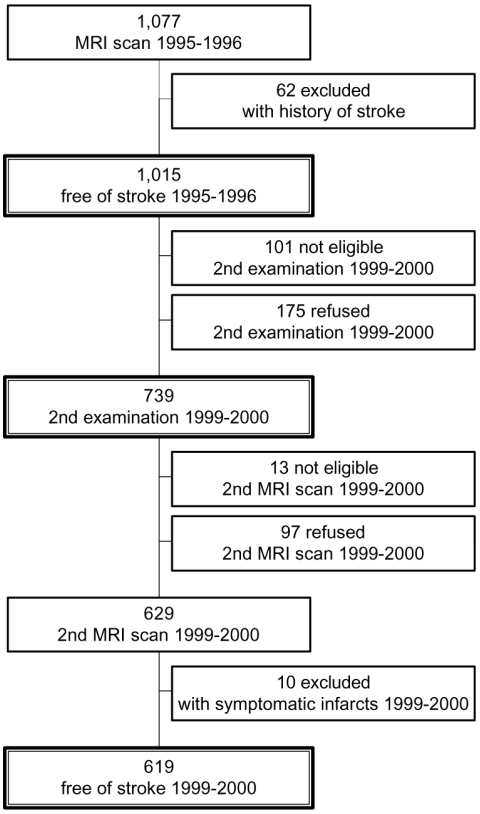


Figure 1. **Flow diagram of the study population.** The various study samples are indicated by double-lined boxes. MRI denotes magnetic resonance imaging.

significantly older, were less highly educated, and performed worse on the neuropsychological tests at baseline than participants in the second examination. People who declined to undergo the second examination did not differ significantly from those who participated with respect to the presence or absence of silent brain infarcts at baseline, whereas ineligible participants had a nonsignificantly higher prevalence of silent brain infarcts than participants (absolute age- and sex-adjusted difference, 5 percent; 95 percent confidence interval, -3 to 14 percent). Thirteen of the 739 participants were ineligible to undergo a second MRI of the brain because of a contraindication to MRI, and 97 declined to undergo the procedure. In total, 629 of the 901 eligible participants (70 percent) underwent a second MRI in 1999 to 2000.

Cerebral infarcts and other MRI measures

All 1015 participants underwent MRI of the brain at baseline in 1995 to 1996. We made axial T1-weighted, T2-weighted, and proton-density-weighted scans on 1.5-Tesla MRI scanners (MR Gyroscan, Philips, or MR VISION, Siemens).[11] In 1999 to 2000, 629 participants underwent a second MRI with use of the MR VISION scanner and the same sequences.

The presence of brain infarcts was rated similarly at baseline and follow-up. We defined brain infarcts as areas of focal hyperintensity on T2-weighted images that were at least 3 mm in diameter. Proton-density scans were used to distinguish infarcts from dilated perivascular spaces. Areas of hyperintensity in the white matter also had to have corresponding prominent hypointensity on T1-weighted images, in order to distinguish them from cerebral white matter lesions. A single trained physician who was unaware of the patients' history of stroke and transient ischemic attack scored infarcts on both the baseline and second MRI with respect to their location and size. An intrarater study for detecting infarcts (110 images randomly selected from both scanners) showed good agreement (κ=0.80).

We obtained information on any history of stroke and transient ischemic attack from the participants themselves and by checking medical records of all participants, independently of their MRI results. An experienced neurologist subsequently reviewed the participants' medical history and scans and categorized infarcts as silent or symptomatic. We defined silent brain infarcts as evidence on MRI of one or more infarcts, without a history of a (corresponding) stroke or transient ischemic attack. If a prior stroke or transient ischemic attack did correspond with a lesion, the latter was defined as a symptomatic infarct. The intrarater reliability for the classification of infarcts as silent or symptomatic was excellent (κ=1.0). If participants had both symptomatic and silent infarcts, they were included in the group with symptomatic infarcts.

White matter lesions and subcortical atrophy of the brain were rated on the baseline MRI scans.[12] White matter lesions were considered present if they were hyperintense on proton-density and T2-weighted images, without prominent hypointensity on T1-weighted scans. The severity of periventricular white matter lesions was determined by adding three region-specific scores (grades ranged from 0 to 9, with higher grades indicating greater severity). The volume of subcortical white matter lesions was approximated on the basis of the number and size of lesions (volume range, 0 to 29.5 ml). The severity of subcortical atrophy of the brain was estimated by calculating the ratio of ventricle to brain (the average of assessments at the frontal and occipital horns and the caudate nucleus) on T1-weighted images.[17] Both intrareader and interreader studies (100 of each) showed good-to-excellent agreement.[12]

Dementia

All participants were free of dementia at baseline. We screened all participants for dementia at follow-up using the Mini–Mental State Examination and the Geriatric Mental State Schedule.[1] Participants who were positive at screening underwent additional cognitive testing with the Cambridge Mental Disorders of the Elderly Examination. People who were then thought to have dementia were examined by a neurologist and underwent extensive neuropsychological testing. In addition, we continually monitored the medical records of all participants at their general practitioners' offices and the Regional Institute for Ambulatory Mental Health Care to obtain information on newly diagnosed dementia until March 1, 2000. Dementia and its subtypes were diagnosed by a panel that reviewed all available information according to standardized criteria.[18-20] The onset of dementia was defined as the date on which the clinical symptoms allowed the diagnosis of dementia to be made. We had complete follow-up data for dementia on all participants through our system of monitoring general practitioners.

Cognitive decline

Participants underwent the following neuropsychological tests at the baseline examination: the Mini Mental State Examination, the 15-word verballearning test, the Stroop test, the Pa-

per-and-Pencil Memory Scanning Task, and the Letter–Digit Substitution Task.[15] We used alternative versions of the same neuropsychological tests at the second examination. For each participant, we calculated z scores (individual test score minus mean test score divided by the standard deviation) for the neuropsychological tests at baseline and at follow-up using the mean and standard deviation of the baseline tests. We constructed compound scores for memory performance by averaging the z scores of the total of three immediate recall trials and the delayed-recall trial of the 15-word verbal-learning test. The compound score for psychomotor speed was the average of the z scores for the reading subtask of the Stroop test, the one-letter subtask of the Paper-and-Pencil Memory Scanning Task, and the Letter–Digit Substitution Task. The compound score for global cognitive function was constructed by calculating the average of the z scores for all the above tests.[15] Cognitive decline was calculated by subtracting the z scores for memory performance, psychomotor speed, and global cognitive function at baseline from the z scores at follow-up.

Statistical analysis

First, we used Cox proportional-hazards regression analysis to examine the relation between the presence of silent brain infarcts at baseline and the risk of subsequent dementia in the 1015 participants who were free of dementia and stroke at baseline. The duration of follow-up was calculated from the date of the MRI at baseline until death, the diagnosis of dementia, or the end of follow-up, whichever came first. We also investigated the association of white matter lesions and subcortical atrophy of the brain with dementia and whether these structural changes in the brain affected the relation between silent brain infarcts and dementia. Second, we estimated the association between the presence of silent brain infarcts at baseline and subsequent cognitive decline by multiple linear-regression analysis in the subsample of 739 participants who underwent neuropsychological tests at follow-up. We also investigated whether this relation with cognitive decline differed between silent infarcts in the thalamus and infarcts elsewhere, because thalamic nuclei are involved in storage and short-term memory.[21,22] Third, we examined the contribution of newly detected silent infarcts to the rate of cognitive decline. This analysis was based on 619 participants without symptomatic infarcts on the second MRI (Fig. 1).

We adjusted all analyses for age, sex, and level of education. In the analyses of cognitive decline, we also adjusted for the interval between the two sets of neuropsychological tests.

Results

During 3697 person-years of follow-up (mean per person, 3.6 years), dementia developed in 30 participants (3 percent), 26 of whom had Alzheimer's disease (1 with cerebrovascular disease), 2 vascular dementia, and 1 multisystem atrophy; in 1, the subtype was unknown. Four patients with dementia died, but no autopsy was performed.

Table 1. **Baseline characteristics of all participants who were free of dementia and stroke in 1995 to 1996, those who underwent the second neuropsychological examination, and those who underwent the second MRI scan in 1999 to 2000.***

Characteristic	All participants (N = 1015)	Participants who underwent 2nd examination (N = 739	Participants who underwent 2nd MRI (N = 619)
Age — yr	72.1 ± 7.4	70.9 ± 7.0	70.7 ± 7.0
Women — no. (%)	526 (52)	390 (53)	320 (52)
Primary education only — no. (%)	357 (35)	235 (32)	191 (31)
MMSE score†	27.4 ± 2.2	27.6 ± 2.1	27.6 ± 2.0
Hypertension — no. (%)	517 (51)	357 (48)	291 (47)
Diabetes mellitus — no. (%)	66 (7)	42 (6)	33 (5)
Use of aspirin — no. (%)	109 (11)	71 (10)	49 (8)
Use of oral anticoagulants — no. (%)	41 (4)	24 (3)	20 (3)
APOE e4 carriers — no. (%)‡	267 (29)	206 (30)	171 (30)
Silent brain infarcts — no. (%)	217 (21)	148 (20)	116 (19)
Thalamic	32 (3)	20 (3)	14 (2)
Nonthalamic	185 (18)	128 (17)	102 (16)
White-matter lesions			
Periventricular — grade	2.3 ± 2.2	2.1 ± 2.1	2.0 ± 2.1
Subcortical — ml	1.3 ± 2.8	1.1 ± 2.4	1.1 ± 2.5
Ratio of subcortical brain atrophy	0.32 ± 0.04	0.31 ± 0.04	0.31 ± 0.04

* Plus–minus values are unadjusted means ± SD. MRI denotes magnetic resonance imaging.
† The score on the Mini–Mental State Examination (MMSE) can range from 0 to 30, with higher scores indicating better cognitive function.
‡ The apolipoprotein E (APOE) genotype was not determined in 97 of the 1015 participants, 63 of the 739 who underwent the second examination, and 55 of the 619 who underwent the second MRI.

Table 1 shows the baseline characteristics of the participants. Eleven of the 217 participants with silent brain infarcts at baseline had cortical infarcts, 202 had lacunar infarcts – 171 in the basal ganglia and 31 in the subcortex – and 4 had infarcts in the cerebellum or brainstem. Fourteen of the 30 participants in whom dementia developed had one or more silent brain infarcts present on the baseline MRI, 7 of whom had multiple infarcts.

The presence of silent brain infarcts at baseline more than doubled the risk of dementia, and this result remained largely unchanged after adjustment for the severity of white matter lesions and subcortical atrophy (Table 2). A greater severity of periventricular white mat-

Table 2. **Relation between the presence of silent brain infarcts at baseline, the severity of periventricular and subcortical white matter lesions, and the risk of dementia.**

Variable	Hazard ratio (95% confidence interval)	
	Adjusted for age, sex, and level of education	Adjusted for age, sex, level of education, and MRI measures*
Silent brain infarcts (yes vs. no)	2.26 (1.09–4.70)	2.03 (0.91–4.55)
Severity of periventricular white matter lesions (per SD increase)	1.59 (1.13–2.25)	1.47 (0.92–2.35)
Severity of subcortical white matter lesions (per SD increase)	1.21 (0.96–1.53)	0.92 (0.65–1.29)

* The magnetic resonance imaging (MRI) measures adjusted for were presence or absence of silent brain infarcts, severity of periventricular and subcortical white matter lesions, and severity of subcortical brain atrophy.

ter lesions was also associated with an increased risk of dementia (Table 2), as was greater severity of subcortical atrophy of the brain hazard ratio per increase of 1 SD in severity, 1.78; 95 percent confidence interval, 1.26 to 2.51).

There was no significant difference in risk between participants with Mini–Mental State Examination scores below 26 and those with a score of 26 or above at baseline or between carriers of the apolipoprotein E $\varepsilon 4$ allele and noncarriers. The exclusion of participants who used aspirin or oral anticoagulants at baseline did not materially change the results. Nineteen of the 30 participants in whom dementia developed underwent a second cerebral MRI or computed tomographic scan; a symptomatic infarct was found in 3 (16 percent) and a new silent brain infarct was found in 4 (21 percent). This rate was higher than that among the 618 participants without dementia at follow-up, of whom 8 (1 percent) had a symptomatic brain infarct and 71 (11 percent) a silent brain infarct on the second MRI scan.

Global cognitive function was significantly worse in participants with silent brain infarcts on the baseline MRI than in those without such infarcts (adjusted mean difference in z score, -0.11; 95 percent confidence interval, -0.20 to -0.01). The presence of silent brain infarcts at baseline was associated with a steeper decline in cognitive function (Table 3). The presence of multiple silent infarcts showed a stronger relation with cognitive decline than the presence of single silent infarcts (adjusted mean difference in z score for multiple infarcts, -0.34; 95 percent confidence interval, -0.51 to -0.17; and for single infarcts, -0.07; 95 percent confidence interval, -0.20 to 0.06). Silent infarcts in the thalamus were associated with a greater decline in memory performance, whereas infarcts located elsewhere resulted in a greater decline in psychomotor speed (Table 3). There was no association between the presence of silent brain infarcts at baseline and a decline in the Mini–Mental State Examina-

Table 3. **Association between the presence of silent brain infarcts on magnetic resonance imaging in 1995–1996 and subsequent cognitive decline.***

Variable	Silent brain infarcts		
	All	Thalamic	Nonthalamic
	decline in z score (95% CI)		
Memory performance	-0.01 (-0.16 to 0.15)	-0.50 (-0.87 to -0.13)	0.06 (-0.10 to 0.23)
Psychomotor speed	-0.19 (-0.34 to -0.04)	-0.11 (-0.36 to 0.13)	-0.20 (-0.36 to -0.05)
Global cognitive function	-0.15 (-0.27 to -0.02)	-0.28 (-0.50 to -0.06)	-0.13 (-0.26 to 0.001)

* Values are the mean differences in the z scores between follow-up and baseline, with 95 percent confidence intervals (CIs) between those with and those without silent brain infarcts, adjusted for age, sex, level of education, and interval between neuropsychological tests. A positive value indicates an increase in the z score.

tion score (adjusted mean difference in the score, -.01; 95 percent confidence interval, -0.44 to 0.33).

When participants were subdivided into four groups according to the presence or absence of silent brain infarcts on the baseline and follow-up MRI, the decline in cognitive function was restricted to those with new silent brain infarcts on the follow-up scan, regardless of whether they had silent infarcts at baseline (Fig. 2). Memory performance improved for all participants, as expected owing to the learning effect. There were no significant changes in scores on the Mini–Mental State Examination among the various groups.

Discussion

We found that the presence of silent brain infarcts on MRI at baseline in the general population doubled the risk of dementia. People with silent infarcts had a steeper decline in cognitive function than those without silent infarcts, but this decline was confined to people who had additional silent brain infarcts after baseline.

The strengths of this study are the large number of elderly participants and its population-based design. Furthermore, we had no losses to follow-up for the analyses of dementia. Notwithstanding good-to-excellent intrareader agreement, we still may have incorrectly identified brain infarcts or misclassified infarcts as silent or symptomatic. However, because silent brain infarcts were identified and classified in a blinded fashion from data on dementia and neuropsychological tests, any misclassification would have resulted in an underestimation of the associations.

The dementia diagnoses in our study were clinical diagnoses. We intentionally refrained

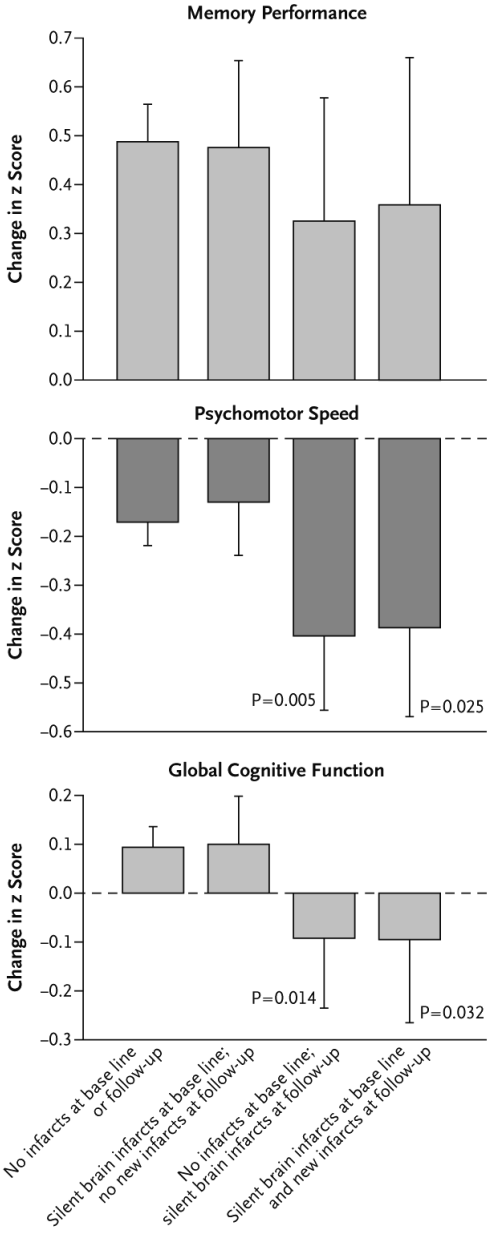


Figure 2. **Mean change in memory performance, psychomotor speed, and global cognitive function among participants with and those without silent brain infarcts on magnetic resonance imaging at baseline (1995 to 1996) and at follow-up (1999 to 2000), after adjustment for age, sex, level of education, and interval between neuropsychological tests.**
Bars are 95 percent confidence intervals. P values are for the comparison with participants who did not have infarcts at baseline or follow-up.

from analyzing subtypes of dementia, because a distinction based on clinical information is hard to make, especially in elderly people, in whom dementia often is a heterogeneous disorder. There is increasing evidence that vascular factors may contribute to the development of Alzheimer's disease.[23,24] After a stroke, dementia, including Alzheimer's disease, develops in approximately 30 percent of patients with symptomatic infarcts.[2-4] We found that silent brain infarcts increase the risk of dementia, the majority of cases of which in our study were of the Alzheimer's subtype. Furthermore, we showed that a greater severity of periventricular white matter lesions, also thought to result from small vessel disease, was associated with an increased risk of dementia.

Our findings of a large number of new infarcts in the participants in whom dementia developed and a steeper decline in cognition in those with a new infarct support the notion that people with silent brain infarcts are at high risk for additional infarcts, both silent and symptomatic,[25] which may contribute to dementia. Perhaps an infarct in a brain already affected by Alzheimer's disease–related abnormalities further impairs cognition, leading to clinically evident dementia. This notion is supported by autopsy findings showing that fewer plaques and

tangles led to clinical Alzheimer's disease in the presence of lacunar infarcts.[5] Alternatively, silent brain infarcts may trigger the development of senile plaques and neurofibrillary tangles or reflect cerebral vulnerability or a certain vascular risk profile that enhances the abnormalities associated with Alzheimer's disease. However, several clinicopathological studies found that patients with Alzheimer's disease who had infarcts had a similar amount of plaques and tangles or even fewer than those without infarcts.[26-29]

We found that silent brain infarcts – those without relevant stroke symptoms – are associated with worse cognition, confirming the results of a cross-sectional study.[9] Recently, we reported that the presence of periventricular white matter lesions is associated with a steeper cognitive decline,[30] and we have now found that this is also true for silent brain infarcts. That the relation between infarcts and cognitive decline was stronger for multiple infarcts than for single infarcts strengthens these findings. Furthermore, we found that this decline in cognitive function was confined to persons with incident silent infarcts, which may suggest a stepwise decline after an infarct occurs.

The reason that we found no relation between a decline in the score on the Mini–Mental State Examination and the presence of silent brain infarcts is probably that this test, although useful as a screening tool for dementia, is not a very sensitive means of detecting subtle changes in cognitive function. The Cardiovascular Health Study did find an association between evidence of infarcts on MRI and a decline in a modified Mini–Mental State Examination score, which comprised 100 rather than 30 questions and examined a broader range of cognitive function.[31] Furthermore, we found that the decline in different cognitive domains varied with the location of silent brain infarcts on MRI. Strategic infarcts in the thalamus, which is involved in storage and short-term memory,[21,22] were associated with a worse performance in memory tasks.

Our finding that in both participants with and those without silent brain infarcts memory performance improved at the second examination may be explained by a learning effect.[32] This learning effect does not seem to have a major role in tests specific for psychomotor speed. The presence of silent infarcts that were not in the thalamus resulted in a decline in psychomotor speed. These infarcts probably interrupt various connecting fibers in the white matter that are involved in these psychomotor tasks.

In conclusion, the presence of silent brain infarcts on MRI identifies persons at increased risk for dementia, probably because these people continue to have additional brain infarcts, both silent and symptomatic, that decrease their cognitive function.

References

1. Ott A, Breteler MMB, van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia: the Rotterdam Study. Am J Epidemiol 1998;147:574-80.
2. Pohjasvaara T, Erkinjuntti T, Ylikoski R, Hietanen M, Vataja R, Kaste M. Clinical determinants of poststroke dementia. Stroke 1998;29:75-81.

3. Desmond DW, Moroney JT, Paik MC, et al. Frequency and clinical determinants of dementia after ischemic stroke. Neurology 2000;54:1124-31.
4. Hénon H, Durieu I, Guerouaou D, Lebert F, Pasquier F, Leys D. Poststroke dementia: incidence and relationship to prestroke cognitive decline. Neurology 2001;57:1216- 22.
5. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer's disease: the Nun Study. JAMA 1997;277:813-7.
6. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet 2001;357:169-75.
7. Skoog I, Nilsson L, Palmertz B, Andreasson L-A, Svanborg A. A population-based study of dementia in 85-year-olds. N Engl J Med 1993;328:153-8.
8. Barber R, Scheltens P, Gholkar A, et al. White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. J Neurol Neurosurg Psychiatry 1999;67:66-72.
9. Longstreth WT Jr, Bernick C, Manolio TA, Bryan N, Jungreis CA, Price TR. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. Arch Neurol 1998;55: 1217-25.
10. Howard G, Wagenknecht LE, Cai J, Cooper L, Kraut MA, Toole JF. Cigarette smoking and other risk factors for silent cerebral infarction in the general population. Stroke 1998;29:913-7.
11. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MMB. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke 2002;33:21-5.
12. de Leeuw FE, de Groot JC, Achten E, et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study: the Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001;70:9-14.
13. Hofman A, van Laar A, Klein F, Valkenburg HA. Coffee and cholesterol. N Engl J Med 1983;309:1248-9.
14. Hofman A, Ott A, Breteler MM, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet 1997;349: 151-4.
15. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. Ann Neurol 2000;47:145-51.
16. Vermeer SE, van Dijk EJ, Koudstaal PJ, et al. Homocysteine, silent brain infarcts, and white matter lesions: the Rotterdam Scan Study. Ann Neurol 2002;51:285-9.
17. den Heijer T, Oudkerk M, Launer LJ, van Duijn CM, Hofman A, Breteler MMB. Hippocampal, amygdalar, and global brain atrophy in different apolipoprotein E genotypes. Neurology 2002;59:746-8.
18. Diagnostic and statistical manual of mental disorders, 3rd ed. rev.: DSM-III-R. Washington, D.C.: American Psychiatric Association, 1987.
19. McKahnn G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939-44.
20. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDSAIREN International Workshop. Neurology 1993;43: 250-60.
21. Bogousslavsky J, Regli F, Uske A. Thalamic infarcts: clinical syndromes, etiology, and prognosis. Neurology 1988;38:837-48. [Erratum, Neurology 1988;38:1335.]
22. Tatemichi TK, Steinke W, Duncan C, et al.

Paramedian thalamopeduncular infarction: clinical syndromes and magnetic resonance imaging. Ann Neurol 1992;32:162-71.

23. Sparks DL, Scheff SW, Liu H, Landers TM, Coyne CM, Hunsaker JC III. Increased incidence of neurofibrillary tangles (NFT) in non-demented individuals with hypertension. J Neurol Sci 1995;131:162-9
24. Breteler MMB. Vascular risk factors for Alzheimer's disease: an epidemiologic perspective Neurobiol Aging 2000;21:153-60
25. Bernick C, Kuller L, Dulberg C, et al. Silent MRI infarcts and the risk of future stroke: the Cardiovascular Health Study Neurology 2001;57:1222-9
26. Heyman A, Fillenbaum GG, Welsh-Bohmer KA, et al. Cerebral infarcts in patients with autopsy-proven Alzheimer's disease: CERAD, part XVIII. Neurology 1998; 51:159-62. [Erratum, Neurology 1998;51: 1809.]
27. Berg L, McKeel DW Jr, Miller JP, et al. Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease: relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. Arch Neurol 1998;55:326-35
28. Petrovitch H, White LR, Izmirilian G, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS: Honolulu-Asia aging Study. Neurobiol Aging 2000;21:57- 62
29. de la Monte SM, Lu BX, Sohn YK, et al. Aberrant expression of nitric oxide synthase III in Alzheimer's disease: relevance to cerebral vasculopathy and neurodegeneration. Neurobiol Aging 2000;21:309-19
30. de Groot JC, de Leeuw FE, Oudkerk M, et al. Periventricular cerebral white matter lesions predict rate of cognitive decline. Ann Neurol 2002;52:335-41
31. Kuller LH, Shemanski L, Manolio T, et al. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. Stroke 1998;29:388- 98
32. Small SA, Stern Y, Tang M, Mayeux R. Selective decline in memory function among healthy elderly. Neurology 1999;52:1392-6

2.3

Cerebral white matter lesions and the risk of dementia

Abstract

Objective – To study the association between white matter lesions (WML) in specific locations and the risk of dementia.
Design – The Rotterdam Scan Study, a prospective population-based cohort study. We scored periventricular and subcortical WML on MRI, and followed participants until January 2002 for incident dementia.
Setting – General population.
Participants – 1,077 elderly people aged 60 to 90 years, who were non-demented at base line.
Main outcome measure – Incident dementia by DSM III-R criteria.
Results – During a mean follow-up of 5.2 years, 45 participants developed dementia. Higher severity of periventricular WML increased the risk of dementia, whereas the association between subcortical WML and dementia less prominent. The adjusted hazard ratio of dementia for each standard deviation increase in periventricular WML severity was 1.67 (95% CI 1.25 - 2.24). This increased risk was independent of other risk factors for dementia and partly independent of other structural brain changes on MRI.
Conclusions – WML, especially in the periventricular region, increase the risk of dementia in elderly people.

Introduction

Cerebral white matter lesions (WML) in elderly people are thought to result from small-vessel disease, and are considered to be a risk factor for dementia.[1] Evidence relating WML to dementia is mainly derived from studies in stroke patients and from cross-sectional studies in patients with dementia. WML increase the risk of post-stroke dementia, and together with lacunar infarcts, WML are considered the primary type of brain lesions in subcortical ischemic vascular dementia.[1,2] Small-vessel disease may also contribute to the development of Alzheimer's disease (AD), since patients with AD were found to have more WML than controls.[3]

WML are also frequently seen on MRI of non-demented elderly, but only few studies investigated the extent to which WML increase the risk of dementia in the general population.[4,5] We investigated the risk of dementia for WML in specific locations in the Rotterdam Scan Study. Furthermore, we assessed whether the association between WML and dementia is independent of other risk factors for dementia and other structural brain changes on MRI.

Methods

Study population

The Rotterdam Scan Study is a prospective, population based cohort study, designed to study causes and consequences of age-related brain changes in the elderly. The characteristics of the 1077 participants have been described previously.[6] All participants were free of dementia at base line.[5] Base line examination in 1995 to 1996 comprised a structured interview, neuropsychological tests, physical examination, blood sampling, and all participants underwent an MRI scan of the brain. In 1999 to 2000, 787 of the 973 participants who were alive and eligible were re-examined at the research center similar to the baseline examination (response 81%). All participants were continually monitored for mortality, dementia and stroke until January 1st 2002.

MRI procedure

Details of the MRI examinations in the Rotterdam Scan Study have been published.[6] We considered WML to be in the periventricular region if they were directly adjacent to the ventricle; otherwise we considered them subcortical. Periventricular WML were scored semiquantitatively for locations at the frontal and occipital horns, and the lateral walls of the ventricles, in order to obtain a total periventricular score (range: 0 to 9). For subcortical WML, a total volume as appearing on hardcopy was approximated, based on number and size of lesions in the frontal, parietal, temporal and occipital lobes (range: 0 to 29.5 ml).[6] We rated cortical atrophy on a semiquantitive scale (range 0 to 15), and assessed subcortical

atrophy by the ventricle-to-brain ratio (range: 0.21 to 0.45). Cerebral infarcts were defined as focal hyperintensities on T2-weighted images, 3 mm in size or larger, and with a corresponding prominent hypointensity on T1-weighted images if located in the white matter.[5]

Ascertainment of incident dementia

Participants with dementia were carefully excluded at base line.[5] We screened all participants for dementia at follow-up with the Mini-Mental State Examination (MMSE)[7] and the Geriatric Mental State Schedule[8] Screen positives were subsequently evaluated using the Cambridge Mental Disorders of the Elderly Examination (CAMDEX).[9] Participants who were then thought to have dementia were examined by a neurologist, and underwent extensive neuropsychological testing. In addition, we continually monitored the medical records of all participants at their general practitioners' office, and at the Regional Institute for Outpatient Mental Health Care (RIAGG) to obtain information on newly diagnosed dementia until January 1st 2002.[5] A panel that reviewed all available information diagnosed dementia and its subtypes according to standardized criteria.[10,11,12] We defined the onset of dementia as the date on which the clinical symptoms first allowed the diagnosis of dementia to be made.

Other baseline measurements

The following variables assessed at baseline were used as possible confounders: age, sex, educational status,[13] hypertension, diabetes mellitus, smoking, APOE genotype,[14] history of stroke and incident stroke.[5]

Data analysis

We assessed the association between WML and measures of generalized brain atrophy with Pearson's correlation coefficient, and the association between WML and presence of cerebral infarcts with linear regression analysis. To examine the relationship between WML and the risk of dementia and AD, we used Cox' proportional hazards regression models.[15] We analyzed periventricular and subcortical WML in categories of severity to analyze the shape of the relationship, and as a continuous variable (per standard deviation). Adjustments were made for age and sex, and analyses were repeated with possible confounders and measures of other structural brain changes added to the models. Additionally, we excluded participants with a history of stroke at baseline, and participants with a baseline MMSE score of 25 or lower. We examined possible effect modification by APOE genotype through stratified analysis.

