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Measurement of carotid plaque burden: A tool for predicting and preventing dementia?

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ABSTRACT

Introduction: Carotid plaque burden is a strong predictor of stroke risk, and preventing stroke reduces the risk of dementia. Treating carotid plaque burden markedly reduces the risk of stroke.

Methods: Among patients age 65–80 years attending a stroke prevention clinic, we identified those with a carotid plaque burden in the top 20% of Total Plaque Area (High TPA) and the bottom 20% (Low TPA) and performed cognitive tests: The Montreal Cognitive Assessment test (MoCA), the WAIS-III Digit Symbol-Coding Test (DSST) and Trail-Making Test (TMT) part A and B.

Results: There were 31 patients recruited; 11 Low TPA (5 men) and 20 High TPA (17 men), $p = 0.04$. TPA was 35 ± 25 mm^2 in the Low TPA vs.392 ± 169 mm^2 in the High TPA group (0.0001). Patients with a high plaque burden had significantly worse performance on all the cognitive tests, all $p < 0.05$

Discussion: A high carotid plaque burden identifies patients at risk of cognitive impairment. Because carotid plaque burden is treatable, and treating it markedly reduces the risk of stroke, we suggest that measurement of plaque burden is a useful tool for both prediction of cognitive impairment, and prevention of dementia.

1. Background

It is well established that hypertension is a major risk factor for cognitive dysfunction [1]. Indeed, management of hypertension can decrease the 5-year progression of dementia by half in patients presenting with executive dysfunction [2], and reduce .dementia due to Alzheimer's Disease (AD) by half [3]. In the Nun Study [4], participants with AD pathology and silent infarction were more than 20 times more likely to have been demented during life than those with equivalent AD pathology but without an infarct [4].

A third of community-dwelling elderly persons with intermediate and high level of AD pathologies are not yet demented [5], but they are at high risk of dementia, and targeted treatment of vascular risk factors can prevent or delay their cognitive decline [6].

Besides hypertension, atherosclerosis is a common cause of stroke. Persons with atherosclerosis in the circle of Willis had a greater prevalence of AD, and arterial stiffness—a marker of arterial disease—was strongly associated with cognitive decline [7,8]. Silent strokes are highly prevalent, affecting 6–28% of the general population, and markedly increase the risk of cognitive impairment and the development of dementia [4,6].

The Rotterdam Scan Study, a population-based study of participants aged 60–90 years old, found that approximately 75% of silent strokes were lacunar infarctions in the basal ganglia [9].

The Tromsø study related carotid plaque area to prediction of lower scores on tests of verbal memory [10], but the participants were healthy volunteers with a much smaller plaque burden than our vascular patient population [11], and executive function was not assessed. In the Northern Manhattan study, another population-based study with less severe atherosclerosis than our patients, carotid plaque burden was not associated with impaired cognitive function [12].

We reported in 2002 that carotid plaque burden, measured as total plaque area (TPA) by ultrasound, is a strong predictor of risk of stroke, myocardial infarction, and vascular death. After adjustment for

Abbreviations: ADAS, Alzheimer's Disease Assessment Scale; ANOVA, Analysis of variance; DSST, WAIS-III Digit Symbol-Coding Test; MMSE, Mini mental state examination; MOCA, Montreal Cognitive Assessment test; SPARC, Stroke Prevention & Atherosclerosis Research Centre; TMT, Trail-Making Test; TPA, Carotid Total Plaque Area.

