Folia Cardiologica 2016
tom 11, nr 4, strony 261–267
DOI: 10.5603/FC.2016.0067

ISSN 2353–7752

Metabolic syndrome as a useful tool in the identification of persons with an increased risk of nonfatal cardiovascular events in the Polish urban population — a prospective study

Zespół metaboliczny jako przydatne narzędzie w identyfikacji osób ze zwiększonym ryzykiem niezakończonych zgonem incydentów sercowo-naczyniowych w wielkomiejskiej populacji polskiej — badanie prospektywne

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Abstract

Introduction. The increasing worldwide prevalence of lifestyle diseases, including cardiovascular disorders, makes preventive measures more and more important. The identification of risk factors for cardiovascular events (CVEs) allows for determination of people requiring implementation of effective primary prevention.

The aim of the present study was to assess the prevalence of metabolic syndrome (MS) in the urban population of Poland. The second aim was to assess which of the MS definition increased the risk of development of CVEs.

Material and methods. 798 people were included in the prospective study. In all study participants anthropometric measurements, blood pressure, biochemical tests and standardized questionnaire history of actual physical condition as well as lifestyle and family history of cardiovascular diseases and diabetes were examined.

Results. During the baseline study, MS according to World Health Organization criteria was diagnosed in 13.6% people. When considering third report of the National Cholesterol Education Program — Adult Treatment Panel (NCEP-ATP III) criteria, the prevalence of the MS raised up to 32.7% of the participants. According to the International Diabetes Federation (IDF) criteria, 43.7% of the people were diagnosed with MS. In the follow-up study, the prevalence of nonfatal cardiovascular events was 5.8%. Male gender, body mass index ≥ 25 kg/m^2, abdominal obesity (measured by waist-to-hip ratio), glucose 120' oral glucose tolerance test, high-density lipoprotein cholesterol and MS (NCEP and IDF criteria) were significantly and independently related to myocardial infarction (MI) and/or stroke.

Conclusions. Taking into account potential risk factors of CVEs, the most valuable in the identification of people with increased risk of developing MI and/or stroke was the MS definition according to NCEP-ATP III and IDF.

Key words: metabolic syndrome, cardiovascular events, obesity

Folia Cardiologica 2016; 11, 4: 261–267

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Introduction

The increasing worldwide prevalence of lifestyle diseases, including cardiovascular disorders, makes preventive measures more and more important. The identification of risk factors for myocardial infarction (MI) and stroke allow for determination of people requiring implementation of effective primary prevention. This will definitely help to reduce the incidence and morbidity due to cardiovascular diseases.

In Poland cardiovascular diseases are still the leading cause of death, including a significant percentage of premature deaths. The Polish Forum for Prevention stresses the need to implement an effective primary prevention strategy at the level of the general population [1]. Metabolic syndrome (MS) is much more common among patients with cardiovascular disease, including coronary artery disease, hypertension and ischemic stroke [2–6]. Conversely, individuals who meet the criteria for the diagnosis of MS have an increased risk of developing cardiovascular diseases. A meta-analysis of 37 studies that used the definition by World Health Organization (WHO) and third report of the National Cholesterol Education Program — Adult Treatment Panel (NCEP-ATP III) found that the presence of MS increases the risk of cardiovascular events (CVEs) and death 1.78 times in total [7].

The aim of the study was to assess the prevalence of MS in the urban population of Poland and to assess which of the MS criteria (WHO, NCEP-ATP III or International Diabetes Federation [IDF]) correlate with an increased risk of nonfatal CVEs development.

Material and methods

The present analysis is based on the data gathered within the framework of the Project ordered by the Ministry of Health entitled: "Primary and secondary prevention and its impact on epidemiological and economic indicator in type 1 and type 2 diabetes in the Polish population" in the 1998–2000, and then extended to the follow-up study conducted in 2007–2009. Contractor for the project was the Department of Endocrinology Jagiellonian University Collegium Medicum (UJCM). The study protocol was approved by the Bioethics Committee of the Jagiellonian University in Krakow.

