ORIGINAL ARTICLE

Silent Brain Infarcts and the Risk of Dementia and Cognitive Decline

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ABSTRACT

BACKGROUND

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

METHODS

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

RESULTS

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

CONCLUSIONS

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

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

METHODS

PARTICIPANTS

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

The base-line examination in 1995 to 1996 comprised a structured interview, physical examination, blood sampling, and neuropsychological tests at the research center, as well as a cerebral MRI scan. For the present study we excluded 62 participants with a history of stroke before the base-line evaluation (Fig. 1).[16] We monitored all 1015 participants throughout the study by reviewing medical records from their general practitioners after base line for death and major complications, including cognitive
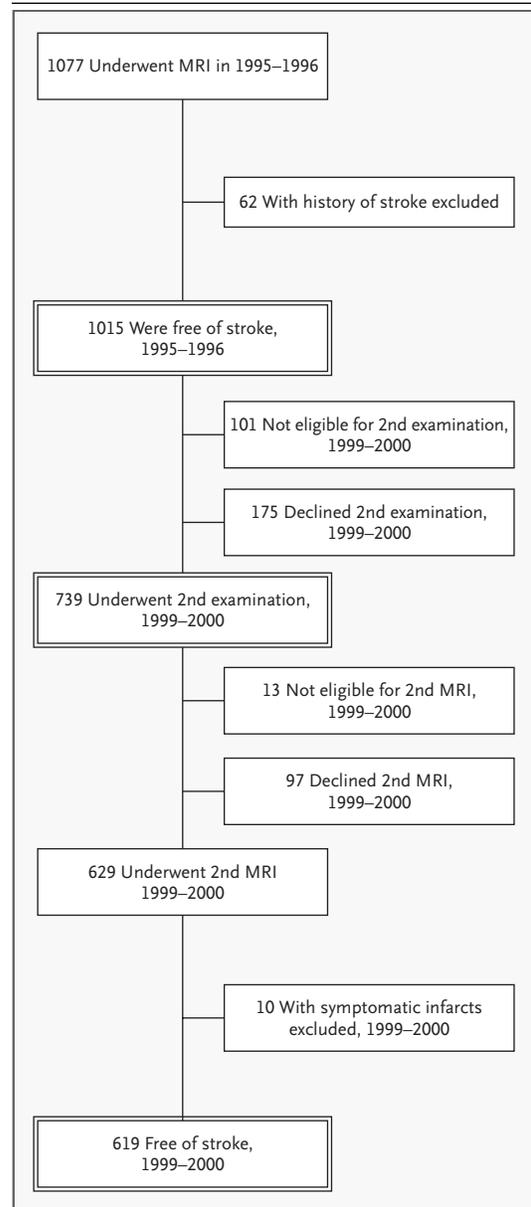

Figure 1. Flow Diagram of the Study Population.
The various study samples are indicated by double-lined boxes. MRI denotes magnetic resonance imaging.

problems, dementia, stroke, and transient ischemic attack. In 1999 to 2000, we reinvited 914 of the 1015 participants for a second examination, of whom 739 participated (81 percent) (Fig. 1). The remaining 101 participants were not reinvited, for the following reasons: 75 had died, 15 had been institutionalized for dementia, 7 had already been examined in 1999 as part of the regular examination for the Rot-

terdam Study,[14] 3 had moved abroad, and 1 could not be reached.

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

CEREBRAL INFARCTS AND OTHER MRI MEASURES

All 1015 participants underwent MRI of the brain at base line in 1995 to 1996. We made axial T_1-weighted, T_2-weighted, and proton-density–weighted scans on 1.5-Tesla MRI scanners (MR Gyroscan, Philips, or MR VISION, Siemens).[11] In 1999 to 2000, 629 participants underwent a second MRI with use of the MR VISION scanner and the same sequences.

The presence of brain infarcts was rated similarly at base line and follow-up. We defined brain infarcts as areas of focal hyperintensity on T_2-weighted images that were at least 3 mm in diameter. Proton-density scans were used to distinguish infarcts from dilated perivascular spaces. Areas of hyperintensity in the white matter also had to have corresponding prominent hypointensity on T_1-weighted images, in order to distinguish them from cerebral white-matter lesions. A single trained physician who was unaware of the patients' history of stroke and transient ischemic attack scored infarcts on both the base-line and second MRI with respect to their location and size. An intrarater study for detecting infarcts (110 images randomly selected from both scanners) showed good agreement ($\kappa=0.80$).

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

White-matter lesions and subcortical atrophy of the brain were rated on the base-line MRI scans.[12] White-matter lesions were considered present if they were hyperintense on proton-density and T_2-weighted images, without prominent hypointensity on T_1-weighted scans. The severity of periventricular white-matter lesions was determined by adding three region-specific scores (grades ranged from 0 to 9, with higher grades indicating greater severity). The volume of subcortical white-matter lesions was approximated on the basis of the number and size of lesions (volume range, 0 to 29.5 ml). The severity of subcortical atrophy of the brain was estimated by calculating the ratio of ventricle to brain (the average of assessments at the frontal and occipital horns and the caudate nucleus) on T_1-weighted images.[17] Both intrareader and interreader studies (100 of each) showed good-to-excellent agreement.[12]

DEMENTIA

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

mentia to be made. We had complete follow-up data for dementia on all participants through our system of monitoring general practitioners.

