Chapter 4

Atherosclerosis and cognitive impairment are linked in the elderly. The Leiden 85-plus Study

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In press Atherosclerosis

ABSTRACT

Background Post-mortem analyses suggest that atherosclerosis more often contributes to late-onset dementia than hitherto expected. We set out to further unravel the relation between atherosclerosis and cognitive impairment. We therefore tested the hypothesis that number the of cardiovascular pathologies is positively associated with cognitive impairment in elderly subjects, and that the smaller number of cardiovascular pathologies in women explains for the better cognitive function of elderly women.

Methods Within the Leiden 85-plus Study, we assessed the atherosclerotic burden by counting the number of cardiovascular pathologies in the medical histories of a population-based sample of 599 subjects aged 85 years (response 87%).

Results Significantly more men than women had a history of cardiovascular pathologies (67% compared to 59%, $p<0.001$). In addition, cognitive function was assessed. All subjects completed the Mini-Mental State Examination (MMSE). Cognitive speed and memory were determined with specific neuro-psychological tests in those with a MMSE-score above 18 points. There was a highly significant dose-response relationship between the number of cardiovascular pathologies and cognitive impairment for both men and women. The median MMSE-score was 26 points in subjects without cardiovascular disease and decreased to 25 points for subjects who had two or more cardiovascular pathologies (p for trend =0.003). Similar associations were found for cognitive speed but not for memory.

Conclusion Our data confirm that at old age atherosclerosis significantly contributes to cognitive impairment. Since treatments for atherosclerosis appear to be particularly effective in elderly people, we consider our finding of utmost clinical importance to possibly preventing cognitive impairment and late-onset dementia.

Introduction

The risk of dementia is increased in patients who have suffered a stroke [1,2]. Moreover, recent post mortem analyses suggest that cerebrovascular disease more often contributes to late-onset dementia than hitherto expected [3,4]. Examination of brains of patients diagnosed with late-onset dementia, as well as the brains of patients with autopsy proven Alzheimer's disease, often show multiple vascular lesions when compared to brains of subjects without dementia. Furthermore, amyloid plaques and tau pathology are often found in the brains of elderly people who did not suffer from dementia [4]. Taken together, these post mortem correlates suggest that the various entities of late-onset type dementia are not mutually exclusive and that the differences between vascular dementia and Alzheimer's disease are not distinct. A unifying hypothesis is that atherosclerotic changes of heart, peripheral and cerebral arteries cause clinical and subclinical ischemic disease in the brain contributing to the development of late onset dementia [5]. Such a multicausal interpretation of the observational data provides an explanation for the experimental finding that treating systolic hypertension at old age decreases the risk of both clinically diagnosed vascular dementia and Alzheimer's disease [6].

In an earlier study, we found that elderly women had better cognitive function than men [7]. This is highly remarkable as women born at the beginning of the 20th century have, in general, lower levels of formal education than men, which increases the risk of late-onset dementia [8]. Women have on average a lower atherosclerotic burden compared to men of the same age [9,10]. Evidence indicates that elderly women and men with atherosclerosis are more likely to be cognitively impaired [11-14]. Therefore, differences in atherosclerotic burden between women and men might explain the gender differences in cognitive function at old age.

To further unravel the relation between atherosclerosis and cognitive impairment at old age, we assessed the atherosclerotic burden by counting the number of cardiovascular pathologies in the medical history and assessed cognitive function in a large population-based sample of 85 year olds. We also analyzed the data to test the hypothesis that a lesser atherosclerotic burden in women may explain for the better cognitive function of women at old age.

Methods

Subjects

The Leiden 85-plus Study is a population-based study of inhabitants of Leiden, in the Netherlands. Since 1997, all members of the 1912 to 1914-birth cohort were enrolled in the month of their 85th birthday. There were no selection criteria related to health or demographic characteristics. Subjects were visited three times at their place of residence. During these visits, face-to-face interviews were conducted and an electrocardiogram was recorded. The study was approved by the Medical Ethical Committee of the Leiden University Medical Center.

