# Sex Differences of Cardiovascular Risk Factors in Patients with Symptomatic Carotid Disease

Miloš Maksimović[1], Hristina Vlajinac[2], Djordje Radak[3,4], Jelena Marinković[5],
Jadranka Maksimović[2], Jagoda Jorga[1]

[1]Institute of Hygiene and Medical Ecology, School of Medicine, University of Belgrade, Belgrade, Serbia;
[2]Institute of Epidemiology, School of Medicine, University of Belgrade, Belgrade, Serbia;
[3]Department of Vascular Surgery, Dedinje Cardiovascular Institute, Belgrade, Serbia;
[4]School of Medicine, University of Belgrade, Belgrade, Serbia;
[5]Institute of Medical Statistics and Informatics, School of Medicine, University of Belgrade, Belgrade, Serbia

**SUMMARY**
**Introduction** Cardiovascular diseases, especially heart disease and stroke are the cause of more than a half of the total number of deaths in Serbia.
**Objectives** The aim of the present study was to determine sex differences of atherosclerotic risk factors in patients with symptomatic carotid disease.
**Methods** The cross-sectional study, involving 657 consecutive patients with verified carotid atherosclerotic disease, was performed in Belgrade, Serbia. Sex differences of anthropometric parameters and atherosclerotic risk factors were analyzed by means of the univariate logistic regression.
**Results** In comparison with men, lower education and physical inactivity were significantly more frequent in women, and the frequency of metabolic syndrome (MetS), lower high-density cholesterol, abdominal obesity, body mass index ≥30.0 kg/m², hypercholesterolemia and depression were also significantly higher in women. Smoking and high serum uric acid level were significantly more frequent in men than in women. Women had significantly higher number of MetS components per person, but there were no significant sex differences in the number of other risk factors. Out of all observed risk factors, including MetS components, physical inactivity and hypertension were most frequent in both sexes followed by ever smoking and low education in men and low education and dyslipidemia in women.
**Conclusion** There were significant sex differences in the distribution of some atherosclerotic risk factors, but not in their number per person. Only the number of MetS components was significantly higher in women.
**Keywords:** carotid disease; atherosclerotic risk factors; gender

## INTRODUCTION

It is estimated that cardiovascular diseases, especially heart disease and stroke, are the cause of nearly half (48%) of the total number of deaths in Europe [1].

The population of Serbia is in the third stage of the "epidemiological transition," with noncommunicable diseases being the predominant cause of death and disability [2]. In 2011, cardiovascular diseases were responsible for 54% of all causes of death (49% in men and 59% in women). Crude mortality rates were 720.9 per 100,000 in men and 806.4 per 100,000 in women. [3].

Apparent sex differences in morbidity and mortality from atherosclerotic diseases have been attributed to unequal exposure to atherosclerotic risk factors [4, 5], hormonal differences [6, 7] and differences in vessels anatomy [8].

**Correspondence to:**
Miloš MAKSIMOVIĆ
Institute of Hygiene and Medical Ecology
School of Medicine
Dr Subotića 8, 11000 Belgrade
Serbia
**milos.maksimovic@mfub.bg.ac.rs**

## OBJECTIVE

The aim of this study was to determine sex differences in atherosclerotic risk factors in patients with the symptomatic carotid disease who have undergone endarterectomy.

## METHODS

This cross-sectional study involved 657 consecutive patients with verified carotid atherosclerotic disease referred to the Vascular Surgery Clinic Dedinje in Belgrade during the period April 2006 – November 2007. The study included subjects who had signs and/or symptoms of cerebral ischemia and carotid stenosis of ≥50%, according to NASCET criteria [9]. Carotid atherosclerosis was estimated by high resolution B-mode ultrasonography HDI, ATL 3500.

Patients under eighteen years of age, with malignant disease, previous endarterectomy or rheumatoid arthritis, were excluded.

Anthropometric parameters and data on cardiovascular risk factors were collected for all participants.

Body weight and height, measured by standard procedures, were used to calculate body mass index (BMI) as weight (kg) divided by height (m²). BMI was categorized according to World Health Organization (WHO) criteria [10].

Waist circumference (WC) was measured at the midline between lower rib and crista iliaca. According to WHO criteria, patients with the abdominal obesity were defined as those with WC >102 cm (men) and >88 cm (women) [10].

Blood pressure was measured using the method recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [11].

