Carotid atherosclerosis and cognitive function in a general population aged 63-65 years:

Data from the Akershus Cardiac Examination (ACE) 1950 Study

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ABSTRACT

BACKGROUND: Studies on the relationship between carotid atherosclerosis and cognitive function in subjects from the general population are few and results have been inconsistent.

OBJECTIVES: We aimed to investigate the association between carotid atherosclerotic burden and cognitive function in a cross-sectional analysis of a population-based cohort aged 63-65 years..

METHODS: All habitants born in 1950 from Akershus County, Norway were invited to participate. A linear regression model was used to assess the association between carotid atherosclerosis and cognitive function. We used carotid plaque score as a measure of carotid atherosclerotic burden and the Montreal Cognitive Assessment (MoCA) for global cognitive function.

RESULTS: We analysed 3,413 individuals aged 63-65 with mean MoCA score 25.3 ± 2.9 and 87% visible carotid plaques. We found a negative correlation between carotid plaque score and MoCA score ($r = -0.14$, $p < 0.001$), but this association was lost in multivariable analysis. In contrast, diameter or area of the thickest plaque was independently associated with MoCA score. Lower educational level, male sex, current smoking and diabetes were also associated with lower MoCA score in multivariable analysis.

CONCLUSION: Carotid atherosclerotic burden was, unlike other measures of advanced carotid atherosclerosis, not independently associated with global cognitive function.

Keywords: Atherosclerosis, Carotid plaque, Cognition, Cognitive function, Montreal Cognitive Assessment, Cardiovascular risk factors

INTRODUCTION

The number of people with cognitive impairment and dementia is expected to surge in the coming decades due to a large increase in number of older adults [1]. Understanding the etiology and identifying risk factors for cognitive impairment is the first step towards prevention strategies and potential treatment. Several studies over the past decades have emphasized the importance of vascular risk factors in the development of cognitive impairment, and modifiable cardiovascular risk factors like hypertension, diabetes, obesity, hypercholesterolemia, smoking and atrial fibrillation in midlife have been identified as predictors of dementia in later-life [2-6]. Established atherosclerosis has also been identified as an independent risk factor for dementia [7-14].

The extent to which atherosclerosis is related to cognition is not fully understood. There is uncertainty whether atherosclerosis has an impact on cognition in dementia-free individuals [15]. While end-stage and occlusive atherosclerosis have been linked to poorer cognitive performance in dementia-free individuals [12, 16], the evidence is scarce and conflicting for subclinical atherosclerosis defined as the presence of carotid plaques or increased intima-media thickness (IMT) [15, 17].

Subclinical atherosclerosis begins early in life and develops slowly over time [18], and is commonly studied in the carotid arteries using ultrasound. We have previously reported that that carotid atherosclerosis is frequent at the age of 65 years as almost nine out of 10 subjects have detectable atherosclerotic plaques located in the carotid arteries [19].

Few studies have investigated to which extent subclinical carotid atherosclerosis contribute to reduced cognitive performance in subjects without known cognitive impairment [20, 21].

Accordingly, we aimed to explore if carotid atherosclerosis at the age of 65 years was associated with cognitive performance in an unselected cohort from the general population. In addition, we investigated the association between cardiovascular risk factors and cognitive function.

MATERIALS AND METHODS

Participants

The Akershus Cardiovascular Examination (ACE) 1950 study is a prospective population-based cohort study of the cerebrovascular and cardiovascular health of all men and women born in 1950 in Akershus County, Norway.

All eligible subjects were invited to participate, and were upon acceptance examined at one of the two hospitals in the region, Akershus University Hospital or Bærum Hospital, in the period between 2013-2015. The study design has been published previously [22]. After inviting 5,827 individuals, a total of 3,706 accepted the invitation and were enrolled in the ACE 1950 study (attendance rate 64%). The present study is a cross-sectional analysis of the cohort at baseline, and included all 3,413 participants completing the Montreal Cognitive Assessment (MoCA) test. The 293 subjects without results were not capable (language difficulties, n=73), not willing to perform the test (n=213), or were excluded due to self-reported cognitive impairment (n=8). The study was approved by the Regional Committees for Medical and Health Research Ethics in Norway (Reference number 2011/1475). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and all participants signed a written, informed consent before entering the study.