Results

Characteristics of the participants are shown in table 1. Periventricular and subcortical WML

Table 1: **Baseline characteristics of participants of the Rotterdam Scan Study**

Characteristic	N = 1077
Age, years	72.2 (7.4)
Sex, % female	51.5
Education, % primary education only	34.8
Mini-Mental State Examination (score)	27.4 (2.2)
Hypertension, %	52.0
Diabetes, %	5.8
Current smoking, %	15.7
Periventricular white matter lesions (score)	2.4 (2.2)
Subcortical white matter lesions (ml)	1.4 (2.9)
Cortical brain atrophy (grade)	5.6 (2.9)
Subcortical brain atrophy (ventricle-to-brain ratio)	0.316 (0.036)
Cerebral infarcts, %	24.0
APOE genotype*	N = 971
ε2/ε2 or ε2/ε3 or ε3/ε3, %	70.9
ε2/ε4 or ε3/ε4 or ε4/ε4, %	29.1

Values are unadjusted means (standard deviation) or percentages.
*The APOE genotype was not determined in 106 of the 1077 participants

were positively correlated with cortical brain atrophy (Pearson correlation coefficient 0.40, $p<0.01$ and 0.25, $p<0.01$) and subcortical brain atrophy (Pearson correlation coefficient 0.21, $p<0.01$ and 0.14, $p<0.01$). Presence of cerebral infarcts was associated with a higher severity of periventricular and subcortical WML (age and sex adjusted mean difference in periventricular WML severity 1.6 points, 95% CI 1.3 to 1.9 points; in subcortical WML severity 2.0 ml, 95% CI 1.6 to 2.4 ml).

During 5,572 person-years of follow-up (mean per person 5.2 years), 45 participants developed dementia (incidence rate 8.1/1000 person-years). AD was diagnosed in 34 (76 %) patients, vascular dementia in 6 (13%), and another 5 (11%) were diagnosed with other types of dementia (Parkinson's disease dementia (3), multiple system atrophy (1), and unspecified dementia (1)). One-hundred-seventy-four participants died. The risk of dementia increased linearly with severity of periventricular WML (figure 1 and table 2). Increasing severity of subcortical WML tended to increase the risk of dementia, but this association was less strong (figure 1 and table 2). The hazard ratio for dementia per standard deviation increment in periventricular WML score remained largely the same after exclusion of participants with a history of stroke (n=58) (hazard ratio for dementia 1.66, 95% CI 1.22 to 2.27), and after adjustment for incident stroke (hazard ratio for dementia 1.63, 95% CI 1.21 to 2.19). After exclusion of participants with a baseline MMSE score of 25 or lower (n=173) the association remained (hazard ratio for dementia 1.50, 95% CI 1.04 to 2.16).

Table 2: **Relation between the severity of periventricular and subcortical white matter lesions (WML) and the risk of dementia.**

Variables adjusted for	Periventricular WML		Subcortical WML	
	Hazard ratio	95%CI	Hazard ratio	95% CI
Age and sex	1.67	(1.25-2.24)	1.20	(0.98-1.46)
Age, sex and education	1.67	(1.25-2.23)	1.20	(0.98-1.46)
Age, sex, hypertension, diabetes and smoking	1.69	(1.25-2.29)	1.21	(0.99-1.48)
Age, sex and APOE genotype	1.66	(1.23-2.25)	1.18	(0.97-1.44)
Age, sex and cerebral infarcts	1.60	(1.17-2.18)	1.13	(0.91-1.40)
Age, sex and generalized brain atrophy	1.51	(1.13-2.03)	1.15	(0.93-1.41)
Age, sex, cerebral infarcts and generalized brain atrophy	1.42	(1.04-1.94)	1.08	(0.86-1.35)
Age, sex, and WML in other location*	1.91	(1.31-2.78)	0.90	(0.68-1.19)

Numbers are hazard ratios and 95% confidence intervals per standard deviation (SD) increment in periventricular white matter lesion score (range 0 to 9; SD 2.2), and subcortical white matter lesion volume (range 0 to 29.5; SD 2.9).
*Periventricular WML conditional on subcortical WML and vice versa.

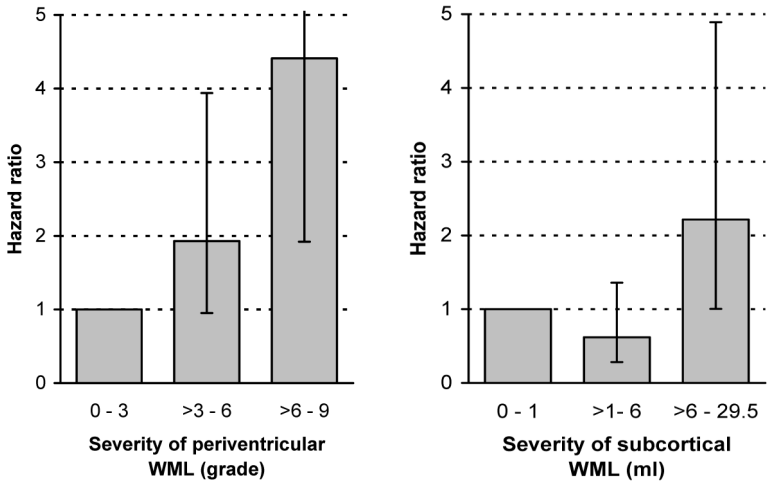


Figure 1. **Relation between white matter lesion (WML) severity in the periventricular and subcortical region, and the risk of dementia.**
Severity of white matter lesions (WML) is divided in three categories based on the distribution of periventricular WML scores. The risk of dementia is expressed as age and sex adjusted hazard ratios. The number of dementia cases and total number of participants in consecutive periventricular WML severity categories were 16 and 749 (grade 0-3), 18 and 261 (grade >3-6), 11 and 66 (grade >6-9), and in consecutive subcortical WML severity categories 24 and 763 (0-1 ml), 10 and 244 (>1-6 ml), 10 and 65 (>6-29.5 ml).

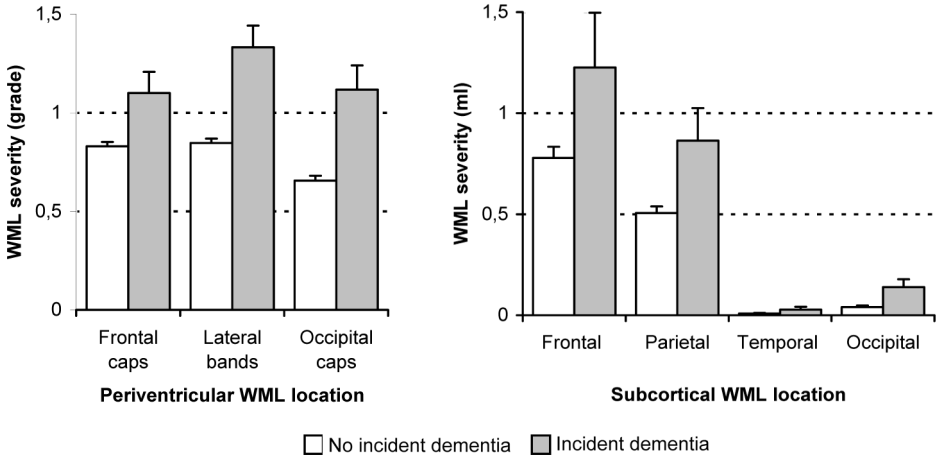


Figure 2. **Relation between white matter lesion (WML) severity and incident dementia for different locations of WML in the periventricular and subcortical region.**
Bars represent age and sex adjusted mean white matter lesion severity (standard error) at baseline for participants without (n = 1032) and participants with (n = 45) incident dementia during follow-up.

Participants who developed dementia during follow-up had on average more severe WML at baseline in all locations within the periventricular and subcortical region (figure 2). Periventricular WML also increased the risk of AD (hazard ratio for AD 1.41, 95% CI 1.01 to 1.98). The association of periventricular WML and AD was similar for those with and without an APOE ε4 allele (data not shown).

Comment

Higher severity of periventricular WML increased the risk of dementia, whereas the association between subcortical WML and dementia was less prominent. The association between periventricular WML and dementia was independent of possible confounders, and partly independent of other structural brain changes on MRI. The strengths of this study are the large number of participating elderly, its population-based design, and the fact that we had a complete follow-up for dementia through our monitoring system. Another important feature is the distinction between WML in the periventricular and subcortical region.

A preclinical phase of many years often precedes a diagnosis of dementia, especially in the case of AD.[16] It is therefore likely that our study population contained participants with a preclinical stage of dementia that remained below detection at base line. The association of periventricular WML and the risk of dementia did not change after exclusion of participants

with a low MMSE score at baseline, which suggests that the association is not confined to participants with a preclinical stage of dementia.

Our results are in line with those from previous studies on the relationship between WML and dementia. Cross-sectional case-control studies reported positive associations of the severity of WML on MRI with AD and vascular dementia.[3,17] In the Cardiovascular Health Study, participants with more severe WML had a two-fold increased risk of dementia.[4]

Several potential mechanisms may underlie the observed associations between WML and dementia. Histopathological studies demonstrated that irregular and confluent WML correspond to ischemic tissue damage including infarction, gliosis and rarefaction and loss of myelin.[18] This tissue damage is likely to cause disconnection of functionally related cortical and subcortical structures that are important to cognitive functioning.[19] It has been suggested that periventricular WML are just an epiphenomenon of brain atrophy, and are not independently related to disease.[20,21] We found that the association between periventricular WML and the risk of dementia was partly independent of generalized brain atrophy. Furthermore, we found that the association between periventricular WML and incident dementia was largely independent of presence of cerebral infarcts, of which in our study the majority was lacunar, and was not mediated by incident stroke.

Subcortical WML were not as strongly associated with dementia as periventricular WML, which is in line with previous reports.[3] Several possible pathophysiologic mechanisms may explain this finding. Firstly, WML close to the ventricles may interrupt bundles of cholinergic fibers, which extend from the nucleus basalis to the cerebral cortex, resulting in cholinergic denervation.[22] Secondly, the white matter in the periventricular region has a high density of long association fibers, whereas subcortical white matter has a high density of U-fibers. Diffusion tensor MRI studies found that white matter pathology in patients with AD selectively involved fiber tracts connecting cortical association areas, such as the cingulate bundles and the corpus callosum.[23,24] Periventricular WML may reflect vascular damage to these fiber tracts, or alternatively, represent wallerian degeneration of these tracts.

Extensive WML alone is sufficient for a diagnosis of vascular dementia,[12] and this leads to circularity when associations between WML and subdiagnoses of dementia are studied. However, the observed association between periventricular WML and AD suggest that WML may contribute to clinical AD. This is compatible with the view that most elderly people with dementia have mixed disease.[25] Because of the small number of cases with vascular dementia, we cannot provide reliable estimates for the association between WML and the risk of vascular dementia. In conclusion, we found that higher severity of periventricular WML is independently associated with an increased risk of dementia. Longer follow-up with repeated MRI is needed to gain insight in whether, and to what extent, progression of WML increases the risk of dementia.

References

1. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. The Lancet Neurology. November 2002 2002;1:426-436.
2. Leys D, Henon H, Pasquier F. White matter changes and poststroke dementia. Dement Geriatr Cogn Disord. Jul 1998;9 Suppl 1:25-29.
3. O'Brien JT, Ames D. White matter changes in depression and Alzheimer's disease: a review of Magnetic Resonance Imaging studies. International Journal of Geriatric Psychiatry. 1996;11.
4. Kuller LH, Lopez OL, Newman A, et al. Risk factors for dementia in the cardiovascular Health Cognition Study. Neuroepidemiology. 2003;22:13-22.
5. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med. Mar 27 2003;348(13):1215-1222.
6. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. Ann Neurol. 2000;47(2):145-151.
7. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-198.
8. Copeland JR, Kelleher MJ, Kellett JM, et al. A semi-structured clinical interview for the assessment of diagnosis and mental state in the elderly: the Geriatric Mental State Schedule. I. Development and reliability. Psychol Med. 1976;6(3):439-449.
9. Roth M, Tym E, Mountjoy CQ, et al. CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. Br J Psychiatry. 1986;149:698-709.
10. American Psychiatric Association., American Psychiatric Association. Work Group to Revise DSM-III. Diagnostic and statistical manual of mental disorders : DSM-III-R. 3rd rev. ed. Washington, DC: American Psychiatric Association; 1987.
11. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34(7):939-944.
12. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993;43(2):250-260.
13. UNESCO. International Standard Classification of Education (ISCED). Paris: UNESCO; 1976.
14. Wenham PR, Price WH, Blandell G. Apolipoprotein E genotyping by one-stage PCR. Lancet. 1991;337(8750):1158-1159.
15. Cox D. Regression models and life-tables. J R Stat Soc [B]. 1972;34:187-220.
16. Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB. The preclinical phase of alzheimer disease: A 22-year prospective study of the Framingham Cohort. Arch Neurol. 2000;57(6):808-813.
17. Barber R, Scheltens P, Gholkar A, et al. White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. J Neurol Neurosurg Psychiatry. 1999;67(1):66-72.
18. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke. Mar 1997;28(3): 652-659.
19. Filley CM. The behavioral neurology of cerebral white matter. Neurology. 1998;50(6): 1535-1540.
20. Fazekas F, Kapeller P, Schmidt R, Offenbacher H, Payer F, Fazekas G. The relation of cerebral magnetic resonance signal hyperin-

tensities to Alzheimer's disease. J Neurol Sci. 1996;142(1-2):121-125.

21. Barber R, Gholkar A, Scheltens P, Ballard C, McKeith IG, O'Brien JT. MRI volumetric correlates of white matter lesions in dementia with Lewy bodies and Alzheimer's disease. Int J Geriatr Psychiatry. 2000;15(10):911-916.
22. Selden NR, Gitelman DR, Salamon-Murayama N, Parrish TB, Mesulam MM. Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. Brain. Dec 1998;121 (Pt 12):2249-2257.
23. Bozzali M, Falini A, Franceschi M, et al. White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging. J Neurol Neurosurg Psychiatry. Jun 2002;72(6):742-746.
24. Takahashi S, Yonezawa H, Takahashi J, Kudo M, Inoue T, Tohgi H. Selective reduction of diffusion anisotropy in white matter of Alzheimer disease brains measured by 3.0 Tesla magnetic resonance imaging. Neurosci Lett. Oct 25 2002;332(1):45-48.
25. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Lancet. Jan 20 2001;357(9251):169-175.

2.4

Homocysteine and cognitive function in the elderly

Abstract

Background – Elevated plasma total homocysteine (tHcy) concentrations are associated with AD and vascular dementia, but the relation with cognitive performance in nondemented elderly people is not known.

Objective – To examine the association of tHcy and cognitive function in the elderly, and assess whether this may be mediated by structural brain changes on MRI.

Methods – The Rotterdam Scan Study is a population-based study of 1,077 nondemented elderly. Cognitive performance was assessed, and compound scores were constructed for psychomotor speed, memory function, and global cognitive function. Cerebral infarcts, white matter lesions, and generalized brain atrophy were measured on MRI. The cross-sectional relationship between tHcy levels and neuropsychological test scores was assessed by multiple regression.

Results – Mean tHcy level was 11.5 μmol/L (SD 4.1). Increasing tHcy levels were associated with lower scores for psychomotor speed, memory function, and global cognitive function, and this was largely due to the association with tHcy levels in the upper quintile (>14 μmol/L). Adjusted differences between test scores of participants in the upper quintile as compared with the lower four quintiles of tHcy were -0.26 (95% CI: -0.37; -0.14) for psychomotor speed, -0.13 (95% CI: -0.27; 0.01) for memory function, and -0.20 (95% CI: -0.30; -0.11) for global cognitive function. These associations were not mediated by structural brain changes on MRI.

Conclusion – Elevated tHcy levels are associated with decreased cognitive performance in nondemented elderly people, and the relation was most marked for psychomotor speed. This association was independent of structural brain changes on MRI.

Introduction

Homocysteine is a sulfur-containing amino acid derived from methionine. Plasma total homocysteine (tHcy) concentrations are increased in patients with AD and vascular dementia.[1,2] In a large longitudinal study, increased tHcy was a risk factor for the development of dementia and AD.[3] Previous studies in nondemented elderly have reported that higher tHcy levels are associated with worse cognitive performance4-6 and with cognitive decline,[7] but many of these studies have been small or the instruments used to measure cognitive function were unspecific to assess these associations reliably.

The adverse effects of tHcy on cognitive function may arise as a consequence of direct neurotoxicity[8] or indirectly through cerebrovascular disease.[9] The relevance of structural brain changes as assessed by MRI, such as cerebral infarcts, white matter lesions (WML), and generalized brain atrophy, as possible intermediates in the association of tHcy with cognitive function has not been previously studied. We investigated the relation between elevated tHcy levels and cognitive performance in a nondemented elderly population and assessed the extent to which any association may be mediated by structural brain changes on cerebral MRI.

Subjects and methods

Subjects

The Rotterdam Scan Study was designed to study the causes and consequences of age-related brain changes in the elderly.[10] Participants were recruited from the Rotterdam Study[11] and the Zoetermeer Study,[12] which are ongoing prospective cohort studies. In 1995 through 1996, 1,904 elderly aged 60 to 90 years were randomly selected after stratification by sex and by age in 5-year age groups. Among the invited subjects, 187 were excluded (owing to presence of dementia, a contraindication for MRI scanning, or blindness). Assessment of dementia was performed by using a stepped approach. All participants were initially screened with the Mini-Mental State Examination (MMSE)[13] and the Geriatric Mental Schedule (GMS), organic section.[14] Subsequently, participants who scored below a cutoff of 26 on the MMSE or above 0 on the GMS were further evaluated using more extensive neuropsychological tests, including an informant interview, and review of medical records. Of the 1,717 eligible participants, 1,077 completed all examinations (overall response 63%). Each participant gave informed consent to protocol, which was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam.

Total plasma homocysteine level

We collected nonfasting blood samples from participants into Vacutainers (Becton-Dickinson, Oxford, UK) containing sodium citrate in 1995 through 1996; these whole blood sam-

ples were put on ice immediately and centrifuged within 60 minutes, and aliquots of plasma were stored at -80°C. Plasma total tHcy concentrations were determined, 3 years after storage, by fluorescence polarization immunoassay on an IMx analyzer (Abbott Laboratories, Chicago, IL). This method has an intralaboratory imprecision of less than 5%.[15] Blood samples were unavailable for tHcy measurement in 39 participants, either owing to inability to collect the blood sample or loss of samples after collection. Seven participants whose tHcy levels were greater than 45 μmol/L were excluded.

Neuropsychological testing

Neuropsychological tests were administered in 1995 through 1996. We used the following three tests to assess executive function: an abbreviated Stroop test,[16,17] the Letter-Digit Substitution Task (a modified version of the Symbol Digit Modalities Test),[18] and a verbal fluency test.[19] A Paper-and-Pencil Memory Scanning Task consisting of four subtasks was used to measure attention.[20,21] We assessed memory function by means of a 15-word verbal learning test (based on Rey's recall of words),[22] which consists of three immediate recall trials and a delayed recall of words. An average or compound cognitive test score was made by transforming individual test scores into standardized Z-scores (Z-score = test score – mean test score/SD). Compound scores were estimated for psychomotor speed, memory performance, and global cognitive function.[23] Compound scores for psychomotor speed were calculated by averaging the Z-scores of the reading subtask of the Stroop test, the one letter subtask of the Paper-and-Pencil Memory Scanning Test, and the Letter-Digit Substitution Task. Compound scores for memory function were calculated by averaging the Z-scores of the total of three immediate recall trials and the delayed recall trial of the 15-word verbal learning tests. Compound scores for global cognitive performance were calculated by averaging the Z-scores of the reading subtask of the Stroop test, the one letter subtask of the Paper-and-Pencil Memory Scanning Test, the Letter-Digit Substitution Task, and the immediate and delayed recall of the 15-word verbal learning test. The MMSE[13] was used as a general indicator of cognitive function.

MRI procedure

Cranial MRI scanning was performed in all participants with 1.5-Tesla scanners at two centers to assess the presence of cerebral infarcts, WML, and generalized brain atrophy, as previously published.[23,24] Cerebral infarcts were defined as focal hyperintensities on T2-weighted images, 3 mm or larger. Lesions in the white matter also had to have corresponding prominent hypointensities on T1-weighted images. WML were considered present if visible as hyperintense on proton density and T2-weighted images, without prominent hypointensity on T1-weighted images. WML were scored for periventricular and subcortical areas, resulting in a total periventricular score (range 0 to 9) and an index for total subcortical WML volume (range 0 to 29.5). Generalized brain atrophy was scored on T1- weighted images. Subcortical atrophy was measured by the ventricle-to-brain ratio (range 0.21 to 0.45) and cortical atro-

phy was rated on a semiquantitative scale (range 0 to 15) using reference scans.

Duplex ultrasonography

Both the right and left carotid arteries were examined for the presence of plaques in the common carotid artery, the bifurcation, and the internal carotid artery using a 7.5 MHz linear array transducer and a Duplex scanner (ATL Ultra-Mark IV, Advanced Technology Laboratories, Bethel, WA).[25] Plaques per region were defined as being present or absent, and the data were used to estimate a carotid plaque score of 0 to 6.

Other measurements

The following variables were considered as possible confounding variables in the relationship between tHcy and cognition: age, sex, the highest level of education achieved (according to the United Nations Educational, Scientific, and Cultural Organization [UNESCO]),[26] disturbances of mood (determined with the Center of Epidemiologic Studies Depression Scale [CES-D]),[27] serum creatinine level (enzymatic assay),[28] and use of cigarettes (pack-years) and alcohol (units/day).

Data analysis

Among the 1,077 study participants, 1,031 had tHcy levels within the reliable 5 to 45 μmol/L range. All neuropsychological data were missing in four participants. Of the remaining 1,027, data on one or more tests were incidentally missing or incomplete due to physical handicap, insufficient motivation, or technical problems. The association of tHcy level with cognitive performance, as assessed using neuropsychological test scores, was assessed using multivariate linear regression, treating tHcy as a continuous variable. To assess whether the relationship between tHcy and cognitive performance was linear, we analyzed this relationship using tHcy categorized into quintiles of its distribution. Limits in tHcy level for the different quintiles were as follows: first quintile <8.54 μmol/L (median 7.57 μmol/L, n = 203), second quintile 8.55 to 9.87 μmol/L (median 9.12 μmol/L, n = 207), third quintile 9.88 to 11.44 μmol/L (median 10.54 μmol/L, n = 208), fourth quintile 11.45 to 13.95 μmol/L (median 12.47 μmol/L, n = 208), fifth quintile >13.96 μmol/L (median 16.34 μmol/L, n = 201). Because of an apparent threshold, tHcy was also dichotomized into the lower four quintiles versus the upper quintile (>14.0 μmol/ L). Analysis of covariance was used to obtain adjusted mean cognitive performance by quintiles of tHcy and adjusted mean difference in cognitive performance between tHcy levels of 14.0 μmol/L or lower and tHcy levels >14.0 μmol/L. All analyses were adjusted for age, sex, educational level, depression (CES-D score of 16 or higher), and serum creatinine to exclude confounding, and analyses were also adjusted for current alcohol use (units/day) and cigarette smoking (pack-years). To elucidate whether and to what extent the observed associations of tHcy with cognitive performance might be explained by structural intermediates, further analyses also adjusted for WML, cerebral infarcts, generalized brain atrophy, and carotid atherosclerosis.

Table 1. **Characteristics of the study population.**

Characteristics	All participants (n = 1,077
Age, y, mean (SD)	72.2 (7.4)
% Female	51.5
tHcy, μmol/L, mean (SD)	11.5 (4.1)
Education, % primary education only	34.8
Serum creatinine, μmol/L, mean (SD)	88.9 (18.5)
Alcohol use, units/d, median (interquartile range)	0.3 (0.0; 2.0)
Smoking, pack-years, median (interquartile range)	10.0 (0.0; 31.5)
Depression, % CES-D positive	7.4
Cerebral infarcts, %	24.0
White matter lesions, mean (SD)	
Periventricular, grade	2.4 (2.2)
Subcortical, mL	1.4 (2.9)
Generalized brain atrophy, mean (SD)	
Cortical atrophy, grade	5.6 (2.9)
Ventricle-to-brain ratio	0.314 (0.035)
Carotid plaque score, median (interquartile range)	1 (0; 3)

tHcy = plasma total homocysteine; CES-D = Center for Epidemiologic Studies Depression Scale.

Results

Selected characteristics of the study participants are shown in table 1. The mean plasma total tHcy level was 11.5 (SD 4.1) and values varied from 5.1 μmol/L to 40.1 μmol/L. Plasma tHcy levels increased with age (1.5 μmol/L increase per 10 years, 95% CI 1.2 to 1.9), and were higher in men then in women (mean difference 1.2 μmol/L, 95% CI 0.7 to 1.7). Increasing tHcy levels were associated with lower neuropsychological compound scores. Each SD (4.1 μmol/L) increase in tHcy level was associated with a decrease in compound scores for psychomotor speed by 0.06 points (95% CI 0.02 to 0.11), for memory function by 0.03 points (95% CI -0.02 to 0.08), and for global cognitive performance by 0.05 points (95% CI 0.01 to 0.09). With increasing tHcy, participants had more WML, more cerebral infarcts, and more cortical atrophy, after adjustment for age and sex.[29]

The figure shows the relationship between tHcy in quintiles and compound scores for psychomotor speed, memory function, and global cognitive function, adjusted for age, sex, education, depression, and serum creatinine. There was an apparent threshold in the relation of cognitive performance between the lowest four quintiles and the upper quintile (>14.0 μmol/L) of tHcy. The association of tHcy and test scores for individual neuropsychological tests showed a similar pattern. We therefore performed subsequent analyses with tHcy dichotomized into the top quintile and the lower four quintiles. Table 2 shows the relation between neuropsychological tests and tHcy level dichotomized at the upper

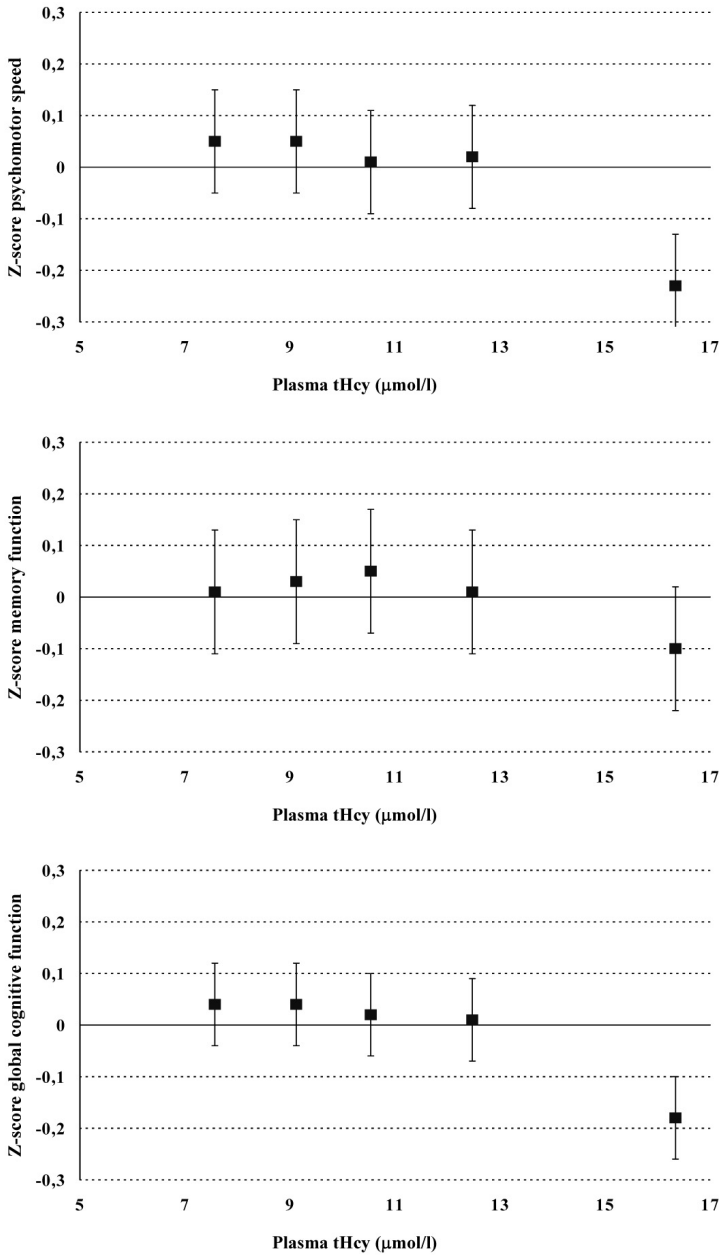


Figure. **Relation between plasma total homocysteine (tHcy) in quintiles and cognitive function (expressed as mean Z-scores [+SEM]) adjusted for age, sex, education, depression, and serum creatinine.**

Mean Z-scores are plotted at the median tHcy levels of the different quintiles. Limits in tHcy level for the different quintiles were as follows: first quintile <8.54 μmol/L, second quintile 8.55 to 9.87 μmol/L, third quintile 9.88 to 11.44 μmol/L, fourth quintile 11.45 to 13.95 μmol/L, fifth quintile >13.96 μmol/L.

Table 2. **The relation between total plasma tHcy and neuropsychological test outcome.**

Neuropsychological test	n	Mean (SD)	Difference (95% CI) upper quintile vs lower four quintiles of tHcy
Mini-Mental State Examination (score)*	1,027	27.5 (2.1)	-0.29 (-0.62; 0.05)
Stroop test†			
Reading (part 1 in sec)	1,019	18.6 (5.2)	0.83 (0.02; 1.64)
Naming (part 2 in sec)	1,015	25.5 (7.0)	1.34 (0.24; 2.44)
Interference (part 3 in sec)	995	58.1 (23.2)	4.68 (1.08; 8.28)
Letter Digit Substitution Task*			
No. of letters/min	995	26.7 (6.9)	-1.64 (-2.64; -0.65)
Verbal fluency*			
No. of animals/min	1,021	20.4 (5.1)	-1.53 (-2.32; -0.75)
Paper and Pencil Memory Scanning Task†			
1 letter (sec)	1,000	31.7 (9.7)	2.97 (1.52; 4.42)
2 letters (sec)	1,000	46.1 (15.4)	3.71 (1.35; 6.07)
3 letters (sec)	997	57.6 (18.0)	2.46 (-0.34; 5.26)
15-word verbal learning test*			
Total in three trials (no. of words)	1,016	20.1 (5.4)	-0.67 (-1.47; 0.14)
Delayed recall (no. of words)	1,014	5.9 (2.7)	-0.33 (-0.74; 0.08)

Values are mean test scores (SD) and mean adjusted differences (95% CI) in test score between upper quintile (>14 μmol/L) and lower four quintiles of plasma total homocysteine (tHcy). Adjustments were made for age, sex, education, depression, and serum creatinine.
* Lower scores indicate worse performance.
† Higher scores indicate worse performance.

quintile (>14.0 μmol/L) compared with the lower four quintiles. Individuals with elevated tHcy levels in the upper quintile had worse performance on all individual neuropsychological tests, although this difference in test performance was not significant for the MMSE, the three-letter subtask of the Paper-and- Pencil Memory Scanning Test, and the immediate and delayed recall of the 15-word verbal learning test. Further adjustment for use of alcohol and for smoking did not alter these associations (data not shown).

