УДК 616.12-005.4-02:613.84
https://doi.org: 10.20538/1682-0363-2021-1-7-15

Association of smoking with coronary artery disease depending on other cardiovascular risk factors

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ABSTRACT

Aim. To study the possibility of the presence of coronary artery disease (CAD) depending on the smoking status, as well as to estimate the association of smoking with other traditional risk factors in residents of Kemerovo region aged 25–64 years.

Materials and methods. We analyzed the results of the multicenter epidemiological study "Epidemiology of cardiovascular diseases and their risk factors in the Russian Federation" in Kemerovo region obtained from a random sample of 1,599 subjects aged 25–64 years. Besides the smoking status, the following parameters were analyzed: gender, age, education, diabetes mellitus (DM) and arterial hypertension (AH) history, hypercholesterolemia, hypertriglyceridemia, high level of low-density lipoproteins (LDL), low level of high-density lipoproteins (HDL), hyperglycemia, obesity, alcohol abuse, and depression.

Results. Three groups were formed depending on the smoking status: group 1 included 484 (30.3%) current smokers, group 2 included 317 (19.8%) former smokers and group 3 consisted of 798 (49.9%) individuals who had never smoked. The groups did not differ in the prevalence of CAD. When determining the rank significance of the impact of risk factors on the possibility of CAD development in the overall population, it was revealed that the age affected the risk of CAD the most, while smoking and low HDL had minimal impact. The impact of the smoking factor on CAD was higher in the representatives of the older age group; however, even in the subjects aged ≥ 50 years, the smoking factor was not the leading one and followed DM, hypertriglyceridemia, depression, and obesity. The possibility of CAD development in smokers, as opposed to individuals who had never smoked, increased when smoking was accompanied by hypercholesterolemia, hypertriglyceridemia, male sex, lack of higher education, depression, and age of ≥ 50 years. The possibility of CAD development in former smokers, as opposed to non-smokers increased when smoking was accompanied by hyperglycemia.

Conclusion. Smoking is not the primary risk factor in CAD detection in the studied sample. In the presence of additional risk factors, the impact of smoking on the possibility of CAD detection increases.

Key words: coronary artery disease, smoking, risk factors.

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study.

Conformity with the principles of ethics. All individuals were notified of the objectives of the study and signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at the Research Institute for Complex Issues of Cardiovascular Diseases (Protocol No. 71 of 02.09.2013).

For citation: Bazdyrev E.D., Maksimov S.A., Galimova N.A., Mulerova T.A., Indukaeva E.V., Artamonova G.V., Barbarash O.L. Association of smoking with coronary artery disease depending on other cardiovascular risk factors. *Bulletin of Siberian Medicine.* 2021; 20 (1): 7–15. https://doi.org: 10.20538/1682-0363-2021-1-7-15.

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Связь курения с ишемической болезнью сердца в зависимости от других факторов сердечно-сосудистого риска

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РЕЗЮМЕ

Цель. Изучение вероятности наличия ишемической болезни сердца (ИБС) в зависимости от статуса курения, а также оценка связи курения с другими традиционными факторами риска у жителей Кузбасского региона в возрасте 25–64 лет.

Материалы и методы. Проведен анализ результатов многоцентрового эпидемиологического исследования «Эпидемиология сердечно-сосудистых заболеваний и их факторов риска в Российской Федерации» в Кемеровской области, полученных на случайной выборке 1 599 человек в возрасте 25–64 лет. Помимо статуса курения анализировались пол, возраст, образование, наличие сахарного диабета (СД) и артериальная гипертензия, гиперхолестеринемия, гипертриглицеридемия, высокий уровень липопротеидов низкой плотности, низкий уровень липопротеидов высокой плотности (ЛПВП), гипергликемия, ожирение, злоупотребление алкоголем и депрессия.

