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Gender and age related features of metabolically healthy obesity phenotype prevalence

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ABSTRACT

Aim. The study objective was to assess the age and gender characteristics of the metabolically healthy obesity phenotype (MHO) prevalence, taking into account various classifications.

Materials and methods. The materials used are the cross-sectional studies of the population cohort (Health, Alcohol and Psychosocial factors in Eastern Europe (HAPIEE) project, Novosibirsk), with the total of 3,197 people, among them 857 men (26.8%) and 2,340 women (73.2%), with BMI ≥30 kg/m². The MHO is defined according to different classifications: 1. IDF (International Diabetes Federation, 2005) – Waist circumference (WC) ≥ 94 cm in men and ≥80 cm in women and one or none of the components of metabolic syndrome (MS); 2. NCEP ATP III (the National Cholesterol Education Program Adult Treatment Panel III, 2001) in the presence of 2 and / or less components of the metabolic syndrome and 3. RSC (The Royal Society of Chemistry) - the index of waist circumference / hip circumference (WC / HC) ≤0.9 in men and ≤0.85 in women.

Results. According to IDF the frequency of MHO in the group was 23.2%; NCEP ATP III – 41.8; RSC criteria – 27.1%. The frequency of MHO was higher in women than in men, and it significantly decreased with the age in women population. In all classifications, increased average blood pressure (BP) level, with normal average values of the level of triglycerides (TG) and high-density lipoprotein (HDL) is typical for persons with MHO. The surveyed according to the RSC criteria people with MHO demonstrate higher frequency levels of all cardio metabolic risk factors than those surveyed with the use of other criteria of MHO.

Conclusion. The frequency of MHO varies depending on the used classification. In women, the frequency of MHO is reliably higher than in men. With the age, a significant reduction of the frequency of MHO in women is manifested. The frequency of arterial hypertension and abdominal obesity, the level of fasting blood glucose and LDL (low density lipoprotein), hypertriglyceridemia is higher in persons with MHO according to the criteria RSC.

Key words: obesity, prevalence, sex differences, metabolically healthy obesity phenotype.

Conflict of interests. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at IIPM (Protocol No. 1 of 03.14.2002).

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Половозрастные особенности распространенности метаболически здорового фенотипа ожирения

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РЕЗЮМЕ

Цель. Изучить половозрастные особенности метаболически здорового фенотипа ожирения (МЗФО).

Материалы и методы. Использованы материалы кросс-секционного исследования популяционной когорты (проект HAPIEE, г. Новосибирск) (n = 3 197 человек, среди них 857 (26,8%) мужчин и 2 340 (73,2%) женщин, с индексом массы тела (ИМТ) ≥30 кг/м^2). МЗФО определен в соответствии с различными классификациями: 1) IDF (2005) – окружность талии (ОТ) ≥94 см у мужчин и ≥80 см у женщин и любой компонент метаболического синдрома (МС) по IDF или без него; 2) NCEP ATP III (2001) при наличии 2 и (или) менее компонентов МС; 3) критерии РКО (2017) – индекс окружность талии/окружность бедер (ОТ/ОБ) ≤0,9 у мужчин и ОТ/ОБ ≤ 0,85 у женщин.

Результаты. Среди лиц с ожирением частота МЗФО по критериям IDF – 23,2%; NCEP ATP III – 41,8%; РКО – 27,1%. Частота МЗФО выше у женщин, чем у мужчин, и она значимо снижается с возрастом в женской популяции. Для лиц с МЗФО по всем классификациям характерны повышенное среднее значение артериального давления при нормальных средних значениях уровня триглицеридов и холестерина липопротеидов высокой плотности. Обследованные с МЗФО по критериям РКО демонстрируют более высокие показатели частоты всех изучаемых кардиометаболических факторов риска, чем при использовании других критериев МЗФО.

Выводы. Частота МЗФО варьирует в зависимости от используемой классификации. У женщин частота МЗФО достоверно выше, чем у мужчин. С возрастом отмечается значимое снижение частоты МЗФО у женщин. Частота артериальной гипертонии, абдоминального ожирения, уровень глюкозы крови натощак, холестерина липопротеидов низкой плотности и гипертриглицеридемия выше у лиц с наличием МЗФО по критериям РКО.