A random sample of 2838 participants was recruited at the baseline survey (response ratio of 47%) from the residents of the district Podgórze in Krakow. After the mean of 8.8 (standard deviation [SD] = 1.76) years the subjects who in the baseline study did not have diagnosed diabetes or did not report a history of CVEs were included in the present study (Figure 1). The final sample comprised 798 participants.

In both, the baseline and the follow-up study, participants fulfilled a structured questionnaire and were invited at clinical investigation. The physical investigation included measurements of blood pressure, height, weight, waist and hip circumference. Body mass index (BMI — m/kg^2) and waist-to-hip ratio (WHR) were calculated according to the standard protocol. Biochemical examination included fasting glucose (mmol/l) and insulin (μU/ml), total cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides. For the measurement of fasting plasma glucose and fasting plasma insulin a blood sample was taken after an overnight fast. In people not treated due to diabetes mellitus type 2 (DM2) oral glucose tolerance test with testing of blood glucose and insulin at 120 min after administration of 75 g glucose was performed. Information on lifestyle and

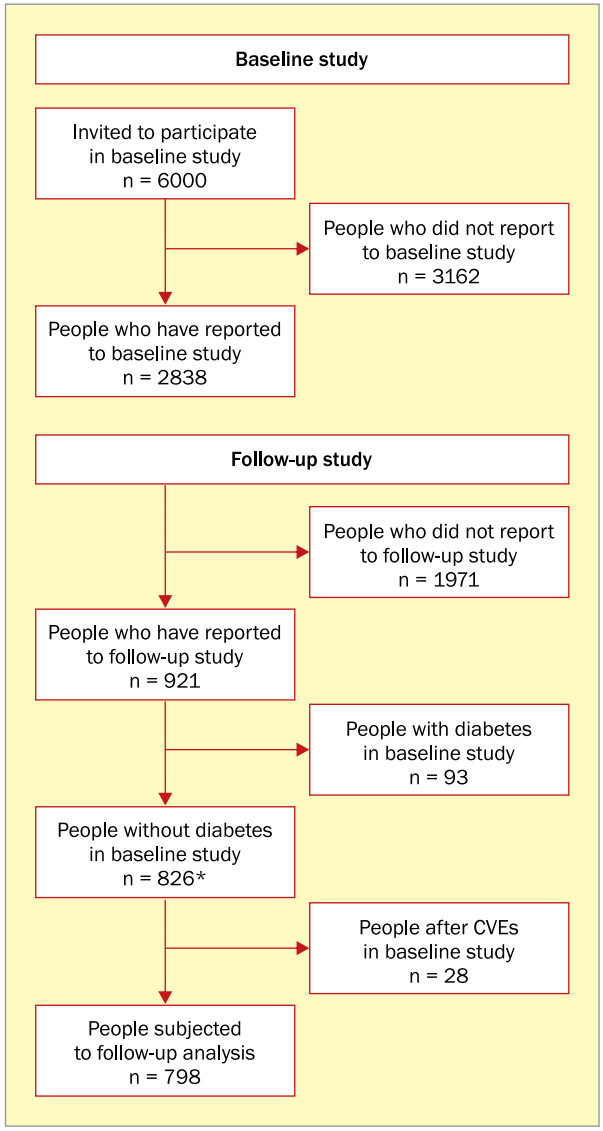

Figure 1. Characteristics of groups in baseline and follow-up studies; *2 people were excluded, because of the lack of anthropometric measurements and/or biochemical results in follow-up study; CVEs — cardiovascular events; n — numbers

healthy behaviors, the current state of health and family history of CVEs and DM2 were obtained by the structured questionnaire.