Carotid atherosclerosis and carotid plaque burden

B-mode ultrasound examination of the extra-cranial arteries was performed to assess atherosclerosis using a Vivid E9 machine (GE Healthcare, Horten, Norway). The carotid ultrasound protocol is described in detail elsewhere [19]. Atherosclerosis was defined according to the latest version of the

Mannheim Carotid Intima-Media Thickness and Plaque Consensus, as a local thickening of the IMT of >50% compared to the surrounding vessel wall, an IMT>1.5 mm, or a local thickening >0.5 mm, as measured from the media-adventitia interface to the intima-lumen interface [23]. We aimed to explore if carotid atherosclerotic burden was associated with cognitive performance measured with the MoCA test. In order to quantify the total carotid atherosclerotic burden, we calculated a carotid plaque score, used as the main explanatory variable in the present study. Increasing carotid plaque score is regarded as a surrogate measure of increasing cardiovascular burden and vascular disease, and a plaque score is, unlike measuring total plaque area, easy to perform and less operator-dependent [18]. Briefly, the carotid artery was divided in four segments on both sides (common carotid artery, bifurcation, internal and external carotid artery), and plaques were assessed in each segments. The largest plaque in each segment was given a point score. Plaque diameters ≥ 1.5 , ≥ 2.5 , and ≥ 3.5 mm were given 1, 2, and 3 points, respectively, from 1-3. The total carotid plaque score was calculated as the sum of the scores of each segment, ranging from a minimum of 0 points to a maximum of 24 points [24]. In addition the diameter and area of the thickest plaque were manually measured. Inter-rater and intra-rater reliability test was performed twice during the inclusion period, both with excellent results (Cronbach`s kappa 0.999).

Cognitive function

Cognitive function was assessed with the MoCA test, a brief screening instrument of global cognitive function [25]. The score varies between zero and 30, and higher score denotes better cognitive function. MoCA was originally developed to detect mild cognitive impairment [25], and cognitive deficits in persons with increased cardiovascular risk [26], which makes the MoCA test suitable for the study purpose.

Cardiovascular risk

Hypertension was defined as the mean systolic blood pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg in sitting position after 10 minutes' rest or use of blood pressure lowering agents [27].

Diabetes was defined as a self-reported diagnosis or, use of antidiabetic agents, or glycated hemoglobin A1c (HbA1c) ≥ 6.5 % and fasting plasma glucose ≥ 7.0 mmol/L [28]. Obesity was defined as body mass index (BMI) ≥ 30 kg/m². Hypercholesterolemia was defined as total cholesterol ≥ 6.2 mmol/L and/or Low-Density-Lipoprotein (LDL) cholesterol ≥ 4.1 mmol/L [29], or use of lipid-lowering agents. Current medication, history of stroke and smoking were self-reported. Physical inactivity was self-reported with the answer "never" to the multiple choice question "How often do you exercise?". Atrial fibrillation (AF) was self-reported and validated by ECG documentation in hospital records or at baseline. Higher education was defined as > 12 years of formal education.

Statistics

Descriptive demographic and clinical measures are shown as mean $\pm$ standard deviation (SD), or as numbers and frequencies as appropriate. Student's t-test was used to compare means of continuous variables and the Chi-square test was used to compare categorical variables. The plaque score showed a right-skewed distribution. However, the large number of subjects provided good approximation to normal distribution, so that the association between carotid plaque score and the MoCA test was assessed by the Pearson product-moment correlation coefficient. The linear regression assumptions were not violated as MoCA test score residuals were approximately normally distributed, the variance of error terms were similar across the values of the independent variables (homoscedasticity) and there were no pairs of independent variables with high correlation (no multicollinearity). Variables with a p-value $p \leq 0.1$ in univariable analysis were included in multivariable analyses. A significance level was set at $p < 0.05$. As education level is known to influence MoCA test performance [30-34], a hierarchical multiple regression was used to assess the amount of variation before and after entering education in the model. Further, a three-step mediation analysis was performed to investigate whether cardiovascular risk factors (diabetes and smoking) affect cognition in part through

atherosclerosis. First, MOCA was regressed on the risk factors (step 1). Then, atherosclerosis was regressed on the risk factors (step 2). Finally, MOCA was regressed on both the risk factors and atherosclerosis (step 3). The Sobel test was used to examine whether the coefficients of the risk factors were significantly reduced after inclusion of atherosclerosis (i.e from step 1 to step 3), which would indicate partial mediation of the effect of the risk factors on MOCA through atherosclerosis. . All analyses were performed using IBM SPSS Statistics for Windows version 25.0.

