Medical Research | Published by Faculty of Medicine University of Belgrade

ORIGINAL ARTICLE

The association of physical activity with the severity of carotid disease

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Submitted: 26 January 2026
Revised: 10 February 2026
Accepted: 13 February 2026
Online First: 24 February 2026

Check for updates

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Summary

Introduction: Regular physical activity reduces the risk of cardiovascular diseases (CVD). The aim of this study was to examine the association of physical activity with the severity of carotid disease.

Materials and methods: This cross-sectional study involved 506 patients from the Vascular Surgery Clinic at the Institute for Cardiovascular Diseases "Dedinje", who underwent carotid endarterectomy from 2012 - 2017. The severity of carotid disease was assessed based on the degree of carotid stenosis, plaque type, and patients' symptomatic status before surgery. Patient physical activity data were collected using the standardized Baecke questionnaire. Univariate and multivariate logistic regressions were performed to examine the association between physical activity and the severity of carotid disease.

Results: According to univariate analysis, there was no statistically significant association between any form of physical activity (occupational, sports, or recreational) and the degree of carotid stenosis, nor with other characteristics. Also, physical activity was not associated with complicated carotid plaque. The only characteristic associated with complicated carotid plaque was the use of oral anticoagulants in therapy (OR=2.91; 95% CI=1.12-7.52; p=0.028). The relationship between physical activity and symptomatic carotid disease was not observed, but according to multivariate analysis, the following factors were associated with symptomatic status: age (OR=0.97; 95% CI 0.94-0.99; p=0.016), gender (OR=0.64; 95% CI 0.44-0.99; p=0.028), family history of CVD (OR=0.63; 95%CI 0.43-0.94; p=0.022), use of clopidogrel (OR 1.79; 95% CI 1.18-2.71; p=0.006) and ACEIs in therapy (OR=1.60; 95% CI 1.02-2.53; p=0.041).

Conclusion: Physical activity was not associated with carotid disease severity.

Keywords: physical activity, carotid disease, carotid stenosis, carotid plaque

Cite this article as: Vukasinovic D, Maksimovic M, Tanaskovic S, Cirkovic A, Vlajinac H. The association of physical activity with the severity of carotid disease; Medicinska istraživanja 2026; DOI: 10.5937/medi0-64316

INTRODUCTION

In modern society, marked by a global obesity pandemic and with cardiovascular disease remaining the leading cause of morbidity and mortality, physical activity is needed more than ever before. However, the results of global physical activity assessments are devastating. Nearly one-third of adults and up to 81% of adolescents do not meet the World Health Organization (WHO) recommendations for physical activity (1). According to Eurostat data, two-thirds of adult Europeans are physically inactive (2). In Serbia, according to the latest health survey from 2019 (3), nearly two-thirds of individuals aged 18 to 64 meet the WHO recommendations for physical activity.

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure (1). The WHO recommends at least 150–300 minutes of moderate-intensity aerobic physical activity per week, or 75–150 minutes of high-intensity aerobic activity per week (1). For additional health benefits, muscle-strengthening exercises are recommended at least twice a week (1).

Carotid disease is a major contributor to stroke, one of the leading causes of death and disability worldwide. Numerous studies have examined the association between physical activity and the severity of carotid disease (4–10). Most studies indicate an inverse association between physical activity and carotid atherosclerosis (5–9), although some have not observed this link (4, 10) or have found an association only with advanced carotid atherosclerosis (11). Therefore, the relationship between physical activity and carotid disease remains unclear. Moreover, current guidelines for CVD prevention recommend regular physical activity, but they are mainly aimed at the general population. There is insufficient data from studies in populations with a high risk for CVD, such as patients with carotid disease. Additionally, the association between physical activity and the severity of carotid disease has been insufficiently examined, which can affect the disease course and progression.

The aim of this study was to examine the association between physical activity and the severity of carotid disease, assessed by the degree of carotid stenosis, plaque type, and patients' symptomatic status.

MATERIALS AND METHODS

This cross-sectional study included 506 patients treated at the Vascular Surgery Clinic of the Institute for Cardiovascular Diseases "Dedinje" who underwent carotid endarterectomy between January 1, 2012, and December 31, 2017. All participants were interviewed to provide information on their levels of physical activity during the year preceding surgery.

