Carotid artery plaque progression and cognitive decline: the Tromsø Study 1994–2008

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Background: Carotid atherosclerosis is a risk factor for stroke and cognitive decline, but knowledge on how progression of carotid atherosclerosis affects cognitive function in stroke-free individuals is scarce.

Methods: In the population-based Tromsø study, we calculated the change in ultrasound-assessed carotid plaque number and total plaque area from baseline (survey 4) to follow-up 7 years later (survey 5) in 4274 middle-aged stroke-free subjects. Cognitive function was assessed at follow-up by the verbal memory test, the digit-symbol coding test, and the tapping test and repeated after an additional 6 years in a subgroup of 2042 subjects (survey 6). Associations between the average of survey 4 and survey 5 plaque scores and the progression of plaque scores and cognitive test scores were assessed in regression analyses adjusted for baseline age, sex, education, depression, and cardiovascular risk factors.

Results: Progression of total plaque area was associated with lower scores in the digit-symbol coding test (multivariable adjusted standardized $\beta$, $-0.03; 95\%$ CI, $-0.05$ to $-0.00; P = 0.04$) and the tapping test ($\beta$, $-0.03; 95\%$ CI, $-0.06$ to $-0.00; P = 0.03$). Similar results were seen for progression of plaque number. The average plaque scores were associated with lower scores in all cognitive tests ($P$-values $\leq 0.01$). No association was found between plaque scores and cognitive decline.

Conclusions: The average plaque scores were associated with lower scores in all cognitive tests. Progression of plaque scores was associated with lower scores in the digit-symbol coding test and the tapping test, but not with the verbal memory test or with cognitive decline.

Introduction

Cognitive decline and dementia are major health problems worldwide. Understanding the pathology and discovering risk factors is the first step toward treatment or preventive strategies. Research in the last 20 years has outlined a number of both genetic and non-genetic risk factors of the two major subtypes of dementia, Alzheimer’s disease (AD), and vascular dementia. Vascular risk factors are associated with both subtypes, although weakest associated with AD [1]. Carotid atherosclerosis is a major risk factor of stroke and subsequent cognitive decline [2], but some epidemiological studies have indicated an association between carotid intima-media thickness (IMT) and stenosis and cognitive decline also in stroke-free individuals [3,4]. The mechanisms behind these associations are not fully understood, and results are conflicting as some studies did not observe the same relationship [5,6]. Previous carotid ultrasound studies have focused on a baseline IMT or carotid stenosis as predictors of cognitive decline, and we found no other population-based studies assessing the progression of carotid plaques in relation to cognitive function and decline. Measuring the progression of carotid atherosclerosis over years in relation to cognitive function could bring stronger evidence of a causal association between carotid atherosclerosis and cognitive function. Also, little is known about how progression of carotid atherosclerosis in middle-aged subjects affects cognitive function, as most studies are performed in the elderly (>65 years).

In this study, we followed a large middle-aged cohort of the general population in the Tromsø study and assessed the progression of carotid atherosclerosis...
over 7 years in relation to cognitive test scores and also followed a subgroup of these for an additional 6 years to see whether carotid plaque progression could predict cognitive decline.

**Methods**

**Subjects**

Subjects were participants in the Tromsø study, a longitudinal population-based study in the municipality of Tromsø, Norway [7]. Cross-sectional screening surveys of the population of Tromsø have been performed every 6–7 years since 1974, altogether six surveys. Carotid ultrasonography was performed in the 4th (1994/1995) and 5th surveys (2001/2002), and cognitive testing was carried out in the 5th and 6th (2007/2008) surveys.

