

ATHEROSCLEROSIS AND DEMENTIA DEVELOPMENT: AN EPIDEMIOLOGICAL CASE-CONTROL STUDY

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SUMMARY

Objectives: With increasing life expectancy, the prevalence of atherosclerosis and dementia is expected to rise in the future and as such represents a public health threat. This study focused on analysis of atherosclerosis risk factors and the protective factors of leisure-time activities in the development of dementia.

Methods: The sample comprised 1,298 participants that were selected from university hospitals and outpatient clinics between 2019–2023. All participants completed a questionnaire and medical data were obtained. We used logistic regression to identify dementia risk factors and we also compared the leisure-time protective factors between four groups based on the presence of atherosclerosis and/or dementia.

Results: Hypercholesterolemia (aOR = 3.25, $p > 0.001$), stroke (aOR = 1.43, $p = 0.015$), and carotid stenosis (aOR = 2.23, $p > 0.001$) were significantly associated with risk of dementia whereas age (aOR = 0.93, $p < 0.001$) and female gender (aOR = 0.70, $p = 0.012$) were negatively associated. The model of these factors demonstrated moderate discriminatory ability of AUC 0.737 (95% CI: 0.702–0.769). Higher education levels and regular cognitive and physical activities such as reading and exercise had positive effects against dementia.

Conclusion: These findings accentuate the importance of cardiovascular health in reducing risk of dementia. Preventive strategies targeting hypercholesterolemia, carotid stenosis and inactivity, along with promotion of cognitive engagement and education, could substantially reduce the global burden of dementia.

Key words: cognitive decline, dementia, epidemiology, public health, prevention, atherosclerosis

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INTRODUCTION

According to the World Health Organization (WHO), approximately one billion people worldwide reached the age of 60 years or more in 2020. This figure is expected to double by 2050, with the majority of this age group living in low- and middle-income countries. The number of individuals aged 80 years and older will triple over the same time period, reaching 426 million. As the population ages, the number of people with dementia is increasing

and is projected to rise from 55 million in 2019 to 139 million in 2050. The burden of providing care for these patients has likewise been increasing substantially. By 2030, costs are expected to more than double to 2.8 trillion US dollars (1). As neurodegenerative diseases remain incurable, preventive strategies targeting their risk factors must be implemented (2).

The Lancet Commission reported increasing evidence of an association with 12 modifiable risk factors, namely lower levels of education, poor social contact, hypertension, hearing impairment,

smoking, obesity, depression, physical inactivity, diabetes mellitus (DM), air pollution, excessive alcohol consumption, and traumatic brain injury. Globally, these risk factors account for approximately 40% of all dementia cases. Although complete elimination of these risk factors is unlikely, even modest reductions may confer substantial benefits (2, 3). Another modifiable factor contributing to cognitive decline is atherosclerosis. Pathological changes such as carotid artery stenosis, changes in carotid intima-media thickness, and increased carotid artery stiffness are associated with a higher risk of cognitive decline and dementia. Lipid homeostasis of oxysterols and apolipoproteins is implicated in the pathogenesis of Alzheimer's disease (AD). Accumulating evidence suggests that low HDL levels are associated with poor brain health due to arterial plaque build-up, damage to the blood-brain barrier and cerebral artery thrombosis. These changes all act via different mechanisms and are potential predictors of dementia (4, 5).

The prevalence of risk factors for atherosclerotic cardiovascular disease such as smoking, hypertension, physical inactivity, and DM is steadily increasing. Smoking represents one of the major public health concerns globally. Numerous studies suggest that smoking affects endothelial homeostasis, leading to structural changes in blood vessels (6, 7).

Patients with DM are 1.4 to 2.2 times more likely to develop dementia, as indicated by Litkowski et al. in their prospective study (8). Evidence from epidemiological studies is inconsistent and does not show associations that could integrate a single pathophysiological mechanism (9).

The paper aims to investigate the relationship between atherosclerosis and dementia by analysing common risk factors and leisure-time activities for their impact on cognitive decline.

