THE RELATIONSHIP BETWEEN ATHEROSCLEROSIS AND DEMENTIA

Jana Janoutová[1], Ondřej Machaczka[2, 3], Martina Kovalová[2, 3, 9], Anna Zatloukalová[2, 3], Petr Ambroz[2, 3], Veronika Koutná[1], Eva Mrázková[9], Michal Bar[4], Martin Roubec[4, 5], Petra Bártová[4], Richard Novobilský[4, 5], Martin Sabela[4, 5], Pavlína Kušnierová[6, 7], David Stejskal[6, 7], Lucie Faldynová[8], Sylwia Walczysková[8], Martin Vališ[11, 12], Lukáš Školoudík[11, 12], Petra Šolínová[12], David Školoudík[10], Vladimír Janout[1]

[1]Department of Public Health, Faculty of Medicine and Dentistry, Palacký University Olomouc, Olomouc, Czech Republic
[2]Science and Research Centre, Faculty of Health Sciences, Palacký University Olomouc, Olomouc, Czech Republic
[3]Department of Health Management and Public Health, Faculty of Health Sciences, Palacký University Olomouc, Olomouc, Czech Republic
[4]Department of Neurology, University Hospital Ostrava, Ostrava, Czech Republic
[5]Department of Clinical Neurosciences, Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic
[6]Department of Laboratory Medicine, University Hospital Ostrava, Ostrava, Czech Republic
[7]Institute of Laboratory Medicine, Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic
[8]Department of Molecular and Clinical Pathology and Medical Genetics, University Hospital Ostrava, Ostrava, Czech Republic
[9]Department of Epidemiology and Public Health, Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic
[10]Centre for Health Research, Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic
[11]Faculty of Medicine in Hradec Králové, Charles University, Hradec Králové, Czech Republic
[12]University Hospital Hradec Králové, Hradec Králové, Czech Republic

SUMMARY

Objective: The main objective is to confirm a hypothesis that atherosclerosis, through various mechanisms, considerably influences cognitive impairment and significantly increases the risk for developing dementia. Complete sample should be 920 individuals. The present study aimed to analyse epidemiological data from a questionnaire survey.

Methods: The work was carried out in the form of an epidemiological case control study. Subjects are enrolled in the study based on results of the following examinations carried out in neurology departments and outpatient centres during the project NU20-09-00119 from 2020 to 2023. Respondents were divided into four research groups according to the results of clinical examination for the presence of atherosclerosis and dementia. The survey was mainly concerned with risk factors for both atherosclerosis and dementia. It contained questions on lifestyle factors, cardiovascular risk factors, leisure activities, and hobbies.

Results: Analysis of the as yet incomplete sample of 877 subjects has yielded the following selected results: on average, 16% of subjects without dementia had primary education while the proportion was 45.2% in the group with both dementia and atherosclerosis. Subjects with dementia did mainly physical work. Low physical activity was more frequently noted in dementia groups (Group 2 – 54.4% and Group 3 – 47.2%) than in subjects without dementia (Group 1 – 19.6% and Group 4 – 25.8%). Coronary heart disease was more frequently reported by dementia patients (33.95%) than those without dementia (16.05%).

Conclusion: Cognitively impaired individuals, in particular those with vascular cognitive impairment, have poorer quality of life and shorter survival. Risk factors contributing to such impairment are similar to those for ischaemic or haemorrhagic stroke. It may be concluded that most of the analysed risk factors play a role in the development of both atherosclerosis and dementia.