The 4th survey comprised two screening visits 4–12 weeks apart. All citizens aged 25 and above were invited to the first visit, and 27,158 attended (77% attendance rate). All participants who were between 55 and 74 years old and 5–10% samples of the remaining 5-year birth cohorts aged 25–85 years were invited to the second visit, where 7,965 subjects attended (76% of the eligible). At the time of the 4th survey, the Tromsø population was mainly Caucasian; <2% of the population were immigrants of non-Western origin. In 2001/2002, all 6,969 subjects who attended the second of two visits of the 4th survey, and who were still registered as inhabitants of Tromsø, were invited to the 5th survey, and 5,939 (85%) subjects attended [8]. A total of 5,493 subjects attended cognitive testing in 2001/2002. Subjects without valid written consent to medical research in September 2011 (n = 31) were excluded. Information on stroke was obtained through linkage to the diagnosis registry at the University Hospital of North Norway (UNN), as previously described [9]. Event ascertainment followed a detailed protocol, according to established diagnostic criteria [10]. We identified 195 subjects who had ever had a clinical stroke prior to cognitive testing in the 5th survey, and these subjects were excluded from the study. Subjects with incomplete data on baseline and follow-up carotid examination and/or baseline vascular risk factors (n = 993) were excluded, leaving 4,274 subjects (2,073 men and 2,201 women) to be included in the total cohort of the present study.

Of the total cohort of 4,274 subjects, 2,100 were retested in the 6th survey with at least one of the three cognitive tests. Subjects with a diagnosis of clinical stroke in the follow-up period from the 5th to the 6th survey (n = 58) were excluded from analyses, leaving a subgroup of 2,042 subjects who were included in the second part of the study.

The study was approved by the Regional Committee for Medical and Health Research Ethics, the Data Inspectorate, and the Norwegian Directorate of Health. All participants gave written consent to medical research.

**Carotid ultrasound measurements**

Details about the ultrasound methods and reproducibility have previously been published [11]. High-resolution B-mode ultrasonography was performed with a duplex scanner (Acuson Xp10 128, ART-upgraded) equipped with a 7.5-MHz linear array transducer. The far and near walls of the right common carotid artery (CCA), the bifurcation (bulb), and the internal carotid artery (ICA) were scanned for plaque presence. A plaque was defined as a localized protrusion into the vessel lumen with thickening of the vessel wall of more than 50% compared to the adjacent intima-media thickness. The total plaque area was calculated as the sum of all plaque areas [11]. Only the right carotid artery was examined to reduce study time, expense, and participant burden.

**Cardiovascular risk factors**

At baseline, information on education, smoking, physical activity, diabetes, coronary heart disease, medication, and depression was obtained from questionnaires. Blood pressure was recorded with an automatic device by specially trained personnel, and non-fasting serum cholesterol and triglycerides were analyzed by standard enzymatic methods as previously described [8].

**Cognitive testing**

Cognitive function was assessed by three standardized tasks sensitive to and predictive of cognitive decline in other population-based studies [5,12,13]. The cognitive tests are previously described in detail [8]. The 12-word memory test is a test of short-time verbal memory with immediate free recall of 12 nouns. The Digit-Symbol Coding test examines psychomotor speed, attention, and mental flexibility. The task consists of rows containing blank squares, each paired with a randomly assigned number from one to nine, and a printed key above that pair, each number with a different nonsense symbol. Subjects were asked to consecutively fill in as many as possible of the blank spaces with the corresponding symbol as quickly as possible for 90 s. In the tapping test, a test mainly of psychomotor tempo, the subjects were instructed to tap as many times as possible in 10 s with their index fingers.
finger on a computer. The task was repeated four times with both dominant hand and non-dominant hand. The mean of the average score of the three last trials on each hand was used in the analyses.

**Statistical analysis**

The SAS statistical software package (SAS®, V9.2; SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. Baseline characteristics were presented with mean (SD) or numbers (%) of the total cohort and the subgroup. Each individual’s plaque score at survey 4 and survey 5 was averaged to create average plaque scores (number of plaques and total plaque area) for those two visits and is referred to as average plaque scores (number of plaques and total score at survey 4 and survey 5 was averaged to create cohort and the subgroup. Each individual’s plaque represented with mean (SD) or numbers (%) of the total statistical analyses. Baseline characteristics were pre-

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SAS statistical software package (SAS®