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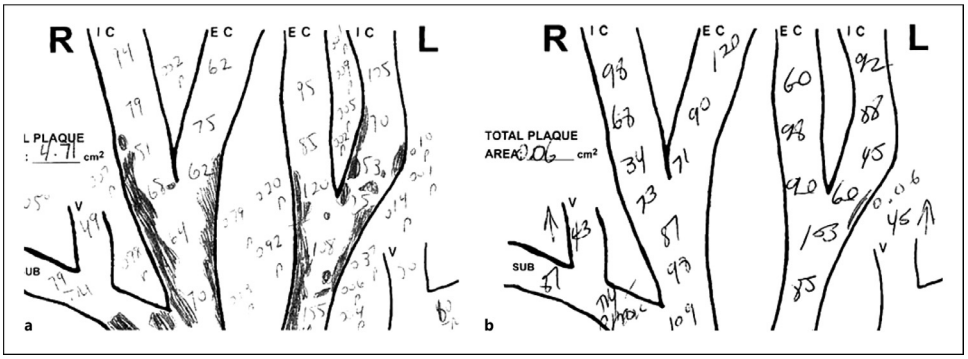

Fig. 1. Examples of patients with high vs. low carotid total plaque area (TPA)
These are composite drawings of plaques in the carotid arteries, from ultrasound reports. The black areas represent plaques in the wall of the artery; the numbers in the lumen represent peak velocity in cm/s.
a. A 79-year old woman with 471 mm^2 of plaque; 9 times normal for age and sex. b. A 72-year old man with only 6 mm^2 of plaque; normal for age and sex would be 40 mm^2.
(Reproduced by permission of Karger Publishers from: Bogiatzi C, Wannarong T, McLeod AI, Heisel M, Hackam D, Spence JD. SPARKLE (Subtypes of Ischaemic Stroke Classification System), incorporating measurement of carotid plaque burden: a new validated tool for the classification of ischemic stroke subtypes. Neuroepidemiology. 2014;42(4):243–51.

age, sex, cholesterol, blood pressure, smoking, total homocysteine, diabetes, and treatment of cholesterol and blood pressure [13], the 5-year risk of those events by quartile of TPA was 5.6%, 10.7%, 13.9%, and 19.5% [13]. That finding was validated by the Tromsø study, a Norwegian population-based study in which over 6000 participants were followed for 12 years [14,15]. Carotid plaque burden is a stronger predictor of stroke than either IMT [15] or stenosis [16,17].

Since atherosclerotic burden is such a strong risk factor for stroke, and stroke is strongly related to cognitive dysfunction, atherosclerotic burden may also be a strong predictor of dementia. Furthermore, as discussed below, treating atherosclerotic burden markedly reduces the risk of stroke [18]. Therefore, in this study, we explored whether a high carotid plaque burden is associated with impaired cognitive function.

2. Objectives

Our objective was to determine whether carotid plaque burden was associated with impairment in cognitive function.

3. Methods

This was a prospective cross-sectional study. We recruited patients being followed at the Stroke Prevention & Atherosclerosis Research Centre (SPARC) who had measurements of their carotid plaque in successive years before recruitment. We excluded any patients who were clinically suspected of already having cognitive impairment, a history of stroke, or conditions that may reduce their life expectancy below two years. The participants' data on risk factors and carotid plaque area were obtained from the clinical records of SPARC.

The participants were scheduled on the same day as their routine annual ultrasound appointments to minimize inconvenience. All subjects completed a socioeconomic status survey about their years and level of education completed, their career either at present or prior to retirement, and their annual household income. They were then guided through three cognitive assessments tasks. Tests were scored according to the guidelines provided with each test.

3.1. Study population

Participants were age 65 to 80 years, and were recruited from two groups. The low plaque burden group (Low TPA) had a TPA ≤ 40 mm^2; the high plaque burden group (High TPA) had a TPA ≥ 268 mm^2, based on the bottom 20th and the top 20th percentile of TPA of patients in our database within that age range. These conditions were in line with the Tromsø study, which found normal TPA to be 40 mm^2 in patients at age 65, 45 mm^2 at age 70–74, and 80 mm^2 at age ≥ 75 years [14,15]. Therefore, TPA in the Low TPA group was within the normal TPA range for age, while the High TPA group had a much higher TPA than the highest TPA value found in the Tromsø study. Examples of patients with high and low TPA are shown in Fig. 1

3.2. Carotid plaque measurement

Carotid TPA was measured by ultrasound as previously described [13,19], by two extremely experienced registered vascular technologists. Plaques are measured in longitudinal views, panning around the artery to find the plane in which each plaque was biggest, freezing the frame, magnifying it, and tracing the contour of each plaque with a cursor. The sum of the areas of all plaques seen from the clavicle to the angle of the jaw in both carotids and the right subclavian artery was TPA. A Philips HDI 5000 scanner was used in earlier studies and a Philips IU-22 scanner in more recent studies. Intraobserver reliability (intraclass correlation) was 0.94 for repeated measurements [13].