Cognitive impairment

The Mini-Mental State Examination (MMSE) was administered in all subjects [15]. We defined good cognitive function as a score on the MMSE equal or above 28 points; cognitive impairment was defined as an MMSE-score below 28 points. A cut-off point of 28 points on the MMSE was used, since there is strong evidence that subjects aged 85 years with MMSE scores of 28 points or higher are cognitively intact [16].

To further investigate the various domains of cognitive function, we used a set of four neuro-psychological tests that are widely utilized in observational studies and have proven clinical value [17]. Cognitive speed was measured with two neuro-psychological tests, the Letter Digit Coding test (processing speed) and an abbreviated 40-item version of the Stroop test (attention). Memory was measured with the 12-Word Learning test, assessing immediate and delayed recall. The neuro-psychological tests were not conducted in subjects with an MMSE score of 18 points or lower, because in these subjects neuro-psychological tests cannot be accurately administered [18]. All neuro-psychological tests were conducted by the same trained research nurse, who gave her impression of whether the tests went well and whether the test scores reflected the subject's ability to perform the test at that time.

As described earlier, subjects were defined as having a good cognitive speed when they had a score below the median on the Stroop test and a score above the median on the Letter Digit Coding test [7]. Subjects were defined as having poor cognitive speed when they had a score above the median on the Stroop test or a score below the median on the Letter Digit test. Good memory was defined as a score above the median on both the immediate recall test and the delayed recall test. Poor memory was defined as a score below the median on either the immediate recall test or the delayed recall test. Subjects with MMSE scores of 18 points and lower and subjects who, for cognitive reasons, were unable to complete some of the neuro-psychological tests were also classified as having a poor cognitive speed and memory [7]. Subjects who, for other reasons such as low vision, or physical disabilities, were unable to complete the set of neuro-psychological tests were excluded from the analyses.

Atherosclerosis

All subjects' general practitioners or subject's nursing home physicians were interviewed to assess the medical history for number of cardiovascular pathologies for each subject. In addition, electrocardiograms were recorded on a Siemens Siccard 440 and transmitted by telephone to the ECG Core Lab in Glasgow for automated Minnesota coding [19].

In line with the Second Manifestations of Arterial disease (SMART) study [20] the atherosclerotic burden of each subject was expressed by the total number of cardiovascular pathologies. Each cardiovascular pathology was classified into one of five categories: (1) arterial surgery, (2) stroke, (3) intermittent claudication, (4) myocardial infarction, or (5) angina pectoris or myocardial ischemia. Arterial surgery,

stroke, and intermittent claudication were considered present when there was a positive medical history. Myocardial infarction was considered present when there was a positive medical history of myocardial infarction or when the ECG revealed myocardial infarction (Minnesota codes 1-1, 1-2, or 1-3) [20]. Subjects with a medical history of angina pectoris or myocardial ischemia on the ECG (Minnesota codes 4-1, 4-2, 4-3, 5-1, 5-2 and 5-3) [21] were also classified as having one cardiovascular pathology. In addition, subjects with both a medical history of myocardial infarction and myocardial ischemia on the ECG were classified as having myocardial infarction only, not myocardial ischemia [21]. Transient ischemic attacks were not included in the cardiovascular pathologies, since they may not always be distinguished from other disorders such as migraine, epilepsy, or syncope.

We classified the atherosclerotic burden of subjects by counting the total number of cardiovascular pathologies they had; i.e. subjects without cardiovascular pathology, subjects with one cardiovascular pathology, and subjects with two or more cardiovascular pathologies.

Possible confounders

Socio-demographic characteristics such as gender or level of education were considered as possible confounders. Education was divided into two levels: a lower education level, including individuals without schooling or with primary school education only (with a maximum of 6 years of schooling), and those with a higher education level (equivalent to more than 6 years of schooling). We used the 15-item Geriatric Depression Scale [22] to adjust for the effect of depressive symptoms on cognitive function. A score of four points or above on the Geriatric Depression Scale indicates that the presence of depression is likely. The Geriatric Depression Scale was not administered in subjects with a Mini-Mental State Examination score of 18 points or lower, because in these subjects depressive symptoms cannot be accurately assessed [23]. We also had to ascertain that our findings were not due to the use of cardiovascular drugs or non-steroidal anti-inflammatory drugs. These drugs, which are mainly prescribed for cardiovascular disease and arthritis, may also affect cognitive function [24,25]. The use of cardiovascular drugs (diuretics, calcium channel blockers, beta blockers, digoxin, nitrates) and non-steroidal anti-inflammatory drugs was obtained from the records of subjects' pharmacists.