Statistical analysis

The SAS statistical software package (SAS®, V9.2; SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. Baseline characteristics were presented with mean (SD) or numbers (%) of the total cohort and the subgroup. Each individual’s plaque score at survey 4 and survey 5 was averaged to create average plaque scores (number of plaques and total plaque area) for those two visits and is referred to as the average survey4–survey5 plaque scores. The independent relations between the average survey4–survey5 plaque scores and the change in plaque scores and cognitive test results at survey 5, as well as cognitive decline from survey 5 to survey 6, were assessed in multivariable linear regression models. Adjustments were made for sex, age, education, systolic blood pressure, total cholesterol, HDL cholesterol, body mass index, current smoking, physical activity, diabetes, coronary heart disease, and depression. Adjustment for the use of lipid- and blood pressure–lowering drugs at baseline or follow-up did not change estimates or P-values significantly; therefore, it was not included in the final analyses. Standardized regression coefficients were used as effect size to compare results between models and between each cognitive test. The model assumptions were confirmed by graphical inspection of residuals. Possible two-way interactions were assessed by adding to the models cross product terms between each of the carotid variables and each of the adjustment variables. No significant interaction was seen except between age and the number of plaques on the verbal memory test and the tapping test, and between age and the total plaque area and sex and the total plaque area on the tapping test in analyses of the total cohort. No interaction was seen in analyses of the subgroup with repeated cognitive testing. Multicollinearity between the independent variables was low, with a variance inflation factor <1.4 for all variables. Differences in estimates between gender were small; therefore, results are presented for the total population.

**Results**

Baseline characteristics of the total cohort followed for 7 years from baseline to the 5th survey and the subgroup followed for 13 years with cognitive retesting in the 6th survey are presented in Table 1. Compared with the total cohort, the subgroup followed for 13 years were younger at baseline (mean age, 56.9 vs. 59.0 years) and had a slightly better health profile and less carotid atherosclerosis.

The change in the number of plaques and total plaque area over 7 years is shown in Table 2. The presence of plaques increased from 44.5% to 61.0%, the average total plaque area increased from 8.7 to

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of the total cohort and the subgroup</th>
<th>Total cohort</th>
<th>Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, woman</td>
<td>2201 (51.5)</td>
<td>1035 (50.7)</td>
</tr>
<tr>
<td>Age, years</td>
<td>59.0 (9.7)</td>
<td>56.9 (8.7)</td>
</tr>
<tr>
<td>Education:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary/secondary/modern secondary school</td>
<td>2206 (51.6)</td>
<td>936 (45.8)</td>
</tr>
<tr>
<td>Technical/middle/vocational/senior high school</td>
<td>1105 (25.9)</td>
<td>570 (27.9)</td>
</tr>
<tr>
<td>High school diploma or college/university &lt;4 years</td>
<td>620 (14.5)</td>
<td>340 (16.7)</td>
</tr>
<tr>
<td>College/university ≥4 years</td>
<td>343 (8.0)</td>
<td>196 (9.6)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>124.2 (21.2)</td>
<td>139.3 (19.3)</td>
</tr>
<tr>
<td>Total cholesterol, mM</td>
<td>6.71 (1.3)</td>
<td>6.64 (1.2)</td>
</tr>
<tr>
<td>HDL cholesterol, mM</td>
<td>1.55 (0.4)</td>
<td>1.55 (0.4)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.0 (3.7)</td>
<td>25.9 (3.4)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>1294 (30.3)</td>
<td>570 (27.9)</td>
</tr>
<tr>
<td>Physically active</td>
<td>2270 (53.1)</td>
<td>1128 (55.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>88 (2.1)</td>
<td>28 (1.4)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>91 (2.1)</td>
<td>32 (1.6)</td>
</tr>
<tr>
<td>Depression</td>
<td>165 (3.9)</td>
<td>82 (4.0)</td>
</tr>
<tr>
<td>Carotid ultrasound measures:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque presence</td>
<td>1902 (44.5)</td>
<td>773 (37.9)</td>
</tr>
<tr>
<td>Number of plaques:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2372 (55.5)</td>
<td>1269 (62.1)</td>
</tr>
<tr>
<td>1</td>
<td>1204 (28.2)</td>
<td>513 (25.1)</td>
</tr>
<tr>
<td>2</td>
<td>499 (11.7)</td>
<td>203 (9.9)</td>
</tr>
<tr>
<td>≥3</td>
<td>199 (4.7)</td>
<td>57 (2.8)</td>
</tr>
<tr>
<td>Total plaque area (mm²)</td>
<td>8.7 (15.2)</td>
<td>6.3 (11.9)</td>
</tr>
</tbody>
</table>