Key words: dementia, atherosclerosis, risk factors, prevention, epidemiology

Address for correspondence: J. Janoutová, Department of Public Health, Faculty of Medicine and Dentistry, Palacký University Olomouc, Hněvotínská 3, 775 15 Olomouc, Czech Republic. E-mail: jana.janoutova@upol.cz

https://doi.org/10.21101/cejph.a7848

INTRODUCTION

Dementia is a neurological condition characterized by cognitive and functional decline that includes impaired memory and at least one other cognitive domain (1). According to the American Psychiatric Association and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, the term dementia has been replaced by major neurocognitive disorder, referring to a broad spectrum of cognitive and functional impairment, as a basis for diagnostic criteria. For certain aetiological subtypes, however, the term dementia is routinely used. According to current criteria, cognitive impairment must be characterized by significantly decreased cognitive performance (e.g., memory, learning, attention, executive function, perceptual and motor skills related to language or social knowledge) compared to the level a year ago that cognitive decline must interfere with daily activities (2–4).

Even though the incidence of atherosclerosis-related cardiovascular disease (CVD) and its death rates continue to decrease in Europe, they remain the main cause of morbidity and mortality. In 2020, the World Health Organization (WHO) reported coronary heart disease and stroke as the two main causes of death globally.

In the past, the main risk factors for atherosclerosis were identified. Prevention should be focused on promoting a healthy lifestyle, in particular smoking cessation. Unfortunately, unhealthy behaviours are rather common. The main causal and modifiable factors for atherosclerosis are hyperlipidaemia, hypertension, cigarette smoking, and diabetes mellitus (DM). Another significant risk factor is obesity, increasing the risk for CVD via the main common risk factors and other mechanisms (5, 6).

Numerous epidemiological studies have suggested that the development of dementia is greatly contributed to by arterial atherosclerosis, with this being especially true for vascular dementia and Alzheimer's disease (AD), the most common form of dementia. Manifestations of cognitive impairment and dementia tend to be associated with carotid artery disease that has been studied as a potential predictor of the risk for developing dementia. Even mild carotid artery disease or subclinical atherosclerosis have been shown to be associated with greater cognitive impairment in middle-aged adults after adjustment for other vascular risk factors (7–10).

Accelerated brain aging is also associated with higher homocysteine levels or increased carotid intima-media thickness, a measure of subclinical atherosclerosis (11, 12).

Research studies have repeatedly shown that hyperlipidaemia may affect cerebral vascular tone through mechanisms unrelated to proatherogenic properties of hyperlipidaemia (7).

Vascular cognitive impairment stems from decreased blood flow to the brain, causing ischaemia in various areas of brain tissue (e.g., the hypothalamus or frontal lobe) or results in modifications such as small vessel fibrosis with white matter strokes, either clinically silent or accompanied by neurological nonspecific signs. White matter damage is associated with disruption of cortical and subcortical circuits with impairment of complex attention, information processing speed and executive skills and abilities. At the same time, there are cortical-subcortical border zone infarcts resulting from restricted blood flow due to atherosclerosis, as well as episodes of arterial hypertension that may be accompanied by impaired cognition. Thus, cerebrovascular disease leads to a large group of manifestations from the cognitive vascular sphere (2, 13, 14). Over 80% of the global burden of stroke may be attributed to modifiable risk factors. If people adjusted their habits, the associated vascular risk factors for atherosclerosis could be mitigated and the rates of stroke and the related risk for cognitive impairment and dementia could be reduced (15).

The aim of the study is to present interim results of an epidemiological study as a part of the Czech Health Research Council (Ministry of Health of the Czech Republic) project Possible Influence of Atherosclerosis on Dementia Development (NU20-09-00119).

The project's principal investigator is the Science and Research Centre (Faculty of Health Sciences, Palacký University Olomouc), cooperating with University Hospital Neurology Departments in Ostrava and Hradec Králové where patients enrolled in the study have been examined.

The project's main objective is to confirm a hypothesis that atherosclerosis, through various mechanisms, is considerably associated with cognitive impairment and significantly increases the risk for developing dementia. The present study aimed to analyse epidemiological data from a questionnaire survey.