Table 3 shows the relation between tHcy and neuropsychological compound scores after further adjustment for cerebral infarcts, WML, and generalized brain atrophy. The difference in neuropsychological compound scores between people with tHcy levels in the upper quintile compared to the lower four quintiles was only slightly attenuated after adjustment for these radiologic variables. Furthermore, the relation of tHcy with cognitive performance was unaltered by further adjustment for carotid artery plaques (data not shown).

Table 3. **The influence of structural brain changes on the association of tHcy and neuropsychological compound scores.**

Compound score	Difference in cognitive performance (95% CI) for people in the upper quintile vs lower four quintiles of tHcy		
	Model 1*	Adjusted for cerebral infarcts and WML†	Adjusted for generalized brain atrophy†
Speed	-0.26 (-0.37; -0.14)	-0.24 (-0.36; -0.12)	-0.24 (-0.35; -0.12)
Memory	-0.13 (-0.27; 0.01)	-0.10 (-0.24; 0.05)	-0.12 (-0.26; 0.02)
Cognitive Index	-0.20 (-0.30; -0.11)	-0.18 (-0.28; -0.08)	-0.19 (-0.29; -0.09)

Values are adjusted mean differences in compound score between the highest quintile (>14.0 μmol/L) of total plasma homocysteine (tHcy) and the lower four quintiles and 95% CI.
* Adjusted for age, sex, education, depression, and serum creatinine.
† Additional to model 1.

Discussion

Elevated plasma tHcy levels were significantly associated with adverse cognitive function in this large population-based study of elderly people. The associations of tHcy were strongest for psychomotor speed, but were also present for memory function. There was an apparent threshold for tHcy of about 14 μmol/L, above which it was significantly associated with adverse cognitive performance. This association of tHcy with cognitive function appeared to be independent of the presence of cerebral infarcts, WML, or generalized brain atrophy on MRI.

Using a cross-sectional study design for these analyses, the current report cannot refute the possibility that high tHcy levels were a consequence of cognitive impairment rather than being causally related to cognitive impairment. It is possible that dementia can lead to a deterioration of diet, resulting in insufficient intake of folate and vitamin B_{12} and elevated tHcy levels. Because people with dementia were excluded from our study, we consider it unlikely that cognitive dysfunction may have caused elevation in tHcy levels. A large follow-up study found that increased tHcy levels were strongly and independently related to the development of dementia and AD,[3] suggesting that high tHcy levels may be causally related, rather than being a consequence of impaired cognitive function.

The use of a single tHcy measurement to classify persons may have underestimated the strength of any associations due to regression dilution by 15 to 30%.[30] Furthermore, we could not assess the relative importance of vitamin status (such as vitamin B_{12} and folate) or free thyroxine levels for cognitive function.

The overall response rate to invitation to participate in this study was 63%. Nonparticipants were older and had a higher frequency of hypertension, and had lower MMSE scores than participants.[23] Consequently, the proportion of people with cognitive impairment may

have been underestimated in our study. However, we have no reason to believe that the association of tHcy with cognitive function may be materially different between participants and nonparticipants.

The results of the current analyses confirm the findings suggested by the results of previous studies on the association of high tHcy levels with cognitive dysfunction and dementia.[1-6] We found a threshold effect in the relation between tHcy and cognitive function above tHcy levels of 14 μmol/L.[31] The possibility that tHcy levels under 14 μmol/L may affect cognitive function cannot be excluded, but the extent that this occurs remains below threshold of detection using the neuropsychological tests used in this report. We found that participants with high tHcy levels tended to have lower MMSE scores, although this association was not significant. We previously reported a lack of association between tHcy and cognitive impairment (defined as a MMSE score of 25 or lower) and cognitive decline (defined as a drop in MMSE of more than one point per year) in a random sample of participants from the Rotterdam study.[32] These findings may be explained by a low sensitivity of the MMSE to detect subtle differences in cognitive function in healthy elderly populations, and a short follow-up period with a mean of 2.7 years. Another study with a longer follow-up and older subjects did find a significant association between tHcy and decline in MMSE.[7]

There are several plausible biological mechanisms that may explain the relationship between tHcy levels and cognitive function. Elevated tHcy is an independent risk factor for cerebrovascular disease,[33] which in turn is a risk factor for cognitive decline and dementia.[34] We recently reported on the association of tHcy and silent brain infarcts and WML in the Rotterdam Scan Study.[29] Previously we reported on the association of WML and cognitive function.[23] In the current study we found that the association between tHcy and cognitive function was not mediated by cerebral infarcts, WML, or generalized brain atrophy. Although we cannot exclude that measurement error involved in the assessment of structural brain changes was associated with a failure to establish such an intermediate role, we suggest that other mechanisms play a role in the association of tHcy and cognitive function. tHcy may have a direct neurotoxic effect.[8] Additionally, high tHcy levels may be a marker of impaired methylation reactions in brain tissue, which play an important role in the production of neurotransmitters, phospholipids, and myelin.[35] Finally, high tHcy may promote β-amyloidpeptide mediated toxic effects on neuronal cells.[36]

Further prospective and intervention studies are needed to confirm whether the association between high tHcy levels and cognitive dysfunction is causal, and whether lowering of the plasma tHcy level reduces the risk of cognitive decline and dementia.

References

1. Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol 1998;55:1449–1455.
2. Fassbender K, Mielke O, Bertsch T, Nafe B,

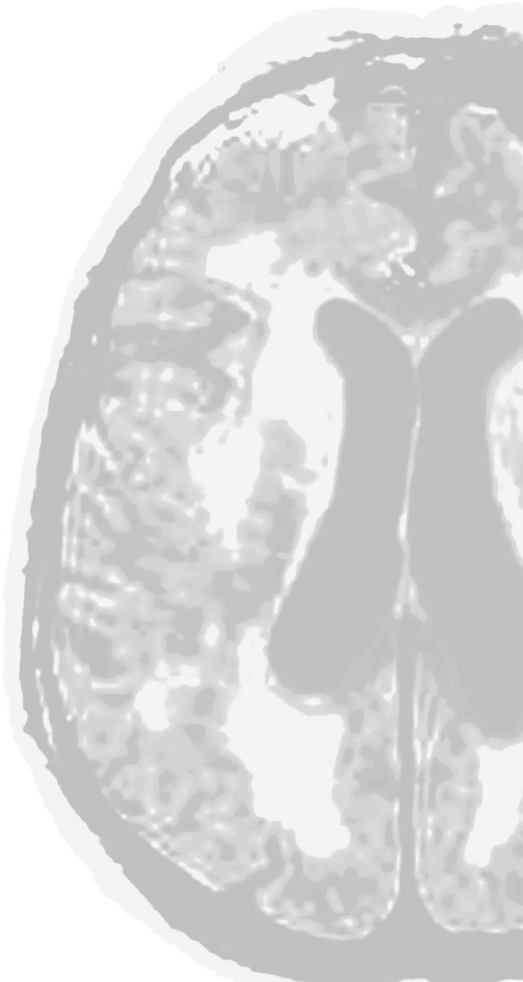
Froschen S, Hennerici M. Homocysteine in cerebral macroangiography and microangiopathy. Lancet 1999;353:1586–1587.
3. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002; 346:476–483.
4. Morris MS, Jacques PF, Rosenberg IH, Selhub J. Hyperhomocysteinemia associated with poor recall in the third National Health and Nutrition Examination Survey. Am J Clin Nutr 2001;73:927–933.
5. Riggs KM, Spiro A, Tucker K, Rush D. Relations of vitamin B-12, vitamin B-6, folate, and homocysteine to cognitive performance in the Normative Aging Study. Am J Clin Nutr 1996;63:306–314.
6. Budge M, Johnston C, Hogervorst E, et al. Plasma total homocysteine and cognitive performance in a volunteer elderly population. Ann NY Acad Sci 2000;903:407–410.
7. McCaddon A, Hudson P, Davies G, Hughes A, Williams JH, Wilkinson C. Homocysteine and cognitive decline in healthy elderly. Dement Geriatr Cogn Disord 2001;12:309–313.
8. Lipton SA, Kim WK, Choi YB, et al. Neurotoxicity associated with dual actions of homocysteine at the N-methyl-Daspartate receptor. Proc Natl Acad Sci USA 1997;94: 5923–5928.
9. Diaz-Arrastia R. Hyperhomocysteinemia: a new risk factor for Alzheimer disease? Arch Neurol 1998;55:1407–1408.
10. de Groot JC, de Leeuw FE, Oudkerk M, Hofman A, Jolles J, Breteler MM. Cerebral white matter lesions and subjective cognitive dysfunction: The Rotterdam Scan Study. Neurology 2001;56:1539–1545.
11. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403–422.
12. Hofman A, van Laar A, Klein F, Valkenburg H. Coffee and cholesterol (letter). N Engl J Med 1983;309:1248–1249.
13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
14. Copeland JR, Kelleher MJ, Kellett JM, et al. A semistructured clinical interview for the assessment of diagnosis and mental state in the elderly: the Geriatric Mental State Schedule. I. Development and reliability. Psychol Med 1976;6:439–449.
15. Nexo E, Engbaek F, Ueland PM, et al. Evaluation of novel assays in clinical chemistry: quantification of plasma total homocysteine. Clin Chem 2000;46:1150–1156.
16. Bohnen N, Twijnstra A, Jolles J. Performance in the Stroop color word test in relationship to the persistence of symptoms following mild head injury. Acta Neurol Scand 1992; 85:116–121.
17. Hammes J. De Stroop Kleur-Woord Test. Lisse: Swets & Zeitlinger, 1971.
18. Lezak MD. Neuropsychological assessment. 3rd ed. New York: Oxford University Press, 1995.
19. Luteijn F, van der Ploeg F. Groninger Intelligentie Test. Lisse: Swets & Zeitlinger, 1983.
20. Houx PJ, Vreeling FW, Jolles J. Rigorous health screening reduces age effect on memory scanning task. Brain Cogn 1991;15: 246–260.
21. Sternberg S. Memory-scanning: mental processes revealed by reaction-time experiments. Am Sci 1969;57:421–457.
22. Brand N, Jolles J. Learning and retrieval rate of words presented auditorily and visually. J Gen Psychol 1985;112:201–210.
23. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. Ann Neurol 2000;47:145–151.
24. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam scan study. Stroke 2002;33:21–25.
25. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media

thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation 1997;96:1432–1437.

26. UNESCO. International Standard Classification of Education (ISCED) (Report No: IgC/3). Paris: UNESCO, 1976.
27. Radloff L. The CES-D Scale. A self-report depression scale for research in the general population. Appl Psychol Meas 1977;1: 385–401.
28. Mazzachi BC, Peake MJ, Ehrhardt V. Reference range and method comparison studies for enzymatic and Jaffe creatinine assays in plasma and serum and early morning urine. Clin Lab 2000;46:53–55.
29. Vermeer SE, van Dijk EJ, Koudstaal PJ, et al. Homocysteine, silent brain infarcts, and white matter lesions: The Rotterdam Scan Study. Ann Neurol 2002;51:285–289.
30. Clarke R, Woodhouse P, Ulvik A, et al. Variability and determinants of total homocysteine concentrations in plasma in an elderly population. Clin Chem 1998;44: 102–107.
31. Selhub J, Jacques PF, Rosenberg IH, et al. Serum total homocysteine concentrations in the third National Health and Nutrition Examination Survey (1991–1994): population reference ranges and contribution of vitamin status to high serum concentrations. Ann Intern Med 1999;131:331–339.
32. Kalmijn S, Launer LJ, Lindemans J, Bots ML, Hofman A, Breteler MM. Total homocysteine and cognitive decline in a community-based sample of elderly subjects: the Rotterdam Study. Am J Epidemiol 1999;150:283–289.
33. Clarke R, Daly L, Robinson K, et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. N Engl J Med 1991; 324:1149–1155.
34. Breteler MM, Bots ML, Ott A, Hofman A. Risk factors for vascular disease and dementia. Haemostasis 1998;28:167–173.
35. Selhub J, Bagley LC, Miller J, Rosenberg IH. B vitamins, homocysteine, and neurocognitive function in the elderly. Am J Clin Nutr 2000;71:614S–620S.
36. White AR, Huang X, Jobling MF, et al. Homocysteine potentiates copper- and amyloid beta peptide-mediated toxicity in primary neuronal cultures: possible risk factors in the Alzheimer's-type neurodegenerative pathways. J Neurochem 2001;76:1509–1520.

Chapter 3

Cerebral small vessel disease and depression



Brain infarcts, white matter lesions and the risk of depression in the general population

Abstract

Background – Cerebrovascular pathology may contribute to late-life depression. Whether brain infarcts and white matter lesions increase the risk of depressive disorders in the general population has not been studied longitudinally.

Methods – The Rotterdam Scan Study is a prospective, population-based cohort study among 1,077 non-demented elderly people. The presence of brain infarcts and severity of white matter lesions were scored on cerebral MRI scans obtained at baseline in 1995-1996. We assessed depressive disorders during follow-up by re-examination of the cohort in 1999-2000, and by monitoring medical records. We used logistic regression analysis to estimate relative risks of depressive disorders associated with the presence of brain infarcts and severity of white matter lesions.

Findings – During a mean follow-up of 3.6 years, 48 participants had an incident, and 30 participants a chronic (recurrent or persistent) depressive disorder. Brain infarcts were associated with a three-fold increased risk of chronic depressive disorders (all infarcts: odds ratio 2.9, 95% confidence interval 1.1-7.6, asymptomatic infarcts: odds ratio 3.2, 95% confidence interval 1.2-8.9). Severe subcortical white matter lesions more than doubled the risk of incident depressive disorders (odds ratio 2.2, 95% confidence interval 1.1-4.5). Periventricular white matter lesions were not related to depressive disorders.

Interpretation – In elderly people, both symptomatic and asymptomatic brain infarcts are associated with chronicity of depressive disorders, whereas severe subcortical white matter lesions are associated with an increased risk of incident depressive disorders. Our findings suggest that cerebral small-vessel disease plays a role in the pathophysiology of late-life depression.

Introduction

There is a convergence of evidence suggesting a causal link between cerebrovascular disease and depression in late life.[1] This has led to the 'vascular depression' hypothesis, which implies that there is a subtype of depression arising in later life that is characterized by a distinct clinical presentation and an association with cerebrovascular disease.[2] About a third of hospitalized stroke patients develop a depressive disorder.[3] The question remains whether in these patients depression is a direct consequence of vascular brain damage, or is a psychological reaction to physical disability or perceived disease. Epidemiological and neuroimaging studies suggest that also asymptomatic brain infarcts and white matter lesions, which typically result from cerebral small vessel disease, are related to depression in elderly people.[4,5] We previously showed that white matter lesions on MRI are associated with the presence of depressive symptoms.[6] One longitudinal population-based study examined the relationship between cerebral small vessel disease and self-reported depressive symptoms over time. This study showed that cerebral small vessel disease was associated with worsening and persistence of depressive symptoms, but not with incident depressive symptoms.[7] Whether cerebral small vessel disease increases the risk of clinical depressive disorders in the general population has not been studied prospectively. We therefore examined the association of asymptomatic and symptomatic brain infarcts and white matter lesions with the risk of depressive disorders in a population-based follow-up study among elderly people. Since the risk of depression may be related to lesion location, we additionally investigated if relationships were different for specific locations of cerebral small vessel disease.[3]

Methods

Participants

The Rotterdam Scan Study was designed to study causes and consequences of brain changes in the elderly. The study design has been described in detail.[8] In 1995-1996, we randomly selected participants aged 60 to 90 years in strata of age (5 years) and sex from two large ongoing population-based studies, the Zoetermeer Study and the Rotterdam Study.[9,10] A total of 1,077 non-demented elderly participated in our study (overall response 63%). The medical ethics committee of the Erasmus Medical Center approved the study, and each participant gave written informed consent.

Baseline examination in 1995-1996 comprised a structured interview, screening for depressive symptoms, physical examination, blood sampling, and neuropsychological tests at the research center, as well as a cerebral MRI scan. In 1999-2000, we re-examined 787 of the 973 participants who were alive and eligible (not institutionalized, not moved abroad) at the research center with a protocol similar to that used at the baseline examination (response 81%). Compared to participants in the second examination, people who were ineligible or

who declined to undergo the second examination were significantly older (mean age difference 4.2 years), and were less educated (percentage primary education only 56% versus 32%). The percentage of people with depressive symptoms at baseline did not differ among participants and non-participants.

We monitored all 1,077 participants throughout the study by reviewing medical records from their general practitioners and from the Regional Institute for Ambulatory Mental Health for death and major complications, including depression and dementia. Follow-up for depression was virtually complete until March 1st, 2000 (99.4%; for 7 participants we had no information on depression).

Cerebral infarcts and white matter lesions

All participants underwent MRI of the brain in 1995-1996. We made axial T1-weighted, T2-weighted, and proton-density-weighted scans on 1.5 Tesla MRI scanners (for participants from Zoetermeer: MR Gyroscan, Philips, Best, the Netherlands and for participants from Rotterdam: MR VISION, Siemens, Erlangen, Germany). The slice thickness was 5 or 6 mm with an interslice gap of 20%.

Infarcts were defined as focal hyperintensities on T2-weighted images, 3 mm in size or larger. Proton-density scans were used to distinguish infarcts from dilated perivascular spaces. Lesions in the white matter also had to have corresponding prominent hypointensities on T1-weighted images, in order to distinguish them from cerebral white matter lesions. A single trained physician scored infarcts both on baseline and second MRI, including their location and size. An intrarater study (n=110) for detecting infarcts showed good agreement (κ=0.80).[11] An experienced neurologist subsequently reviewed the medical history and scans and categorized the infarcts as asymptomatic or symptomatic. We defined asymptomatic brain infarcts as evidence of one or more infarcts on MRI, without a history of a (corresponding) stroke or TIA. Participants with both symptomatic and asymptomatic infarcts were categorized in the symptomatic infarct group.

White matter lesions were considered present if visible as hyperintense on proton-density- and T2-weighted images, without prominent hypointensity on T1-weighted scans. Two raters scored periventricular and subcortical located white matter lesions independently. Both intrarater and interrater studies (n=100) showed a good to excellent agreement (κ=0.79-0.90, r=0.88-0.95). A detailed description of the scoring method has been reported previously.[8] Severity of periventricular white matter lesions was rated semi-quantitatively in three regions (grade range 0-9). A total volume of subcortical white matter lesions was approximated based on number and size of lesions in the frontal, parietal, occipital, and temporal lobes (volume range 0-29.5 ml).

Assessment of depressive disorders

We assessed whether participants had a psychiatric history in 1995-1996 by interview and by checking medical records and indications of prescribed drugs in all 1,077 participants.

A history of depression was defined as a depressive episode before the baseline examination lasting for more than two weeks. We also assessed presence of depressive symptoms at baseline with a validated Dutch version of the original Center for Epidemiologic Studies Depression (CES-D) scale (range 0-60).[12]

We acquired information on depression during follow-up in two ways. Firstly, we administered the CESD in all participants but one who were re-examined in 1999-2000 (n=786). Participants with a CES-D score of 16 or more were considered screen-positive.[12] To ascertain a Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) diagnosis,[13] a psychiatrist interviewed screen positives with a semi-structured psychiatric interview, a Dutch version of the Present State Examination.[14] Secondly, as mentioned previously, we continually monitored the medical records of all 1,077 participants at the general practitioner's offices and the Regional Institute for Ambulatory Mental Health for depressive episodes. Prevalent depressive symptoms were defined as depressive symptoms (CES-D score $\geq$16) or the use of antidepressant medication for the indication of depression at baseline. We defined incident depressive disorders as depressive disorders at follow-up without prevalent depressive symptoms (CESD <16) at baseline. Chronic (persistent or recurrent) depressive disorders were defined as depressive disorders at follow-up in persons with prevalent depressive symptoms (CESD $\geq$16) at baseline.

Other measurements

The following variables assessed at baseline were used as possible confounders: age (continuously per year); sex; educational status (defined as the highest education according to UNESCO, and dichotomized into primary education only, and more than primary education);[15] cognitive function (defined as score on the Mini-Mental State Examination (MMSE) (score range 0-30).)[16] All participants were followed for the development of dementia, which was diagnosed according to standardized criteria.[17]

Data analysis

In order to estimate the relative risks of depressive disorders associated with the presence of brain infarcts and the severity of white matter lesions, we used multiple logistic regression analysis to calculate odds ratios and 95% confidence intervals. We excluded participants of whom we had no information on depression (n=7), those who were screen-positive but received no psychiatric work-up (n=7), and those who were diagnosed with a psychiatric disorder other than a depressive disorder during follow-up (n=8), leaving 1,055 participants in the analyses. We studied incident depressive disorders in 968 participants without prevalent depressive symptoms, and chronic depressive disorders in 87 participants with prevalent depressive symptoms at baseline.

In the analyses we adjusted for age, sex, education and baseline MMSE score. We used separate models for presence of asymptomatic brain infarcts, and for severity of periventricular and subcortical white matter lesions. For the analyses with brain infarcts, the ref-

erence group comprised participants without brain infarcts and no distinction was made between participants with one or multiple infarcts. Periventricular and subcortical white matter lesions were analyzed both continuously per standard deviation, and as presence versus absence of severe white matter lesions (five points or more for periventricular white matter lesions; two milliliter or more for subcortical white matter lesions).[8] In order to investigate the risk of incident late-onset depression, we excluded all participants with a history of early-onset depression (n=21). Early-onset depression was defined as a depressive episode with an onset before the age of 60 years. Additionally, we excluded participants with any history of depression. We repeated the analyses after exclusion of participants who became demented during follow-up (n=34), because depressive symptoms may be a prodrome of dementia, and this might confound the associations of interest. Finally, we examined whether the relationship between severity of subcortical white matter lesions and the risk of depressive disorders was different for white matter lesions in different locations. In order to evaluate this, we used multiple linear regression modeling to compare the white matter lesion severity in the frontal, parietal, occipital, and temporal lobes, between participants with and without incident depression during follow-up.

Table 1. **Baseline characteristics of all participants.**

	Participants		
	All n = 1055*	No depressive symptoms at baseline n = 968	Depressive symptoms at baseline n = 87
Age, years	72.2 (7.4)	72.1 (7.4)	73 (7.8)
Women	542 (51%)	477 (49%)	65 (75%)
Primary education only	366 (35%)	325 (34%)	40 (47%)
History of depression	66 (6%)	37 (4%)	29 (33%)
Use of antidepressant medication	19 (2%)	0 (0%)	23 (26%)
CES-D score, range 0-60	5.8 (6.1)	4.6 (4.3)	18.9 (7.7)
CES-D score $\geq$ 16	74 (7%)	0 (0%)	74 (85%)
MMSE score, range 0-30	27.4 (2.2)	27.5 (2.2)	27.0 (2.4)
Brain infarcts on MRI:	252 (24%)	220 (23%)	32 (37%)
Symptomatic	39 (4%)	33 (3%)	6 (7%)
Asymptomatic	213 (20%)	187 (19%)	26 (30%)
Periventricular white matter lesions, grade, range 0-9	2.4 (2.2)	2.3 (2.2)	2.9 (2.0)
Subcortical white matter lesions, volume, range 0-29.5 ml	1.4 (2.9)	1.4 (2.9)	1.6 (2.8)

Values are unadjusted means (standard deviation) or number of participants (percentages).
*Excludes participants without information on depression (n = 7), screen-positives without a psychiatric work-up (n = 7), and participants who were diagnosed with a psychiatric disorder other than a depressive disorder during follow-up (n = 8).

Results

The baseline characteristics of the study population are shown in Table 1. During a mean follow-up of 3.6 years, 78 of the 1,055 participants (7.4%) were diagnosed with a depressive disorder. The mean age of these 78 participants was 72.1 years, and 55 (71%) were women. Of the 968 participants without prevalent depressive symptoms at baseline, 48 (5.0%) had an incident depressive disorder. Thirty (34%) of the 87 participants with prevalent depressive symptoms had a chronic (recurrent or persistent) depressive disorder.

The presence of brain infarcts, including asymptomatic infarcts, at baseline was associated with a three-fold increased risk of a chronic depressive disorder, whereas brain infarcts were not associated with incident depressive disorder (Table 2). Severe subcortical white matter lesions more than doubled the risk of incident depressive disorders (Table 2). Severe periventricular white matter lesions tended to increase the risk of incident depression, but this association was less strong (Table 2). White matter lesions were not associated with chronic depression (Table 2). Exclusion of participants with early-onset depression in history (n=21) did not change any of the results, nor did exclusion of participants with any history of depression (data not shown). Exclusion of participants who developed dementia during follow-up (n=34), of whom 6 were diagnosed with a depressive disorder before the dementia diagnosis, did not change the association between infarcts and chronic depressive disorders (age, sex, education and MMSE adjusted OR 2.9, 95% CI 1.0-7.9), nor between severe subcortical white matter lesions and incident depressive disorders (age, sex, education and MMSE adjusted OR 2.5, 95% CI 1.2-5.0).

Table 2. **Association between presence of asymptomatic brain infarcts and severity of white matter lesions and the risk of incident or chronic (recurrent or persistent) depressive disorder, estimated by odds ratios (OR) with 95% confidence intervals (CI).**

	Incident depressive disorder OR* (95% CI)	Chronic depressive disorder OR* (95% CI)
Infarcts (present/absent)		
All infarcts	1.0 (0.5-2.1)	2.9 (1.1-7.6)
Asymptomatic infarcts	1.0 (0.4-2.1)	3.2 (1.2-8.9)
White matter lesions		
Periventricular (per SD†)	1.2 (0.9-1.7)	1.2 (0.7-2.1)
Severe periventricular (present/absent)	1.4 (0.7-2.9)	0.9 (0.3-2.8)
Subcortical (per SD†)	1.2 (1.0-1.7)	0.9 (0.6-1.6)
Severe subcortical (present/absent)	2.2 (1.1-4.5)	0.6 (0.2-1.9)

*Adjusted for age, sex, education and baseline Mini-Mental State Examination (MMSE) score
† Standard deviation

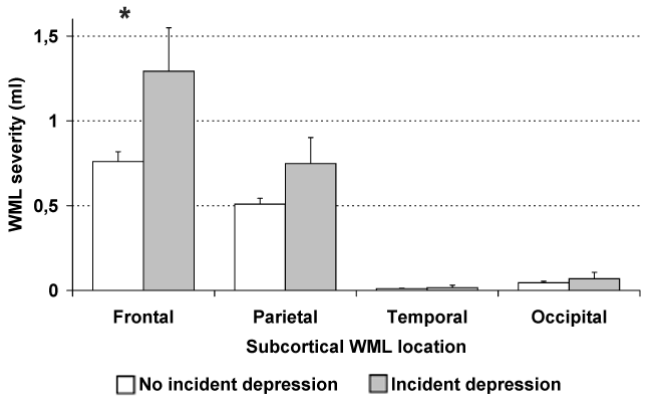


Figure. **Relationship between white matter lesions and incident depression for different locations of white matter lesions in the subcortical region.**
Bars represent age and sex adjusted mean white matter lesion severity (standard error) at baseline for participants without (n = 920) and with (n = 48) incident depression during follow-up. *The mean white matter lesion severity in the frontal region was significantly higher (p-value 0.04) in participants with incident depression, compared to participants without incident depression.

The figure shows the age and sex adjusted baseline severity of white matter lesions at different locations in the subcortical region for participants with and without incident depression. Participants who developed depression during follow-up had on average more severe subcortical white matter lesions at all locations. The largest difference was found for subcortical white matter lesions in the frontal lobe (adjusted mean difference 0.53 ml, 95% confidence interval 0.02-1.05).

Discussion

In this prospective study in community dwelling elderly people, we found that the presence of brain infarcts was associated with a three-fold increased risk of chronic depressive disorders, but was not associated with incident depressive disorders. In contrast, subcortical white matter lesions were associated with incident depressive disorders. This was most marked for white matter lesions in the frontal lobe. White matter lesions did not increase the risk of chronic depressive disorders.

The strengths of this study are the large number of participating elderly people, and its prospective population-based design. Furthermore, follow-up for depressive disorders was nearly complete. A potential methodological limitation of our study is misclassification. Participants tend to underreport depressive symptoms, and physicians probably underdiagnose depressive disorders, which may have resulted in an underestimation of the true

number of events. In addition to information from medical records, we actively screened participants for the presence of depressive symptoms, which will have reduced this underestimation. Another issue that needs to be addressed is that, in order to study incident depression, we excluded participants with a CES-D score of 16 or higher at baseline. This cut-off represents clinically significant depressive symptoms and has a very high sensitivity for major depression in elderly subjects.[12] Exclusion of participants with a CES-D score of 16 or higher may have led to an underestimation of the incidence of depressive disorders, and possibly to an attenuation of the associations between brain infarcts, white matter lesions and depression.

In the present study, we found that the presence of brain infarcts, of which the majority is asymptomatic (85%), was associated with chronicity of depressive disorders. As in other studies, we found that the prognosis of depression was poor.[18] Thirty-four percent of participants who had significant depressive symptoms at baseline were diagnosed as depressed during follow-up. This was particularly the case for participants with a brain infarct on MRI who were three times as likely to have persistent depression. However, brain infarcts were not associated with de novo occurrence of depressive disorders.

We report an association between increasing severity of subcortical white matter lesions and the incidence of depressive disorders in elderly people. This is consistent with our earlier cross-sectional findings, and with those from the Cardiovascular Health Study.[6,7] We found that the association between subcortical white matter lesions and depression was most marked for white matter lesion localization in the frontal lobe. This is in agreement with neuropathological evidence for ischaemia in frontal-subcortical areas in the brains of elderly people with depression.[19] However, in clinical stroke patients, the risk of depression seems to be unrelated to the location of the brain lesions,[20] which suggests that other mechanisms play a role in depression following a large vessel stroke.

