Silent brain infarcts

Frequency, risk factors, and prognosis

Sarah Elisabeth Vermeer

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 Centre, Rotterdam.

The Rotterdam Scan Study was supported by grants from the Netherlands Heart Foundation and the Netherlands Organisation for Scientific Research. Financial support for 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 Clinical Trial Service Unit, University of Oxford, United Kingdom (Prof. dr R. Clarke), and the Regional Institute for Ambulatory Mental Health and the general practitioners of Rotterdam and Zoetermeer.

The Departments of Epidemiology & Biostatistics and Neurology of the Erasmus Medical Centre supported the publication of this thesis.

Further financial support for publication of this thesis
was provided by the Remmert Adriaan Laan Fonds,
AstraZeneca BV, and Servier Nederland BV.

Cover design: Jeep Brongersma
Printed by: Optima Grafische Communicatie, Rotterdam

ISBN 90-77017-98-4

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Stille herseninfarcten

Frequentie, risicofactoren en prognose

Proefschrift

ter verkrijging van de graad van doctor aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus Prof. dr ir J.H. van Bemmel
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 2 oktober 2002 om 13:45 uur

door

Sarah Elisabeth Vermeer

geboren te Leiden.

Promotiecommissie

Promotores:	Prof. dr P.J. Koudstaal
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The studies described in this thesis were supported by grants of the Netherlands Heart Foundation (NHF 97.152) and the Netherlands Organisation for Scientific Research (NWO 904.61.096).

Financial support by the Netherlands Heart Foundation and the Netherlands Organisation for Scientific Research for the publication of this thesis is gratefully acknowledged.

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Chapter 2.2
Vermeer SE, van Dijk EJ, Koudstaal PJ, Oudkerk M, Hofman A, Clarke R, Breteler MMB. Homocysteine, silent brain infarcts and white matter lesions. The Rotterdam Scan Study. Ann Neurol 2002;51:285-289.

Chapter 2.3
Vermeer SE, den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MMB. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Submitted.

Chapter 3.1
Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MMB. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Submitted.

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Vermeer SE, den Heijer T, Hofman A, Koudstaal PJ, Breteler MMB. Silent brain infarcts and the risk of dementia and cognitive decline. The Rotterdam Scan Study. Submitted.

Chapter 3.3
Vermeer SE, Prins ND, Tiemeier H, Hofman A, Koudstaal, PJ, Breteler MMB. Brain infarcts, white matter lesions and the risk of depression in the general population. The Rotterdam Scan Study. Submitted.

Chapter 4
Vermeer SE, Koudstaal PJ, Hofman A, Breteler MMB. Silent brain infarcts: a review. Submitted.

Chapter 1

Introduction

Silent — i.e. asymptomatic — brain infarcts are frequently seen on cerebral magnetic resonance imaging (MRI) scans in patients admitted to the hospital with their first stroke. With the increasing use and improvement of imaging techniques, these silent lesions are more often found in people without stroke-like symptoms.[1] In contrast to symptomatic brain infarcts, the relevance of these so-called silent brain infarcts is not known. Because knowledge of the consequences of silent infarcts is lacking, special treatment regimens have not been developed yet for patients with these lesions. In selected patient groups however, silent brain infarcts seem to increase the risk of stroke and death.[2] Furthermore, hospital-based studies found that they are more frequently present in elderly patients with dementia and depression than in other patients.[3,4] Prospective longitudinal research in which large groups of asymptomatic people undergo brain imaging is needed to examine the clinical relevance of silent brain infarcts in the general population.

In this thesis the following questions are investigated:

1. How frequent are silent brain infarcts in the general population?
2. What are the risk factors for silent brain infarcts?
3. What are the clinical consequences of silent brain infarcts?

To answer these questions, data was used from the Rotterdam Scan Study, a large cohort study among elderly people from the general population who underwent MRI scanning of the brain. The presence of (silent) brain infarcts was scored on MRI, as were other brain abnormalities including white matter lesions and global brain atrophy. Both are thought to have a vascular pathogenesis and frequently coexist in ischaemic brains.[5,6] In chapter 2, the prevalence and incidence of silent brain infarcts is presented. Furthermore, this chapter describes studies on the risk factors for silent brain infarcts, in which a comparison with the classical risk factors for symptomatic infarcts is made. The investigation of the relationship with one of the relative new risk factors, the potentially modifiable homocysteine, is also reported here. For studies described in chapter 3, this cohort is followed over time and monitored for mortality and major morbidity. This chapter describes the relationship between silent brain infarcts and the risk of three frequent and

disabling disorders in elderly people, namely stroke, dementia, and depression. In chapter 4, I discuss and review all findings and make suggestions for further research.

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Chapter 2

Frequency and risk factors

PREVALENCE AND RISK FACTORS OF SILENT BRAIN INFARCTS

Chapter **2.1**

Abstract

Background Silent brain infarcts are commonly seen on MRI both in patients with a first stroke and in healthy elderly persons. These infarcts seem associated with an increased risk of stroke. It is unclear whether risk factors for silent infarcts differ from those for symptomatic stroke. We investigated the prevalence of, and cardiovascular risk factors for, silent brain infarcts.

Methods The Rotterdam Scan Study is a population-based cohort study among 1,077 participants 60 to 90 years of age. Participants underwent cerebral MRI. We assessed cardiovascular risk factors by interview and physical examination. Associations between risk factors and presence of infarcts were analysed by logistic regression and adjusted for age, sex, and relevant confounders.

Results For 259 participants (24%) one or more infarcts on MRI were seen; 217 persons had only silent and 42 had symptomatic infarcts. The prevalence odds ratio of both silent and symptomatic infarcts increased with age by 8% per year (95% confidence interval 1.06-1.10 and 1.04-1.13, respectively). Silent infarcts were more frequent in women (age-adjusted odds ratio 1.4, 95% confidence interval 1.0-1.8). Hypertension was associated with silent infarcts (age- and sex-adjusted odds ratio 2.4, 95% confidence interval 1.7-3.3), but diabetes mellitus and smoking were not.

Conclusions Silent brain infarcts are five times as prevalent as symptomatic brain infarcts in the general population. Their prevalence increases with age and seems higher in women. Hypertension is associated with silent infarcts, but other cardiovascular risk factors are not.

Prior brain infarctions are commonly seen on MRI in patients with their first stroke. Silent, that is asymptomatic, brain infarcts are often found in healthy elderly as well. In selected patient groups, silent brain infarcts seem associated with an increased risk of stroke.[1] It is unclear whether risk factors for silent infarcts are similar to those for symptomatic stroke. Thus far, two US-based studies have investigated the presence of silent brain infarcts in the elderly.[2,3] Both studies addressed the association between cardiovascular risk factors and silent infarcts. They showed conflicting results about risk factors such as sex and smoking. Therefore, we further studied the prevalence of and cardiovascular risk factors for silent brain infarcts in the population-based Rotterdam Scan Study, in the Netherlands.

Participants and Methods

Participants

The Rotterdam Scan Study is designed to study causes and consequences of brain changes in the elderly. The participants originated from two large ongoing prospective population-based cohort studies, the Zoetermeer Study and the Rotterdam Study. The baseline data collection for the Zoetermeer Study took place from 1975 to 1978, and that for the Rotterdam Study occurred in 1990 to 1993. Both studies included independently and institutionalised living persons. The rationale for both studies has been described elsewhere.[4,5]

In 1995 to 1996, we randomly selected participants 60 to 90 years of age from both studies in strata of age (5 years) and sex. People with MRI contraindications were not eligible for our study and were excluded. A total of 1,077 non-demented elderly individuals participated in our study (overall response 63%). The main reasons for not participating in the Rotterdam Scan Study were old age, too much trouble, not wanting to participate in brain research, and claustrophobia. The study design has been described in detail.[6] Each participant gave informed consent. The medical ethics committee of the Erasmus Medical Centre approved the study.

Cerebral infarcts

All participants underwent MRI of the brain. 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 with an interslice gap of 20%. Laser hardcopies were printed with a reduction factor of 2.7.

We defined infarcts 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 for us to distinguish them from cerebral white matter lesions. Lesions were defined as possible infarcts, if this distinction between infarcts and white matter lesions could not be made. We did not consider possible infarcts as infarcts in our analyses; participants with only possible infarcts (n=73) were included in the reference group. A single trained physician who was blinded to history of stroke and transient ischaemic attack (TIA) scored infarcts, including their location and size. Intrarater study for detecting infarcts showed good agreement (κ=0.80).

We obtained a history of stroke and TIA by self-report, and by checking medical records in all 1,077 participants, independently on their MRI outcome. Stroke was defined as an episode of typical focal neurological deficits with acute onset and lasting for more than 24 hours. TIA was similarly defined, but with symptoms lasting less than 24 hours. An experienced neurologist with knowledge of the participants' medical history subsequently reviewed the scans and categorised the infarcts on MRI 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 TIA. If prior stroke or TIA did correspond with a lesion, the latter was defined as a symptomatic infarct. Participants with both symptomatic and silent infarcts were included in the symptomatic infarct group. Intrarater reliability for the classification of infarcts as silent or symptomatic was excellent (κ=1.0).

Cardiovascular risk factors

We obtained the cardiovascular risk factors by interview and physical examination in 1995 to 1996. Blood pressure was measured twice on the right arm with a random-zero sphygmomanometer. We used the average of these two measurements. We calculated pulse pressure by subtracting diastolic blood pressure from systolic blood pressure.[7] Participants had hypertension if the systolic blood pressure $\geq$ 160 mm Hg, if the diastolic blood pressure $\geq$ 95 mm Hg, or if they reported the use of blood pressure-lowering medication. We considered diabetes

Silent infarcts were more frequent in women than in men (Table 2). Ninety-one of 522 men (17%) had one or more silent infarcts on MRI compared to 126 of the 555 participating women (23%). This higher prevalence in women was constant over all age groups. No clear differences could be detected in the prevalence of symptomatic infarcts between men and women.

Table 2. Association between cardiovascular risk factors and subtypes of infarcts.

	Silent infarcts		Symptomatic infarcts	
	Crude OR* (95% CI)	Adjusted OR† (95% CI)	Crude OR* (95% CI)	Adjusted OR† (95% CI)
Age (per year)	1.08 (1.06-1.10)	1.08 (1.05-1.10)	1.08 (1.04-1.13)	1.07 (1.03-1.12)
Women	1.4 (1.0-1.8)	1.3 (0.9-1.9)	0.8 (0.4-1.5)	1.2 (0.6-2.6)
Hypertension	2.4 (1.7-3.3)	2.3 (1.6-3.2)	3.7 (1.8-8.0)	3.3 (1.5-7.2)
Diabetes mellitus	1.0 (0.5-1.9)	0.7 (0.4-1.5)	3.3 (1.4-7.8)	2.5 (1.0-5.9)
Smoking:				
No smoking	1 (reference)	1 (reference)	1 (reference)	1 (reference)
< 20 pack-years	1.1 (0.7-1.7)	1.2 (0.8-1.8)	1.3 (0.5-3.6)	1.5 (0.5-4.0)
≥ 20 pack-years	0.9 (0.6-1.4)	1.0 (0.6-1.5)	3.0 (1.2-7.5)	3.1 (1.2-7.6)

* Odds ratios (OR) and 95% confidence intervals (CI), adjusted for age and sex.

† Additionally adjusted for hypertension, diabetes mellitus, and smoking.

Hypertension was strongly associated with the presence of both silent and symptomatic infarcts (Table 2). The presence of diabetes mellitus and pack-years of smoking were associated with symptomatic, but not with silent, infarcts. Further adjustments for alcohol consumption did not alter this association with smoking. The adjusted odds ratio of silent infarcts for the highest compared to the lowest category of systolic blood pressure, irrespective of blood pressure-lowering medication, was 1.9 (95% confidence interval 1.0-3.7; Figure 3). For diastolic blood pressure the odds even tripled (odds ratio 2.8, 95% confidence interval 1.6-4.9). The presence of silent infarcts was also higher when we compared the highest with the lowest category of pulse pressure (odds ratio 4.3, 95% confidence interval 2.1-8.9). Table 3 shows the relations between the blood pressure measures and brain infarcts when they were analysed continuously. To allow comparison of the strength of the associations, they are all expressed as adjusted odds ratio per standard deviation increase in blood pressure measure. Systolic and diastolic blood

pressure and pulse pressure were all associated with presence of silent brain infarcts. For symptomatic infarcts, no significant associations were found between systolic or diastolic blood pressure levels and presence of infarcts. Analysis in strata of antihypertensive treatment showed that in participants without treatment the proportion of participants with silent infarcts increased with increasing blood pressure (data not shown). The strength of the association of pulse pressure with symptomatic infarcts was very similar to that for silent infarcts, albeit not statistically significant. Pulse pressure was no longer related to silent brain infarcts after adjustment for systolic blood pressure level (odds ratio 0.95 per standard deviation 95% confidence interval 0.71-1.27). The strong colinearity between these blood pressure measures limits the interpretability of this finding. However, the effect of systolic blood pressure seems larger than that of pulse pressure (Table 3), which suggests that the latter may be mainly driven by the effect of systolic blood pressure.

Figure 3. Association between categories of systolic blood pressure, diastolic blood pressure, and pulse pressure and presence of silent brain infarcts (odds ratios and 95% confidence intervals, adjusted for age, sex, diabetes mellitus, and smoking).

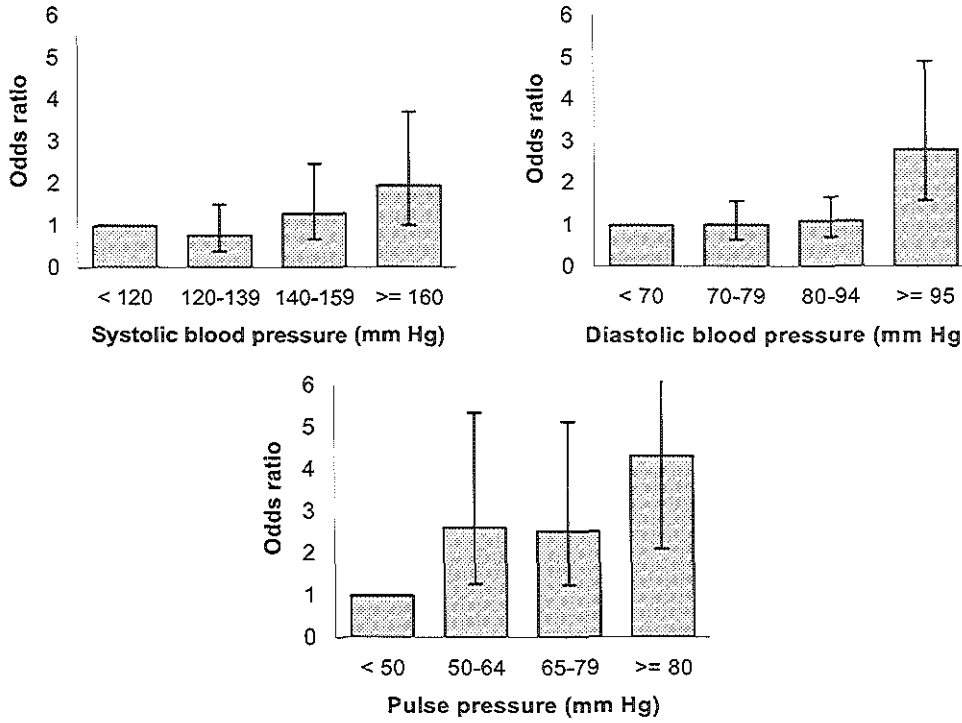

Table 3. Association between systolic blood pressure, diastolic blood pressure, and pulse pressure and subtypes of infarcts.

	Silent infarcts Adjusted OR (95% CI)*	Symptomatic infarcts Adjusted OR (95% CI)*
Systolic blood pressure	1.45 (1.23-1.71)	1.30 (0.94-1.79)
Diastolic blood pressure	1.27 (1.08-1.49)	1.08 (0.78-1.50)
Pulse pressure	1.34 (1.13-1.58)	1.31 (0.96-1.79)

* Odds ratios (OR) per standard deviation increase and 95% confidence intervals (CI), adjusted for age, sex, diabetes mellitus, and smoking.

All analyses were also performed with exclusion of participants with possible infarcts on MRI. This did not alter the strength of any of the associations described above.

Discussion

We found in our population-based study a prevalence of silent brain infarcts that gradually increased with age from 8% in the 60- to 64-year-old participants to 35% in the oldest (85 to 90 years of age). Silent infarcts were five times as frequent as symptomatic infarcts. The prevalence of silent infarcts was higher in women than men. Hypertension was an additional independent risk factor for the presence of silent infarcts. Other cardiovascular risk factors were only related to symptomatic infarcts.

Some potential methodological limitations of our study need to be discussed first. The response rate in our study was high, but not 100%. Hence, there is a possibility of selection bias. The participating persons were significantly younger than non-responders.[6] Because we found the prevalence of silent brain infarcts to be higher with increasing age, the prevalence may be even higher in the highest age category. Non-participation because of cognitive or functional deficits may also have introduced bias, probably leading to an underestimation of the prevalence of brain infarctions. There was no difference in response rate between men and women. Therefore, it is unlikely that the difference in silent brain infarcts between sexes is due to selection bias.

Furthermore, we may have misclassified brain infarcts in two different ways. First, we might have incorrectly identified them on the MRI scan. Despite our good

intrarater agreement, it is possible that we systematically over- or underrated infarcts. Second, we may have misclassified infarcts as being silent or symptomatic. We tried to minimise error by obtaining participants' history of stroke and TIA not only by self-report, but also by checking medical records. Both the reader of the MRI scans and the experienced neurologist who classified the silent and symptomatic infarcts were blinded to all other data. Therefore, any misclassification will have resulted in an underestimation of the strength of the associations. The strengths of our study are the large number of participating elderly and its population-based design.