RESULTS

Characteristics

The mean age of the study population was 63.9 ± 0.6 years, and 1,639 (48%) were women. Higher education was reported among 1,615 (47%). The mean MoCA score was 25.3 ± 2.9 . Atherosclerotic carotid plaques were detected in 2,977 (87%) subjects. The median plaque score was 2 (interquartile range [IQR] 3), mean diameter of the thickest carotid plaque 2.4 ± 0.7 mm, and the mean area of the thickest plaque 16.6 ± 11.2 mm². Women achieved a higher MoCA score, and had lower prevalence of cardiovascular risk factors and a lower plaque score compared to men. Prevalence of cardiovascular risk factors and comorbidities are presented in Table 1.

Carotid plaque and cognition

Increasing carotid plaque score was associated with decreasing MoCA scores (Figure 1), with a weak but significant negative correlation between carotid plaque score and MoCA score ($r = -0.14$, $p < 0.001$). Participants without any detectable atherosclerotic plaque had significantly higher MoCA score (25.6 ± 2.8) compared to their counterparts (25.2 ± 3.0 , $p = 0.008$). Individuals with a plaque score > 4 (representing the quarter with the highest carotid atherosclerotic burden) had significantly lower mean MoCA score (24.9 ± 3.0) compared to those with a plaque score ≤ 4 (25.4 ± 2.9 , $p < 0.001$).

In linear univariable analysis, carotid plaque score showed a significant association with reduced MoCA score; B -0.14, 95% CI -0.19- -0.09, $p < 0.001$. However, the association did not persist in multivariable analysis (Table 2). In the multivariable analysis, in descending order of impact, lower education level (B -1.72, 95% CI -1.91- -1.53, $p < 0.001$), male sex (B -0.53, 95% CI -0.73- -0.34, $p < 0.001$), current smoking (B -0.45, 95% CI -0.74- -0.17, $p = 0.002$) and diabetes mellitus (B -0.42, 95% CI -0.78- -0.07, $p = 0.02$) were independently associated with decreasing MoCA score. The mediation model suggest that the effect of smoking and diabetes on the MoCA score were partly mediated through plaque score ($p < 0.001$) (Table 3 and Figure 2). The variance explained by our model changed from 3% to 11% after adding educational level. If carotid plaque score was replaced with diameter of thickest plaque (B -0.17, 95% CI -0.32- -0.01, $p = 0.04$) or area of the thickest plaque (B -0.02, 95% CI -0.03- -0.01, $p = 0.001$) as explanatory variable respectively, the association with MoCA score remained statistically significant in multivariable analysis (Table 2). Other variables remained unchanged. Although women had higher MoCA score and lower plaque score, we could not find any statistically impact of gender in the relation plaque score to MoCA score ($p = 0.98$).

DISCUSSION

In our cohort from the general population aged 63-65 years, a nearly linear association between carotid plaque score and MoCA score was observed in univariate analysis. In multivariable analysis, lower educational level, male sex, current smoking and diabetes remained independently associated with lower MoCA scores, while carotid plaque score was no longer significant. Mediation analysis suggested that the effect of diabetes and smoking on cognitive performance was partly mediated by atherosclerosis.

We failed to show that carotid atherosclerotic score as a continuous variable was independently associated with cognitive performance. Adjusting for cardiovascular and lifestyle variables resulted in a change in effect estimate and loss of significance. However, previous studies have shown that atherosclerosis is independently associated with reduced cognitive performance, but these studies have used other neuropsychological tests and different definitions of atherosclerosis, or have failed to perform multiple adjustments [11, 15, 20, 21, 35, 36]. The heterogeneity in available data complicates comparison between studies. However, our results showed that other markers of advanced atherosclerosis such as diameter and area of the largest plaque remained significant after multiple adjustments. This suggests that mean plaque score is a less sensitive marker compared to area and diameter of the thickest plaque. To summarize, our findings confirm previous studies, suggesting that carotid atherosclerosis is weakly correlated with MoCA test score [11, 15] and indicating that those with advanced atherosclerotic disease may have an increased risk of reduced cognitive performance [16, 37].

Presence of carotid plaque was common in our study population, but only a relative small proportion had a high carotid plaque burden. This clustering around a plaque score of 1-3 may be the reason why we failed to detect a significant association between carotid plaque score and global cognitive function when adjusting for confounders.