Data collected from the patients' medical records included: demographics (age and sex), body mass index (BMI), smoking habits, comorbidities, family history of cardiovascular disease, biochemical parameters (triglyceride levels and total cholesterol levels at the time of hospital admission), and prescribed medications (aspirin, clopidogrel, OACs, ACEIs, beta-blockers, and statins). Data on preoperative ultrasound findings of the carotid arteries (degree of stenosis and plaque type) and carotid disease symptoms were also retrieved from medical documentation. The severity of carotid disease was assessed based on the degree of stenosis in the ipsilateral and contralateral carotid arteries, plaque type, and patients' symptomatic status.

Carotid artery stenosis, assessed based on NASCET (*North American Symptomatic Carotid Endarterectomy Trial*) criteria, was categorized as significant or non-significant. A narrowing of the carotid artery lumen by ≥70% was considered significant stenosis. Patients with retinal or focal cerebral ischemia (*amaurosis fugax* or transient ischemic attack–TIA) or stroke within the six months preceding the planned surgery were considered symptomatic patients. Based on the ultrasound findings, carotid plaques were classified as complicated or uncomplicated. Carotid plaques with ulceration, intraplaque hemorrhage, or parietal thrombus were categorized as complicated.

Patient physical activity data were collected using the standardized Baecke questionnaire (12). This questionnaire comprises three groups of scored questions, each assessing one of three dimensions of physical activity: occupational, sports, and recreational. The first group consists of eight questions used to determine the occupational physical activity index. The other two groups contain four questions each and serve to determine the sports and recreational physical activity indices.

The Ethics Committees of the Faculty of Medicine, University of Belgrade (No 1322/XII-1, date December 30, 2021) and Institute for Cardiovascular Diseases "Dedinje (No 6037, date December 21, 2021) approved this study. This study has been conducted in full accordance with national and international ethical guidelines and standards relevant to this type of study.

Categorical data are described by absolute and relative numbers in the form of percentages. For the description of numerical data, arithmetic means with standard deviation were used because they meet the criteria for normal distribution (*Sapiro-Willk* test, histogram and box plot). To test the hypothesis of a difference in the frequency of categories, the chi-square test was used, while to examine differences in numerical data, the Student's t-test for two independent samples was used. Univariate and multivariate logistic regression analyses were performed to examine the association of factors with significant carotid artery stenosis, complicated carotid plaque, and symptomatic carotid disease. Variables with p-values ≤0.1 in the univariate analysis were included in the multi-

variate analysis, with multicollinearity assessed using the VIF method (variables with VIF >5 were excluded from the multivariate model). A p value <0.05 was considered statistically significant. IBM SPSS version 29 was used for the analysis.

RESULTS

The study included 506 patients who underwent carotid endarterectomy. The patients' average age was 67.4 (±7.2) years. Males were more prevalent (56.5%) than females (43.5%).

Demographic characteristics, smoking habits, family history of cardiovascular disease (CVD), comorbidities, therapy used, and laboratory values of the study population, according to the presence of significant stenosis, complicated plaque, and symptomatic status of carotid disease, are shown in **Table 1**. Patients with significant stenosis, compared to those with a <70% degree of stenosis, did not differ statistically significantly in any of the aforementioned characteristics. The only difference between patients with and without complicated plaque was the use of OACs in therapy (p = 0.022). Symptomatic patients (those with TIA, stroke, or *amaurosis fugax*) were more often male (p = 0.026), compared to patients

Table 1. Demographic characteristics, smoking, family history of cardiovascular disease, comorbidities, therapy and laboratory values, according to the presence of significant stenosis, complicated plaque and symptomatic status