Two other population-based studies, the Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study, have found overall prevalences of silent brain infarcts of 11%[3] and 28%,[8] respectively. A Japanese community study, among participants who wished to receive health screening at their own expense, reported also a prevalence of 11%.[9] However, in both the ARIC Study and the Japanese study the mean age of participants was much lower than in our study. The participants of the Cardiovascular Health Study had the same mean age, but had more women participating,[10] compared to the Rotterdam Scan Study. Comparisons between all four studies are further hampered in that the MRI scanning protocol was not uniform; with important differences in slice thickness, interslice gap and type of scanner. Studies additionally differ in that none but ours verified the self-reported history of stroke and TIA by checking medical records. Besides, none of the other three studies checked whether prior stroke-like symptoms corresponded to the infarcts, as we did. When we take the age and sex differences into account, the prevalences of silent infarcts in the three studies mentioned above accord, however, largely with ours. Our prevalence also fits with what a Japanese autopsy study found, although they report slightly lower age-specific prevalences, but that might be due to the thick slices they used.[11]

Consistent with the study of silent lacunar infarcts in the Cardiovascular Health Study,[2] but not with those authors' results regarding overall silent infarcts,[8] we observed a 30% to 40% higher prevalence among women. This in contrast to common observations regarding symptomatic stroke that is reportedly more frequent in men. Although the sex difference was no longer statistically significant when we adjusted for other risk factors, our data are compatible with a higher prevalence of silent infarcts in women than men. Such a sex difference may be due

to differences in reporting and interpreting symptoms of stroke or TIA by both patients and physicians, similar to what has been observed for acute myocardial infarction.[12,13] Recent studies reported about this sex difference in the treatment of cerebrovascular disease.[14,15] Furthermore, women of this age more often live without a partner. Especially for transient neurological symptoms, one may hypothesise that those women will not report their symptoms at all. This might explain why the reverse is seen for symptomatic stroke, namely a higher prevalence in men,[16] although we could not duplicate this finding, which probably results from the small number of stroke survivors in our study. This higher prevalence of silent brain infarcts in women was not found in the younger cohorts of the Japanese study,[9] or in the ARIC Study.[3]

Hypertension was the only additional risk factor associated with silent brain infarcts in our study. The strong association with hypertension suggests that hypertensive small-vessel disease plays a crucial role in the pathogenesis of silent brain infarcts. This finding accords with all other studies on silent and symptomatic infarcts. The absence of a significant association between symptomatic infarcts and systolic and diastolic blood pressure may result from the small numbers of participants with symptomatic infarcts or reflect that blood pressure often drops after a symptomatic infarct. Furthermore, the antihypertensive treatment in these participants with prior symptomatic stroke may also have contributed the lack of association. Analysis in strata of antihypertensive treatment showed stronger associations between blood pressure level and presence of infarcts in persons without treatment, albeit, probably because of small numbers, not significantly.

We could not find an association between any other cardiovascular risk factor and silent brain infarcts. Diabetes mellitus — which is known to exacerbate small-vessel disease next to hypertension — was associated only with symptomatic infarcts in our study. We considered that we might have underestimated the prevalence of diabetes mellitus in our population, particularly in subjects without symptomatic infarcts. For persons with symptomatic infarcts, assessment of diabetic status may have been more correct, since these people are more likely to receive more medical attention. We did not have data on blood glucose level at time of the MRI examination. However, half of our cohort was screened for diabetes mellitus just a few years before as part of the Rotterdam Study with an oral glucose load, and associations were similar in this part of the cohort. Although we

cannot exclude that some differential misclassification may have occurred, we do not think that that can fully explain the discrepant findings for symptomatic and silent infarcts. The lack of association was consistent with the ARIC Study[3] and the lacunar infarct study of the Cardiovascular Health Study,[2] although not with the Japanese study.[9] For smoking we likewise found a relation with symptomatic infarcts and not with silent infarcts. We think that a different distribution of infarct types may be the reason why. Smoking is known to enhance atherosclerosis leading to large-vessel disease, and we found a much larger proportion of cortical infarcts among the symptomatic infarcts. The majority of silent infarcts were lacunar, where small-vessel disease is thought to play a more important role. The finding of Uehara et al[17] that risk factors for silent infarcts in the white matter differed from those for basal ganglia infarcts also supports this. An association between smoking and silent infarcts was supported only by the ARIC Study.[3] Unfortunately, the numbers in our study were to small to do risk factor analyses of the different subtypes of infarcts.

In conclusion, silent brain infarcts are common among the elderly. Silent brain infarcts are associated with hypertension, but not with other indicators of small- and large-vessel disease that are related to symptomatic infarcts. The prognosis of silent brain infarcts remains unclear. The study of Kobayashi et al[9] showed that they increased risk of stroke onset tenfold. However, as mentioned above, this study was not population-based. Prospective population studies will have to show the prognostic relevance of silent brain infarcts.

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HOMOCYSTEINE, SILENT BRAIN INFARCTS, AND WHITE MATTER LESIONS

Chapter **2.2**

Abstract

Background Silent brain infarcts and white matter lesions are frequently seen on MRI in healthy elderly people and both are associated with an increased risk of stroke and dementia. Plasma total homocysteine may be a potentially modifiable risk factor for stroke and dementia. We examined whether elevated total homocysteine levels are associated with silent brain infarcts and white matter lesions.

Methods The Rotterdam Scan Study is a population-based study of 1,077 people aged 60 to 90 years who had a cerebral MRI. The cross-sectional relation of total homocysteine with silent infarcts and white matter lesions was analysed with adjustment for cardiovascular risk factors.

Results The mean plasma total homocysteine level was 11.5 μmol/l (standard deviation 4.1). The risk of silent brain infarcts increased with increasing total homocysteine levels (odds ratio 1.24 per standard deviation increase, 95% confidence interval 1.06-1.45). The severity of periventricular white matter lesions and extent of subcortical white matter lesions were also significantly associated with total homocysteine levels, even after excluding those with silent brain infarcts. The overall risk of having either a silent brain infarct or severe white matter lesions was strongly associated with total homocysteine levels (odds ratio 1.35 per standard deviation increase, 95% confidence interval 1.16-1.58).

Conclusions We concluded that total homocysteine levels are associated with silent brain infarcts and white matter lesions independent of each other and of other cardiovascular risk factors.

Silent brain infarcts and white matter lesions are frequently seen on brain MRI in healthy elderly and either is associated with an increased risk of stroke[1] and dementia.[2,3] The presence of these lesions has been associated with several cardiovascular risk factors.[4,5] Both prospective and retrospective studies reported that an elevated total homocysteine concentration is a potentially modifiable risk factor for stroke.[6-9] More recently, several retrospective studies have shown that elevated levels of total homocysteine may also be a risk factor for dementia.[10,11] A recent study suggested that elderly participants with elevated total homocysteine levels had an increased risk of silent brain infarcts, but that study did not examine any associations with white matter lesions.[12] We examined whether elevated plasma total homocysteine, as a potentially modifiable risk factor,[13] is associated with an increased risk of silent brain infarcts and white matter lesions in elderly people and assessed the extent to which any such associations are independent of other cardiovascular risk factors and of each other.

Participants and Methods

Participants

The Rotterdam Scan Study was designed to study the aetiology and natural history of age-related brain changes in the elderly. In 1995 to 1996, we randomly selected participants aged 60 to 90 years by sex and by age in 5-year age strata from the population-based Zoetermeer[14] and Rotterdam[15] studies. A total of 1,077 non-demented elderly participated in our study (overall response 63%).[16] Each person gave informed consent to participate in our study, which had been approved by the medical ethics committee.

Plasma total homocysteine level

We collected non-fasting blood samples into vacutainers containing sodium citrate in 1995 to 1996. Samples were put on ice immediately, centrifuged within 60 minutes, and aliquots of plasma were stored at –80^{0}C. In 1999 to 2000, plasma levels of total homocysteine were determined by fluorescence polarisation immunoassay on an IMx analyser (Abbott Laboratories, Chicago, Illinois, USA). This method has an intralaboratory imprecision of less than 5% and showed linearity throughout the 5 to 45 μmol/l range.[17] Blood samples were not available

for 39 participants due to failure to obtain a sample. Seven participants were excluded, because their total homocysteine level fell outside this range.

Cardiovascular risk factors

We obtained information on the following variables by interview and physical examination in 1995 to 1996: systolic blood pressure, antihypertensive drugs, diabetes mellitus, pack-years of smoking, and vitamin use.[18] The presence of carotid artery plaques, the intima-media thickness of the common carotid artery, and the presence of peripheral arterial disease were assessed as non-invasive markers of atherosclerotic disease.[19]

Cerebral infarcts and white matter lesions

We obtained axial T1-, T2-weighted and proton-density MRI scans of the brain on 1.5 Tesla MRI scanners (MR Gyroscan, Philips, Best, the Netherlands and MR VISION, Siemens, Erlangen, Germany) in 1995 and 1996. The slice thickness was 5 or 6 mm (scanner dependent) with a 20% interslice gap.

Infarcts were rated by a single rater and 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.[18] We obtained a history of stroke and TIA by self-report, and by checking medical records in all 1077 participants. A neurologist subsequently reviewed the medical history and scans and categorised the infarcts as silent or symptomatic. We defined silent 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 silent infarcts were categorised in the symptomatic infarct group. Twenty participants with a confirmed history of stroke had no infarcts on MRI. Three of them experienced a haemorrhagic stroke; the seventeen others with ischaemic (n=12) or unspecified (n=5) stroke had minor symptoms.

White matter lesions were considered present if visible as hyperintense on proton-density and T2-weighted images, without prominent hypointensity on T1-weighted scans. We scored periventricular and subcortical white matter lesions separately. Periventricular white matter lesions were rated semi-quantitatively (grade range 0-9). A total volume of subcortical white matter lesions was approximated based on number and size of lesions (volume range 0-29.5 ml).[20]

Statistical analysis

Participants with symptomatic infarcts were excluded from all analyses. We analysed the association between quintiles of total homocysteine and presence of silent brain infarcts using multiple logistic regression. Using a dichotomous approach, the reference group comprised all participants without infarcts visible on MRI. No distinction was made between participants with one or more infarcts on their scan. We evaluated the association of quintiles of total homocysteine and white matter lesions using analysis of covariance. The relationship of total homocysteine levels and white matter lesions was also analysed continuously using multiple linear regression models. We performed separate analyses for subcortical and periventricular lesions. All analyses were adjusted for age, sex, systolic blood pressure, antihypertensive drugs, diabetes mellitus, and pack-years of smoking. Additionally, we adjusted for markers of atherosclerotic disease to examine whether such associations with total homocysteine were mediated by atherosclerosis.

Because the presence of silent brain infarcts and white matter lesions on MRI are highly correlated, we tested whether the association of total homocysteine with white matter lesions was explained by the relation between total homocysteine and silent brain infarcts. We therefore repeated the above analyses with white matter lesions after exclusion of participants with silent infarcts on MRI, and vice versa for the association with silent brain infarcts. Finally, we analysed the association of total homocysteine with the presence of either silent infarcts or severe white matter lesions, defined as white matter lesions in the upper quintile of their distribution.

Results

Selected characteristics of the study population are shown in Table 1. Twenty percent had one or more silent brain infarcts on MRI, 80% of the 1,077 participants had any periventricular and 92% any subcortical white matter lesions. The mean plasma total homocysteine level was 11.5 µmol/l (standard deviation 4.1). Plasma total homocysteine concentrations significantly increased with age (1.5 µmol/l increase per 10 years) and were about 1.1 µmol/l higher in men than in women, 1.2 µmol/l higher in participants who took antihypertensive drugs, and 1.4 µmol/l lower in participants who used vitamins than those who did not. Plasma

total homocysteine levels were 0.6 µmol/l higher for every increase in plaque category. However, this association disappeared after adjustment for age, sex, and other confounders (0.1 µmol/l per increase in plaque category, 95% confidence interval –0.2-0.4). Plasma total homocysteine was also not associated with intima-media thickness or with peripheral artery disease (data not shown).

Table 1. Characteristics of the study population in 1995 to 1996.

	All participants n=1,077
Age, years	72.2 ± 7.4
Women	51.5
Plasma total homocysteine, µmol/l	11.5 ± 4.1
Systolic blood pressure, mm Hg	147 ± 22
Use of antihypertensive drugs	34.7
Diabetes mellitus	5.8
Smoking:	
Never (0 pack-years)	34.6
> 0 and < 20 pack-years	29.6
≥ 20 pack-years	35.8
Use of vitamins	5.8
Participants with infarcts on MRI:	
Silent	20.1
Symptomatic	2.4
Both	1.5
White matter lesions:	
Periventricular, grade	2.4 ± 2.2
Subcortical, ml	1.4 ± 2.9

Values are unadjusted means ± standard deviation or percentages.

Silent brain infarcts were 2.5 times as common in the top quintile compared with the bottom quintile of plasma total homocysteine levels (Table 2). Since the crude and adjusted risk estimates and 95% confidence intervals were almost identical, only the adjusted risk estimates are presented. The results were unaltered by further adjustment for markers of atherosclerosis (data not shown). Participants were 24% more likely to have silent infarcts per standard deviation increase in total

homocysteine (95% confidence interval 6%-45%). The association of silent brain infarcts with total homocysteine was also significant in participants after exclusion of those with periventricular white matter lesions (odds ratio 1.79 per standard deviation increase, 95% confidence interval 1.08-2.98).

Table 2. Association of quintiles of plasma total homocysteine (tHcy) level with silent brain infarcts (SBI), severe white matter lesions (WML), and both on MRI.

tHcy in quintiles (µmol/l)	SBI OR (95% CI)‡	Severe WML* OR (95% CI)‡	SBI and/or severe WML† OR (95% CI)‡
I 5.0-8.5	1 (reference)	1 (reference)	1 (reference)
II 8.6-9.8	1.4 (0.8-2.5)	1.9 (1.0-3.4)	1.7 (1.0-2.9)
III 9.9-11.3	1.7 (1.0-3.1)	2.1 (1.1-3.7)	2.0 (1.2-3.3)
IV 11.4-13.7	1.6 (0.9-2.9)	2.0 (1.1-3.7)	2.3 (1.4-3.8)
V 13.8-45.0	2.5 (1.4-4.5)	2.3 (1.3-4.2)	3.0 (1.8-5.2)

* Presence of severe periventricular, and/or severe subcortical white matter lesions, defined by the upper quintile of their distribution.

† Presence of silent brain infarcts, and/or severe periventricular, and/or severe subcortical white matter lesions.

‡ Odds ratios (OR) and 95% confidence intervals (CI), adjusted for age, sex, systolic blood pressure, antihypertensive drugs, diabetes mellitus, and smoking.

White matter lesions were also associated with plasma total homocysteine levels (Figure 1). Participants in the top quintile of total homocysteine had more than double the prevalence of severe white matter lesions on MRI compared with those in the bottom quintile (Table 2). Severity of both periventricular and subcortical white matter lesions increased with higher total homocysteine levels (Table 3). These associations were unaltered by further adjustment for atherosclerotic disease. After exclusion of those with silent infarcts on MRI, the association of total homocysteine with periventricular white matter lesions was unaltered; the association of total homocysteine with subcortical white matter lesions was attenuated but remained significant.

A total of 378 (36%) of the 1,077 participants had either infarcts on MRI, severe white matter lesions, or both. Plasma total homocysteine levels were increased in these participants (Table 2). The risk of having either a silent brain infarct or severe white matter lesions was strongly associated with total

homocysteine levels (odds ratio 1.35 per standard deviation increase, 95% confidence interval 1.16-1.58), and further adjustment for atherosclerotic markers did not alter these associations. Exclusion of participants who used vitamins or who had a history of stroke but no infarct on MRI did not change any of the results above.

Figure 1. Association between quintiles of plasma total homocysteine (tHcy) level and periventricular and subcortical white matter lesions (WML; mean grade or volume (ml) and 95% confidence intervals, adjusted for age, sex, systolic blood pressure, antihypertensive drugs, diabetes mellitus, and smoking).

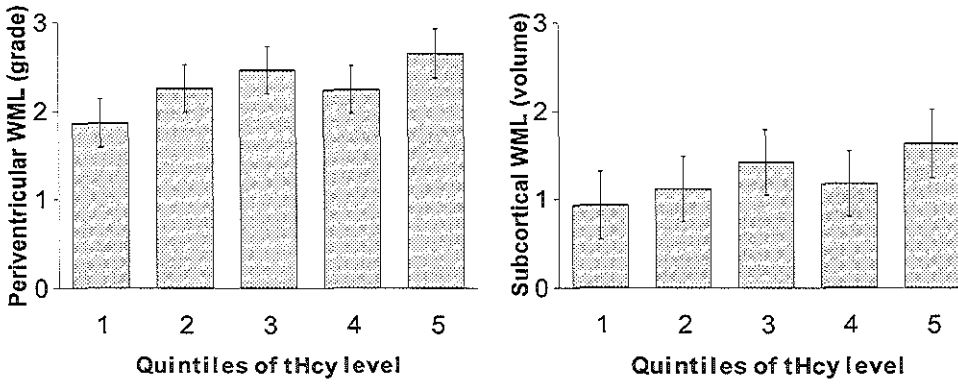

Table 3. Association of plasma total homocysteine (tHcy) levels with periventricular and subcortical white matter lesions (mean increase in grade or volume (ml) per standard deviation increase in total homocysteine level and 95% confidence intervals(CI)).

	Periventricular white matter lesions Mean increase in grade (95% CI)		Subcortical white matter lesions Mean increase in volume (ml) (95% CI)	
	All participants	Participants without infarcts	All participants	Participants without infarcts
Model 1*	0.19 (0.06-0.31)	0.21 (0.08-0.33)	0.24 (0.07-0.42)	0.14 (0.003-0.28)
Model 2†	0.18 (0.05-0.30)	0.19 (0.06-0.32)	0.25 (0.08-0.42)	0.14 (0.001-0.28)
Model 3‡	0.17 (0.05-0.30)	0.16 (0.03-0.29)	0.25 (0.08-0.43)	0.11 (–0.03-0.25)

* Adjusted for age and sex.

