Subjective Memory Complaints and the Risk of Stroke

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**Background and Purpose**—Persons with cognitive impairment, as assessed by cognitive tests, are at a higher risk of stroke. Subjective memory complaints might be an earlier marker for stroke, especially in persons with higher education. Their cognitive reserve might mask their cognitive impairment during cognitive testing. In a population-based setting, we investigated the association between subjective memory complaints and stroke. We simultaneously investigated the association between Mini-Mental State Examination and stroke. We also assessed whether these associations varied with educational level.

**Methods**—9152 participants from the Rotterdam Study (baseline 1990–1993 or 2000–2001) completed the subjective memory complaints questionnaire and underwent Mini-Mental State Examination assessment. Subsequently, the entire cohort was followed for incident stroke until 2012. We used Cox proportional hazard models to estimate the associations between subjective memory complaints and Mini-Mental State Examination, with stroke.

**Results**—During a follow-up of 111593 person years, 1134 strokes were identified, of which 663 were ischemic and 99 hemorrhagic. In the fully adjusted model, presence of subjective memory complaints was independently associated with a higher risk of stroke (hazard ratio, 1.20; 95% confidence interval, 1.04–1.39), but a higher Mini-Mental State Examination was not (hazard ratio per point increase, 0.99; 95% confidence interval, 0.95–1.02). The association between subjective memory complaints and risk of stroke was modified by educational level, with a higher risk of stroke in persons with a higher level of education (hazard ratio, 1.39; 95% confidence interval, 1.07–1.81).

**Conclusions**—Subjective memory complaints might be an early indicator of stroke risk, especially in highly educated individuals. *(Stroke. 2015;46:170-175. DOI: 10.1161/STROKEAHA.114.006616.)*

**Key Words:** cognitive impairment □ education □ stroke

Cognitive impairment and dementia are often long-term sequelae of stroke.¹ This could be because of direct loss of brain parenchyma during stroke, especially when such damage is located at strategic sites in the brain, for instance in the thalamus.² However, cognitive impairment and stroke might also be linked through a shared pathogenesis because vascular risk factors for stroke are also determinants of cognitive impairment and dementia.³,⁴ To test this hypothesis, several studies that investigated how cognitive impairment relates to incident stroke were reviewed and found an increased risk of stroke in persons with lower cognitive performance.⁵

Most studies have used objective cognitive tests, such as the Mini-Mental State Examination (MMSE), to determine the presence of cognitive impairment.⁶-⁹ However, subjective memory complaints may appear earlier and might therefore be an earlier marker of vascular damage that could also lead to stroke.¹⁰ This may apply especially to persons with higher education, who perform well on cognitive testing, probably because of a higher cognitive reserve,¹¹ which can mask subtle changes in cognition. As a result, these persons may continue to harbor subclinical vascular insults to the brain. Previous studies have found an association between subjective memory complaints and risk of dementia,¹²,¹³ mostly in persons with higher education.¹¹ Still, the clinical importance of subjective memory complaints for the prediction of stroke remains unclear.

The aim of the present study was to evaluate the independent association between subjective memory complaints and the risk of stroke. In addition, we used the MMSE as an objective measure to relate with incident stroke. Furthermore, we also sought to determine whether these associations vary with educational level.

**Methods**

**Study Population**

This study was embedded in the Rotterdam Study, a large prospective population-based cohort that started in 1990 among inhabitants aged ≥55 years residing in a district of Rotterdam, the Netherlands.
Assessment of Subjective Memory Complaints and Objective Cognition

Trained investigators interviewed all participants at home. The presence of subjective memory complaints was assessed by the question, “Do you have memory complaints?”

Cognitive function on an objective scale was tested with the 30-point MMSE. The MMSE contains 20 items covering orientation, memory, attention, language, and visuospatial construction.

Assessment and Follow-Up of Stroke

At study entry, history of stroke was assessed using home interviews and confirmed by reviewing medical records. Once participants entered the Rotterdam Study, they were continuously followed up for stroke through automatic linkage of general practitioner files with the study database. Also, nursing home physicians’ files and files from general practitioners of participants who moved out of the district were checked on a regular basis. Of the potential strokes, additional hospital and general practitioner information was collected. Research physicians reviewed the stroke information, and an experienced neurologist adjudicated the strokes using standardized definitions, as described in detail previously.

