Prestroke Cognitive Performance, Incident Stroke, and Risk of Dementia
The Rotterdam Study

Christiane Reitz, MD, PhD; Michiel J. Bos, MD, MSc; Albert Hofman, MD, PhD; Peter J. Koudstaal, MD, PhD; Monique M.B. Breteler, MD, PhD

Background and Purpose—Several studies indicate that stroke increases the risk of dementia. Most of these studies lacked the ability to take accurately assessed prestroke cognitive function into account. Whether the effects of stroke merely unravel an ongoing underlying dementing process or in fact cause the dementia has implications for the prevention of dementia in persons with cerebrovascular disease. We explored in a prospective cohort study whether stroke occurrence was related to a higher risk of subsequent dementia and whether this association was dependent on prestroke slope of cognitive function.

Methods—Cox proportional hazard models were used to relate incident stroke as a time-varying exposure with the risk of dementia in 6724 participants of the Rotterdam Study without dementia or stroke at baseline (49 361 person years of follow-up). Subsequently Cox proportional hazard models were performed to assess whether this association was dependent on slope of prestroke cognitive performance and other risk factors for cognitive decline.

Results—Independent of both level and the rate of change of prestroke cognitive performance and other risk factors for cognitive decline, incident stroke was associated with a more than doubled risk of subsequent dementia (hazard ratio, 2.1; 95% CI, 1.55 to 2.81).

Conclusions—Prestroke cognitive function is not a major determinant of the effect of stroke on the risk of poststroke dementia. (Stroke. 2008;39:36-41.)

Key Words: cognition ■ dementia ■ stroke

Cerebrovascular disease and dementia are among the most common diseases in aging societies. Cerebrovascular disease is the second leading cause of mortality in Western societies and the major cause of long-term disability, leaving 30% disabled.1 About 1% of people 65 to 69 years of age have dementia, and this proportion increases with age, to ≈60% for people ≥90 years of age.2

Epidemiologic evidence is accumulating that both disorders are linked. In their recently published review, Leys et al3 summarized the previous studies that explored the impact of stroke on the risk of poststroke dementia (PSD). According to these studies, stroke considerably increases the risk of dementia, with prevalence rates ranging from 13.6% to 32% within 3 months to 1 year after stroke, and incidence rates of new-onset dementia after stroke ranging from 24% within 3 years to 33.3% within 5 years.3–13

Of essential clinical implication for the prevention of dementia in persons with cerebrovascular disease is the clarification of whether the effects of stroke merely unravel an ongoing underlying dementing process or whether they in fact cause the dementia. If stroke itself would cause the dementia syndrome, neuroprotective intervention after occurrence of stroke would be of major importance. If stroke would merely unravel a masked ongoing dementing process, the expected effect of such intervention would be much smaller and the underlying process should be targeted.

To have the ability to accurately interpret the impact of stroke on the risk of PSD, prestroke level of cognitive function must be taken into account. In turn, this demands several methodological features from the study design: it requires assessment of prestroke cognitive status using an adequate neuropsychological test battery, a long enough follow-up time between prestroke cognitive assessment and occurrence of stroke, and subsequently a long enough follow-up time between the incident stroke and subsequent dementia or censoring. Ideally, the impact of prestroke cognitive status should be assessed using the slope of prestroke cognitive performance over time because the effect of stroke on risk of cognitive impairment may depend on the rate of decline in cognitive function before stroke.

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As stated by Leys et al., the studies that related prestroke cognitive performance with PSD reported a higher risk of PSD after 3 months\(^4\)–\(^7\) and 3 years\(^8\)–\(^9\) in persons with prestroke cognitive decline compared with persons without cognitive impairment before stroke. However, these studies had been obtained from stroke cohorts assessing prestroke cognitive function either by measuring cognitive performance at time of hospital admission or by using dementia diagnoses based on prestroke medical records.\(^4,5,9\)–\(^11\) Thus, they in fact lacked the essential ability to take cognitive function before stroke into account, leaving the true impact of stroke on dementia risk unclear.