The data obtained in the follow-up study were then compared with the data obtained in the baseline study. In order to identify people with MS, three MS definitions were used — the WHO of the 1999, the NCEP-ATP III of the 2001 and IDF of the 2005. Nonfatal CVEs defined as MI or stroke were identified on the basis of the answer to the question "Have cardiovascular disease like myocardial infarction or stroke ever been diagnosed by a doctor?" included in the questionnaire.

Statistics

Difference in baseline demographic and clinical characteristics were assessed by CVEs status with the standard methods: χ^2 test for categorical variables, and *t*-Student or Mann-Whitney tests for continuous variables.

Incidence rates of CVEs were calculated dividing number of events by person-time at risk while the follow-up time was the number of months between the baseline visit and either the first event or last contact. Multivariate proportional hazard regression analysis was applied to model the relationship between MS status assessed by different definitions and CVEs, adjusted to age, gender, and smoking habit. The proportional hazards assumption was tested by inspecting Schoenfeld residuals [8] and found to be satisfactory.

Statistical analysis was performed using Statistica 10PL and SAS for Windows ver. 9.4 (SAS Institute, Cary, NC). A p value < 0.05 was considered as statistically significant [8].

Results

During the baseline study MS by WHO criteria from 1999 was diagnosed in 13.6% of patients, according to the NCEP-ATP III 2001 in 32.7% and by the IDF from 2005 in 43.7% of the study group. In the follow-up study MS by WHO was diagnosed in 15.9%, according to the NCEP-ATP III in 34.6% and by IDF in 49.2% of the study group. In the study group of 798 people, after an average observation period of 8.8 (± 1.75) years, nonfatal CVEs were observed in 5.8% of the patients (n = 46). Anthropometric and metabolic parameters of the baseline study in patients with and without CVEs history identified in the follow-up study are presented in Table 1.

A similar analysis was performed after taking into account gender. Women with CVEs history were older, had higher waist-to-hip ratio, and MS by NCEP and IDF was recognized among them more often. Women after CVEs show higher systolic (p = 0.003) and diastolic blood pressure (p = 0.002), higher levels of LDL (p = 0.016) and lower HDL-cholesterol levels compared with the group of women without CVEs (p = 0.004). All these differences were statistically significant. In the group of men with CVEs no statistically significant differences in anthropometric and metabolic parameters in comparison with the group of men without CVEs was observed. Men with CVEs were significantly more frequently treated for hypercholesterolemia (p = 0.01) and hypertension (p < 0.003) compared with the group of men without completed CVEs. In women, these differences were not observed. In both women and men, there was a higher incidence of CVEs in subjects with previously identified MS compared with those without metabolic disorders. This difference was statistically significant (in women, p < 0.001; in men, p = 0.042). For both, men and women, the cumulative hazard of cardiovascular events related to MS by WHO, NCEP and IDF is presented in (Figures 2–4).

Results of the Cox regression analysis showed that the risk of CVEs was 2-fold higher in men compared with women and increased with age. These associations were statistically significant (Table 2). In the multivariate regression model, after adjustment for age and sex, it was found that the potential factors that increased the risk of CVEs in the study group were: BMI ≥ 25 kg/m^2, abdominal obesity as curtained by waist-to-hip ratio, glucose in 120' OGTT and HDL cholesterol. These associations were statistically significant (Table 3). The greatest risk of CVEs were observed for visceral obesity diagnosed on the basis of WHR (HR 4.44, p = 0.04). For diagnosis of MS according to the NCEP and IDF criteria it was found that individuals with the syndrome was approximately 2.5 times more likely to develop CVE that individuals without the syndrome. In both cases these associations were statistically significant (Table 4).

Discussion

For primary prevention of cardiovascular diseases it is necessary to search for risk factors for these diseases in the population. Many countries developed risk cards using simple parameters such as gender, age, total cholesterol and HDL cholesterol in the blood serum, blood pressure, history of smoking and type 2 diabetes. These cards estimate 5- and 10-year risk of the cardiovascular diseases development [9–11]. In the present study attempts were undertaken to assess which CVEs risk factors are valuable and at the same time simple indicators were sought, which would allow for identification of persons who need primary prevention of cardiovascular diseases in the Polish population.

