**Russian Journal of Cardiology 2021;26(5):**4379
doi:10.15829/1560-4071-2021-4379
https://russjcardiol.elpub.ru

ORIGINAL ARTICLES
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

# Factors associated with carotid plaque burden in the adult general population

Kaveshnikov V. S., Trubacheva I. A., Serebryakova V. N.

**Aim.** To study the relationship between carotid plaque burden and conventional, behavioral, and social cardiovascular risk factors.

**Material and methods.** The object of the study was 469 people (women, 49%) from a representative sample of the general population aged 25-64 years (cross-sectional ESSE-RF study) with the presence of one or more atherosclerotic plaques in the carotid arteries. The study participants underwent cardiac screening and carotid ultrasound. All respondents signed informed consent. The number of involved segments and the average plaque height were studied. The associative analysis included blocks of conventional, social, and behavioral risk factors for cardiovascular diseases. The study of relationships was carried out using linear and log-linear models. An error probability <5% was considered significant.

**Results.** According to multivariate analysis, age (in men), male sex, smoking, systolic blood pressure (SBP), total cholesterol, heart rate, alcohol abuse, statin and β-blocker therapy were interrelated with the number of involved segments. In turn, the average plaque size was associated with age (in men), male sex, higher education, alcohol abuse, smoking, and high-sensitivity C-reactive protein.

**Conclusion.** The results obtained confirm the leading role of age (in men), smoking, SBP, total cholesterol, β-blockers as indicators of the number of involved segments. Alcohol abuse and heart rate have shown associations between the ages of 40-50 years and thus may contribute to premature atherosclerosis. Key role of age (in men), sex (among those ≥50 years old), and educational status in average plaque height in this study was confirmed. A significant contribution was also made by alcohol abuse, smoking, high-sensitivity C-reactive protein. The obtained data do not confirm the hypothesis about the contribution of atherogenic lipoproteins and SBP to average plaque height. The study results can be useful for studying the plaque burden role in risk stratification and further development of cardiovascular prevention.

**Keywords:** population study, ultrasound examination, carotid atherosclerosis, plaque burden, risk factors.

**Relationship and Activities:** none.

**Acknowledgments.** The authors are grateful to all participants of the ESSE-RF study (Tomsk) for their invaluable contribution to this work. The authors express their special gratitude to Doctor of Medical Science, Professor T. V. Balakhonova (Moscow) for consulting on the ultrasound measurements; Yu. V. Zhernakova (Moscow) for coordinating the ESSE-RF study, T. I. Kotkina (Moscow) for the determination of high-sensitivity C-reactive protein and lipid profile parameters in the ESSE-RF study.

Cardiology Research Institute, Tomsk National Research Medical Center, Tomsk, Russia.

Kaveshnikov V. S.* ORCID: 0000-0002-0211-4525, Trubacheva I. A. ORCID: 0000-0003-1063-7382, Serebryakova V. N. ORCID: 0000-0002-9265-708X.

*Corresponding author: kave@ngs.ru

**Received:** 01.03.2021
**Revision Received:** 22.03.2021
**Accepted:** 28.03.2021



**For citation:** Kaveshnikov V. S., Trubacheva I. A., Serebryakova V. N. Factors associated with carotid plaque burden in the adult general population. *Russian Journal of Cardiology*. 2021;26(5):4379. (In Russ.) doi:10.15829/1560-4071-2021-4379

The current trends in cardiovascular diseases (CVD) in Russia and other countries of the world continue to indicate its leading contribution to the premature mortality of the working-age population. In view of the significant socioeconomic damage, CVD prevention by early detection and correction of their risk factors (RFs) is considered as one of the priorities of the long-term socioeconomic development of Russia [1].

Known to date, 50-60% of mortality among population is due to classical RFs of CVD [2]. In various directions, the search for additional RFs continues, which can be influenced or used to develop prognostic tools. The promising tools include peripheral vascular ultrasound [3]. From the early research of carotid stenosis, current papers is increasingly devoted to subclinical atherosclerosis, quantitative assessment and its role in cardiovascular risk stratification. To determine the severity of atherosclerotic involvement, parameters of plaque burden (PB) are used. Research indicates the relationships between such parameters and cardiovascular events [3, 4].

It is known that the development of atherosclerosis and CVD is promoted by major RFs. However, it remains unclear why, with the same susceptibility to major RFs, the individual severity of atherosclerosis varies widely? What additional factors influence the atherogenesis, and to what extent does PB measurement help in predicting cardiovascular risk?