For estimation of metabolic parameters, fasting plasma glucose (FPG) and lipoproteins, the blood samples were obtained after an overnight fast and avoidance of liquids. Levels of fasting plasma glucose (FPG), total cholesterol (TC), serum triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and serum uric acid level were estimated using the commercial kits (Abbot, IL,USA) on an automated analyzer (AEROSET™, Abbot, IL, USA). Levels of high sensitivity C-reactive protein (hsCRP) and fibrinogen were measured by using the Immunoturbidimetric fixed time test (Olympus Diagnostics, O`Callaghan`s Mills Co. Clare, Ireland), and high value of hsCRP was assessed according to CDC recommendation (≥3 mg/L) [12].

Metabolic syndrome (MetS) was defined according to NCEP III criteria [13]. Patients were classified as having MetS if they fulfilled 3 or more of the following criteria: 1) triglycerides ≥1.69 mmol/L; 2) HDL-C<1.03 mmol/L (men) and <1.29 mmol/L (women); 3) systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or antihypertensive drug therapy; 4) obesity, defined as waist circumference >102 cm (men) and >88 cm (women); and 5) abnormal glucose metabolism defined as fasting glucose ≥6.11 mmol/L.

Data on formal educational status, smoking habit, physical activity and depression of study participants were collected by questionnaire.

Participants were classified into two educational groups: ≤12 years and >12 years of schooling.

With reference to smoking, each subject was classified as a non-smoker, former smoker, or current smoker. Current smokers were defined as individuals who smoked at least one cigarette per day, or stopped smoking within the past 12 months. Former smokers were defined as those who quitted smoking more than a year earlier. The number of cigarettes smoked and duration of smoking were expressed as pack-years of smoking.

Physical activity was assessed in two ways:

1. Any type of non-occupational physical exercise lasting more than 30 minutes per day, during the previous month. Individuals who exercised more than once per week were considered physically active. The rest of the participants were classified as physically inactive.

2. Baecke questionnaire [14] was used for assessing the work, sport and leisure physical activity of each participant.

For the assessment of depression, Beck Depression Inventory (BDI) score was used [15]. BDI consists of 21 questions and answers are given on a four-point scale (valued from 0 to 3). BDI score theoretically ranges from 0 to 63 points and a score higher than 10 points indicates depression. BDI reliability and validity have been proven in previous psychometric studies.

Continuous variables were described as means ± standard deviation (SD), and categorical variables were presented by counts and percentages. For data analysis, univariate logistic regression was used. Data were analyzed using SPSS package version 15 with significance level set at p≤0.05.

The study was reviewed and approved by the Ethics Board at the Faculty of Medicine in Belgrade. All patients gave their written, informed consent.

## RESULTS

Study group comprised 657 patients with carotid atherosclerotic disease, 245 (37.29%) women and 412 (62.71%) men.

Stroke was significantly more frequent in men than in women (Table 1).

Severe form of stenosis was also more frequent in men, but this difference was not significant.

Men and women significantly differed in some sociodemographic and lifestyle characteristics (Table 2). In comparison with men, women were significantly more wid-

**Table 1.** Carotid stenosis and clinical manifestation of carotid atherosclerotic disease according to sex

| Variable | | Number (%) | | p[a] |
|---|---|---|---|---|
| | | Women (n=245) | Men (n=412) | |
| Carotid stenosis ≥70% | | 193 (79.6) | 349 (84.7) | 0.093 |
| Clinical manifestation of carotid disease | Amaurosis fugax | 102 (41.6) | 147 (35.7) | |
| | Transient ischemic attack | 63 (25.7) | 85 (20.6) | |
| | Stroke | 80 (32.7) | 180 (43.7) | 0.017 |

[a] according to univariate logistic regression analysis
n – number of patients

**Table 2.** Sociodemographic and some lifestyle characteristics of patients with carotid atherosclerotic disease, according to sex