Characteristics	Total	Significant stenosis		p*	Complicated plaque		p*	Symptomatic status		p*
		NO (n=72)	YES (n=434)		NO (n=423)	YES (n=83)		NO (n=334)	YES (n=172)	
Age	67.4 ± 7.2	67.9 ± 6.3	67.3 ± 7.3	0.157	67.4 ± 7.1	67.5 ± 7.3	0.790	68.0 ± 6.8	66.3 ± 7.8	0.074
Gender, n (%)							0.332			**0.026**
Male	286 (56.5)	35 (48.6)	251 (57.8)	0.144	235 (55.6)	51 (61.4)		177 (53.0)	109 (63.4)	
Female	220 (43.5)	37 (51.4)	183 (43.4)		188 (44.4)	32 (38.6)		157 (47.0)	63 (36.6)	
BMI, n (%)				0.494			0.675			0.196
18.5-24.9	160 (31.6)	23 (31.9)	137 (31.6)		137 (32.4)	23 (27.7)		114 (43.1)	46 (26.7)	
25-29.9	243 (48)	33 (45.8)	210 (48.4)		200 (47.3)	43 (51.8)		152 (45.5)	91 (52.9)	
≥30	101 (20)	15 (20.8)	86 (19.8)		84 (19.9)	17 (20.5)		66 (19.8)	35 (20.3)	
Smoking, n (%)	258 (51.0)	34 (47.2)	224 (51.6)	0.490	211 (49.9)	47 (56.6)	0.261	160 (47.9)	98 (57.0)	0.053
Family history of CVD, n (%)	246 (48.6)	39 (54.2)	207 (47.7)	0.309	210 (49.6)	36 (43.4)	0.296	175 (52.4)	71 (41.3)	**0.018**
Comorbidities, n (%)										
Myocardial infarction	34 (6.7)	2 (2.8)	32 (7.4)	0.149	29 (6.9)	5 (6.0)	0.782	26 (7.8)	8 (4.6)	0.182
Congestive heart failure	6 (1.2)	0 (0.0)	6 (1.4)	0.316	5 (1.2)	1 (1.2)	0.986	5 (1.5)	1 (0.6)	0.367
Peripheral arterial disease	83 (16.4)	16 (22.2)	67 (15.4)	0.150	66 (15.6)	17 (20.5)	0.272	60 (18.0)	23 (13.4)	0.186
Aneurysmal aortic disease	23 (4.5)	3 (4.2)	20 (4.6)	0.868	20 (4.7)	3 (3.6)	0.656	19 (5.7)	4 (2.3)	0.085
Hyperlipidemia	450 (88.9)	63 (87.5)	387 (89.2)	0.676	377 (89.1)	73 (88.0)	0.755	298 (89.2)	152 (88.4)	0.773
Hypertension	478 (94.5)	70 (97.2)	408 (94.0)	0.269	401 (94.8)	77 (92.8)	0.460	315 (94.3)	163 (94.8)	0.832
Diabetes mellitus	148 (29.2)	16 (22.2)	132 (30.4)	0.157	123 (29.1)	25 (30.1)	0.849	97 (29.0)	51 (29.6)	0.887
Therapy, n (%)										
Aspirin	416 (82.2)	57 (79.2)	359 (82.7)	0.465	346 (81.8)	70 (84.3)	0.580	267 (79.9)	149 (86.6)	0.062
Clopidogrel	138 (27.3)	22 (30.6)	116 (26.7)	0.499	113 (26.7)	25 (30.1)	0.524	77 (23.0)	61 (35.5)	**0.003**
OACs	20 (3.9)	4 (5.6)	16 (3.7)	0.451	13 (3.1)	7 (8.4)	**0.022**	16 (4.8)	4 (2.3)	0.178
ACEIs	376 (74.3)	52 (72.2)	324 (74.6)	0.662	314 (74.2)	62 (74.7)	0.929	239 (71.6)	137 (79.6)	**0.048**
β-blockers	239 (47.2)	36 (50.0)	203 (46.8)	0.612	202 (47.7)	37 (44.6)	0.596	162 (48.5)	77 (44.8)	0.425
Statins	331 (65.4)	43 (59.7)	288 (66.4)	0.273	276 (65.2)	55 (66.3)	0.859	210 (62.9)	121 (70.3)	0.094
Laboratory values, n (%):										
Cholesterol ≥ 5.2 mmol/L	231 (45.6)	36 (50.0)	195 (44.9)	0.485	190 (44.9)	41 (49.4)	0.384	158 (47.3)	73 (42.4)	0.336
Triglycerides ≥ 1.7 mmol/L	275 (54.3)	35 (48.6)	204 (47.1)	0.239	228 (53.9)	47 (56.6)	0.550	179 (53.6)	96 (55.8)	0.562