† Additionally adjusted for systolic blood pressure, antihypertensive drugs, diabetes mellitus, and smoking.

‡ Adjustments as in model 2, with atherosclerotic markers included in the model.

Discussion

The present study demonstrated a strong and significant association between plasma total homocysteine levels and silent brain infarcts and white matter lesions on MRI. We showed that plasma total homocysteine is an independent risk factor for the presence of either silent brain infarcts, white matter lesions, and both. The relationships of these MRI lesions with total homocysteine levels were continuous and graded, with no obvious threshold below which lower total homocysteine levels were not associated with lower risks of disease.

The strengths of this study are the population-based design and the large number of elderly participants. However, because the response rate in our study was about 63%, it is possible that selection bias may have influenced the results. Those people who agreed to participate were significantly younger and had a lower prevalence of hypertension compared with non-responders.[20] Old age and hypertension are known risk factors for the presence of both silent brain infarcts and white matter lesions. Hence, people with infarcts and severe white matter lesions on MRI may be somewhat underrepresented in our study. This bias might be expected to result in an attenuation of any association of total homocysteine with MRI lesions.

The plasma total homocysteine level was measured without knowledge of other risk factors or presence of lesions on MRI. Silent brain infarcts and white matter lesions were scored also blind to all other data. Therefore, any misclassification will be random and result in an underestimation of the strength of any risk associations. The use of a single total homocysteine measurement to classify persons may have underestimated the strength of any associations due to regression dilution by 10% to 15%.[21]

Elevated total homocysteine levels reflect nutritional deficiencies, genetic defects, or renal impairment. We do not have data on any of these determinants of total homocysteine concentrations and hence the present study is unable to address these issues. Further studies are required to address the extent to which the differences caused by total homocysteine levels reflect vitamin B12 or folate deficiency or renal impairment.

Recently, a study involving 153 participants reported a fourfold-increased risk of silent brain infarcts in elderly with a total homocysteine greater than 15

µmol/l, but it did not present an odds ratio of silent brain infarcts after adjustment for all other confounders.[12] This study showed no attenuation of the association between total homocysteine and silent brain infarcts after adjustment for renal function. We could not adjust for cholesterol level or history of myocardial infarction, because we did not have data on these measures at time of this study. However, because the association with cholesterol and stoke is debated and myocardial infarction has a similar risk profile as stroke, but does not increase stroke risk in itself, we do not think this will have biased our results. The strong association between total homocysteine and silent brain infarcts is consistent with results from previous studies that showed that total homocysteine is a risk factor for symptomatic infarcts.[6,7,22] There have been no previous published studies that have examined the relationship between total homocysteine and white matter lesions. Plasma total homocysteine levels showed a significant relationship with both periventricular and subcortical white matter lesions, although the latter association was attenuated after exclusion of those without infarcts on MRI. We previously suggested periventricular and subcortical white matter lesions might have a different pathophysiology.[23] The vascular supply to the subcortical white matter is believed to be superior to the periventricular region, which as an arterial border zone may be more vulnerable to hypoperfusion.[24,25] We hypothesise that this may render the periventricular white matter more susceptible to damage caused by elevated total homocysteine levels. This might explain our finding of a stronger relationship of total homocysteine levels with periventricular than with subcortical white matter lesions.

The mechanisms through which elevated total homocysteine levels might cause vascular damage to the brain are unclear. Elevated total homocysteine levels may promote atherosclerosis by damaging the vascular wall[26] or by its direct toxic effect on nerve cells.[27] We tested whether the action of total homocysteine may be mediated via peripheral atherothrombosis by adjusting for the additional effects of markers of atherosclerosis. This did not modify the effect of total homocysteine on risk of silent brain infarcts or white matter lesions in any of the analyses. This is consistent with Fassbender's finding that total homocysteine was associated with small-vessel disease, but not with large-vessel disease.[28] However, Clarke et al reported in a study of patients with histologically confirmed Alzheimer's disease, that both patients with and without macroscopic cerebral infarcts had higher total

homocysteine concentrations than age-matched controls.[10] Further histopathological studies in patients with suspected dementia are needed to examine the associations of total homocysteine (and other risk factors) with microvascular disease. Whether plasma total homocysteine causes direct neurotoxicity cannot be tested in vivo, so the underlying mechanism remains unclear.

In conclusion, we found a strong relation between plasma total homocysteine levels with silent brain infarcts and with white matter lesions. However, this is a cross-sectional study and the results should be confirmed by prospective longitudinal studies. While randomised controlled trials have shown that vitamin supplements can effectively reduce plasma total homocysteine levels,[29] the results of ongoing large-scale trials are needed to determine whether lowering total homocysteine levels reduces the risk of stroke and other cardiovascular disease. Several such trials designed to assess the effects of folic acid-based vitamin supplements on cardiovascular risk include an assessment of cognitive function. However, further trials in high-risk elderly populations are needed to assess whether such therapy may reduce the risk of dementia.

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INCIDENCE AND RISK FACTORS OF SILENT BRAIN INFARCTS

Chapter 2.3

Abstract

Background The prevalence of silent brain infarcts in healthy elderly people is high and these lesions are associated with an increased risk of stroke. The incidence of silent brain infarcts is unknown. We investigated the incidence and cardiovascular risk factors for silent brain infarcts.

Methods The Rotterdam Scan Study is a prospective population-based cohort study among 1077 participants, aged 60 to 90 years. All participants underwent cranial MRI in 1995 to 1996 and 668 participants had a second MRI in 1999 to 2000 (response rate 70%) with a mean interval of 3.4 years. We assessed cardiovascular risk factors by interview and physical examination at baseline. Associations between risk factors and incident silent infarcts were analysed by multiple logistic regression.

Results Ninety-three participants (14%) had one or more new infarcts on the second MRI, of whom 81 had only silent, and 12 had symptomatic infarcts. The incidence of silent brain infarcts strongly increased with age and was five times higher than that of symptomatic stroke. A prevalent silent brain infarct strongly predicted a new silent infarct on the second MRI (age- and sex-adjusted odds ratio 2.9, 95% confidence interval 1.7-5.0). Age, blood pressure, diabetes mellitus, cholesterol and homocysteine levels, intima-media thickness, carotid plaques, and smoking were associated with new silent brain infarcts in participants without prevalent infarcts.

Conclusions The incidence of silent brain infarcts on MRI in the general elderly population strongly increases with age. The cardiovascular risk factors for silent brain infarcts are similar to those for stroke.

Silent brain infarcts are frequently seen on MRI in healthy elderly people. The prevalence of these asymptomatic lesions increases with age from approximately 5% at age 60 to 35% at 90 years of age.[1-3] People with silent brain infarcts have an increased risk of stroke, independent of other stroke risk factors.[4,5] In cross-sectional studies, the presence of silent brain infarcts is associated especially with higher age and hypertension. No prospective longitudinal study examined the incidence of, and risk factors for, silent brain infarcts yet. We investigated the incidence of silent brain infarcts, and examined the cardiovascular risk factors for incident silent brain infarcts in the longitudinal population-based Rotterdam Scan Study, in the Netherlands.

Methods

Participants

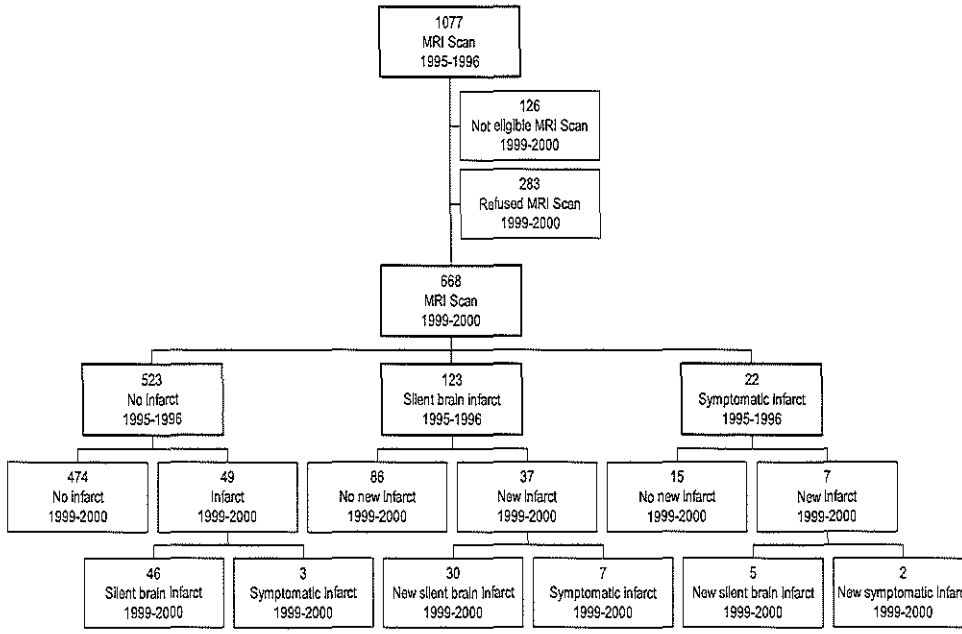
The Rotterdam Scan Study is a prospective follow-up study designed to study causes and consequences of brain changes on MRI in elderly people.[6] In 1995 to 1996, we randomly selected participants aged 60 to 90 years in strata of age (5 years) and sex from two large ongoing population-based studies.[7,8] People with MRI contraindications or dementia at baseline were not eligible for our study and were excluded. A total of 1,077 non-demented elderly people participated in our study (overall response 63%). Each participant gave informed consent. The medical ethics committee of the Erasmus Medical Centre approved the study.

Cerebral infarcts

All participants underwent MRI of the brain at baseline in 1995 to 1996. We made axial T1-, T2- 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 with comparable pulse sequences).[6] For every participants we made 60 slices (20 per acquisition) of 5 or 6 mm thick with an interslice gap of 20%. In 1999 to 2000, all eligible participants were reinvited for a second MRI using the MR VISION with the same MR sequences and protocol. Of the 1,077 participants at baseline 126 people were not eligible to participate in the second MRI examination (n=82 died, n=19 had MRI contraindications, n=19 were institutionalised, n=3 moved abroad, and n=3 could not be reached, Figure 1). In total, 668 of the 951 eligible persons

underwent the second MRI in 1999 to 2000 with a mean interval of 3.4 years between the two MRI examinations (response rate 70%). The reasons for refusal to undergo the second MRI examination were claustrophobia developed at the baseline MRI (n=98), too much trouble (n=90), no interest (n=77), and other reasons (n=18).

Figure 1. Flow diagram of the study population.



The presence of infarcts was rated similarly at baseline and follow-up. We defined infarcts 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 who was blinded to history of stroke and TIA scored infarcts on both the baseline and second MRI, including their location and size. Intrarater study (n=110) for detecting infarcts showed good agreement (κ=0.80).

We obtained a history of stroke and TIA by self-report, and by checking medical records in all 1,077 participants, independently on their MRI outcome. Stroke was defined as an episode of typical focal neurological deficits with acute

onset and lasting for more than 24 hours. TIA was defined similarly, but with symptoms lasting less than 24 hours. An experienced neurologist, with knowledge of the participants' medical history, subsequently reviewed the scans and categorised the infarcts on MRI 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 TIA. If prior stroke or TIA did correspond with a lesion, the latter was defined as a symptomatic infarct. Participants who had both symptomatic and silent infarcts were included in the symptomatic infarct group. Intrarater reliability (n=50) for the classification of infarcts into silent or symptomatic was excellent (κ=1.0).

Cardiovascular risk factors

We obtained cardiovascular risk factors by interview and physical examination in 1995 to 1996. Blood pressure was measured twice on the right arm with a random-zero sphygmomanometer. We used the average of these two measurements. Participants were asked to bring all prescribed drugs to the research centre, where a physician checked the use. Hypertension was defined as a systolic blood pressure of 140 mm Hg or over, a diastolic blood pressure of 90 mm Hg or over, or the use of antihypertensive medication. We considered diabetes mellitus to be present if the random glucose level was 11.1 mmol/l or higher, or if a person was taking oral antidiabetics or insulin. The presence of atrial fibrillation was assessed by MEANS interpretation of a 12-lead electrocardiogram (ACTA electrocardiograph, ESAOTE, Florence, Italy).[9] Serum total cholesterol and high-density lipoprotein was determined using an automated enzymatic procedure (Hitachi analyser, Roche Diagnostics, Mannheim, Germany). Plasma total homocysteine levels were determined by fluorescence polarisation immunoassay on an IMx analyser (Abbott Laboratories, Chicago, Illinois, USA).[10] 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, Bethel, Washington, USA). 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. The 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 four locations: the near and far wall of both the right and left common carotid

artery.[11] A physician assessed participants' smoking habits using a structured questionnaire and classified smoking status as current or not.

Data analysis

The follow-up time between the date of the baseline MRI and the second MRI was calculated. We estimated the cumulative incidence of silent brain infarcts in 10-year age strata. We analysed the associations between potential risk factors at baseline and incident silent brain infarcts by multiple logistic regression, adjusted for age and sex. Separate analyses were done in participants with and without infarcts at baseline MRI. We excluded participants with symptomatic infarcts at baseline (n=22) and those with a history of stroke but without infarcts on the baseline MRI (n=10) for the risk factor analyses.[3] No distinction was made between participants with one or more infarcts on their scan.

Table 1. Baseline characteristics (1995-1996) of all 1,077 participants.

	Participants with 2nd MRI n=668	Participants who refused 2nd MRI n=283	Non-eligible participants n=126
Age, years	71 ± 7	74 ± 7*	77 ± 8*
Women	344 (52%)	160 (57%)	51 (41%)*
Systolic blood pressure, mm Hg	147 ± 21	149 ± 22	146 ± 23
Diastolic blood pressure, mm Hg	79 ± 12	79 ± 12	75 ± 12*
Use of antihypertensive drugs	200 (30%)	120 (42%)*	54 (43%)*
Hypertension	468 (70%)	218 (77%)*	96 (76%)
Diabetes mellitus	36 (5%)	22 (8%)	16 (13%)*
Atrial fibrillation	17 (3%)	4 (1%)	11 (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	48 (7%)	23 (8%)	3 (2%)*
Total homocysteine, µmol/l	11.0 ± 3.6	11.7 ± 4.2	13.9 ± 5.4*
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*
Current smoking	106 (16%)	37 (13%)	26 (21%)
Presence of silent brain infarcts	123 (18%)	58 (21%)	36 (29%)*
Presence of symptomatic infarcts	22 (3%)	13 (5%)	7 (6%)

Values are unadjusted means ± standard deviation or number of participants (percentages).

* Mean or percentage is significantly different ($P < 0.05$) from participants with a 2nd MRI.

Results

The characteristics of all 1,077 participants at baseline are listed in Table 1. Participants who underwent the second MRI did not differ in the presence of infarcts on the baseline MRI from those who refused this second examination.

Overall, 93 of the 668 participants (14%) had one or more new infarcts on MRI, of whom 81 (12%) had only silent infarcts, 8 (1%) only symptomatic infarcts, and 4 (1%) both symptomatic and silent infarcts (Figure 1). Sixty-three of these 93 participants (68%) had a single new infarct and 30 (32%) had multiple new infarcts on MRI. The incidence of silent infarcts was higher for participants with multiple silent infarcts at baseline (29%; 12 of 42 participants) than for those with single infarcts on baseline MRI (22%; 18 of 81 participants). The cumulative incidence of silent brain infarcts over a mean period of 3.4 years increased from 8% in the 60- to 70-year-olds at baseline, to 22% in the oldest participants (Figure 2). No difference in incidence was observed between sexes.

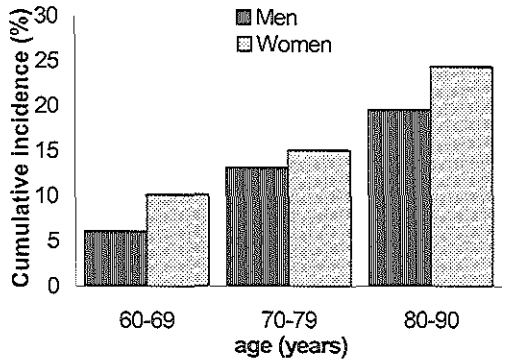


Figure 2. Cumulative incidence (%) of silent brain infarcts over a period of 3.4 years for men and women in 10-year age groups.

The majority of the participants with incident silent brain infarcts had lacunar infarcts in the basal ganglia (Figure 3). The distribution of location of new silent infarcts was similar for participants with or without silent infarcts on the baseline MRI.

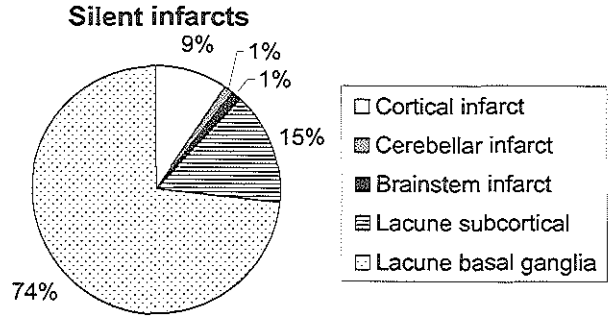


Figure 3. Distribution of infarct location in participants with incident silent brain infarcts on MRI 1999-2000.

A silent brain infarct at baseline strongly predicted a new silent infarct (age- and sex-adjusted odds ratio 2.9, 95% confidence interval 1.7-5.0). Additional adjustment for hypertension, diabetes mellitus, atrial fibrillation, cholesterol, homocysteine, intima-media thickness, carotid plaques, and smoking did not essentially change this estimate (fully adjusted odds ratio 2.6, 95% confidence interval 1.4-4.9). Further risk factor analyses were done in strata of presence of infarcts at the baseline MRI. In 46 of the 523 (9%) participants without prevalent infarcts, silent brain infarcts were seen on the second MRI (Figure 1). In these participants the risk of silent brain infarcts increased with all vascular risk factors (Table 2). This was statistically significant for age, the presence of diabetes mellitus, and increasing intima-media thickness. Additional exclusion of participants using antihypertensive drugs or lipid-lowering drugs did not essentially change the risk estimates of the blood pressure measures or cholesterol measures (data not shown).