| Characteristics | | Women (n=245) | Men (n=412) | p[a] |
|---|---|---|---|---|
| Age (years) | | 64.89±8.30 | 65.54±8.41 | 0.335 |
| Marital status | Married | 141 (57.6) | 348 (84.5) | <0.001 |
| | Divorced | 13 (5.3) | 14 (3.4) | 0.237 |
| | Widowed | 86 (35.1) | 35 (8.5) | <0.001 |
| | Single | 5 (2.0) | 15 (3.6) | 0.255 |
| Years of education | ≤12 | 203 (82.9) | 293 (71.1) | |
| | >12 | 42 (17.1) | 119 (28.9) | <0.001 |
| Occupation | Blue collar worker | 132 (53.9) | 232 (56.3) | |
| | White collar worker | 113 (46.1) | 180 (43.7) | 0.544 |
| Smoking | Non-smoker | 116 (47.3) | 109 (26.5) | <0.001 |
| | Current smoker | 77 (31.4) | 124 (30.1) | 0.720 |
| | Former smoker | 52 (21.2) | 179 (43.4) | <0.001 |
| Pack-years of smoking | | 31.18±20.86 | 47.09±29.22 | <0.001 |
| Physical activity (times per month) | 0–4 | 236 (96.3) | 366 (88.8) | 0.003 |
| | 5–8 | 9 (3.7) | 40 (9.7) | 0.006 |
| | >9 | 0 | 6 (1.4) | - |
| Index[b] | Work | 2.74±0.59 | 2.91±0.64 | 0.001 |
| | Sport | 1.88±0.25 | 1.97±0.39 | 0.001 |
| | Leisure | 2.30±0.59 | 2.47±0.71 | <0.001 |

The values are expressed as mean value ± standard deviation (SD) or number of patients (%).

[a] according to univariate logistic regression analysis
[b] according to Baecke questionnaire

**Table 3.** Some clinical and biochemical characteristics, nutritional state and inflammatory markers in patients with carotid atherosclerotic disease according to sex

| Characteristics | Number (%) | | $p^a$ |
| --- | --- | --- | --- |
| | Women (n=245) | Men (n=412) | |
| Metabolic Syndrome | 160 (65.3) | 205 (49.8) | <0.001 |
| Hypertension[b] | 223 (91.0) | 359 (87.1) | 0.132 |
| Triglycerides ≥1.7 mmol/L | 118 (48.2) | 189 (45.9) | 0.570 |
| HDL-C (<1.03 mmol/L in men, <1.29 mmol/L in women) | 185 (75.5) | 224 (54.4) | <0.001 |
| Abdominal obesity | 152 (62.0) | 172 (41.7) | <0.001 |
| Fasting glucose ≥6.1 mmol/L | 54 (22.0) | 107 (26.0) | 0.251 |
| Self reported diabetes | 81 (33.1) | 152 (36.9) | 0.321 |
| BMI ≥30 kg/m² | 66 (26.9) | 75 (18.2) | 0.009 |
| Total cholesterol ≥5.2 mmol/L | 134 (54.7) | 187 (45.4) | 0.021 |
| LDL-C ≥3.4 mmol/L | 115 (46.9) | 191 (46.4) | 0.886 |
| Lipid lowering drug intake | 109 (44.5) | 189 (45.9) | 0.644 |
| Serum uric acid >6.8 mg/dL | 31 (12.7) | 121 (29.4) | <0.001 |
| hsCRP ≥3 mg/L | 85 (34.7) | 161 (39.1) | 0.262 |
| Fibrinogen ≥4 g/L | 63 (25.8) | 96 (23.5) | 0.510 |
| Depression | 75 (30.7) | 77 (19.0) | 0.001 |

[a] according to univariate logistic regression analysis
[b] systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or antihypertensive drug therapy

ows, less educated, non-smokers, and physically inactive according to all examined parameters. Men were significantly more married and former smokers, and pack-years of smoking were significantly greater in men.

Some clinical and biochemical characteristics, nutritional state and inflammatory markers in patients with the carotid atherosclerotic disease according to sex were presented in Table 3. Compared to men, women had significantly higher frequency of MetS, and out of MetS components, lower HDL-C and abdominal obesity were also significantly more frequent in women. In addition, obesity, when expressed by BMI, was significantly more frequent in women as well as hypercholesterolemia and depression. High serum uric acid level (>6.8 mg/dL) was significantly more frequent in men than in women.

There was also statistically significant (p=0.002) difference in the clustering of MetS components between women and men: 71 (29.0%) women had 3 components of the MetS, 66 (26.9%) had 4 components and 23 (9.4%) had 5 components. In men, corresponding numbers were 107 (26.0%), 82 (19.9%) and 16 (3.9%). Women and men did not significantly differ in the number of other atherosclerotic risk factors per person. There were also no significant sex differences in the number of all observed risk factors, including MetS components, per person.

## DISCUSSION

In the present study, out of 657 consecutive patients with the carotid atherosclerotic disease, there were 1.7 times more men than women (412 men vs. 245 women). The majority of atherosclerotic risk factors (low education, physical inactivity, MetS, low HDL-C level, hypercholesterolemia, abdominal obesity, BMI≥30 kg/m² and depression)

were significantly more frequent in women in comparison with men. High level of serum uric acid and smoking were significantly more frequent in men. Women and men did not differ in the number of risk factors observed (including MetS components) per person, but the clustering of MetS components was significantly more frequent in women.