Ключевые слова: ожирение, распространенность, половые различия, метаболически здоровый фенотип ожирения

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

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INTRODUCTION

The modern obesity epidemy is one of the most serious public health problems of our century. Usually, obesity is accompanied by an unfavorable metabolic profile, such as carbohydrate metabolism disorders, altered lipid profile, increased blood pressure (BP), systemic inflammation, altered liver enzymes, etc. [1]. The cluster of changes caused by obesity is also known as metabolic syndrome (MS).

However, recent evidence suggests that obesity does not always lead to adverse metabolic effects and it is increasingly recognized not as not being a homogeneous condition [2]. Approximately 10–30% of obese people are metabolically healthy despite excessive body fat accumulation. This phenomenon is referred to in modern literature as a metabolically healthy obesity phenotype (MHO) [3]. However, the main obstacle to understanding the epidemiology of MHO and its long-term perspective is the contradictory definition in various studies [4–6]. For example, some studies show that the prevalence of MHO varies depending on the definition used. This circumstance contributes to the discrepancy between this phenotype and the health consequences. Rey-Lopez and coauthors conducted a systematic review of the prevalence of MHO and they reported that the frequency of this phenotype varies from 6% to 75%. They also suggested that prevalence may vary depending on several socio-demographic factors, such as gender, age, and ethnicity. The authors then stratified the analysis by gender and age, and found that the prevalence of MHO was higher in women and younger individuals [7].

Thus, it is important to understand that researchers may introduce overweight and/or obesity and/or different MS criteria into this concept. Thus, participants with the absence of metabolic changes, or with the presence of one/two components of metabolic syndrome (MS), depending on the definitions of the latter, may fall under the definition of metabolically healthy individuals [6].

Despite different study designs and population differences, the variability in the frequency of MHO reported in both comparative studies and meta-analyses underscores the need for larger representative population studies and the need for a global consensus on a standard definition of MHO.

The aim was to assess the age and gender characteristics of MHO prevalence, taking into account various classifications.

MATERIALS AND METHODS

The survey of a representative sample of Novosibirsk residents was conducted in 2003-2005, within the framework of the international project HAPIEE (Health, Alcohol and Psychosocial factors In Eastern Europe), which is a prospective cohort study designed to study the impact of classical and non-traditional risk factors, as well as social and psychosocial factors on cardiovascular and other non-communicable diseases in Eastern Europe and the CIS countries [8]. The analysis included persons with a body mass index (BMI) ≥ 30 kg / m2: There were 3,197 people, 857 (26.8%) males and 2,340 (73.2%) females. In the initial survey the following data was analyzed: age, anthropometry, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), fasting plasma glucose (BG), table 1.

Table 1

Main characteristics of the studied sample of 45–69 years, $M \pm \sigma$

Parameters	Male, $n = 857$	Female, $n = 2.40$	Both genders, $n = 3.197$	$p_{м/ж}$
SPB (mmHg)	151.6 ± 23.3	151 ± 26.5	151.2 ± 25.7	0.573
DBP (mmHg)	96.5 ± 13.1	94.6 ± 13.1	95.1 ± 13.1	<0.001
BMI (kg/m²)	33.1 ± 3.0	34.9 ± 4.2	34.4 ± 4.0	<0.001
BG (mmol/l)	6.8 ± 2.3	6.3 ± 1.8	6.4 ± 2.0	<0.001
TC (mmol/l)	6.2 ± 1.1	6.6 ± 1.3	6.5 ± 1.2	<0.001
LDL-C (mmol/l)	4.0 ± 1.0	4.3 ± 1.1	4.2 ± 1.1	<0.001
HDL-C (mmol/l)	1.4 ±0.3	1.5 ± 0.3	1.4 ± 0.3	<0.001
TG (mmol/l)	1.9 ± 1.0	1.8 ± 0.9	1.8 ± 0.9	<0.001

BP was mesasured three times with an interval of two minutes in the right hand in a sitting position after a 5-minute rest using an automatic to-

nometer Omron M5-I (Japan). The average value of three measurements was recorded. We found out the awareness of the screening participants about the presence of previously elevated blood pressure and about taking antihypertensive drugs during the last two weeks. Persons with previously diagnosed arterial hypertension (AH), but with normotonia on screening, in cases of taking drugs that reduce blood pressure, were also considered as patients with AH.

Standing height was measured without outer clothing and shoes with a standard height meter. Body weight was determined without clothing and shoes with a doctor's scales that passed metrological control. The measurement accuracy was 0.1 kg. Body mass index (BMI) was calculated by the formula: BMI (kg/m^2) = weight (kg) / height (m)^2 (WHO (World Health Organization), 1997).

