ISSN 1607-419X
ISSN 2411-8524 (Online)
УДК 616.056.52

Metabolically healthy obesity: predictors of transformation to unhealthy phenotype in St Petersburg population (according to the ESSE-RF study)

M. A. Boyarinova[1], O. P. Rotar[1], A. M. Erina[1], N. A. Paskar[1], A. S. Alieva[1], E. V. Moguchaia[1], E. P. Kolesova[1], A. O. Konradi[1, 2]
[1] Almazov National Medical Research Center, St Petersburg, Russia
[2] ITMO University, St Petersburg, Russia

Corresponding author:
Maria A. Boyarinova,
Almazov National Medical Research Centre,
2 Akkuratov str., St Petersburg,
197341 Russia.
Phone: 8(812)702–37–56.
E-mail: boyarinova@almazovcentre.ru

Received 22 April 2021;
accepted 27 May 2021.

Abstract

Objective. The purpose of the study was to determine the dynamics of the metabolically healthy obesity (MHO) status according to the Meigs criteria, and to establish the predictors of the transformation of healthy obesity phenotype into an unhealthy (MUHO) one in the population of residents of St Petersburg (Russia) at 6,5-year follow-up. **Design and methods.** Within the epidemiology study ESSE-RF a random sample of 1600 St Petersburg inhabitants stratified according to gender and age was formed. Examination of participants included anthropometry with measurement of waist circumference and calculation of body mass index (BMI), measurement of blood pressure (BP), fasting blood glucose, insulin (index of insulin resistance was calculated), creatinine, cortisol, lipid spectrum, C-reactive protein, adiponectin, leptin, and uric acid. Meigs MHO criteria (2006) were used in obese subjects (BMI > 30 kg/m²). Obese patients, who were identified as metabolically healthy in 2012–2013, were invited for follow-up in 2018–2019. **Results.** At the first stage obesity was diagnosed in 430 (26,9 %) participants, according to the BMI, 116 (27,0 %) of them were metabolically healthy according to the Meigs criteria. At follow-up, 44,4 % individuals with the MHO phenotype transformed to the MUHO category on average after 6,5 years. Individuals who retained the MHO phenotype over time had significantly lower baseline systolic BP and diastolic BP levels, more favorable lipid levels and lower levels of uric acid, insulin, and index of insulin resistance. Glucose increase by every 0,5 mmol/l and higher was associated with elevated probability of transformation MHO to MUHO phenotype by 10,9 times (adjusted for sex and age). **Conclusions.** Significantly higher levels of BP, insulin resistance, low density lipoprotein and uric acid at baseline, as well as an increase in glucose levels over time, were associated with the transformation of the metabolically healthy to the unhealthy phenotype in obese individuals at 6,5-year follow-up.

In all individuals with the MHO phenotype, there was a significant increase in waist circumference over time, accompanied by an increase in BMI only in those who transformed into the MUHO status.

Key words: obesity, metabolically healthy obesity, obesity dynamics, metabolic status

For citation: Boyarinova MA, Rotar OP, Erina AM, Paskar NA, Alieva AS, Moguchaia EV, Kolesova EP, Konradi AO. Metabolically healthy obesity: predictors of transformation to unhealthy phenotype in St Petersburg population (according to the ESSE-RF study). Arterial'naya Gipertenziya = Arterial Hypertension. 2021;27(3):279–290. ***doi:10.18705/1607-419X-2021-27-3-279-290***

Метаболически здоровое ожирение: предикторы трансформации в нездоровый фенотип в популяции жителей Санкт-Петербурга (по данным исследования ЭССЕ-РФ)

М. А. Бояринова[1], О. П. Ротарь[1], А. М. Ерина[1], Н. А. Паскарь[1], А. С. Алиева[1], Е. В. Могучая[1], Е. П. Колесова[1], А. О. Конради[1, 2]

[1] Федеральное государственное бюджетное учреждение «Национальный медицинский исследовательский центр имени В. А. Алмазова» Министерства здравоохранения Российской Федерации, Санкт-Петербург, Россия

[2] Федеральное государственное автономное образовательное учреждение высшего образования «Санкт-Петербургский национальный исследовательский университет информационных технологий, механики и оптики» (Университет ИТМО), Санкт-Петербург, Россия

Контактная информация:
Бояринова Мария Анатольевна,
ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России,
ул. Аккуратова, д. 2, Санкт-Петербург, Россия, 197341.
Тел.: 8(812)702–37–56.
E-mail: boyarinova@almazovcentre.ru

Статья поступила в редакцию 22.04.21 и принята к печати 27.05.21.