Iemolo et al. [16] have found that men and women differ in the frequency of carotid stenosis and carotid plaque. Both stenosis and carotid plaque area increase with age in both sexes, but at any age women have more carotid stenosis and men have more carotid plaque, plaque area being a stronger predictor of outcome than stenosis. Men also have higher prevalence of high-risk carotid plaque features (including a thin-ruptured fibrous cap, larger lipid-rich/ necrotic core, and hemorrhage) associated with stroke in comparison with women [17]. According to Iemolo et al. [16], these differences may be related to the effects of sex hormones on arterial remodeling (compensatory enlargement maintaining the normal lumen in the face of plaque development). There are also suggestions [8] that sex differences in the prevalence of atherosclerotic plaque and their distribution may be partly explained by sex differences in the anatomy of the carotid bifurcation - absolute vessels size, and in addition, vessel diameter and area ratios vary markedly between sexes. Many studies, epidemiological and experimental [7, 18] indicate that estrogen has beneficial effect on endothelial function, although it seems that this effect depend on age and time since menopause [18].

Accumulating data suggest that MetS can influence the progression of atherosclerosis and that subjects with MetS have increased risk of atherosclerotic disease morbidity and mortality [19]. Lin et al. [20] and Kawamoto et al. [21] found that the effect of MetS in early carotid stenosis was more pronounced in women than in men, but there are other reports which do not confirm this finding [22]. Sex hormones are considered a partial explanation of gender differences.

The strength of the association between MetS components and carotid intima media thickness (IMT) also differ between men and women. In Kawamoto et al. study [21], hypertension and dyslipidemia showed the strongest impact on carotid IMT in men, whereas hypertension ranked first in women. In the present study, hypertension and low HDL-C were the most frequent MetS components in both sexes followed by abdominal obesity in women and hypertriglyceridemia in men.

There are numerous data showing adverse effects of obesity, especially on cardiovascular health [23]. According to many studies, abdominal obesity, expressed as waist circumference or waist-hip ratio, is more important than BMI in predicting the cardiovascular events. These two measures of obesity are usually correlated, but Kawamoto et al. [24] found that not BMI but abdominal obesity itself and the interaction between abdominal obesity and BMI were significantly associated with carotid atherosclerosis. Harmful effect of abdominal obesity is believed to be due to visceral adipose tissue (VAT) [25]. According to the results of the Multicultural Community Health Assessment Trial (M-CHAT) in men, but not in women, VAT

was associated with IMT after adjusting for established risk factors. Authors suggested that differing findings in men and women might be explained by the existence of an absolute or relative VAT threshold that was reached in men at an earlier age than in women [25]. Song et al. [26] found that BMI and WC in men, but not in women, could be indicators predicting the carotid IMT regardless of age and cardiovascular risk factors. Obesity seems to be associated with cardiovascular disease in two ways, as an independent risk factor and through its association with other cardiovascular risk factors. Risk factors tend to cluster in obese individuals and may act synergistically to increase their risk of CVD [27].

In a large cohort study conducted in population representative of Italy [28], there was an inverse relationship between the educational level and major cardiovascular risk factors in both genders. Authors concluded that preventive interventions on cardiovascular risk should be addressed mostly to people with less education, although during follow-up no relationship between the incidence of cardiac events and education was observed.

In the study with 5084 subjects without atherosclerotic disease, Veronesi et al. [29] showed that men and women in the low educational class had a 2-fold increase in ischemic stroke and CHD incidence, respectively, after controlling for major risk factors. It has been suggested that this association may be due to undesirable health behavior (such as smoking, inadequate diet, and physical inactivity) and psychosocial stress [30]. In the present study, women with lower education, compared to men, were more frequently non-smokers. They were more frequently physically inactive, although the number of physically active was very low in both sexes. We did not collect data on nutrition but as previously mentioned, women were more obese. We do not know whether education status was related to psychological stress in our participants, but the compared groups differed in the frequency of depression, that is, depression being significantly more frequent in women.

The association of smoking and atherosclerosis is well known, as well as the fact that men more frequently smoke and smoke greater number of cigarettes than women. In the present study ever smoking was among the most frequent risk factors in men.

High serum uric acid level has been associated with cardiovascular disease [31]. The results of recently published meta-analysis by Kim et al. [32], including 16 prospective cohort studies, suggest that hyperuricemia may modestly increase the risks of both stroke incidence and mortality. However, pooled estimate of RRs (relative risks), adjusted for known risk factors such as age, hypertension, diabetes, and cholesterol did not differ much by sex.