MATERIALS AND METHODS

Subjects are enrolled in the study based on results of the following examinations carried out in neurology departments and outpatient centres: test for atherosclerosis including history taking; electrocardiogram; duplex ultrasound of cervical and intracranial cerebral arteries and/or cervical/cranial computed tomography (CT)/CT angiography/magnetic resonance imaging (MRI)/magnetic resonance angiography; neuropsychological tests for dementia – Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Addenbrooke's Cognitive Examination and/or brain CT/MRI and other tests for dementia; and epidemiological questionnaire.

Other inclusion criteria are being 40–90 years of age and signing informed consent. The exclusion criterion is having a serious disease with a poor chance of surviving one year or more.

The criteria for inclusion in atherosclerosis subgroups are having established atherosclerosis with 50% or more stenosis of coronary, carotid, cerebral or leg arteries; angina pectoris; myocardial infarction; stroke including transient ischaemic attack, etc.

The criteria for inclusion in cognitive impairment groups are having an insidious onset of cognitive impairment (or dementia) confirmed by clinical examination (MMSE score <24 points, MoCA score 22–26 points).

Using the above criteria, subjects are classified into those with confirmed atherosclerosis but no cognitive impairment (Group 1); those with both atherosclerosis and cognitive impairment (Group 2); those with cognitive impairment but without atherosclerosis (Group 3); and those with neither cognitive impairment nor atherosclerosis (Group 4). The intention is to test 920 individuals by the end of the project.

The present study analysed epidemiological data from a questionnaire survey containing items related mainly to risk factors for both atherosclerosis and dementia. Those were questions on lifestyle factors, cardiovascular risk factors, leisure activities, and hobbies.

Limitation of the study was the fact that responses were ascertained either from patients able to communicate or from medical records, patients' relatives, or health professionals. Thus, a lot of information may have come from that time and not from the time before disease development.

Data were statistically analysed using a chi-squared test and Fisher's exact test (if chi-squared test criteria were not met); metric variables were compared by ANOVA for testing medians across several groups. The statistical analyses were performed with Microsoft Excel 2017 and Statistica v. 14. The level of significance was set at 5%.

RESULTS

So far, data obtained from 877 subjects have been analysed (Group 1 n = 185, 21.09%; Group 2 n = 151, 17.22%; Group 3 n = 389, 44.36%; Group 4 n = 152, 17.33%).

There was no statistically significant difference in the male-to-female ratio between the groups ($p = 0.080$).

There was a statistically significant difference in the mean age (irrespective of gender) between the groups ($p < 0.001$). Males and females with dementia were approximately six and nine years older, respectively, compared to those without the condition. The highest mean age was noted in both males and females in Group 2.

There was no statistically significant difference in the family history of dementia between the groups ($p = 0.174$), with 9.2% of subjects reporting dementia in their families.

In all the groups, the largest proportion of subjects had secondary education (range 45.7%–77.8%). In Groups 3, this proportion was nearly identical to that of individuals with primary education (45.2%). On average, 16% of subjects without dementia had primary education. There was a statistically significant difference in education level between the groups ($p < 0.001$).

Subjects with dementia did mainly physical work. In Group 3, 46.5% of subjects were blue-collar workers, as compared to only 18.6% of white-collar workers. The combined type was most frequently reported by individuals without dementia. Analysis of data by profession showed that the largest proportion of white-collar workers was among subjects not diagnosed with any of the conditions. The difference was statistically significant ($p < 0.001$).

Cognitive impairment is strongly associated with cardiovascular and metabolic risk factors, often associated with excessive use of tobacco and alcohol as well as inadequate physical activity.

The largest and smallest proportions of smokers were in Group 1 (19.6%) and Group 3 (12.4%), respectively, with the difference being statistically significant ($p < 0.001$). In all groups, non-smokers were the largest category. The mean number of cigarettes smoked per day was 11.3 in smokers, but much higher (16.7) in ex-smokers (ranging from 15.1 in those with atherosclerosis but no dementia to 18.3 in subjects diagnosed with both conditions).