A considerable volume of data on the factors influencing the development and severity of atherosclerosis originates in clinical studies. The extent to which clinical patterns can be extrapolated to the entire population is an important question that can be answered by epidemiological studies. Examples of such studies studying the relationship between PB and RFs are Atherosclerosis Risk in Communities, Malmö Diet and Cancer study, Tromsø Study. In the Russian working-age population, these issues have not been sufficiently studied.

The aim of the current paper was to study the relationships between the key PB indicators in the carotid system and the classical, behavioral and social RFs of CVD in the adult working-age population.

## Material and methods

As part of the ESSE-RF cross-sectional study, the analysis of data from 469 respondents aged 25-64 years (n=1600; women, 59%) with one or more atherosclerotic plaques in the carotid system. The detailed design of the study and sampling methods were published earlier [5]. All subjects signed informed consent. All respondents underwent standard cardiac screening and carotid duplex ultrasound using a high-end ultrasound system with a 7,5 MHz linear transducer. The number of involved carotid segments (common and internal carotid arteries, bifurcation) on the right and left, and the maximum plaque height in each segment were measured. The average plaque height was determined as the sum of plaque sizes in 6 segments divided by the number of involved segments. The number of involved segments and the average plaque height were analyzed. Details of ultrasonic measurements are given in previously published works [6, 7].

The association analysis included age, sex, education, marital status, number of children, income level, type of dwelling; the presence of hypertension, myocardial infarction, stroke, diabetes in first-degree relatives; physical activity, smoking, alcohol consumption; glomerular filtration rate, diabetes; medical appointment in the past year, body mass index, systolic and diastolic blood pressure, heart rate (HR); taking beta-blockers (BB), diuretics, angiotensin-converting enzyme inhibitors, statins; total cholesterol (TC), high density lipoproteins (HDL), triglycerides, highly sensitive C-reactive protein (hs-CRP), glucose.

The boundary between moderate alcohol consumption and abuse was considered to be 168 g of ethanol per week for men and 84 g for women. Intense physical activity was considered an exercise for at least 20-30 minutes, causing the sweating or mild shortness of breath. Glomerular filtration rate was determined using the CKD-EPI equation.

Statistical analysis was performed using SPSS (v.13) and R (v.2.15) programs. Frequencies were compared by the chi-squared method and Fisher's exact test. To compare quantitative variables, Student's t and the Mann-Whitney test were used. To analyze the number of involved segments and the average plaque height, a generalized linear model of the gamma family of distributions with a log link function and a log-linear model were used, respectively. The variables such as sex, age, income level, and statin intake were entered into the model as covariates. An error probability <5% was considered significant.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committees of all participating centers approved this study. All patients signed informed consent.

## Results

Comparative characteristics of the surveyed sample depending on sex are presented in Table 1. Women were on average 2 years older than men, smoked less often, had lower number of involved

**Table 1**

**Comparative characteristics of the surveyed sample**

| Factor | Men (n=239) | Women (n=230) | p |
|---|---|---|---|
| Age, years, m(se) | 54,2 (0,46) | 56,2 (0,41) | 0,001 |
| Sex, % | 51,0 | 49,0 | - |
| Higher education, % | 44,6 | 38,3 | 0,164 |
| Smoking ⩾10 cigarettes per day, % | 42,9 | 10,0 | <0,001 |
| Cardiovascular diseases, % | 20,4 | 20,0 | 0,910 |
| Statins, % | 6,3 | 7,8 | 0,501 |
| Number of plaques, m(se) | 2,03 (0,07) | 1,57 (0,06) | <0,001 |
| Average plaque height, m(se) | 1,96 (0,04) | 1,71 (0,03) | <0,001 |
| SBP, mm Hg | 144,4 (1,43) | 140,4 (1,52) | 0,054 |
| Total cholesterol, mmol/L | 5,9 (0,09) | 6,4 (0,09) | <0,001 |
| Glucose, mmol/L | 5,8 (0,10) | 5,9 (0,11) | 0,450 |

**Abbreviation:** SBP — systolic blood pressure.

segments, average plaque height and a higher level of TC.

To identify the factors associated with the number of involved segments, a multiple stepwise regression model was created ($\chi^2$=184,0; df=14, p<0,001) with the inclusion of significant interactions — (male) sex with age (b=0,037; p<0,001) and systolic blood pressure (SBP) (b=-0,009; p<0,001), age with alcohol abuse (b=-0,030; p=0,008) and heart rate (b=-0,008; p=0,014). The results are shown in Table 2.