COGNITIVE DECLINE

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

STATISTICAL ANALYSIS

First, we used Cox proportional-hazards regression analysis to examine the relation between the presence of silent brain infarcts at base line and the risk of subsequent dementia in the 1015 participants who were free of dementia and stroke at base line. The duration of follow-up was calculated from the date of the MRI at base line until death, the diagnosis of dementia, or the end of follow-up, whichever came first. We also investigated the association of white-matter lesions and subcortical atrophy of the brain with dementia and whether these structural changes in the brain affected the relation between silent brain infarcts and dementia. Second, we estimated the association between the presence of silent brain infarcts at base line and subsequent cognitive decline by multiple linear-regression analysis in the subsample of 739 participants who underwent neuropsychological tests at

follow-up. We also investigated whether this relation with cognitive decline differed between silent infarcts in the thalamus and infarcts elsewhere, because thalamic nuclei are involved in storage and short-term memory.[21,22] Third, we examined the contribution of newly detected silent infarcts to the rate of cognitive decline. This analysis was based on 619 participants without symptomatic infarcts on the second MRI (Fig. 1).

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

RESULTS

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

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

The presence of silent brain infarcts at base line more than doubled the risk of dementia, and this result remained largely unchanged after adjustment for the severity of white-matter lesions and subcortical atrophy (Table 2). A greater severity of periventricular white-matter lesions was also associated with an increased risk of dementia (Table 2), as was a greater severity of subcortical atrophy of the brain (hazard ratio per increase of 1 SD in severity, 1.78; 95 percent confidence interval, 1.26 to 2.51).

There was no significant difference in risk between participants with Mini–Mental State Examination scores below 26 and those with a score of 26 or above at base line or between carriers of the apolipoprotein E ε4 allele and noncarriers. The exclusion of participants who used aspirin or oral anticoagulants at base line did not materially change the results. Nineteen of the 30 participants in whom dementia developed underwent a second cerebral MRI or computed tomographic scan; a symptomat-

Table 1. Base-Line Characteristics of All Participants Who Were Free of Dementia and Stroke in 1995 to 1996, Those Who Underwent the Second Neuropsychological Examination, and Those Who Underwent the Second MRI Scan in 1999 to 2000.*

Characteristic	All Participants (N=1015)	Participants Who Underwent 2nd Examination (N=739)	Participants Who Underwent 2nd MRI (N=619)
Age — yr	72.1±7.4	70.9±7.0	70.7±7.0
Women — no. (%)	526 (52)	390 (53)	320 (52)
Primary education only — no. (%)	357 (35)	235 (32)	191 (31)
MMSE score†	27.4±2.2	27.6±2.1	27.6±2.0
Hypertension — no. (%)	517 (51)	357 (48)	291 (47)
Diabetes mellitus — no. (%)	66 (7)	42 (6)	33 (5)
Use of aspirin — no. (%)	109 (11)	71 (10)	49 (8)
Use of oral anticoagulants — no. (%)	41 (4)	24 (3)	20 (3)
APOE ϵ4 carriers — no. (%)‡	267 (29)	206 (30)	171 (30)
Silent brain infarcts — no. (%)	217 (21)	148 (20)	116 (19)
Thalamic	32 (3)	20 (3)	14 (2)
Nonthalamic	185 (18)	128 (17)	102 (16)
White-matter lesions			
Periventricular — grade	2.3±2.2	2.1±2.1	2.0±2.1
Subcortical — ml	1.3±2.8	1.1±2.4	1.1±2.5
Ratio of subcortical brain atrophy	0.32±0.04	0.31±0.04	0.31±0.04

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

ic infarct was found in 3 (16 percent) and a new silent brain infarct was found in 4 (21 percent). This rate was higher than that among the 618 participants without dementia at follow-up, of whom 8 (1 percent) had a symptomatic brain infarct and 71 (11 percent) a silent brain infarct on the second MRI scan.

Global cognitive function was significantly worse in participants with silent brain infarcts on the baseline MRI than in those without such infarcts (adjusted mean difference in z score, −0.11; 95 percent confidence interval, −0.20 to −0.01). The presence of silent brain infarcts at base line was associated with a steeper decline in cognitive function (Table 3). The presence of multiple silent infarcts showed a stronger relation with cognitive decline than the presence of single silent infarcts (adjusted mean difference in z score for multiple infarcts, −0.34; 95 percent confidence interval, −0.51 to −0.17; and

Table 2. Relation between the Presence of Silent Brain Infarcts at Base Line, the Severity of Periventricular and Subcortical White-Matter Lesions, and the Risk of Dementia.