The paper presents the results of an epidemiological study conducted as part of the project "Possible influence of atherosclerosis on dementia development" (NU20-09-00119), which followed a previous Palacký University Olomouc junior grant project.

The principal investigator of the project was the Science and Research Centre of the Faculty of Health Sciences, Palacký University Olomouc, collaborating with the Department of Neurology, University Hospital Ostrava, and the Department of Neurology, University Hospital Hradec Králové.

The main objective of the project was to confirm the hypothesis that atherosclerosis increases the risk of developing dementia, identify common risk factors for atherosclerosis that may also contribute to risk and evaluate the importance of leisure-time activities for the prevention of cognitive decline.

MATERIALS AND METHODS

Between 2019 and 2023, a total of 1,298 participants were recruited from University Hospitals in Ostrava and Hradec Králové, as well as from neurology outpatient clinics.

Baseline medical history was collected from all patients, who additionally completed an epidemiological questionnaire and underwent neuropsychological testing to confirm cognitive decline.

Additional examinations, including electrocardiography, duplex ultrasonography of the cervical and intracranial cerebral arteries and/or cervical/cerebral CT/CTA/MR/MRA were performed on patients as part of the recommended procedures for diagnosing cognitive decline.

The epidemiological questionnaire focused on risk factors for atherosclerosis and dementia and contained questions related to lifestyle choices, cardiovascular and psychosocial risk factors, interests and hobbies.

To analyse leisure-time activity as a protective factor, all participants were assigned to one of the study groups based on the presence or absence of atherosclerosis and/or cognitive decline. The criteria for inclusion in the atherosclerosis groups were at least 50% presence of carotid stenosis or a disease such as cerebral atherosclerosis, lower-extremity peripheral artery disease, angina pectoris or myocardial infarction and stroke including transient ischaemic attack.

The criterion for inclusion in the cognitive decline groups was cognitive decline or dementia confirmed by clinical tests – MMSE score of less than 24 points or a MoCA Test score between 22 and 26 points.

Statistical Methods

Logistic regression was conducted using NCSS 2024 statistical software (NCSS, LLC, Kaysville, Utah, USA) and the discriminatory ability of the model was assessed through ROC curve analysis. The basic statistical analysis employed the chi-squared test and Fisher's exact test (when the assumptions of the chi-squared test were not met); metric variables were compared using the ANOVA test for multiple means. For data that were not normally distributed (as verified by the Shapiro-Wilk test), the non-parametric Kruskal-Wallis test was used. This statistical analysis was performed using Microsoft Excel 2017 and TIBCO Statistica® 14.1.0. The level of significance was set at 5%.

RESULTS

The study included 1,298 participants with mean age 72.7 (SD= 9.4; min. 27, max. 95).

After excluding 77 cases due to missing predictor data, 1,221 observations remained for the final regression analysis.

The dependent variable was dementia, with 887 cases of identified dementia (reference value = 1), accounting for 72.6% of the study population, whereas 334 (27.4%) participants did not have dementia. Predictor variables are based on research studies suggesting their association with dementia, including hypertension, hypercholesterolemia, stroke and carotid stenosis, whereas age and gender were included as covariates.

This model has shown a significant effect of independent variables (Table 1).