Data analysis

Because the MMSE has a maximum score of 30 points and the delayed Word Learning test has a maximum of 12 words, the distributions of both tests were skewed to the left. Data are thus presented as medians with corresponding confidence intervals for the median. A confidence interval for the median represents the range of values that include the "true" median [26]. Groups were compared with non-parametric tests that do not assume an underlying normal distribution of the data. As the non-parametric equivalent of the one-way ANOVA procedure, we used the Jonckheere-Terpstra test [27] to determine the p-value for trend between the scores of the cognitive tests and the strata representing an increasing number of cardiovascular pathologies. In a secondary analysis, we used dichotomous endpoints, respectively cognitive impairment (MMSE score <28 points) versus good cognitive function (MMSE score ≥ 28 points), poor versus good cognitive speed (Stroop and Letter Digit test) and poor versus the

MMSE score 28 points or higher), poor versus good cognitive speed (Stroop and Letter Digit test) and poor versus good memory (immediate and delayed recall on the Word Learning test).]. In these analyses we compared the cognitive function of elderly subjects over the strata representing an increasing number of cardiovascular pathologies. Statistical significance was assessed by the linear association test to determine the p value for trend. Univariate odds ratios and 95% confidence intervals were obtained by cross-tabulation. Multivariate odds ratios were obtained by logistic regression analysis, adjusting for possible confounders.

Results

Between 1 September 1997 and 1 September 1999, 705 inhabitants of Leiden reached the age of 85 years and became eligible for inclusion in the study. Fourteen inhabitants died before they could be enrolled. Of the remaining 691 subjects, a total of 599 subjects participated (response 87%). The proportion of subjects with high education was 46% in men and 29% in women ($p<0.001$). There were no significant differences for various demographic characteristics between the 599 participants and the source population.

For three subiects we had no information on the presence of the cardiovascular pathologies in medical history. Of the remaining 596 subjects, table 1 shows the prevalence of cardiovascular pathologies. More than half of all subjects (62%) had a medical history of cardiovascular disease. Men had significantly more cardiovascular pathologies than women (table 1).

Table 1 *Prevalence of cardiovascular pathologies in participants of the Leiden 85-plus Study.*

Characteristic	All (n=596)	Men (n=201)	Women (n=395)
Myocardial infarction	139 (23%)	59 (29%)	80 (20%)*
Angina or myocardial ischemia †	277 (46%)	89 (44%)	188 (48%)
Stroke	62 (10%)	22 (11%)	40 (10%)
Arterial surgery	40 (7%)	26 (13%)	14 (4%)*
Intermittent claudication	37 (6%)	22 (11%)	15 (4%)*
Number of cardiovascular pathologies			
No cardiovascular pathology	227 (38%)	66 (33%)	161 (41%)**
one cardiovascular pathology	204 (34%)	65 (32%)	139 (35%)
two or more cardiovascular pathologies	165 (28%)	70 (35%)	95 (24%)

*† diagnosed by a positive medical history of angina pectoris (n=108) or ECG revealed ischemia (Minnesota codes 4-1, 4-2, 4-3, 5-1, 5-2, 5-3). * Chi square tests between men and women, df=1, p <0.05.** Chi square tests between men and women, df=2, p <0.05*

One might argue that physicians tend to diagnose cardiovascular disease more frequently in men than in women. For that reason, we also compared the proportion of men and women with a silent myocardial infarction, i.e. a myocardial infarction that was not recorded in subjects' medical history, but was revealed by ECG only. There was no significant difference in the proportion of men and women with silent myocardial infarctions (16% vs. 13%, chi-square p=0.4).

Severe cognitive impairment (MMSE ≤ 18 points) was present in 99 (16.6%) subjects, whereas the other 497 subjects had a MMSE score higher than 18 points. The set of neuro-psychological tests to measure cognitive speed and memory could not be completed in 53 subjects because of visual impairment (n=17), technical failure (n=1), refusal (n=31) and persistent misunderstanding of the instructions as given by the research nurse (n=4). The median scores for the tests of cognitive speed and memory showed that, after stratification for level of education, women had better cognitive function than men (Table 2) .