Table 2. Association between cardiovascular risk factors and risk of incident silent brain infarcts on MRI in 1999-2000 in strata of presence of infarcts on MRI in 1995-1996.

	Risk of incident silent brain infarcts 1999-2000 OR (95% CI)*	
	No prevalent infarcts 1995-1996 n=513	Prevalent silent infarcts 1995-1996 n=123
Age, per year	1.08 (1.04-1.13)	1.00 (0.94-1.06)
Women	1.0 (0.5-1.9)	1.4 (0.6-3.2)
Systolic blood pressure, per SD	1.29 (0.92-1.82)	0.66 (0.42-1.04)
Diastolic blood pressure, per SD	1.21 (0.87-1.69)	0.79 (0.52-1.20)
Hypertension	1.2 (0.6-2.4)	1.0 (0.3-3.6)
Diabetes mellitus	2.9 (1.0-8.5)	1.9 (0.4-8.4)
Total cholesterol, per SD	1.08 (0.76-1.53)	1.07 (0.70-1.63)
High-density lipoprotein, per SD	0.81 (0.56-1.15)	1.03 (0.68-1.57)
Total homocysteine, per SD	1.31 (0.95-1.82)	0.86 (0.54-1.36)
Intima-media thickness, per SD	1.31 (1.01-1.71)	1.12 (0.66-1.90)
Plaques in carotid artery, per SD	1.20 (0.85-1.68)	1.10 (0.72-1.68)
Current smoking	1.4 (0.6-3.3)	0.6 (0.2-2.2)

Standard deviation (SD).

* Odds ratios (OR) with 95% confidence intervals (CI), adjusted for age and sex.

Numbers were too small to allow risk factor analysis with the presence of atrial fibrillation. In participants with prevalent silent brain infarcts, of whom 30 had one or more new silent infarcts, none of the cardiovascular factors was associated with incident silent brain infarcts.

Discussion

We found that the incidence of silent brain infarcts in the general population strongly increases with age. A prevalent silent brain infarct strongly predicts a new silent infarct during follow-up. The risk factors for silent brain infarcts are similar to those for reported for symptomatic stroke.

Several methodological issues should be addressed first. There is a possibility of selection bias, since we have incomplete follow-up. The participating persons were significantly younger and less often had vascular risk factors than the non-eligibles and those who refused the second scan. Therefore, the incidence of silent brain infarcts will be even higher in the general elderly population than what is reported here, since we found an increase in the incidence with increasing age. Furthermore, this also might have led to an attenuation of the associations between risk factors and incident silent brain infarcts. The true incidence of symptomatic infarcts will also be higher, because people with a fatal or disabling stroke during follow-up could not undergo the second MRI. Secondly, we may have incorrectly identified brain infarcts, or misclassified infarcts into silent or symptomatic. However, both the intrarater agreement of scoring infarcts and of classifying silent or symptomatic infarcts was good. We tried to minimise misclassification of infarcts into silent or symptomatic by obtaining participants' history of stroke and TIA by self-report, and by checking their medical records. If anything, any misclassification will have resulted in an underestimation of the strength of the associations. Although our study does not include people with MRI contraindications, we think our findings can be generalised to these people as well. Merits of our study are the large number of participating elderly from the general population and its prospective design.

We found a steep rise in the incidence of silent brain infarcts with increasing age. The incidence of silent infarcts was similar for men and women. No other population-based study examined the incidence of silent infarcts yet. Compared

with the incidence of symptomatic stroke in similar populations, the incidence of silent brain infarcts is approximately five times higher for all age groups.[12-14]

A prevalent silent brain infarct nearly tripled the risk of a new silent infarct. This effect remained highly significant after adjustment for other stroke risk factors, suggesting that the presence of silent brain infarcts is a strong indicator of advanced vascular pathology. When we analysed risk factors for first-ever silent brain infarcts separately, all cardiovascular risk factors showed an increased risk estimate for silent brain infarcts, although probably due to small numbers only age, diabetes mellitus, and intima-media thickness showed a significant association. All risk estimates for silent brain infarcts were comparable with those for symptomatic stroke.[15,16] In the participants with prevalent silent brain infarcts, none of the risk factors was associated with an increased risk of subsequent silent infarcts. We earlier showed in a cross-sectional study that these participants already had a vascular risk profile at baseline.[3] This is probably the reason why cardiovascular risk factors do not discriminate any further in these high-risk participants. Age and cardiovascular risk factors do not seem to play a major role in predicting subsequent stroke in stroke patients also,[17,18] whereas infarct-related factors are of greater importance in recurrent stroke. Unfortunately, numbers were too small to analyse if the risk of incident silent infarcts differed with varying location and size of the silent brain infarcts at baseline.

In conclusion, the incidence of silent brain infarcts on MRI is five times higher than that of symptomatic stroke in the general population and steeply increases with age. The presence of silent brain infarcts triples the risk of a new silent infarct. Most cardiovascular risk factors known to increase the stroke risk — both indicators of small- and large-vessel disease — do also increase the risk of silent brain infarcts. This suggests that silent brain infarcts differ from symptomatic stroke only with respect to the lack of acute stroke-like symptoms. Which infarct characteristics result in it being symptomatic or silent needs further study.

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Chapter 3

Prognosis

SILENT BRAIN INFARCTS, WHITE MATTER LESIONS AND THE RISK OF STROKE

Chapter **3.1**

Abstract

Background Silent brain infarcts and white matter lesions are associated with an increased risk of subsequent stroke in minor stroke patients. In healthy elderly people silent brain infarcts and white matter lesions are common, but little is known about their relevance. We examined the risk of stroke associated with these lesions in the general population.

Methods The Rotterdam Scan Study is a population-based prospective cohort study among 1,077 elderly people. The presence of silent brain infarcts and white matter lesions was scored on cerebral MRI scans obtained in 1995-1996. Participants were followed for stroke for on average 4.2 years. We estimated the risk of stroke in relation to presence of brain lesions with Cox proportional hazards regression analysis.

Results Fifty-seven participants (6%) experienced a stroke during follow-up. Participants with silent brain infarcts had a five times higher stroke incidence than those without. The presence of silent brain infarcts increased the risk of stroke more than threefold, independently of other stroke risk factors (adjusted hazard ratio 3.9, 95% confidence interval 2.3-6.8). People in the upper tertile of the white matter lesion distribution had an increased stroke risk compared with those in the lowest tertile (adjusted hazard ratio for periventricular lesions 4.7, 95% confidence interval 2.0-11.2 and for subcortical lesions 3.6, 95% confidence interval 1.4-9.2). Silent brain infarcts and severe white matter lesions increased the stroke risk independently of each other.

Conclusions Elderly people with silent brain infarcts and white matter lesions are at a strongly increased risk of stroke, which could not be explained by the major stroke risk factors.

Prior brain infarctions and cerebral white matter lesions are frequently seen on MRI scans in patients admitted with a first stroke. In patients with a minor stroke, both silent brain infarcts and white matter lesions increased the risk of recurrent stroke.[1,2] With the increased use of imaging techniques these lesions are more often seen in non-stroke patients as well. Silent brain infarcts and white matter lesions are thought to have a vascular origin and are frequently seen in neurologically asymptomatic elderly people.[3-9] Little is known about the relevance of these lesions in the general population. Recently, a population-based study reported a twofold-increased risk of stroke in elderly people with silent brain infarcts.[10] We examined whether the presence of silent brain infarcts and white matter lesions increased the rate and risk of stroke in the general population. Furthermore, we quantified this relation and investigated if this was independent of the established stroke risk factors and of each other.

Methods

Participants

The Rotterdam Scan Study was designed to study causes and consequences of brain changes in the elderly. In 1995 to 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.[11,12] A total of 1,077 non-demented elderly people participated in our study (overall response 63%). The study design has been described in detail.[8] The medical ethics committee of the Erasmus Medical Centre approved the study and each participant gave informed consent.

Cerebral infarcts and white matter lesions

All participants underwent MRI of the brain in 1995 to 1996. We made axial T1-, T2-weighted and proton-density 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 with an interslice gap of 20%.

Infarcts were rated by a single rater and 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.

Intrarater study (n=110) for detecting infarcts showed good agreement (κ=0.80).[9] We obtained a history of stroke and TIA by self-report, and by checking medical records in all 1077 participants. An experienced neurologist subsequently reviewed the medical history and scans and categorised the infarcts as silent or symptomatic. We defined silent 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 silent infarcts were categorised in the symptomatic infarct group. Twenty participants with a confirmed history of stroke had no infarcts on MRI. Three of them experienced a haemorrhagic stroke; the seventeen others with ischaemic (n=12) or unspecified (n=5) stroke had minor symptoms. Participants with symptomatic infarcts on MRI (n=42; 16 of whom symptoms of a TIA corresponded to the infarct)[9] and participants with a previous stroke without infarcts on MRI (n=20) were excluded from all analyses.

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 white matter lesions separately. Periventricular white matter lesions were rated semi-quantitatively (grade range 0-9). A total volume of subcortical white matter lesions was approximated based on number and size of lesions (volume range 0-29.5 ml). Both intrareader and interreader studies (n=100) showed a good to excellent agreement (κ=0.79-0.90, r=0.88-0.95).[8]

Cardiovascular risk factors

We obtained the cardiovascular risk factors by interview and physical examination in 1995 to 1996. Blood pressure was measured twice on the right arm with a random-zero sphygmomanometer. We used the average of these two measurements. Participants were asked to bring all prescribed drugs to the research center, where a physician checked the use. Hypertension was defined as a systolic blood pressure of 140 mm Hg or over, a diastolic blood pressure of 90 mm Hg or over, and/or the use of blood pressure lowering medication. We considered diabetes mellitus to be present if the random glucose level was 11.1 mmol/l or higher, or if a person used antidiabetic medication. Serum total cholesterol was determined using an automated enzymatic procedure (Hitachi analyser, Roche Diagnostics, Mannheim, Germany). Plasma total homocysteine levels were determined by fluorescence polarisation immunoassay on an IMx analyser (Abbott

Laboratories, Chicago, Illinois, USA).[13] The presence of atrial fibrillation was assessed by MEANS interpretation of a 12-lead electrocardiogram (ACTA electrocardiograph, ESAOTE, Florence, Italy).[14] The intima-media thickness was measured by longitudinal 2-dimensional ultrasound of the carotid artery. We calculated the mean common carotid artery intima-media thickness as the mean of four locations: the near and far wall of both the right and left common carotid artery.[15] A physician assessed participants' smoking habits using a structured questionnaire and classified smoking status as current or not.

Follow-up for incident stroke

In 1999 to 2000, we reinterviewed 787 of the participants that were alive about symptoms of stroke and TIA using a structured questionnaire (response rate 81%). In addition, we continuously monitored the medical records of all 1,077 participants at the general practitioner's office to obtain information on the occurrence of stroke since the last visit until January 1st, 2001. For all reported strokes we recorded information about signs and symptoms, date of onset, duration, and hospital stay. If participants had been hospitalised for a stroke, we retrieved discharge letters and radiology reports from the hospital where they had been treated. By reviewing all available information, an experienced neurologist assessed the exact day of onset and classified the stroke. Stroke was defined as an episode of relevant focal deficits with acute onset, documented by neurological examination, and lasting for more than 24 hours. On the basis of radiological findings strokes were further subdivided into haemorrhagic or ischaemic stroke subtypes. Follow-up was complete.

Data analysis

We used the Kaplan–Meier method to estimate the rates of stroke. The follow-up time was calculated from the date the MRI scan was made until the date of stroke, death, or end of follow-up whichever came first. We did Cox proportional hazards regression analysis to determine whether the presence of brain lesions on MRI was predictive of subsequent stroke, by estimation of its hazard ratio and 95% confidence interval. Adjustments were made for age, sex, and for the established stroke risk factors hypertension, diabetes mellitus, atrial fibrillation, common carotid intima-media thickness, smoking, and history of TIA.[16] Separate models were used for presence of silent brain infarcts, periventricular and subcortical white matter lesions. For silent brain infarcts, no distinction was made between

participants with one or more infarcts on MRI. We did a subanalysis to examine whether the risk of stroke was different between participants with more than one silent infarct and those with only one infarct on MRI, by comparing them both to participants without infarcts. The association with periventricular and subcortical white matter lesions was analysed in tertiles of their distribution, and continuously if the relation was linear. Furthermore, we investigated whether silent brain infarcts and white matter lesions predicted future stroke independently of each other, by including them in one model. In addition, we repeated the above analyses after exclusion of participants with previous TIA without infarcts on MRI (n=33).

Results

The baseline characteristics of the study population are shown in Table 1. Fifty-seven participants (6%) experienced at least one stroke during 4,260 person-years (mean follow-up 4.2 years). Six of these strokes were haemorrhagic, 42 ischaemic, and in 9 the stroke subtype was unspecified. Thirty-one of these 57 participants (54%) had one or more silent brain infarcts present on MRI. They had more severe periventricular and subcortical white matter lesions.

Table 1. Baseline characteristics of all participants who were free of stroke and symptomatic infarcts on MRI at baseline.

	All participants n=1,015
Age, years	72 ± 7
Women	526 (52%)
Hypertension	727 (72%)
Diabetes mellitus	66 (7%)
Atrial fibrillation	28 (3%)
Mean intima-media thickness, mm	0.87 ± 0.15
Current smoking	163 (16%)
History of TIA	33 (3%)
Presence of silent brain infarcts	217 (21%)
Periventricular white matter lesions, grade	2.3 ± 2.2
Subcortical white matter lesions, ml	1.3 ± 2.8

Values are unadjusted means ± standard deviation or number of participants (percentages).

The 4-years mortality was 7% (95% confidence interval 6%-9%). The overall stroke rate was 11 per 1,000 person-years (95% confidence interval 8-15). The absolute risk of developing stroke within 4 years was 11.7% for participants with silent brain infarcts and 2.3% for those without. This absolute risk was 5.0 times higher (95% confidence interval 2.7-9.2) for participants with one or more silent brain infarcts on MRI compared with those without, both for participants younger and older than 75 years of age (Figure 1).

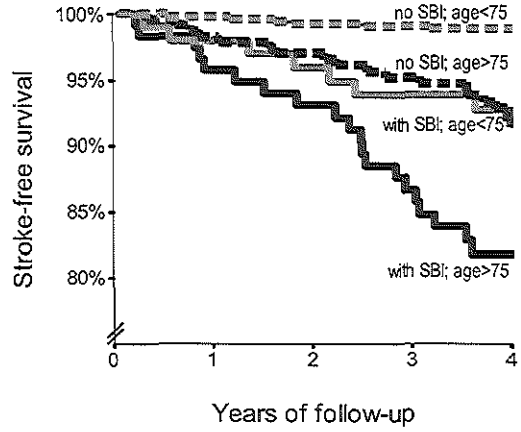

Figure 1. Kaplan–Meier curves of the stroke-free survival, stratified for the presence of silent brain infarcts (SBI) on MRI.

The presence of silent brain infarcts more than tripled the risk of stroke after adjustment for the established stroke risk factors (Table 2). Participants with more than one silent infarct had a higher stroke risk than those with only one infarct on MRI, although this difference was not significant (age- and sex-adjusted hazard ratio 4.9, 95% confidence interval 2.5-9.4 and 2.8, 95% confidence interval 1.5-5.3, respectively). Both participants in the upper tertile of the distribution of periventricular and subcortical white matter lesions had an increased stroke risk, independent of other stroke risk factors (Table 2). When silent brain infarcts, tertiles of periventricular and subcortical white matter lesions were all included in the same model, the associations with stroke risk remained for silent brain infarcts, but diminished for periventricular and especially subcortical white matter lesions. For subcortical white matter lesions, the risk of stroke did not increase linearly. The largest risk difference was between no and very small volumes of subcortical white matter lesions (0.05 ml). With larger volumes the stroke risk only marginally increased further. The relationship between periventricular white matter lesions and the risk of stroke was linear, and remained after adjustment for stroke risk factors (adjusted hazard ratio per grade increase of periventricular lesions 1.36, 95%

confidence interval 1.20-1.54), and after additional adjustment for silent brain infarcts and subcortical white matter lesions (adjusted hazard ratio 1.27, 95% confidence interval 1.10-1.47). Results of above analyses were similar after exclusion of participants with previous TIA (data not shown). Additional adjustment for the less established stroke risk factors homocysteine and cholesterol levels did not change any of the associations (data not shown).

Table 2. Relationship between the presence of silent brain infarcts, and tertiles of periventricular and subcortical white matter lesions (WML) and the risk of stroke.

	Risk of stroke Hazard ratio (95% confidence interval)		
	Adjusted for age and sex	Adjusted for stroke risk factors*	Adjusted for MRI lesions†
Silent brain infarcts			
Absent	1 (reference)	1 (reference)	1 (reference)
Present	3.6 (2.1-6.1)	3.9 (2.3-6.8)	3.3 (1.8-5.9)
Periventricular WML			
1st tertile (grade 0-1.0)	1 (reference)	1 (reference)	1 (reference)
2nd tertile (grade 1.5-3.0)	2.5 (1.0-6.3)	2.5 (1.0-6.2)	2.0 (0.8-5.3)
3rd tertile (grade 3.5-9.0)	4.7 (2.0-11.2)	4.7 (2.0-11.2)	2.8 (1.0-7.6)
Subcortical WML			
1st tertile (0-0.05 ml)	1 (reference)	1 (reference)	1 (reference)
2nd tertile (0.05-0.6 ml)	2.2 (0.8-5.7)	2.3 (0.9-6.1)	1.4 (0.5-4.0)
3rd tertile (0.6-29.5 ml)	3.7 (1.5-9.1)	3.6 (1.4-9.2)	1.4 (0.5-4.0)

* Age, sex, hypertension, diabetes mellitus, atrial fibrillation, mean intima-media thickness, smoking, and history of TIA.