3.3. Assessment of cognitive function

Three cognitive tests were chosen for the assessment, in accordance with the Harmonization Standards of the US National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network, which recommended the use of test batteries that are sensitive for evaluating executive function [20]. The Montreal Cognitive Assessment test (MoCA) was used, a screening tool developed and widely used for detecting Mild Cognitive Impairment (MCI) in epidemiological studies and clinical trials. The MoCA evaluates various cognitive domains including attention, concentration, executive function, memory, language, visuospatial skills, abstraction, calculation and orientation. The WAIS-III Digit Symbol-Coding Test (DSST) is a neuropsychological test sensitive for detecting cognitive dysfunction that examines attention, visual perception, learning, and overall executive function. It consists of a key of number and symbol pairs from 1 to 9 followed by rows of blank boxes with numbers on top. The participant is asked to fill out the empty boxes with the corresponding symbols as quickly as possible in 90 s. Lastly, Trail-Making Test (TMT) part A and B are extensions of the visuo-spatial and executive function tasks in MoCA. Trail Making A (TMA) asks participants to connect numbers in circles in an ascending order while Trail Making B (TMB) asks participants to connect numbers and letters in circles in an ascending and alternating order. The time taken for the participants to complete each trail is recorded.

Cognitive tests were administered by JS, after watching training videos and being trained and certified by a research coordinator experienced in cognitive testing.

3.4. Data analysis

With regard to TMT score analysis, the scores were inversed and scaled to ~100 by multiplying by a factor of (shortest time taken)/100

Table 1
Risk factors in the low total plaque area (Low TPA) vs. high plaque area (High TPA) groups.

	Low TPA	High TPA	Significance
Continuous variables Mean ± SD			Anova
Age (years)	72.82 ± 2.67	75.75 ± 5.87	0.13
Systolic BP (mmHg)	136.82 ± 17.79	143.65 ± 18.73	0.35
Diastolic BP (mmHg)	77.36 ± 9.71	79.76 ± 10.54	0.55
Total cholesterol (mmol/L)	4.70 ± 1.40	4.31 ± 0.92	0.37
Triglycerides (mmol/L)	1.66 ± 1.18	1.79 ± 1.06	0.77
HDL-C (mmol/L)	1.55 ± 1.18	1.34 ± 0.30	0.15
LDL-C (mmol/L)	2.35 ± 1.23	2.12 ± 0.87	0.56
Creatinine (μmol/L)	78.22 ± 19.48	90.06 ± 23.29	0.21
Hemoglobin A1C (%)	5.81 ± 0.32	6.00 ± 0.8	0.52
Total homocysteine (μmol/L)	11.83 ± 3.05	13.09 ± 5.09	0.41
Smoking (pack-years)	1.82 ± 6.03	22.33 ± 19.33	0.002
Carotid total plaque area (mm^2)	35 ± 25	392 ± 169	0.0001
Categorical variables (N%)			Chi-Square
Men	5 (45%)	17 (85%)	0.04
Smoker: Never	10 (91%)	6 (30%)	0.005
Quit	1 (9%)	11 (55%)	
Still smoking	0	3 (15%)	
Diabetic	1 (9%)	3 (15%)	1

BP, blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

in order to take into account that a longer time taken to complete the task is a poorer score. When calculating the composite score of the three cognitive assessments, the raw MoCA and DSST scores were first scaled to ~100 by multiplying by a factor of 100/(top score), and then summated with the scaled scores of TMT. Scaling the scores to 100 allowed for a relatively equal weighting of each cognitive test. To determine the significance of the data, one-way ANOVA was conducted using IBM SPSS version 25.