Blood for biochemical studies was taken by venipuncture using vacutainers in fasting state, after 12-hour fasting. The content of TG, HDL-C and glucose was determined by enzymatic methods using an automatic biochemical analyzer "KoneLab 300". Conversion of fasting serum glucose into blood plasma values was carried out according to the formula proposed by experts of the European Association for the study of diabetes in 2007: plasma glucose concentration (mmol/l) = −0.137 + 1.047 × serum glucose concentration (mmol / l).

Three variants of criteria were used to single out the metabolically healthy phenotype of obesity: presence of BMI ≥30 kg/m^2 and

1. (IDF, 2005) from ≥ 94 cm in men and ≥80 cm in women and in the presence or absence of one of the following MS components: TG≥1.7 mmol/l or prior treatment (hyperTG); HDL-C − <1.0 mmol / l in men and <1.3 mmol / l in women or prior treatment (hypo-HDL); Blood pressure ≥130/85 mmHg or previous antihypertensive therapy (AH); Fasting plasma glucose ≥5.6 mmol / l or presence of D2.

2. (NCEP ATP III, 2001) presence of one or 2 of the following MS components: FROM >102 cm in men and >88 cm in women; TG ≥1.7 mmol/l; HDL-C <1.0 mmol / l in men and <1.3 mmol / l in women; Blood pressure≥130/85 mmHg; Blood plasma glucose ≥ 6.1 mmol / l (BG) or prior treatment.

3. Project (RSC, 2017) index of waist circumference / hip circumference (WC/HC) ≤0.9 in men and WC/HC ≤0.85 in women.

Statistical analysis was carried out using the statistical software package SPSS (Statistical Product and Service Solutions) 13.0 for Windows (1 Sep. 2004). The level of statistical significance of the differences was assessed by the Student's criterion (t) in the presence of two groups. The distribution of features obeyed the normal distribution (Kolmogorov − Smirnov criterion was used to assess the normality of the distribution), in the case of distribution other than normal, for analysis using parametric criteria, the transformation of indicators using natural logarithm was carried out. The data obtained are presented in the tables and the text as absolute and relative values (n, %), as well as ($M \pm \sigma$), where M is the arithmetic mean; σ is the standard deviation. Differences were considered as statistically significant at $p < 0.05$; $p \leq 0.01$-very significant; $p \leq 0.001$-highly significant.

RESULTS

The sample of obese persons (BMI ≥30 kg/m^2) was 3,197 people: 857 males (26.8%) and 2,340 females (73.2%). The frequency of the metabolically healthy obesity phenotype varies significantly depending on the criteria used, as shown in Fig. 1.

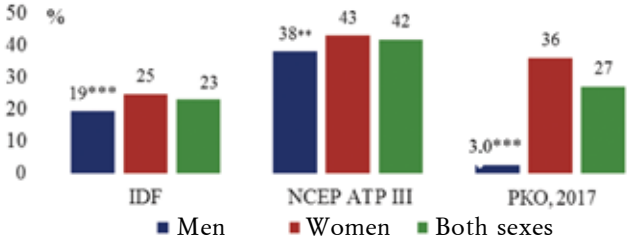

Fig. 1. The prevalence of the metabolically healthy obesity phenotype by different classifications. ** $p < 0.01$, *** $p < 0.001$ statistical significance between men and women

The frequency of MHO according to IDF criteria, 2005 was 23% (n = 743 people), NCEP ATP III, 2001 − 41.8% (n = 1,338 people), RSC, 2017 − 27% (n = 867 people), $p < 0.001$. At the same time, according to the criteria of the RSC, an interesting peculiarity was obtained in men. The frequency of MHO in them is 3%, which indicates a high prevalence of abdominal obesity.

According to the data obtained MHO is more common in women than in men, Fig. 1. Since age and gender are important factors in the development of MHO, we estimated the frequency of MHO in different age groups, Figure 2–4. In women, the highest frequency of MHO was determined in the age range of 45–49 – 34.1% (IDF, 2005), 54.0% (NCEP ATP III), 52.9% (RSC, 2017), $p < 0.001$, is significantly less common in women at the age of over 55, compared with the age of 45–49. In men, no statistical significance of differences in the frequency of MHO in all age groups was obtained ($p > 0.05$), Fig. 2–4.