Chronic vascular pathology is primarily known to affect subcortical brain areas and frontal lobe functions. Measures of executive functions, psychomotor speed, mental flexibility and attention have been linked to vascular pathology [38]. For this reason, most previous studies have used domain-specific cognitive tests to assess the impact of atherosclerosis on cognition [11, 15]. Memory has been linked to atherosclerosis because the mesial temporal lobes are vulnerable to hypoperfusion [39]. Our use of a global function test could possibly explain why the results of previous studies were not replicated in the present study.

Our results show a strong association between cardiovascular risk factors and cognitive performance. Individuals affected by vascular risk factors, such as diabetes, before old age occurs, are at increased risk of cognitive impairment in late life, but only a few studies have documented an association between cardiovascular risk and cognitive performance before old age occurs [40]. Our data support that the presence of cardiovascular risk factors, particularly smoking and diabetes, already before the age of 65 years, is associated with reduced cognitive ability. Lower education, male sex and smoking were the variables with the greatest impact on cognitive performance. This is in line with a recent Lancet Commissions paper, reporting that 35% of the risk of dementia can be attributed to modifiable risk factors. The four most important risk factors are; ApoE ϵ 4, early hearing loss, lower education and smoking [41].

Mechanisms leading to cognitive impairment are complex, and cardiovascular risk factors such as diabetes and smoking may exert their negative effects on cognition in part through increased atherosclerosis. In our study, the total effect of carotid atherosclerosis and cardiovascular risk factors on MoCA performance was relatively small. Only 3% of the variance was explained by the variables in our model, before education was added to the model. Such minor effects are most likely not of clinical importance. However, in a multifactorial disease, risk factors may have an additive effect, and we hypothesize that cardiovascular risk factors could impact subclinical cognitive disease development by mechanisms not explained by association studies. For this reason, and based on current understanding and evidence, we may still suggest that prevention of atherosclerosis and cardiovascular risk factors is paramount in preserving brain health.

In line with other studies, we found that men had a higher burden of cardiovascular risk factors than women. Premenopausal women tend to have lower age-specific risk due to the protective effect of estrogen, and experience a postmenopausal exponential increase, while men have a more linear progression of cardiovascular risk throughout life [42]. Furthermore, the education level was higher

among men, compared to women. Still, the MoCA score was significantly higher among women. An effect of sex on MoCA performance, even after adjusted for education, has been described previously [34]. However, with this sample size we could not observe any sex differences in the association between carotid plaque score, cardiovascular risk factors and MoCA score.

Associations identified by a cross-sectional study design may be difficult to interpret, and the design is susceptible for recall bias and selection bias. However, a participation rate of 64% is acceptable, and in line with other population-based studies in Norway and internationally [43-45]. The mediation analysis indicates that the negative effect of diabetes and smoking is partly mediated through atherosclerosis, although caution should be taken to such causal inferences in cross-sectional studies. The study population had a narrow age range, 63-65 years, and the results cannot be generalized to other age groups. Further, we did not collect information about the participant's cognitive function from family members or friends, hence cognitive changes and impairment may be underreported. The present study use definition of cardiovascular risk factors according to the current guidelines. The definitions does not distinguish between satisfactory controlled risk factors or not, and does not take into account the actual time of onset of drug treatment. This may have affected result. The strength of the study is first of all the large number of participants from an unselected population, the assessment of the carotid artery at both sides, systematic measures of carotid plaque, and the multiple adjustments performed. Whether each unit in the MoCA test score represent equal value and thus makes this variable suitable for use in linear regression analysis could be disputed; however given the linear relation of the MoCA scores in relation to plaque score in our cohort we believe that the linear regression analysis gives the best representation of our data.

CONFLICTS OF INTEREST:

The authors have no conflict of interest to report

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Table 1: Baseline characteristics