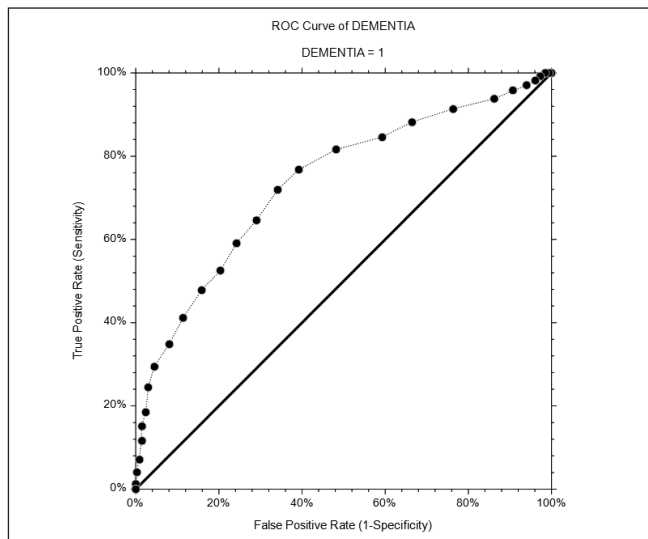
Hypercholesterolemia had the highest significant positive effect, indicating increased odds of the outcome (aOR = 3.25, 95% CI: 2.18–4.85), stroke (aOR = 1.43, 95% CI: 1.07–1.91) and carotid stenosis (aOR = 2.23, 95% CI: 1.66–2.97). In contrast, age (aOR = 0.93, 95% CI: 0.92–0.95) and female gender (aOR=0.70, 95% CI: 0.52–0.92) were associated with reduced odds. Whilst hypertension showed a trend toward increased aOR = 1.34 (95% CI: 0.92–1.94), its effect was not statistically conclusive. The non-significant result should be interpreted with caution.

The performance of the logistic regression model was assessed using the area under the receiver operating characteristic curve (AUC). In this analysis, the AUC was 0.737 (95% CI:

Table 1. Logistic regression results

Independent variable	Regression coefficient B(i)	Odds ratio Exp B(i)	95% confidence interval limits for odds ratio	p-value*
Age	-0.068	0.93	0.92–0.95	<0.001
Gender	-0.356	0.70	0.53–0.92	0.012
Hypertension	0.290	1.34	0.92–1.94	0.127
Hypercholesterolemia	1.178	3.25	2.18–4.85	<0.001
Stroke	0.360	1.43	1.07–1.91	0.015
Carotid stenosis	0.799	2.23	1.66–2.97	<0.001

*p-value at 5% level significance

**Fig. 1. Performance of logistic regression using the ROC curve and AUC.**

0.702–0.769), indicating moderate discriminatory ability, with an AUC of 0.737 meaning that the model correctly ranks a positive case over a negative case in 73.7% (Fig. 1).

Table 2 shows the analyses of protective factors associated with leisure-time activities. Leisure-time activities and physical activities were analysed using 1,298 participants who were enrolled in the following groups: group 1 consisted of 182 (14%) participants with atherosclerosis but no cognitive decline; group 2 included 317 (24%) participants with both atherosclerosis and cognitive decline; group 3 comprised 636 (49%) participants with cognitive decline but no atherosclerosis; and group 4 consisted of 163 (13%) participants without either of the diagnoses.

There was a statistically significant difference in the level of education between the groups ($p < 0.001$), patients with dementia were more likely to have a primary education. We found that previous book reading and crossword puzzle-solving activities were significantly higher ($p < 0.001$) in groups without dementia with atherosclerosis. There were no differences among the groups regarding cultural activities.

Table 2. Results of protective leisure time activity by groups

	Group 1 n = 182 n (%)	Group 2 n = 317 n (%)	Group 3 n = 636 n (%)	Group 4 n = 163 n (%)	Total	p-value*	Responses n (%)
Gender							
Male	101 (55.5)	155 (48.8)	253 (39.8)	94 (57.7)	603	<0.001	1,298 (100.0)
Female	81 (44.5)	162 (51.2)	383 (60.2)	69 (42.3)	695		
Age (years), mean, SD (min.–max.)	70.00 7.818 (31–89)	73.61 9.122 (29–92)	74.14 8.785 (40–95)	68.20 11.589 (27–89)	72.7 9.38 (29–95)	<0.001	1,298 (100.0)
Education							
Primary	27 (14.9)	105 (33.2)	243 (38.6)	23 (14.1)	398	<0.001	1,289 (99.3)
Secondary	136 (75.1)	193 (61.1)	319 (50.7)	119 (73)	767		
Higher or university	18 (10)	18 (5.7)	67 (10.7)	21 (12.9)	124		
Reading	149 (81.4)	207 (65.1)	451 (70.8)	109 (66.5)	916	<0.001	1,155 (89.0)
Crossword activity	108 (59.3)	235 (74.1)	486 (76.4)	109 (66.5)	938	<0.001	938 (72.3)
Culture active	29 (15.9)	78 (24.6)	155 (24.4)	31 (19.0)	293	0.124	723 (55.7)
Physical activity							
Regular	14 (7.8)	34 (10.8)	64 (10.1)	12 (7.4)	124	<0.001	1,272 (98.0)
Leisure time	130 (72.2)	153 (48.2)	308 (48.3)	110 (67.5)	701		
None	35 (19.6)	122 (38.6)	250 (39.5)	40 (24.7)	447		