The objective of the present study was to elucidate the impact of stroke on the risk of PSD as a function of prestroke cognitive performance by assessing the impact of prestroke cognitive performance on the association between incident stroke and risk of subsequent dementia in the large prospective population-based Rotterdam Study. We also sought to assess the effect of prestroke measures of other common risk factors for cognitive decline on the risk of dementia after stroke. Because the clinical distinction between dementia subtypes Alzheimer's disease (AD) and VaD is difficult, in particular, when a stroke has occurred, and persons with a diagnosis of stroke are by definition more likely to receive a diagnosis of VaD rather than AD, we focused on the risk of dementia rather than on the dementia subtypes AD or VaD.

Materials and Methods

Participants

The Rotterdam Study is a population-based prospective cohort study that has been described previously.\(^12\) From 1990 to 1993, all 10,275 residents \(\geqslant 55\) years of age living in Ommoord, a district of the city of Rotterdam, were invited to participate, and 7983 (78%) men and women agreed. During the baseline examination (1990 to 1993), a research assistant interviewed participants in their homes and obtained information on current and past health, medication, lifestyle, and risk factors for chronic diseases. In addition, participants visited the research center twice for baseline clinical examinations. Follow-up examinations took place in 1993 to 1994, 1997 to 1999, and 2002 to 2004. Through linkage with records of general practitioners, the entire cohort was monitored continuously for morbidity and mortality. This follow-up information was available for all participants until January 1, 2005.

From the 7983 participants who underwent baseline examination, 7528 were screened for dementia (94.3%). From these, 482 persons (6.4%) were diagnosed with prevalent dementia, 175 persons (2.2%) had a history of stroke at baseline, and 147 persons (2.0%) did not agree to give informed consent for collecting stroke information. The final analytic sample included in this study comprised 6724 persons without dementia or stroke at baseline. Follow-up with respect to dementia and stroke was nearly complete (96.7%).

Diagnosis of Dementia

Diagnostic procedures for dementia have been described in detail.\(^13\) At baseline and both follow-up examinations, a three-stage protocol was used to screen all participants cognitively with the Mini-Mental State Examination (MMSE)\(^14\) and the Geriatric Mental State schedule organic level.\(^15\) If subjects scored <26 on the MMSE or \(\geqslant 0\) on the Geriatric Mental State schedule organic level, the Cambridge Examination of Mental Disorders in the Elderly\(^16\) was administered. The Cambridge Examination of Mental Disorders in the Elderly also included an informant interview. Finally, participants in whom dementia was suspected were examined by a neurologist and neuropsychologist and, if possible, underwent MRI of the brain. In addition, the total cohort was continuously monitored for incident dementia cases through computerized linkage between the study database and computerized medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care.\(^13\) The diagnoses of dementia and AD were based on Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria\(^17\) and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria,\(^18\) respectively, and were made by a panel composed of a neurologist, neuropsychologist, and research physicians who reviewed all existing information.\(^19\) The diagnosis of vascular dementia was based on Association Internationale pour la Recherche et l’Enseignement en Neurologie (NINDS-AIREN) criteria.\(^19\)

Assessment of Stroke

History of stroke at time of enrollment in the Rotterdam Study was assessed by the question “Did you ever suffer from a stroke, diagnosed by a physician?” Positive answers to this question were verified by review of medical records. After baseline assessment, participants were monitored continuously for major events through automated linkage of the study database with files from general practitioners and the municipality. In addition, nursery home physicians’ files and files from general practitioners of participants who moved out of the district were scrutinized. For reported events, additional information including brain imaging was obtained from hospital records. Research physicians discussed information on all potential strokes and transient ischemic attacks with an experienced stroke neurologist to verify all diagnoses. Subarachnoid hemorrhages and retinal strokes were excluded from the stroke diagnosis. Strokes were subclassified into hemorrhagic or ischemic stroke based on neuroimaging. Strokes that could not be subclassified as ischemic or hemorrhagic were called unspecified.

Assessment of Other Covariates

Level of education was categorized into 3 groups: low (primary education only); intermediate (lower vocational or general education); and high (intermediate or higher vocational or general education, college, or university). Smoking habits were categorized as ever smoking and nonsmoking. Body mass index was calculated using the formula \([\text{weight (kg)/length (m)}^2]\). Blood pressure was measured at the right brachial artery using a random-zero sphygmomanometer with the participant in sitting position. Diabetes mellitus was defined as a random or postload glucose level \(\geqslant 11.1\) mmol/L or a history of diabetes or the use of blood glucose–lowering medication.