In all groups, occasional alcohol drinkers were the largest subgroup (range 51.7%–68.2%). Abstainers were more frequently seen among individuals without dementia (approximately 45%) than among dementia patients (approximately 30%). There was a statistically significant difference in alcohol consumption between the groups ($p = 0.014$).

Low physical activity was more frequently noted in dementia groups (Group 2 – 54.4% and Group 3 – 47.2%) than in subjects without dementia (Group 1 – 19.6% and Group 4 – 25.8%, a statistically significant difference ($p < 0.001$).

Hypercholesterolemia was found in 72% of subjects, with the proportion being the highest (82.5%) in Group 1 and the lowest among subjects without the two diagnoses. The difference in hypercholesterolemia status between the groups was statistically significant ($p = 0.004$). However, only three patients with hypercholesterolemia did not report statin use.

Hypertension was reported by 76.3% of subjects, with the proportion being the highest in Group 1 (84.3%). There was a statistically significant difference between the groups ($p = 0.001$). In all groups, hypertension was diagnosed in subjects older than 57 years of age.

Coronary heart disease or angina pectoris was more frequently reported by dementia patients (33.95%) than those without dementia (16.05%).

There was a statistically significant difference in the history of stroke between the groups ($p \leq 0.001$), with the condition being considerably more common in subjects with dementia.

In the three groups with diagnoses, the proportions of diabetics were nearly identical. However, the mean age of DM diagnosis was higher in dementia patients (66 years) than in subjects without dementia (62 years). The above results are summarized in Table 1.

DISCUSSION

The article presents interim results of a study analysing the relationship between atherosclerosis and cognitive impairment. The association between cognitive decline and diseases linked to atherosclerosis has been reported by many authors (2, 16–19).

The analysis included data on 877 individuals obtained from an epidemiological questionnaire as well as from cognitive and imaging tests.

Advanced age is an important factor influencing both cognitive impairment and atherosclerosis-related chronic non-infectious diseases such as hypertension and cerebrovascular disease (20, 21). In the present study, the mean age of patients with dementia was higher than that of subjects without dementia, the differences being approximately six and nine years in males and females, respectively. The oldest mean age of both males and females was noted in the group with dementia and atherosclerosis.

There were statistically significant differences in education level and profession ($p < 0.001$). In Group 3, the most common level of education was primary (45.2%). In the groups without dementia, subjects with primary education accounted for an average of 16%. Consistently with these findings, multiple epidemiological studies have reported a higher risk for dementia in less educated individuals than in those with higher education (22, 23). At the same time, dementia patients in the present study were predominantly blue-collar workers. Analysis of data by profession showed that the largest proportion of white-collar workers was among subjects not diagnosed with any of the conditions.

Important lifestyle risk factors that are also easily preventable are smoking and excessive alcohol consumption. Some clinical studies claim that nicotine may stimulate the action of certain neurotransmitters involved in the development of various types of dementia, in particular AD. This relationship, however, may only exist in the short term. From a long-term perspective, nicotine may affect blood vessel walls and modify the chemical composition of blood nutrients needed for proper brain function (2). Tobacco smoke contains toxic substances causing oxidative stress and inflammation that increase the risk of AD (24, 25). According to many studies, smokers are twice as likely to develop dementia (26–28). The present study failed to confirm a similar association. The proportion of smokers was the highest in Group 1 (19.6%) and the lowest in Group 3 (12.4%), a statistically significant difference between the groups ($p < 0.001$). However, the validity of obtained results is questionable. Despite accurate criteria for classifying subjects as current smokers or ex-smokers, it is difficult to obtain more precise information on smoking before disease development, as is the case with pinpointing the exact onset of cognitive impairment. In all groups, non-smokers were the largest category. Interestingly, the mean number of cigarettes smoked per day was much higher in ex-smokers than in current smokers. Today, there is no doubt that smoking considerably reduces life expectancy.