The follow-up was complete until January 1, 2012, for 97% of potential person-years.

Assessment and Follow-Up of Dementia

Participants were screened for dementia at baseline and follow-up examinations using a 3-step protocol. Screening was done using the MMSE and the Geriatric Mental Schedule organic level. Screen-positives (MMSE <26 or Geriatric Mental Schedule organic level >0) subsequently underwent an examination and informant interview with the Cambridge Examination for Mental Disorders in the Elderly. Participants who were suspected of having dementia underwent, if necessary, further neuropsychological testing. Additionally, the total cohort was continuously monitored for dementia through computerized linkage between the study database and digitized medical records from general practitioners and the Regional Institute for Outpatient Mental Healthcare. When information on neuroimaging was required and available, it was used for decision making on the diagnosis. For all suspected cases of dementia, a consensus panel, led by a neurologist, decided on the final diagnosis in accordance with standard criteria for dementia (DSM-III-R) and Alzheimer’s disease (NINCDS-ADRDA).

Follow-up for incident dementia was virtually complete until September 2, 2011.

Measurement of Covariates

We used covariates measured at baseline. Smoking status and information on the number of cigarettes smoked per day in each decade of life was obtained by a self-administered questionnaire during the home interview. Smoking status was characterized as never, past, and current smoking. Participants were also invited to visit the research center for clinical examinations and laboratory assessments. Body mass index was measured using weight in kilograms divided by the square of height in meters. Total cholesterol and high-density lipoprotein-cholesterol levels were acquired by an automated enzymatic procedure. Diabetes mellitus type-2 was defined as having a fasting glucose level of ≥7.0 mmol/L, or using blood glucose-lowering medication.

Blood pressure was measured at the research center twice in the sitting position on the right arm with a random zero sphygmomanometer. The average of the 2 measurements was used in the analyses. Data on indication for use of blood pressure-lowering medication were based on information collected by a physician at the research center. In the case of missing information, data from the home interview was taken. Information on APOE-ε4 genotype (2 ε4 APOE-ε4 alleles versus no APOE-ε4 alleles) was determined from blood samples. Basic activities of daily living was assessed using the Dutch version of the disability index from the Stanford Health Assessment Questionnaire.

The disability index consists of 20 items constituting 8 components: dressing and grooming, arising, eating, walking, hygiene, grip, reach, and activities. Two of the 3 items belonging to the eating component were combined into 1 item. Each item was scored from 0 to 3, with higher scores indicating worse ability: 0, without any difficulty; 1, with some difficulty; 2, with much difficulty; and 3, unable to.

Statistical Analysis

We investigated the associations of subjective memory complaints and MMSE, as a continuous measure, with stroke incidence using Cox proportional hazards models. The proportional hazard assumption was evaluated using Schoenfeld residuals. The underlying time-scale in these models was the follow-up time in years. Participants who did not have stroke were censored at date of death, date of loss to follow-up, or January 1, 2012, whichever occurred first. All models were adjusted for age, sex, and cohort. We subsequently adjusted for body mass index, diabetes mellitus type-2, smoking status, systolic blood pressure, diastolic blood pressure, blood pressure lowering medication, total serum cholesterol, high-density lipoprotein-cholesterol, lipid lowering medication, basic activities of daily living, APOE-ε4 allele carrier status, and MMSE or subjective memory complaints (where applicable). To examine whether subclinical subjective memory complaints are associated with stroke, 2 sensitivity analyses were performed: first, we censored for incident dementia during follow-up. Second, we additionally excluded participants with an MMSE score of <26 at baseline.

To investigate whether education level affected the association between subjective memory complaints and MMSE with stroke, we constructed interaction terms with education and performed stratified analyses. We categorized level of education into 3 groups: low education (primary education only), intermediate education (primary education plus a not completed higher education, lower vocational education, intermediate vocational education, or general secondary education), and high education (higher vocational education or university training).