3.5. Ethics

The study was approved by the Western University Human Subjects Research Ethics Board, protocol number 104473. Participants all gave signed informed consent.

4. Results

We recruited 31 patients; 11 in the low TPA group (5 men) and 20 in the high TPA group (17 men); $p = 0.04$. Mean age was 70 years in the low TPA group and 72 years in the high TPA group. TPA was 35 ± 25 mm^2 in the Low TPA vs.392 ± 169 mm^2 in the High TPA group (0.0001). There were few significant differences between the two groups for various measures of vascular risk factors (Table 1).

The high TPA group had poorer cognitive abilities as assessed by all three cognitive tests. On the MoCA test, the high TPA group had a mean score of 22.26, which was significantly lower compared to the mean score of 26.00 for the low TPA group ($P<0.05$). According to the MoCA guideline, the standard for a normative score is any score greater than 25, which indicates that the mean score of the low TPA group was in the normal range while the mean score of the high TPA group was in the abnormal, or early cognitive dysfunction range [21]. Similarly, the high TPA group had poorer performance in the executive function-sensitive tests.

For the DSST, the high TPA group had a mean score of 28.68 while the low TPA group had a mean score of 39.75; the high TPA group had significantly worse mean scores ($P<0.05$, one-way ANOVA). However, both mean scores were within normative standards [22]. For the TMT, the high TPA group had better mean scores of 48.71 and 41.49 s for part A and B respectively, while the low TPA group had worse mean scores of 68.25 and 72.63 s ($P<0.05$, one-way ANOVA). According to Tombaugh et al., for TMT a normative range for people aged 65–90 was 33.84–63.46 s for part A, and 67.12–167.69 s for part B [23]. Prior to scaling the scores, the high TPA group had mean times of 72.85 s and 267.11 s for part A and B respectively, while the low TPA group had mean times of 43.94 s and 127.21 s. Therefore, while both groups were within the normal range or better for part A, only the high TPA group was outside the normal range for part B, which indicates executive dysfunction.

Overall, the cognitive abilities of the high TPA group were significantly worse compared to the low TPA group; their composite score of the three cognitive assessments was 27.8% lower ($P<0.05$, one-way ANOVA). Fig. 2 compares results of the cognitive tests in the low TPA and high TPA groups.

5. Discussion

We found that high carotid plaque burden was strongly associated with cognitive impairment. Our findings are compatible with a report from the Rotterdam study, in which carotid plaque burden was not measured, but vessel wall thickness and the presence of plaques in the carotid arteries assessed by ultrasonography, and the ratio of ankle-to-brachial systolic blood pressure were associated with the diagnosis of AD [24].

The high TPA group, with plaque area in the top quintile, performed significantly worse on the MoCA test, demonstrating a substantial deficit in various cognitive abilities ($P<0.05$, one-way ANOVA). Moreover, while the mean score of the low TPA group was within the normal range, the mean score of the high TPA group was within the dementia range. This exhibits a strong association between high TPA and a greater prevalence of dementia, as the MoCA test is known to show excellent sensitivity in detecting MCI and AD, at 90% and 100% respectively [21].

Similar results were found for the executive dysfunction-sensitive DSST and TMT tests. Subjects in the high TPA group had significantly poorer scores on both assessments and were outside the normal range in TMB, signifying executive function impairments ($P<0.05$, one-way ANOVA). The findings were in accordance with previous results from our clinic, which showed that greater carotid plaque burden was associated with an increased prevalence of neurodegenerative events [22]. Although a strong relationship between carotid plaque burden and cognitive function was observed, the underlying mechanism is unclear. There are, however, a number of possible explanations for the observed association.