Nonfasting blood samples were drawn and immediately frozen. Total cholesterol, high-density lipoprotein cholesterol, and glucose were measured within 2 weeks, as described previously.\(^20\) Levels of serum C-reactive protein were determined by the rate near infrared particle immunoassay method (Immage high-sensitivity C-reactive protein; Beckman Coulter).

Ultrasonography of both carotid arteries was performed. As an indicator of atherosclerosis of the carotid arteries, we used intima media thickness (IMT). Common carotid IMT was determined as the average of the maximum IMT of near- and far-wall measurements, and the average of left and right common carotid IMT was computed.\(^21\) Apolipoprotein E (apoE) genotype was assessed on coded DNA samples using polymerase chain reaction without knowledge of the diagnosis.\(^22\) We dichotomized apoE genotype into presence or absence of the (apoE*4) allele. ApoE2*4 carriers were excluded from the analyses.

Statistical Methods

First, we evaluated the demographic and clinical characteristics of the study sample at baseline. Then we performed Kaplan–Meier analyses to determine the proportion of participants surviving free of dementia among persons without incident stroke, persons with incident stroke with normal prestroke cognitive function (last MMSE score before stroke \(\geqslant 26\)), and persons with incident stroke with low prestroke cognitive function (last MMSE score before stroke \(<26\)).
Table 1. Baseline Characteristics of the Study Sample in 6724 Persons Followed Prospectively

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>4033 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), year</td>
<td>69.2 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2493 (37.1)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>1797 (26.7)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2320 (34.5)</td>
<td></td>
</tr>
<tr>
<td>ApoE 4/- or 4/4 genotype, n (%)</td>
<td>1724 (25.6)</td>
<td></td>
</tr>
<tr>
<td>MMSE score, mean (SD)</td>
<td>27.7 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>672 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg), (SD)</td>
<td>139.1 (22.3)</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg), mean (SD)</td>
<td>73.8 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>26.3 (3.9)</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/L), mean (SD)</td>
<td>3.3 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL), mean (SD)</td>
<td>256.4 (47.0)</td>
<td></td>
</tr>
<tr>
<td>High-density lipoprotein (mg/dL), mean (SD)</td>
<td>52.1 (13.9)</td>
<td></td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>4281 (63.7)</td>
<td></td>
</tr>
<tr>
<td>IMT (mm), mean (SD)</td>
<td>0.8 (0.2)</td>
<td></td>
</tr>
</tbody>
</table>

In these analyses, the date of onset of dementia was considered to be the date of the visit on which dementia was diagnosed. We explored the individual effects of incident stroke and prestroke cognitive function on the risk of PSD with Cox proportional hazards analyses. For the analysis regarding the effect of stroke on subsequent dementia, incident stroke was entered as a time-varying exposure. For the analysis regarding the effect of prestroke cognitive function on the risk of dementia after stroke, we first used baseline measures of MMSE, and in a subsequent analysis, rate of decline in MMSE over time before occurrence of stroke or censoring.

To explore the individual effects of incident stroke and prestroke cognitive function on the risk of PSD with Cox proportional hazards analyses in which we added an interaction term to the model that contained both main effects as described in the previous paragraph (ie, the term relating incident stroke to PSD and the term relating prestroke cognitive impairment to PSD). Prestroke cognitive function was again assessed first using baseline measures of MMSE and then using rate of decline in MMSE over time before occurrence of stroke or censoring.

In the Cox models relating incident stroke as a time-varying exposure with the risk of PSD, persons with incident stroke had a significantly higher risk of subsequent dementia than persons remaining free of stroke during follow-up (age- and sex-adjusted hazard ratio, 2.1; 95% CI, 1.55 to 2.81; P<0.0001; Table 2). This association remained stable in the group without incident stroke was 97.6% (Figure). The cumulative proportion in the group without incident stroke was 97.6% (Figure).