Abbreviations: ACEIs – angiotensin-converting enzyme inhibitors; BMI – body mass index; CVD – cardiovascular disease; OACs – oral anticoagulants.
*For significance level of 0.05 according to Students t-test and Chi-square test

Table 2. Physical activity, according to the presence of significant stenosis, complicated plaque and symptomatic status

Characteristics	Total, n (%)	Significant stenosis, n (%)		p*	Complicated plaque, n (%)		p*	Symptomatic status, n (%)		p*
		NO (n=72)	YES (n=434)		NO (n=423)	YES (n=83)		NO (n=334)	YES (n=172)	
Occupational physical activity index	2.05 ± 0.69	1.95 ± 0.70	2.06 ± 0.68	0.958	2.05 ± 0.68	2.02 ± 0.70	0.967	2.05 ± 0.69	2.04 ± 0.69	0.972
Sports physical activity index	1.39 ± 0.51	1.42 ± 0.61	1.39 ± 0.50	0.057	1.38 ± 0.51	1.44 ± 0.54	0.542	1.38 ± 0.52	1.43 ± 0.51	0.877
Recreational physical activity index	2.57 ± 0.55	2.56 ± 0.58	2.57 ± 0.55	0.433	2.57 ± 0.57	2.56 ± 0.58	0.492	2.58 ± 0.55	2.54 ± 0.57	0.857

*For significance level of 0.05 according to Students t-test

Table 3. Univariate regression analysis for outcomes: significant stenosis, complicated plaque, and symptomatic status

Characteristics	Significant stenosis			Complicated plaque			Symptomatic status		
	OR	95%CI OR	p*	OR	95%CI OR	p*	OR	95%CI OR	p*
Age	0.99	0.95 - 1.02	0.463	1.00	0.97 – 1.03	0.924	**0.97**	**0.94 – 0.99**	**0.017**
Gender:									
Female	Ref.			Ref.			Ref.		
Male	1.45	0.88 – 2.39	0.145	1.27	0.79 – 2.06	0.323	**1.53**	**1.05 – 2.24**	**0.026**
BMI:									
18,5-24,9	Ref.			Ref.			Ref.		
25-29,9	1.04	0.51 – 2.10	0.915	0.83	0.42 – 1.64	0.592	0.76	0.45 – 1.30	0.316
≥30	1.11	0.57 – 2.15	0.757	1.06	0.570 – 1.97	0.848	1.13	0.69 – 1.83	0.624
Smoking	1.19	0.72 – 1.96	0.490	1.31	0.82 – 2.11	0.262	**1.44**	**1.00 – 2.07**	**0.054**
Family history of CVD	0.77	0.47 – 1.27	0.310	0.78	0.48 – 1.25	0.297	**0.64**	**0.44 – 0.92**	**0.018**
Comorbidities:									
Myocardial infarction	2.77	0.65 - 11.88	0.166	0.87	0.33 – 2.32	0.782	0.58	0.26 – 1.30	0.187
Congestive heart failure	2.72	0.77 - 9.98	0.999	1.02	1.12 – 8.84	0.986	0.38	0.04 – 3.32	0.385
Peripheral arterial disease	0.64	0.35 - 1.18	0.153	1.39	0.77 – 2.52	0.274	0.70	0.42 – 1.19	0.188
Aneurysmal aortic disease	1.11	0.32 - 3.84	0.868	0.76	0.22 – 2.60	0.657	**0.39**	**0.13 – 1.18**	**0.096**
Hyperlipidemia	1.18	0.55 – 2.52	0.676	0.89	0.43 – 1.84	0.755	0.92	0.51 – 1.64	0.773
Hypertension	0.45	0.10 – 1.93	0.282	0.70	0.28 – 1.80	0.462	1.09	0.48 – 2.47	0.832
Diabetes mellitus	1.53	0.85 - 2.76	0.159	1.05	0.63 – 1.76	0.849	1.03	0.69 – 1.54	0.887
Therapy:									
Aspirin	1.26	0.67 – 2.34	0.466	1.20	0.63 – 2.28	0.580	**1.63**	**1.00 – 2.72**	**0.064**
Clopidogrel	0.83	0.48 – 1.43	0.500	1.18	0.71 – 1.98	0.524	**1.83**	**1.23 – 2.74**	**0.003**
OACs	0.65	0.21 – 2.00	0.454	**2.91**	**1.12- 7.52**	**0.028**	0.47	0.16 – 1.44	0.187
ACEIs	1.13	0.65 – 1.98	0.662	1.02	0.60 – 1.76	0.929	**1.56**	**1.01 – 2.42**	**0.049**
β-blockers	0.88	0.53 – 1.45	0.612	0.88	0.55 – 1.41	0.596	0.86	0.59 – 1.24	0.425
Statins	1.33	0.80 – 2.22	0.274	1.05	0.64 – 1.72	0.859	**1.40**	**0.94 – 2.08**	**0.095**
Laboratory values, n (%):									
Cholesterol ≥ 5,2 mmol/L	0.84	0.51 – 1.38	0.485	1.23	0.77 – 1.99	0.384	0.83	0.57 – 1.21	0.336
Triglycerides ≥ 1,7 mmol/L	1.35	0.82 – 2.22	0.240	1.16	0.72 – 1.87	0.550	1.12	0.77 – 1.62	0.562
Physical activity:									
Occupational physical activity index	1.27	0.87 – 1.86	0.212	0.93	0.66 – 1.32	0.692	0.99	0.76 – 1.27	0.951
Sports physical activity index	0.88	0.55 – 1.41	0.596	1.22	0.79 – 1.89	0.374	1.21	0.85 – 1.71	0.294
Recreational physical activity index	1.04	0.66 – 1.64	0.865	0.97	0.63 – 1.49	0.900	0.87	0.62 – 1.22	0.436