The MoCA assessment includes a variety of tasks that require the activation of several parts of the brain. The major brain structures involved are the four major lobes of the cerebral cortex, as well as sub-cortical

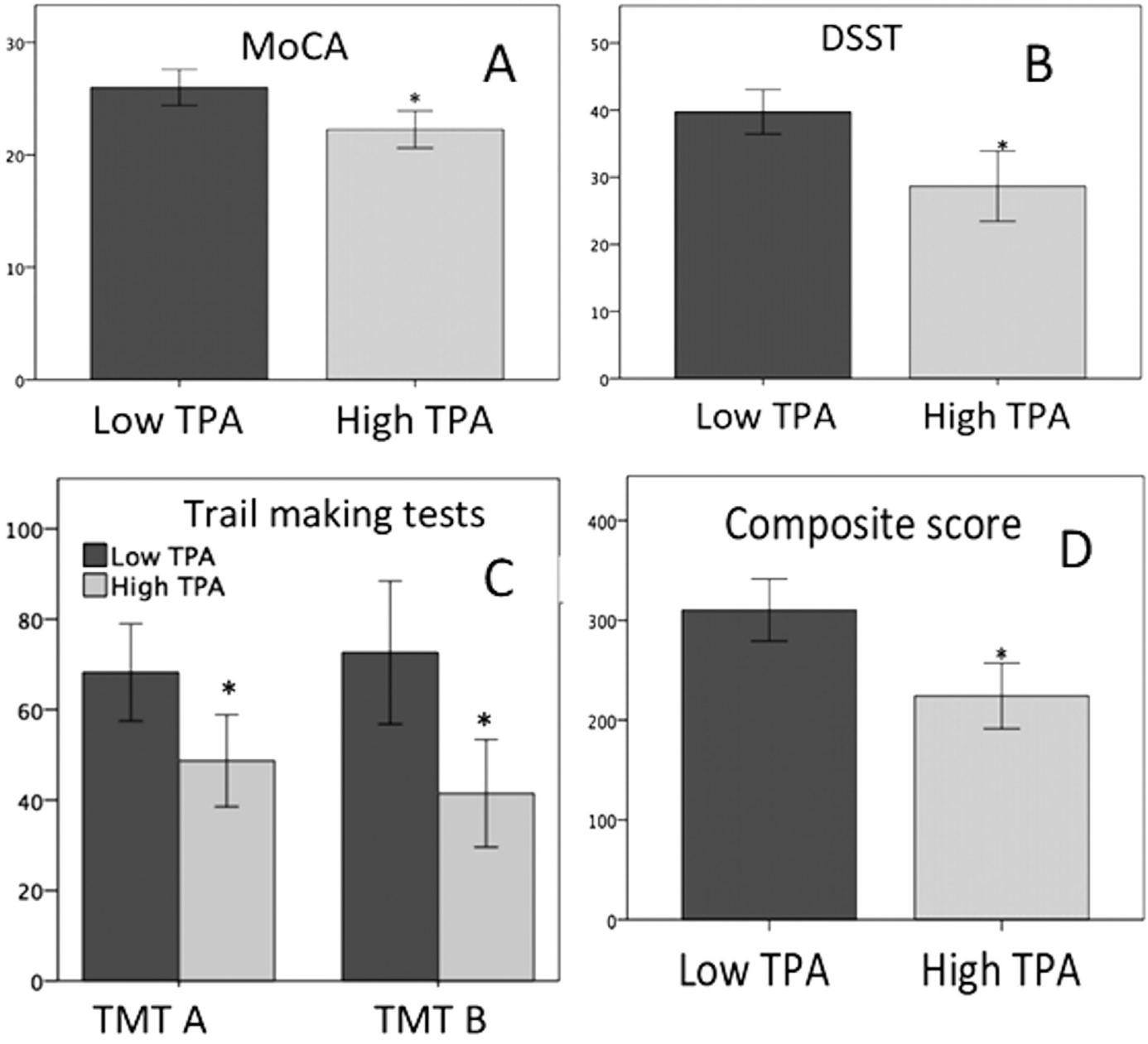

Fig. 2. Cognitive function was significantly better with low plaque burden (Low TPA) than with high plaque burden (High TPA).
A. Montreal Cognitive Assessment; MoCA; B. WAIS-III Digit Symbol-Coding Test, DSST; C. Trail making A and B test scores for the Low TPA and High TPA groups; D. A composite score combining all three tests. All $p<0.05$, ANOVA.