In the study group, taking into account the three definitions of MS, the percentage of people with MS is much higher compared with other epidemiological studies [12–16]. It should be emphasized that the study group included a significant proportion of people with overweight and obesity, and that the average age was higher compared with most large population studies. Many studies have shown that MS is more common in people with obesity and

Table 1. Anthropometric and metabolic parameters from the baseline study by volunteers without and with cardiovascular events examined during the follow-up study*

Anthropometric and metabolic parameters from the baseline study		The follow-up study		p**
		Without cardiovascular events	After cardiovascular events	
Number [%]		n = 752 (94.2%)	n = 46 (5.8%)	
Age, years		50 (13)	53 (10)	0.011
BMI [kg/m^2]		27 (5.6)	28.8 (4.0)	0.011
Fasting glucose [mmol/l]		5.5 (0.9)	5.7 (0.8)	0.16
Glucose 120' OGTT [mmol/l]		6.1 (2.2)	6.4 (2.1)	0.06
Fasting insulin [µIU/ml]		8.2 (8.4)	9.6 (9.5)	0.11
Insulin 120' OGTT [IU/ml]		24.0 (47.9)	51.4 (62.2)	0,17
HOMA-IR		2.02(2.16)	2.36(2.63)	0,10
Diastolic BP [mm Hg]		80.9 (10.2)	85.7 (12.2)	< 0.001
Systolic BP [mm Hg]		124.4 (10.2)	135.4 (24.7)	< 0.001
Total cholesterol [mmol/l]		6.1 (1.1)	6.4 (1.2)	0.053
HDL [mmol/l]		1.3 (0.3)	1.1 (0.3)	< 0,001
LDL [mmol/l]		4.0 (1.0)	4.4 (1.2)	< 0.001
Triglycerides [mmol/l]		1.41 (1.13)	1.81 (1.12)	0.06
Volunteers during hypercholesterolemia treatment		118 (18.6%)	14 (35.9%)	0.02
Volunteers during hypertension treatment		191 (28.4%)	22 (51.6%)	0.006
Smoking	Non-smoker	352 (46.8%)	16 (34.8%)	0.05
	Smoker	196 (26.0%)	10 (21.7%)	
	Former smoker	204 (27.2%)	20 (43.5%)	
Positive family history of heart disease		512 (68%)	35 (76%)	0.26
Positive family history of diabetes		196 (26.1%)	11 (23.9%)	0.75

*Data are presented as mean ± standard deviation; **a p value of < 0.05 is considered statistically significant; BMI — body mass index; OGTT — oral glucose tolerance test; HOMA-IR — homeostatic model assessment — insulin resistance; BP — blood pressure; HDL — high-density lipoprotein; LDL — low-density lipoprotein

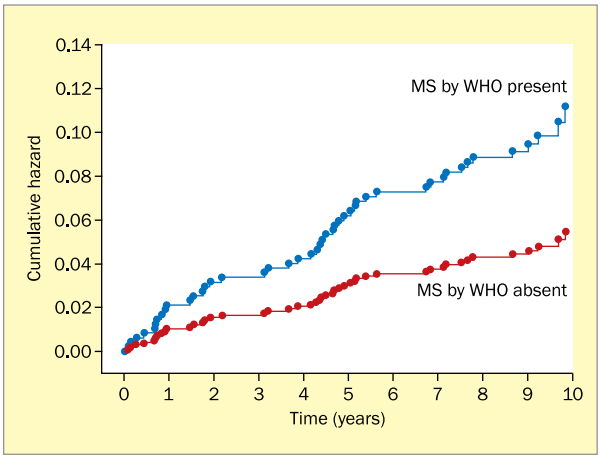

Figure 2. Cumulative hazard of cardiovascular events related to metabolic syndrome (MS) by World Health Organization (WHO), adjusted to age and sex