As can be seen from the table, age is associated with the number of involved segments only in men, and the SBP level — only in women, respectively. Regular smoking of 10 or more cigarettes a day, TC showed a direct association, while BB intake — an inverse association, respectively. The sex effect varied depending on age and SBP. With an average SBP and an adjustment for other RFs, significant sex differences were revealed only for patents aged ⩾60 years.

A significant contribution to the studied parameter was made by alcohol abuse and heart rate. Such associations were limited in age to 50 and 55 years, respectively.

To study the factors interrelated with the average plaque height, a multiple stepwise regression model (F=9,85; df=10, p<0,001; $R^2$=0,18) was created with the inclusion of significant interactions — age with the (male) sex (b=0,008; p=0,014) and alcohol abuse (b=-0,012; p=0,042), respectively. The results are shown in Table 3.

Age in men, smoking 10 or more cigarettes a day, hs-CRP, and alcohol abuse under the age of 55 were associated with higher average plaque height. The contribution of alcohol abuse to the studied parameter was higher in the young age than in the middle one. Higher education has been shown to be the only protective factor. After adjusting for significant covariates, the sex difference in the average plaque height was observed already at the age of 50, and it increased further.

## Discussion

The development of approaches to improving the cardiovascular health of the population requires not only knowledge of RFs associated with cardiovascular morbidity and mortality, but also a more substantive understanding of the relationship between factors and structural vascular defects.

Measurement of peripheral arterial plaque burden is possible using such integral parameters as the total plaque height. However, to study various atherogenesis aspects, it is advisable to separately consider the number of involved segments and the average plaque height, reflecting the extent of atherosclerosis and the average severity of atheromatosis, respectively. The aim of this work was to study plaque burden patterns from this point of view.

Evidence from epidemiological studies on the plaque burden determinants is controversial. In most of them, the role of major RFs is described — age, male sex, TC, HDL, smoking, SBP, etc. [8-11].

In this study, age (in men) and smoking made the greatest contribution to this indicator, which is consistent with other papers [8-10]. In women, the relationship with age was not noted, which confirms the results of univariate analysis [6]. It should be noted the weak effect of sex on the of involved segments, observed only in persons aged ⩾60 years.

**Table 2**

**Factors associated with the number of involved segments according to multivariate analysis**

| Factor | Coefficient | t-test | p |
|---|---|---|---|
| Age* (men) | 0,034 | 6,589 | <0,001 |
| Age* (women) | -0,003 | -0,663 | 0,507 |
| Male sex* : | | | |
| — age of 50 years | -0,017 | 0,109 | 0,914 |
| — age of 55 years | 0,169 | 1,080 | 0,280 |
| — age of 60 years | 0,355 | 2,138 | 0,033 |
| SBP (men) | -0,001 | -1,040 | 0,298 |
| SBP (women) | 0,008 | 6,452 | <0,001 |
| Regular smoking ⩾10 cigarettes | 0,315 | 6,422 | <0,001 |
| Total cholesterol | 0,049 | 3,177 | 0,001 |
| Alcohol abuse: | | | |
| — age of 40 years | 0,418 | 2,545 | 0,011 |
| — age of 45 years | 0,270 | 2,267 | 0,023 |
| — age of 50 years | 0,122 | 1,439 | 0,150 |
| Heart rate | | | |
| — age of 45 years | 0,099 | 2,481 | 0,013 |
| — age of 50 years | 0,057 | 2,118 | 0,034 |
| — age of 55 years | 0,016 | 0,812 | 0,417 |
| Beta blockers | -0,137 | -2,162 | 0,031 |
| Statins | 0,263 | 3,099 | 0,002 |
| Income status | 0,019 | 0,866 | 0,375 |

**Note:** * — mean values of other factors.
**Abbreviation:** SBP — systolic blood pressure.

A strong association with the studied parameter is demonstrated by SBP in women. The important role of this factor is noted in most works [8-11]. In a population study performed in Japan, age and SBP were the only determinants of plaque number in women [8]. The absence of such effect in men is inconsistent with research data, which requires further study.

Atherogenic lipoproteins are considered key factors in atherogenesis. In this study, TC showed a significant association with the number of involved segments, which confirms the data of previous works [8-10] and indirectly indicates its effect on the formation of new plaques ABP. This talking point is confirmed in the prospective study by Johnsen SH, et al. [12], demonstrating the relationship of TC with the formation of new plaques.