Результаты. В зависимости от статуса курения сформированы три группы. Первая группа – курящие в настоящее время, 484 человека (30,3%), вторая – курившие в прошлом, 317 (19,8%), и третья группа – никогда не курившие, 798 человек (49,9%). Группы не имели различий по распространенности ИБС. При определении ранговой значимости влияния факторов риска на вероятность ИБС в общей популяции выявлено, что возраст является самым сильным фактором, а курение и низкий уровень ЛПВП – минимальными. Степень влияния на ИБС фактора курения выше у представителей старшей возрастной группы, однако даже у лиц в возрасте 50 лет и старше факт курения не занял лидирующие позиции и следовал за СД, гипертриглицеридемией, депрессией и ожирением. Вероятность ИБС у курящих в сравнении с никогда не курившими усиливается при сочетании курения с гиперхолестеринемией, гипертриглицеридемией, мужским полом, отсутствием высшего образования, наличием депрессии и возрастом 50 лет и старше. У куривших в прошлом к не курящим – при сочетании с гипергликемией.

Заключение. Курение является не первостепенным фактором риска при выявлении ИБС в исследуемой выборке, а при наличии дополнительных факторов риска влияние курения на вероятность выявления ИБС усиливается.

Ключевые слова: ишемическая болезнь сердца, курение, факторы риска.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом НИИ КПССЗ (протокол № 71 от 02.09.2013).

Для цитирования: Баздырев Е.Д., Максимов С.А., Галимова Н.А., Мулерова Т.А., Индукаева Е.В., Артамонова Г.В., Барбараш О.Л. Связь курения с ишемической болезнью сердца в зависимости от других факторов сердечно-сосудистого риска. *Бюллетень сибирской медицины.* 2021; 20 (1): 7–15. https://doi.org: 10.20538/1682-0363-2021-1-7-15.

INTRODUCTION

Coronary artery disease (CAD) has been a leading cause of death and disability for many years, not only in the Russian Federation, but all over the world. It is generally accepted that risk factors, such as impaired lipid and carbohydrate metabolism, arterial hypertension (AH), excessive alcohol intake, low physical activity, obesity, and smoking, play a crucial role in the development of cardiovascular diseases (CVD). Research in recent years has focused primarily on the analysis of cause-and-effect relationships from the point of view of the isolated influence of these factors on the possibility of developing CAD. Unfortunately, there are not enough studies that demonstrate a comprehensive approach to assessing a possible impact of smoking in combination with other traditional cardiovascular risk factors.

MATERIALS AND METHODS

The analysis was based on the results of the study "Epidemiology of cardiovascular diseases and their risk factors in the Russian Federation" in Kemerovo region, where a random sample of male and female adults aged 25–64 years (1,628 people) was investigated. The final sample size was 1,599 people after exclusion of individuals with incomplete data. Their influence on the final results was not analyzed, since the percentage of missing data was less than 2%.

The study was conducted in accordance with the standards of good clinical practice and the principles of the Helsinki Declaration. The patients signed an informed consent approved by the institution's Ethics Committee before being included in the study.

The presence of CAD was assessed according to the sum of 3 epidemiological criteria: ECG encoded changes later classified according to the Minnesota code and the Rose questionnaire and myocardial infarction (MI) in the medical history.

Depending on smoking habits, the respondents were divided into three groups. Current smokers were those who smoked at least one cigarette a day or quit smoking less than a year ago. "Former" smokers were patients who had quit smoking a year or more before inclusion in the study, non-smokers were those who had never smoked [1].

In addition to smoking, the following cardiovascular risk factors were analyzed: sex, age, education, diabetes mellitus (DM) and AH, hypercholesterolemia, hypertriglyceridemia, high LDL, low HDL, hyperglycemia, obesity, alcohol abuse, and depression.

The smoking status (non-smokers / former smokers / smokers), education (higher education / lack of higher education), diabetes (according to the respondent), peculiarities of alcohol consumption, and the level of depression were assessed according to the survey data. Alcohol consumption was assessed based on the data on the frequency, amount and type of alcoholic beverages consumed. The volume of alcohol consumption for the year was calculated, followed by conversion to average daily values in grams of ethanol. Alcohol abuse was classified with estimated average daily ethanol consumption of more than 72 grams.

The hospital scale of anxiety and depression (HADS), validated in Russia, was used to assess depression. The 75th percentile of depression in this sample was calculated, in case values were above it, the level of depression was considered to be increased. AH was classified at systolic blood pressure (SBP) ≥140 mm Hg and / or diastolic blood pressure (DBP) ≥ 90 mm Hg, regardless of the level of blood pressure during the intake of antihypertensive drugs. The person was considered to be obese if the value of the Body Mass Index was ≥ 30 kg / m^2. Hypercholesterolemia was defined when the concentration of total cholesterol was over 5.0 mmol / l, hypertriglyceridemia was detected if the triglyceride level was more than 1.7 mmol / l, high LDL was registered if values were greater than 3.0 mmol / l, low HDL – if values were less than 1.0 mmol / l, and fasting hyperglycemia was classified at the glucose level of more than 5.6 mmol / l.