structures such as the hippocampus and basal ganglia [21]. A functional MRI study revealed that executive function tests require planning in the frontal lobe and integration with the visual and fine motor sequences from the fronto-parieto-occipital cortices [25]. Infarction in these regions results in deficits in cognition and increased risk for developing vascular cognitive impairment [26]. Since greater carotid plaque area is a strong predictor of stroke, it is likely that the High TPA group is also at greater risk of developing vascular cognitive impairment. In a related study, MRI scans revealed that increasing severity of lacunar strokes is related to deteriorating cognitive scores on the mini mental state examination (MMSE) and Alzheimer's Disease Assessment Scale (ADAS) [27].

Likely explanations for the observed association of atherosclerotic burden and cognitive dysfunction include the shared risk factors for atherosclerosis and dementia; most notably age; [26,28] atherosclerosis, stroke and AD pathologies commonly co-exist in autopsy specimens of longitudinal studies. Furthermore, there is an important interaction between stroke and Alzheimer disease, due to interactions of inflammation, amyloid, stroke and dementia; this topic was reviewed in 2014 [29].

6. Limitations

An important limitation is the small sample size; the reason for this is that this study was a student summer research project by JS. Nevertheless, the significant differences we observed suggest that this approach is very powerful, and that the findings would not have differed by much with a larger sample.

Secondly, while the three cognitive assessments differed, there may be overlaps in the type of cognitive ability required to complete the tasks.

While these results are preliminary, the relationship between carotid plaque area and cognitive dysfunction seems to be very strong. Therefore, measuring carotid plaque burden may be a valuable addition to the methods for identification of patients at high risk of cognitive decline. High-risk patients tend to benefit more from treatment, so improving the ability to accurately identify such patients could help focus intensive preventative therapies on patients more likely to benefit [13]. De Bruijn et al. reported from the Rotterdam study [30] that approximately a third of dementia would have been avoidable by lifestyle changes and elimination of cardiovascular risk factors. It may be possible to achieve even better results with an approach to treatment of atherosclerosis based on measurement of plaque burden.

Among high-risk patients with asymptomatic carotid stenosis, a process called “Treating arteries instead of treating risk factors” [31], based on measurement of carotid plaque burden, was associated with a >80% reduction in the 2-year risk of stroke and myocardial infarction [18]. The process of treating arteries involves intensive medical therapy, with the objective of stopping progression of plaque or achieving regression, not simply being content with achieving target levels of risk factors such as blood pressure and cholesterol. A key part of the process is showing patients images of their arteries, explaining the severity of their atherosclerosis compared to healthy individuals of the same age, and their level of risk;, that their arteries can actually improve, and that their risk can be markedly reduced by the process [32]. Two studies have reported that showing patients images of their carotid plaques markedly improves compliance with medical advice in vascular prevention [33,34]. That approach holds great promise for prevention of dementia, since preventing strokes prevents dementia [35]. Brookmeyer et al. [36] estimated that a 2-year delay of dementia would reduce prevalence of dementia by 22%, and a 5-year delay by 47%. Moreover, the process of measuring carotid plaque area itself is quick, inexpensive, reproducible and non-invasive. Thus, the inclusion of measurement of atherosclerotic burden as a tool in preventative therapy holds promise for prevention of dementia.

7. Conclusions

Greater carotid plaque burden was significantly associated with impaired cognitive function. Patients with carotid plaque area in the lowest quintile scored 27.8% lower on a composite score of cognitive function than patients in the highest quintile of plaque burden. Thus, measurement of carotid plaque burden may be useful not only as a strong predictor of cognitive dysfunction, to identify patients in whom intensive therapy of atherosclerosis may delay/prevent dementia, but also to improve the efficacy of preventive therapy. Further research would be required to assess this. A randomized controlled trial of usual care vs. intensive therapy of atherosclerosis based on measurement of plaque burden for prevention of dementia is planned.

Declaration of Competing Interest

JS, MRA, AS and VH have no interests to declare.

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