Group 1 – patients with atherosclerosis but no cognitive decline; group 2 – patients with both atherosclerosis and cognitive decline; group 3 – patients with cognitive decline but no atherosclerosis; group 4 – patients with neither cognitive decline nor atherosclerosis; *p-value at significance level 5%

The groups had a statistically significant difference in physical activity ($p < 0.001$). People with dementia were generally less physically active than their counterparts without dementia. Group 1 (atherosclerosis without dementia) reported the highest leisure activity participation and the lowest inactivity, while groups 2 and 3 (dementia groups) had the highest proportions of inactivity.

DISCUSSION

This paper presents results from a study focused on risk factors for atherosclerosis and cognitive decline involving 1,298 participants.

Ageing is associated with both an increase in chronic diseases caused by atherosclerosis and cognitive decline. In the present study, dementia was present in older participants.

Another important factor influencing the development of AD and dementia appears to be education. Our sample showed a statistically significant difference ($p < 0.001$) in the levels of education. Patients diagnosed with dementia were significantly more likely to have a primary education (33.2% and 38.6% in groups 2 and 3, respectively), which is consistent with findings in several other studies (10–12).

A substantial part of the relationship between education and dementia is mediated by midlife vascular risk factors. However, modifying these risk factors is unlikely to fully resolve the large educational differences in dementia risk. Prevention efforts must also address differences in socioeconomic resources that lead to disparities in early-life education and other structural determinants of midlife vascular risk factors (13).

In a prospective study Hoenig et al. (14) used positron emission tomography (PET) to examine patients with mild to moderate AD. Focusing on neuronal dysfunction in AD patients, the authors found that individuals with higher levels of education have less tau pathology necessary to induce neuronal dysfunction. Leibovici et al. (15) have concluded that secondary memory and language function are more resistant to decline in highly educated persons, whilst attention, implicit memory, and spatial skills decline regardless of education level.

Chronic hypertension is undoubtedly an important risk factor for a number of cardiovascular diseases (16–18).

The pooled results of studies examining midlife hypertension and the risk of all-cause dementia have found a significant positive association (19, 20). Chronic hypertension in midlife is associated with reduced cerebral white matter integrity and impaired cerebral autoregulation (e.g., through reduced arterial elastance), which is linked to dementia (21). People with controlled hypertension have significantly lower progression of white matter lesions than those with untreated hypertension, suggesting that treatment of hypertension plays an important role in slowing the progression of these lesions (22).

The present study showed a higher risk of hypertension in people with dementia, but this was not statistically significant. Carotid plaque and stenosis are significantly associated with cognitive dysfunction and dementia, as demonstrated by studies and meta-analyses showing increased odds and hazard ratios for these conditions. The findings indicate that carotid plaque, as a potentially modifiable risk factor, warrants further study regarding its role in dementia (4, 23). Elevated plasma cholesterol, particu-

larly low-density lipoprotein cholesterol, is a major risk factor for chronic heart disease (CHD) and ischaemic stroke, with an estimated prevalence of approximately 39% among adults worldwide (24). In the present study, dyslipidaemia (hypercholesterolemia) was treated in 69.92% of participants with dementia. The vast majority of these subjects were taking statins, which are known to significantly reduce the risk of dementia, as some authors have reported (25, 26). Wee et al. (27) in their systematic review, found that high versus low total cholesterol (age > 65 years) was associated with an increased incidence of all-cause dementia. When total cholesterol was assessed as a continuous variable, each 1 mmol/L increase was associated with a 5% increase in the incidence of dementia. Similarly, each 1 mmol/L increase in low-density lipoprotein was associated with an 8% increase in the incidence of dementia (ES 1.08, 95% CI: 1.03–1.14).