The observation that infarcts and white matter lesions are related to depression in a distinct way, i.e. white matter lesions are related to incident, whereas infarcts are related to chronic depression may be explained by the difference in pathogenesis of these vascular lesions. Infarcts are acute events, and therefore a depressive disorder may develop directly after the infarct has occurred, due to disconnection in neural circuits involved in mood regulation.[21] Participants with an infarct on MRI are therefore more likely to be depressed at baseline, which may become chronic during follow-up. White matter lesions on the other hand, may represent a more gradual process of brain damage, which might result in a depressive disorder after the damage has reached a certain threshold. This is in line with the Cardiovascular Health Study that reported that MRI infarcts were associated with persistence of depressive symptoms, whereas white matter lesions were associated with worsening of depressive symptoms.[7]

Depressive disorders are frequently found in patients with dementia.[22] Brain infarcts and white matter lesions are thought to be risk factors for dementia,[17,23] and the association between these lesions and depression may therefore be explained by the coexistence of de-

mentia. In our study, the risk increase of depressive disorders with the presence of brain lesions remained largely unchanged after exclusion of participants who developed dementia during follow-up. This suggests that in the present study the associations of brain infarcts and white matter lesions with depression are not confined to participants who developed dementia during follow-up. However, there is evidence that late-onset depression is often a prodromal disorder for dementia, and people who developed a depressive disorder in our study may be predisposed to the later development of dementia.[24]

Several mechanisms have been proposed for the association between cerebrovascular disease and depression.[25] First, depressive disorders may be a direct consequence of ischemic brain damage. Second, depressive disorders may be a reaction to deficits associated with serious cerebrovascular disease such as stroke. Third, it has been suggested that depression may contribute to the evolution of vascular risk factors and may increase the risk of cerebrovascular disease. We found an increased risk of depressive disorders for people with brain infarcts and subcortical white matter lesions. These associations were independent of a history of depression, suggesting that cerebral small vessel disease precedes the depressive disorder, rather than being a consequence of depression. Furthermore, asymptomatic brain infarcts and white matter lesions, reflect mainly small vessel disease.[11,26] This indicates that in elderly people depression may be a direct consequence of vascular brain damage, and is not only a psychological reaction to physical disability or perceived disease. Ischemic damage of striatal and prefrontal cortical systems may disrupt neurotransmitter circuitry involved in mood regulation.[19,21]

In conclusion, we found an increased risk of depressive disorders in elderly people with brain infarcts and white matter lesions in the general population. This supports that vascular brain damage plays an important role in depression in elderly people. It also suggests that prevention of cerebral small vessel disease may diminish the number of depressive disorders in elderly people.

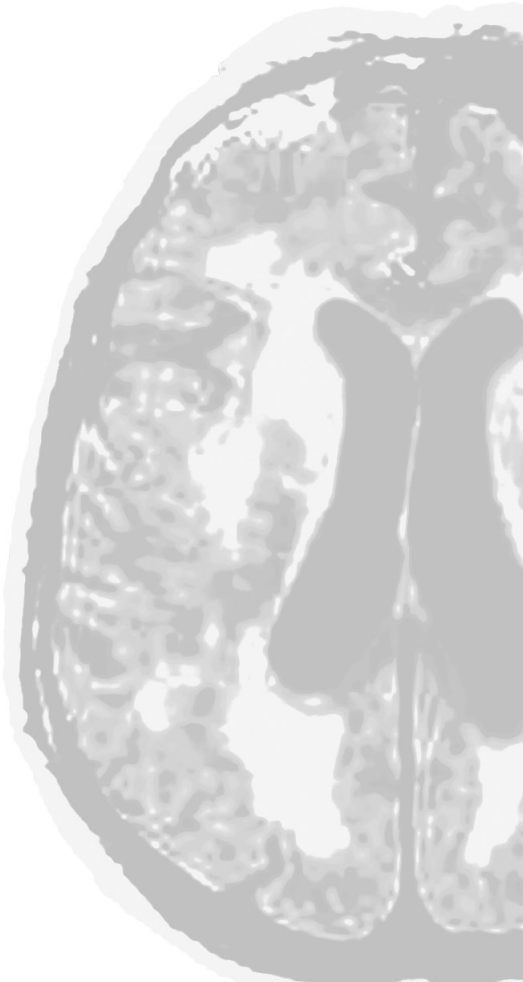
References

1. Baldwin RC, O'Brien J. Vascular basis of late-onset depressive disorder. Br J Psychiatry 2002;180:157-60.
2. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. Arch Gen Psychiatry 1997;54(10):915-22.
3. Chemerinski E, Robinson RG. The neuropsychiatry of stroke. Psychosomatics 2000;41(1): 5-14.
4. Fujikawa T, Yamawaki S, Touhouda Y. Incidence of silent cerebral infarction in patients with major depression. Stroke 1993;24(11): 1631-4.
5. Soares JC, Mann JJ. The anatomy of mood disorders--review of structural neuroimaging studies. Biol Psychiatry 1997;41(1):86-106.
6. de Groot JC, de Leeuw FE, Oudkerk M, Hofman A, Jolles J, Breteler MM. Cerebral white matter lesions and depressive symptoms in elderly adults. Arch Gen Psychiatry 2000; 57(11):1071-6.
7. Steffens DC, Krishnan KR, Crump C, Burke

GL. Cerebrovascular disease and evolution of depressive symptoms in the cardiovascular health study. Stroke 2002;33(6):1636-44.
8. de Leeuw FE, de Groot JC, Achten E, et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001;70(1):9-14.
9. Hofman A, van Laar A, Klein F, Valkenburg H. Coffee and cholesterol (letter). N Engl J Med 1983;309(20):1248-9.
10. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991;7(4): 403-22.
11. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population- based rotterdam scan study. Stroke 2002;33(1):21-5.
12. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. Psychol Med 1997;27(1):231-5.
13. Diagnostic and statistical manual of mental disorders, 4th ed. Washington D.C.: American Psychiatric Association, 1994.
14. WHO.SCAN. scedules for clinical assessment in neuropsychiatry, version 2.1. Distribution from trainig centers. 2nd ed. Geneva: World Health Organisation, 1997.
15. UNESCO. International Standard Classification of Education (ISCED). Paris: UNESCO, 1976.
16. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-98.
17. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348(13): 1215-22.
18. Beekman AT, Geerlings SW, Deeg DJ, et al. The natural history of late-life depression: a 6-year prospective study in the community. Arch Gen Psychiatry 2002;59(7):605-11.
19. Thomas AJ, Perry R, Kalaria RN, Oakley A, McMeekin W, O'Brien JT. Neuropathological evidence for ischemia in the white matter of the dorsolateral prefrontal cortex in late-life depression. Int J Geriatr Psychiatry 2003;18(1):7-13.
20. Carson AJ, MacHale S, Allen K, et al. Depression after stroke and lesion location: a systematic review. Lancet 2000;356(9224): 122-6.
21. Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol 2001;11(2):240-9.
22. Ritchie K, Lovestone S. The dementias. Lancet 2002;360(9347):1759-66.
23. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Lancet 2001;357(9251):169-75.
24. Schweitzer I, Tuckwell V, O'Brien J, Ames D. Is late onset depression a prodrome to dementia? Int J Geriatr Psychiatry 2002;17(11): 997-1005.
25. Ramasubbu R. Relationship between depression and cerebrovascular disease: conceptual issues. J Affect Disord 2000;57(1-3): 1-11.
26. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke 1997;28(3):652-9.

Chapter 4

Progression of white matter lesions



4.1

Measuring progression of cerebral white matter lesions on MRI; visual rating and volumetrics

Abstract

Objective – To evaluate the concordance of a volumetric method for measuring white matter lesion (WML) change with visual rating scales.

Methods – We selected a stratified sample of 20 elderly people (mean age 72 years, range 61-88 years) with an MRI examination at baseline and at 3-year follow-up from the community based Rotterdam Scan Study. Four raters assessed WML change with four different visual rating scales: the Fazekas scale, the Scheltens scale, the Rotterdam Scan Study scale, and a new visual rating scale that was designed to measure change in WML. We assessed concordance with a volumetric method with scatter plots and correlations, and interobserver agreement with intraclass correlation coefficients.

Results – For assessment of change in WML, the Fazekas-, the Scheltens- and periventricular part of the Rotterdam Scan Study scale showed little correlation with volumetrics, and low interobserver agreement. Our new WML change scale and the subcortical part of the Rotterdam Scan Study scale showed good correlation with volumetrics. After additional training, the new WML change scale showed good interobserver agreement for measuring WML change.

Conclusions – Commonly used visual rating scales are not well suited for measuring change in white matter lesion severity. Our new white matter lesion change scale is more accurate and precise, and may be of use in studies focusing on progression of white matter lesions.

Introduction

Cerebral white matter lesions (WML) are thought to result from small vessel disease, and their presence and severity increase with age and the presence of arterial hypertension.[1-3] Although the clinical significance of these lesions remains to be fully understood, WML have been associated with dementia, depression and stroke.[4-6] In healthy elderly people, WML are associated with adverse cognitive function and the presence of depressive symptoms.[7-9] Patients with Alzheimer's disease, vascular dementia and depression have more severe WML than controls.[4,5] It has been suggested that WML progress gradually over time, and may ultimately lead to subcortical vascular dementia and vascular depression or contribute to the clinical expression of Alzheimer's disease.[10] Studies that have determined progression of WML over time are limited, and comparison of their findings is difficult due to the use of different visual rating scales for the assessment of WML progression.[11-13] Evaluation of WML progression is of clinical importance, since it is needed to determine the natural course of these lesions, and to study the effect of intervention studies. Visual rating scales have proven their value in cross-sectional studies, but very little is known about the sensitivity and reliability of these scales for measuring change in WML over time. Volumetric methods may provide the most objective assessment method, but are often time consuming, and therefore not always feasible in large studies. The objective of the present study was to evaluate three commonly used visual rating scales, the Fazekas scale,[14] the Rotterdam Scan study scale,[3] and the Scheltens scale,[15] in terms of accuracy and precision in measuring change of WML in a defined population. We compared the degree of concordance with a volumetric method, and the reproducibility of these scales. In addition, we introduce a simple visual rating scale that was designed to measure change in WML over time. We compared the performance of this WML change scale with the other three visual rating scales, and with the volumetric method.

Methods

Subjects

The scan material used in the present study originates from subjects participating in the Rotterdam Scan Study, a population based study that was designed to study causes and consequences of age related brain changes in elderly people.[7] In 1995 through 1996, 1,077 nondemented elderly people aged 60 to 90 years underwent a baseline examination that included a cranial MRI scan. In 1999 through 2000, 787 of the 973 participants who were alive and eligible (not institutionalized, not moved abroad) were re-examined (response rate 81%). Of these participants, 668 underwent a second MRI (response rate 69%). We selected scan pairs from 10 participants, in a non-random manner, to serve as a training set. Additionally, we randomly selected 20 participants who had a baseline and follow-up scan, in three strata of

baseline subcortical WML severity, as assessed with the Rotterdam Scan Study scale.[3] We selected seven participants from the first tertile of subcortical WML severity, seven from the second tertile, and six from the third tertile to cover the whole range of the WML distribution. The mean age of participants was 72 years (range 61-88 years), 10 (50%) were women and 8 (40%) had hypertension. The mean time between the first and second MRI was 3.3 years (range 2.9-4.0 years).

MRI scanning and white matter lesions

Axial T1-, T2-, and proton-density(PD)-weighted cerebral MR scans were made on a 1.5-Tesla scanner (Siemens, Erlangen, Germany). The following pulse sequences were applied: T1 (700 ms/14 ms/ 2 [TR/TE/excitations]), T2 (2200 ms/80 ms), PD (2200 ms/20 ms). Slice thickness was 5 mm, with an interslice gap of 1 mm, and a matrix size of 192 x 256 pixels. MRI protocols were identical at baseline and at follow-up. We defined WML as hyperintense lesions, located in the cerebral white matter, that are visible on both T2- and PD-weighted images, and do not have a hypointense center on PD-weighted images (as in lacunes). Lesions were considered being periventricular in location when directly adjacent to the ventricles;otherwise we considered them as subcortical. If periventricular lesions extended 10 mm perpendicularly from the ventricular border, the extending part was per definition scored as a subcortical lesion.

Rating scales

We assessed WML severity at baseline and WML progression with four different visual rating scales. The Fazekas scale rates WML both in the periventricular and subcortical region on a 0 to 3 scale.[14] The Scheltens scale rates WML in the periventricular region on a 0 to 6 scale, and in the subcortical region on a 0 to 24 scale, on the basis of the size and number of the lesions.[15] It also includes ratings for basal ganglia and infratentorial areas, which were not used in this report. The Rotterdam Scan Study scale rates WML in the periventricular region on a 0 to 9 scale, and for subcortical WML a lesion volume is approximated based on number and size of the lesions.[3] In addition, we designed and used a new simple scale to measure WML change: the WML change scale. In this scale change in WML (-1 decrease, 0 no change, +1 increase) is scored in three periventricular locations (frontal caps, lateral bands, occipital caps) resulting in a periventricular score of -3 to +3, and in four subcortical locations (frontal, parietal, temporal and occipital), resulting in a subcortical score of -4 to +4. Increase is defined as the occurrence of a new focal lesion or the enlargement of a previously visible lesion;decrease is defined as the reverse (i.e. disappearance or shrinkage).

Visual rating system

All ratings were performed at the VU medical center. The MRI studies were in digital format. Four raters analyzed WML on baseline and follow-up images, using the four different visual rating scales. Raters were blinded to clinical information, but not to name, age and

scan year. WML were rated on PD- and T2-weighted images, by direct scan comparison on a personal computer, using the viewing program Radworks (version 5.1, Applicare, Zeist, the Netherlands). To optimize the comparability of the baseline and follow-up scans, images had been registered and resliced using the software package Mirit, that uses mutual information as optimization criteria.[16] After a training session in which the four raters in couples assessed ten scan pairs of the training set, a consensus meeting was held among the authors to identify and resolve any possible differences in application of the various scales. Following this training stage, each rater then individually scored the 20 series of baseline and follow-up MRI studies. The rating scales were always applied in the same order: firstly the Fazekas scale, secondly the Rotterdam Scan Study scale, thirdly the Scheltens scale and finally our WML change scale. Raters were aware which was the baseline and follow-up scan, and this may lead to bias towards finding a positive change in WML severity. In order to estimate this potential systematic measurement error, two raters reassessed the 20 series with the WML change scale in the native domain, first blinded to scan date, and two weeks later not-blinded to scan date.

Volumetric assessments

We used PD images for the volumetric quantification of WML volume on a workstation (Sparc 5;SUN, Palo Alto, Calif.). One reader identified lesions on the registered images, and then determined the areas of the lesions using home-developed software (Show_Images, version 3.6.1) in the native domain to avoid artificial enlargement of lesion areas due to reslicing. We used a seed growing method to determine WML areas on each slice for periventricular WML (frontal caps, lateral bands, occipital caps), and subcortical WML (frontal, parietal, temporal and occipital).[17] WML areas were not recorded separately for the right and left hemisphere. By summing the areas of each slice multiplied by the interslice distance, we calculated total WML volumes for the different regions. The volumetric assessments were performed twice, with an interval of six months, and the mean value of the two assessments was used in the analyses. The intraclass correlation coefficients reflecting the intrarater agreement for the baseline assessment were 0.84 for periventricular and 0.97 for subcortical WML volume respectively, with a standard deviation of the difference between the two ratings of 1.4 ml for periventricular and 0.86 ml for subcortical WML.[18]

Data analysis

For the volumetric assessment, change in WML volume was calculated by subtracting the baseline WML volume from the follow-up volume.[19] Pearson's correlation coefficient was used to assess the relation between baseline WML severity and WML change in the periventricular and subcortical region. For the visual rating scales (Fazekas scale, Scheltens scale, Rotterdam Scan Study scale), change in WML score was calculated by subtracting the baseline from the follow-up rating for each rater separately. Progression on the visual rating scales was defined as an increase of 1 point or more on the scale. We made scatter plots

to visualize the relation between the change in WML assessed with the volumetric method (in ml), and the visual rating scales. Furthermore, we assessed concordance between visual scales and volumetrics by the nonparametric Spearman's rho. Spearman's rho values of 0 were considered no relationship between the variables;values equal to 1 were considered to reflect perfect correlation. We quantified the interobserver agreement on the visual rating scales with intraclass correlation coefficients. The intraclass correlation coefficient is the biological variation between participants divided by the sum of the variation between participants and the rater variation. We estimated the possible bias in the visual ratings that may have been intoduced by being aware which were the baseline and follow-up images. Bias was expressed as the mean difference in scores on the WML change scale between not-blinded ratings and blinded ratings.[18] Furthermore, we assessed the 95% limits of agreement between the not-blinded and blinded method.

Results

White matter lesion severity at baseline and change

The median WML volumes as assessed with the volumetric method were 3.3 ml (range 1.6;10.4) at baseline and 0.7 ml (range -2.1;6.7) increase for the periventricular region, and 0.2 ml at baseline (range 0;15.2) and 0.1 ml (range -0.4;3.5) increase for the subcortical region. Mean increase in the periventricular region was 1.4 (SD 2.2) and in the subcortical region 0.5 (SD 0.9). This corresponds to a mean WML increase at a rate of 0.42 ml per year in the peri-

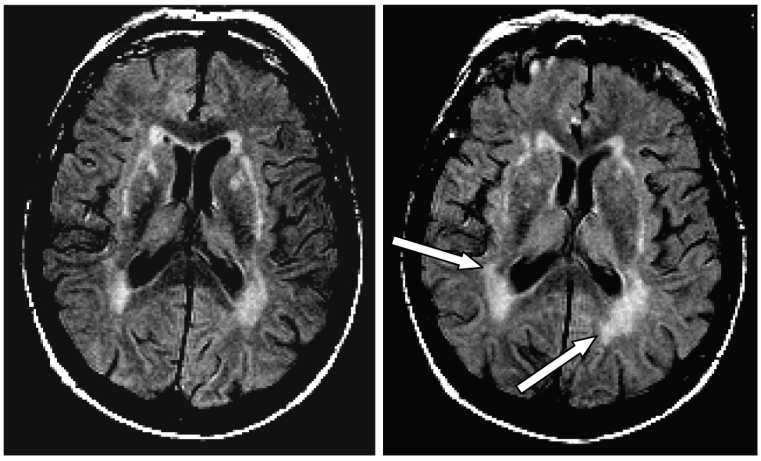


Figure 1. **WML progression in an 88-year-old woman who participated in our study.**
The composite shows a slice from the baseline study (left), and a corresponding slice from the follow up study (right). After 3 1/2 years WML progression has occurred (arrows) in the left and right occipital cap (periventricular region), extending into the parietal subcortical regions.

Table 1A. **Periventricular WML severity at baseline, change and number of participants with progression for the four visual rating scales and for the four raters**

Rating scale	Rater 1	Rater 2	Rater 3	Rater 4
Fazekas scale, 0 to 3				
Baseline, median (rg)	2(2;3)	2(1;3)	2(1;3)	2(2;3)
Change, median (rg)	0(0;1)	0(0;1)	0(0)	0(0)
Progression, n (%)	2(10%)	3(15%)	0(0%)	0(0%)
RSS scale, 0 to 9				
Baseline, median (rg)	6(4;9)	5(3;9)	5(3;9)	5.5(3;9)
Change, median (rg)	0(0;1)	0(0;2)	0(0)	0(0;1)
Progression, n (%)	6(30%)	6(30%)	0(0%)	6(30%)
Scheltens scale, 0 to 6				
Baseline, median (rg)	4(3;6)	3(3;6)	3(2;6)	3(2;6)
Change, median (rg)	0(0;2)	0(0;3)	0(0;1)	0(0;1)
Progression, n (%)	2(10%)	3(15%)	1(5%)	3(15%)
WML change scale, -3 to 3				
Change, median (rg)	1(0;3)	1(-1;3)	0(0;3)	0(0;3)
Progression, n (%)	11(55%)	11(55%)	5(25%)	8(40%)

Values are medians (range) or absolute numbers (percentage).
Progression on the visual rating scales, including the WML change scale, was defined as a positive change of 1 point or more on the scale.

Table 1B. **Subcortical WML severity at baseline, change and number of participants with progression for the four visual rating scales and for the four raters**

Rating scale	Rater 1	Rater 2	Rater 3	Rater 4
Fazekas scale, 0 to 3				
Baseline, median (rg)	1(0;3)	1(0;3)	1(0;3)	1(0;3)
Change, median (rg)	0(0;1)	0(0;1)	0(0;1)	0(0)
Progression, n (%)	3(15%)	3(15%)	2(10%)	0(0%)
RSS scale, ml				
Baseline, median (rg)	0.2(0;9.8)	0.4(0;6.4)	0.7(0;9.9)	0.6(0;7.0)
Change, median (rg)	0.2(0;1.4)	0.2(-0.1;3.8)	0.0(-0.2;2.2)	0.6(-0.1;3.4)
Progression, n (%)	2(10%)	5(25%)	1(5%)	6(30%)
Scheltens scale, 0 to 24				
Baseline, median (rg)	5.5(0;23)	6(0;20)	4(0;23)	7(1;21)
Change, median (rg)	1(0;3)	1.5(-2;4)	0(-2;6)	2(-1;12)
Progression, n (%)	11(55%)	11(55%)	5(25%)	18(90%)
WML change scale, -4 to 4				
Change, median (rg)	1(0;3)	2(-1;4)	0(-1;3)	1(0;3)
Progression, n (%)	16(80%)	17(85%)	9(45%)	17(85%)

Values are medians (range) or absolute numbers (percentage).
Progression on the visual rating scales, including the WML change scale, was defined as a positive change of 1 point or more on the scale.

ventricular region and 0.15 ml per year in the subcortical region. Figure 1 shows an example of WML progression in the periventricular and subcortical region.

WML volumes at baseline were positively correlated with WML change (Pearson correlation coefficient 0.70, p =0.001 for periventricular WML;0.90 p<0.001 for subcortical WML). Table 1 gives the WML severity at baseline and WML change as well as the number of participants with WML progression, as assessed with the different visual rating scales for the four raters. Several methods showed on average an increase in WML in both the periventricular and subcortical region, but the number of participants showing progression varied largely between the different methods applied.

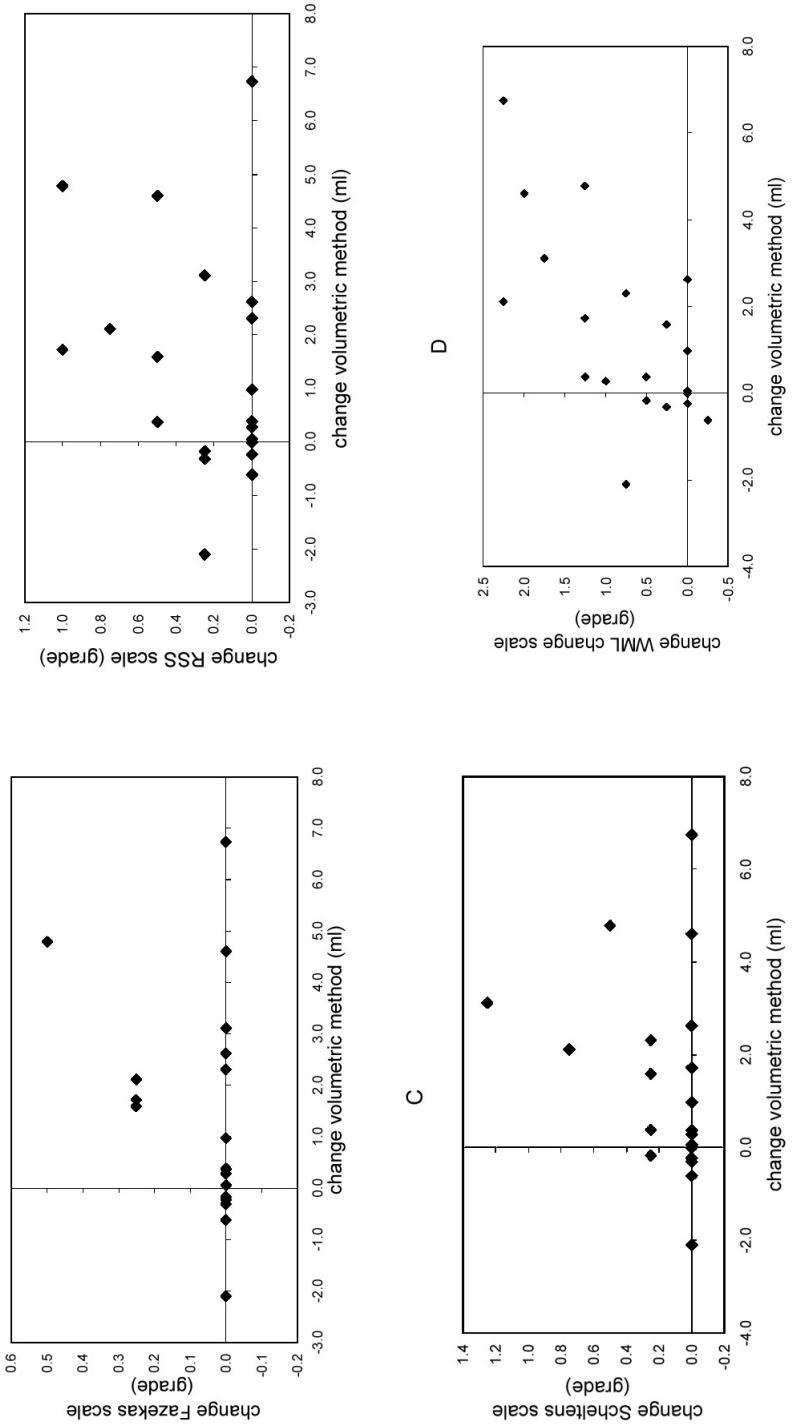
Correlation between volumetric assessment and visual rating scales

We evaluated the concordance between the volumetric WML change and the change assessed with the visual rating scales. This was done separately for the four raters, and after averaging the visual rating of the four raters in order to reduce noise due to interobserver disagreement. Figure 2 shows the scatter plots of the relationship between WML change measured with the volumetric assessment and the visual rating scales (average of four raters) in the periventricular and subcortical region. Visual inspection of the scatter plots shows comparatively good agreement between the WML change scale and the volumetric method, although the WML change scale tends to overestimate lesion change in the subcortical region (figure 2 D), and may systemetically underestimate lesion change in the periventricular region as volume change gets larger (figure 2H). Table 2 gives the nonparametric Spearman's rho between the volumetric method and the four visual rating scales on WML change. Only the subcortical part of the Rotterdam Scan Study scale and the WML change scale showed significant correlation with the volumetric method for raters 1, 2 and 3, and for the average of the four raters (table 2).

Interobserver agreement

The intraclass correlation coefficients for the interobserver agreement on baseline WML severity and change for the visual rating scales including our new WML change scale are presented in table 3. Values <0.20 were considered to reflect poor agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 good agreement, and 0.81-1.00 very good agreement.[18] The interobserver agreement for the baseline ratings on the Fazekas, Scheltens, and Rotterdam Scan Study scales was fair to good for the periventricular region and good to very good for the subcortical region (table 3). However, agreement on change was poor for the Fazekas and Scheltens scales, fair for the WML change scale and the periventricular part of the Rotterdam Scan Study scale, and moderate for the subcortical part of the Rotterdam Scan Study scale.

The raters had been using the existing rating scales by Fazekas, Scheltens, and the Rotterdam Scan Study previously and thus were better acquainted with it. In a post-hoc study that was performed using the new WML change scale after additional training, two of the


A
change Fazekas scale (grade)
change volumetric method (ml)
B
change RSS scale (grade)
change volumetric method (ml)
C
change Schelten scale (grade)
change volumetric method (ml)
D
change WML change scale (grade)
change volumetric method (ml)

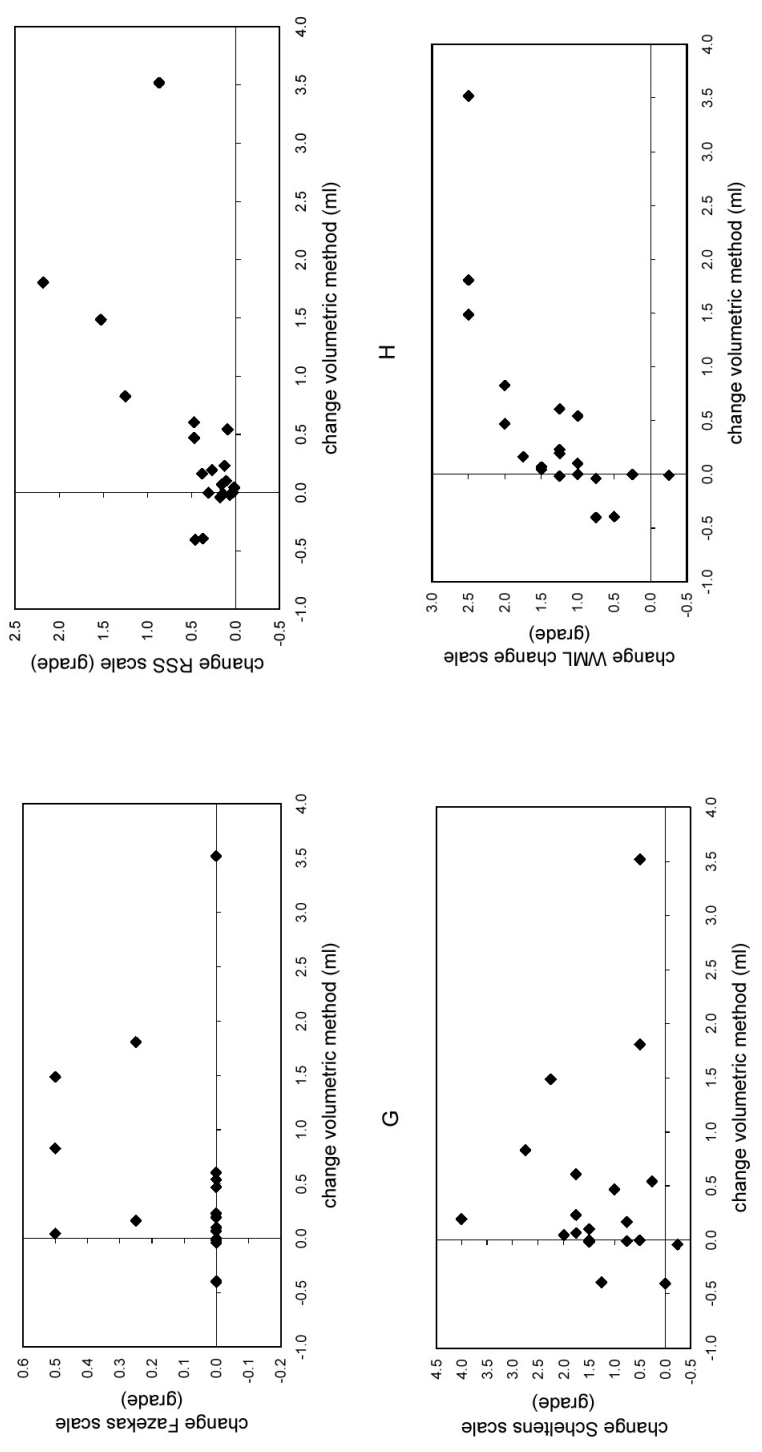


Figure 2. **Scatter plots showing the relation between change in WML measured with the volumetric method (x-axis) and the different visual rating scales (y-axis).**
In the periventricular region: A. Fazekas scale, B. Rotterdam Scan Study scale, C. Scheltens scale, D. WML change scale.
In the subcortical region: E. Fazekas scale, F. Rotterdam Scan Study scale, G. Scheltens scale H. WML change scale.