Abbreviations: ACEIs – angiotensin-converting enzyme inhibitors; BMI – body mass index; CVD – cardiovascular disease; CI - confidence interval; OACs – oral anticoagulants; OR - odds ratio.
* For significance level of 0.1

without symptoms of carotid disease. However, a family history of cardiovascular disease was less common in the symptomatic group (p = 0.018). Regarding medication, symptomatic patients used clopidogrel (p = 0.003) and ACEIs (p = 0.048) more often than those without symptoms of the disease.

Table 2 presents the physical activity indices according to the presence of significant stenosis, complicated plaque, and symptomatic status of carotid disease. There were no statistically significant differences in any of the examined physical activity indices between the compared groups.

Results of univariate logistic regression analysis are shown in **Table 3**. According to these results, none of the analyzed characteristics was associated with significant stenosis. The only characteristic associated with a complicated plaque was the use of OACs in therapy (OR = 2.91; 95% CI = 1.12–7.52; p = 0.028). Regarding the symptomatic status, patients with TIA, stroke, or *amaurosis fugax* were younger (OR = 0.97; 95% CI = 0.94-0.99; p = 0.017), more often male (OR = 1.53; 95% CI = 1.05–2.24; p = 0.026), and smoked more frequently (OR = 1.44; 95% CI=1.00-2.07; p=0.054) than patients without symptoms of carotid disease. However, a family history of cardiovascular disease was less common in the symptomatic group (OR = 0.64; 95% CI = 0.44-0.92; p = 0.018). Additionally, these patients were less likely to have aneurysmal aortic disease in their personal medical history (OR = 0.39; 95% CI = 0.13-1.18; p = 0.096). Also, symptomatic patients used aspirin (OR = 1.63; 95% CI = 1.00-2.72; p = 0.064), clopidogrel (OR = 1.83; 95% CI = 1.23-2.74; p = 0.003), ACEIs (OR = 1.56; 95% CI = 1.01-2.42; p = 0.049), and statins (OR = 1.40; 95% CI = 0.94-2.08; p = 0.095) more often than those without symptoms of the disease.