The distribution of quantitative indicators was evaluated, taking into account that the distribution did not deviate significantly from the normal value. Descriptive statistics methods were used to calculate the average value (*M*) and standard deviation (*SD*) for quantitative indicators and frequency for qualitative indicators. The Kruskall – Wallis test and the Pearson Chi-square test were used to evaluate differences in quantitative indicators. The ranking of the risk factor influence on the probability of developing CAD was determined using decision trees. The method of discriminant one-dimensional

branching for categorical and ordinal predictors was applied.

Equal cost of misclassification of objects and a priori probabilities proportional to the size of classes of the dependent variable were taken as the forecast accuracy criteria. Pruning according to the classification error initiated a branching stop, the minimum number of misclassified objects was 12, and the value of a standard error was 1.0. The importance of risk factors in the analysis of classification trees was estimated according to a conventional 100-point scale, 100 conventional units (c.u.) were accepted as an important predictor that impacted most on the classified object.

Logistic regression analysis was used to assess a relationship between smoking and CAD; the results were adjusted for sex, age, hypertriglyceridemia, education, depression, obesity, diabetes, and hypertension. Odds ratio (OR), 95% confidence interval (CI), and *p*-level of OR were calculated. At the first stage, the relationship of smoking with CAD was evaluated in the total sample. At the second stage, it was assessed alternately in groups based on the presence / absence of risk factors.

Statistical analysis was performed using Statistica 6.1 software. The critical level of statistical significance was 0.05. At the level of $0.05 < p < 0.10$, the trend was considered to be statistically significant.

RESULTS

In the sample of 1,599 subjects, CAD was verified in 264 (16.5 %) respondents, of which 28 (10.6 %) previously had MI. It should be noted that 801 (50.1 %) respondents were former or current smokers. Comparative analysis (Table 1) shows that groups did not differ in the prevalence of CAD, prior MI, and stroke. Notably, current smokers were males of younger age with no signs of cholesterol or carbohydrate metabolism disorders. At the same time, fewer people among them had higher education and more people among them abused alcohol.

Table 1

Clinical and anamnestic characteristics of groups depending on smoking habits

Parameter	Current smokers 484 (30.3 %)	Former smokers 317 (19.8 %)	Non-smokers 798 (49.9 %)	*p*-level difference in the groups
Age, years, (M ± SD)	44.5±11.0	46.6±11.6	48.3±11.3	< 0.0001
Sex, male, (*n*, %)	312 (64.5)	195 (61.5)	182 (22.8)	< 0.0001
CAD, (*n*, %)	83 (17.1)	50 (15.8)	131 (16.4)	0.87
MI, (*n*, %)	8 (1.6)	10 (3.1)	10 (1.2)	0.090
Chronic bronchitis, (*n*, %)	92 (19.0)	54 (17.0)	108 (13.5)	0.028
Bronchial asthma, (*n*, %)	15 (3.1)	9 (2.8)	36 (4.5)	0.28
Digestive diseases, (*n*, %)	136 (28.1)	103 (32.5)	346 (43.4)	< 0.0001
Kidney diseases, (*n,* %)	74 (15.3)	74 (23.3)	258 (32.3)	< 0.0001
AH, (*n*, %)	185 (38.2)	156 (49.2)	352 (44.1)	0.0074
DM, (*n*, %)	11 (2.3)	19 (6.0)	33 (4.1)	0.028
Stroke, (*n*, %)	7 (1.4)	11 (3.5)	14 (1.7)	0.11
Cardiac arrhythmia, (*n*, %)	77 (15.9)	60 (18.9)	179 (22.4)	0.016
Obesity, (*n*, %)	132 (27.3)	114 (36.0)	312 (39.1)	< 0.0001
Depression, (*n*, %)	100 (20.7)	51 (16.1)	153 (19.2)	0.27
Alcohol abuse, (*n*, %)	146 (30.2)	66 (20.8)	56 (7.0)	< 0.0001
Higher education, (*n*, %)	153 (31.6)	127 (40.1)	349 (43.7)	< 0.0001
Hypercholesterolemia,(*n*, %)	232 (47.9)	176 (55.5)	441 (55.3)	0.024
Hypertriglyceridemia, (*n*, %)	98 (20.2)	76 (24.0)	150 (18.8)	0.15
Low HDL level, (*n*, %)	11 (2.3)	8 (2.5)	6 (0.7)	0.032
High LDL level, (*n*, %)	297 (61.4)	215 (67.8)	542 (67.9)	0.041
Hyperglycemia, (*n*, %)	76 (15.7)	59 (18.6)	141 (17.7)	0.52