† Adjusted for stroke risk factors and additionally for the presence of silent brain infarcts, and tertiles of periventricular and subcortical white matter lesions.

Discussion

We found that elderly people with silent brain infarcts have a more than threefold-increased risk of stroke, compared with those without infarcts on MRI in the general population. The presence of more severe white matter lesions also increased stroke risk. This was independent of other established stroke risk factors and of each other.

The strengths of this study are the large number of participating elderly people and its population-based design. Furthermore, we had no losses to follow-up, and therefore no selection bias. A potential methodological limitation of our study is misclassification. Despite good agreement, we may have systematically over- or underrated infarcts or white matter lesions on MRI. We do not have pathological verification of the lesions seen on MRI. Furthermore, infarcts may have been erroneously classified as silent or symptomatic. Both the readers who identified white matter lesions and infarcts and the neurologist who classified infarcts into silent or symptomatic were blinded to all other data. Misclassification may also have occurred in the identification of strokes during follow-up. People probably underreport symptoms of TIA and minor stroke, which will have resulted in an underestimation of the true number of events. But because we obtained information about these events both by self-report and from medical records, without knowledge of baseline MRI findings, it is unlikely that this has introduced a major bias in our study. If anything, this non-differential misclassification will have resulted in an attenuation of the relation.

We report a more than threefold-increased risk of stroke in elderly people with silent brain infarcts on MRI in the general population. This is in line with the finding of the Cardiovascular Health Study, the only other population-based study that examined this relationship.[10] They showed that people with white matter lesions defined by cluster analysis had an increased risk of stroke.[17] We extended this finding and found that more severe white matter lesions, both periventricular and subcortical located, also increased the risk of stroke. A Japanese study of healthy volunteers found an increased stroke risk when silent brain infarcts and white matter lesions were present on MRI, but this study was based on adults who wished to receive health screening at their own expense and it obtained information about 19 incident strokes by self-report only.[18] Unfortunately, numbers were too small in our study to do separate analyses for stroke subtypes.

Both silent brain infarcts, of which the majority are lacunar infarcts,[6,9] and white matter lesions reflect mainly small-vessel disease. We showed however that the increased stroke risk with the presence of silent infarcts and white matter lesions remained after adjustment for cardiovascular risk factors. These risk factors did not explain the effect of silent brain infarcts and white matter lesions on stroke risk. There may be residual confounding by the way we adjusted for these stroke

risk factors, because we did not account for duration and severity of exposure. However, we do not think it will account totally for the strong risk increase of stroke by the presence of silent brain infarcts and white matter lesions. This suggests that silent brain infarcts and white matter lesions are not just intermediates in the relation of vascular risk factors and the risk of stroke, but that these lesions are markers for other — yet unknown — factors that lead to symptomatic stroke.

In conclusion, we found that elderly people with silent brain infarcts and white matter lesions from the general population are at a high risk of stroke. The major stroke risk factors only accounted for part of this increased stroke risk. Because the clinical relevance of these lesions was unknown, no special treatment regimen has been developed for these people. However, if these lesions are found by coincidence in people without symptoms of a TIA or stroke, these people should at least be screened for the presence of well treatable risk factors, such as hypertension, diabetes mellitus, and smoking. Further research will have to show if treatment of these people, comparable to the treatment regimen for people with TIA, effectively prevents stroke.

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SILENT BRAIN INFARCTS AND THE RISK OF DEMENTIA AND COGNITIVE DECLINE

Chapter **3.2**

Abstract

Background Silent brain infarcts are frequently seen on 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 1,015 participants of the prospective population-based Rotterdam Scan Study, who were aged 60 to 90 years 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 continuously monitored for incident dementia. We performed Cox proportional hazards and multiple linear regression analyses, adjusted for age, sex, and education.

Results During 3,697 person-years of follow-up (mean follow-up 3.6 years), 30 participants developed dementia. Baseline presence of silent brain infarcts doubled the risk of dementia (hazard ratio 2.3, 95% confidence interval 1.1-4.7). Silent brain infarcts on baseline MRI were 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 non-thalamic infarcts to a decline in psychomotor speed. When participants with prevalent silent brain infarcts were subdivided in those with and without additional incident infarcts, decline in cognitive function was restricted to those with incident silent infarcts.

Conclusions Elderly people with silent brain infarcts have an increased risk of dementia and decline more steeply in cognitive function than contemporaries without such lesions. Cognitive function seems to decline stepwise after an infarct occurs.

Dementia is a major health problem in western countries. Now every fourth 55-year-old person will develop dementia[1] and the number of dementia patients will still rise with increasing life expectancy. Evidence has accumulated over the last decade that vascular pathology plays a role in the development of dementia. Stroke patients are known to be at an increased risk of developing dementia, both vascular dementia and Alzheimer's disease.[2-4] People with lacunar cerebral infarcts at autopsy had a higher prevalence of dementia compared to those without infarcts, and they needed fewer neuropathologic lesions of Alzheimer's disease to result in the clinical symptoms of dementia.[5,6] Patients with Alzheimer's disease more frequently have asymptomatic, i.e. silent, brain infarcts on MRI than non-demented controls.[7,8] The prevalence of these silent brain infarcts on MRI is high in non-demented elderly populations as well.[9-11] Whether the presence of silent brain infarcts increases the risk of dementia has not been investigated. We examined the relationship 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 causes and consequences of brain changes in the elderly.[12] In 1995 to 1996, we randomly selected 1,717 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.[13,14] A total of 1,077 non-demented elderly people participated in our study (response 63%). The medical ethics committee of the Erasmus Medical Centre approved the study and each participant gave informed consent.

Baseline examination in 1995 to 1996 comprised a structured interview, physical examination, blood sampling, and neuropsychological tests at the research centre, as well as a cerebral MRI scan. All 1,077 participants were continuously monitored after baseline for mortality and major morbidity including cognitive problems, dementia, stroke, and TIA. We had complete follow-up of all participants. In 1999 to 2000, we reinvited 965 of the 1,077 participants for a second examination. The remaining 112 participants were not reinvited, because

they had died (n=82), were institutionalised for known dementia (n=18), were seen in 1999 as part of the regular examination for the Rotterdam Study (n=8), moved abroad (n=3), or could not be reached (n=1). In total, 778 of the invited participants underwent neuropsychological testing at the second examination (response 81%). Participants who were non-eligible (n=112) or those who refused the second examination (n=187) were significantly older, less educated, and performed worse on the neuropsychological tests at baseline compared with those who did participate. The participants who refused the second examination did not differ with respect to presence of silent brain infarcts, whereas non-eligible participants had a higher prevalence of silent brain infarcts on baseline MRI than participants, but this was no longer significant different after adjustment for age and sex (age- and sex-adjusted difference 4%, 95% confidence interval –4%-12%). Fourteen participants were non-eligible to undergo a second MRI of the brain because of a MRI contraindication. In total, 668 underwent this second MRI scan in 1999 to 2000 (response 70%).

Cerebral infarcts

Participants underwent MRI scanning of the brain at baseline. We made axial T1-, T2-, 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).[11] In 1999 to 2000, participants underwent a second MRI using the MR VISION with the same MR sequences and protocol.

The presence of brain infarcts was rated similarly at baseline and follow-up. We defined brain infarcts 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 who was blinded to history of stroke and TIA scored infarcts both on baseline and second MRI, including their location and size. An intrarater study for detecting infarcts showed good agreement (κ=0.80).

We obtained a history of stroke and TIA by self-report, and by checking medical records in all 1,077 participants, independently of their MRI outcome. An experienced neurologist subsequently reviewed the medical history and scans and

categorised the 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 TIA. If prior stroke or TIA did correspond with a lesion, the latter was defined as a symptomatic infarct. The intrarater reliability for the classification of infarcts into silent or symptomatic was excellent (κ=1.0). If participants had both symptomatic and silent infarcts, they were included in the symptomatic infarct group. Participants with a history of stroke at baseline either with (n=42) or without infarcts on MRI (n=20) were excluded from all analyses.[15]

Follow-up for incident dementia

We screened all participants for dementia both at baseline and follow-up examinations.[1] In short, we screened all participants with brief tests of cognitive function (Mini-Mental State Examination (MMSE) and Geriatric Mental State Schedule). Participants who were screen-positive for low cognitive function underwent further cognitive testing using the Cambridge Examination for Mental Disorders of the Elderly. People who were suspected of dementia were examined by a neurologist, underwent neuropsychological testing, and if possible, cerebral MRI scanning. In addition, we continuously monitored the medical records of all 1077 participants at the general practitioner's office and the Regional Institute for Ambulatory Mental Health Care to obtain information on incident dementia until March 1st, 2000. Dementia was diagnosed according to standardised criteria (DSM-III-R, NINCDS-ADRDA, NINDS-AIREN) by a panel that reviewed all available information. Onset of dementia was defined as the date the clinical symptoms allowed the diagnosis of dementia. Follow-up was complete.

Cognitive decline

Participants underwent the following neuropsychological tests at baseline examination: MMSE, 15-word verbal learning test, Stroop test, Paper-and-Pencil Memory Scanning Task, Letter-Digit Substitution Task, and a verbal fluency test.[16] The neuropsychological tests at the second examination were similar, but we used alternative versions for the MMSE, 15-word verbal learning test, Paper-and-Pencil Memory Scanning Task, and Letter-Digit Substitution Task in order to reduce learning effects. From these tests we constructed compound scores for memory performance, psychomotor speed, and global cognitive function by transforming individual test scores into standardised *Z*-scores.[16] We calculated *Z*-scores for the neuropsychological tests at follow-up using the mean and standard deviation of the

baseline tests, which allowed comparison of participants' test scores at follow-up with their baseline scores. Cognitive decline was calculated by subtracting the *Z*-scores for memory performance, psychomotor speed, and global cognitive function at follow-up from the *Z*-scores at baseline.

Other baseline measures

Potential confounding factors for the relationship between silent brain infarcts and dementia were the following: age, sex, level of education, subcortical brain atrophy, and periventricular white matter lesions. The MRI measures may be associated with dementia and were rated on the baseline MRI scans using a standardised protocol.[12] Briefly, we estimated subcortical atrophy by calculating the mean of the ventricle-to-brain ratio at three locations. Total periventricular white matter lesions was rated as the sum of three region specific scores (grade range 0-9). We also determined the *APOE* genotype in DNA-samples taken from participants at baseline.[17]

Data analysis

We excluded participants with a history of stroke (n=62) from all analyses. This resulted in a study sample of 1,015 participants who were free of dementia and stroke at baseline. The follow-up time was calculated from the date the MRI scan was made at baseline until death, diagnosis of dementia, or end of follow-up, whichever came first. Firstly, we examined the relation between presence of silent brain infarcts and risk of dementia with Cox proportional hazards regression analysis in the entire sample. Secondly, we estimated the association between presence of silent brain infarcts and cognitive decline by multiple linear regression analysis in the subsample of 739 participants without stroke at baseline and who underwent neuropsychological tests at follow-up. We also investigated whether this relationship with cognitive decline was different for silent infarcts located in the thalamus and infarcts elsewhere, because thalamic nuclei are involved in storage and short-term memory.[18,19] Thirdly, we examined the contribution of incident silent infarcts to the rate of cognitive decline, because we suspected that an incident infarct might impair cognition. This analysis was based on all participants without stroke at baseline that underwent the second MRI. We excluded 10 participants with incident symptomatic infarcts, leaving 619 participants for this analysis.

In all analyses adjustments were made for age, sex, and education and additionally for subcortical atrophy, and periventricular white matter lesions. In the cognitive decline analyses, we also adjusted for the interval between the two

neuropsychological tests. No distinction was made between participants with one or more silent infarcts on MRI.

Results

During 3,697 person-years of follow-up (mean follow-up 3.6 years), 30 participants (3%) developed dementia, of whom 26 had Alzheimer's disease (1 with cerebrovascular disease), 2 vascular dementia, 1 multiple system atrophy, and in 1 the subtype was unknown.

The baseline characteristics of all participants who were free of dementia and stroke at start of the study are shown in Table 1. Fourteen of the 30 demented participants (47%) had one or more silent brain infarcts present on the baseline MRI. The presence of silent brain infarcts at baseline increased the risk of dementia more than twofold (hazard ratio 2.3, 95% confidence interval 1.1-4.7, adjusted for age, sex, and education; Figure 1). This result largely remained after additional adjustment for subcortical brain atrophy and periventricular white matter lesions (hazard ratio 2.0, 95% confidence interval 0.9-4.5). There was no significant difference in risk between participants with MMSE-scores below 26 and those with a score of 26 or above at baseline or between *APOE* ε4 carriers and non-ε4 carriers

Table 1. Baseline characteristics of all participants who were free of dementia and stroke in 1995 to 1996.

	All participants n=1,015
Age, years	72.1 ± 7.4
Women	526 (52%)
Primary education only	357 (35%)
MMSE-score, range 0-30	27.4 ± 2.2
APOE ε4 carriers*	267 (29%)
Presence of silent brain infarcts:	217 (21%)
Thalamic	32 (3%)
Non-thalamic	185 (18%)
Subcortical brain atrophy, ratio	0.32 ± 0.04
Periventricular white matter lesions, grade	2.3 ± 2.2

Values are unadjusted means ± standard deviation or number of participants (percentages).
* *APOE* genotype was not determined in 97 participants.

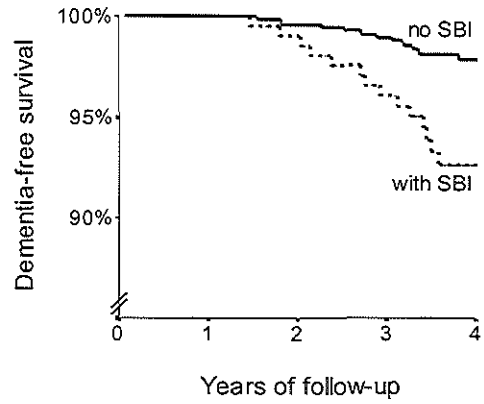

Figure 1. Kaplan–Meier curve of the dementia-free survival, for participants with and without silent brain infarcts (SBI) on MRI in 1995 to 1996.

(data not shown). Nineteen of the 30 participants with incident dementia underwent a second cerebral MRI or CT scan, of whom in three (16%) an incident symptomatic infarct and in four (21%) a new silent brain infarct was found. This was higher than in participants withour dementia at follow-up, of whom 8 (1%) had a symptomatic and 71 (11%) a silent brain infarcts on the second MRI scan.

Of the 739 participants who completed the second neuropsychological examination, 148 (20%) had silent brain infarcts on baseline MRI, of whom 20 (14%) had thalamic infarcts. The presence of silent brain infarcts was associated with a steeper decline in global cognitive function (Table 2). Silent infarcts located in the thalamus were associated with a decline in memory performance, whereas infarcts located elsewhere resulted in a decline in psychomotor speed. There was no relationship between silent brain infarcts on MRI and a decline in MMSE-score (adjusted difference in MMSE-score −0.01, 95% confidence interval −0.44-0.33). The cognitive function was significantly worse in participants with silent brain infarcts on baseline MRI (Table 3).

Table 2. Association between the presence of silent brain infarcts on MRI in 1995 to 1996 and cognitive decline.

Cognitive decline in	Silent brain infarcts*		
Z-score for	All	Thalamic	Non-thalamic
Memory performance	–0.01 (–0.16;0.15)	–0.50 (–0.87;–0.13)	0.06 (–0.10;0.23)
Psychomotor speed	–0.19 (–0.34;–0.04)	–0.11 (–0.36;0.13)	–0.20 (–0.36;–0.05)
Global cognitive function	–0.15 (–0.27;–0.02)	–0.28 (–0.50;–0.06)	–0.13 (–0.26;0.001)

* Mean difference in *Z*-score of follow-up and baseline (95% confidence interval) between those with or without silent brain infarcts, adjusted for age, sex, education, and interval between neuropsychological tests.

Figure 2. Mean change (and 95% confidence interval) in memory performance, psychomotor speed, and global cognitive function for participants with or without silent brain infarcts (SBI) on MRI in 1995 to 1996 and 1999 to 2000, adjusted for age, sex, education, and interval between neuropsychological tests.

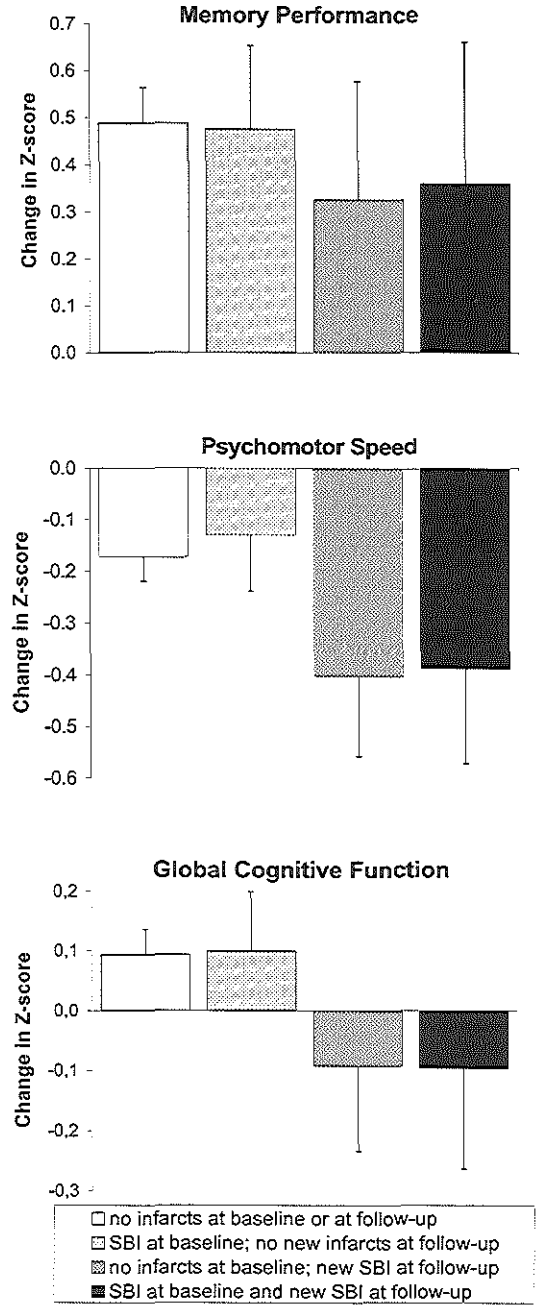

Table 3. Baseline characteristics (1995 to 1996) of participants who underwent both neuropsychological tests and MRI of the brain in 1995 to 1996, and 1999 to 2000

	Without infarcts in 1995 to 1996 n=503	With silent infarcts in 1995 to 1996 n=116
Age, years	69.8 ± 6.8	74.5 ± 6.7
Women	253 (50%)	67 (58%)
Primary education only	150 (30%)	41 (35%)
MMSE-score, range 0-30	27.6 ± 2.1	27.7 ± 1.7
Memory performance, *Z*-score	0.15 ± 0.94	0.01 ± 0.92
Psychomotor speed, *Z*-score	0.19 ± 0.74	–0.18 ± 0.79
Global cognitive index, *Z*-score	0.17 ± 0.67	–0.10 ± 0.65

Values are unadjusted means ± standard deviation or number of participants (percentages). Participants with prevalent or incident stroke were excluded.