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Table 2. Hazard Ratios and 95% CIs Relating Incident Stroke and Clusters of Incident Stroke With Baseline Measures of Risk Factors for Cognitive Decline With the Risk of Incident Dementia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 HR (95% CI)</th>
<th>Model 2 HR (95% CI)</th>
<th>P Value for Interaction Between Incident Stroke and Risk Factor††</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident stroke</td>
<td>2.1 (1.55–2.81)</td>
<td>2.1 (1.54–2.93)</td>
<td>–</td>
</tr>
<tr>
<td>+ MMSE</td>
<td>2.0 (1.45–2.69)</td>
<td>1.9 (1.36–2.68)</td>
<td>0.7</td>
</tr>
<tr>
<td>+ Rate of decline in MMSE over time†</td>
<td>2.0 (1.41–2.87)</td>
<td>2.0 (1.34–2.87)</td>
<td>0.5</td>
</tr>
<tr>
<td>+ ApoE4 genotype</td>
<td>2.1 (1.53–2.84)</td>
<td>2.1 (1.54–2.93)</td>
<td>0.3</td>
</tr>
<tr>
<td>+ Diabetes</td>
<td>2.1 (1.55–2.81)</td>
<td>2.1 (1.54–2.93)</td>
<td>0.9</td>
</tr>
<tr>
<td>+ Systolic blood pressure</td>
<td>2.1 (1.52–2.82)</td>
<td>2.0 (1.43–2.78)</td>
<td>0.4</td>
</tr>
<tr>
<td>+ Diastolic blood pressure</td>
<td>2.1 (1.51–2.81)</td>
<td>2.0 (1.44–2.81)</td>
<td>0.7</td>
</tr>
<tr>
<td>+ Serum CRP *</td>
<td>2.0 (1.47–2.81)</td>
<td>1.9 (1.37–2.77)</td>
<td>0.1</td>
</tr>
<tr>
<td>+ Total cholesterol</td>
<td>2.2 (1.59–2.91)</td>
<td>2.2 (1.57–2.99)</td>
<td>0.7</td>
</tr>
<tr>
<td>+ HDL</td>
<td>2.2 (1.61–2.92)</td>
<td>2.1 (1.54–2.93)</td>
<td>0.4</td>
</tr>
<tr>
<td>+ Smoking</td>
<td>2.1 (1.54–2.81)</td>
<td>2.1 (1.55–2.95)</td>
<td>0.8</td>
</tr>
<tr>
<td>+ IMT</td>
<td>2.2 (1.54–3.99)</td>
<td>2.1 (1.46–4.19)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Cox proportional hazards model.
HR indicates hazard ratio; CRP, C-reactive protein; HDL, high-density lipoprotein cholesterol.
Model 1, Adjusted for sex and age; model 2, adjusted for sex, age, education, and apoE4 genotype.
*Serum CRP was used as a logarithmic transformed continuous variable; †β coefficient for rate of decline in MMSE score over time before occurrence of incident stroke, derived by linear regression; ††adjusted for sex, age, education, and apoE4 genotype.

Discussion

We found that an incident stroke doubled the risk of subsequent dementia independent of prestroke level of cognitive function and prestroke rate of cognitive decline.

This study has limitations. We restricted our analyses to persons with complete information on the occurrence of incident stroke. Individuals who were excluded because of incomplete information were older and had a higher frequency of vascular risk factors. However, this will only have biased our results if the association among incident stroke, prestroke cognitive function, and dementia is completely different in the people with incomplete data compared with people with complete data, which we consider highly unlikely. We only had data on symptomatic stroke. Given that the frequency of asymptomatic infarcts is much higher than that of symptomatic stroke,23 we may have underestimated the impact of subclinical cerebrovascular disease. Information on imaging from hospital records was available on ≈92% of all hospitalized stroke patients but in only 65% of all persons with stroke. The lack of brain imaging in approximately one third of stroke patients implies the possibility of misclassification of stroke subtype, but we consider it unlikely that it led to a misclassification of stroke itself. As measure of prestroke cognitive function, we used the MMSE test, which can be insensitive to early deficits attributable to cerebrovascular disease and prone to practice effects. Thus, there remains the possibility that the estimation of slope of prestroke cognitive decline was rather rough.