The influence of cardiovascular risk factors on the probability of CAD was ranked. In the total sample, with all the considered risk factors taken into account, age criteria had the maximum rank (100 c.u.) of influence on the probability of CAD (Table 2).

Table 2

Ranking of the impact of risk factors on the probability of CAD

Parameter	Risk factor ranking of the probability of CAD (c.u.)		
	Total sample	Persons < 50 years	Persons ≥ 50 years
Sex, male	8	100	32
Age	100	83	45
Smoking	1	31	52
Higher education	15	66	43
DM	14	8	100
AH	13	76	12
Hypercholesterolemia	2	16	15
Hypertriglyceridemia	13	39	96
High LDL level	2	14	25
Low HDL level	1	21	11
Hyperglycemia	13	41	42
Obesity	19	56	67
Alcohol abuse	6	23	30
Depression	27	53	80

Other risk factors had lesser impact (in the descending order): depression – 27 c.u., obesity – 19 c.u., higher education – 15 c.u., etc. Ranking assessment of the risk factor influence on the probability of CAD was performed in two age groups due to the overwhelming influence of age. Sex, age, AH, higher education, and depression had the influence rank of more than 50 c.u. in the < 50-year-old group.

It is worth noting that smoking as one of the leading factors determining the probability of CAD has the lowest rank in the general population. However, with age differentiation, the influence of this risk factor increases. Thus, in people younger than 50 years, the rank influence of smoking was 31 c.u., and in the older age group (50 years and older) it elevated to 52 c.u. Besides smoking, the rank influence of more than 50 c.u. was registered for DM (100 c.u.), hypertriglyceridemia (96 c.u.), depression (80 c.u.), and obesity (67 c.u.).

Age influenced CAD the most, while smoking and low HDL levels had the lowest rank influence in the general population. The degree of influence of smoking on CAD was greater in the older age group, but even in people aged ≥ 50 years it was not the greatest and followed DM, hypertriglyceridemia, depression, and obesity.

Further, the probability of CAD was calculated depending not only on smoking, but also on smoking combined with other risk factors. Due to the large volume of data obtained, Table 3 shows only statistically significant relationships.

Table 3

Probability of CAD depending on smoking in combination with other cardiovascular risk factors

Parameter	OR	95 % CI	*p*-level
Smokers vs. non-smokers			
Smoking	1.53	1.05–2.22	0.025
Hypercholesterolemia	1.74	1.05–2.89	0.031
Hypertriglyceridemia	2.39	1.11–5.12	0.025
Male sex	1.92	1.01–3.68	0.049
Lack of higher education	1.71	1.07–2.72	0.024
Depression	2.36	1.15–4.83	0.018
Age ≥ 50 years	1.82	1.11–2.99	0.028
Former smokers vs. non-smokers			
Smoking	1.31	0.86–1.99	0.20
Hyperglycemia	2.79	1.10–7.11	0.030
Smokers vs. former smokers			
Smoking	1.47	0.96–2.27	0.078
Male sex	2.16	1.18–3.96	0.012
Lack of higher education	1.74	1.02–2.97	0.041
Depression	2.58	1.01–6.61	0.047
Age ≥ 50 years	1.87	1.08–3.24	0.024

Current smokers were 53% more likely to have CAD than non-smokers. In addition, a direct statistically significant association was found between the probability of CAD if smoking was combined with other cardiovascular risk factors, such as hypercholesterolemia, hypertriglyceridemia, male sex, lack of higher education, depression, and age over 50 years. When smoking was combined with other risk factors, the association with CAD became close to statistically significant: AH (OR = 1.63, 95% CI 0.94–2.83, $p = 0.082$), hyperglycemia (OR = 2.63, 95% CI 0.98–7.04, $p = 0.053$), obesity (OR = 1.83, 95% CI 0.99–3.38, $p = 0.054$).