The analysis shows a direct association of heart rate and alcohol abuse with the number of involved segments among people aged 40-50 years. The influence of these factors has been less often discussed in population studies. It has been reported that there is a relationship between resting heart rate and the occurrence of plaques in the Chinese population [13]. The results obtained indirectly confirm the prospective study by Kiechl S, et al. [14], demonstrating the association of alcohol abuse with the involvement of new carotid segments in the northern Italian population.

An inverse association of the studied parameter with BB intake was revealed. One of the reasons of this effect may be the achievement of lower heart rate among older people, in whom the prescription rate of these drugs increases. Antihypertensive therapy, as well as individual antihypertensive drugs of other classes did not show significant relationships in this aspect.

The most significant predictors in average plaque height were age (in men), male sex among people aged ⩾50 years, and higher education. In contrast to the number of involved segments, the sex effect was observed 10 years earlier. The epidemiological studies on the effect of sex in this aspect are very ambiguous, while foreign studies showed less significant sex differences [8-10]. The education influence on plaque burden was rarely studied in

**Table 3**

**Factors associated with the average plaque height according to multivariate analysis**

| Factor | Coefficient | t-test | p |
|---|---|---|---|
| Age (men) | 0,112 | 4,847 | <0,001 |
| Age (women) | 0,003 | 1,278 | 0,201 |
| Male sex: | | | |
| — age of 45 years | 0,029 | 0,673 | 0,501 |
| — age of 50 years | 0,070 | 2,265 | 0,024 |
| — age of 55 years | 0,111 | 4,394 | <0,001 |
| Statins | 0,082 | 1,828 | 0,068 |
| Income status | 0,003 | 0,278 | 0,781 |
| Higher education | -0,078 | -3,244 | 0,001 |
| Regular smoking ⩾10 cigarettes | 0,068 | 2,408 | 0,016 |
| C-reactive protein (log) | 0,024 | 2,406 | 0,017 |
| Alcohol abuse: | | | |
| — age of 45 years | 0,183 | 2,762 | 0,006 |
| — age of 50 years | 0,120 | 2,544 | 0,011 |
| — age of 55 years | 0,057 | 1,339 | 0,181 |

foreign publications. The data obtained indicate the protective effect of higher education on plaque burden.

Alcohol abuse, regular smoking of 10 or more cigarettes and hs-CRP were associated with higher average plaque height. Compared to the number of involved segments, the effect of alcohol abuse in this regard covered a wider age segment and up to 50 years was at least as important or more significant than smoking. The relationship between the studied parameter and hs-CRP confirms the role of chronic inflammation in the atheroma progression.

There was no significant associations of average plaque sizes with lipid profile parameters. TC is the leading modifiable factor effecting carotid plaque formation in the general population [15]. TC can be associated with the number of involved segments in men [8], the severity of maximal stenosis [10], and the total plaque height [8]. There is a relationship between the total plaque area and low density lipoproteins to HDL ratio [9]. In prospective studies, the relationship of TC with the total plaque area progression is confirmed in the study by Header M, et al. [16] and refuted by Johnsen SH, et al. [12]. The association of the factor with the average plaque height indirectly indicates the contribution of this factor to plaque burden progression due to the increase in plaque size. In most of the above papers, however, authors studied associations in relation to the total plaque burden, which does not allow us to fully determine the influence of RF on its individual components. Thus, the results obtained are consistent with other papers demonstrating the leading role of atherogenic lipoproteins in plaque burden progression due to the formation of new atherosclerotic plaques.

Study limitations include its cross-sectional design, which does not give a complete picture of the cause-and-effect relationship. The assumptions made are probabilistic in nature. The revealed relationships with TC, SBP, heart rate, alcohol abuse require further study, including as part of prospective studies.

## Conclusion

The results obtained confirm the leading role of age (in men), smoking, SBP and total cholesterol as indicators of the number of involved segments. Alcohol abuse and heart rate have shown associations between the ages of 40-50 years and thus may contribute to premature atherosclerosis. Key role of age (in men), sex (among those ⩾50 years old), and educational status in average plaque height in this study was confirmed. A significant contribution was also made by alcohol abuse, smoking, high-sensitivity C-reactive protein. The obtained data do not confirm the hypothesis about the contribution of atherogenic lipoproteins and SBP to average plaque height. The study results can be useful for studying the plaque burden role in risk stratification and further development of cardiovascular prevention.