Values are mean (SD) for continuous variables and n (%) for categorical variables.

| Table 2 Plaque progression from the 4th to the 5th survey in the total cohort, The Tromsø study |
|---------------------------------------------------------------|-------------|----------|
| Age | 59.0 (9.7) | 66.0 (9.7) |
| Plaque presence (yes/no) | 1902 (44.5) | 2607 (61.0) |
| No. of plaques | | |
| 0 | 2372 (55.5) | 1667 (39.0) |
| 1 | 1204 (28.2) | 1190 (27.8) |
| 2 | 499 (11.7) | 852 (19.9) |
| ≥3 | 199 (4.7) | 565 (13.3) |
| Total plaque area, mm² | 8.7 (15.2) | 14.8 (19.5) |

Values are mean (SD) for continuous variables and n (%) for categorical variables.
14.8 mm$^2$, and there was a shift toward a higher number of plaques between the surveys.

In all cognitive tests, we observed a decline in average test results over 6 years from the 5th to the 6th survey (Table 3). The number of subjects who had a follow-up testing in each test is given in the table.

Table 3 shows the association between the average survey4–survey5 number of plaques and total plaque area and the change in plaque numbers and total plaque area from survey 4 to survey 5 and cognitive test scores in survey 5 in a regression model adjusted for sex, age, education, depression, and cardiovascular risk factors. Progression of both total plaque area and plaque numbers was independently associated with lower scores in the digit-symbol coding test and the tapping test at follow-up. The average survey4–survey5 number of plaques and total plaque area were associated with lower scores in all cognitive tests. No associations were found between the average survey4–survey5 plaque scores or progression of plaque scores and decline in cognitive test scores between 5th and 6th surveys (Table 5).

### Discussion

The main results in this study were that the average survey4–survey5 number of plaques and total plaque area were associated with lower scores in all cognitive tests and the progression of total plaque area and plaque numbers was associated with lower scores in the digit-symbol coding test and the tapping test, but not in the verbal memory test. No associations were found between carotid plaque scores and cognitive decline in a subgroup followed for 13 years.

To our knowledge, no other population-based studies have examined the progression of carotid atherosclerosis in relation to cognitive test results. The associations found between the average survey4–survey5 carotid plaque scores and lower cognitive test results and the progression of carotid plaque scores...
and lower scores in two cognitive tests in the 5th survey are in line with the results from some previous epidemiological studies that have assessed the impact of a one-time measure of atherosclerosis on cognitive function. One cross-sectional study found that subjects with carotid stenosis (≥35%) performed weaker on cognitive tests than subjects without stenoses [14], and in a large cohort study, a high-grade stenosis (≥75%) in the left carotid artery at baseline was seen as a significant predictor of cognitive decline. The results were independent of vascular changes on brain MRI [15]. Several population-based studies of elderly subjects (>65 year) have found associations between carotid IMT in the CCA and ICA and subsequent cognitive decline [16,17], but conflicting results were found in middle-aged populations. Two studies found no association between baseline mean carotid IMT and cognitive decline after 6- and 14-year follow-up [5,6], whereas one study found that mean carotid IMT at baseline was significantly associated with poorer cognitive test performance after 4-year follow-up, independent of MRI markers of silent cerebral infarcts or white matter hyperintensities [3].