Characteristic	Total (n=3,413)	Men	Women	P value
Sex	3,413 (100)	1,774 (52.0)	1,639 (48.0)	<0.001
Age	63.9±0.65	63.9±0.66	63.9±0.63	0.174
Cardiovascular risk factors				
Hypertension	2,103 (61.6)	1171 (66.0)	932 (56.9)	<0.001
Hypercholesterolemia	1,796 (52.8)	894 (55.2)	902 (50.5)	0.016
Diabetes	276 (8.1)	195 (11.0)	81 (4.9)	<0.001
Obesity	775 (22.7)	424 (23.9)	351 (21.4)	0.083
Atrial fibrillation	151 (4.4)	111(6.3)	40 (2.4)	<0.001
Self-reported history of stroke	129 (3.8)	87 (4.9)	42 (2.6)	<0.001
Lifestyle variables				
Physical inactivity	151 (4.5)	89 (5.1)	62 (3.8)	0.083
Higher education	1,615 (47.4)	912 (51.6)	703 (43.0)	<0.001
Current smoking	481 (14.2)	237 (13.4)	244 (14.9)	0.200
Medication				
Antihypertensive agents	1,232 (36.1)	718 (40.59)	514 (31.4)	<0.001
Lipid lowering agents	892 (26.1)	523 (52.0)	369 (22.5)	<0.001
Antidiabetic agents	174 (5.1)	126 (7.1)	48 (2.9)	<0.001
Carotid ultrasound measures				
Plaque score, median (IQR)	2 (1-4=3)	3 (2-4=2)	2 (1-3=2)	
Thickest plaque diameter, mm	2.4±0.7	2.4±0.7	2.3±0.7	<0.001
Plaque area, mm²	16.6±11.2	17.9±12.1	14.9±9.6	<0.001
Cognitive tests results				
MoCA score	25.3±2.9	25.0±2.9	25.5±2.9	<0.001

NOTE. Categorical variables reported as counts with percentages in parentheses. Normally distributed variables are reported as mean±SD. IQR, interquartile range.

Table 2: Linear regression; MoCA score in relation to measurement of carotid atherosclerosis

	Univariable				Multivariable			
	B	95% CI		P value	B	95% CI		P value
		Lower	Upper			Lower	Upper	
Plaque score	-0.14	-0.19	-0.09	<.0001	-0.04	-0.09	0.01	0.12
<i>Plaque score 0 (n=435)</i>	<i>0.40</i>	<i>0.69</i>	<i>0.10</i>	<i>0.008</i>	<i>0.02</i>	<i>-0.27</i>	<i>0.30</i>	<i>0.92</i>
Plaque score 1-4 (n=2,446)	0.12	0.10	0.34	0.281				
Plaque score>4 (n=532)	-0.52	-0.80	-0.25	<0.001	-0.1	-0.18	0.36	0.50
<i>Diameter largest plaque</i>	<i>-0.4</i>	<i>-0.56</i>	<i>-0.24</i>	<i><0.001</i>	<i>-0.17</i>	<i>-0.32</i>	<i>-0.01</i>	<i>0.039</i>
<i>Area largest plaque</i>	<i>-0.03</i>	<i>-0.04</i>	<i>-0.02</i>	<i><0.001</i>	<i>-0.02</i>	<i>-0.03</i>	<i>-0.01</i>	<i>0.001</i>

NOTE. Univariable analysis, unadjusted. The multivariable model adjusted for potential confounders; gender, hypertension, hypercholesterolemia, diabetes, obesity, current smoking, physical inactivity, history of stroke and lower education. CI, confidence interval.

Table 3: Mediation model analysis to examine whether diabetes and smoking affect cognition through mediation by atherosclerosis

	B	95% CI	P value
Step 1: MoCA as dependent variable, linear regression			
Diabetes	-0.82	-1.17- -0.46	<0.001
Smoking	-0.82	-1.10- -0.54	<0.001
Step 2: Plaque score as dependent variable			
Diabetes	0.86	0.61-1.11	<0.001
Smoking	1.34	1.14-1.53	<0.001
Step 3: MoCA as dependent variable, linear regression			
Diabetes	-0.73	-1.09- -0.37	<0.001
Smoking	-0.68	-0.97- -0.39	<0.001
Plaque score	-0.10	-1.15- -0.06	<0.001

The effect of diabetes and smoking is significant reduced in Step 3 compared to Step 1 (using Sobel's test)

Figure 1: MoCA score in relation to the carotid plaque score

Black line indicates mean observed measures; CI=confidence interval of the observed measures; Solid gray line indicates the negative correlation

Figure 2: Possible effect of diabetes and smoking on cognition through mediation by atherosclerosis

Total effect of Smoking on MoCA = Direct effect + Mediated effect (through plaque score) = $-0.68 + 1.34 \times (-0.10) = -0.82$

Total effect of Diabetes on MoCA = Direct effect + Mediated effect (through plaque score) = $-0.73 + 0.86 \times (-0.10) = -0.82$