In the present study, contrary to MetS components, the number of which per person was greater in women than in men, there were no differences between sexes in the number of other observed risk factors. There were only significant differences in the distribution of some risk factors by sex. In Debing et al. study [33] conducted in carotid endarterectomy population, the number of classical atherosclerotic risk factors (diabetes, smoking, hypertension and hyperlipidemia) per patient was higher in men than in women, the difference being significant only in subjects <75 years old. Out of these factors, the most frequent were ever smoking and hypertension in men, and hypertension and hyperlipidemia in women. In a population-based study conducted in Sweden, the number of risk factors (smoking, hypertension, dyslipidemia, obesity and increased fasting blood glucose/diabetes) was higher in men than in women. With the exception of current smoking, which was more frequent in women, all these factors were more frequently present in men [4].Out of classical risk factors, in our study hypertension was on the first place in both sexes followed by ever smoking in men and dyslipidemia in women. Out of all observed risk factors, including MetS components, physical inactivity and hypertension were most frequent in both sexes followed by ever smoking and low education in men and low education and dyslipidemia in women.

Our study has certain limitations. One of them is the cross-sectional design, which makes it difficult to judge causal relations. In addition, study participants were taken from a single hospital and they did not represent all patients with carotid atherosclerotic disease. There is also a possibility that analyzed variables might be changed after the cardiovascular events.

## CONCLUSION

There were significant sex differences in the distribution of some cardiovascular risk factors, but not in their number per person. Only the number of MetS components was significantly higher in women.

## ACKNOWLEDGMENTS

**762**

Maksimović M. et al. Sex Differences of Cardiovascular Risk Factors in Patients with Symptomatic Carotid Disease

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# Разлике по полу у факторима ризика за настанак обољења кардиоваскуларног система код особа оболелих од симптоматске каротидне болести

Милош Максимовић[1], Христина Влајинац[2], Ђорђе Радак[3,4], Јелена Маринковић[5], Јадранка Максимовић[2], Јагода Јорга[1]

[1]Институт за хигијену и медицинску екологију, Медицински факултет, Универзитет у Београду, Београд, Србија;
[2]Институт за епидемиологију, Медицински факултет, Универзитет у Београду, Београд, Србија;
[3]Одсек за васкуларну хирургију, Институт за кардиоваскуларне болести „Дедиње", Београд, Србија;
[4]Медицински факултет, Универзитет у Београду, Београд, Србија;
[5]Институт за медицинску статистику и информатику, Медицински факултет, Универзитет у Београду, Београд, Србија

**КРАТАК САДРЖАЈ**

**Увод** Кардиоваскуларне болести, а посебно срчана обољења и мождани удар, узрочник су више од половине смртних случајева у Србији.

**Циљ рада** Циљ студије био је да се процени разлика између мушкараца и жена у факторима ризика за развој атеросклеротских обољења код оболелих од симптоматске каротидне болести.

**Методе рада** Студија пресека, која је изведена у Београду, обухватила је 657 испитаника са дијагностикованом каротидном болешћу, који су сукцесивно укључивани у студију. Разлике по полу у антропометријским параметрима и атеросклеротским факторима ризика су анализиране коришћењем униваријантне логистичке регресије.

**Резултати** У поређењу с мушкарцима, жене су значајно чешће биле са нижом школском спремом и физички неактивне и имале су значајно чешће метаболички синдром, снижени ниво липопротеина велике густине, абдоминалну гојазност, индекс телесне масе већи од 30,0 $kg/m^2$, хиперхолестеролемију и депресију. Пушење и висок ниво мокраћне киселине били су значајно чешћи код мушкараца. Жене су имале значајно већи број компоненти метаболичког синдрома по особи, али међу половима није постојала разлика у броју осталих фактора ризика. Од свих испитиваних фактора ризика, укључујући и компоненте метаболичког синдрома, физичка неактивност и хипертензија су биле најчешће код оба пола, а следили су их пушење и низак ниво образовања код мушкараца, односно низак ниво образовања и дислипидемија код жена.

**Закључак** Мушкарци и жене су се значајно разликовали у расподели појединих фактора ризика за развој атеросклеротских обољења, али не и у њиховом броју по особи. Само је број компоненти метаболичког синдрома био значајно већи код жена.

**Кључне речи:** каротидна болест; атеросклеротски фактори ризика; пол