Table 1. *Selected risk factors in respondents by group*

	Group 1		Group 2		Group 3		Group 4		p-value*	Responses N (%)
Gender	**Male n (%)**	**Female n (%)**	**Male n (%)**	**Female n (%)**	**Male n (%)**	**Female n (%)**	**Male n (%)**	**Female n (%)**		
	91 (10.38)	94 (10.72)	76 (8.67)	75 (8.55)	170 (19.38)	219 (24.97)	57 (6.5)	95 (10.38)	0.080	
Age (min, max)	69.8 (29, 82)	68.3 (31, 83)	75.1 (55, 92)	76.3 (47, 94)	74.1 (44, 93)	76.1 (40, 91)	67.4 (33, 83)	65.5 (27, 83)	**< 0.001**	877 (100)
SD	7.79	9.39	8.33	8.74	8.73	8.16	9.23	10.17		
Family history of dementia	15 (8.2)		11 (7.4)		33 (8.6)		21 (13.9)		**0.174**	867 (98.9)
Education										
Primary	26 (14.1)		62 (41.6)		174 (45.2)		28 (18.4)		**< 0.001**	871 (99.3)
Secondary	144 (77.8)		76 (51.0)		176 (45.7)		102 (67.1)			
Tertiary	15 (8.1)		11 (7.4)		35 (9.1)		22 (14.5)			
Profession										
White-collar	25 (13.6)		24 (16.2)		71 (18.6)		49 (32.7)		**< 0.001**	863 (98.4)
Blue-collar	74 (40.2)		63 (42.6)		177 (46.5)		40 (26.7)			
White/blue-collar	85 (46.2)		61 (41.2)		133 (34.9)		61 (40.7)			
Smoking status										
Non-smoker	84 (45.7)		77 (51.0)		277 (71.6)		97 (64.2)		**< 0.001**	873 (99.5)
Smoker	36 (19.6)		27 (17.9)		48 (12.4)		27 (17.9)			
Ex-smoker	64 (34.8)		47 (31.1)		62 (16.0)		27 (17.9)			
Alcohol consumption										
Abstainer	61 (33.3)		65 (44.2)		172 (45.1)		43 (28.5)		**0.014**	862 (98.3)
Occasional drinker	118 (64.5)		76 (51.7)		197 (51.7)		103 (68.2)			
Daily drinker	3 (1.6)		4 (2.7)		6 (1.6)		4 (2.6)			
Weekly drinker	1 (0.5)		2 (1.4)		6 (1.6)		1 (0.7)			
Physical activity										
Regular activity	26 (14.1)		12 (8.2)		29 (7.6)		21 (13.9)		**< 0.001**	863 (98.4)
Leisure time activity	122 (66.3)		55 (37.4)		172 (45.1)		91 (60.3)			
None	36 (19.6)		80 (54.4)		180 (47.2)		39 (25.8)			
Hypercholesterolemia	151 (82.5)		108 (72.0)		265 (68.8)		101 (67.3)		**0.004**	868 (99.0)
Arterial hypertension	156 (84.3)		117 (77.5)		293 (75.9)		99 (66.0)		**0.001**	872 (99.4)
Angina pectoris or coronary heart disease	25 (22.3)		19 (17.0)		87 (50.9)		11 (9.8)		**0.095**	664 (75.7)
Stroke	25 (13.5)		56 (37.3)		181 (47.1)		45 (30.0)		**< 0.001**	869 (98.6)
Diabetes mellitus	62 (33.7)		50 (33.1)		122 (31.7)		34 (22.7)		**0.117**	870 (99.2)

Numbers in bold indicate statistically significant values.

Therefore, deaths from smoking-related diseases (cardiovascular disease, cancer, etc.) may in the end conceal the actual effect of smoking on the risk of dementia.