When participants were subdivided into four groups according to the presence of silent brain infarcts on baseline and follow-up MRI, decline in cognitive function was restricted to those with new silent brain infarcts on the follow-up scan, either with or without silent infarcts at baseline (Figure 2). Memory performance improved for all participants, as expected due to learning effect. There were no significant changes in MMSE-score between the different groups (data not shown).

Discussion

We found that presence of silent brain infarcts on MRI in the general population doubled the risk of dementia. People with silent infarcts declined more steeply in cognitive function than those without infarcts, but this decline was confined to people who acquired additional silent brain infarcts after baseline, suggesting that cognitive function declines in a stepwise fashion after an infarct occurs.

The strengths of this study are the large number of elderly people participating and its population-based design. Furthermore, we had no losses to follow-up for the analyses on dementia, and therefore no selection bias. Not all persons underwent the second neuropsychological tests and cerebral MRI scan, but because the percentage silent brain infarcts was similar to that for participants, we consider it unlikely that the relationship between silent brain infarcts and cognitive decline will be different for non-participants. Notwithstanding good to excellent

intrareader agreements, we still may have incorrectly identified brain infarcts, or misclassified infarcts into silent or symptomatic. However, because identification and classification of silent brain infarcts was performed blindly from data on dementia and neuropsychological tests, any misclassification will have resulted in an underestimation of the associations.

Subclassification of dementia diagnoses is very difficult. We intentionally refrained from analysing subtypes, because distinction is arbitrary, especially in elderly people in whom dementia often is a heterogeneous disorder. There is increasing evidence over the last decade that vascular factors may contribute to the development of dementia and Alzheimer's disease.[20,21] Approximately 30% of patients with symptomatic infarcts develop dementia after their stroke, including Alzheimer's disease.[2-4] We now have found that also silent brain infarcts increase the risk of dementia, of whom the majority was diagnosed with Alzheimer's disease. Our finding of a high number of new infarcts in the incident dementia cases and the stepwise decline in cognition after the occurrence of an incident infarct support the notion that people with prevalent silent brain infarcts are at high risk of developing new infarcts, both silent and symptomatic,[22] which may further impair their cognition and lead towards the clinical diagnosis of (vascular) dementia. Another explanation might be that silent brain infarcts trigger the development of senile plaques and neurofibrillary tangles or do they reflect cerebral vulnerability or a certain vascular risk profile that enhances Alzheimer's pathology. However, several clinicopathological studies found that Alzheimer patients with infarcts had a similar amount of plaques and tangles or even less.[23-26] Perhaps an infarct in a brain already affected by Alzheimer's pathology will simply further impair cognition, leading to clinically manifest 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]

We showed that silent brain infarcts, i.e. without relevant TIA or stroke symptoms, are not innocent as they were associated with worse cognition, confirming an earlier cross-sectional finding.[9] More importantly, we showed that this decline in cognitive function was confined to persons with incident silent infarcts, which suggests a stepwise decline. Although the observed change in cognition in the general population was very small, it may be relevant, because people who decline in cognition have a high risk of dementia. The reason that we

found no relationship with MMSE-score is probably that this test, although useful as a screening tool for dementia, is not very sensitive for subtle changes in cognitive function. The Cardiovascular Health Study did find an association between MRI infarcts and decline in a modified MMSE-score, which comprised 100 instead of 30 questions and examines a broader range of cognitive function.[27] Furthermore, we found that decline in different cognitive domains varied with the location of silent brain infarcts on MRI. Strategic infarcts in the thalamus, of which the anterior and medial dorsal nuclei are involved in storage and short-term memory,[18,19] were associated with a worse performance in memory tasks. Our finding that both in participants with and those without silent brain infarcts memory performance improved at the second examination may be explained by learning effect.[28] This learning effect does not seem to play a major role in tests specific for psychomotor speed. The presence of silent infarcts that were not located in the thalamus resulted in a decline in psychomotor speed. These infarcts most likely interrupt various connecting fibres in the white matter involved in these psychomotor tasks.

In conclusion, presence of silent brain infarcts on MRI identifies persons at risk for dementia. This is most likely due to the fact that these people develop new brain infarcts, both silent and symptomatic, that further lower their cognition.

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BRAIN INFARCTS, WHITE MATTER LESIONS AND THE RISK OF DEPRESSION

Chapter **3.3**

Abstract

Context Vascular pathology may contribute to late-onset depression. Cross-sectional studies showed that elderly patients with depression more frequently have cerebral infarcts and white matter lesions on MRI. The relationship between cerebrovascular disease and depressive disorders has not been studied in the general population longitudinally.

Objective To prospectively examine the association between (a)symptomatic brain infarcts, white matter lesions and the risk of depressive disorders.

Design and Setting The Rotterdam Scan Study, a large population-based prospective cohort study conducted in the Netherlands.

Participants 1,077 elderly people, aged 60 to 90 years, who all underwent MRI of the brain in 1995 to 1996 on which the presence of infarcts and severity of white matter lesions was scored. Participants were followed for on average 3.6 years.

Main Outcome Measure Depressive disorders, assessed by psychiatric work-up of participants with CES-D score $\geq$ 16 and monitoring of medical records of all 1,077 participants for the development of depressive disorders during follow-up.

Results Seventy-eight participants were diagnosed with a depressive disorder during follow-up. The presence of (a)symptomatic brain infarcts at baseline nearly doubled the risk of depressive disorders (odds ratio 1.8, 95% confidence interval 1.1-3.1). Severity of subcortical white matter lesions was associated with an increased risk of incident depressive disorders (odds ratio per ml increase in subcortical lesions 1.08, 95% confidence interval 1.00-1.17).

Conclusions The presence of brain infarcts and white matter lesions increases the risk of depressive disorders in elderly people. Our findings support the hypothesis that cerebrovascular disease plays an important role in late-onset depression.

Late-onset depression may have a different aetiology than early-onset depression. It has been postulated that vascular factors may play a role in the onset of depression in elderly people.[1] Epidemiological and neuroimaging studies have shown that cerebrovascular lesions are more frequently present in depressive elderly patients than in controls.[2,3] We showed earlier that white matter lesions on MRI were associated with depressive symptoms.[4] Furthermore, one third of stroke patients develop a major depression.[5] These findings support the 'vascular depression' hypothesis[6] that cerebrovascular disease contributes to the pathogenesis of late-onset depression. However, these studies were all cross-sectional and most were hospital-based. Recently, a large longitudinal population-based study examined the relationship with cerebrovascular disease, but it was restricted to depressive symptoms.[7] We examined the association between brain infarcts, white matter lesions and the risk of depressive disorders in an elderly population. Because the risk of depression may be related to lesion location,[5,8] we additionally investigated if this relationship was influenced by different locations of these cerebrovascular lesions on MRI.

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.[9] In 1995 to 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.[10,11] A total of 1,077 non-demented elderly participated in our study (overall response 63%). The medical ethics committee of the Erasmus Medical Centre approved the study and each participant gave informed consent.

Baseline examination in 1995 to 1996 comprised a structured interview, screening for depressive symptoms, physical examination, blood sampling, and neuropsychological tests at the research centre, as well as a cerebral MRI scan. All 1,077 participants were continuously monitored after baseline for mortality and major morbidity including depressive and other psychiatric disorders, dementia, stroke, and TIA. Follow-up was virtually complete until March 1st, 2000 (99.4%; of

7 participants we had no information on depression). In 1999 to 2000, we re-examined 787 of the participants at the research centre with a protocol similar to the baseline examination (response 81%). Participants who were non-eligible (n=104) or those who refused the second examination (n=186) were significantly older and less educated compared to those who did participate; the latter had also more depressive symptoms at baseline. In total, 668 underwent a second MRI scan in 1999 to 2000 (response 70%).

Cerebral infarcts and white matter lesions

All participants underwent MRI of the brain in 1995 to 1996. We made axial T1-, T2-weighted, and proton-density 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%. In 1999 to 2000, participants underwent a second MRI using the MR VISION with the same sequences and protocol as at baseline.

The presence of infarcts was rated similarly at baseline and at follow-up. 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).[12] We obtained a history of stroke and TIA by self-report, and by checking medical records in all 1,077 participants. An experienced neurologist subsequently reviewed the medical history and scans and categorised the infarcts as silent or symptomatic. We defined silent 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 silent infarcts were categorised 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 intrareader and interreader 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.[9] Briefly, severity of periventricular white matter lesions was rated semi-quantitatively at 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 obtained whether participants had a psychiatric history in 1995 to 1996 by interview and by checking medical records and indications of prescribed drugs in all 1,077 participants. We also screened the participants for depressive symptoms with a validated Dutch version of the original Centre for Epidemiologic Studies Depression (CES-D) scale (range 0-60).[13,14] A history of depression was defined as a depressive episode before the baseline examination lasting for more than two weeks, diagnosed by a psychiatrist, clinical psychologist, or general practitioner and treated with antidepressant medication.

Information on persistent and incident depressive disorders was obtained in two ways. Firstly, we re-examined 787 participants for depressive symptoms with the CES-D scale in 1999 to 2000. Participants with a CES-D score of 16 or more were considered screen-positive,[14] and received a psychiatric work-up. A psychiatrist visited these participants at home and evaluated them with the Dutch version of the Present State Examination, a semi-structured psychiatric interview included in the Schedules for Clinical Assessment in Neuropsychiatry.[15] Psychiatric disorders including major depression, minor depression, and dysthymia were classified according to the DSM-IV criteria. Six participants were screen-positive on the CES-D scale, but received no psychiatric work-up and were subsequently excluded. Secondly, we continuously monitored the medical records of all 1,077 participants at the general practitioner's office to obtain information on depressive episodes. Depressive disorders were diagnosed either by our screening and psychiatric work-up or by information from medical records if diagnosed by a psychiatrist, clinical psychologist, or general practitioner and treated with antidepressant medication. Persistent depression was defined as a depressive disorder during follow-up, with depressive symptoms (CES-D score $\geq$ 16) or antidepressant medication at baseline. If participants did not have depressive symptoms or antidepressant medication at baseline, the depressive disorder during follow-up was considered to be incident.

Other measurements

Neuropsychological tests at baseline included the Mini-Mental State Examination (MMSE) (score range 0-30) as measure of global cognitive function. All participants were followed for the development of dementia according to standardised criteria.

Data analysis

We first examined the cross-sectional association between the presence of brain infarcts and depressive symptoms at baseline (defined as CES-D $\geq$ 16 or antidepressant medication at baseline) by estimation of the odds ratio and 95% confidence interval with multiple logistic regression analyses. For the longitudinal analyses, 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=6), and those who were diagnosed having an anxiety or other psychiatric disorders during follow-up (n=8). We examined whether the presence of brain lesions on MRI was predictive of a depressive disorder, persistent or incident, with multiple logistic regression analyses. In all analyses we adjusted for age, sex, education, and baseline MMSE score. Separate models were used for presence of symptomatic and silent brain infarcts, and for severity of periventricular and subcortical white matter lesions. For (a)symptomatic brain infarcts, no distinction was made between participants with one or more infarcts on MRI. Periventricular and subcortical white matter lesions were analysed in tertiles of their distribution, and continuously if the association was linear. In addition, we examined the risk of incident depressive disorders by excluding all participants on antidepressant medication and those with depressive symptoms at baseline, defined as CES-D score of 16 or over (n=92). In order to investigate the risk of incident late-onset depression, we additionally 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. Because depressive symptoms often precede dementia and this might confound the associations of interest, we repeated the analyses after exclusion of participants who became demented during follow-up (n=34). We further explored the contribution of incident brain infarcts on the second MRI to the onset of depressive disorders during follow-up, because we suspected that an incident infarct might result in depression.

Finally, we investigated the relationship between location of MRI lesions and risk of depressive disorders. According to some studies, patients with basal ganglia

lesions in the left hemisphere have a higher risk of post-stroke depression.[5,8] We examined if the relationship with the risk of depressive disorders was different for infarcts located in the left basal ganglia compared to infarcts located elsewhere. In this respect, we also looked at subcortical white matter lesions in the frontal, parietal, occipital, and temporal lobes in relation to the risk of depressive disorders.

Results

The baseline characteristics of the study population are shown in Table 1. Brain infarcts on baseline MRI were associated with depressive symptoms at baseline in cross-sectional analysis (adjusted odds ratio 1.9, 95% confidence interval 1.2-3.0). The risk of depressive symptoms was higher for participants with symptomatic infarcts than for those with silent brain infarcts when compared with participants without infarcts on MRI at baseline, although these risk estimates were not statistically different (adjusted odds ratio for symptomatic infarcts 2.9, 95% confidence interval 1.2-7.0 and for silent infarcts 1.7, 95% confidence interval 1.0-2.8).

Table 1. Baseline characteristics of all participants.

	All participants n=1,077
Age, years	72.2 ± 7.4
Women	555 (52%)
Primary education only	375 (35%)
History of depression	67 (6%)
Use of antidepressant medication	23 (2%)
CES-D score, range 0-60	5.9 ± 6.2
CES-D score ≥ 16	79 (7%)
MMSE score, range 0-30	27.4 ± 2.2
Brain infarcts on MRI:	259 (24%)
Symptomatic	42 (4%)
Silent	217 (20%)
Periventricular white matter lesions, grade	2.4 ± 2.2
Subcortical white matter lesions, ml	1.4 ± 2.9

Values are unadjusted means ± standard deviation or number of participants (percentages).

Seventy-eight participants (7%) were diagnosed with a depressive disorder during a mean follow-up of 3.6 years, of whom 30 had a persistent and 48 had an incident depressive disorder. In 39 participants the depressive disorder was assessed by information from medical records and in 39 participants the depressive disorder was diagnosed during re-examination, of whom 18 had a major depression, 18 a minor depression, and 3 dysthymia. The mean age of the 78 participants with a depressive disorder during follow-up was 72.1 years and 55 (71%) were women. Twenty-six of these 78 participants had a history of depression. Twenty-seven (35%) of them had one or more brain infarcts present on baseline MRI, of whom 23 had silent brain infarcts only. They also had more severe periventricular and subcortical white matter lesions.

The presence of brain infarcts at baseline nearly doubled the risk of a persistent or incident depressive disorder (Table 2). Risks were similar for participants with symptomatic and those with silent brain infarcts, although the risk increase for symptomatic infarcts was not significant due to small numbers. The risk of depressive disorders increased linearly with increasing periventricular and subcortical white matter lesions, which was borderline significant (Table 2).

Table 2. Association between presence of brain infarcts (symptomatic and silent) and white matter lesions (periventricular and subcortical) on baseline MRI and the risk of depressive disorders during follow-up, estimated by odds ratios (OR) with 95% confidence intervals (CI) adjusted for age, sex, education, and cognitive function.

	Persistent or incident depressive disorder* OR (95% CI)	Incident depressive disorder† OR (95% CI)
Infarcts (yes/no):		
All infarcts	1.8 (1.1-3.1)	1.0 (0.5-2.1)
Symptomatic infarcts	1.9 (0.6-5.8)	1.4 (0.3-6.2)
Silent infarcts	1.8 (1.0-3.1)	1.0 (0.4-2.1)
White matter lesions:		
Periventricular (per grade increase)	1.11 (0.99-1.24)	1.09 (0.95-1.25)
Subcortical (per ml increase)	1.06 (0.99-1.13)	1.08 (1.00-1.17)

* Analyses are based on 1,056 participants with complete follow-up of depressive disorders.
† Analyses are restricted to 969 participants without antidepressant medication and without depressive symptoms (CES-D score < 16) at baseline.

Exclusion of participants who developed dementia during follow-up, of whom 6 were diagnosed with a depressive disorder before the dementia diagnosis, did not change any of the above risk estimates (data not shown). When analyses were restricted to those participants without antidepressant medication and depressive symptoms at baseline, the relationship between brain infarcts and the risk of depressive disorders disappeared (Table 2). Subcortical white matter lesions remained associated with incident depressive disorders, whereas the association with periventricular lesions diminished (Table 2). Additional exclusion of participants with early-onset depression in history did not change any of the results (data not shown).

Participants with infarcts on baseline MRI that acquired new infarcts during follow-up (n=35) had a threefold-increased risk of depressive disorders compared with those without infarcts and those with baseline infarcts only (adjusted odds ratio 3.4, 95% confidence interval 1.3-8.9). These participants had twice the risk of incident depressive disorders, although no longer significant, after exclusion of participants with antidepressant medication or depressive symptoms (adjusted odds ratio 1.9, 95% confidence interval 0.5-7.2).