**Acknowledgments.** The authors are grateful to all participants of the ESSE-RF study (Tomsk)

for their invaluable contribution to this work. The authors express their special gratitude to Doctor of Medical Science, Professor T. V. Balakhonova (Moscow) for consulting on the ultrasound measurements; Yu. V. Zhernakova (Moscow) for coordinating the ESSE-RF study, T. I. Kotkina (Moscow) for the determination of high-sensitivity C-reactive protein and lipid profile parameters in the ESSE-RF study.

**Relationships and Activities:** none.

## References

1. Kontsevaya AV, Drapkina OM, Balanova YA, et al. Economic burden of cardiovascular diseases in the Russian Federation in 2016. Rational Pharmacotherapy in Cardiology. 2018;14(2):156-66. (In Russ.) doi:10.20996/1819-6446-201814-2-156-166.
2. Ford ES, Capewell S. Proportion of the decline in cardiovascular mortality disease due to prevention versus treatment: public health versus clinical care. Annu. Rev. Public. Health. 2011;32:5-22. doi:10.1146/annurev-publhealth-031210-101211.
3. Ershova AI, Meshkov AN, Deev AD, et al. Atherosclerotic plaque in carotid arteries as a risk marker for cardiovascular events risk in middle aged population. Cardiovascular Therapy and Prevention. 2018;17(4):34-9. (In Russ.) doi:10.15829/1728-8800-2018-4-34-39.
4. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur. Heart. J. 2020;41(1):111-88. doi:10.1093/eurheartj/ehz455.
5. Chazova IE, Trubacheva IA, Zhernakova YuV, et al. The prevalence of arterial hypertension as a risk factor of cardiovascular diseases in one of the cities in siberian federal district. Systemic Hypertensions. 2013;10(4):30-7. (In Russ.)
6. Kaveshnikov VS, Serebryakova VN, Trubacheva IA. Carotid atherosclerosis severity in unorganized adult population. Rational Pharmacotherapy in Cardiology. 2019;15(1):84-9. (In Russ.) doi:10.20996/1819-6446-2019-15-1-84-89.
7. Zhernakova YuV, Kaveshnikov VS, Serebriakova VN, et al. The prevalence of carotid atherosclerosis in spontaneous populations in Tomsk. Systemic Hypertensions. 2014;11(4):37-42. (In Russ.)
8. Mannami T, Konishi M, Baba S, et al. Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factors in the general population of a Japanese city: the Suita study. Stroke. 1997;28(3):518-25. doi:10.1161/01.str.28.3.518.
9. Kuo F, Gardener H, Dong C, et al. Traditional cardiovascular risk factors explain the minority of the variability in carotid plaque. Stroke. 2012;43(7):1755-60. doi:10.1161/STROKEAHA.112.651059.
10. Fabris F, Zanocchi M, Bo M, et al. Carotid plaque, aging, and risk factors. A study of 457 subjects. Stroke. 1994;25(6):1133-40. doi:10.1161/01.str.25.6.1133.
11. Pan XF, Lai YX, Gu JQ, et al. Factors Significantly Associated With the Increased Prevalence of Carotid Atherosclerosis in a Northeast Chinese Middle-aged and Elderly Population: A Cross-sectional Study. Medicine. (Baltimore). 2016;95(14):e3253. doi:10.1097/MD.0000000000003253.
12. Johnsen SH, Ellisiv BM. Ultrasound imaging of carotid atherosclerosis in a normal population. The Tromso Study. Norsk Epidemiologi. 2009;19(1):17-28.
13. Wang L, Zhang N, Sun BG, et al. Elevated Resting Heart Rate Is Associated with Carotid Atherosclerosis in Middle-Aged and Elderly Chinese Population. J. Stroke. Cerebrovasc. Dis. 2016;25(1):34-40. doi:10.1016/j.jstrokecerebrovasdis.2015.08.030.
14. Kiechl S, Willeit J, Rungger G, et al. Alcohol consumption and atherosclerosis: what is the relation? Prospective results from the Bruneck Study. Stroke. 1998;29(5):900-7. doi:10.1161/01.str.29.5.900.
15. Kaveshnikov VS, Serebryakova VN, Trubacheva IA, et al. Descriptive model of carotid atherosclerosis prevalence in adult urban population of Siberian region. The Siberian Medical Journal. 2015;30(2):131-6. (In Russ.)
16. Herder M, Arntzen KA, Johnsen SH, et al. Long-term use of lipid-lowering drugs slows progression of carotid atherosclerosis: the Tromso study 1994 to 2008. Arterioscler. Thromb. Vasc. Biol. 2013;33(4):858-62. doi:10.1161/ATVBAHA.112.300767.