Missing values on blood measurements were because of failure of blood draw, or the blood sample was inadequate to run all tests. Blood pressure measurements and anthropometry measures were missing because of physical inability of persons. Missing values on smoking status, education level, use of medication were missing because of time constraints in administering the questions at the time of home interview. Missing values for the confounding variables (0.1%–5.8% missing data; Figure I in the online-only Data Supplement) were imputed by multiple imputation using chained equations in which 40 completed data sets were generated and analyzed by using the standard combination rules for multiple imputation. Each variable was used as a predictor in the imputation model. All continuous variables in our data had normal distribution. No interactions were included in the final analysis; thus, no interactions were included in the imputation models. The data were imputed assuming that the data were missing at random. All analyses were performed using Stata13 (Stata Corp, College Station, TX).

Results

Baseline characteristics of the study population are presented in Table 1. Individuals with any missing data on covariates (n=999) were compared with persons with complete data (n=8153); persons with incomplete data were older in age (72.2 years [10.2] compared with 67.1 years [8.4], P<0.001).
The association between subjective memory complaints and stroke did not change significantly after adjustment for lifestyle factors, vascular risk factors, and APOE-ε4 and MMSE, HR 1.20 (95% CI, 1.04–1.39). The association between subjective memory complaints and ischemic stroke was similar in strength, HR 1.22 (95% CI, 1.10–1.49) in the fully-adjusted model.

An increase in MMSE score was not significantly associated with the risk of stroke: fully adjusted HR per point higher MMSE score 0.99 (95% CI, 0.95–1.02). The effect sizes for the association between MMSE with ischemic and hemorrhagic stroke were also nonsignificant. Mutual adjustment (model 2) showed that subjective memory complaints were associated with stroke independently of MMSE. Additional analyses (censoring at the date of diagnosis of incident dementia and excluding persons with MMSE <26 at baseline) showed virtually unchanged results.

We found a significant interaction between the level of education and subjective memory complaints in relation to stroke (P=0.007). The education-stratified analyses showed that subjective memory complaints were significantly associated with stroke only in persons with high education, HR 1.39 (95% CI, 1.07–1.81 fully adjusted; Table 3 and Figure). Time to incident stroke was also shorter in persons with high education level who complained about their memory (Figure). The effect sizes of MMSE with stroke were similar across the strata of education.

### Discussion

We found that individuals with subjective memory complaints, especially those with a high level of education, had an increased risk of stroke compared with those who did not complain about their memory. The association between subjective memory complaints and stroke was independent of the MMSE score. All associations remained similar after censoring for incident dementia and excluding persons with an MMSE score <26 at baseline.

Subjective memory complaints are common in the elderly with prevalence rates reported from 11% in persons above 65 years to 88% in those aged above 85 years.26,27 In our population of community-dwelling individuals of an average age 67 years, the prevalence was 17% and is comparable to numbers in the literature.

The associations between subjective memory complaints and the risk of stroke are probably mainly explained by shared vascular risk factors. Subjective memory complaints may be a marker of cerebral microvascular injuries, which may ultimately lead to clinical stroke.28 Previous studies have found associations between subjective memory complaints and cerebral microbleeds or white matter lesions.28,29 This supports our hypothesis that early vascular damage presenting as memory complaints, which are not yet evident in cognitive tests, may lead in future to clinical stroke. Similarly, it has been shown among hypertensive patients that those with subjective memory complaints have more arterial stiffness and white matter lesions than patients without subjective memory complaints.30 One study showed the presence of amyloid-β protein deposition in people with subjective memory complaints, who were otherwise cognitively unimpaired (MMSE ≥28). Yet in the
same study, no association was found between objective memory measures and amyloid burden.31 Thus, the deposition of amyloid-β proteins in the vessels of the brain can compromise their integrity, which may lead to leakage and subsequently contribute to clinical stroke.32

We found that the association between subjective memory complaints and stroke was strongest in highly educated persons. This is comparable to a previous finding that the association between subjective memory complaints and Alzheimer’s disease is strongest in highly educated persons.11 An explanation may be that persons who are highly educated are more likely to notice subtle changes in their cognitive performance than the less educated. This makes the perception of memory changes of highly educated persons a suitable measure to assess subtle cerebrovascular degeneration. This is evident in our data after adjustment for age, sex, and MMSE at baseline; we found that the odds of having subjective memory complaints is 1.56× in the high education group compared with low education group. A counterargument against this reasoning is that, in our population, memory complaints were more frequent in the low educated group compared with the highly educated group. Another explanation is that education reflects cognitive reserve.33 Higher cognitive reserve allows persons to cope better with accumulating vascular injury in the brain, thereby maintaining their performance on cognitive testing. Subjective memory complaints in these highly educated persons might therefore be a better marker than cognitive testing to assess vascular brain injury.