Some studies have also found that high carotid IMT could predict AD. In the Rotterdam Study, the risk of AD was increased in the highest quintile of CCA-IMT compared with the lowest quintile (HR, 1.54; 95% CI, 1.03–2.30) after 9-year follow-up in 5399 subjects, but carotid plaque number at baseline did not predict dementia [18]. Similar results were found in the Cardiovascular Health Study where the highest quartile of baseline IMT in the CCA and ICA, but not carotid stenosis, was associated with increased risk of AD [19]. One clinical study of 66 patients with AD found that the progression of carotid plaques over 12 months correlated with increased cognitive impairment [14].

Only the right carotid artery was examined in our study. Previous epidemiological and clinical studies have found that left carotid stenosis, in contrast to stenosis on the right side, is more strongly associated with lower performance on cognitive tests involving language [20] and on the Modified Mini-Mental State Examination [15], and with the progression of AD assessed by Mini-Mental State Examination [21]. This could be one reason why no association was found between the progression of atherosclerosis of the right carotid artery and the verbal memory test, whereas the digit-symbol coding test and the tapping test that assess both left and right hemispheric pathology were associated. However, in a previous study, we found that both high number of plaques and total plaque area at baseline were associated with lower scores on the verbal memory test after 7-year follow-up [22], and the average plaque scores between baseline and follow-up in the present study were associated with scores in all cognitive tests and seem like better predictors for cognitive test results than both the change in plaque scores and baseline plaque scores. This could be due to the measurement errors when assessing change in measurements, whereas an average score may align these errors.

We found no association between carotid atherosclerosis and cognitive decline. Even though there was 7–8% decline in test scores in the verbal memory test and the tapping test, this is not much more than the expected effect of aging [22]. The prevalence of dementia and cognitive decline mainly increases from the age of seventy, which was the mean age at the second cognitive testing, and may explain why cognitive decline was modest [23]. Lower statistical power in the smaller subgroup combined with modest effects of carotid atherosclerosis on cognitive test scores may also have influenced the lack of association. The small decline observed in scores in the digit-symbol coding test could be caused by measurement errors.

Several possible mechanisms may explain the association found between carotid plaque progression and lower scores in the digit-symbol coding test and the tapping test. Individuals with a confirmed stroke were excluded from our study, but embolisms from carotid atherosclerosis could cause silent strokes leading to vascular cognitive impairment [24]. Carotid atherosclerosis may also act as a marker of intracerebral atherosclerosis, cerebral small vessel disease, or microangiopathy with reduced intracerebral perfusion as a result. Small vessel disease and MRI detectable white matter lesions have been associated with cognitive decline [25]. However, three population-based studies found significant associations between carotid stenosis and reduced cognitive function independently of lesions detected on brain MRI [3,14,15]. Theoretically, neuropsychological test results could be more sensitive to microembolic lesions than MRI. Cerebral hypoperfusion owing to high-grade stenosis (>70%) could be a possible mechanism for lower cognitive scoring, but as the prevalence of high-grade stenosis in the general population is low, this is less likely [26]. In addition to the possible effect of subclinical carotid atherosclerosis on silent ischaemic cerebral lesions in this study, the association between carotid atherosclerosis and cognitive test results could perhaps relate to AD pathology as cases with mild cognitive impairment because of preclinical AD and some cases with early AD probably were included in our general population cohort. Associations between carotid atherosclerosis and AD have been found in previous studies [18,19], and two large autopsy studies found an association between...
intracranial atherosclerosis and Alzheimer’s pathology [27,28], whereas one did not [29]. The large sample size, repeated assessment of sensitive cognitive tests, standardized carotid ultrasound measurements, and the prospective design are the major strengths of this study. Some degree of selection is likely to have occurred because of lower participation rate amongst persons with dementia at baseline and persons who developed dementia during follow-up. MRI of the cohort would have added valuable information to the interpretation of our results, but was not feasible in this setting. We mainly studied Caucasians, and generalizability could be restricted by ethnicity.

Conclusion

The average survey4–survey5 carotid plaque scores were associated with lower scores in all cognitive tests in the 5th survey. Progression of total plaque area and plaque number was associated with lower scores in the digit-symbol coding test and the tapping test, but not in the verbal memory test. No associations were found between carotid plaque scores and cognitive decline in a subgroup followed for 13 years.

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Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

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