In all groups in the study, occasional drinkers predominated. Abstainers were more frequently seen among dementia patients (approximately 45%) than among those without dementia. There was a statistically significant difference in alcohol consumption between the groups ($p=0.014$). Once again, the validity of information obtained is questionable. As patients with established dementia may lose interest in drinking alcohol, the questionnaire rather reflects the current status and cannot be applied to the past. Some large studies have suggested that excessive use of alcohol is associated with cognitive decline and the development of dementia (28).

Another factor claimed to be responsible for both dementia and atherosclerosis is low physical activity. Movement is an integral part of healthy lifestyle. Unfortunately, people today get little exercise. According to the WHO, more people have died due to overnutrition than undernutrition since 2012. It is a well-known fact that the lack of activity and excessive food consumption result in overweight and obesity (29). Some studies have shown that adults over 60 years of age with high triglyceride levels and obesity have a higher risk for short-term memory loss and dementia (26, 30). Other epidemiological studies have confirmed that physical activity protects against the negative impact of aging and lowers the risk of AD and related dementia. Regular physical activity that includes walking is associated with cognitive improvements in the elderly (31–36). In the present study, poor physical activity was reported significantly more frequently by subjects with dementia than those without the condition.

Dyslipidaemia, known to be an important cardiovascular risk factor, is associated with AD. Elevated serum cholesterol levels in middle age increase the risk of dementia in older age. However, many epidemiological studies suggest that increased levels of high-density lipoprotein and its main apolipoprotein A-I are associated with a lower risk for dementia in elderly individuals (37). Metabolic syndrome is defined by the presence of several cardiovascular risk factors such as dyslipidaemia, obesity, hypertension, and DM. Metabolic syndrome has been reported to be associated with a higher risk of developing vascular neurocognitive disorders, especially in the elderly (aged 70 or more years). Hypercholesterolemia is linked to a higher risk for dementia in middle-aged individuals but to a low risk in the elderly. Prospective statistical studies have shown that statin therapy for dyslipidaemia has no impact on the development of neurocognitive diseases (2). In the present study, almost three quarters of subjects were found to have elevated cholesterol levels. The highest proportion (82.5%) was noted in Group 1, that is subjects with atherosclerosis but without dementia. Nearly all participants reported the use of statins.

Mechanisms related to cerebral atherosclerosis in patients diagnosed with arterial hypertension result in cerebral ischaemic lesions in various locations and neurocognitive disorders (38, 39). Blood pressure above 160/95 mmHg represents a considerable risk for developing vascular dementia. Untreated hypertension leads to dysfunction of blood vessels in the brain due to modification of the vascular endothelium, flat myocytes and blood-brain barrier, causing large white matter lesions that may be associated with cognitive impairment. Numerous recent studies have shown vascular dementia to be less frequent in patients with hypertension receiving antihypertensive medications (21, 40–42). Also Westmannia Cardiovascular Risk Factors Study results suggest that middle-age hypertension is responsible for a higher risk of dementia. This supports the need for preventive tests in middle-aged adults aimed at early detection of hypertension, allowing early initiation of antihypertensive therapy (43). In the present study, hypertension was reported by more than 76% of subjects, with the proportion being the highest in Group 1 comprising individuals with atherosclerosis and without dementia. In all groups, hypertension was diagnosed in subjects older than 57 years of age. The results support the above claims about the need for cardiovascular disease prevention and early recognition of hypertension.

In the present study, chronic coronary heart disease was reported by a much higher proportion of patients with dementia (33.95%) than those without the condition (16.05%). There was also a statistically significant difference in stroke events between the groups ($p \leq 0.001$), with stroke being considerably more common in dementia patients.