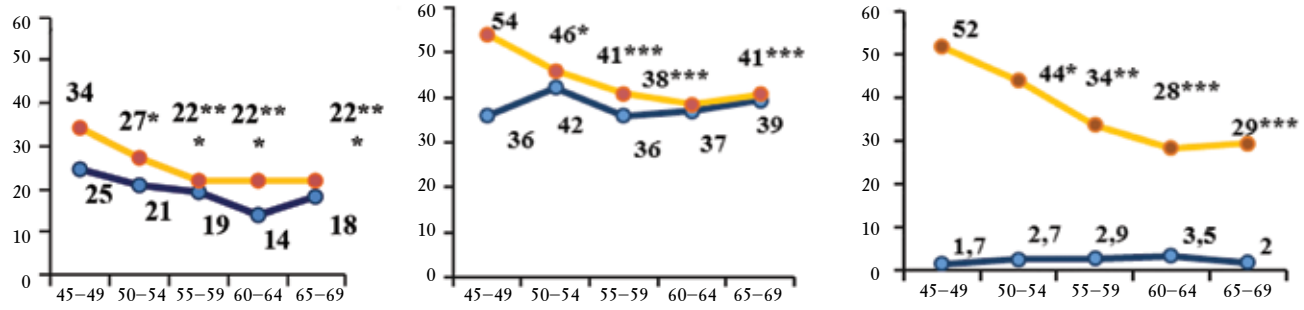

Fig. 2. Age characteristics and gender characteristics of the prevalence of MHO: * $p < 0.05$, *** $p < 0.001$, the statistical significance of the differences in age ranges compared with age 45–49

Thus, our results indicate a higher incidence of MHO in women than in men, as well as a decrease in the incidence of MHO in women over the age of 55.

The analysis of the main components was carried out in persons with MHO according to different classifications where it was found that the average values of SPB, DBP presented in Table 2 are higher than recommended by modern recommendations for the diagnosis and treatment of hypertension [15]. The analysis of lipid spectrum components showed normal values of TG and HDL-C levels in all analyzed classifications, in contrast to the levels of TG and LDL-C, which exceed the reference values for the general population, in persons with low cardiovascular risk [16].

Table 2

The main characteristics of the components in persons with MH, $M \pm \sigma$

Parameters	IDF $n = 743$	NCEP ATP III $n = 1.338$	RSC $n = 867$
SPB (mmHg)	142.9 ± 25.5	145.4 ± 26.1	146.7 ± 25.3
DBP (mmHg)	90.8 ± 13.0	92.0 ± 13.5	92.5 ± 12.5
BMI (kg/m²)	33.7 ± 3.6	33.7 ± 3.6	34.1 ± 4.1
WC (cm)	101.0 ± 9.6	101.3 ± 9.6	96.1 ± 7.9
BG (mmol/l)	5.3 ± 0.7	5.5 ± 0.7	5.8 ± 1.2
TC(mmol/l)	6.0 ± 1.0	6.1 ± 1.1	6.4 ± 1.2
LDL-C (mmol/l)	3.9 ± 0.9	4.0 ± 1.0	4.2 ± 1.1
HDL-C (mmol/l)	1.5 ± 0.2	1.5 ± 0.2	1.5 ±0.3
TG(mmol/l)	1.1 ± 0.3	1.2 ± 0.3	1.5 ± 0.8

The highest rates of cardiometabolic risk factors were determined in individuals with MHO according to the criteria proposed by the RSC 2017, despite lower mean values of WC.

The analysis of the frequency of risk factors in individuals with MHO showed a high prevalence of abdominal obesity (AO) in both men and women. At the same time, a comparative analysis of gender characteristics revealed that AO is more common in women than in men: NCEP ATP III – 90% and 71%, respectively, $p < 0.001$; IDF – 99% and 97 %, respectively, $p < 0.001$;

RSC – 99% and 86%, respectively, $p < 0.001$, Figure 3.

The frequency of AH in the NCEP ATP III group in men and women is the same, $p < 0.01$. We found a higher prevalence of AH in men (91%) than in women (84%) according to the criteria of the MHO RSC, $p < 0.001$. In the MHO group, IDF AH is more often determined in women than in men: 70% and 67%, respectively, $p < 0.05$.