Table 4. Results of multivariate logistic regression analysis for the association of various factors with symptomatic carotid disease

Characteristics*	OR	95% CI	p value
Age	**0.97**	**0.94–0.99**	**0.016**
Sex	**0.64**	**0.44–0.99**	**0.028**
Smoking	1.31	0.88–1.93	0.175
Family history of CVD	**0.63**	**0.43–0.94**	**0.022**
Aneurysmal aortic disease	0.36	0.12–1.10	0.074
Aspirin therapy	1.36	0.79–2.33	0.262
Clopidogrel therapy	**1.79**	**1.18–2.71**	**0.006**
ACEIs therapy	**1.60**	**1.02–2.53**	**0.041**
Statins therapy	1.21	0.78–1.87	0.391

Abbreviations: ACEIs – angiotensin-converting enzyme inhibitors; OR – odds ratio; CI – confidence interval; CVD – cardiovascular disease; OACs - oral anticoagulants.

Table 4 presents the results of the multivariate logistic regression analysis examining the association between the studied characteristics and symptomatic status of carotid disease. According to the results of this analysis, age (OR=0.97; 95% CI=0.94–0.99; p=0.016), gender (OR = 0.64; 95% CI = 0.44–0.99; p = 0.028), family history of CVD (OR = 0.63; 95% CI = 0.43–0.94; p = 0.022), as well as use of clopidogrel (OR = 1.79; 95% CI = 1.18–2.71; p = 0.006) and ACEIs in therapy (OR = 1.60; 95% CI = 1.02–2.53; p = 0.041), were independently associated with the symptomatic form of this disease.

DISCUSSION

In this study, we examined the association between physical activity and the severity of carotid disease. The severity of carotid disease was evaluated based on the degree of carotid artery stenosis, the type of carotid plaque, and the patients' symptomatic status. We found that physical activity was not associated with any of the three parameters used to assess carotid disease severity.

It is well known that regular physical activity reduces the risk of cardiovascular morbidity and mortality (13–15). The beneficial effect of physical activity on the cardiovascular system is primarily reflected in the improvement of cardiorespiratory fitness. Furthermore, physical activity positively influences traditional cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes mellitus, and obesity (16). In the literature, the positive effects of physical activity on carotid disease are explained through several mechanisms. Primarily, physical activity reduces insulin resistance (17), and reduced insulin sensitivity is a known independent predictor of increased carotid intima–media thickness (CIMT) (18).

Additionally, physical activity promotes weight loss and has a favorable effect on lipid metabolism and the adipocytokine profile (19), which play significant roles in the development and progression of atherosclerotic lesions in the carotid arteries (20). Moreover, physical activity has been shown to improve endothelial function by increasing nitric oxide (NO) bioavailability (21). Furthermore, favorable effects of physical activity have been reported on blood pressure, systemic inflammation, and platelet aggregation (22, 23), all of which are critical processes in the onset and progression of carotid atherosclerosis.

Numerous studies have examined the link between physical activity and the severity of carotid disease (4–10). Most of these investigations established an inverse association between physical activity and carotid disease severity (5–9); however, some studies, including ours, did not detect such an association (4, 10). A recent Chinese study involving nearly 11,000 high-cardiovascular-risk subjects confirmed an inverse association between physical activity and both CIMT and carotid plaque, particularly among the elderly (24). *Boss et al.* reported similar findings when investigating the impact of physical activity on the carotid artery wall in high-risk patients (25). In that study, higher levels of leisure-time physical activity were associated with a lower risk of carotid artery stenosis.

Furthermore, patients engaged in light physical activity exhibited lower carotid artery stiffness, whereby no additional benefit was observed in patients with higher levels of activity. Additionally, in patients with cardiovascular diseases, physical activity was inversely associated with CIMT, whereas this was not the case for patients with cardiovascular risk factors (25). Results from a recent longitudinal study suggest a positive effect of physical activity on the progression of carotid disease (26). Specifically, higher levels of physical activity, particularly the total step count, were independently associated with a reduction in the progression of CIMT over an eight-year follow-up period. On the contrary, a recent cross-sectional study found no association between moderate-to-vigorous physical activity and abnormal CIMT (4). Similar results were obtained in the SABPA Study (10), where physical activity levels were not related to CIMT (10).