Резюме

Цель исследования — определить динамику статуса метаболически здорового ожирения (МЗО) согласно критериям Meigs и предикторы трансформации здорового фенотипа в нездоровый в популяции жителей Санкт-Петербурга через 6,5 года наблюдения. **Материалы и методы.** В рамках российского эпидемиологического исследования ЭССЕ-РФ была сформирована случайная выборка 1600 жителей Санкт-Петербурга, стратифицированная по полу и возрасту. В 2012–2013 годах всем участникам были выполнены антропометрия с оценкой окружности талии (ОТ) и индекса массы тела (ИМТ), измерение артериального давления (АД), анализы крови натощак: глюкоза, инсулин (с расчетом индекса инсулинорезистентности), креатинин, кортизол, липидный состав крови, С-реактивный белок, адипонектин, лептин, мочевая кислота. У лиц с ожирением (ИМТ > 30 кг/м²) использовались критерии МЗО по Meigs (2006). Часть участников была приглашена на второй этап обследования в 2018–2019 годах. Явка составила 288 человек (18 % от исходной выборки). В анализ включались пациенты с ожирением по критерию ИМТ, у которых был выявлен метаболически здоровый статус в 2012–2013 годах. **Результаты.** На первом этапе в 2012–2013 годах у 430 (26,9 %) человек было выявлено ожирение согласно критерию ИМТ, 116 (27,0 %) из которых были метаболически здоровыми (по критерию Meigs). 44,4 % лиц с МЗО фенотипом перешли в категорию метаболически нездоровых лиц с ожирением (МНЗО) в среднем через 6,5 лет наблюдения. У лиц, сохранивших с течением времени МЗО фенотип, отмечался

значимо более низкий исходный уровень систолического АД и диастолического АД, более благоприятный липидный профиль, более низкий уровень мочевой кислоты, инсулина и индекса инсулинорезистентности. При увеличении уровня глюкозы на 0,5 ммоль/л и более вероятность трансформации МЗО в МНЗО фенотип повышалась в 10,9 раза с поправкой на пол и возраст. **Выводы.** Исходно значимо более высокие уровни АД, инсулинорезистентности, липопротеинов низкой плотности и мочевой кислоты, а также рост уровня глюкозы с течением времени были ассоциированы с трансформацией метаболически здорового в нездоровый фенотип у лиц с ожирением через 6,5 лет наблюдения. У всех лиц с МЗО фенотипом происходило значимое увеличение ОТ в динамике, сопровождаясь увеличением ИМТ только у лиц, перешедших в категорию метаболического нездоровья.

Ключевые слова: ожирение, метаболически здоровое ожирение, динамика ожирения, метаболический статус

Для цитирования: Бояринова М.А., Ротарь О.П., Ерина А.М., Паскарь Н.А., Алиева А.С., Могучая Е.В., Колесова Е.П., Конради А.О. Метаболически здоровое ожирение: предикторы трансформации в нездоровый фенотип в популяции жителей Санкт-Петербурга (по данным исследования ЭССЕ-РФ). Артериальная гипертензия. 2021;27(3):279–290. ***doi:10.18705/1607-419X-2021-27-3-279-290***

Introduction

Despite the scientific and technological progress observed in the medical field, obesity remains a cardiometabolic risk factor, the importance of which cannot be overestimated. In the course of numerous, including large prospective epidemiological studies, the association of obesity with such socially and economically significant diseases as cardiovascular diseases (CVD), type 2 diabetes mellitus (DM) and some types of oncological diseases has been repeatedly demonstrated [1, 2]. The steadily progressing spread of obesity, which currently has the scale of an epidemic throughout the world, demonstrates the low effectiveness of measures taken to treat and prevent overweight and confirms the need to change the paradigm of management of this pathological condition. It is possible that the use of a personalized approach, taking into account the peculiarities of a specific pathophysiological situation, will make it possible to qualitatively change the tactics of managing obese patients, prevent the development of cardiometabolic complications and reduce cardiovascular mortality in the future.

Obesity has long been regarded as a marker of metabolic ill health, being the central link in metabolic syndrome (MS). Nevertheless, obesity is heterogeneous in its structure — there is a variation in the individual risk of pathological conditions accompanying obesity, and this variability is not explained only by the degree of obesity. Currently, it is known that there is a group of people who, despite the excess amount of fat mass, have a favorable glucose and lipid profile, maintain normal blood pressure and have no cardiovascular diseases [3]. Such patients are considered metabolically healthy obese individuals (MHO). The prevalence of the MHO phenomenon, depending on the diagnostic criteria, is 10–40 % among obese individuals [4], 12–41.8 % — in the Russian population [5, 6]. Most authors use the criteria for MS and / or the presence of other cardiometabolic disorders to determine the MHO [3]. Most often, the presence of 2 or less criteria for metabolic syndrome in obese individuals, established by the body mass index (BMI) (BMI ≥30 m²), is taken for the presence of a MHO. MHO in comparison with metabolically unhealthy persons with obesity (MUHO) demonstrate a significantly lower risk of developing CVD, type 2 diabetes and a lower risk of death from all causes [7, 8]. It is currently not completely clear what factors determine the metabolic health of a person in the presence of obesity. It is assumed that the distribution of adipose tissue is of the greatest importance in the formation of one or another metabolic response in obesity — the MUHO phenotype is characterized by an excessive accumulation of visceral fat — and its functional activity; some genetic and epigenetic factors, as well as changes in the gastrointestinal microbiota, play an important role [9–11]