Table 2. Subjective Memory Complaints, Mini-Mental State Examination and Risk of Incident Stroke

<table>
<thead>
<tr>
<th></th>
<th>Total Strokes, HR (95% CI)</th>
<th>Ischemic Strokes, HR (95% CI)</th>
<th>Hemorrhagic Strokes, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>n/N=1134/9152</td>
<td>n/N=663/9152</td>
<td>n/N=99/9152</td>
</tr>
<tr>
<td>Subjective memory complaints (yes vs no)</td>
<td>Model 1 1.19 (1.03–1.38)</td>
<td>1.17 (0.96–1.42)</td>
<td>1.32 (0.81–2.15)</td>
</tr>
<tr>
<td></td>
<td>Model 2 1.20 (1.04–1.39)</td>
<td>1.22 (1.01–1.49)</td>
<td>1.39 (0.85–2.26)</td>
</tr>
<tr>
<td>MMSE (per point increase)</td>
<td>Model 1 0.97 (0.94–1.00)</td>
<td>1.02 (0.98–1.07)</td>
<td>0.96 (0.86–1.07)</td>
</tr>
<tr>
<td></td>
<td>Model 2 0.99 (0.95–1.02)</td>
<td>1.04 (0.99–1.09)</td>
<td>0.97 (0.87–1.09)</td>
</tr>
<tr>
<td>Censoring for dementia</td>
<td>n/N=1000/9152</td>
<td>n/N=630/9152</td>
<td>n/N=91/9152</td>
</tr>
<tr>
<td>Subjective memory complaints (yes vs no)</td>
<td>Model 1 1.17 (1.00–1.37)</td>
<td>1.15 (0.94–1.41)</td>
<td>1.35 (0.81–2.25)</td>
</tr>
<tr>
<td></td>
<td>Model 2 1.19 (1.01–1.39)</td>
<td>1.20 (0.98–1.47)</td>
<td>1.42 (0.85–2.37)</td>
</tr>
<tr>
<td>MMSE (per point increase)</td>
<td>Model 1 0.98 (0.95–1.02)</td>
<td>1.01 (0.97–1.06)</td>
<td>0.95 (0.85–1.07)</td>
</tr>
<tr>
<td></td>
<td>Model 2 0.99 (0.96–1.03)</td>
<td>1.02 (0.98–1.07)</td>
<td>0.97 (0.86–1.09)</td>
</tr>
<tr>
<td>Censoring for dementia and excluding MMSE &lt;26</td>
<td>n/N=891/8200</td>
<td>n/N=577/8200</td>
<td>n/N=82/8200</td>
</tr>
<tr>
<td>Subjective memory complaints (yes vs no)</td>
<td>Model 1 1.17 (0.99–1.39)</td>
<td>1.14 (0.92–1.41)</td>
<td>1.33 (0.77–2.31)</td>
</tr>
<tr>
<td></td>
<td>Model 2 1.20 (1.02–1.42)</td>
<td>1.19 (0.96–1.48)</td>
<td>1.39 (0.80–2.41)</td>
</tr>
<tr>
<td>MMSE (per point increase)</td>
<td>Model 1 0.99 (0.93–1.04)</td>
<td>1.01 (0.94–1.08)</td>
<td>1.00 (0.83–1.20)</td>
</tr>
<tr>
<td></td>
<td>Model 2 1.00 (0.95–1.06)</td>
<td>1.02 (0.95–1.10)</td>
<td>1.02 (0.85–1.23)</td>
</tr>
</tbody>
</table>

Model 1, Adjusted for age, sex, education, and cohort; Model 2, Model 1+BMI, diabetes mellitus, smoking, systolic blood pressure, diastolic blood pressure, blood pressure lowering medication, total serum cholesterol, HDL-cholesterol, lipid lowering medication, APOE-ε4, basic activities of daily living, and MMSE or subjective memory complaints. APOE indicates apolipoprotein E; BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; MMSE, Mini-Mental State Examination; n, number of stroke events; and N, number of persons in the total population.