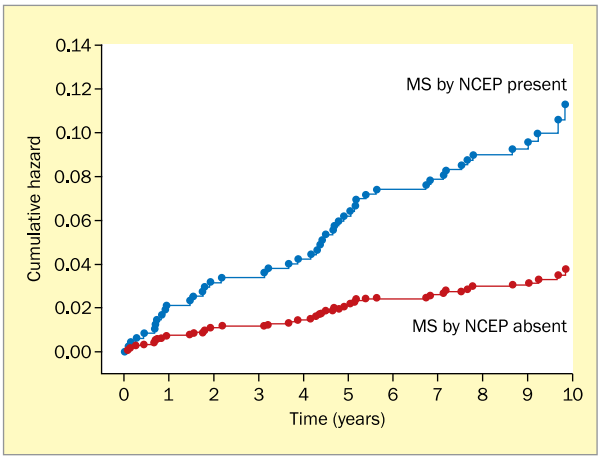

Figure 3. Cumulative hazard of cardiovascular events related to metabolic syndrome (MS) by National Cholesterol Education Program (NCEP), adjusted to age and sex

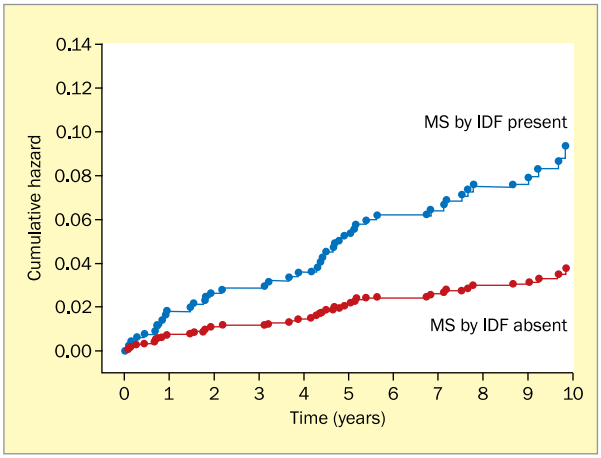

Figure 4. Cumulative hazard of cardiovascular events related to metabolic syndrome (MS) by International Diabetes Federation (IDF), adjusted to age and sex

Table 2. The risk of cardiovascular events related to age and gender estimated by univariate Cox regression analysis in the whole study group

	The risk of cardiovascular events		
	HR	95% CI	p*
Age	1.03	1.003–1.07	0.03
Sex (male vs. female)	2.10	1.17–3.78	0.01

*A p value of < 0.05 is considered statistically significant; CI — confidence interval; HR — hazard ratio

in the elderly [17]. In a study of only patients with obesity, MS by NCEP-ATP III was found in 60.6% of patients. In the cited work the average BMI was 42.3 (± 7.4) kg/m^2 [18].

In our work, nonfatal CVEs were observed in 5.8% of patients during the 9-year follow-up. In a Danish prospective study, in which the median follow-up time was 9.4 years and the average age of the respondents was 51 years, at the end of the follow-up, CVEs were observed in 9.4% of patients [19]. According to a Swedish prospective study, among more than 5 thousand people without DM at baseline, MI and/or stroke was observed in 6.9% of the study population during the 11 years follow-up [20]. On the other hand, in a prospective study of the Framingham Offspring Study, CVEs occurred in 6.5% of the study population, during the average 7 years of follow-up [21]. In a nationwide study performed by POLSCREEN in outpatient centers throughout the country (mean age for women 60.7 ± ± 11.7; mean age for men 58 ± 11.6), 16% of men and 7% of women reported in an interview MI and/or stroke. This high percentage of people with a history of CVEs in the cited study results from the analysis of only such persons who were registered by Primary Health Care for advice. The profile of the risk factors studied by this research group was also much more negative, with a large percentage of people treated for DM (16% of women and 15% men) and a large percentage of people with BMI ≥ 25 kg m^2 [22].