Questions remain extremely relevant: is the MHO phenotype only a transitional stage to metabolically unhealthy obesity, and what are the pre-

dictors of of transformation to unhealthy phenotype. Epidemiological studies have shown that about 50% of individuals with the MHO phenotype "progress" to the MUHO status gradually [8, 12, 13]. The same studies reported an increase in the incidence of cardiovascular events and a higher risk of long-term mortality from all causes in the MHO group compared with metabolically healthy individuals of normal weight. It is possible that the development of CVD and other complications in individuals with the initial MHO status can be partially explained by their transition to the category of MUHO. On the other hand, it has been shown that the MUHO phenotype can be transformed into MHO under certain influences, in particular, with a sufficient level of physical activity, which is accompanied by a decrease in the waist circumference (WC) [14]. Thus, MHO and MUHO phenotypes should not be considered as separate groups in the long term — a mutual transition between these states is possible. Preventing the transition of a healthy phenotype to an unhealthy one and potentiating the transformation of MUHO into MHO status can become therapeutic goals in real clinical practice. Identification of predictors of the transition from a metabolically healthy to an unhealthy phenotype will allow the identification of new therapeutic targets and may contribute to better prevention of cardiometabolic complications among obese individuals. Studies of the stability of the MHO phenotype are relevant and are carried out all over the world, however, no data for the Russian population was previously presented, which served as the basis for this work.

The objective of our study was to determine the dynamics of the status of metabolically healthy obesity according to the Meigs criteria and predictors of transformation to unhealthy phenotype in the population of St. Petersburg residents after 6.5 years of follow-up.

Materials and methods

In 2012–2013 in 12 regions of Russia, different in climatic, geographic, economic and demographic characteristics, a national study "Epidemiology of cardiovascular diseases in various regions of the Russian Federation" (ESSE-RF) has been launched. Within the framework of this study, a stratified multistage random sample of 1600 residents (the adult population — men and women aged 25–65 years) was formed in St. Petersburg [15]. All participants signed informed consent and completed a standard questionnaire based on adapted and validated international methods.

All participants underwent anthropometry: height was measured (once with an accuracy of 0.5 cm in a standing position and body weight (once with an accuracy of 100 g) with the calculation of BMI according to the Quetelet formula; WC in a standing position. Blood pressure (BP) and frequency heart rate (HR) was measured by the OMRON apparatus (Japan) twice on the right hand in a sitting position, calculating the average blood pressure and average heart rate. Fasting blood was taken to determine the lipid composition, levels of glucose, creatinine, uric acid (Abbott Architect 8000, USA; reagents Abbot Diagnostic), C-reactive protein (CRP), insulin, cortisol (Cobas Integra 400 plus, Switzerland; Roche-diagnostics reagents), leptin and adiponectin levels were determined by enzyme-linked immunosorbent assay using DRG reagents (Germany)/ Insulin resistance index was calculated using the formula: fasting blood glucose × insulin × 0.138 (coefficient used to convert pmol / L to μU / ml) / 22.5 (HOMA-IR (Homeostasis Model Assessment of Insulin Resistance)) [16].

For the diagnosis of obesity, a BMI of ≥ 30 kg / m^2 was used. The MHO phenotype was determined according to the Meigs criteria [17] (Table 1) in combination with the absence of CVD and diabetes at the time of inclusion in the study, according to the history and information about the absence of therapy with hypoglycemic drugs. Obese patients who did not meet these criteria were considered as patients with MUNO phenotype.

Some of the participants were invited to the second stage of the survey in 2018–2019. The analysis included obese patients according to the BMI criterion (BMI ≥ 30 m^2), who had a metabolically healthy status in 2012–2013. The condition for inclusion in the final analysis was the presence of obesity at stages 1 and 2 of the survey, the absence of CVD and DM at the first (excluded 100 people with obesity and previously diagnosed CVD and DM) and the second (excluded 7 people with CVD and DM) stages of the survey. Some of the individuals with the initial MHO status "left" the category of obesity, having reduced body weight

Table 1

CRITERIA FOR THE MHO PHENOTYPE

Parameter	Criteria
BP, mm Hg	SBP ≥ 130 or DBP ≥ 85, or antihypertensive therapy
TG, mmol / L	≥ 1.7
HDL, mmol / L	< 1.04 (M) / 1.30 (F) or statin therapy
Glucose, mmol / L	≥ 5.6 or hypoglycemic therapy
WC, cm	> 102 (M) / 88 (W)
MHO criteria: sum of <3 criteria	

Note: MHO — metabolically healthy obesity; BP — blood pressure; SBP — systolic blood pressure; DBP — diastolic blood pressure; TG — triglycerides; HDL — high density lipoprotein; WC — waist circumference; M — men; F — women.