Table 3. Subjective Memory Complaints, Mini-Mental State Examination, and Risk of Incident Stroke Stratified by the Level of Education

<table>
<thead>
<tr>
<th></th>
<th>Low Education, HR (95% CI)</th>
<th>Intermediate Education, HR (95% CI)</th>
<th>High Education, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N=276/1724</td>
<td>n/N=478/4551</td>
<td>n/N=355/2743</td>
</tr>
<tr>
<td>Subjective memory complaints (yes vs no)</td>
<td>Model 1 1.05 (0.79–1.39)</td>
<td>1.15 (0.91–1.44)</td>
<td>1.45 (1.12–1.87)</td>
</tr>
<tr>
<td></td>
<td>Model 2 1.09 (0.82–1.45)</td>
<td>1.17 (0.93–1.47)</td>
<td>1.39 (1.07–1.81)</td>
</tr>
<tr>
<td>MMSE (per point increase)</td>
<td>Model 1 0.97 (0.92–1.03)</td>
<td>0.98 (0.93–1.03)</td>
<td>0.96 (0.90–1.03)</td>
</tr>
<tr>
<td></td>
<td>Model 2 0.97 (0.92–1.03)</td>
<td>1.00 (0.95–1.06)</td>
<td>0.97 (0.91–1.05)</td>
</tr>
</tbody>
</table>

Model 1, Adjusted for age, sex, cohort; Model 2, Model 1+BMI, diabetes mellitus, smoking, systolic blood pressure, diastolic blood pressure, blood pressure lowering medication, total serum cholesterol, HDL-cholesterol, lipid lowering medication, APOE-ε4, basic activities of daily living, and MMSE or subjective memory complaints. APOE indicates apolipoprotein E; BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; MMSE, Mini-Mental State Examination; n, number of stroke events; and N, number of persons in each education category.
The strengths of our study are its population-based prospective design and availability of data on >9000 participants at baseline with a long follow-up. The main novelty of our study is that we describe subjective memory complaints in addition to objective cognitive testing as an independent predictor of stroke. Furthermore, we also assess the association between subjective memory complaints and stroke in a population without stroke and dementia at baseline. Our study is limited by the use of MMSE as the only comparative objective measure of cognitive impairment because the severity of cognitive impairment cannot be reliably assessed by MMSE alone. Future studies with more extensive cognitive testing batteries are needed to determine the associations between cognitive impairment and stroke. Because different cognitive tests target different cognitive domains, it would be mandatory to apply a variety of objective measurements to determine which cognitive domains are particularly associated with a higher risk of stroke. Our study is limited by the unavailability of neuroimaging data. Future studies should include MRI findings to explore the evidence of small vessel disease as an underlying mechanism of the associations between subjective memory complaints and stroke. Among the 372 unspecified strokes, silent strokes were not diagnosed because all strokes being clinical strokes were reported at the hospital. Furthermore, although we adjusted for a variety of vascular risk factors, we cannot exclude residual confounding by measurement error or unmeasured factors. Moreover, the covariates in our list may not be exhaustive of all vascular risk factors and there may also be some risk factors that do not go through the vascular risk factor pathways. The unavailability of data on depression and depressive symptoms as an unmeasured confounder is also a major limitation of this study because it has been suggested that the associations with subjective indicators of health especially memory may be confounded by prevalence of depression.34

In conclusion, subjective memory complaints are associated with a higher risk of incident stroke, especially in persons with a high level of education. In these persons, cognitive tests are not of incremental value because they might perform well, despite their subjective memory dysfunction. This suggests the importance of a single self-rated question about memory complaints that can prompt clinicians to consider screening for and treatment of vascular risk factors. People with high level of education who complain about changes in their memory should be a primary target for further risk factor screening and prevention of stroke.

Acknowledgments
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Disclosures
None.

References


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