There was also a direct association of smoking with CAD (OR higher than 1.00) in former smokers and non-smokers who did not have other risk factors, but it was statistically insignificant. In this regard, it is appropriate to say that the influence of smoking is more pronounced in people with comorbidities and additional cardiovascular risk factors.

Next, respondents who had quit smoking for more than a year before the study and non-smokers were analyzed. In former smokers, the association of smoking with CAD was direct, but statistically insignificant. Of all the factors considered, a combination of the former smoker status only with hyperglycemia was significantly associated with CAD.

Additionally, a combination of the former smoker status with disorders of lipid metabolism, such as hypercholesterolemia (OR = 1.68, 95% CI 0.96–2.94, p = 0.071), hypertriglyceridemia (OR = 2.31, 95% CI 0.96–5.58, p = 0.060), and obesity (OR = 1.82, 95% CI 0.95–3.52, p = 0.072), was approaching the statistical significance level. Therefore, lower probability of CAD is not strongly associated with smoking cessation in case these risk factors are present.

Statistically insignificant trends in smoking cessation among men and women are worth noting. In the "smokers vs. non-smokers" analysis, prominent association of CAD with sex was registered among men (men OR = 1.92, 95% CI 1.01–3.68, p = 0.049 compared to women OR = 1.20, 95% CI 0.74–1.94, p = 0.45). In the "former smokers vs. non-smokers" analysis, the probability of CAD was higher among women (women OR = 1.33, 95% CI 0.79–2.25, p = 0.8 compared to men OR = 0.94, 95% CI 0.45–1.98, p = 0.87), although no statistical significance was shown. This may indirectly indicate that smoking cessation and reduced probability of CAD are less likely associated in women than in men.

Changes in the association with CAD during smoking cessation are more evident when associations with CAD are compared in current smokers and former smokers. In the total sample, the decrease in the strength of the association with CAD in former smokers, is reflected in high values of the OR of current smokers, as opposed to former smokers (the differences are close to statistically significant values, OR = 1.47, 95 % CI 0.96–2.27, p = 0.078).

According to the conducted logistic regression analysis, low probability of CAD in combination with smoking cessation is associated with male sex, lack of higher education, age of over 50 years, and depression. Additionally, during smoking cessation, a number of factors become almost statistically significant in relation to reduced probability of CAD: AH (OR = 1.47, 95% CI 0.96–2.27, p = 0 .078), absence of hyperglycemia (OR 1.52, 95% CI 0.93–2.48, p = 0.095), and absence of obesity (OR = 1.68, 95% CI 0.94–2.98, p = 0.077). The presence or absence of such factors as hypercholesterolemia and hypertriglyceridemia does not affect reduction of CAD probability even during smoking cessation.

DISCUSSION

Smoking is the leading risk factor for CVD. According to the study "Epidemiology of cardiovascular diseases and their risk factors in the Russian Federation", 27.7% of people smoke in Russia. The prevalence of this risk factor in Kemerovo region was higher than in other regions, both among men (49.8 %) and women (22.9 %) [1]. Similar data were demonstrated in 2016, in the global survey of adult population of the Russian Federation. It showed that in Russia 36.4 million (30.5 %) people use tobacco products on a regular basis (14.5% of women and 49.8% of men) [2]. The use of tobacco products is the cause of death for 5.4 million people annually and accounts for 1 in 10 deaths among adults worldwide [3]. Smoking plays a leading role in the development of atherosclerosis and, thereafter, CAD. Smoking has been shown to have a negative effect on the endothelial function, stimulate thrombosis, potentiate oxidative stress and inflammation, and cause impairment of lipid metabolism [4].

The study found that smoking is associated with the probability of CAD. However, in the general population, smoking was not classified as a highly significant factor, giving the leading role instead to age, depression, and obesity. Taking into account division of the sample by age, smoking association became more important in people over 50 years. It was demonstrated that the probability of CAD was 53% higher in smokers compared to those who had never smoked. There were no differences in the probability of CAD when comparing former smokers and current smokers. In addition, there were no differences in the probability of CAD in former smokers and non-smokers. However, the study was limited by the absence of analysis on the time frames of smoking cessation. It is known that CVD risk is lowered after 10–15 years of smoking cessation (the values approach those of non-smokers) [4]. This may explain the results of the study.