Participants with basal ganglia infarcts in the left hemisphere at baseline (n=62) had a threefold-increased risk of depressive disorders compared with participants without infarcts on MRI (adjusted odds ratio 2.9, 95% confidence interval 1.4-6.2). This was higher than for participants with brain infarcts located elsewhere when compared with those without infarcts (adjusted odds ratio 1.5, 95% confidence interval 0.8-2.7), although these risk estimates were not significantly different. The risk of depressive disorders was similar for subcortical white matter lesions in the frontal lobes as for lesions in the parietal, occipital, and temporal lobes (data not shown).

Discussion

We found that elderly people with brain infarcts, both symptomatic and silent, have twice the risk of persistent or incident depressive disorders compared with those without infarcts in the general population. The risk of depressive disorders also increased with increasing severity of white matter lesions. Subcortical white matter lesions predicted the risk of incident depressive disorders in people without

depressive symptoms at baseline, whereas brain infarcts did not.

The strengths of this study are the large number of participating elderly people and its prospective population-based design. Furthermore, we hardly had any losses to follow-up. However, a potential methodological limitation of our study is misclassification. Despite good agreement, we may have systematically over- or underrated infarcts or white matter lesions on MRI. Misclassification may also have occurred in the diagnosis of depressive disorders during follow-up. Participants tend to underreport depressive symptoms and physicians probably underdiagnose depressive disorders, which will have resulted in an underestimation of the true number of events. However, in addition to information from medical records we actively screened participants for the presence of depressive symptoms, and this will have reduced the underdiagnosis of depression. Furthermore, the readers and neurologist who identified and classified white matter lesions and infarcts and the psychiatrist who diagnosed the depressive disorders were blinded to all other data. If anything, this non-differential misclassification will have attenuated the associations and will not have introduced a major bias in our study.

We report an increased risk of persistence and incidence of depressive disorders in elderly people with brain infarcts and severe white matter lesions on MRI in the general population. We found that people with symptomatic infarcts had the same risk as those with asymptomatic lesions, i.e. silent brain infarcts or white matter lesions. This suggests that the depression may be a direct consequence of vascular brain damage and is not only a psychological reaction to physical disability. Ischaemic damage of striatal and prefrontal cortical systems may disrupt neurotransmitter circuitry involved in mood regulation.[16] Several hospital-based studies found that 30% of the stroke patients develop a depression,[5] and this is three times higher than the 10% of the participants with symptomatic brain infarcts that acquired a depressive disorder in our study. We have to keep in mind that participants with symptomatic brain infarcts in our study have less severe stroke symptoms than patients in hospital-based studies. Furthermore, our participants with symptomatic infarcts may have experienced their stroke or TIA years before the baseline examination, so it could well be that people who developed a depression directly after their stroke did not participate in our study. Therefore, our study cannot unravel the psychological impact of experiencing a stroke on the development of depression after a stroke. Still, the increased risk in neurologically

asymptomatic participants with silent brain infarcts and white matter lesions suggests that brain lesions themselves play a role in late-onset depression, extending our earlier cross-sectional findings.[4] We found that severity of subcortical white matter lesions did, while the presence of brain infarcts did not increase the risk of incident depressive disorders. This is in line with the Cardiovascular Health Study that recently reported that MRI infarcts were associated with persistence of depressive symptoms, whereas white matter lesions were associated with worsening of depressive symptoms.[7] Infarcts are acute events and perhaps a depressive disorder develops directly after an infarct has occurred due to total cell loss in the infarcted area. White matter lesions on the other hand might represent a more gradual process of brain damage that might result in a depressive disorder after the damage has reached a certain threshold. This implies that many people with baseline infarcts already have depression at baseline, which is supported by our cross-sectional findings and those of the Cardiovascular Health Study.[17,18] Our finding that the risk of depressive disorders was confined to people with baseline infarcts who acquired new infarcts during follow-up supports this. We did not find a relationship with location of white matter lesions, which can be explained by the involvement of so many brain structures in mood regulation. The risk of depressive disorders seemed to be higher for people with basal ganglia infarcts in the left hemisphere, although this was not significantly different from that for persons with elsewhere located infarcts.

Silent brain infarcts, of which the majority is lacunar,[12,19] and white matter lesions reflect mainly small-vessel disease.[20] Both are related to an increased stroke risk[21] and might be risk factors for dementia and cognitive decline.[22] Depressive symptoms often precede the development of dementia.[23] The relationship between depressive symptoms and silent brain infarcts disappeared after adjustment for physical disability and cognitive impairment in the Cardiovascular Health Study.[18] In our study, the risk increase of depressive disorders with the presence of brain lesions remained both after adjustment for cognitive function and after exclusion of participants who developed dementia during follow-up.

In conclusion, we found an increased risk of depressive disorders in elderly people with cerebrovascular lesions in the general population. The associations were the same for symptomatic and asymptomatic brain lesions. This supports that vascular brain damage plays an important role in late-onset depression. Whether

prevention of brain infarcts and white matter lesions will diminish the number of depressive disorders in elderly people needs to be examined.

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Chapter 4

General discussion

The aim of this thesis was to gain knowledge on the frequency, risk factors and prognosis of silent brain infarcts in the general population. The limitations and merits of these studies have been discussed in the previous chapters. In this chapter, I discuss and review the main findings and their clinical relevance. Furthermore, I consider two methodological issues that pertain to studies as described in this thesis. The first issue concerns loss to follow-up, which is of great significance in prospective longitudinal studies. The second matter deals with the coexistence of other cerebrovascular abnormalities in ischaemic brains, which is especially relevant to prognostic research of silent brain infarcts. Finally, I give suggestions for further research.

MAIN FINDINGS

Frequency and risk factors

Prevalence of silent brain infarcts

Silent brain infarcts are frequently seen on MRI in elderly patients with stroke, dementia, or major depression. We found in the general population an overall prevalence of silent infarcts of 20% with a strong increase with age from 8% in the 60- to 64-year-old persons to 35% in the oldest (85 to 90 years of age). This prevalence is five times higher than the prevalence of stroke.[1] The prevalences of silent brain infarcts in two other population-based studies conducted in the United States, the Cardiovascular Health Study and the Atherosclerosis Risk in Communities Study, and that of a Japanese community study accorded with our prevalence, after taking age and sex differences into account.[2-4]

We observed a 30% to 40% higher prevalence among women; this is consistent with the study of silent lacunar infarcts in the Cardiovascular Health Study,[5] but differs from observations regarding symptomatic infarcts, which are more frequent in men.[6] This discrepancy may be explained by differences in reporting and interpreting symptoms of stroke or TIA by both patients and physicians. This has been observed for diagnosis and treatment of acute myocardial infarction,[7,8] as well as for treatment of cerebrovascular disease.[9,10] Furthermore, women of this age more often live without a partner. One may hypothesise that these single women will not report transient neurological symptoms at all. This

might clarify why men have a higher prevalence of symptomatic infarcts and women a higher prevalence of silent infarcts.

Incidence of silent brain infarcts

We found a steep increase in the incidence of silent brain infarcts with increasing age. The incidence of silent infarcts was the same in men and women. No other population-based study reported on the incidence of silent infarcts yet. Similar to the prevalence, the incidence of silent brain infarcts was approximately five times higher for all age groups when compared with the incidence of stroke in similar populations.[11-13]

Three-quarters of the participants with incident silent infarcts had lacunar infarcts in the basal ganglia; less than 10% had cortical infarcts in our study. This distribution of infarct location was similar for people with or without silent infarcts on baseline MRI.

Risk factors for silent brain infarcts

Cross-sectional studies found silent brain infarcts to be associated with the following classical risk factors for stroke: hypertension, diabetes mellitus, smoking, carotid stenosis, and coronary heart disease, which are all indicators of small- and large-vessel disease that are also related to symptomatic infarcts.[3-5] Hypertension and elevated homocysteine levels were the only risk factors cross-sectionally associated with silent brain infarcts in our study. The strong association with hypertension suggests that hypertensive small-vessel disease plays a crucial role in the pathogenesis of silent brain infarcts, of which the vast majority is lacunar infarcts. Elevated homocysteine levels reflect nutritional deficiencies, genetic defects, or renal impairment, but unfortunately we did not have data on any of these determinants of homocysteine and were unable to address these issues. The strong association between homocysteine and silent brain infarcts is consistent with the results of a recent Japanese study.[14] The mechanisms through which homocysteine, a relative new risk factor for stroke,[15-17] might cause vascular damage to the brain are unclear. It may promote atherosclerosis by damaging the vascular wall,[18] or may be toxic for nerve cells.[19] We also found that homocysteine levels were strongly associated with severity of periventricular and subcortical white matter lesions, which are thought to have a vascular origin.[20-23]

In longitudinal analyses, cardiovascular risk factors known to increase the stroke risk — both indicators of small- and large-vessel disease — also increase the

risk of silent brain infarcts, with the exception of atrial fibrillation as indicator of cardioembolic disease. Furthermore, all risk estimates for silent brain infarcts were comparable with those for symptomatic stroke.[6,24] This suggests that silent brain infarcts differ from symptomatic infarcts only with respect to the lack of acute stroke-like symptoms.

Prognosis of silent brain infarcts

Risk of stroke

Silent brain infarcts are associated with an increased risk of subsequent stroke in minor stroke patients with atrial fibrillation.[25] The clinical relevance of silent brain infarcts in neurologically asymptomatic elderly was unknown until recently. The Cardiovascular Health Study found that elderly people with silent brain infarcts had an increased stroke risk compared with those without infarcts.[26] We similarly found that the presence of silent brain infarcts increased the risk of stroke in the general population. Furthermore, the stroke risk increased with increasing severity of white matter lesions, both periventricularly and subcortically located. This is in line with a Japanese study of healthy volunteers, who wished to receive health screening at their own expense, which found an increased stroke risk when silent brain infarcts and severe white matter lesions were present on MRI.[4] Importantly, the known stroke risk factors only accounted for part of this threefold-increased stroke risk in our study. This suggests that silent brain infarcts and white matter lesions are not just intermediates in the relation between vascular risk factors and the risk of stroke, but that these lesions may be markers for other — yet unknown — factors that lead to stroke.

Risk of dementia

Many studies have been performed to identify risk factors for dementia, but the aetiology remains unclear. Awareness has increased over the last decade that vascular pathology plays a role in the development of dementia, and in particular Alzheimer's disease.[27-29] Our finding of a twofold-increased risk when silent brain infarcts are present supports this vascular hypothesis of Alzheimer's disease. The mechanism behind this risk increase remains unclear. It may be that these vascular lesions lower cognition itself or that these infarcts somehow enhance the development of plaques and tangles, or a combination of the two. That silent brain

infarcts can result in cognitive decline was shown earlier in the Cardiovascular Health Study.[30] We confirmed this finding and extended it by showing that this decline was confined to people who acquired additional silent brain infarcts after baseline. This suggests that cognitive function declines in a stepwise fashion after an infarct occurs.

Furthermore, we found that cognitive function of the different domains varied with the location of silent brain infarcts. Strategic silent infarcts in the thalamus, of which the anterior and medial dorsal nuclei are involved in storage and short-term memory,[31,32] were associated with a worse performance in memory tasks. The presence of silent infarcts that were not located in the thalamus resulted in a decline in psychomotor speed.

Risk of depression

Similar to dementia, the vascular depression hypothesis is supported by several cross-sectional studies the last decade.[33-35] We examined longitudinally whether cerebrovascular disease contributes to the pathogenesis of late-onset depression. Our findings of an increased risk of depressive disorders in elderly people with brain infarcts and severe white matter lesions supports this hypothesis. Furthermore, we found that people with symptomatic infarcts had the same risk as those with asymptomatic lesions, i.e. silent brain infarcts and white matter lesions. This suggests that the ischaemic brain damage itself may lead to depressive symptoms. The strength of the association with brain infarcts disappeared when we excluded persons with depressive symptoms at baseline, suggesting that many people with brain lesions already had depressive symptoms before their depression became clinically manifest. Cross-sectional studies showed that silent brain infarcts and severity of both periventricular and subcortical white matter lesions are associated with depressive symptoms.[36,37] Recently, the Cardiovascular Health Study reported that MRI infarcts were associated with persistence of depressive symptoms, whereas white matter lesions were associated with worsening of depressive symptoms,[38] which is in line with our findings with depressive disorders.

CLINICAL RELEVANCE

Silent brain infarcts, although without acute stroke-like symptoms, are not 'silent' as they are associated with worse cognition and depressive symptoms. Moreover, they

are thus not innocuous. Above results show that elderly people with silent brain infarcts or severe white matter lesions are at high risk for developing stroke, dementia, and depression. Because the clinical relevance of these silent lesions was unknown until now, no special treatment regimen has been developed for these people. We cannot ignore the presence of silent brain infarcts any longer. Routine MRI screening of all elderly persons will not be cost-effective, although it might be for high-risk groups. However, if a silent infarct is found by coincidence in people without symptoms of a TIA or stroke, we should at least screen them for the presence of well treatable risk factors, such as hypertension, diabetes mellitus, smoking, and carotid stenosis. Because the known stroke risk factors can only partly explain the effect of silent brain infarcts and white matter lesions on stroke risk, screening and treatment of these risk factors will diminish stroke risk but probably will not take it away. Therefore, we should consider extra treatment of this new high-risk group, comparable to the treatment regimen for people with TIA who have a similar risk increase, to prevent stroke. Furthermore, we should investigate if screening of people with mild cognitive impairment or depressive symptoms for the presence of silent brain infarcts and giving them preventive treatment is effective in reducing the risk of dementia and depression.

METHODOLOGICAL CONSIDERATIONS

The methodological issues of the studies described in this thesis are discussed in chapters 2, and 3. In this paragraph, I will focus on two important methodological aspects involved in studies on cerebrovascular disease.

The first issue is of importance to every prospective longitudinal study, namely loss to follow-up. Loss to follow-up of patients or participants can result in a bias, if this loss is selective. Unfortunately, this usually is the case, because those who are lost to follow-up tend to be older, and have more morbidity. We can distinguish loss to follow-up in studies that examine silent brain infarcts as outcome variable and as a determinant of other diseases. In the incidence study, which investigated silent brain infarcts as outcome variable (chapter 2.3), many participants did not undergo the second MRI because of death or refusal. These people were significantly older and more often had vascular risk factors than those who participated to the second scan. The incidence of silent brain infarcts may

therefore be even higher in the general elderly population than what we have found, because the incidence increases with age. When examining the prognostic relevance of silent brain infarcts (chapter 3), selective participation is a major issue in the assessment of diseases during follow-up too. Not all participants fulfilled the second examination that comprised neuropsychological tests and an interview about depressive symptoms and major morbidity since baseline. Again, non-participants were significantly older, more often had vascular risk factors, and performed worse on the neuropsychological tests than those who did participate. This might have led to an attenuation of the associations between cerebrovascular lesions and cognitive decline, which was based on the neuropsychological tests at baseline and follow-up examination. For the major diseases, we continuously monitored the medical records from the general practitioners of all participants and encountered no losses to follow-up. The bias will therefore be minimal, although minor events still may be missing. Information on 'hard' events, such as stroke, can be reliably obtained from medical records. The diagnoses of the 'soft' diseases dementia and depression are based on symptom severity and by checking medical records only one will miss early-stage dementia and minor depression especially. By screening participants ourselves with a diagnostic work-up if participants were screen-positive, we tried to minimise misclassification of these diseases.

Secondly, in this thesis I have focussed on silent brain infarcts, which is one of the cerebrovascular abnormalities visible on MRI. White matter lesions, discussed in chapters 2.2 and 3, and global brain atrophy are other abnormalities of the brain, that often coexist in ischaemic brains. Both are thought to have a vascular pathogenesis.[23,39] Not only do these abnormalities have the same risk factors, they also show similar associations with diseases, such as stroke and dementia. Pathological studies show that severity of white matter lesions correspond to increasing severity of ischaemic tissue damage.[40-42] Furthermore, white matter lesions strongly correlate with subcortical brain atrophy, i.e. ventricular enlargment.[43,44] Ventricular enlargement and sulcal widening might result from collapsing diseased white matter. I hypothesise that white matter lesions, brain infarcts, and global atrophy are probably one continuum of cerebrovascular brain damage. The coexistence of all these cerebrovascular abnormalities may hamper the investigation of silent brain infarcts in two ways. When studying the determinants of silent brain infarcts, the associations with risk

factors might be confounded if misclassification of silent infarct has occurred. The distinction between lacunar infarcts in the cerebral white matter and subcortical white matter lesions is sometimes hard to make. Because of our good intrarater agreement, we do not think this will be a major problem in our study. For studies on silent brain infarcts as an aetiological factor, the coexistence of all these vascular brain abnormalities is a more important problem. The independent effect of silent brain infarcts, and that of white matter lesions and global brain atrophy, is hard to estimate. It is questionable if it is relevant to obtain the prognostic relevance of silent brain infarcts alone. More important is to consider people with silent brain infarcts, severe white matter lesions, and severe brain atrophy as one vascular compromised group in further research.

FUTURE RESEARCH

Frequency and risk factors

The prevalence of silent brain infarcts is now well known in Caucasians in western countries, but still has to be investigated in other populations of which the stroke occurrence is known to be different. Which infarct characteristics result in it being symptomatic or silent needs further study. The incidence should also be established with repeated MRI scans in all populations, including western countries to support our findings. In addition, data on progression of white matter lesions and brain atrophy is scarce in the general population; so far there is one longitudinal study that found white matter lesions to progress using a simple scale.[45] The magnitude of progression of white matter lesions and brain atrophy should be quantified as well, ideally with volumetric methods.