Variable	Hazard Ratio (95% Confidence Interval)	
	Adjusted for Age, Sex, and Level of Education	Adjusted for Age, Sex, Level of Education, and MRI Measures*
Silent brain infarcts (yes vs. no)	2.26 (1.09–4.70)	2.03 (0.91–4.55)
Severity of periventricular white-matter lesions (per SD increase)	1.59 (1.13–2.25)	1.47 (0.92–2.35)
Severity of subcortical white-matter lesions (per SD increase)	1.21 (0.96–1.53)	0.92 (0.65–1.29)

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

Table 3. Association between the Presence of Silent Brain Infarcts on Magnetic Resonance Imaging in 1995–1996 and Subsequent Cognitive Decline.*

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

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

for single infarcts, –0.07; 95 percent confidence interval, –0.20 to 0.06). Silent infarcts in the thalamus were associated with a greater decline in memory performance, whereas infarcts located elsewhere resulted in a greater decline in psychomotor speed (Table 3). There was no association between the presence of silent brain infarcts at base line and a decline in the Mini–Mental State Examination score (adjusted mean difference in the score, –0.01; 95 percent confidence interval, –0.44 to 0.33).

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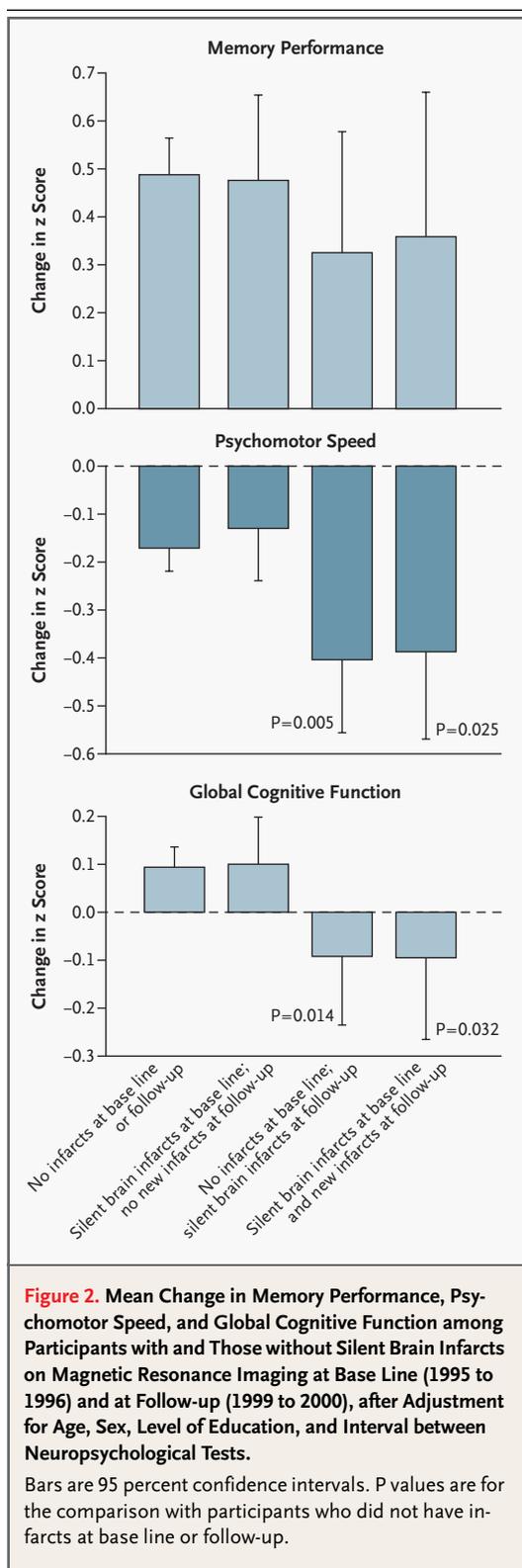
DISCUSSION

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

The strengths of this study are the large number of elderly participants and its population-based design. Furthermore, we had no losses to follow-up for the analyses of dementia. Notwithstanding

good-to-excellent intrareader agreement, we still may have incorrectly identified brain infarcts or misclassified infarcts as silent or symptomatic. However, because silent brain infarcts were identified and classified in a blinded fashion from data on dementia and neuropsychological tests, any misclassification would have resulted in an underestimation of the associations.

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

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

Figure 2. Mean Change in Memory Performance, Psychomotor Speed, and Global Cognitive Function among Participants with and Those without Silent Brain Infarcts on Magnetic Resonance Imaging at Base Line (1995 to 1996) and at Follow-up (1999 to 2000), after Adjustment for Age, Sex, Level of Education, and Interval between Neuropsychological Tests.

Bars are 95 percent confidence intervals. P values are for the comparison with participants who did not have infarcts at base line or follow-up.

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

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

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

Our finding that in both participants with and those without silent brain infarcts memory performance improved at the second examination may be explained by a learning effect.[32] This learning effect does not seem to have a major role in tests specific for psychomotor speed. The presence of silent in-

farcts that were not in the thalamus resulted in a decline in psychomotor speed. These infarcts probably interrupt various connecting fibers in the white matter that are involved in these psychomotor tasks.

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

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