Table 2 *Gender differences in cognitive function, stratified for level of education.*

Characteristic	Men (n=156)	Women (n=288)	p-value
Low level of education (n)	80	187	
Cognitive speed			
Stroop Test (seconds)	89.6 (77.9-101.5)	78.4 (72.3-83.4)	0.008
Letter Digit Test (digits/minute)	14 (12-15)	14 (14-15)	0.2
Memory			
Immediate Word Learning test (words)	23 (21-24)	26 (24-26)	0.003
Delayed Word Learning test (words)	8 (8-9)	9 (9-10)	0.05
High level of education (n)	76	101	
Cognitive speed			
Stroop Test (seconds)	72.6 (64.7-79.1)	63.1 (60.4-66.5)	0.07
Letter Digit Test (digits/minute)	20 (18-23)	19 (18-22)	0.9
Memory			
Immediate Word Learning test (words)	24 (23-26)	27 (24-28)	0.05
Delayed Word Learning test (words)	9 (8-10)	10 (9-10)	0.4

Data are presented as medians and corresponding 95% confidence intervals.

The median MMSE score showed a gradual decline over the number of cardiovascular pathologies. Subjects without cardiovascular pathology had a median MMSE score of 26 points, whereas subjects with two or more cardiovascular pathologies had a MMSE score of 25 points (Table 3, p for trend = 0.003). This decline in MMSE score was also present when we stratified for gender and for level of education. The decline remained similar when we excluded subjects who had suffered a stroke (n=62).

Table 3 *Mini-Mental State Examination scores in relation to number of cardiovascular pathologies.*

	Number of cardiovascular pathologies			
	0	1	≥2	p for trend
All subjects (n=596)	26 (26-27)	26 (26-27)	25 (24-27)	0.003
Gender				
Female (n=395)	26 (25-27)	26 (25-27)	24 (23-27)	0.005
Male (n=201)	26.5 (26-28)	27 (26-28)	26 (25-27)	0.1
Education †				
Low (n=384)	25 (24-26)	25 (24-26)	24 (22-26)	0.02
High (n=206)	28 (27-28)	28 (27-29)	27 (26-28)	0.4

Data are presented as medians and corresponding 95% confidence intervals.

** Cardiovascular pathologies; myocardial infarction, angina or ischemia, stroke, arterial surgery, and intermittent claudication. † Level of education was missing for 6 subjects (all had MMSE-scores ≤ 18 points).*

Figure 1 presents the neuro-psychological test scores related to the number of cardiovascular pathologies. Subjects with cardiovascular pathologies performed significantly worse on the tests measuring cognitive speed (Stroop test and Letter Digit Coding test). The median time needed to complete the Stroop test increased from 69.9 seconds in subjects without cardiovascular pathology to 84.2 seconds in subjects with two or more cardiovascular pathologies (p for trend < 0.001). The median number of digits scored on the Letter Digit test in one minute was 17 in subjects without cardiovascular pathology and 15 in subjects with two or more cardiovascular pathologies (p for trend = 0.005). Subjects with cardiovascular pathologies performed not different on the memory tests (immediate and delayed Word Learning test).