Table 2. **Correlation between volumetrics and visual rating of WML change assessed by the nonparametric Spearman's rho test.**

	Spearman's rho				
	Rater 1	Rater 2	Rater 3	Rater 4	Mean four raters
Periventricular WML					
Fazekas scale	0.29	0.30	N.A.	N.A.	0.37
Rotterdam Scan Study scale	0.42	0.24	N.A.	0.13	0.27
Scheltens scale	0.29	0.40	0.18	0.11	0.39
WML change scale	0.55*	0.70†	0.38	0.13	0.62†
Subcortical WML					
Fazekas scale	0.28	0.13	0.43	N.A.	0.40
Rotterdam Scan Study scale	0.62†	0.59†	0.19	0.50*	0.54*
Scheltens scale	0.12	0.28	0.25	-0.18	0.27
WML change scale	0.65†	0.61†	0.60†	0.35	0.79†

*$p<0.05$
†$p<0.01$
N.A. not assessed because none of the participants showed change on the visual scale.

Table 3. **Interobserver agreement for the visual rating scales for baseline and change measurements**

	Baseline	Change
Periventricular WML		
Fazekas scale	0.37	0.08
Rotterdam Scan Study scale	0.64	0.23
Scheltens scale	0.56	0.18
WML change scale		0.39
Subcortical WML		
Fazekas scale	0.84	0.18
Rotterdam Scan Study scale	0.90	0.47
Scheltens scale	0.84	0.003
WML change scale		0.24

Numbers are intraclass correlation coefficients.

raters rated 200 additional pairs of scans. In this second sample, the interobserver agreement was 0.73 for the periventricular region, and 0.72 for the subcortical region, indicating good agreement.

Effect of blinding to the scan date

Mean difference in score on the WML change scale between the not-blinded and blinded method were +0.075 (SD 0.40) points in the periventricular region, and -0.025 (SD 0.44) in the subcortical region. This indicates there is no substantial bias towards higher progression when images are scored with knowledge of which are the baseline and which are the follow-up images. The 95% limits of agreement between the not-blinded and the blinded method were (-0.71 to +0.86) for the periventricular region, and (-0.84 to +0.89) for the subcortical region, which suggests that for an individual the not-blinded and blinded methods are unlikely to disagree more than one point on the WML change scale.

Discussion

We evaluated three commonly used visual rating scales, and one new simple visual rating scale in terms of their ability to measure change in WML severity on MRI. We assessed the concordance of the visual assessments with volumetric change, and quantified the reproducibility of the scales for measuring WML change. In a stratified sample from a defined population, during a 3-year time period, both the volumetric method and the visual rating scales showed, on average, an increase in WML. We found significant correlations with volumetric change for the subcortical part of the Rotterdam Scan Study scale and for the new WML change scale. The interobserver agreement was moderate for change on the subcortical part of the Rotterdam Scan Study scale, and fair for the WML change scale. In a post-hoc study, the interobserver agreement for the WML change scale improved to good agreement after observers had become familiarized with the scale. The Fazekas, Scheltens, and periventricular part of the Rotterdam Scan Study scales showed poor correlation with volumetric change, and poor to fair interobserver agreement on the change measurements.

Several methodological issues need to be addressed. First, there is currently no gold standard for the assessment of WML change, and our volumetric method cannot be interpreted as such. Second, the comparison between volumetric WML change and WML change measured with different visual scales is complicated by differences in type of data (continuous versus categorical) obtained with the different methods. We used rank correlation to evaluate the relationship between the visual scales and volumetrics. Unlike agreement, correlation is not affected by the scale of measurement, but does depend on the range of the quantity of the sample.[19] Therefore, the presented correlations cannot be interpreted as agreement between the visual scales and volumetrics, although they do allow for comparison between the visual scales. Third, visual rating was performed side by side, and with knowledge of the time sequence of scans, which may have led to some bias towards a higher progression rating. However, we evaluated this possible bias in a post-hoc analysis, and found that this effect was very small. Fourth, registration of the follow-up scans on the baseline scans may have caused blurring effect, and although this effect was judged to be small, it may have contributed to higher progression rating with the visual rating scales.

The Fazekas, Scheltens, and Rotterdam Scan Study scales were designed for cross-sectional assessments of WML. When applied in a cross-sectional fashion these scales show both good intra- and interobserver agreement, which largely corresponds to our findings of fair to very good interobserver agreement for the baseline assessments.[3,15,20] A previous study reported that visual rating with the Fazekas and Scheltens scales shows significant correlation with quantitative volumetric assessments.[20] However, visual assessment of WML change with these scales is problematic. There are several explanations for the disappointing performance of these scales in measuring WML change. As shown in our and other data sets, baseline WML severity is positively correlated with WML change.[11] WML that were already rated in the highest category at baseline (and which are most likely to progress) cannot con-

tribute to progression on these scales due to a ceiling effect. Furthermore, new lesions may develop or lesions may grow without crossing the limits of the categories of the scales, and thereby remain below detection on the visual scales. The subcortical part of the Rotterdam Scan study scale performed better in capturing change, most likely because it incorporates the number and size of lesions in more detail, thus avoiding a ceiling effect. However, the subcortical part of this scale is elaborate and time consuming. Our new WML change scale that was designed to measure WML change not only seemed to be valid, but also takes less time to apply. Although agreement on progression initially was fair, it approved to good agreement after additional training.

We found that during a three-year time period WML volume increased at a mean rate of 0.42 ml per year in the periventricular region and 0.15 ml per year in the subcortical region. These figures on rate of change do not directly reflect the rate of change in the population at large because of the way we constructed our sample for this validation study. The NHLBI Twin study reported a mean WML volume increase of 0.38 ml per year in 168 individual male twins with a mean age of 72 years,[21] which is comparable to the range of our findings on rate of change.

When we compare the interobserver agreement on the visual scales for the baseline assessments in the present study to those reported in the literature, interobserver agreement was comparable for periventricular WML on the Fazekas scale (0.37 vs. 0.35-0.74) and for subcortical WML on the Rotterdam Scan Study scale (0.90 vs. 0.88), higher for subcortical WML on the Fazekas scale (0.84 vs. 0.34-0.78) and Scheltens scale (0.84 vs. 0.69), but lower for periventricular WML on the Scheltens scale (0.56 vs. 0.71) and Rotterdam Scan Study scale (0.64 vs. 0.79-0.90).[3,15,20]

References

1. Longstreth WT, Jr., Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke 1996;27(8):1274-1282.
2. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke 1997;28(3):652-659.
3. de Leeuw FE, de Groot JC, Achten E, et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001;70(1):9-14.
4. Barber R, Scheltens P, Gholkar A, et al. White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. J Neurol Neurosurg Psychiatry 1999;67(1):66-72.
5. O'Brien J, Desmond P, Ames D, Schweitzer I, Harrigan S, Tress B. A magnetic resonance imaging study of white matter lesions in depression and Alzheimer's disease. Br J Psychiatry 1996;168(4):477-485.
6. Leys D, Englund E, Del Ser T, et al. White matter changes in stroke patients. Relationship with stroke subtype and outcome. Eur Neurol 1999;42(2):67-75.
7. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and cognitive

function: the Rotterdam Scan Study. Ann Neurol 2000;47(2):145-151.

8. DeCarli C, Murphy DG, Tranh M, et al. The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. Neurology 1995;45(11):2077-2084.
9. Steffens DC, Krishnan KR, Crump C, Burke GL. Cerebrovascular disease and evolution of depressive symptoms in the cardiovascular health study. Stroke 2002;33(6):1636-1644.
10. Awad IA, Johnson PC, Spetzler RF, Hodak JA. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. II. Postmortem pathological correlations. Stroke 1986;17(6):1090-1097.
11. Schmidt R, Fazekas F, Kapeller P, Schmidt H, Hartung HP. MRI white matter hyperintensities: three-year follow-up of the Austrian Stroke Prevention Study. Neurology 1999;53(1):132-139.
12. Veldink JH, Scheltens P, Jonker C, Launer LJ. Progression of cerebral white matter hyperintensities on MRI is related to diastolic blood pressure. Neurology 1998;51(1):319-320.
13. Wahlund LO, Almkvist O, Basun H, Julin P. MRI in successful aging, a 5-year follow-up study from the eighth to ninth decade of life. Magn Reson Imaging 1996;14(6):601-608.
14. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987;149(2):351-356.
15. Scheltens P, Barkhof F, Leys D, et al. A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. J Neurol Sci 1993;114(1): 7-12.
16. Maes F, Collignon A, Vandermeulen D, Marchal G, Suetens P. Multimodality image registration by maximization of mutual information. IEEE Trans Med Imaging 1997;16(2): 187-198.
17. van Walderveen MA, Barkhof F, Hommes OR, et al. Correlating MRI and clinical disease activity in multiple sclerosis: relevance of hypointense lesions on short-TR/short-TE (T1-weighted) spin-echo images. Neurology 1995;45(9):1684-1690.
18. Altman DG. Practical statistics for medical research. Boca Raton: Chapman & Hall; 1999.
19. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1(8476):307-310.
20. Kapeller P, Barber R, Vermeulen RJ, et al. Visual rating of age-related white matter changes on magnetic resonance imaging: scale comparison, interrater agreement, and correlations with quantitative measurements. Stroke 2003;34(2):441-445.
21. DeCarli C, Swan GE, Park M, Reed T, Wolf PA, Carmelli D. Longitudinal changes in brain and white matter hyperintensity volumes among elderly male twins from the NHLBI twin study. Neurology 2002;58 (Suppl 3):A399.

4.2

Progression of cerebral white matter lesions in the population-based Rotterdam Scan Study

Abstract

Background and purpose – Cerebral white matter lesions in elderly people are mostly caused by cerebral small-vessel disease and have been associated with an increased risk of stroke, dementia and depression. We studied the rate of white matter lesion progression over time, and its relation with cardiovascular risk factors.

Methods – Six hundred sixty-eight people, aged 60 to 90 years, underwent repeated MRI scanning within a 3-year follow-up, as part of the prospective population-based Rotterdam Scan Study. We rated change in periventricular and subcortical white matter lesion severity with a semiquantitative scale, and graded progression as no, minor or marked. We assessed risk factors for white matter lesion progression with logistic and multinomial logistic regression analysis.

Results – Twenty-seven percent of participants showed any and 9% showed marked progression of white matter lesions in the periventricular region. Thirty-two percent showed any and 10% showed marked progression in the subcortical region. White matter lesion severity and presence of brain infarcts at baseline, higher age, high blood pressure, and current smoking were positively associated with progression of white matter lesions. Women had more marked progression of subcortical white matter lesions compared to men.

Conclusion – Approximately one-third of elderly people have progression of white matter lesions in 3 years. Presence and severity of white matter lesion and brain infarcts, higher age, female sex, elevated blood pressure and current cigarette smoking are associated with white matter lesion progression.

Introduction

Cerebral white matter lesions are frequently seen on magnetic resonance imaging (MRI) scans in elderly people.[1,2] These lesions mostly reflect demyelination and axon loss due to chronic ischemia associated with cerebral small vessel disease.[3-5] People with more severe white matter lesions have an increased risk of stroke, dementia, and depression.[6-8]

Cross-sectional studies reported on the higher prevalence and increased severity of white matter lesions with older age. Hypertension is considered the main risk factor, but other cardiovascular risk factors may be related to these lesions as well.[1,5,9-15] Data on change of white mater lesions in community dwelling people are however scarce.[16] The Austrian Stroke Prevention Study reported progression of white matter lesions within three years in 18% of the 273 participants. Diastolic blood pressure and severe white matter lesions at baseline were the only predictors of lesion progression.[16,17]

We investigated in a large population-based sample of elderly people, the rate, location and configuration of change of cerebral white matter lesions. Furthermore, we studied the association of age, sex, severity and presence of white matter lesions and brain infarcts at baseline, and cardiovascular risk factors with progression of cerebral white matter lesions.

Methods

Subjects

The Rotterdam Scan Study is a prospective population-based cohort study designed to study the causes and consequences of age related brain changes in elderly people.[18] We randomly selected people 60 to 90 years of age, stratified on age and sex, from two ongoing population based studies, the Rotterdam Study and the Zoetermeer study.[19,20] A total of 1,077 elderly people without dementia participated (response rate 63%). The medical ethics committee of the Erasmus Medical Center approved the study, and each participant gave written informed consent. The baseline examination in 1995 to 1996 comprised a structured interview, physical examination, blood sampling, and neuropsychological tests, as well as a cerebral MRI scan.

In 1999 to 2000, we re-invited 951 people who were eligible for a second MRI examination from the cohort of 1,077 people who had a MRI examination at baseline. In total 668 participated (response rate 70%). One-hundred-twenty-six participants were ineligible to undergo a second MRI for the following reasons: 82 died, 19 were institutionalized, 19 had MRI contraindications, 3 moved abroad, and 3 could not be reached. The reasons for refusal to participate in the second examination were as follows: claustrophobia developed at the baseline MRI (n=98), too much trouble (n=90), no interest (n=77), and other reasons (n=18).

MRI scanning

At baseline, we made axial T1-, T2-, and proton-density- (PD) weighted cerebral MR scans on a 1.5-Tesla scanner (for participants from Zoetermeer, MR Gyroscan, Philips; for participants from Rotterdam MR VISION, Siemens, with comparable pulse sequences).[18] In 1999 to 2000 all second MRI scans were made with the MR VISION scanner and the same sequences.

Lesion rating

We considered white matter lesions to be periventricular if they were directly adjacent to the ventricle; otherwise we considered them subcortical. At baseline, we scored white matter lesions severity on hardcopy as described previously.[18] We scored periventricular white matter lesions semiquantitatively in order to obtain a total periventricular score (range 0-9). For subcortical white matter lesion, we approximated a total volume (range 0-29.5 ml). We defined infarcts as focal hyperintensities on T2-weighted images, 3 mm in size or larger. Lesions in the white matter also had to have corresponding prominent hypointensities on T1-weighted images, in order to distinguish them from cerebral white matter lesions. We defined lacunar infarcts as infarcts sized 3 to 20 mm and located in the subcortical white matter or basal ganglia.

To assess change of white matter lesions, we transferred digital images to a Linux PC, and used a Matlab software (Mathworks) viewing tool. Two raters independently analyzed progression of white matter lesions severity on PD- and T2-weighted images by direct scan comparison. We used a new white matter lesions change scale, since commonly used rating scales designed for cross-sectional assessments of white matter lesions are not well suited for measuring change.[21] Baseline and follow-up series were downloaded side-by-side, with the baseline and follow-up scan randomly appearing on the right or left side of the screen. We assessed the difference in white matter lesion severity between the right and left images. In the periventricular region, we assessed difference in size of lesions in the frontal caps, lateral bands, and occipital caps, in the left and right hemisphere (negative difference -1 point, no difference 0 points, positive difference +1 point, resulting in a score of -6 to +6). In the subcortical region, we assessed difference in number, size, or confluence of lesions in the frontal, parietal, temporal and occipital lobes of the left and right hemisphere (negative difference -1 point, no difference 0 points, positive difference +1 point, resulting in a score of -8 to +8). If periventricular lesion change extended beyond 10 mm outside the border of the ventricle, we considered the change to have occurred in both the periventricular and subcortical region. Raters were blinded to all clinical information, including scan date, for participants derived from the Rotterdam Study. This was not possible for participants derived from the Zoetermeer Study due to the change in MRI between baseline and follow-up. If raters disagreed one point or less on the scale, we used the mean of the ratings, otherwise we held a consensus meeting. The change rating showed good interobserver agreement (intraclass correlation coefficient periventricular region 0.79; subcortical region 0.75), and good to

very good intraobserver agreement (intraclass correlation coefficient periventricular region 0.70-0.89; subcortical region 0.78-0.93). Digital images were not available in 52 participants due to technical problems. In these participants, we assessed white matter lesion change on hardcopy. We defined progression as an increase of 1 point or more between baseline and follow-up. Progression was categorized into minor progression (score 1-2.5) and marked progression (score 3 or higher).

We evaluated the effect of non-blinding of the scan date.[21] The difference between non-blinded and blinded scores was 0.075 (95%CI -0.71; +0.86) points for periventricular white matter lesions, and 0.025 (95%CI -0.84; +0.89) points for subcortical white matter lesions. Therefore, non-blinding in the Zoetermeer Study part of our study did not introduce bias.

Cardiovascular risk factors

Blood pressure was measured twice on the right arm with a random-zero sphygmomanometer. The two measurements were averaged. Hypertension was defined according to WHO-ISH guidelines, as systolic blood pressure of ≥ 160 mmHg, diastolic blood pressure of ≥ 100 mmHg, or the use of blood pressure lowering medication.[22] Smoking habits were classified as never, former and current cigarette smoking. We considered diabetes mellitus to be present if the random glucose level was ≥ 11.1 mmol/l or if a person was taking oral antidiabetics or insulin. The presence of atrial fibrillation was assessed by MEANS interpretation of a 12-lead ECG (ACTA ECG, ESAOTE).[23] Serum total cholesterol and high-density lipoprotein were determined with an automated enzymatic procedure (Hitachi analyzer, Roche Diagnostics). To determine plasma total homocysteine levels, we used a fluorescence polarisation immunoassay on an IMx analyser (Abbott Laboratories).[9] Partial arterial oxygen saturation was measured twice, with a pulse oximeter (Andos, Oxycount). The two measurements were averaged (range 86-99%).15 Participants underwent ultrasonography of both carotid arteries with a 7.5-MHz linear-array transducer and a Duplex scanner (ATL Ultra-Mark IV, Advanced Technology Laboratories). We examined the right and left carotid arteries for the presence of plaques in the common carotid artery, bifurcation, and internal carotid artery and calculated the total number of sites with plaques present (range 0-6). Intima-media thickness was measured by longitudinal 2-dimensional ultrasound of the common carotid artery. We calculated the mean common carotid intima-media thickness as the mean of the near and far walls of both the right and left common carotid arteries.[13] Apolipoprotein E (APOE) genotyping was done on coded genomic DNA samples.[24] The distribution of the APOE genotype in this population was in Hardy-Weinberg equilibrium.

Data analysis

We used age and sex adjusted analysis of covariance to assess whether baseline risk factors differed between people with and without a second MRI assessment. We calculated Spearman's rho for correlation between periventricular and subcortical white matter lesion progression. We used logistic and multinomial logistic regression analyses to study the

association of risk factors with any, minor and marked white matter lesion progression. People with a negative difference in white matter lesion severity over time were added to the group of people with no progression. All analyses were adjusted for age and sex, and additionally for cardiovascular risk factors. Baseline white matter lesion severity could confound the relation between risk factors and white matter lesion progression. However since it could also be an intermediate factor, adjustment for baseline severity may result in over adjusted estimates as well. To evaluate these effects we additionally adjusted the analyses for baseline white matter lesion severity.

Table 1. **Baseline characteristics of people who had a 2nd MRI assessment and for those who refused or were ineligible.**

	People with 2nd MRI assessment n = 668	People that refused 2nd MRI assessment n = 283	People ineligible for 2nd MRI assessment n = 126
Age, year	71 (7)	74 (7)*	77 (8)*
Women	52	57	41*
Systolic blood pressure, mmHg	147 (21)	149 (22)	146 (23)
Diastolic blood pressure, mmHg	79 (12)	79 (12)	75 (12)*
Use of antihypertensive medication	30	42*	43
Hypertension	47	57	58
Current smoking	16	13	21*
Former smoking	51	50	52
Diabetes	5	8	13*
Atrial fibrillation	3	1	9*
Total cholesterol, mmol/l	5.9 (1.0)	5.9 (1.0)	5.7 (1.3)
High-density lipoprotein, mmol/l	1.3 (0.3)	1.3 (0.4)	1.2 (0.3)*
Use of lipid-lowering drugs	7	8	2*
Total homocysteine, μmol/l	11.0 (3.6)	11.7 (4.2)	13.9 (5.4)*
Oxygen saturation, $\%SpO_2$	96.4 (1.3)	96.3 (1.2)	96.3 (1.5)
Intima media thickness, mm	0.86 (0.15)	0.87 (0.13)	0.93 (0.17)
Plaques in carotid artery (range 0-6)	1.5 (1.6)	1.8 (1.6)	2.3 (1.7)*
Periventricular white matter lesions (range 0-9)	2.2 (2.1)	2.5 (2.1)	3.5 (2.5)*
Subcortical white matter lesions, ml	1.2 (2.5)	1.5 (3.1)	2.1 (4.1)
Brain infarcts	22	25	34
Lacunar infarcts	20	23	28
APOE ε4 allele	30	30	22

Values are unadjusted means (SD) or percentages
*Age and sex adjusted mean or percentage is significantly different ($p < 0.05$) from people with 2nd MRI assessment

Results

People who underwent a second MRI were younger and less often used blood pressure lowering medication than people who refused a second examination (table 1). They were also younger, healthier and more often female than people who were ineligible for a second MRI (table 1). The mean follow-up between the two MRI assessments was 3.3 (SD 0.2) years.

Twenty seven percent of the people had any progression of periventricular white matter lesions and 32% had any progression of subcortical white matter lesions, whereas 39% had any progression of white matter lesions in either region (table 2). Spearman's rho for the correlation between progression in the periventricular and subcortical region was 0.60 ($p<0.001$)). Two people had minor regression of white matter lesions in the periventricular and 13 in the subcortical region. Within people with periventricular white matter progression, 17% had progression of the frontal caps, 56% of the bands and 73% of the occipital caps. Within the people with subcortical white matter lesion progression, 71% had progression in the frontal, 63% in the parietal, 12% in the occipital and 7% in the temporal lobe. The hemispheres were equally affected. Marked subcortical white matter progression predominantly consisted of growth and confluence of lesions, whereas minor progression mostly consisted of new small lesions (figure 1).

Table 2. **Relationship between periventricular and subcortical white matter lesion (WML) progression.**

		Periventricular WML progression			
		no	minor	marked	totals
Subcortical WML Progression	no	407 (61)	38 (6)	6 (1)	451 (68)
	minor	72 (11)	59 (9)	19 (3)	150 (23)
	marked	9 (1)	23 (3)	35 (5)	67 (10)
	totals	488 (73)	120 (18)	60 (9)	668 (100)

Numbers are absolute numbers of people and percentages of overall total.

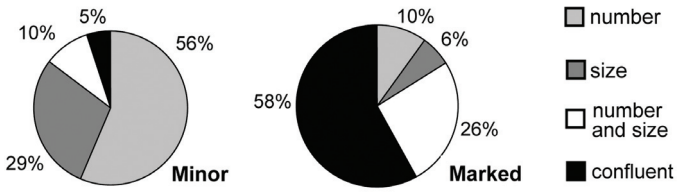


Figure 1. **Configuration of minor and marked subcortical white matter lesion progression.**

Table 3. **Relationship between baseline brain lesions and progression of white matter lesions.**

Baseline brain lesions	Odds ratio periventricular WML progression (95%CI)			Odds ratio subcortical WML progression (95%CI)		
	Any	Minor	Marked	Any	Minor	Marked
Periventricular WML (range 0-9)	1.90 (1.69; 2.14)	1.77 (1.56; 2.00)	2.35 (1.97; 2.80)	1.64 (1.48; 1.81)	1.45 (1.30; 1.62)	2.33 (1.97; 2.76)
Subcortical WML (per ml)	1.77 (1.54; 2.04)	1.67 (1.41; 1.89)	2.03 (1.73; 2.39)	1.74 (1.51; 2.01)	1.63 (1.41; 1.89)	2.03 (1.73; 2.39)
Infarcts	3.20 (2.12; 4.84)	2.38 (1.48; 3.82)	5.84 (3.21; 10.60)	3.11 (2.06; 4.70)	2.13 (1.35; 3.36)	5.62 (3.18; 9.91)
Lacunar infarcts	3.05 (1.99; 4.69)	2.13 (1.29; 3.52)	5.95 (3.24; 10.94)	2.94 (1.98; 4.37)	2.17 (1.35; 3.50)	6.22 (3.49; 11.09)

Age and sex adjusted odds ratio per grade increase in periventricular and per millilitre increase in subcortical white matter lesions and for presence of infarcts with people without progression as the reference (95% confidence intervals)

White matter lesion severity and the presence of brain infarcts, of which 90% were lacunar, on baseline MRI were strongly related to progression of white matter lesions (table 3). None of the people without lesions at baseline, and three people with only small punctate lesions (<3 mm) at baseline, had marked subcortical white matter lesion progression. The extent of progression of both periventricular and subcortical white matter lesions was strongly related to age (figure 2). Women had a higher risk of subcortical white matter lesions progression than men, and this difference reached significance for marked subcortical white matter lesions (table 4). Systolic and diastolic blood pressure were positively associated with white matter lesion progression (table 4), which remained after adjustment for use of blood pressure lowering medication (data not shown). Current cigarette smoking was positively associated with marked white matter lesion progression (table 4). We did not observe a relation between atrial fibrillation, carotid atherosclerosis, homocysteine levels, oxygen saturation and white matter lesion progression.

Additional adjustment for baseline white matter lesion severity, strongly diminished the strength of the associations between white matter lesion progression and age (odds ratios per year increase in age for progression in the periventricular region 1.05 (95%CI 1.02; 1.08), in the subcortical region 1.02 (95%CI 1.00; 1.05)), sex (odds ratio of women for marked pro-

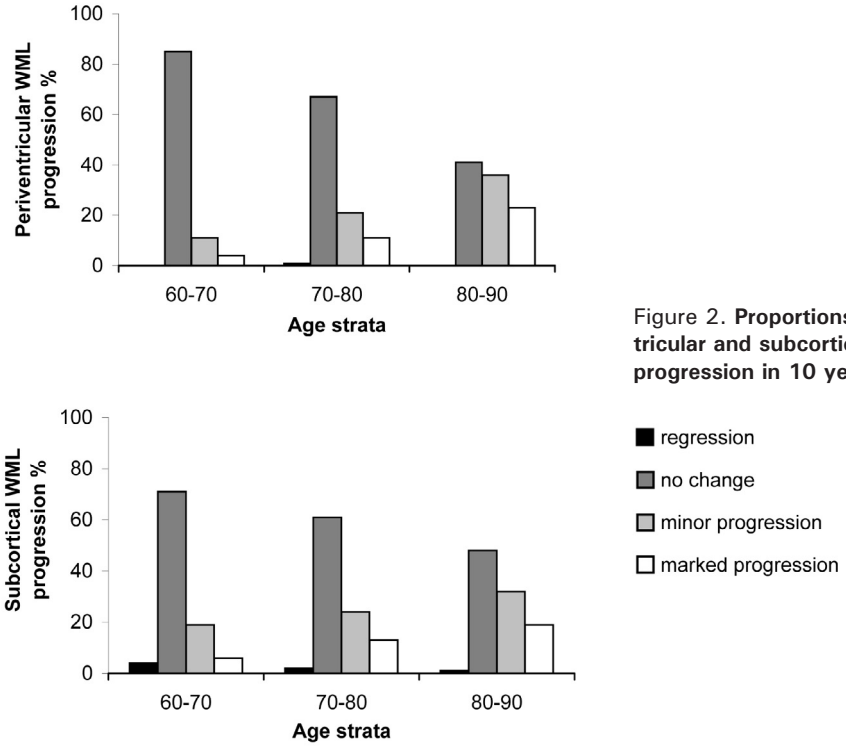


Figure 2. **Proportions of periventricular and subcortical white lesion progression in 10 years age strata.**

Table 4 Relationship between baseline determinants and progression of white matter lesions

	Odds ratios periventricular WML progression (95%CI)			Odds ratios subcortical WML progression (95%CI)		
	Any	Minor	Marked	Any	Minor	Marked
Age (per year)	1.12 (1.09; 1.15)	1.11 (1.07; 1.14)	1.15 (1.11; 1.20)	1.07 (1.04; 1.09)	1.06 (1.03; 1.08)	1.10 (1.06; 1.14)
Sex (women)	1.21 (0.84; 1.74)	1.10 (0.72; 1.66)	1.58 (0.89; 2.79)	1.09 (0.78; 1.52)	0.89 (0.61; 1.29)	1.80 (1.05; 3.10)
SBP (per SD)	1.23 (1.02;1.48)	1.24 (1.00; 1.53)	1.21 (0.90; 1.61)	1.18 (0.99; 1.40)	1.13 (0.93; 1.37)	1.28 (0.98; 1.67)
DBP (per SD)	1.32 (1.10; 1.59)	1.29 (1.05; 1.59)	1.38 (1.04; 1.84)	1.21 (1.03; 1.44)	1.14 (0.95; 1.39)	1.38 (1.06; 1.80)
Hypertension	1.41 (0.97; 2.04)	1.48 (0.97; 2.26)	1.26 (0.71; 2.25)	1.22 (0.87; 1.73)	1.37 (0.93; 2.01)	1.01 (0.60; 1.75)
Current smoking	1.87 (1.04; 3.34)	1.51 (0.77; 2.95)	2.96 (1.25; 7.04)	1.45 (0.86; 2.45)	1.08 (0.59; 1.98)	2.82 (1.25; 6.36)
Former smoking	1.06 (0.66; 1.70)	0.99 (0.58; 1.70)	1.21 (0.58; 2.51)	0.96 (0.62; 1.46)	0.77 (0.47; 1.24)	1.58 (0.81; 3.12)
Diabetes	0.79 (0.35; 1.78)	0.53 (0.18; 1.56)	1.38 (0.48; 3.95)	0.61 (0.28; 1.33)	0.39 (0.13; 1.14)	1.14 (0.41; 3.17)
AF	0.66 (0.21; 2.10)	0.85 (0.25; 2.87)	0.31 (0.03; 2.71)	0.61 (0.20; 1.82)	0.57 (0.16; 2.08)	0.68 (0.14; 3.35)
Cholesterol (per SD)	0.90 (0.74; 1.08)	0.87 (0.70; 1.08)	0.94 (0.71; 1.26)	0.93 (0.78; 1.11)	0.89 (0.73; 1.09)	1.03 (0.78; 1.35)
HDL (per SD)	1.00 (0.83; 1.21)	0.95 (0.76; 1.18)	1.12 (0.84; 1.47)	1.13 (0.95; 1.35)	1.14 (0.93; 1.39)	1.12 (0.86; 1.47)
Homocysteine (per SD)	1.08 (0.90; 1.30)	1.13 (0.92; 1.39)	0.98 (0.73; 1.31)	0.95 (0.80; 1.14)	0.97 (0.79; 1.18)	0.92 (0.70; 1.22)
Oxygen saturation (per SD)	0.87 (0.72; 1.06)	0.85 (0.69; 1.05)	0.92 (0.69; 1.24)	1.05 (0.88; 1.25)	1.05 (0.86; 1.28)	1.05 (0.80; 1.39)
Carotid IMT (per SD)	1.00 (0.82; 1.23)	0.98 (0.78; 1.24)	1.05 (0.78; 1.42)	1.12 (0.33; 3.82)	1.03 (0.84; 1.27)	0.97 (0.72; 1.32)
Carotid plaques (range 0-6)	1.09 (0.97; 1.24)	1.15 (1.00; 1.32)	0.98 (0.81; 1.19)	1.11 (0.99; 1.25)	1.16 (1.03; 1.32)	0.98 (0.81; 1.18)
APOE e4 carrier	0.91 (0.59; 1.40)	0.84 (0.51; 1.38)	1.07 (0.55; 2.07)	1.07 (0.73; 1.58)	1.11 (0.72; 1.70)	1.00 (0.53; 1.87)

Age and sex adjusted odds ratios with people without progression as the reference (95% confidence intervals). WML = white matter lesion; SBP = systolic blood pressure; DBP = diastolic blood pressure; AF = atrial fibrillation; HDL = high density lipoprotein; IMT = intima-media thickness

gression of subcortical white matter lesions 1.67 (95%CI 0.89; 3.12)), systolic blood pressure (odds ratio per standard deviation increase for progression in the periventricular region 1.09 (95%CI 0.87;1.36), in the subcortical region 1.07 (95%CI 0.88;1.29)), and diastolic blood pressure (odds ratio per standard deviation increase for progression in the periventricular region 1.17 (95%CI 0.94;1.45), in the subcortical region 1.09 (95%CI 0.91;1.31)). The associations between current cigarette smoking and marked white matter lesion progression did not change after adjustment for white matter lesion severity at baseline. The association of blood pressure, hypertension, and smoking with progression of white matter lesions hardly changed after additional adjustment for other cardiovascular risk factors (data not shown).