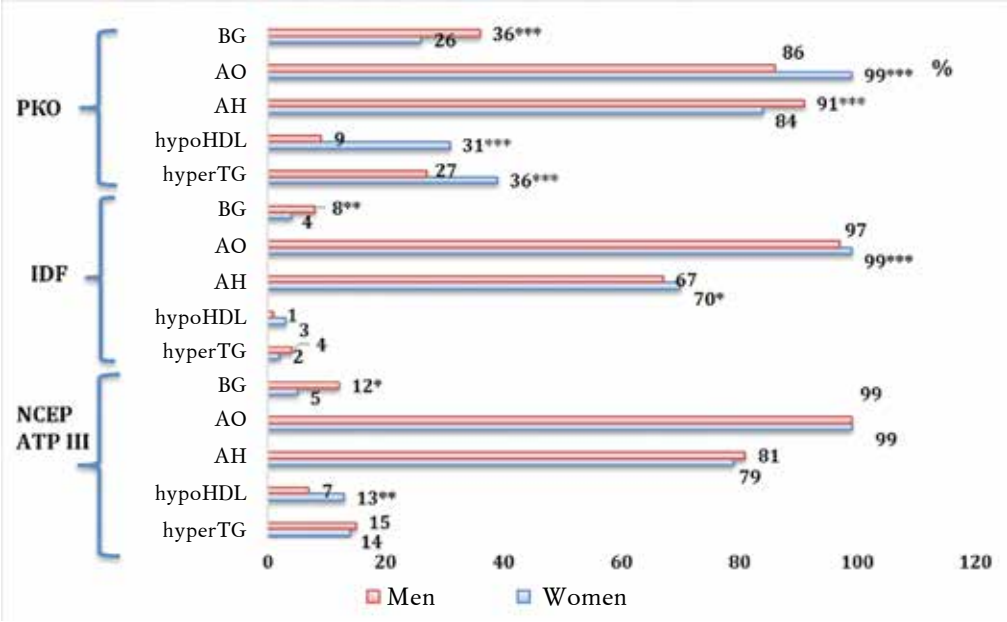

Fig. 3. Frequency of MS components in individuals with MHO according to IDF and NCEP ATP: III criteria
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ statistical significance of differences between men and women within the same classification of MHO

Carbohydrate metabolism disorders have a low incidence in individuals with MHO, according to NCEP ATP III and IDF criteria. However, according to the RSC criteria, the prevalence of hyperglycemia in men was 36%, in women – 26%, $p < 0.001$. Various lipid spectrum disorders such as hyperTG and hypoHDL have a low incidence in MHO according to IDF and NCEP ATP III criteria and no statistical significance of differences between men and women was obtained, $p < 0.05$. However, according to the RSC criteria, the prevalence of hyperTG and hypoHDL in women is quite high: 39% and 31%, respectively, while in men the frequency of hyperTG is lower (27%), and hypoHDL is 9%, $p < 0.001$.

Based on the above, a high frequency of such components of the metabolic syndrome as AO and AH in all studied classifications was revealed in persons with MHO. At the same time, in accordance with the criteria of RSC, MHO demonstrates higher rates of all cardiometabolic risk factors.

DISCUSSION

Recently, the lack of a standard approach to the use of the same criteria and limit values sets in order to determine metabolic disorders has been identified as the main source of the high variability in the prevalence of MHO obesity, which was reported earlier [3].

Both around the world and in the Russian Federation, experts are searching for the criteria of the MHO. The Russian cardiological society published a draft of recommendations relating to obesity in 2017. This paper actively discusses the feasibility of isolating a group of patients with a metabolically healthy obesity phenotype. The authors propose to allocate this phenotype of obesity in each category of BMI on the basis of the index WC/HC [9]. This may be due to the fact that a number of data suggests that body fat distribution is a strong metabolic and cardiovascular risk factor [10-11]. The HUNT-II study suggested that indicators of abdominal obesity, such as the WC/HC index, may serve as better

predictors of coronary heart disease than BMI [12]. A similar data was obtained in the Australian national representative cross-sectional study (AusDiab), among 11,247 thousand participants aged ≥25, it was revealed that those with a larger WC and a small HC had the highest prevalence of undiagnosed diabetes. A similar pattern was shown for the prevalence of undiagnosed hypertension and undiagnosed dyslipidemia [13].