increasing number of cardiovascular pathologies. Statistical significance

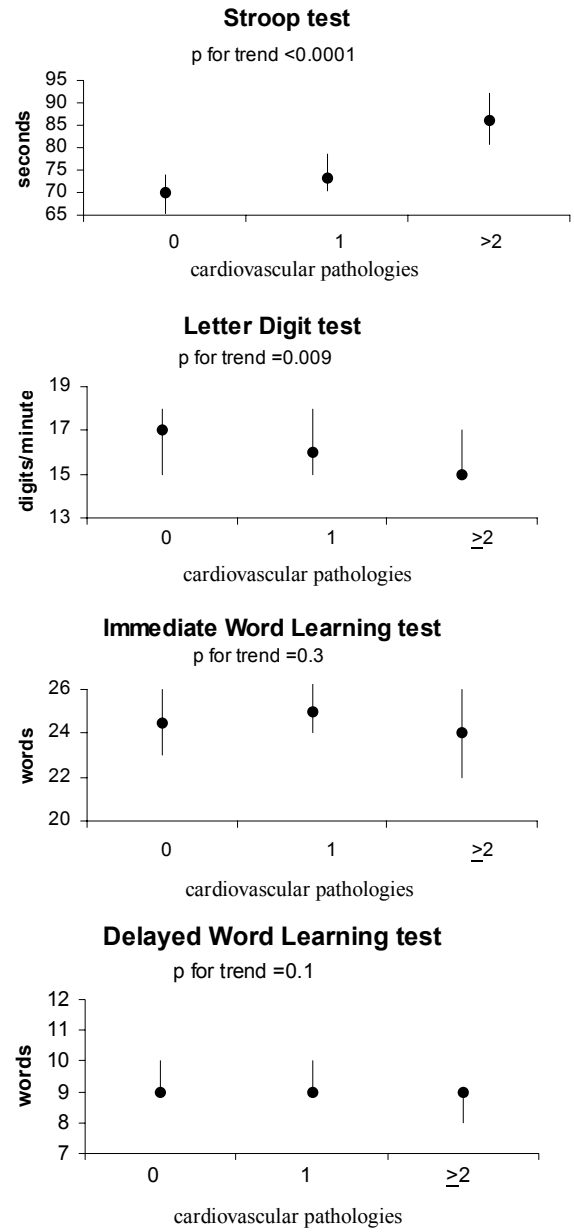

Figure 1 *Test scores of neuro-psychological tests measuring cognitive speed (Stroop test, Letter Digit test) and memory (Immediate and Delayed Word Learning test) dependent on the number of cardiovascular pathologies. Data are presented as medians and corresponding 95% confidence intervals. A confidence interval for the median represents the range of values with a 95% probability of containing the "true" median.*

The odds ratios of cognitive impairment (MMSE <28) and poor cognitive speed gradually increased to 2.0 (95% CI 1.3-3.0) and 2.1 (95% CI 1.0-3.5) over strata of increasing number of cardiovascular pathologies (Table 4). Comparable odds ratios were found for both men and women. Adjusting for possible confounders such as education, depressive symptoms, use of non-steroidal anti-inflammatory drugs, and use of cardiovascular drugs did not alter the odds ratios (data not shown). Memory was not affected by the number of cardiovascular pathologies (Table 4). Since it could be argued that the observed cognitive impairment in subjects with cardiovascular disease was due only to subjects with a medical history of stroke, we did an additional analysis excluding these subjects (n=62). The odds ratio for cognitive impairment (MMSE<28) and poor cognitive speed gradually increased to 1.7 (95% CI 1.0-2.6) and 1.8 (95% CI 1.1-3.2) respectively over increasing number of cardiovascular pathologies.

Table 4 *Odds ratios to have cognitive impairment (MMSE ≤28), poor cognitive speed, or poor memory dependent on the number of cardiovascular pathologies.*

	Number of cardiovascular pathologies			
	0	1	≥2	p for trend
MMSE <28				
All (n=596)	1*	1.2 (0.8-1.8)	2.0 (1.3-3.0)	0.003
Men (n=201)	1*	1.1 (0.6-2.2)	2.1 (1.0-4.3)	0.02
Women (n=395)	1*	1.3 (0.8-2.1)	2.0 (1.1-3.5)	0.04
Poor cognitive speed†				
All (n=547)	1*	1.2 (0.7-1.8)	2.1 (1.2-3.5)	0.07
Men (n=177)	1*	1.6 (0.7-3.5)	3.2 (1.3-7.6)	0.009
Women (n=370)	1*	1.0 (0.6-1.7)	1.8 (0.9-3.4)	0.1
Poor memory‡				
All (n=547)	1*	0.8 (0.5-1.2)	0.7 (0.4-1.2)	0.3
Men (n=177)	1*	1.2 (0.5-2.7)	1.7 (0.7-3.8)	0.6
Women (n=370)	1*	0.6 (0.3-1.1)	0.5 (0.3-0.9)	0.2