Discussion

We found that approximately 30% of people between 60 and 90 years of age had any progression and 10% had marked progression of periventricular and subcortical white matter lesions within a period of 3-years. Older age, female sex, higher blood pressure, current cigarette smoking and high white matter lesion severity and the presence of brain infarcts at baseline were associated with progression of white mater lesions. The associations were independent of other cardiovascular risk factors.

The strengths of the present study are its large number of participating elderly people from the general population, its prospective design, and the assessment of a large number of risk factors. Still, several methodological issues should be considered. First, there is a possibility of selection bias. People who participated were younger and healthier compared to those who were ineligible or refused a second MRI scan. Therefore, the progression of white matter lesions in our study may be an underestimation of the progression in the population at large. The same selection may also have attenuated the estimates for the associations between risk factors and progression of white matter lesions. Second, we changed MRI scanner in half of our cohort, which made it not possible to blind for study date in that part. However, we evaluated the effect of non-blinding and found that it did not cause overestimation of progression in our study.[21] Furthermore, the rate of progression and the strength of the associations between risk factors and white matter lesion progression were not different for the blinded and non-blinded group. Third, adjustment for baseline lesions could in theory introduce overestimated risk associations. This results from regression towards the mean as a result of measurement error.[25] We consider this effect to be small, firstly because we used a change scale instead of calculated differences between repeated measurements, and secondly because none of the risk estimates increased after adjustment for lesions at baseline.

It is hard to compare the distribution of white matter lesions between studies, due to differences in study population, imaging techniques, lesion rating, lesion categorization and risk factor distributions, and the same holds for comparing progression of white matter le-

sions.[26] In the Austrian Stroke Prevention Study,1[6,17] 18% of the participants had any and 8% had marked progression within 3 years of follow-up. The lower proportion of progression of white matter lesions in this study compared to our findings could be explained by the exclusion of people with cerebrovascular disease, the 10 years lower mean age of the participants and the lower response rate.

In cross-sectional studies, older age and higher blood pressure, in particular diastolic blood pressure, were strongly associated with white matter lesion severity.[2,18] Furthermore, women tended to have more severe white matter lesions.[2] We observed that these risk factors are also associated with progression of white matter lesions. The Austrian Stroke Prevention study reported the same associations of age and diastolic blood pressure with progression of white matter lesions.[16,17] In addition, we found that current cigarette smoking was also associated with periventricular and subcortical white matter lesion progression.

Our data confirm that white matter lesion severity and presence of brain infarcts at baseline are strongly associated with lesion progression.[16,17,27] The association between brain infarcts and progression of white matter lesions can be explained by a shared exposure to risk factors and susceptibility for these factors, resulting in a common pathological substrate.[27,28] Baseline white matter lesions and lacunar infarcts reflect small vessel disease and chronic hypoperfusion. Continuation of a state of hypoperfusion could, without additional vessel damage, result in lesion progression. We adjusted for baseline white matter lesions to assess whether risk factors were associated with progression independent of the severity of small vessel damage that was already present. This adjustment strongly diminished the strength of the associations between risk factors and progression of white matter lesions, suggesting that the effect of age and high blood pressure on white matter lesion progression in a 3-year period is for a large part explained by the relation with severity of small vessel disease at baseline.

We reported previously on the cross-sectional association between atrial fibrillation,[11] carotid atherosclerosis,[12] homocysteine levels,[9] oxygen saturation[15] and white matter lesions. We did not observe an association between these factors and progression of white matter lesions. This could be explained by selective follow-up as noted earlier. We repeated the cross-sectional analyses with these risk factors in the 668 people with a second MRI and found no significant associations (data not shown), confirming selective follow-up. Alternative explanations for these distinct findings are the smaller samples size, and the possibility that baseline white matter lesion distribution is a more robust measure of small vessel disease since it reflects accumulation of lesions over a longer period of time.

In this study we considered progression of white matter lesions as an increase in number, size or confluence of lesions. This "lesion volume"-based paradigm may not cover the complete pathofysiology, since progression could, apart from increase in volume, also be increase in tissue damage within existing lesions. Confluent white matter lesion show histopathological similarity to lacunar infarcts, whereas smaller lesions correspond to no or incomplete infarction.[3,4] A prospective study in patients with CADASIL showed progression

in tissue damage with diffusion tensor imaging.[29] Future studies on the development of progression of white matter lesions should therefore not only examine change in number and size of lesions, but should also take change in integrity of the white matter into account.

References

1. Liao D, Cooper L, Cai J, et al. The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC Study. Neuroepidemiology 1997; 16:149-62.
2. de Leeuw FE, de Groot JC, Achten E, et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001; 70:9-14.
3. Fazekas F, Kleinert R, Offenbacher H, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology 1993; 43:1683-9.
4. van Swieten JC, van den Hout JH, van Ketel BA, Hijdra A, Wokke JH, van Gijn J. Periventricular lesions in the white matter on magnetic resonance imaging in the elderly. A morphometric correlation with arteriolosclerosis and dilated perivascular spaces. Brain 1991; 114 (Pt 2):761-74.
5. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke 1997; 28:652-9.
6. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. Lancet Neurol 2003; 2:89-98.
7. Vermeer SE, Hollander M, Van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the rotterdam scan study. Stroke 2003; 34: 1126-9.
8. Prins ND, van Dijk EJ, Den Heijer T, et al. Cerebral white matter lesions and the risk of dementia. The Rotterdam Scan Study. Arch Neurol; (in press).
9. Vermeer SE, van Dijk EJ, Koudstaal PJ, et al. Homocysteine, silent brain infarcts, and white matter lesions: The Rotterdam Scan Study. Ann Neurol 2002; 51:285-9.
10. de Leeuw FE, de Groot JC, Oudkerk M, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. Brain 2002; 125:765-72.
11. de Leeuw FE, de Groot JC, Oudkerk M, et al. Atrial fibrillation and the risk of cerebral white matter lesions. Neurology 2000; 54: 1795-801.
12. de Leeuw FE, de Groot JC, Bots ML, et al. Carotid atherosclerosis and cerebral white matter lesions in a population based magnetic resonance imaging study. J Neurol 2000; 247: 291-6.
13. Bots ML, van Swieten JC, Breteler MM, et al. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. Lancet 1993; 341:1232-7.
14. Longstreth WT, Jr., Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke 1996; 27:1274-82.
15. van Dijk EJ, Vermeer SE, De Groot JC, et al. Arterial oxygen saturation, COPD and cerebral small vessel disease. JNNP (in press).
16. Schmidt R, Fazekas F, Kapeller P, Schmidt H, Hartung HP. MRI white matter hyperintensities: three-year follow-up of the Austrian Stroke Prevention Study. Neurology 1999; 53:132-9.
17. Schmidt R, Enzinger C, Ropele S, Schmidt H, Fazekas F. Progression of cerebral white matter lesions: 6-year results of the Austrian Stroke Prevention Study. Lancet 2003; 361: 2046-8.

18. de Leeuw FE, de Groot JC, Oudkerk M, et al. A follow-up study of blood pressure and cerebral white matter lesions. Ann Neurol 1999; 46:827-33.
19. Hofman A, van Laar A, Klein F, Valkenburg H. Coffee and cholesterol (letter). N Engl J Med 1983; 309:1248-1249.
20. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991; 7:403-22.
21. Prins ND, van Straaten ECW, van Dijk EJ, et al. Measuring progression of cerebral white matter lesions on MRI; A comparison of visual rating scales in relation to volumetric change. Neurology (in press).
22. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. J Hypertens 1999; 17:151-83.
23. de Bruyne MC, Kors JA, Hoes AW, et al. Diagnostic interpretation of electrocardiograms in population-based research: computer program research physicians, or cardiologists? J Clin Epidemiol 1997; 50:947-52.
24. Wenham PR, Price WH, Blandell G. Apolipoprotein E genotyping by one-stage PCR. Lancet 1991; 337:1158-9.
25. Vollmer WM. Comparing change in longitudinal studies: adjusting for initial value. J Clin Epidemiol 1988; 41:651-7.
26. van Dijk EJ, Prins ND, Vermeer SE, Koudstaal PJ, Breteler MM. Frequency of white matter lesions and silent lacunar infarcts. J Neural Transm Suppl 2002:25-39.
27. van Zagten M, Boiten J, Kessels F, Lodder J. Significant progression of white matter lesions and small deep (lacunar) infarcts in patients with stroke. Arch Neurol 1996; 53: 650-5.
28. Vermeer SE, Den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke 2003; 34:392-6.
29. Molko N, Pappata S, Mangin JF, et al. Monitoring disease progression in CADASIL with diffusion magnetic resonance imaging: a study with whole brain histogram analysis. Stroke 2002; 33:2902-8.

4.3

Progression of cerebral white matter lesions and the risk of stroke, dementia and depression

Abstract

Background and purpose – Cerebral white matter lesions (WML) are common in elderly people and mostly reflect ischemic damage due to cerebral small-vessel disease. We examined whether progression of WML is associated with the risk of stroke, dementia, cognitive decline, and depressive symptoms in the general population.

Methods – In 668 participants from the Rotterdam Scan Study we performed MRI of the brain both at baseline in 1995 to 1996 and again in 1999 to 2000. We assessed progression of WML with a semi-quantitative rating scale by direct scan comparison. At both visits participants underwent a structured interview, physical examination and neuropsychological testing. Throughout the study period, we monitored participants for stroke and dementia. We used multiple logistic and linear regression analysis to examine the association between WML progression and clinical outcomes.

Results – The mean follow-up period between the first and second MRI was 3.3 years. In this period about one third of participants showed WML progression. WML progression was associated with a more than three-fold increased risk of stroke and a steeper decline in global cognitive function and psychomotor speed. Marked WML progression increased the risk of dementia and depressive symptoms, which was partly explained by the occurrence of stroke during follow-up.

Conclusions – Elderly people with WML progression have an increased risk of stroke, dementia, cognitive decline and depressive symptoms in comparison to those without WML progression.

Introduction

Cerebral white matter lesions are frequently observed on MRI in elderly people. These lesions mostly reflect incomplete infarction of the cerebral white matter as a result of ischemic damage caused by cerebral small vessel disease.[1] The presence and severity of WML increases with age and the presence of arterial hypertension.[2] Although the clinical importance of WML remains to be fully understood, evidence accumulates that WML are associated with the development of stroke, dementia and depression.[3,4] However, most evidence relating WML to clinical outcomes is derived from studies that used a single WML measurement. Studying progression of WML over time in relation to clinical outcomes may provide stronger arguments for a causal relationship between WML and clinical outcomes. The population-based Austrian Stroke Prevention Study reported progression of white matter lesions in 18% of individuals over 3 years.[5] In this study, lesion progression had no influence on the course of neuropsychological test performance, and this lack of association asks for further exploration. A study in patients with symptomatic carotid artery disease found that progression of WML on CT was associated with the occurrence of stroke.[6] The purpose of the present study was to examine the association between WML progression on MRI and the risk of stroke, dementia, cognitive decline, and depressive symptoms in a population-based follow-up study among elderly people.

Methods

Subjects

The Rotterdam Scan Study is a prospective, population based cohort study, designed to study causes and consequences of age-related brain changes in the elderly. The characteristics of the 1,077 participants have been described previously.[7] All participants were free of dementia at baseline. Baseline examination in 1995 to 1996 comprised a structured interview, neuropsychological tests, physical examination, blood sampling, and an MRI scan of the brain. In 1999 to 2000, of the 951 participants who were alive and eligible, 668 (70%) underwent a second MRI and were re-examined at the research center similar to the baseline examination.[8] All participants were continuously monitored after baseline for mortality, dementia and stroke until April 1st 2002.

MRI scanning

Participants underwent MRI of the brain at baseline in 1995 to 1996. We made axial T1-, T2-, and proton density (PD)-weighted cerebral MR scans on a 1.5-Tesla scanner (MR VISION, Siemens, MR Gyroscan, Philips).[7] In 1999 to 2000, participants underwent a second MRI with the use of the MR VISION scanner and the same sequences. Digital data was available for 616 participants (92%) of the 668 participants (286 of the 320 participants scanned with

the MR VISION at baseline, and 330 of the 348 participants scanned with the MR Gyroscan at baseline).

WML rating scheme

We considered WML to be in the periventricular region if they were directly adjacent to the ventricle; otherwise we considered them subcortical. Baseline WML severity was scored on hardcopy with a visual rating scale as described previously.[7] We scored periventricular WML semiquantitatively in order to obtain a total periventricular score (range: 0 to 9). For subcortical WML, we approximated a total volume based on number and size of lesions (range: 0 to 29.5 ml).

Two raters independently assessed progression of WML severity on digital T2-weighted and PD-weighted images by direct scan comparison, using a semiquantitative scale.[8,9] In the periventricular region, we assessed change in size (negative change -1 point, no change 0 points, positive change +1 point) of lesions in the frontal caps, lateral bands, and occipital caps, in the left and right hemisphere, resulting in a score of -6 to +6. In the subcortical region, we assessed change in either number, size, number and size, or confluence (negative change -1 point, no change 0 points, positive change +1 point) in the frontal, parietal, temporal and occipital lobes of the left and right hemisphere, resulting in a score of -8 to +8. If periventricular lesion change extended beyond 10 mm outside the border of the ventricle, we considered the change in both the periventricular and subcortical region. Raters were blinded to all clinical information, including scan date, for the 286 participants (43%) who had digital data available and were scanned with the MR VISION at baseline. This was not possible for the remaining 382 participants (57%) either because they changed MRI between baseline and follow-up, or because digital data was not available. The change rating showed good interobserver agreement (intraclass correlation coefficient periventricular region 0.79; subcortical region 0.75), and good to very good intraobserver agreement (intraclass correlation coefficient periventricular region 0.70-0.89; subcortical region 0.78-0.93). Progression was defined as an increase of 1 point or more between baseline and follow-up. We categorized progression into no progression (score<1), minor progression (score 1-2.5), and marked progression (score 3 or higher).[8] Hyperintensities on PD- and T2-weighted images around an incident infarct were not considered as progression of white matter lesions

New brain infarcts on MRI

The presence of brain infarcts was rated similarly at the baseline and second MRI. We defined brain infarcts as areas of focal hyperintensity on T2-weighted images that were at least 3 mm in diameter. Areas of hyperintensity in the white matter also had to have corresponding prominent hypointensity on T1-weighted images, in order to distinguish them from WML. We defined lacunar infarcts as infarcts sized 3 to 20 mm and located in the subcortical white matter or basal ganglia.

Incident stroke

In 1999 to 2000, we reinterviewed all 668 participants about symptoms of stroke using a structured questionnaire. In addition, we continuously monitored the medical records of all participants at the general practitioner's office to obtain information on the occurrence of stroke until April 1st 2002. For all reported strokes, we recorded information about signs and symptoms, date of onset, duration and hospital stay. If participants had been hospitalized for a stroke, we retrieved discharge letters and radiology reports from the hospital where they had been treated. An experienced neurologist assessed the day of onset and classified the stroke by reviewing all available information. Stroke was defined as an episode of relevant focal deficits with acute onset, documented by neurological examination, and lasting for >24 ours. On the basis of radiological findings strokes were further subdivided into hemorrhagic or ischemic stroke subtypes.[3]

Incident dementia

Participants with dementia were excluded at baseline in 1995 to 1996.[10] At the second examination, we screened all participants for dementia with the Mini-Mental State Examination (MMSE) and the Geriatric Mental State Schedule.[11,12] Screen positives were subsequently evaluated using the Cambridge Mental Disorders of the Elderly Examination (CAMDEX).[13] Participants who were then thought to have dementia were examined by a neurologist, and underwent extensive neuropsychological testing. In addition, we continuously monitored the medical records of all participants at their general practitioners' office, and at the Regional Institute for Outpatient Mental Health Care (RIAGG) to obtain information on newly diagnosed dementia until April 1st 2002.[10] A panel that reviewed all available information diagnosed dementia and its subtypes according to standardized criteria.[14-16] We defined the onset of dementia as the date on which the clinical symptoms first allowed the diagnosis of dementia to be made.

Cognitive decline

Participants underwent the following neuropsychological tests at the baseline and second examination: the Mini-Mental State Examination,[11] the Stroop test,[17] the Paper-and-Pencil Memory Scanning Task, the Letter-Digit Substitution Task,[18] a verbal fluency test (animal categories),[19] and a 15-word verbal learning test (based on Rey's recall of words).[20] We used alternative versions of the same tests at the second examination. For each participant, we calculated z scores (individual test score minus mean test score divided by the standard deviation) for the tests at baseline and follow-up using the mean and standard deviation of the baseline tests. We constructed compound scores for global cognitive function, psychomotor speed and memory. The compound score for global cognitive function was the average of the z scores of all the above tests, except the MMSE. The compound score for psychomotor speed was the average of the z scores for the reading subtask of the Stroop test, the one letter subtask of the Paper-and- Pencil Memory Scanning Task, and the Letter-Digit Substitution

Task. The compound score for memory was the average of the z scores for the immediate and delayed recall of the 15-word verbal learning test. We calculated the rate of cognitive decline by subtracting the scores at baseline from the scores at the second examination, and dividing this difference by the follow-up time between the baseline and second examination.

Incident depressive symptoms

We assessed presence of depressive symptoms at baseline and at the second examination with a validated Dutch version of the original Center for Epidemiologic Studies Depression (CES-D) scale (range 0-60).[21] We used a score of 16 as a cut-off, which indicates clinically significant depressive symptoms.[22] We defined incident depressive symptoms as depressive symptoms at the second examination without prevalent depressive symptoms (CESD <16) or the use of antidepressant medication at baseline.

Other baseline measurements

The following variables assessed at baseline were used as possible confounders: age, sex, education, hypertension, diabetes, atrial fibrillation, current smoking, serum total cholesterol, and carotid artery plaques.[8]

Data analysis

We assessed whether baseline characteristics differed between people with and without a second MRI assessment with analysis of covariance. We used Spearman's rho for the correlation between baseline WML severity and WML progression, and a Chi-square test for the association between WML progression and new brain infarcts. To examine the relationship between progression of WML and the risk of stroke, dementia and incident depressive symptoms, we used multiple logistic regression analysis. We used multiple linear regression analysis to estimate the association between progression of WML and cognitive decline.

Results

Compared to people with a second MRI examination, people who refused a second MRI examination were on average older and less educated, and those who were ineligible for a second MRI assessment were less frequent female, on average older, and less healthy (table 1). The mean follow-up period between the first and second MRI was 3.3 years (standard deviation 0.2 years, range 2.5-4.3 years). During this period, 180 participants (27%) showed WML progression in the periventricular region, of whom 120 (18%) showed minor and 60 (9%) showed marked progression. Two-hundred-seventeen participants (32%) showed progression in the subcortical region, of whom 150 (22%) showed minor and 67 (10%) showed marked progression. One-hundred-and-thirty-six participants (20%) had progression in

Table 1. **Baseline characteristics of participants of the Rotterdam Scan Study with and without a second MRI assessment.**

Characteristic	People with 2nd MRI assessment n = 668	People who refused 2nd MRI assessment n = 283	p-value for difference*	People ineligible for 2nd MRI assessment n = 126	p-value for difference*
Age, years	71 (7)	74 (7)	<0.01	77 (8)	<0.01
Women, %	52	57	0.20	41	0.02
Primary education only, %	31	42	0.02	39	0.39
Mini-Mental State Examination (score)	28 (2)	27 (2)	0.25	27 (3)	0.12
CES-D score ≥ 16	7	9	0.53	6	0.58
Hypertension, %	47	57	0.12	58	0.45
Diabetes, %	5	8	0.34	13	0.02
Atrial fibrillation, %	3	1	0.14	9	<0.01
Current smoking, %	16	13	0.79	21	0.02
Total cholesterol, mmol/l	5.9 (1.0)	5.9 (1.0)	0.45	5.7 (1.3)	0.13
Carotid artery plaques (0-6)	1.5 (1.6)	1.8 (1.6)	0.16	2.3 (1.7)	0.01
Baseline MRI variables					
Periventricular WML (score)	2.2 (2.1)	2.5 (2.1)	0.76	3.5 (2.5)	<0.01
Subcortical WML (score)	1.2 (2.5)	1.5 (3.1)	0.78	2.1 (4.1)	0.32
Brain infarcts, %	22	25	0.85	34	0.23

Values are unadjusted means (standard deviation) or percentages
*After adjustment for age and sex

both the periventricular and subcortical region, of whom 36 (5%) had marked progression in both regions. Baseline WML severity was correlated with WML progression (periventricular region: Spearman's rho 0.55, p<0.001; subcortical region: Spearman's rho 0.53, p<0.001). Ninety-three participants (14%) had a new brain infarct on the follow-up MRI, of whom 79 (12%) had a new lacunar infarct. Participants with WML progression more often developed new infarcts on MRI, in comparison to participants without WML progression (for periventricular WML progression 31% versus 8% (p<0.001); for subcortical WML progression 25% versus 9% (p<0.001)).

The mean follow-up time for stroke and dementia was 4.9 years (standard deviation 0.8 years, range 3.2-6.5 years). During follow-up, 28 participants (3.6%) developed a stroke, of whom 25 had a brain infarct. WML progression increased the risk of stroke, which was most marked for WML progression in the periventricular region (table 2). This association remained after adjustment for WML severity at baseline (table 2). The association between

Table 2. **Association between WML progression and the risk of stroke.**

	Odds ratio and 95% confidence interval	
	Model 1*	Model 2†
Periventricular WML		
No progression	1 (ref)	1 (ref)
Any progression	5.4 (2.2-13.2)	2.9 (1.1-7.8)
Minor progression	3.3 (1.1-9.2)	2.0 (0.7-6.2)
Marked progression	10.7 (3.9-29.5)	5.2 (1.6-16.9)
Subcortical WML		
No progression	1 (ref)	1 (ref)
Any progression	3.1 (1.4-6.9)	2.9 (1.2-6.8)
Minor progression	2.6 (1.0-6.4)	2.6 (1.0-6.5)
Marked progression	4.1 (1.5-11.3)	3.9 (1.2-12.1)

*Adjusted for age and sex
† Adjusted for age, sex, and WML severity at baseline

Table 3. **Association between WML progression and the risk of dementia.**

	Odds ratio* and 95% confidence interval
Periventricular WML	
No progression	1 (ref)
Any progression	1.9 (0.7-5.0)
Minor progression	1.1 (0.3-4.0)
Marked progression	3.4 (1.1-10.9)
Subcortical WML	
No progression	1 (ref)
Any progression	2.1 (0.8-5.5)
Minor progression	1.4 (0.4-4.4)
Marked progression	3.9 (1.2-12.4)

* Adjusted for age and sex

WML progression and stroke did not change after adjustment for stroke risk factors (data not shown). Nineteen participants (2.8%) developed dementia, of whom 17 (90%) were classified as Alzheimer's disease, and two as vascular dementia. Participants with marked WML progression had a more than three-fold increased risk of dementia (table 3). However, confidence intervals were wide due to the limited number of dementia cases. In order not to over-fit our models we only adjusted for age and sex. The association of marked WML progression in the periventricular and subcortical region with dementia attenuated after exclusion of participants with incident stroke (n=28): odds ratio for marked periventricular WML progression 2.9 (95% confidence interval 0.8-10.8), odds ratio for marked subcortical WML progression 3.4 (95% confidence interval 0.9-12.8). WML progression, in particular in the periventricular

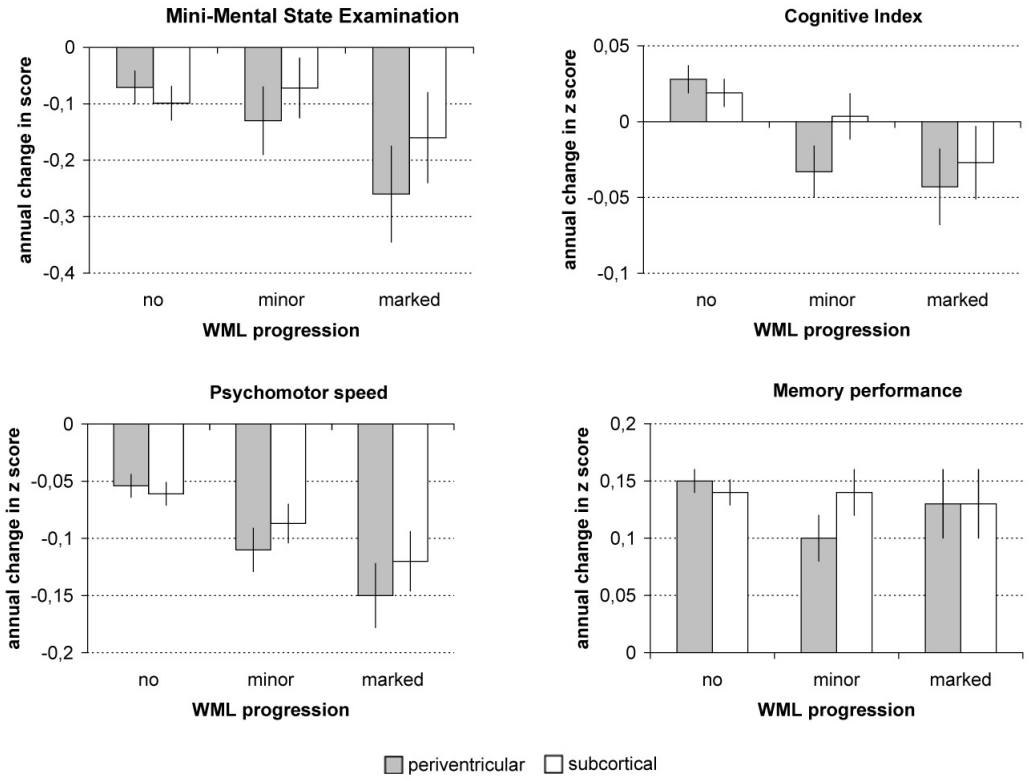


Figure. **Relationship between WML progression in the periventricular and subcortical region and decline in MMSE score, Cognitive Index, Psychomotor Speed, and Memory.** Bars represent age, sex, and education adjusted mean annual change (standard error) in z scores for cognitive performance.

* for significant difference ($p < 0.05$) with no progression

region, was associated with steeper decline in global cognitive function and psychomotor speed, but was not associated with decline in memory (figure). At the second examination 43 people had incident depressive symptoms. WML progression in the periventricular region increased the risk of depressive symptoms, whereas the association between subcortical WML progression and depressive symptoms was less strong and not significant (table 4). These associations did not change after exclusion of participants with incident dementia (n=19; data not shown). The association between marked WML progression in the periventricular region and incident depressive symptoms slightly attenuated after adjustment for WML severity at baseline and for new brain infarcts on MRI (table 4), and was strongly reduced after exclusion of participants with an incident stroke (n=28): odds ratio for marked periventricular WML progression 1.9 (95% confidence interval 0.6-5.7), odds ratio for marked subcortical WML progression 1.2 (95% confidence interval 0.4-3.5).

Table 4. **Association between WML progression and the risk of incident depressive symptoms.**

	Odds ratios and 95% confidence interval		
	Model 1*	Model 2†	Model 3‡
Periventricular WML			
No progression	1 (ref)	1 (ref)	1 (ref)
Any progression	2.1 (1.1-4.3)	2.0 (0.9-4.4)	2.0 (1.0-4.0)
Minor progression	1.9 (0.8-4.2)	1.8 (0.7-4.3)	1.8 (0.8-4.0)
Marked progression	2.7 (1.1-6.6)	2.5 (0.9-7.2)	2.3 (0.9-6.3)
Subcortical WML			
No progression	1 (ref)	1 (ref)	1 (ref)
Any progression	1.7 (0.9-3.2)	1.3 (0.6-2.7)	1.6 (0.8-3.0)
Minor progression	1.5 (0.7-3.2)	1.3 (0.6-2.9)	1.5 (0.7-3.1)
Marked progression	2.0 (0.9-4.9)	1.3 (0.5-3.6)	1.8 (0.7-4.4)

* Adjusted for age and sex
† Adjusted for age, sex, and WML severity at baseline
‡ Adjusted for age, sex, and new brain infarcts on MRI

Discussion

We found that WML progression in elderly people increased the risk of stroke more than three-fold. People with WML progression showed a steeper decline in global cognitive function and psychomotor speed. Marked WML progression increased the risk of dementia and depressive symptoms, which was partly explained by the occurrence of stroke during follow-up.

The strengths of this study are the large number of elderly people with a follow-up MRI measurement, its population-based design, and the fact that we had a complete follow-up for stroke and dementia through our monitoring system. Several other methodological issues need to be addressed. First, we assessed WML progression with a semiquantitative rating scale. Volumetrics may be more accurate and precise for assessment of WML progression. However, our visual method for measuring change showed good correlation with volumetrics (Spearman's rho: periventricular region 0.62, $p<0.01$; subcortical region 0.79, $p<0.01$), and good interobserver agreement.[9] Second, although the total number of participants was large, the number of cases with stroke, dementia, and incident depressive symptoms was relatively small, which has reduced the precision of our estimates. Third, selection may have influenced our results. Participants were younger and healthier than non-participants, which may have led to an underestimation of the percentage of people with WML progression, and an attenuation of the estimates for the associations between

WML progression and clinical outcomes. Fourth, we presented our estimates for the association between progression of WML and the risk of stroke and depressive symptoms both unadjusted and adjusted for WML severity at baseline, because baseline WML severity may be considered as a confounder. However, since WML severity at baseline and progression of WML are both parameters of the same pathofysiological process, adjustment for baseline WML severity may lead to overadjusting, which should be kept in mind when interpreting our findings.