Targeting dyslipidaemia as part of a comprehensive primary prevention strategy that includes modifiable risk factors has the potential to reduce the global burden of not only dementia but also mild cognitive impairment. Dyslipidaemia is an ideal risk factor to address because of its prevalence in the community at about $\approx 27\%$ to 77% (27).

Cardiovascular risk factors such as diabetes, stroke, heart failure, and atrial fibrillation are significantly associated with an increased risk of dementia in all age groups studied. For diabetes, stroke, and heart failure, the strength of this association diminishes with advancing age (28).

In the present study, participants with dementia manifested a higher prevalence of myocardial infarction, angina pectoris, and other CHDs, whereas those without dementia were free of any of these conditions. There were no statistically significant differences in the mean age.

Cardiovascular risk factors such as diabetes, stroke, heart failure, and atrial fibrillation are significantly associated with an increased risk of dementia (28). This aligns with our findings which show that participants with dementia had a higher prevalence of myocardial infarction, angina pectoris, and other CHDs.

Stroke is closely connected to an increased risk of dementia, especially vascular dementia, due to brain damage caused by interrupted blood flow.

Our study revealed that the highest number of participants reporting stroke was in the group with dementia. There was a statistically significant difference in data distribution ($p < 0.001$). We found a higher risk of stroke in dementia patients (OR = 1.43, 95% CI: 1.07–1.91).

In many cases, the risk factors for cognitive decline and stroke are the same. They include atrial fibrillation, hypertension, DM, and hypercholesterolemia. Therefore, it is reasonable to assume that they are also risk factors for AD itself (29).

Given the evidence that the pathologies leading to dementia begin developing 10 to 20 years before the onset of clinical signs, there is considerable interest in timely identification so that midlife interventions could prevent the lifelong onset of dementia (27). The findings from the present study provide further evidence of the high-risk relationship of these factors. As regards leisure-time activities, lower engagement in reading books, solving cross-words or engaging in physical activities represent a risk factor ($p < 0.001$). However, as people may stop exercising because of prodromal dementia, inactivity may either be the consequence or the cause of dementia, or both (30). Physical inactivity has been

linked to impaired performance in episodic memory, processing speed, semantic memory, verbal fluency, working memory, attention, and executive functions, as highlighted by various researchers (31).

Limitations of the Study

Firstly, our study was limited by the fact that the answers to our questions were obtained either from the participants, if they were capable of communication, from medical records, or from relatives or clinical staff. Therefore, in many cases, the information provided about leisure-time activities may have reflected the current period but not past medical history.

The risk of selection bias in this type of epidemiological study must be recognised. Since participants were recruited in hospitals (a hospital-based study), the results may have been partially influenced by the distribution of patients and their diagnoses.

CONCLUSION

Age-related diseases are a growing public health concern. The period of the past nearly 100 years is often referred to as the age of degenerative, particularly neurodegenerative, diseases. As the population ages, and life expectancy increases, the incidence of atherosclerosis and cognitive decline is expected to rise steadily.

In conclusion, hypercholesterolemia and carotid stenosis emerge as particularly strong modifiable risk factors for dementia, while stroke and hypertension are also significant contributing factors. These findings underscore the importance of cardiovascular health in reducing the risk of dementia, reinforcing the role of proactive management of blood pressure, cholesterol, and vascular health as part of dementia prevention strategies.

Conflicts of Interest

None declared

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Data Availability Statement

The data that support the findings of this study are not publicly available because their content could compromise the privacy of the research participants. Data are available from the author Jana Janoutová, email: jana.janoutova@upol.cz, upon reasonable request.

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