Previous studies have confirmed that vascular diseases are significantly associated with the development and progression of AD. In a Gothenburg study published as early as in 1996, individuals developing dementia at an older age had higher blood pressure levels 15 years earlier but those were lower than in non-demented persons of the same age (44). In the past, a number of other studies (e.g., Uppsala, CAIDE or Framingham) analysed data on cardiovascular risk factors in middle-aged subjects followed-up until the age of 65 years. Those studies confirmed the association of the currently known risk factors such as hypertension, obesity or hypercholesterolemia present in middle age with the later development of dementia. The association between the above factors and dementia appears to be credible as hypertension, dyslipidaemia, obesity, and type 2 DM predispose to coronary heart disease and cerebrovascular disease including cortical and subcortical infarcts and white matter lesions. In their systematic review, Meng et al. showed a higher risk for AD associated with cardiovascular risks in middle age (45).

Vascular cognitive impairment (VCI) represents a range of cognitive disorders associated with various forms of damage to brain blood vessels, from mild cognitive impairment to full dementia. Dysfunction of the neurovascular unit and mechanisms regulating blood flow in the brain are likely to be important components of pathophysiological processes underlying VCI. Cerebral amyloid angiopathy has been identified as an important marker of the risk of AD, microinfarcts, cerebral microbleeds, and haemorrhage and VCI. In many cases, the risk factors for VCI are identical to those for stroke. These may include atrial fibrillation, hypertension, DM, and hypercholesterolemia. Additionally, the same vascular risk factors may be risk factors for AD. Carotid intima-media thickness and arterial stiffness are markers of arterial aging and thus of VCI risk (46).

As mentioned above, another condition significantly associated with the risk for developing dementia is DM. It is the main risk factor for myocardial infarction, thrombosis and cerebrovascular diseases such as ischaemic or haemorrhagic stroke that are linked to various degrees of vascular neurocognitive disorder. The association between type 2 DM and arterial hypertension increases the risk for cerebrovascular disease. At the same time, this type of DM is linked to a higher risk for developing neurocognitive disorders (21). Findings from studies on central obesity support

the hypothesis that the association between obesity and dementia may be linked to type 2 DM mediated by insulin resistance and hyperinsulinaemia (47, 48). In the three groups with diagnoses, the proportion of diabetics was nearly identical. Interestingly, the age of subjects with dementia at DM diagnosis was approximately four years older than that of individuals without dementia. Šerý et al. reported that on average, AD patients developed DM more than 10 years later than controls ($p < 0.001$) (49). The question is, however, whether this refers to the onset of the condition or whether the diagnosis was made later. In any event, this interesting fact deserves further study.

CONCLUSION

Cognitively impaired individuals, in particular VCI patients, have poorer quality of life and shorter survival. Risk factors contributing to the development of VCI are similar to those for ischaemic or haemorrhagic stroke, that is arterial hypertension, DM, dyslipidaemia, smoking, obesity, older age, alcohol consumption, and cerebral atherosclerosis. Progressive atheromatous plaque formation and carotid artery stenosis may cause stroke and contribute to the development of dementia, either directly or as a result of stroke (2, 50).

The preliminary study results have shown that the above risk factors play a role in the development of both atherosclerosis and dementia. Therefore, it is necessary to increase the health literacy of the population as a number of risk factors, especially lifestyle, are preventable. Given the severity of the two conditions and many uncertainties present, possible risks need to be studied extensively, analysed and confirmed. Understanding the interrelationships between vascular risk factors, cerebrovascular disease and vascular neurocognitive disorders pose a challenge for prevention, early detection and therapy of cognitive impairment.

Adherence to Ethical Standards

The project was approved by the Ethics Committees of the Faculty of Health Sciences, Palacký University Olomouc (UPOL-90360/1030-2019), Faculty Hospital Ostrava, and Faculty Hospital Hradec Králové. All subjects have given their written informed consent.

Conflicts of Interest

None declared

Funding

The study is supported by the Czech Ministry of Health project NU20-09-00119 – Possible influence of atherosclerosis on dementia development; NU – Programme to support applied medical research for the years 2020–2026.

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Received April 22, 2023
Accepted in revised form February 15, 2024