Studying risk factors of silent brain infarcts, white matter lesions, and global brain atrophy may be helpful in finding causes of end-stage diseases such as stroke and dementia. These brain abnormalities are often present years before stroke occurs or dementia becomes clinically manifest. Because the prevalence of these lesions by far exceeds that of stroke and dementia, it will be easier to identify new risk factors in people with these brain abnormalities than in smaller patient groups. A newly established and potentially modifiable risk factor for stroke and dementia is an elevated homocysteine level.[46-48] We found in a cross-sectional study that

homocysteine was related to both silent brain infarcts and white matter lesions, but these results await confirmation by prospective longitudinal studies. Further studies are also required to examine what underlies the relationship between homocysteine and the risk of (silent) stroke and dementia. Randomised controlled trials have shown that vitamin supplements reduce homocysteine levels effectively.[49] Results of ongoing large-scale intervention trials will determine whether lowering homocysteine levels reduces the risk of stroke.[50,51] Trials in high-risk elderly populations are needed to assess if such therapy reduces the risk of dementia.

Prognosis of silent brain infarcts

Our results of an increased risk of dementia and late-onset depression when silent brain infarcts or severe white matter lesions are present need to be confirmed in other populations. Unfortunately, numbers were too small in our study to do separate analyses for stroke subtypes. Similarly, we were not able to analyse the risk of dementia other than Alzheimer's disease and to discriminate between major and minor depression. Larger studies, such as the Cardiovascular Health Study with 3,600 participants, are needed to examine subtype specific risks. A longer follow-up will also increase the number of people with stroke, dementia, and depression, although then the interval between the MRI assessment and disease onset may be too long to show associations. Ideally, these studies should re-examine the cohort and score new brain lesions on follow-up scans and allow this risk factor to have a time-varying exposure in the analyses. The cross-sectional relationship between white matter lesions and the dementia and depression should be confirmed in longitudinal studies. Furthermore, the mechanism behind the risk increase of Alzheimer's disease when silent brain infarcts are present remains unclear and should be studied.

Finally, our and other studies have shown that silent brain infarcts and severe white matter lesions are neither silent nor innocuous. Therefore, we cannot ignore these lesions any longer, once we have found them by coincidence. A special treatment regimen should be developed for this high-risk group. Randomised controlled trials should elucidate which treatment will be most effective in these people. However, the presence of silent brain infarcts can be obtained only by brain imaging. Power calculations show that in order to show a 20% risk reduction

of for instance stroke, 15,000 elderly people must undergo a MRI of the brain to obtain 3,000 people with silent brain infarcts for randomisation into two treatment arms. Such a trial is hardly feasible. Therefore, we might consider treating this new high-risk group according to what has been shown to be optimal for TIA patients.

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Chapter 5

Summary

Silent — that is asymptomatic — brain infarcts are frequently seen on cerebral MRI scans in patients admitted with a first stroke. With the increasing use and improvement of imaging techniques, these silent lesions are more often found in people without stroke-like symptoms. The relevance of these so-called silent infarcts is not known. The aims of this thesis were to examine the frequency, risk factors and prognosis of silent brain infarcts in the general population. To investigate these issues, we used data from the Rotterdam Scan Study, a large ongoing population-based study among elderly people who underwent brain MRI scanning.

In **chapter 2**, studies on frequency of silent brain infarcts and the risk factors for these lesions are described. **Chapter 2.1** describes the prevalence of silent brain infarcts in the general population. Silent brain infarcts are five times as prevalent as symptomatic stroke. Increasing age and hypertension are associated with silent infarcts in cross-sectional analysis, but other cardiovascular risk factors are not. **Chapter 2.2** shows the relationship between total homocysteine levels and the presence of silent brain infarcts and white matter lesions. Homocysteine may be a potentially modifiable risk factor for stroke and dementia. Increasing total homocysteine levels are associated with silent brain infarcts and white matter lesions independent of other cardiovascular risk factors. **Chapter 2.3** reports on the incidence of silent brain infarcts and what baseline risk factors are associated with new silent infarcts. The incidence of silent brain infarcts is five times higher than that of symptomatic stroke in the general population and strongly increases with age. Most cardiovascular risk factors known to increase the stroke risk — both indicators of small- and large-vessel disease — do also increase the risk of silent brain infarcts.

In **chapter 3**, the studies on the prognosis of silent brain infarcts are reported, in which the relationship is examined between silent brain infarcts and the risk of three frequent and disabling disorders in elderly people, namely stroke, dementia, and depression. **Chapter 3.1** describes the association between silent brain infarcts, white matter lesions and the risk of stroke. Elderly people with silent brain infarcts have triple the risk of those without infarcts. Severity of white matter lesions also strongly increased stroke risk. This could not be explained by the major stroke risk factors. **Chapter 3.2** presents data on the relationship between silent brain infarcts and the risk of dementia and cognitive decline. The presence of silent

brain infarcts doubles the risk of dementia. Elderly persons who develop new silent brain infarcts decline more steeply in cognition than contemporaries without such lesions. Cognitive function seems to decline stepwise after a silent infarct occurs. **Chapter 3.3** shows data on brain infarcts and white matter lesions in relation to the risk of depressive disorders. The presence of silent brain infarcts and severity of white matter lesions increase the risk of depression in elderly people. Silent brain infarcts are associated with persistence of depressive disorders, whereas white matter lesions are associated with incident depressive disorders. Our findings support the vascular depression hypothesis in late-onset depression.

In **chapter 4**, our findings are discussed and placed in broader context. Furthermore, this chapter considers two important methodological issues and describes suggestions for further research.

Stille — dat wil zeggen zonder bijpassende symptomen — herseninfarcten worden vaak gezien op hersenscans bij patiënten die worden opgenomen vanwege een eerste beroerte. Met de toenemende beschikbaarheid en verbetering van beeldvormend onderzoek, worden deze stille infarcten steeds vaker gezien in mensen zonder symptomen van een beroerte. De klinische relevantie van deze zogenaamde stille herseninfarcten is onbekend. Het doel van dit proefschrift was het bestuderen van de frequentie, risicofactoren en prognose van stille herseninfarcten in de algemene bevolking. Om dit te kunnen onderzoeken, hebben we gegevens gebruikt van de Rotterdam Scan Studie, een groot langlopend bevolkingsonderzoek onder ouderen die een hersenscan hebben ondergaan.

In **hoofdstuk 2** worden de onderzoeken beschreven over de frequentie, ofwel het vóórkomen, van stille herseninfarcten en de risicofactoren voor deze infarcten. **Hoofdstuk 2.1** beschrijft de prevalentie, ofwel het aantal ziektegevallen in een populatie op een bepaalde tijd, van stille herseninfarcten in de algemene bevolking. Stille herseninfarcten blijken vijf maal vaker voor te komen dan beroertes. Toenemende leeftijd en een hoge bloeddruk lieten een verband zien met de aanwezigheid van stille herseninfarcten in dwarsdoorsnede onderzoek, terwijl er geen relatie te zien was met andere risicofactoren voor hart- en vaatziekten. **Hoofdstuk 2.2** laat het verband zien tussen het totaal homocysteine gehalte in het bloed en de aanwezigheid van stille herseninfarcten en witte stofafwijkingen. Homocysteine zou een beïnvloedbare risicofactor voor beroerte en dementie kunnen zijn. Bij hogere homocysteine gehaltes worden meer stille herseninfarcten en witte stofafwijkingen gezien en dit was onafhankelijk van andere risicofactoren voor hart- en vaatziekten. **Hoofdstuk 2.3** beschrijft de incidentie, ofwel het aantal nieuwe ziektegevallen in een populatie in een bepaalde periode, van stille herseninfarcten in de algemene bevolking. Tevens wordt laten zien welke van de risicofactoren, gemeten bij het begin van de studie, een relatie vertoonden met het krijgen van nieuwe stille herseninfarcten gedurende het onderzoek. De incidentie van stille herseninfarcten is vijf maal hoger dan die van beroerte in de algemene bevolking en neemt sterk toe met de leeftijd. De meeste risicofactoren voor hart- en vaatziekten die er om bekend staan de kans op beroerte te vergroten — zowel risicofactoren voor ziekten van de kleine als de grote hersenvaten — verhogen ook het risico van nieuwe stille herseninfarcten.

In **hoofdstuk 3** worden vervolgonderzoeken beschreven over de prognose van stille herseninfarcten, waarbij gekeken is naar de relatie tussen stille herseninfarcten en de kans op drie bij ouderen veel voorkomende en invaliderende ziekten, te weten beroerte, dementie en depressie. **Hoofdstuk 3.1** beschrijft het verband tussen de aanwezigheid van stille herseninfarcten en witte stofafwijkingen en de kans op een beroerte. Ouderen met stille herseninfarcten hebben een driemaal verhoogd risico van beroerte vergeleken met leeftijdsgenoten zonder herseninfarcten. Ook ernstige witte stofafwijkingen verhogen de kans op een beroerte. Dit was niet te verklaren door de aanwezigheid van reeds bekende risicofactoren voor beroerte. **Hoofdstuk 3.2** laat de gegevens zien van het verband tussen stille herseninfarcten en het risico van dementie en mentale achteruitgang. De aanwezigheid van stille herseninfarcten verdubbelt de kans op dementie. Ouderen die nieuwe stille herseninfarcten doormaken gaan harder achteruit in het mentaal functioneren dan leeftijdsgenoten zonder herseninfarcten. Het mentaal functioneren lijkt stapsgewijs te verslechteren na het optreden van een stil herseninfarct. **Hoofdstuk 3.3** laat de resultaten zien van de relatie tussen herseninfarcten en witte stofafwijkingen en het risico van depressieve stoornissen. De aanwezigheid van stille herseninfarcten en ernst van witte stofafwijkingen verhogen de kans op depressie bij ouderen. Stille herseninfarcten laten een verband zien met voortduren van depressieve stoornissen, terwijl witte stofafwijkingen verband houden met het ontstaan van nieuwe depressieve stoornissen. Onze bevindingen ondersteunen dat vaatziekten een rol spelen bij ouderdomsdepressie.

In **hoofdstuk 4** worden onze bevindingen besproken en in een bredere context geplaatst. Tevens komen in dit hoofdstuk twee belangrijke methodologische aspecten aan de orde en worden suggesties gegeven voor verder onderzoek.

Gezeten op het Alzheimer congres, wil ik vooral niet vergeten om de mensen te bedanken die bijgedragen hebben aan dit proefschrift. Om te beginnen mijn promotoren, Prof. dr P.J. Koudstaal en Prof. dr A. Hofman, en mijn co-promotor Dr M.M.B. Breteler. Beste Peter, jouw supersnelle beoordeling van de TIA-verhalen en manuscripten is niet te evenaren. Dank ook voor het morele support; ik had geen betere promotor kunnen wensen. Ik zoek graag verder met jou naar een oplossing voor de vele beroerte-vraagstukken en ben blij dat ik bij jou de opleiding tot neuroloog kan volgen. Beste Bert, nooit gedacht dat ik zo zou warmlopen voor de epidemiologie, maar jouw enthousiasme is voorgoed overgestraald. Veel dank voor de goede begeleiding toen Monique in Boston zat. Beste Monique, wat ben ik blij dat je mij destijds hebt aangenomen voor dit onderzoek. Jouw heldere blik maakte dat mijn stukken er keer op keer beter van zijn geworden. Ik heb veel van je geleerd en vind het erg leuk dat ik met jou onderzoek kan blijven doen in dit mooie MRI project.

Prof. dr M. Oudkerk wil ik ook hartelijk danken voor het verwezenlijken van dit grote MRI onderzoek. Bart en Peter, bedankt voor het scannen van al die mensen in de avonduren en weekenden. Neuroradioloog H.L.J. Tanghe, bedankt voor de hulp bij de definitie van infarcten en meebeoordeling van 'moeilijke' scans.

Prof. dr R. Clarke, dear Robert. I really enjoyed working with you and I hope we can continue our collaboration in exploring what underlies the risk increase by homocysteine. Carole, thanks for measuring homocysteine levels in over 1800 samples, and even more for our pleasant e-mail contact. Jeanette, dank voor je hulp bij het terugvinden van kwijtgeraakte blood samples. Theo Stijnen, bedankt voor je waardevolle advies over hoe deze relatie met homocysteine het best te analyseren.

Dit vervolgonderzoek was nooit zo goed gelopen zonder de voortreffelijke inzet van Ingrid van Vuuren, Saskia Hoornweg, Bernadette van Ast en Els Halbmeijer. Ik denk met plezier terug aan de supergezellige tijd op de beide onderzoekscentra in Zoetermeer en Ommoord. Anneke en Joke, ook bedankt voor de warme ontvangst. Ingrid, zonder jou waren de huisartsen-fupdata lang niet zo compleet en waren we de Bonsema's (ergoid ?) zeker nog kwijt. Jolande, dank je wel voor je hulp binnen ERGO.

Ook de jongens van de automatisering, Eric, Nano, René, Frank en René, wil ik bedanken voor hun hulp in barre computertijden. Eric, ik vond het erg leuk om samen met jou zo'n mooie poster te ontwerpen. Tot ziens in onze buurt.

Mijn promotietijd is ondenkbaar zonder mijn steun- en toeverlaten Tom den Heijer en Monika Hollander. Tom, als wetenschappelijke wederhelft en tevens kamergenoot zijn we samen begonnen aan het vervolgonderzoek (jij als computer-whizzkid en ik als organisatietrutje waren we een fantastisch team) en hebben we ons samen ieder apart door duizenden scans geworsteld. Het chatten via de ICQ was onmisbaar voor het goede verloop van het onderzoek. ;-) Jammer dat je me twee jaar alleen achterliet, al maakt ons eerste (!) gezamenlijke congresbezoek veel goed. Leuk dat je over 1½ jaar ook naar de neurologie komt! Monika, als maatje op het beroerte-onderzoek hebben we veel geouwehoerd over ons onderzoek (sommigen noemen dat brainstormsessies), maar vooral ook over veel daarbuiten. Onze levens lopen vrijwel parallel, en dat geeft genoeg gespreksstof..... Gelukkig hoefde ik maar twee maanden zonder jouw gezelligheid en zie ik je vanaf augustus weer iedere dag in de kliniek. Succes met de laatste lootjes van jouw boek en ik sta zeker ook m'n mannetje bij jouw promotie! Ik ben blij dat jullie beiden naast me staan op 2 oktober!

Niet te vergeten zijn de andere co-promovendi van de Scan Studie en kamergenoten van het eerste uur, Jan Cees, Frank-Erik en Sanjay, en van het tweede uur, Ewoud en Niels. Het was heerlijk vertoeven met jullie op de mannen-kamer met tenminste goede straffe koffie! JC en FE, dank voor het opzetten van dit mooie MRI onderzoek. Ewoud en Niels, succes met het meten van een positieve delta; die komt er zeker! Ingrid, dank voor wat vrouwelijk tegengas aan al dit mannelijk 'geweld' op de kamer. En bedankt dat ik er vandaag niet naakt hoef bij te lopen! Ook de andere neuroten, Sandra, Annemieke, Patricia, Marianne, Henning, Zoltán, Mirjam, Muriël en Frank Jan, wil ik bedanken voor de leuke tijd op de neuro-epidemiologie.

Het onderzoek is uitermate veraangenaamd door de vele mede-promovendi op de epidemiologie, waarvan ik er aan aantal met name wil noemen. Melanie, Annette, Marieke en Kristel, bedankt voor de leuke prietpraat in de wandelgangen. Leden van onze vaste borrelploeg, Marjolein, Arjan, Antonio, Henning en Monika, hebben een speciaal plekje in mijn hart gekregen. Marjolein, erg leuk om de aanloop naar onze promoties samen te hebben genomen. Mooi lettertype en opmaak trouwens in jouw (wel twee keer zo dikke) boekje... Succes 18 september! Arjan, mooi om te zien dat iemand van dezelfde dingen in het leven kan genieten (al is mijn lievelingsbiertje wit). Henning, ik heb genoten van onze vele discussies in

de trein en in 't WP. Leuk om samen met jou een paper te hebben geschreven. Succes met je nieuwe lijn! Allemaal bedankt dat jullie mij telkens warm onthaalden als ik me weer eens eenzaam voelde op mijn kamer. Tot gauw in Look!

Mijn toekomstige collega's van de neurologie wil ik bij voorbaat bedanken voor hun begrip en geduld met mijn gebrek aan klinische ervaring na zoveel jaar onderzoek.

Al mijn vrienden en familie ben ik zeer dankbaar voor de steun en vooral aangename afleiding deze jaren. Floor, thanx voor het uitknippen van deze advertentie. Edo en Jacqueline, bedankt voor de heerlijke vakanties en leuke ontspannende weekenden de afgelopen jaren. Papa en mammie, heel veel dank voor jullie onvoorwaardelijk geloof in mijn kunnen enerzijds en het zeer kritisch lezen van mijn stukken anderzijds.

Jeep, ik wil alleen maar bolletje!

Sarah Vermeer was born on April 20th, 1973 in Leiden, the Netherlands. She graduated in 1991 at the Rijnlands Lyceum in Oegstgeest, and studied Pharmacy for one year at the University Utrecht. In 1992, she started Medical School at the University Utrecht, the Netherlands. During this period she did research on subarachnoid haemorrhage at the Department of Neurology (Prof. dr G.J.E. Rinkel). Thereafter, she coordinated a multi-centre study on primary intracerebral haemorrhage at the Departments of Neurology of the University Medical Centre Utrecht (Prof. dr G.J.E. Rinkel), Erasmus Medical Centre (Prof. dr P.J. Koudstaal), and the Atrium Medical Centre, Heerlen (Dr C.L. Franke). She graduated from Medical School in November 1998. In 1998, she started the research project described in this thesis at the Department of Epidemiology & Biostatistics (Prof dr A. Hofman) in collaboration with the Department of Neurology (Prof. dr P.J. Koudstaal) of the Erasmus Medical Centre, Rotterdam. In 2001, she obtained a Master of Science in Clinical Epidemiology at the Netherlands Institute for Health Sciences in Rotterdam. She started her residency in Neurology at the Erasmus Medical Centre, Rotterdam (Prof. dr P.A.E. Sillevis Smitt), August 1st, 2002.

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