Others and we reported previously that WML increase the risk of stroke.[3,23,24] In the present study we found that progression of WML was associated with the occurrence of new brain infarcts on MRI, of which the vast majority was lacunar, and strongly increased the risk of clinical stroke, which is in line with findings from a study in patients with carotid artery disease and leukoaraiosis on computerized tomography.[6] Furthermore, we found that this risk increase was partly independent of baseline WML severity, and independent of stroke risk factors. These findings emphasize that WML, lacunar infarcts, and stroke share common risk factors and pathofysiological mechanisms.

WML progression predicted dementia and cognitive decline, extending earlier findings from studies with a single WML measurement.[25-27] WML may directly contribute to the development of dementia through disconnection of fronto-subcortical and cholinergic pathways.[28,29] Furthermore, WML are closely interrelated with lacunar infarcts with respect to etiology and clinical presentation. We showed that the risk increase for dementia was partly explained by the development of new cerebral infarcts and the occurrence of clinical stroke. Stroke may act both as an intermediate and as a comorbid factor in the relationship between WML and dementia. The finding that WML progression was associated with decline in global cognitive function and psychomotor speed, whereas episodic memory was spared, is characteristic of the profile of vascular cognitive impairment.[4] In contrast with our observations, the Austrian Stroke Prevention Study did not demonstrate an association between WML progression and decline in cognitive function.[5] The reasons for this conflicting result may be differences in subject population and assessment of WML progression. Participants in the Austrian Stroke Prevention Study were on average 10 years younger (mean age 60 ± 6 years) than in our study (mean age 71 ± 7 years), and they excluded people with a history of cerebrovascular diseases at baseline. Both age and brain infarcts are related to WML progression and cognitive decline, and this will have resulted in less power to demonstrate an association between progression of WML and cognitive decline. Furthermore, they made no distinction between progression of WML in the periventricular and subcortical region, whereas we found that the relationship between progression of WML and cognitive decline was most marked for the periventricular region.

We found that participants with WML progression had a two-fold increased risk of depressive symptoms. Late-onset depression may be a prodromal disorder for dementia, but in the present study the association between WML progression and the risk of depression could not be explained by the development of dementia during follow-up. Our findings

support the vascular depression hypothesis, which implies that vascular brain damage plays an important role in depression in elderly people.[30]

In conclusion, we found that elderly people with progression of WML have an increased risk of stroke, cognitive decline and dementia, and depressive symptoms. Further research is needed to show if prevention of the development and progression of WML diminishes the incidence of stroke, dementia and depression in the elderly.

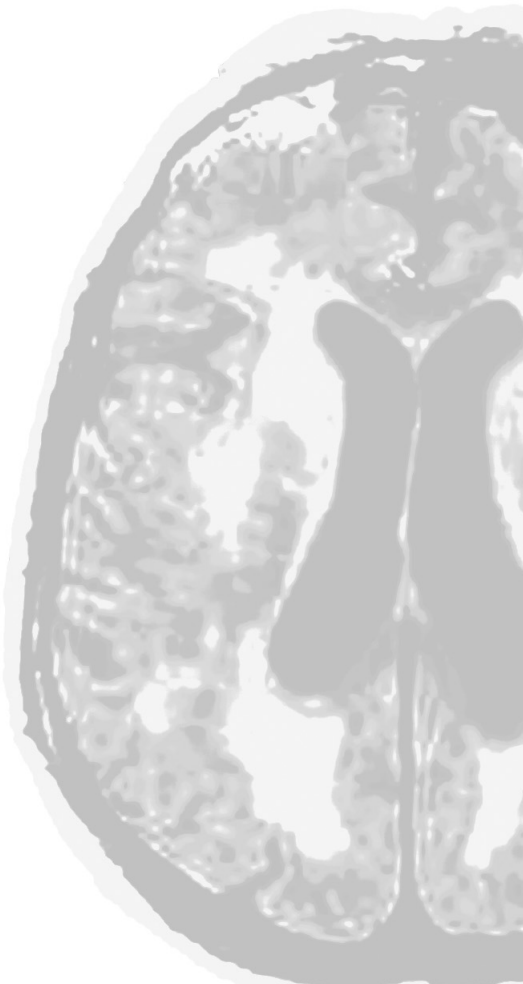
References

1. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke 1997; 28:652-9.
2. de Leeuw FE, de Groot JC, Oudkerk M, et al. A follow-up study of blood pressure and cerebral white matter lesions. Ann Neurol 1999; 46:827-33.
3. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke 2003; 34: 1126-9.
4. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. Lancet Neurol 2003; 2:89-98.
5. Schmidt R, Fazekas F, Kapeller P, Schmidt H, Hartung HP. MRI white matter hyperintensities: three-year follow-up of the Austrian Stroke Prevention Study. Neurology 1999; 53:132-9.
6. Streifler JY, Eliasziw M, Benavente OR, et al. Development and progression of leukoaraiosis in patients with brain ischemia and carotid artery disease. Stroke 2003; 34:1913-6.
7. de Groot JC, de Leeuw FE, Oudkerk M, et al. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. Ann Neurol 2000; 47:145-51.
8. van Dijk EJ, Prins ND, Vrooman H, Hofman A, Koudstaal PJ, Breteler MMB. Progression and risk factors of cerebral white matter lesions in the population-based Rotterdam Scan Study. this thesis.
9. Prins ND, van Straaten E, van Dijk E, et al. Measuring progression of cerebral white matter lesions on MRI; visual rating and volumetrics. Neurology; in press.
10. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003; 348: 1215-22.
11. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189-98.
12. Copeland JR, Kelleher MJ, Kellett JM, et al. A semi-structured clinical interview for the assessment of diagnosis and mental state in the elderly: the Geriatric Mental State Schedule. I. Development and reliability. Psychol Med 1976; 6:439-49.
13. Roth M, Tym E, Mountjoy CQ, et al. CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. Br J Psychiatry 1986; 149:698-709.
14. American Psychiatric Association., American Psychiatric Association. Work Group to Revise DSM-III. Diagnostic and statistical manual of mental disorders : DSM-III-R. Washington, DC: American Psychiatric Association, 1987:xxix, 567.
15. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of

the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34:939-44.
16. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993; 43:250-60.
17. Golden CJ. Identification of brain disorders by the Stroop Color and Word Test. J Clin Psychol 1976; 32:654-8.
18. Lezak MD. Neuropsychological assessment. New York: Oxford University Press, 1995: xviii, 1026.
19. Welsh KA, Butters N, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. Neurology 1994; 44:609-14.
20. Brand N, Jolles J. Learning and retrieval rate of words presented auditorily and visually. J Gen Psychol 1985; 112:201-10.
21. Sawyer-Radloff L. The CES-D scale: a self report depression scale for research in the general population. Appl Psychol Meas 1977; 1:385-401.
22. Blazer D, Burchett B, Service C, George LK. The association of age and depression among the elderly: an epidemiologic exploration. J Gerontol 1991; 46:M210-5.
23. van Swieten JC, Kappelle LJ, Algra A, van Latum JC, Koudstaal PJ, van Gijn J. Hypodensity of the cerebral white matter in patients with transient ischemic attack or minor stroke: influence on the rate of subsequent stroke. Dutch TIA Trial Study Group. Ann Neurol 1992; 32:177-83.
24. Streifler JY, Eliasziw M, Benavente OR, et al. Prognostic importance of leukoaraiosis in patients with symptomatic internal carotid artery stenosis. Stroke 2002; 33:1651-5.
25. de Groot JC, de Leeuw FE, Oudkerk M, et al. Periventricular cerebral white matter lesions predict rate of cognitive decline. Ann Neurol 2002; 52:335-41.
26. Kuller LH, Lopez OL, Newman A, et al. Risk factors for dementia in the cardiovascular Health Cognition Study. Neuroepidemiology 2003; 22:13-22.
27. Prins ND, van Dijk EJ, den Heijer T, et al. Cerebral white matter lesions and the risk of dementia. Archives of Neurology; in press.
28. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. The Lancet Neurology 2002; 1: 426-36.
29. Selden NR, Gitelman DR, Salamon-Murayama N, Parrish TB, Mesulam MM. Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. Brain 1998; 121 (Pt 12):2249-57.
30. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. Arch Gen Psychiatry 1997; 54:915-22.

Chapter 5

General discussion



Introduction

The objective of this thesis was to examine the role of cerebral small vessel disease in the aetiology of cognitive decline, dementia, and depression. For this purpose, I described a number of studies that were performed within the context of the Rotterdam Scan Study, a large prospective population-based cohort study. All 1,077 participants underwent MRI of the brain at baseline in 1995 and 1996, and 668 participants (62%) had a second MRI at 3-year follow-up. We measured the severity of white matter lesions and the presence of brain infarcts at baseline, and assessed the evolution of white matter lesions and the occurrence of new infarcts between the first and second MRI examination. Participants underwent a structured interview, physical examination, neuropsychological testing, and an assessment of depressive symptoms at both the baseline and follow-up examinations. Furthermore, we followed all participants for mortality and for the development of dementia, depression and stroke until April 1st 2002. This design enabled us to relate both the severity of cerebral small vessel disease at baseline and the progression of small vessel disease over time with the development of cognitive decline, dementia and depression.

In the previous chapters I described each specific study in detail. In this chapter, I take a more general viewpoint to discuss several issues related to the topic of this thesis. First, I summarize the main findings of the research described in this thesis. Second, I focus on several methodological issues that are specifically related to our study design. The third part addresses several considerations regarding the pathology underlying our determinants, white matter lesions and brain infarcts on MRI, and also reflects on our outcome measures, namely cognitive decline, dementia and depression. Fourth, I speculate on the implications of our findings and provide recommendations for future research.

Main findings

Cerebral small vessel disease affects cognitive function

People with more severe periventricular white matter lesions and people with brain infarcts showed a steeper decline in cognitive function (chapter 2.1 and 2.2). These brain changes were particularly associated with decline in information processing speed. The association with cognitive decline was also present for asymptomatic infarcts: silent thalamic infarcts were associated with decline in memory, and non-thalamic silent infarcts with decline in information processing speed (chapter 2.2). Furthermore, progression of white matter lesions was associated with decline in global cognition and information processing speed in a dose dependent manner (chapter 4.3).

Although the presented associations were significant, the size of the effects was modest, and may not be regarded as clinically relevant. I shall provide several explanations for the modest effect sizes when I discuss the methodological issues related to the assessment

of cognitive decline. For now, I would like to argue that, despite the size of the effects, our findings are relevant from an etiological point of view, and may be regarded as a proof of principle. One way to appreciate our findings is to look at the effects in relative terms. People with marked periventricular white matter lesion progression decreased almost four-times faster on the MMSE compared to people without marked progression. Another way to view our findings is to compare the effects with those of age. We showed that each standard deviation increase in severity of periventricular white matter lesions had the same effect on change in information processing speed as being 2.5 years older, and that the effect of a brain infarct on MRI was comparable with being 3.3 years older.

Elevated plasma homocysteine concentrations are a risk factor for cerebral small vessel disease and have also been associated with cognitive impairment.[1,2] Therefore, we studied cross-sectionally whether this relationship may be mediated by small vessel disease (chapter 2.4). We found that homocysteine levels greater than 14 µmol/L were associated with decreased information processing speed. However, white matter lesions and cerebral infarcts on MRI did not explain this association.

Cerebral small vessel disease increases the risk of dementia

We prospectively studied the association of cerebral white matter lesions and asymptomatic brain infarcts and the risk of dementia. For each standard deviation increase in periventricular white matter lesion severity, the risk of dementia increased by 70% (chapter 2.3). Furthermore, marked progression of white mater lesions in either the periventricular or subcortical region increased the risk of dementia, which was partly explained by the occurrence of stroke during follow-up (chapter 4.3). The presence of silent brain infarcts at baseline more than doubled the risk of dementia (chapter 2.2). The majority of dementia cases in our studies were of the Alzheimer's type, and the associations of periventricular white matter lesions and silent brain infarcts with dementia remained after analyses were limited to Alzheimer's disease.

Cerebral small vessel disease is associated with depression

We found that people with either symptomatic or asymptomatic brain infarcts on MRI had a three-fold increased risk of chronic depressive disorders. Severe subcortical white matter lesions at baseline more than doubled the risk of incident depressive disorders (chapter 3). Subsequently, marked progression of white matter lesions increased the risk of depressive symptoms (chapter 4.3). Our findings support the 'vascular depression' hypothesis, which implies that there is a subtype of depression arising in later life that is characterized by a distinct clinical presentation and an association with cerebrovascular disease.[3]

Progression of cerebral white matter lesions increases the risk of stroke, dementia and depression

We evaluated the concordance of a volumetric method for measuring white matter lesion

change with several visual rating scales, and found that commonly used visual rating scales are not well suited for measuring change in white matter lesion severity. A new simple visual rating scale that we designed to measure white matter lesion change proved to be more accurate and precise (chapter 4.1). We used this new scale to assess change in white matter lesions in participants from the Rotterdam Scan Study. Approximately one-third of elderly people had progression of white matter lesions over a 3-year period. Risk factors for progression included higher white matter lesion severity at baseline, increasing age, female sex, elevated blood pressure and current cigarette smoking (chapter 4.2). WML progression increased the risk of stroke more than three-fold. People with white matter lesion progression showed a steeper decline in global cognitive function and information processing speed. Marked progression increased the risk of dementia and depressive symptoms, which was partly explained by the occurrence of new brain infarcts on MRI and clinical stroke during follow-up (chapter 4.3).

Methodological issues

For an overview of the general principles related to the quality of epidemiological research I refer to standard texts.[4,5] This paragraph concerns several specific methodological issues related to the studies in this thesis. I first address the advantages and disadvantages of our study design. Next, I discuss the problem of attrition in relation to repeated assessments of cognitive function and mood in population-based studies. The third methodological issue that I will focus on is the question whether or not to adjust for white matter severity at baseline.

The studies that I described in this thesis were performed in the context of a large prospective population-based cohort study. One of the strengths of such a design is that, provided that the response is high enough and loss to follow-up is minimized, selection bias is limited. This holds for our analyses regarding incident dementia and depression (chapter 2.2 and 2.3). Another clear advantage of our design is that the results can be directly generalized to the general population. Furthermore, the prospective nature made it possible to establish temporal relationships between small vessel disease and clinical outcomes, which can provide arguments for causality. In general, a large sample size is the primary way to increase precision in an epidemiological study. However, precision also relates to the efficiency of a study, and despite the large size of the study, the number of people who developed incident dementia and incident depression was modest.[4] Therefore, precision was a concern in our study, particularly regarding the analyses on progression of white matter lesions and the risk of dementia (chapter 4.3).

Attrition is a problem in repeated measurements of cognitive function or mood in a population-based MRI study. People with cognitive impairment or depressive symptoms as well as those who are generally less healthy, are more likely to drop out of the study and

thus not participate in a follow-up neuropsychological examination or psychiatric interview.[6,7] In our study this was illustrated by a higher rate of dementia in people without a second examination (chapter 2.1). This selection will have resulted in an underestimation of cognitive decline and incident depressive symptoms. Furthermore, it might have led to an underestimation of the strength of the association between small vessel disease and cognitive decline and incident depressive symptoms. This may be considered as the paradox of measuring cognitive decline with sensitive neuropsychological tests: people who can be tested repeatedly and reliably are the same ones who are least likely to decline. Learning effects induced by repeated testing also result in an underestimation of cognitive decline in the study population. In order to measure substantial cognitive decline in population-based studies, follow-up should be sufficiently long, alternative versions of tests should be used in order to reduce learning effects, and the response rate should be kept as high as possible.

A methodological issue that is important for the interpretation of our findings on progression of white matter lesions involves the adjustment for white matter lesion severity at baseline. We presented our estimates for the association between progression of white matter lesions and outcomes both unadjusted and adjusted for white matter lesion severity at baseline. One reason for adjusting for baseline is that white matter lesion severity at baseline can be considered a confounder in the relation between progression of white matter lesions and outcome. Theoretically, adjustment for baseline may induce bias due to the phenomenon of regression towards the mean.[8,9] However, we judge this effect to be small in our study because we used a change scale to measure progression instead of calculating the difference between two repeated measurements.[10] It is important to realize that white matter severity at baseline and progression of white matter lesions are both parameters of the same pathofysiological process, and progression can be considered an intermediate in the relationship between white matter severity and outcome.[11] Adjusting for baseline may therefore be considered overadjusting and can lead to an underestimation of the association of interest.

Cerebral white matter lesions and brain infarcts on MRI

In this thesis I refer to white matter lesions and lacunar brain infarcts on MRI as measures of cerebral small vessel disease. However, the pathofysiology of these lesions is still not completely understood. The histological abnormalities associated with white matter lesions in elderly people can be considered nonspecific.[12] The most consistent histological substrates of white matter lesions are a diffuse myelin rarefaction sparing the U fibers, astrogliosis, spongiosis, axonal loss, and widened perivascular spaces.[13] Important risk factors for the development of white matter lesions in our study are increasing age, presence of arterial hypertension and cardiovascular disease.[14,15] Arteriolosclerosis and hyaline wall thickening of the long penetrating arterioles in combination with impaired autoregulation may result in

hypoxia and ischemia of the white matter. Ischemic injury to the blood-brain-barrier permeability may lead to leakage of macromolecules and ensuing activation of astrocytes.[12] Other mechanisms have also been suggested. Deposits of amyloid β in the media and adventitia of meningocortical arteries and arterioles may lead to obliteration of vessel luminae and loss of vascular smooth muscle cells necessary to cerebral autoregulation.[16,17] Collagenous thickening and occlusion of deep periventricular-draining veins has been postulated to be another factor in the production of deep hemispheric white matter lesions.[18] In degenerative dementia, white matter lesions may be attributed to wallerian degeneration.[19] A number of conditions require consideration in the differential diagnosis of white matter changes on MRI.[20] Cerebral white matter changes are present in multiple sclerosis, leukodystrophies, mitochondrial encephalopathies, certain infections, and after cerebral anoxia from cardiac arrest or carbon monoxide poisoning. However, in elderly people they can rarely be attributed to these conditions.[21] Furthermore, white matter lesions are a prominent feature in some hereditary cerebrovascular condition such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and hereditary cerebral hemorrhage with amyloidosis.[22-24] These hereditary conditions are rare, and are characterized by an onset of clinical manifestations around the age of 50, which makes them unlikely to be present in our study population.

In our study the vast majority of brain infarcts were of the lacunar type and asymptomatic.[25] The term lacune refers to a small cavity located deep within the brain. Lacunar infarcts vary in maximal diameter from 3-20 mm, and are most commonly found in the putamen, caudate, thalamus, pons, internal capsule and cerebral white matter.[26] Traditionally, lacunes are classified into type I and type II lacunes.[27] Type I lacunes consist of irregular cavities up to 20 mm in size, and are the most frequent. Type II lacunes are characterized by numerous haemosiderin laden macrophages, and are assumed to represent old, small hemorrhages.[27] These microbleeds may be a significant risk factor for primary intracerebral hemorrhage.[28] In our study we were not able to assess these types of lacunes, since specific MRI acquisitions (gradient echo T2) are needed to visualize these lesions. The most common cause of lacunar infarcts is small vessel atherosclerosis and fibrinoid necrosis (lipohyalinosis). Risk factors for asymptomatic infarcts in our study were increasing age, arterial hypertension and increased total plasma homocysteine concentration.[2,25] Atherosclerosis may be present in the proximal perforating arteries, at their origin, or in the parent artery of the circle of Willis, while lipohyalinosis is thought to be responsible for smaller (40-300 μm) perforating vessels that result in occlusion of lenticulostriate, thalamoperforating and long penetrating arteries.[26,29] Apart from the pathology underlying small vessel stroke described above, many other causes have been described as rare causes of lacunar infarcts such as infective and immune vasculitis, cardiac and large vessel embolism, arterial dissection, and microaneurysm. I consider it unlikely that these rare causes have contributed in an important way to our results.

Assessment of cognitive decline, dementia and depression

We assessed cognitive function with a number of neuropsychological tests that were considered as being sensitive and suitable for use in the elderly population. The question remains how decline in cognitive function relates to the development of dementia. A diagnosis of dementia is often preceded by a preclinical phase of many years, and it has been shown that during this phase, people already have a decreased performance on psychometric tests.[30-32] At the time that the first clinical changes in cognitive functioning and behavior start to interfere with daily living a sharp change in psychometric performance is observed.[33] Cognitive decline in elderly people can therefore be considered as a trajectory. Depending on the progression of underlying pathologies that are responsible for this decline, and the summed effect of cognitive impairment in multiple domains, people may eventually cross the line of clinical dementia.

In our study, since necropsy data was not available, we used clinical diagnoses of dementia and its subtypes according to standardized criteria. The value of such a clinical distinction between Alzheimer's disease and vascular dementia can be challenged. Necropsy confirmed clinical diagnostic accuracy for Alzheimer's disease is reported to be as high as 87%.[34,35] However, it has been argued that such figures contain two fallacies; they include cases in which Alzheimer's disease exists with other diseases affecting cognition and the studies that report these figures excluded cases without necropsy (verification bias). When these two fallacies are taken into account, the positive predictive value of a diagnosis of pure Alzheimer's disease is reported to be no more than 38%.[36] Evidence has been accumulating that most elderly people with dementia have mixed disease.[37-39] As a result, current clinical distinctions into dementia subtypes are both imprecise and arbitrary, and may be of little use in etiologic research.

We assessed depressive symptoms with the Center for Epidemiologic Studies Depression scale (CES-D), a validated depression scale, and used a cut-off that indicates clinically relevant depressive symptoms (chapter 3 and 4.3).[40] To ascertain a Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV)41 diagnosis of depression, a psychiatrist interviewed screen positives with a semi-structured psychiatric interview, a Dutch version of the Present State Examination.[42] Secondly, we monitored the medical records of all participants at the general practitioner's offices and the Regional Institute for Ambulatory Mental Health for depressive episodes (chapter 3). In the analyses on depressive disorders, we combined the diagnostic categories of major depression, dysthymia, and minor depression. In the elderly, these syndromes have similar prognosis and consequences for well-being and disability.[43] Furthermore, these syndromes are difficult to delineate in elderly people.[44]

Implications

The impact of cerebral small vessel disease on cognitive function has long been a matter of debate fuelled by equivocal results from cross-sectional studies.[45-48] Results from prospective studies, including ours, provide strong evidence that small vessel disease causes cognitive decline, and in particular decline in information processing speed.[49-51] Small vessel disease may directly interrupt prefrontal subcortical loops.[52] Our data suggest that small vessel disease also indirectly leads to cognitive decline through the development of stroke.[53] A third mechanism may be through interaction with Alzheimer pathology.[37,39,54]

There is widespread belief that cerebral small vessel disease plays a role in the aetiology of dementia. However, there is hardly any evidence from prospective population based studies on the association of white matter lesions and asymptomatic brain infarcts with the risk of dementia and Alzheimer's disease. We found that both white matter lesions and brain infarcts strongly increased the risk of dementia, including clinical Alzheimer's disease. Furthermore, our study is the first to relate progression of white matter lesions to cognitive decline and dementia. This temporality provides strong evidence for a causal relationship between cerebral white matter lesions and cognitive decline and dementia. Observations from epidemiological studies including ours, and from pathology studies challenge the conventional distinction between Alzheimer's disease and vascular dementia on the basis of diagnostic criteria. Vascular amyloid angiopathy is commonly reported in Alzheimer's disease, and risk factors for vascular disease and stroke such as hypertension, diabetes mellitus, cholesterol, atrial fibrillation, and increased homocysteine have been associated with an increased risk of Alzheimer's disease.[39,54] In a community-based neuropathology study Alzheimer-type and vascular pathology were the major pathological correlates of dementia in elderly people, although most patients had mixed disease. There were no clear thresholds of these features that predicted dementia status.[37] All of these findings strongly suggest that dementia in elderly people is mostly a heterogeneous disorder in which different pathologies contribute to the clinical syndrome of dementia.

We found that patients with small vessel disease had a higher risk for depressive disorders. Patients with vascular depression are reported to experience greater cognitive dysfunction, disability, and retardation, but less agitation and guilt feelings than patients with non vascular depression.[55] What could be the neuroanatomical substrate to explain this difference in clinical phenotype? A possible explanation comes from a recent model for depression involving dysfunctional coordination of limbic-cortical pathways. In this model, a dorsal compartment composed of superior limbic structures is thought to regulate attentional and cognitive symptoms of depression such as apathy, psychomotor retardation, impaired attention, and executive dysfunction. A ventral compartment formed of limbic, paralimbic and subcortical structures is proposed to mediate the vegetative and somatic aspects of depression, such as sleep, appetite and endocrine disturbances. The rostral cingulate area has a regulatory role for the interactions between the two compartments. Dysfunction in

this coordinating area is suggested to result in disintegrated mood, cognitive, somatic and autonomic responses.[56,57] According to this model, it can be hypothesized that in vascular depression there is a differential involvement of superior limbic structures. This may occur either via strategically placed lesions or as a result of an overall burden.[3] Our observation that people who developed depression had a higher severity of subcortical white matter lesions in the frontal lobes is compatible with this view. In summary, small vessel disease may contribute to the development of depression by ischemic damage of prefrontal cortical and striatal systems leading to disruption of neurotransmitter circuitry involved in mood regulation.

Future directions

This thesis has provided some answers on the role of small vessel disease in the aetiology of dementia and depression. However, at the same time it has generated many more questions. What is the next step we should take in neuroimaging studies on brain changes in relation to dementia and depression? Do we need new diagnostic criteria for dementia? What are the possibilities for primary and secondary prevention of cerebral small vessel disease and its consequences?

We showed that the location of small vessel disease is important in relation to the development of dementia and depression. However, the way we defined and assessed lesion location can be considered rather crude. Future imaging studies in the general population as well as in patient populations may use volumetric MRI and automatic lesion assessments, which will provide precise information on extent and localization of lesions. This will result in increased statistical power to further elucidate the interaction between small vessel disease and other brain pathologies at old age, such as atrophy of medial temporal lobe structures. Higher field strength increases the resolution of MRI images, and will provide more detailed anatomical information. Diffusion tensor magnetic resonance imaging can provide important information about the anatomy of white matter tracts, which can be related to function. Techniques for the in vivo visualization of amyloid β are in progress.[58] Future neuroimaging studies may take both small vessel disease and Alzheimer pathology into account when studying risk factors for the development of dementia and depression.

As mentioned previously, there are strong suggestions that dementia in elderly people is mostly a heterogeneous disorder. As a result, the conventional distinction between Alzheimer's disease and vascular dementia is being challenged. This leads to the question whether there is a need for new clinical criteria for dementia. In the clinical setting, criteria are useful to enhance agreement and communication among clinicians. For this purpose, present clinical criteria may be sufficient. According to the DSM IV for example, mixed forms of dementia can be classified as "Dementia due to multiple etiologies".[41] In the setting of aetiological research, one should really question whether clinical criteria, in which

notions about the aetiology are incorporated, are of any use and whether they not only lead to circularity. In the setting of clinical trials, clinical criteria may be useful to reduce heterogeneity, thereby increasing the power of a trial. For vascular dementia, Erkinjuntti and colleagues have summarized the characteristics that new criteria need to fulfill.[59,60] Constructs should be based on homogeneity in the aetiology, brain changes, and clinical syndrome. Criteria for the more homogeneous subtype of subcortical vascular dementia have already been proposed.[59]

In order to prevent small vessel disease, subjects at risk should be identified and risk factors should be treated. Hypertension is the main risk factor and can be effectively controlled. In the double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial, active treatment of elderly people with systolic hypertension with nitrendipine with the possible addition of enalapril and hydrochlorothiazide, reduced the incidence of dementia by 50% compared with placebo.[61] An unhealthy blood lipid profile should be treated with statins to reduce the risk of ischemic heart disease and stroke.[62] People should optimize their cardiovascular health, which means they should avoid obesity and smoking.

There is little evidence regarding secondary prevention in patients with small vessel disease. As discussed previously, lacunar infarcts and white matter lesions, apart from subtle subependymal white matter lesions in the immediate vicinity of the ventricles that are probably non-pathological, are both indicators of small vessel disease.[20,63] These structural brain changes can be used as (surrogate) endpoints in clinical trials. Blood pressure lowering with perindopril and indapamide in patients with prior stroke or transient ischemic attack reduced the risk of dementia and cognitive decline associated with recurrent stroke in the PROGRESS study.[64] The question remains whether these results can be generalized to patients with small vessel disease. Only two trials have reported on the effect of antiplatelet agents in patients presenting with lacunar infarcts. The AICLA trial showed that treatment with aspirin or aspirin with dypiradimole compared to placebo, reduced stroke recurrence in patients with lacunar stroke.[65] A benefit of ticlopidine for stroke prevention in patients with lacunar stroke was shown by the CATS study.[66] Even more than lacunes, white matter lesions have been neglected as a potential endpoint in clinical trials. For this reason, it is not known whether for instance antiplatelet agents are beneficial in patients with extensive white matter lesions. Future studies on secondary prevention of cerebral small vessel disease are needed.

Promising results have been reported from treatment studies in patients with vascular dementia. A recent placebo-controlled trial of memantine, an antagonist of the N-methyl-d-aspartate receptor, in patients with mild to moderate vascular dementia showed improved cognition, stabilization of global functioning and behavior, and good tolerance and safety.[67] Cholinesterase inhibitors have been approved for the treatment of Alzheimer's disease and may also be of use in the treatment for vascular dementia. In two large trials of patients with vascular dementia, patients treated with donepezil showed improvement in cognitive scores (ADAS-cog, MMSE) and global scores (CIBIC-plus) compared with placebo.[68] More

studies are needed to investigate the beneficial effects of these and other agents for dementia patients with cerebral small vessel disease.