It is important to note that a positive correlation between oral anticoagulants (OACs) and complicated plaque was observed in our study. The literature contains inconsistent data on the relationship between OAC use and atherosclerotic plaque status, depending on the specific type of medication (27). On one hand, numerous experimental and clinical studies have shown that vitamin K antagonists, such as warfarin, induce vascular calcification and progression of atherosclerotic plaques (27–30). It is well established that vitamin K deficiency plays a role in the pathogenesis of cardiovascular disease (31). In recent years, the mechanism by which warfarin contributes to systemic vascular calcification has been discovered (30). On the other hand, direct oral anticoagulants reduce inflammatory processes and smooth muscle cell proliferation within the vessel wall, thereby stabilizing plaque (32, 33).

Furthermore, in our study, age, sex, family history of CVD, and the use of clopidogrel and ACEIs were associated with the occurrence of carotid disease symptoms.

It is well known that older patients have stiffer, more calcified carotid arteries, increasing the risk of thromboembolic ischemic events (34). A recent study examining the impact of age on the progression of carotid atherosclerosis in symptomatic patients found that older patients, compared to younger ones, have more calcified carotid plaques that progress faster and are more prone to destabilization (35). Authors of this study also discovered that age is an independent predictor of annual carotid plaque growth, recommending that carotid plaques in older patients be monitored more frequently (35). A similar association was found in the study by *Ren et al.* (Ren 2015). In this study, age was significantly associated with CIMT as well as the degree of carotid stenosis (36), both of which are predictive of stroke as a clinical manifestation of carotid disease (37).

In our study, females were less likely to present with symptomatic carotid disease, which is largely consistent with previous research (38–40). Existing studies have shown that men have a 33% higher risk of stroke than women (41–43). However, when women do experience a stroke, the clinical course is often more severe, with a higher likelihood of permanent disability (41–43). One explanation for this sex difference is carotid atherosclerosis, a frequent cause of stroke (44). A systematic review and meta-analysis examining the impact of sex on carotid atherosclerosis provided compelling evidence of sex-based disparities in carotid atherosclerosis (38). Specifically, men were more likely than women to have larger carotid plaques.

Additionally, their plaques were more frequently vulnerable compared to those of females. It was even established that these sex differences were more pronounced in symptomatic patients compared to asymptomatic ones. When the same group of authors analyzed the impact of sex on the severity of carotid atherosclerosis exclusively in symptomatic patients, male sex remained a risk factor for larger and more vulnerable carotid plaques (39), which may contribute to the higher risk of clinical manifestations of carotid disease in men. In a study investigating factors associated with symptomatic carotid disease status, male sex was identified as an independent risk factor (40). Furthermore, the authors of that study suggested that sex should be a mandatory component of scoring systems for assessing the risk of symptomatic carotid stenosis (40).

Surprisingly, in our study, patients with a family history of CVD had a lower probability of developing carotid disease symptoms, which is largely contrary to the findings of other studies (45). Our findings may be explained by more frequent follow-up examinations and greater health awareness among patients with a positive family history of CVD.

Additionally, in our work, the use of clopidogrel and ACEIs was significantly associated with symptomatic carotid disease. Clopidogrel is frequently prescribed to patients with a history of stroke. In our study, we analyzed patients' symptomatic status, but not the specific type of symptom. Regarding the use of ACEIs, it has long been established that they exert a protective effect on the cardiovascular system through several mechanisms, including hypertension control, inhibition of platelet aggregation, reduction of oxidative stress, stimulation of nitric oxide production, and enhancement of endogenous fibrinolysis (46). Moreover, they have been shown to stabilize carotid plaques (47). In our study, patients using clopidogrel and ACEIs likely had a more severe form of the disease from the outset.

In this research, the standardized Baecke questionnaire was used to assess physical activity. The fact that this method relies on subjects' subjective assessments of their physical activity may be a limiting factor. Another limitation of the study is that we did not investigate the specific type of oral anticoagulant medication used in therapy. Moreover, the study uses a cross-sectional design, which makes it difficult to draw causal conclusions. Additional studies are needed, particularly randomized

controlled trials (RCTs). Bearing in mind the high prevalence of physical inactivity in patients with carotid disease, as well as the fact that CVDs are the leading cause of morbidity and mortality in our country, it is necessary to target this population using preventive approaches. In patients with carotid disease, the implementation of appropriate physical activity programs is strongly recommended to slow disease progression and prevent potential complications.