In our study group, MS assessed by the three definitions increased risk of CVEs, but only in the case of MS according

Table 3. The risk of cardiovascular events associated with individual components of metabolic syndromes, standardized for age and gender. Each factor was estimated in a separate model

Variables (baseline study)	The risk of cardiovascular events		
	HR	95% CI	p*
BMI < 25 [kg/m^2]	1.0		
25 ≤ BMI < 30 [kg/m^2]	2.73	1.03–7.22	0.043
BMI ≥ 30 [kg/m^2]	2.81	1.01–7.84	0.048
WHR female > 0.85, male > 0.9	4.48	1.07–18.82	0.041
Waist circumference female > 88; male > 102 cm	1.20	0.63–2.30	0.58
Waist circumference female ≥ 80, male ≥ 94 cm	1.67	0.81–3.45	0.17
Fasting glucose	1.28	0.79–2.09	0.32
Glucose 120' OGTT	1.20	1.01–1.43	0.034
Fasting hyperinsulinemia**	1.33	0.73–2.44	0.35
Hyperinsulinemia 120' OGTT***	1.47	0.82–2.65	0.20
Insulin resistance****	1.40	0.77–2.53	0.27
HDL	0.16	0.05–0.49	0.001
Triglycerides	1.06	0.82–1.36	0.066

*A p value of < 0.05 is considered statistically significant; **fasting hyperinsulinemia — fasting insulin > 11.7 µIU/ml; ***hyperinsulinemia 120' OGTT — insulin in 120 min OGTT > 57.0 µIU/ml; ****insulin resistance — HOMA-IR > 2.78: HR — hazard ratio; CI — confidence interval; BMI — body mass index; WHR — waist-to-hip ratio; OGTT — oral glucose tolerance test; HDL — high-density lipoprotein; HOMA-IR — homeostatic model assessment — insulin resistance

Table 4. Incidence and hazard ratio (HR) of cardiovascular events associated with presence of metabolic syndrome (MS)

	MS present		MS absent		Incidence rate difference* (95%CI)	p	HR 95%CI		p**	
	No. of events per p-y at risk	Incidence rate#	No. of events per p-y at risk	Incidence rate#			Crude	Adjusted***	Crude	Adjusted***
WHO	10/879	11.4	36/6407	5.6	5.8 (0.1–15.3)	0.043	2.04 (1.003–4.13)	1.58 (0.76–3.29)	0.049	0.22
NCEP	26/2223	11.7	20/5063	3.95	7.7 (3.5–13.3)	< 0.001	2.96 (1.65–5.31)	2.78 (1.53–5.05)	< 0.001	< 0.001
IDF	30/3064	9.8	16/4222	3.8	6,0 (2.2–10.4)	0.0014	2.57 (1.4–4.72)	2.39 (1.29–4.43)	0.002	0.006

*Incidence rate difference = absolute risk; **a p value of < 0.05 is considered statistically significant; ***adjusted to age, sex; #incidence rate per 1000 person-years; CI — confidence interval; p-y — person-years; WHO — World Health Organization; NCEP — National Cholesterol Education Program; IDF — International Diabetes Federation