Data are presented as crude odds ratios with corresponding 95% confidence intervals.
** Reference category. † Poor cognitive speed (n=303); a score above the median on the Stroop or a score below the median on the Letter Digit test or a MMSE score ≤ 18 points (n=99) or testfailure due to cognitive impairment (n=4). ‡Poor memory (n=281); a score below the median on either the immediate recall test or the delayed recall test or a MMSE score ≤ 18 points (n=99) or testfailure due to cognitive impairment (n=4).*

Discussion

The primary aim of this study was to determine whether elderly subjects with increasing number of cardiovascular pathologies are more likely to be cognitively impaired. We showed that there is a dose-response relationship between the number of cardiovascular pathologies and cognitive impairment in both men and women. The findings of our population-based study confirm the post mortem findings that brains of patients with late-onset dementia more often have multiple vascular lesions [3,4]. It is noteworthy that our findings were unaffected when we excluded subjects with a history of stroke.

The association between atherosclerotic burden and cognitive impairment we present here is far greater than previously reported [12,13]. Studies published so far have primarily tested subjects at a younger age. At age 70, for example, cognitive impairment is relatively rare. Incidence of cognitive impairment and dementia particularly starts rising at 70 years of age and exponentially increases far beyond 80 years [28]. All these findings corroborate the outcomes of studies that associate peripheral atherosclerosis with white matter lesions in the brain, which are presumed to be of vascular origin, leading to cognitive impairment [29-31].

The association between atherosclerotic burden and cognitive impairment was found to be the same for men and women, and similar for those with low and high level of education. However, there were important differences in the atherosclerotic burden between women and men. Men significantly had more often cardiovascular pathologies compared to women. Hence the differences in the *prevalence* of cardiovascular pathologies can thus explain why 85-year old women have better cognitive function than 85-year old men, despite a lower level of education [7]. Paradoxically, the difference in the prevalence of cardiovascular pathologies between women and men may also explain the higher incidence of dementia in elderly women than in men [28,32]. Since women of the same age as men are relatively free from cardiovascular disease, women can only "catch up" with men by surviving them. The higher *incidence* of cardiovascular disease in women aged 80 years and over compared to men in the same age range could therefore contribute to the higher incidence of late onset dementia in women.

Based on findings from the Second Manifestations of ARTerial disease (SMART) study [20], we assessed the atherosclerotic burden by counting the number of cardiovascular pathologies in medical history. In the SMART study, it was demonstrated that presence of cardiovascular pathologies in the medical history was related to intima-media thickness and arterial stiffness, both well-accepted markers of generalized vascular pathology. This apparent association, although elegantly visualized, is not principally different from classifications used in former observational studies [33].

Areas of cognitive function that tend to change as a function of (clinical) events include memory, attention, and general cognitive speed. These are listed among the so-called *fluid abilities* [34]. In the elderly, memory remains relatively intact until later stages of cognitive decline. Cognitive speed, consisting of attention and processing speed, is the most sensitive measure because age-related cognitive decline first manifests itself by a decline in attention and processing speed [35,36]. We found that

atherosclerotic burden was associated with cognitive speed, but not with memory, which is in line with the sequence of cognitive decline. An alternative explanation might be that scores on memory tests typically show larger variances, which makes demonstrating significant differences more difficult. As this study is no exception, with this reduced probability of detecting group differences, it remains possible that age related decline of memory is also associated with atherosclerosis.

A question that may arise is whether 85 years is a proper age to study the effect of atherosclerosis on cognitive impairment. Subjects aged 85 are survivors from a far larger birth cohort and present a selection of the population at large. However, it is most important to know the determinants of cognitive impairment in the population aged 85 and over, since the largest increase in cognitive impairment and dementia occurs after this age. We therefore argue that 85-year-old individuals are an optimal population to study causes of cognitive impairment.

In conclusion, our study shows that there is an apparent dose-response relationship between the number of cardiovascular pathologies and cognitive impairment at old age. We suggest that generalized atherosclerosis at old age significantly contributes to cognitive impairment and late-onset dementia. Atherosclerotic disease, and especially cerebrovascular disease, becomes more and more amenable to medical treatment. Since these treatments appear to be particularly effective in elderly people [37,38], we consider our finding of utmost clinical importance to possibly preventing cognitive impairment and late-onset dementia.

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