CONCLUSION

Physical activity was not associated with the severity of carotid disease. However, the use of OACs in therapy was significantly associated with the presence of complicated carotid plaques. Additionally, age, gender, family history of CVD, as well as use of clopidogrel and ACEIs in therapy were independently associated with the symptomatic disease status.

Acknowledgements: N/A

Funding Information: The authors declare that the study received no funding.

Conflicts of interest: The authors have no conflicts of interest to report.

Author Contributions: Conceptualization, D.V. and M.M.; Methodology, D.V. and A.C.; Formal Analysis, A.C.; Investigation, D.V.; Writing–Original Draft Preparation, D.V.; Writing – Review & Editing, H.V.; Supervision, S.T.;

Ethical approval: The Ethics Committees of the Faculty of Medicine, University of Belgrade (No 1322/XII-1, date December 30, 2021) and the Institute for Cardiovascular Diseases "Dedinje (No 6037, date December 21, 2021) approved this study. This study has been conducted in full accordance with national and international ethical guidelines and standards relevant to this type of study.

Informed consent: N/A

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POVEZANOST FIZIČKE AKTIVNOSTI SA TEŽINOM KAROTIDNE BOLESTI

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Sažetak

Uvod: Redovna fizička aktivnost smanjuje rizik od kardiovaskularnih bolesti. Cilj ovog istraživanja je bio da ispitamo povezanost fizičke aktivnosti sa težinom karotidne bolesti.

Materijal i metode: Ovom studijom preseka obuhvaćeno je 506 pacijenata Klinike za vaskularnu hirurgiju, Instituta za kardiovaskularne bolesti Dedinje, kod kojih je urađena karotidna endarterektomija u periodu od 2012. do 2017. godine. Težina karotidne bolesti je procenjena na osnovu stepena stenoze karotidne arterije, vrste karotidnog plaka i simptomatskog statusa pacijenata pre operacije. Podaci o fizičkoj aktivnosti pacijenata prikupljeni su korišćenjem standardizovanog Bekeovog upitnika. Univarijantna i multivarijantna logistička regresija su korišćene za ispitivanje povezanosti fizičke aktivnosti, kao i drugih faktora, sa težinom karotidne bolesti.

Rezultati: Prema univarijantnoj analizi, nije postojala statistički značajna povezanost nijednog oblika fizičke aktivnosti (na poslu, sportske ili rekreativne) sa stepenom stenoze karotidne arterije, kao ni drugih ispitivanih karakteristika. Takođe, fizička aktivnost nije bila povezana ni sa komplikovanim karotidnim plakom. Jedina karakteristika povezana sa komplikovanim karotidnim plakom bila je upotreba OAK u terapiji (OR=2,91; CI=1,12-7,52; p=0,028). Veza između fizičke aktivnosti i simptomatske karotidne bolesti nije uočena, ali su prema rezultatima multivarijantne analize sa simptomatskim statusom bili povezani sledeći faktori: starost (OR=0,97; 95% CI 0,94-0,99; p=0,016), pol (OR=0,64; 95% CI 0,44-0,99; p=0,028), porodično opterećenje KVB (OR=0,63; 95% CI 0,43-0,94; p=0,022), upotreba klopidogrela (OR 1,79; 95% CI 1,18-2,71; p=0,006) i ACEI u terapiji (OR=1,60; 95% CI 1,02-2,53; p=0,041).

Zaključak: Fizička aktivnost nije bila povezana sa težinom karotidne bolesti.

Ključne reči: fizička aktivnost, karotidna bolest, karotidna stenoza, karotidni plak

Primljen: 26. 01. 2026. I **Revidiran**: 10. 02. 2026. I **Prihvać**en: 13. 02. 2026. I **Online First:** 24. 02. 2026.

Medicinska istraživanja 2026