to the NCEP-ATP III and IDF this relationship was statistically significant (HR 2.78; p < 0.001 and HR 2.39, p = 0.002 respectively). In the Framingham Offspring Study a positive correlation between MS defined by NCEP-ATP III and CVEs was found [20]. Jeppesen et al. [19] found in a prospective study lasting over 9 years that MS by NCEP is an independent risk factor for CVEs. A Swedish prospective study assessed the three definitions of MS (NCEP, IDF and EGIR) in predicting CVEs. In this study, after taking into account age, gender, low-density lipoprotein and lifestyle, HR for CVEs was highest for MS according to the NCEP-ATP III (HR 1.59 95% confidence interval [CI] 1.25–2.03) [19]. In the prospective Strong Heart Study with patients with no identified diabetes, MS by WHO and NCEP-ATP III (but not by IDF) increased risk of CVEs. In patients with diabetes, MS by WHO seemed to be the most useful in assessing the risk of CVEs. The authors emphasize that the obtained data come from a population with a large proportion of people with obesity and diabetes [23]. Ahmadi et al. showed that MS (by NCEP) patients have significantly greater prevalence and severity as well as worse prognosis of coronary artery disease compared with patients with one component of metabolic syndrome [24]. Similar relationships showed Suh et al. During 8.1-year follow-up period MS (definition NCEP) was a significant risk factor for the development of cardiovascular disease although its impact varied between sexes [25]. Polish researchers who analyzed a population of more than 750 patients after ischemic stroke, found MS by NCEP in 54.3% of people, and after taking into account the criteria by the IDF 2005, in 60.8% of people. Both, the data available in the literature and our results demonstrate that the use of MS as defined by the NCEP and IDF can identify individuals at increased risk of CVEs. These people need to implement multi-primary prevention in order to prevent cardiovascular events [4].

Conclusions

1. The occurrence MS in the baseline study increases the risk of cardiovascular events in the follow-up study, as defined by NCEP-ATP III 2001 and IDF 2005 almost 2.5-fold.
2. In the urban Polish population it is necessary to identify persons with metabolic syndrome in order to select a group demanding the implementation of primary prevention of cardiovascular events.

Acknowledgment

Nr PBZ-018-11.

Streszczenie

Wprowadzenie. Na całym świecie zwiększa się częstość występowania chorób cywilizacyjnych, w tym zaburzeń układu sercowo-naczyniowego, co sprawia, że działania profilaktyczne stają się coraz istotniejsze. Identyfikacja czynników ryzyka incydentów sercowo-naczyniowych (CVE) umożliwia określenie, które osoby wymagają wdrożenia skutecznej prewencji pierwotnej.

Celem badania była ocena częstości występowania zespołu metabolicznego (MS) w wielkomiejskiej populacji polskiej oraz związku między MS a ryzykiem wystąpienia CVE.

Materiał i metody. W badaniu przeanalizowano dane 798 osób. U wszystkich wykonano pomiary antropometryczne, ciśnienia tętniczego i badania laboratoryjne. Wszyscy uczestnicy badania wypełnili wystandaryzowany kwestionariusz dotyczący między innymi aktualnego stanu zdrowia, przebytych schorzeń oraz wywiadu rodzinnego w kierunku chorób układu sercowo-naczyniowego i cukrzycy.

Wyniki. W badaniu wstępnym MS według Światowej Organizacji Zdrowia stwierdzono u 13,6%, według 3. Raportu *National Cholesterol Education Program — Adult Treatment Panel* (NCEP-ATP III) — u 32,7%, a według *International Diabetes Federation* (IDF) — u 43,7% osób. W badaniu kontrolnym CVE niezakończone zgonem stwierdzono u 5,8% osób. Płeć męska, wskaźnik masy ciała większy lub równy 25 kg/m^2, otyłość brzuszna (oceniana za pomocą wskaźnika talia–biodra), stężenie glukozy w 120. min. doustnego testu tolerancji glukozy, stężenie cholesterolu frakcji lipoprotein o wysokiej gęstości oraz zespół metaboliczny według NCEP I IDF istotnie statystycznie obniżają ryzyko zawału serca (MI) i/lub udaru mózgu.

Wnioski. Biorąc pod uwagę potencjalne czynniki ryzyka CVE, cennym narzędziem w identyfikacji osób obciążonych ryzykiem wystąpienia MI i/lub udaru mózgu jest MS według NCEP-ATP III i IDF.

Słowa kluczowe: zespół metaboliczny, incydenty sercowo-naczyniowe, otyłość

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