Our study has important strengths. It is a prospective population-based study with a large total number of participants, a large number of persons with incident stroke during follow-up, and nearly complete follow-up with respect to incident stroke and subsequent dementia. Previous studies relating stroke to the risk of dementia were mostly observational studies using prevalent information of stroke, or studies assessing cognitive deterioration after acute stroke in clinical settings.4–6,8,19,24,25 To our knowledge, this is the first large population-based study relating incident stroke to the long-term risk of subsequent dementia in persons without dementia or stroke at baseline. This design provides the ability to explore the impact of stroke and other risk factors on the risk of dementia, explicitly taking prestroke cognitive performance into account.

We observed an association between incident stroke and the risk of subsequent dementia, which was independent of level of prestroke cognitive performance. This finding contradicts previous studies reporting a higher risk of PSD in persons with prestroke cognitive impairment compared with persons with normal cognition before stroke.4,8,10,24,26 However, as mentioned previously, these studies either used prevalent information of stroke4,10,25,27 or were conducted in stroke cohorts, with prestroke cognitive function being measured after the stroke through informant questionnaires or by checking prestroke medical records for a diagnosis of dementia.5,8,19,24,28 These studies thus lacked the ability to accurately
assess prestroke cognitive function. Also, because of the difficulties in applying a comprehensive, formal neuropsychological assessment to patients who are physically and neurologically impaired, many of the studies in clinical settings examined only a subsample of the total patients registered and thus may have been biased because of selective attrition. Our study also contradicts the findings of the recently published study by Gamaldo et al. This study reported an increased risk of PSD in persons with prestroke mild cognitive impairment. In persons without mild cognitive impairment before stroke, the risk of dementia was similar to persons without stroke. However, these findings were derived from a highly selected cohort without neuroimaging data, were derived from analyses that were solely adjusted for age and sex, and were based on 32 persons total, leading to very imprecise risk estimates. Also, none of the previous studies took into account change in cognitive function before occurrence of stroke. Our findings are in line with observations in a prospective population-based neuroimaging study in which the occurrence of novel brain infarcts during follow-up was associated with cognitive decline, regardless of presence of baseline infarcts and regardless of baseline cognitive status. The present study, with a mean follow-up time of 6.3 years between first assessment of cognitive function at baseline and time of incident first stroke, in which the slope of cognitive performance before stroke was also taken into account, and which had a nearly complete follow-up with respect to dementia, does not suggest that the prestroke level of cognitive function is a major determinant of the effect of stroke on the risk of PSD. Both prestroke cognitive function and the stroke itself have an effect on the risk of dementia after stroke, but these effects are largely independent.

The association between incident stroke and the risk of subsequent dementia was also independent from all other assessed risk factors for cognitive decline, including diabetes mellitus, apoEε4 genotype, blood pressure levels, body mass index, and IMT. This observation supports the notion that the effects of stroke result in dementia through mechanisms other than those of apoEε4 or other potential risk factors, and that stroke increases the risk of dementia independently of these risk factors. There are alternative explanations for our findings. It is possible that incident stroke is not a risk factor but merely part of a preclinical syndrome of dementia, meaning that persons with preclinical dementia may have a higher frequency of stroke than persons without dementia. However, the mean follow-up time between incident stroke and subsequent dementia in persons developing PSD was relatively long (3.9 years), making this an unlikely explanation for our findings. Also, the association between incident stroke and subsequent dementia was independent from prestroke cognitive function, regardless of length of follow-up time from incident stroke to subsequent dementia.

An alternative explanation for the missing interaction between incident stroke and risk factors for cognitive decline might be that elderly cohorts are too homogeneous to show differences in outcomes related to these risk factors. The measurement of these risk factors in our cohort did not take duration into account. Thus, it is possible that our results tend to underestimate the association among incident stroke, risk factors for cognitive decline, and incident dementia, which could bias the results to the level of no interaction. However, this seems unlikely given the robustness of our findings across all assessed risk factors for cognitive decline.

**Summary**

Stroke seems to exert its effect on dementia risk independent of the prestroke level of cognitive function. It also seems to act through mechanisms other than mechanisms of common potential risk factors for cognitive decline.

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**Disclosures**

None.

**References**


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