This study demonstrated that the influence of smoking on the probability of CAD increased if other risk factors were present. Thus, smoking more than doubled the probability of CAD (in comparison to values in non–smokers) in case the examined individuals had depression and hypertriglyceridemia. Besides, it 1.5 times increased the probability of CAD in males aged ≥ 50, with hypercholesterolemia and lack of higher education. Former smokers were almost 3 times more likely to have CAD than non-smokers, even with hyperglycemia. An important conclusion of this study was that smoking cessation is associated with a lower probability of CAD mainly in men aged ≥ 50, with a lack of higher education and depression. This is a one-stage study, which does not allow for a possibility to discuss similar effect of the interaction between these factors and smoking on the risk of CAD development. In the meantime, the results are consistent with other studies that have shown that age, depression, glucose and cholesterol levels, excessive alcohol consumption, etc. are independent adverse factors in terms of CVD risk [1, 5–7].

The study "The Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries" (INTERHEART) showed that psychosocial factors account for 32% of the overall risk of developing MI, which is comparable to smoking [8]. Based on data from 53 separate studies and 4 meta-analyses, the American Heart Association concluded that depression is a predictive adverse risk factor for both general and cardiovascular mortality, as well as non-fatal cardiovascular events in both men and women [8]. A prospective study (Cardiovascular Health Study) involving 4,493 patients with a 6-year follow-up demonstrated the association between the increase in depression and the risk of developing CAD.

Thus, the risk of developing CAD was 1.15 per every 5 units of increase in the average depression score [7]. In addition, there are studies that indicate that CAD may potentiate depression. An observational study conducted by the Women`s Health Initiative found that postmenopausal women with established CAD risk factors (smoking, obesity, and DM) had a higher risk for concomitant depression after adjustment for age, race, education, and income [9].

There are several mechanisms that can possibly link depression and CAD, such as hypothalamic-pituitary-adrenocortical system dysfunction and increased cortisol levels, platelet activation; proinflammatory cytokines, and genetics [10]. In addition, bad habits and lifestyle associated with depression, such as smoking, excessive alcohol consumption, lack of physical activity, unhealthy diet, lack of social support, and poor compliance are associated with the risk of developing CAD [6].

According to available data, the effect of glucose levels on the risk of developing CVD among women and men is not the same. In the publication by P.W.F. Wilson et al. [11], the analysis of the Framingham study concluded that the frequency of CVD was associated with blood glucose levels in women without diabetes, while no such association was observed in men. S.V. Ahn et al. [12] in the longitudinal 11-year follow-up study of 159,702 individuals demonstrated that the relative risk of CAD in women increased in the pre-diabetes glucose range, whereas in men the risk increased solely with diabetes glucose level. The reason why hyperglycemia in women leads to a higher risk of CAD is unclear. Several mechanisms can explain this phenomenon. Hyperglycemia may have a stronger additive or synergistic effect if coupled with obesity, AH, hypercholesterolemia, and smoking in women [12].

Additionally, a high concentration of glucose increases oxidative stress, causing overproduction of the superoxide radical in the mitochondria [13]. The role of oxidative stress in production in the mitochondria causes further deterioration of endothelial function (endothelial dysfunction) and subsequent changes in vascular wall morphology [14]. Fluctuations in the glucose level can have a big impact on the activation of neutrophils, platelets, and cytokines. Abnormal activation of neutrophils and platelets is the main determinant of vascular catastrophes in patients with diabetes, contributing to high inflammatory reactions and high frequency of thrombotic events [15]. A recent study has also shown that sudden fluctuations in glucose levels can increase levels of interleukin-6, tumor necrosis factor-α, and intercellular adhesion molecule-1, leading to cardiovascular damage [16].

CONCLUSION

Thus, this study demonstrated high frequency of smoking as one of the leading risk factors for developing CVD. Smoking alone is not the primary

risk factor of CAD in the study sample, however, in the presence of additional risk factors, the impact of smoking increases. In this regard, criteria, such as male sex, lack of higher education, age, depression, and carbohydrate and lipid metabolism disorders, are unfavorable.

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Received 18.11.2019
Accepted 30.04.2020