In our study, the analysis of the prevalence revealed that the frequency of MHO according to the criteria of IDF 2005 is 23%, according to NCEP ATP III is 41.8%. In women, the frequency of MHO is determined significantly more often than in men. However, the results of the BioSHaRE researchers, who analyzed data from several epidemiological studies using the same standard criteria, also demonstrate a significant diversity in the prevalence of MHO in Europe. The highest percentage of MHO in men was found in CHRIS and KORA studies, and in women in NCDS, LifeLines, KORA and CHRIS, while the lowest prevalence was found in Finnish cohorts and in HUNT2 [14]. According to Ostrovskaya E. V., in the analysis of 389 case records of patients at the age of 18–60 with obesity, the frequency of MHO, taking into account the criteria of IDF 2005, was 38.6%. It is possible that this difference in frequency is connected with a younger average age of the participants of the study [15]. The group of domestic authors (O. Rotar et al.) studied the prevalence of MHO in 13 regions of Russia (Volgograd, Vologda, Voronezh, Vladivostok, Ivanovo, Kemerovo, Krasnoyarsk, Orenburg, Tomsk, Tyumen, St. Petersburg and the Republic of North Ossetia-Alania) with the participation of 1,600 people aged 25–65. The maximum prevalence of MHO, taking into account the criteria of the IDF MS in 2005, was noted in Tyumen at 52.2%, the minimum in Voronezh at 25.7% with a total prevalence of 41% and no significant gender differences [16]. In another domestic study of scientists from St. Petersburg, the prevalence of MHO was significantly lower at only 8.7% [17]. The lower rates were predetermined by the fact that in this work the combination of the minimum number of manifestations of metabolic syndrome together with normal tissue sensitivity to insulin was assigned to the criteria of MHO.

According to the data we have obtained, gender differences in the frequency of MHO in different age groups were revealed. Thus, women over 55 have a significant decrease in the frequency of MHO, as distinct from men. The obtained data can be explained by the fact that at this age women go through menopause. According to the literature, menopausal women show a greater incidence of MS and an increase in the prevalence of MS components: BP, AO, hyper-LDL-C, hyper-HDL-C, hyper-TG, high levels of glucose [18].

In men, there is a slight decrease in the frequency of MHO in older age groups, perhaps this is connected with the average life expectancy, which in men is 66.5 years in Russia for 2016. This age is an order of magnitude less than that of women: 77.1 years [19].

According to the data we have obtained, the average values of SBP, DBP presented in Table 2 are higher than the levels indicated by modern recommendations for the diagnosis and treatment of hypertension, but the average values of TG and HDL-C the level are in the reference range [20].

It is also worth noting that MHO is a transitional state [6], in which components of the metabolic syndrome may join over time. According to our findings on the frequency of cardiometabolic risk factors, persons with MHO, according to the criteria of RSC, have the highest frequency of all risk factors in both men and women, Figure 3. Traditionally, it is believed that the WC/HC index should reflect the presence of AO, but our data shows a fairly high frequency of AO, despite the normal values of the WC/HC index against MHO. And in the general population of Novosibirsk aged 45–69, the most common components among people with MS, according to the criteria of NCEP-ATP III 2001 in the urban Siberian population aged 45–69, are hypertension (95 %) and abdominal obesity (85%) [21].

Thus, data on variability in the prevalence of MHO, as well as higher prevalence at a younger age, correspond to world sources [24, 25]. This situation makes the future prospects of this condition unclear. So a unified classification of the metabolically healthy phenotype of obesity is needed, in order to determine such outcomes as myocardial infarction, cerebrovascular accident,

type 2 diabetes, etc. And it remains unclear at what stage it is necessary to carry out medical intervention to the change of the lifestyle, in order to obtain further benefits for the health of the patient, which requires further comprehensive study of this problem.

CONCLUSIONS

The frequency of MHO varies depending on the classification used: IDF, 2005 – 23%; RSC, 2017 – 27%; NCEP ATP III – 41.8%.

In the female sample, the frequency of MHO is statistically significantly higher than in men in all classifications.

In women older than 55, there is a statistically significant decrease in the frequency of MHO.

Women, according to the RSC criteria, show higher rates of all cardiometabolic risk factors than when using other MHO criteria.

Persons with MHO are characterized by increased mean values of SBP, DBP, with normal mean values of TG and HDL-C.

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Mustafina S. V. – conception and design; justification of the manuscript and critical revision of the manuscript for important intellectual content; final approval of the manuscript for publication. Vinter D.A. – conception and design; analysis and interpretation of data. Shcherbakova L. V. – conception and design; justification of the manuscript and critical revision of the manuscript for important intellectual content. Malyutina S. K. – conception and design. Ragino Yu. I. – conception and design. Rymar O.D. – conception and design; justification of the manuscript and critical revision of the manuscript for important intellectual content; final approval of the manuscript for publication.

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