References

1. Lehmann M, Gottfries CG, Regland B. Identification of cognitive impairment in the elderly: homocysteine is an early marker. Dement Geriatr Cogn Disord 1999; 10:12-20.
2. Vermeer SE, van Dijk EJ, Koudstaal PJ, et al. Homocysteine, silent brain infarcts, and white matter lesions: The Rotterdam Scan Study. Ann Neurol 2002; 51:285-9.
3. Baldwin RC, O'Brien J. Vascular basis of late-onset depressive disorder. Br J Psychiatry 2002; 180:157-60.
4. Rothman KJ, Greenland S. Modern Epidemiology. Philadelphia: Lippincott Williams & Wilkins, 1998.
5. Vandenbroecke JP, Hofman A. Grondslagen der epidemiologie. Maarssen: Elsevier/ Bunge, 1999.
6. Levin BE, Katzen HL, Klein B, Llabre ML. Cognitive decline affects subject attrition in longitudinal research. J Clin Exp Neuropsychol 2000; 22:580-6.
7. Van Beijsterveldt CE, van Boxtel MP, Bosma H, Houx PJ, Buntinx F, Jolles J. Predictors of attrition in a longitudinal cognitive aging study: the Maastricht Aging Study (MAAS). J Clin Epidemiol 2002; 55:216-23.
8. Cain KC, Kronmal RA, Kosinski AS. Analysing the relationship between change in a risk factor and risk of disease. Stat Med 1992; 11: 783-97.
9. Vollmer WM. Comparing change in longitudinal studies: adjusting for initial value. J Clin Epidemiol 1988; 41:651-7.
10. Prins ND, van Straaten E, van Dijk E, et al. Measuring progression of cerebral white matter lesions on MRI; visual rating and volumetrics. Neurology; Revised version submitted.
11. Schmidt R, Fazekas F, Kapeller P, Schmidt H, Hartung HP. MRI white matter hyperintensities: three-year follow-up of the Austrian Stroke Prevention Study. Neurology 1999; 53:132-9.
12. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke 1997; 28:652-9.
13. Pantoni L, Garcia JH. The significance of cerebral white matter abnormalities 100 years after Binswanger's report. A review. Stroke 1995; 26:1293-301.
14. de Leeuw FE, de Groot JC, Oudkerk M, et al. A follow-up study of blood pressure and cerebral white matter lesions. Ann Neurol 1999; 46:827-33.
15. de Leeuw FE, de Groot JC, Bots ML, et al. Carotid atherosclerosis and cerebral white matter lesions in a population based magnetic resonance imaging study. J Neurol 2000; 247: 291-6.
16. Vinters HV, Secor DL, Pardridge WM, Gray F. Immunohistochemical study of cerebral amyloid angiopathy. III. Widespread Alzheimer A4 peptide in cerebral microvessel walls colocalizes with gamma trace in patients with leukoencephalopathy. Ann Neurol 1990; 28:34-42.
17. van Dijk EJ, Prins ND, Vermeer SE, et al. Plasma Amyloid ß, APOE, Lacunar Brain Infarcts, and White Matter Lesions. Annals of Neurology in press.
18. Moody DM, Brown WR, Challa VR, Anderson RL. Periventricular venous collagenosis: association with leukoaraiosis. Radiology 1995; 194:469-76.
19. Englund E. Neuropathology of white matter changes in Alzheimer's disease and vascular dementia. Dement Geriatr Cogn Disord 1998; 9 Suppl 1:6-12.
20. Roman GC, Erkinjuntti T, Wallin A, Pantoni

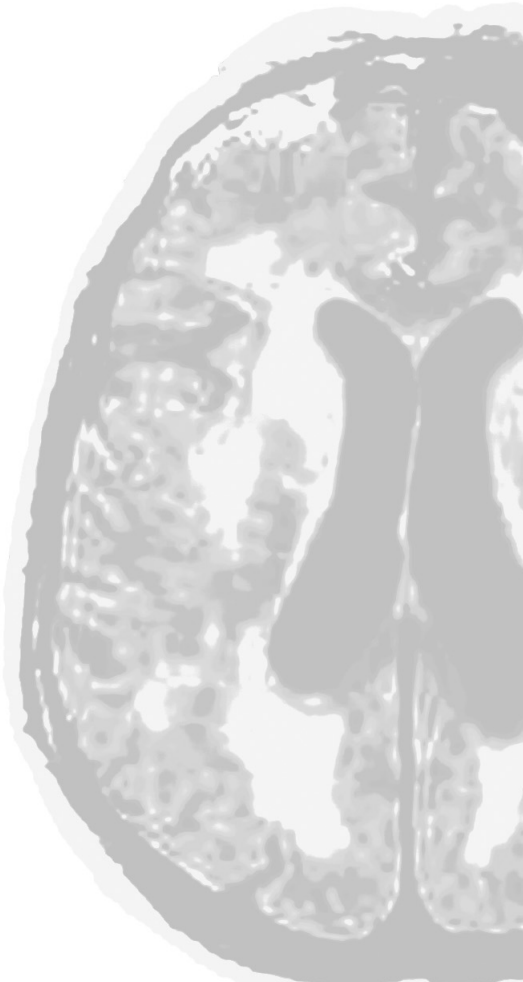
L, Chui HC. Subcortical ischaemic vascular dementia. The Lancet Neurology 2002; 1:426-36.
21. Hijdra A. Vascular dementia. In: Bradley WG, Daroff RD, Marsden CD, Fenichel G, eds. Neurology in clinical practice. Boston: Butterworth Heinemann, 2000.
22. Chabriat H, Vahedi K, Iba-Zizen MT, et al. Clinical spectrum of CADASIL: a study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Lancet 1995; 346:934-9.
23. Dichgans M. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: phenotypic and mutational spectrum. J Neurol Sci 2002; 203-204: 77-80.
24. Bornebroek M, Westendorp RG, Haan J, et al. Mortality from hereditary cerebral haemorrhage with amyloidosis--Dutch type. The impact of sex, parental transmission and year of birth. Brain 1997; 120 (Pt 12):2243-9.
25. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population- based rotterdam scan study. Stroke 2002; 33:21-5.
26. Lammie GA. Pathology of small vessel stroke. Br Med Bull 2000; 56:296-306.
27. Poirier J, Derouesne C. Cerebral lacunae. A proposed new classification. Clin Neuropathol 1984; 3:266.
28. Roob G, Lechner A, Schmidt R, Flooh E, Hartung HP, Fazekas F. Frequency and location of microbleeds in patients with primary intracerebral hemorrhage. Stroke 2000; 31: 2665-9.
29. Fisher CM. Lacunar strokes and infarcts: a review. Neurology 1982; 32:871-6.
30. Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB. The preclinical phase of alzheimer disease: A 22-year prospective study of the Framingham Cohort. Arch Neurol 2000; 57:808-13.
31. Fabrigoule C, Rouch I, Taberly A, et al. Cognitive process in preclinical phase of dementia. Brain 1998; 121 (Pt 1):135-41.
32. Masur DM, Sliwinski M, Lipton RB, Blau AD, Crystal HA. Neuropsychological prediction of dementia and the absence of dementia in healthy elderly persons. Neurology 1994; 44: 1427-32.
33. Rubin EH, Storandt M, Miller JP, et al. A prospective study of cognitive function and onset of dementia in cognitively healthy elders. Arch Neurol 1998; 55:395-401.
34. Gearing M, Mirra SS, Hedreen JC, Sumi SM, Hansen LA, Heyman A. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part X. Neuropathology confirmation of the clinical diagnosis of Alzheimer's disease. Neurology 1995; 45:461-6.
35. Joachim CL, Morris JH, Selkoe DJ. Clinically diagnosed Alzheimer's disease: autopsy results in 150 cases. Ann Neurol 1988; 24:50-6.
36. Bowler JV, Munoz DG, Merskey H, Hachinski V. Fallacies in the pathological confirmation of the diagnosis of Alzheimer's disease. J Neurol Neurosurg Psychiatry 1998; 64: 18-24.
37. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Lancet 2001; 357:169-75.
38. Hachinski V, Munoz DG. Cerebrovascular pathology in Alzheimer's disease: cause, effect or epiphenomenon? Ann N Y Acad Sci 1997; 826:1-6.
39. Breteler MM. Vascular risk factors for Alzheimer's disease: an epidemiologic perspective. Neurobiol Aging 2000; 21:153-60.
40. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. Psychol Med 1997; 27:231-5.
41. American Psychiatric Association., As-

sociation. AP. Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association, 1994.
42. WHO.SCAN. scedules for clinical assessment in neuropsychiatry, version 2.1. Distribution from trainig centers. 2nd ed. Geneva: World Health Organisation, 1997.
43. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. Jama 1989; 262:914-9.
44. Snowdon J. Prevalence of depression in old age. Br J Psychiatry 2001; 178:476-7.
45. Kramer JH, Reed BR, Mungas D, Weiner MW, Chui HC. Executive dysfunction in subcortical ischaemic vascular disease. J Neurol Neurosurg Psychiatry 2002; 72:217-20.
46. Matsubayashi K, Shimada K, Kawamoto A, Ozawa T. Incidental brain lesions on magnetic resonance imaging and neurobehavioral functions in the apparently healthy elderly. Stroke 1992; 23:175-80.
47. Wolfe N, Linn R, Babikian VL, Knoefel JE, Albert ML. Frontal systems impairment following multiple lacunar infarcts. Arch Neurol 1990; 47:129-32.
48. Longstreth WT, Jr., Bernick C, Manolio TA, Bryan N, Jungreis CA, Price TR. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. Arch Neurol 1998; 55: 1217-25.
49. Garde E, Mortensen EL, Krabbe K, Rostrup E, Larsson HB. Relation between age-related decline in intelligence and cerebral white-matter hyperintensities in healthy octogenarians: a longitudinal study. Lancet 2000; 356:628-34.
50. de Groot JC, de Leeuw FE, Oudkerk M, et al. Periventricular cerebral white matter lesions predict rate of cognitive decline. Ann Neurol 2002; 52:335-41.
51. Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Carmelli D. Biobehavioral characteristics of nondemented older adults with subclinical brain atrophy. Neurology 2000; 54:2108-14.
52. Cummings JL. Frontal-subcortical circuits and human behavior. J Psychosom Res 1998; 44:627-8.
53. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke 2003; 34: 1126-9.
54. Kalaria RN. Small vessel disease and Alzheimer's dementia: pathological considerations. Cerebrovasc Dis 2002; 13 Suppl 2: 48-52.
55. Ramasubbu R. Relationship between depression and cerebrovascular disease: conceptual issues. J Affect Disord 2000; 57:1-11.
56. Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. J Psychosom Res 2002; 53: 647-54.
57. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci 1997; 9:471-81.
58. Bennett SA, Pappas BA, Stevens WD, Davidson CM, Fortin T, Chen J. Cleavage of amyloid precursor protein elicited by chronic cerebral hypoperfusion. Neurobiol Aging 2000; 21:207-14.
59. Erkinjuntti T, Inzitari D, Pantoni L, et al. Limitations of clinical criteria for the diagnosis of vascular dementia in clinical trials. Is a focus on subcortical vascular dementia a solution? Ann N Y Acad Sci 2000; 903:262-72.
60. Erkinjuntti T. Diagnosis and management of vascular cognitive impairment and dementia. J Neural Transm Suppl 2002:91-109.
61. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998; 352:1347-51.
62. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipopro-

tein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. Bmj 2003; 326:1423.
63. Sze G, De Armond SJ, Brant-Zawadzki M, Davis RL, Norman D, Newton TH. Foci of MRI signal (pseudo lesions) anterior to the frontal horns: histologic correlations of a normal finding. AJR Am J Roentgenol 1986; 147:331-7.
64. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 2003; 163:1069-75.
65. Bousser MG, Eschwege E, Haguenau M, et al. "AICLA" controlled trial of aspirin and dipyridamole in the secondary prevention of athero-thrombotic cerebral ischemia. Stroke 1983; 14:5-14.
66. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Lancet 1989; 1: 1215-20.
67. Orgogozo JM, Rigaud AS, Stoffler A, Mobius HJ, Forette F. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). Stroke 2002; 33: 1834-9.
68. Pratt RD. Patient populations in clinical trials of the efficacy and tolerability of donepezil in patients with vascular dementia. J Neurol Sci 2002; 203-204:57-65.

Chapter 6

Summary
Samenvatting



Summary

Cerebral small vessel disease may lead to the development of cerebral white matter lesions and brain infarcts. These structural brain changes are common in older people. The presence and severity of white matter lesions and infarcts increase with increasing age, and arterial hypertension is considered as being the most important risk factor. It is a widespread belief that cerebral small vessel disease is involved in the aetiology of dementia. However, the evidence from prospective population based studies to support these notions is scarce. Cerebral small vessel disease may also be involved in the aetiology of depression in older people. Again, this relationship has barely been studied prospectively in the general population. The objective of the research described in this thesis was to relate the presence and severity of small vessel disease on magnetic resonance imaging (MRI) with the development of dementia and depression in older people. The research was carried out within the context of the Rotterdam Scan Study, a prospective cohort-study in 1,077 people aged 60 years and older from the general population. All participants were free from dementia at the start of the study.

Chapter 1 is a general introduction to the topic of this thesis. In **chapter 2.1** we relate the presence and severity of white matter lesions, infarcts, and generalized brain atrophy on MRI to cognitive decline. White matter lesions in the periventricular region, infarcts, and generalized atrophy were associated with cognitive decline, and particularly with decline in information processing speed. Furthermore, our results suggest that stroke may be an intermediate in the association between white matter lesions, infarcts and cognitive decline.

In older people, brain infarcts that have not resulted in stroke-like symptoms are frequently observed on MRI. **Chapter 2.2** describes a study that examined whether or not these asymptomatic infarcts are related to the risk of dementia and cognitive decline. Participants underwent an MRI of the brain both at baseline and on average three years later, and underwent neuropsychological testing. Brain infarcts were assessed on MRI and were classified as either symptomatic or asymptomatic based on medical information. The presence of asymptomatic infarcts at baseline doubled the risk of dementia. Older people who developed new infarcts declined steeper in cognition than contemporaries without such lesions.

We examined the relationship between cerebral small vessel disease in specific locations and the risk of dementia in **chapter 2.3.** We measured the severity of white matter lesions on MRI in the periventricular and subcortical region. All participants were followed over a five-year period for the development of dementia. During the study period, 45 participants became demented. Increasing severity of white matter lesions in the periventricular region increased the risk of dementia. Per standard deviation increase in periventricular white matter lesion severity the risk of dementia increased by 70 percent. This risk increase was independent of other risk factors for dementia, and partly independent of the presence of other structural brain changes on MRI.

In **chapter 2.4,** we explore the association between the concentration of homocysteine in

blood plasma and cognitive function. We found that elderly people with an increased homocysteine concentration performed worse on cognitive tests, in particular tests that measure information processing speed. This association was not explained by structural brain changes on MRI, which may suggest that homocysteine affects cognitive function through a direct neurotoxic effect.

Whether or not brain infarcts and white matter lesions increase the risk of depression is examined in **chapter 3.** We assessed brain infarcts and white matter lesions on MRI, and followed participants over a 3-year period for the development of depressive disorders. We made a distinction between incident and chronic depressive disorders. Brain infarcts tripled the risk of chronic depressive disorders, whereas severe white matter lesions in the subcortical region doubled the risk of incident depressive disorders. These findings support the vascular depression hypothesis, which implies that there is a subtype of depression occurring in late life that is characterized by a distinct clinical presentation and an association with cerebrovascular disease.

Chapter 4.1 focuses on a method comparison study in which the concordance of several visual rating scales with volumetrics for measuring white matter lesion change is evaluated. For assessment of change in white matter lesions, the scales of Fazekas, of Scheltens, and the periventricular part of the Rotterdam Scan Study scale showed little correlation with volumetrics. A new visual scale, which we designed for measuring progression of white matter lesions, and the subcortical part of the Rotterdam Scan Study scale showed good correlation with volumetrics. After observers had become familiarized with the new scale, the measurements with this scale also showed good interobserver agreement.

Although much is known about the frequency and risk factors of white matter lesions in the general population, there is only limited information available about the evolution of these lesions over time. The objective of the study in **chapter 4.2** was to describe the rate of progression of white matter lesions in the general population, and to assess risk factors for this progression. Over a 3-year period, about one third of participants showed progression of white matter lesions. Risk factors for progression were the severity of white matter lesions at baseline, increasing age, female sex, hypertension and cigarette smoking. In **chapter 4.3,** we consider whether progression of white matter lesions is related to the risk of stroke, cognitive decline, dementia and depression. Older people with progression of white matter lesions had a tripled risk of stroke, and declined steeper in global cognitive function and information processing speed. Severe progression increased the risk of dementia and depressive symptoms, which was partly explained by the occurrence of clinical stroke.

Finally, in **chapter 5,** we summarize our main findings, discuss methodological and conceptual issues, and make reccomendations for future research.

SAMENVATTING

Schade aan de kleine bloedvaten in de hersenen, of cerebrale microangiopathie, kan leiden tot het ontstaan van witte stof afwijkingen en infarcten. Deze afwijkingen komen veel voor bij ouderen. De aanwezigheid en ernst van witte stof afwijkingen en infarcten nemen toe met de leeftijd, en hoge bloeddruk wordt beschouwd als de belangrijkste risicofactor. Over het algemeen wordt verondersteld dat cerebrale microangiopathie een rol speelt bij de etiologie van dementie. Tegelijkertijd zijn er echter maar weinig studies die deze relatie prospectief hebben onderzocht in de algemene populatie. Microangiopathie speelt mogelijk ook een rol bij het ontstaan van depressie op oudere leeftijd, maar ook voor deze relatie zijn weinig gegevens bekend uit prospectief bevolkingsonderzoek. Het doel van het in dit proefschrift beschreven onderzoek was om de aanwezigheid en ernst van cerebrale microangiopathie op "magnetic resonance imaging" (MRI) te relateren aan het ontstaan van dementie en depressie bij ouderen. Het onderzoek werd verricht binnen de Rotterdam Scan Studie, een prospectieve cohort-studie onder 1,077 personen van 60 jaar en ouder uit de algemene populatie. Alle deelnemers waren vrij van dementie aan het begin van de studie.

Hoofdstuk 1 is een inleiding over het onderwerp van dit proefschrift. In **hoofdstuk 2.1** relateren we de aanwezigheid en ernst van witte stof afwijkingen, infarcten en globale atrofie op MRI aan achteruitgang in cognitief functioneren. Witte stof afwijkingen in de periventriculaire regio, infarcten en globale atrofie waren geassocieerd met cognitieve achteruitgang, en specifiek met achteruitgang in snelheid van informatieverwerking. Onze resultaten suggereren verder dat een beroerte een tussenliggende stap kan zijn in de relatie tussen witte stof afwijkingen en infarcten enerzijds en cognitieve achteruitgang anderzijds.

Op MRI scans van de hersenen worden bij ouderen vaak infarcten gezien die niet hebben geleid tot symptomen van een beroerte. **Hoofdstuk 2.2** beschrijft een studie waarin wordt onderzocht of deze asymptomatische infarcten gerelateerd zijn aan het risico op dementie en cognitieve achteruitgang. Aan het begin van de studie, en gemiddeld drie jaar daarna, kregen de deelnemers een MRI scan van de hersenen en werden zij neuropsychologisch getest. Herseninfarcten werden beoordeeld op MRI en op basis van medische informatie onderverdeeld in symptomatische en asymptomatische infarcten. De aanwezigheid van asymptomatische infarcten aan het begin van de studie verdubbelde het risico op dementie. Ouderen die nieuwe asymptomatische infarcten doormaakten, gingen harder achteruit in cognitief functioneren dan ouderen zonder nieuwe asymptomatische infarcten.

In **hoofdstuk 2.3** bestuderen we de relatie tussen cerebrale witte stof afwijkingen in specifieke locaties en het risico op dementie. De ernst van cerebrale witte stof afwijkingen in de periventriculaire en subcorticale regio werd gemeten op MRI. Alle deelnemers werden over een periode van gemiddeld vijf jaar gevolgd met betrekking tot het ontwikkelen van dementie. Tijdens de studie-periode werden 45 deelnemers dement. Toenemende ernst van witte stof afwijkingen in de perivertriculaire regio verhoogde het risico op dementie. Voor elke standaard deviatie toename in ernst van periventriculaire witte stof afwijkingen nam

het risico op dementie toe met 70 procent. Dit verhoogde risico was onafhankelijk van andere risicofactoren voor dementie en deels onafhankelijk van de aanwezigheid van andere structurele hersenafwijkingen op MRI.

In **hoofdstuk 2.4** beschrijven we de relatie tussen de concentratie van homocysteine in het bloed en cognitief functioneren. Wij vonden dat ouderen met een verhoogde homocysteine-concentratie slechter presteerden op cognitieve taken, met name op taken voor snelheid van informatieverwerking. Deze relatie werd niet verklaard door de aanwezigheid van structurele hersenafwijkingen op MRI. Dit suggereert mogelijk een direct neurotoxisch effect van homocysteine.

Het verband tussen herseninfarcten, witte stof afwijkingen en depressie wordt beschreven in **hoofdstuk 3.** Infarcten en witte stof afwijkingen werden gemeten op MRI en de deelnemers werden over een periode van drie jaar gevolgd met betrekking tot het ontwikkelen van een depressieve stoornis. Hierbij werd een onderscheid gemaakt tussen incidente en chronische depressieve stoornissen. Herseninfarcten verdrievoudigden het risico op chronische depressieve stoornissen, terwijl ernstige witte stof afwijkingen in de subcorticale regio het risico op incidente depressieve stoornissen verdubbelden. Deze bevindingen ondersteunen de vasculaire depressie hypothese, die veronderstelt dat er bij ouderen een subtype depressieve stoornis bestaat die gekenmerkt wordt door een specifieke klinische presentatie en een associatie met cerebrovasculaire ziekte.

Hoofdstuk 4.1 betreft een studie waarin verschillende visuele schalen werden vergeleken met volumetrie voor het meten van progressie van witte stof afwijkingen. Voor het meten van progressie van witte stof afwijkingen bleken de schalen van Fazekas, Scheltens en het periventriculaire deel van de Rotterdam Scan Studie schaal niet goed overeen te komen met volumetrie. Een nieuwe visuele schaal, specifiek ontworpen voor het meten van progressie van witte stof afwijkingen, en het subcorticale deel van de Rotterdam Scan Studie schaal vertoonden een goede correlatie met volumetrie. Nadat de beoordelaars vertrouwd waren geraakt met de nieuwe schaal, waren de progressie-metingen met deze schaal ook goed reproduceerbaar.

Hoewel er veel bekend is over de frequentie van en risicofactoren voor witte stof afwijkingen onder de algemene populatie, zijn er maar weinig gegevens over de verandering in witte stof afwijkingen over de tijd. Het doel van de in **hoofdstuk 4.2** beschreven studie was om de mate van progressie van witte stof afwijkingen in de algemene populatie te beschrijven en om risicofactoren voor deze progressie te onderzoeken. In een periode van drie jaar vertoonde ongeveer een derde van de ouderen een toename van witte stof afwijkingen. Risicofactoren voor progressie van witte stof afwijkingen waren de ernst van witte stof afwijkingen aan het begin van de studie, hogere leeftijd, vrouwelijk geslacht, hoge bloeddruk en roken.

Het onderzoek in **hoofdstuk 4.3** bestudeert de associatie tussen progressie van witte stof afwijkingen en het risico op beroerte, dementie en depressie. Ouderen met progressie van witte stof afwijkingen hadden een drie keer verhoogd risco op een beroerte en gingen

harder achteruit in globaal cognitief functioneren en snelheid van informatieverwerking. Ernstige progressie verhoogde het risico op dementie en depressieve symptomen, wat bij een deel van de ouderen werd verklaard door een doorgemaakte beroerte.

In **hoofdstuk 5** worden de belangrijkste bevindingen van de in dit proefschrift beschreven onderzoeken samengevat en wordt aandacht besteed aan een aantal methodologische en conceptuele kwesties. Tot slot worden suggesties gedaan voor verder onderzoek.

Dankwoord

Dit proefschrift is het resultaat van drie en een half jaar onderzoek aan de afdeling Epidemiologie & Biostatistiek van het Erasmus MC. Gedurende deze periode hebben veel mensen op de een of andere manier aan dit proefschrift bijgedragen. Nu het is voltooid, is het moment aangebroken om hen te bedanken.

In de eerste plaats wil ik de meer dan duizend deelnemers aan de Rotterdam Scan Studie bedanken. Dank ook aan alle huisartsen uit Rotterdam en Zoetermeer die bij onze studie betrokken waren, en verder aan de medewerkers van de BAVO RNO groep en Circuit Haagrand Parnassia voor hun coöperatie.

Vervolgens gaat mijn dank uit naar mijn promotoren Monique Breteler en Peter Koudstaal. Monique Breteler bood mij de mogelijkheid binnen haar onderzoeksgroep te promoveren en gaf daarmee een beslissende wending aan mijn loopbaan. Onze gedeelde interesse voor hersenafwijkingen in relatie tot cognitie en stemming bleek een goede basis voor een vruchtbare samenwerking. Met haar recente benoeming als hoogleraar neuro-epidemiologie krijgt zij nu de erkenning die zij verdient.

Peter Koudstaal wist gedurende mijn promotieperiode een scherpe wetenschappelijke blik te combineren met een jaloersmakende efficiëntie. Naast zijn onmisbare bijdrage aan mijn onderzoek heeft hij mij gesteund in mijn ambitie voor een carrière in de klinische neurologie. Ik kijk met genoegen uit naar de komende jaren waarin we onze samenwerking zullen continueren.

Ook Bert Hofman ben ik zeer erkentelijk. Als hoofd van de afdeling creëerde hij de voorwaarden voor het in dit proefschrift beschreven onderzoek. Aan het begin van mijn aanstelling gaf hij mijn project de juiste richting en ook gedurende de rest van mijn promotietijd wist hij mij steeds te inspireren.

Een aantal mensen wil ik bedanken voor hun bijdrage aan mijn proefschrift. Jelle Jolles maakte het neuropsychologisch onderzoek mogelijk en gaf waardevolle adviezen over de

analyse en interpretatie van de neuropsychologische gegevens. Matthijs Oudkerk superviseerde het MRI onderzoek. Robert Clarke was verantwoordelijk voor de homocysteine bepalingen en gaf waardevol advies bij de studie naar homocysteine en cognitie. Henning Tiemeier zijn commentaar en advies waren onmisbaar bij de analyse en interpretatie van de depressie-gegevens. Philip Scheltens, Frederik Barkhof en Ilse van Straaten hielpen bij het ontwikkelen en evalueren van een methode voor het meten van progressie van witte stof afwijkingen op MRI. Theo Stijnen gaf waardevolle adviezen met betrekking tot de data analyse. Ewoud van Dijk, Tom den Heijer en Sarah Vermeer speelden een grote rol bij de dataverzameling en de organisatie van de Rotterdam Scan Studie en voorzagen de manuscripten van waardevol commentaar. Bess Leroy las de manuscripten kritisch door op het gebruik van het Engels. Ingrid van Vuuren, Frank-Erik de Leeuw, Jan Cees de Groot, Frank van Rooij, Henri Vrooman en Rik Stokking speelden een belangrijke rol bij het verzamelen en of beheren van de gegevens van de Rotterdam Scan Studie.

Mijn dank gaat verder uit naar alle collega's van de afdeling Epidemiologie & Biostatistiek. Met name bedank ik Marti von Stein, Petra van Rikxoort en Marjolijn Kasi voor de uitstekende secretariële ondersteuning, en Nano Suwarno, Eric Neeleman, René Molhoek, René Vermeeren en Marcel Rond voor hun behulpzaamheid bij alle automatiseringsproblemen. Mijn collega's Ewoud van Dijk en Anna Schut namen de afgelopen jaren een bijzondere plaats in. De zeer nauwe samenwerking met Ewoud groeide uit tot een vriendschap. Anna gaf mijn verblijf op de afdeling glans.

Tot slot bedank ik mijn ouders voor het onbegrensde vertrouwen dat zij altijd in mij hebben gesteld, en mijn zus Anna voor haar liefde en steun tijdens het schrijven van dit proefschrift.

List of publications

Prins ND, Den Heijer T, Hofman A, Koudstaal PJ, Jolles J, Clarke R, Breteler MMB. Homocysteine and cognitive function in the elderly: the Rotterdam Scan Study. Neurology 2002;59:1375-80.

van Dijk EJ, Prins ND, Vermeer SE, Koudstaal PJ, Breteler MMB. Frequency of white matter lesions and silent lacunar infarcts. J Neural Transm Suppl 2002:25-39.

Prins RS, Prins ND, Visch-Brink EG. Taalstoornissen bij dementie. Stem,-Spraak- en Taalpathologie 2002;17:B9.4.2:1-50.

Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MMB. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348:1251-22.

van Straaten EC, Scheltens P, Knol DL, van Buchem MA, van Dijk EJ, Hofman PA, Karas G, Kjartansson O, de Leeuw FE, Prins ND, Schmidt R, Visser MC, Weinstein HC, Barkhof F. Operational definitions of the NINDS-AIREN criteria for vascular dementia: an interobserver study. Stroke 2003;34:1907-12.

den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, Breteler MMB. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. Diabetologica 2003 Dec;46(12):1604-10.

van Dijk EJ, Vermeer SE, de Groot JC, van de Minkelis J, Prins ND, Oudkerk M, Hofman A, Koudstaal PJ, Breteler MMB. Arterial oxygen saturation, COPD, and cerebral small vessel disease. J Neurol Neurosurg Psychiatry 2004. In press.

Prins ND, van Straaten EC, van Dijk EJ, Simoni M, van Schijndel R, Vrooman HA, Koudstaal PJ, Hofman A, Breteler MMB. Measuring progression of cerebral white matter lesions on MRI; visual rating and volumetrics. Neurology 2004. In press.

Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MMB. Cerebral white matter lesions and the risk of dementia. Arch Neurol 2004. In press.

van Dijk EJ, Prins ND, Vermeer SE, Hofman A, van Duijn CM, Koudstaal PJ, Breteler MMB. Plasma β amyloid, APOE, brain infarcts and white matter lesions. Ann Neurol 2004. In press.

Artero S, Tiemeier H, Prins ND, Sabatier R, Breteler MMB, Ritchie K. Neuroanatomical correlates of white matter lesions in the elderly. J Neurol Neurosurg Psychiatry 2004. In press.

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Niels Prins was born on August 30, 1971 in Amsterdam, the Netherlands. He graduated in 1989 at the "Barlaeus Gymnasium" in Amsterdam. In 1990, he started his medical studies at the University of Amsterdam, where he obtained his medical degree in 1998. During his studies, he went to Boston, U.S.A., for an internship at the Massachusets General Hospital. He spent five months in South-East Sulawesi, Indonesia, where he performed a study on drug compliance in leprosy-patients for Dutch Leprosy Relief. After obtaining his medical degree, he worked for three months as a resident in Psychiatry, and from 1999 to 2000 as a resident in Neurology, at the OLVG hospital in Amsterdam. Subsequently, he briefly worked as a resident in Neurology at the VU Medical Center, Amsterdam.

In August 2000, he started the work described in this thesis in the Neuroepidemiology group of the Department of Epidemiology & Biostatistics (Prof.dr. M.M.B. Breteler), in collaboration with the Department of Neurology (Prof.dr. P.J. Koudstaal) of the Erasmus Medical Center, Rotterdam. During this work, he obtained a Master of Science in Clinical Epidemiology at the Netherlands Institute of Health Sciences in 2003. He started his specialist training in neurology at the Erasmus Medical Center, Rotterdam (Prof. P.A.E. Sillevis Smitt), February 2004.