Table 2

CARDIOMETABOLIC PROFILE OF OBESE PATIENTS WITH DIFFERENT METABOLIC STATUS ACCORDING TO THE MEIGS CRITERIA

Parameter	MHO		MUHO		p
	Mean ± SD	95 % CI	Mean±SD	95 % CI	
WC, cm	100.7 ± 11.3	98.6–102.8	106.6 ± 10.7	105.1–109.1	< 0.0001**
Cholesterol, mmol / l	5.4 ± 1.0	5.2–5.6	5.6 ± 1.2	5.4–5.8	0.12
Uric acid, μmol / l	312.6 ± 76.0	298.7–326.6	360.7 ± 87.1	348.6–372.9	< 0.0001*
	Me	Q1-Q3	Me	Q1-Q3	
Age, years	51	44–56	51	42–57	0.916
Body weight, kg	90.9	82.4–101.5	97.65	86.35–108.80	0.001*
BMI, kg / m^2	32.4	31.2–34.3	33.1	31.4–36.3	0.019*
WC/HC	0.89	0.82–0.97	0.92	0.86–0.98	0.008*
SBP, mm Hg	123.3	117.8–136.0	140.0	130.0–150.0	< 0.0001**
DBP, mm Hg	80.0	73.3–85.2	87.8	80.0–94.8	< 0.0001**
Heart rate, beats per minute	69.3	63.8–76.5	72.0	66.0–79.5	0.048
LDL, mmol / l	3.5	2.9–3.9	3.5	2.9–4.3	0.318
HDL, mmol / l	1.4	1.2–1.6	1.1	1.0–1.3	< 0.0001**
TG, mmol / l	1.1	0.9–1.4	1.8	1.3–2.5	< 0.0001**
Glucose, mmol / l	5.1	4.8–5.4	5.6	5.1–6.1	< 0.0001**
Creatinine, mmol / l	65.5	60.5–70.0	67.0	61.0–74.0	0.096
CRP, mg / ml	1.7	1.0–2.7	2.2	1.0–4.7	0.019*
Insulin, pmol / l	84.6	59.2–114.2	105.7	77.6–155.8	< 0.0001*
HOMA-IR	2.6	1.9–3.7	3.6	2.5–5.5	< 0.0001*
Cortisol, nmol / l	447.8	355.5–563.5	467.1	357.9–591.1	0.502
Leptin, ng / ml	24.6	16.7–41.0	24.4	14.1–43.3	0.667
Adiponectin, μg / ml	10.6	6.1–16.9	6.8	4.5–12.0	< 0.0001*

Note: MHO — metabolically healthy obesity; MUHO — metabolically unhealthy obesity; BP — blood pressure; SBP — systolic blood pressure; DBP — diastolic blood pressure; TG — triglycerides; Cholesterol — total cholesterol; HDL — high density lipoprotein; LDL — low density lipoprotein; WC — waist circumference; WC / HC — the ratio of the waist circumference to the hip circumference; BMI — body mass index; CRP — C reactive protein; HOMA-IR — index of insulin resistance Homeostasis Model Assessment of Insulin Resistance.

* — differences in indicators are statistically significant ($p < 0.05$).

** — the values of the indicators included in the criteria for determining the MHO, the statistical significance is predetermined.

in dynamics, and were not included in the analysis of the dynamics of the MHO (10 people).

The following mathematical and statistical methods were used: standard descriptive statistics (mean, standard error of the mean with a normal distribution and median, quartiles with a distribution other than normal). To compare related populations, the paired t-test method was used for indicators with normal distribution and Wilcoxon's test for non-normal distribution. Methods of checking the distribution normality were applied: Kolmogorov-Smirnov test with Lilliefors' correction — for n> 50 and Shapiro-Wilk test for n <50. To assess the odds ratio (OR), one-way and multivariate models of binary logistic regression were used. The reliability of the models was assessed using the maximum likelihood method. The calculation of 95 % confidence intervals (CI) was performed. Mathematical and statistical data analysis was carried out using the IBM SPSS Statistics version 26.0.

Results

1600 residents of St. Petersburg were included in the study in 2012–2013. Among the surveyed persons, women predominated (n=1027, 64 %), the average age for women and men did not differ significantly: 48.1 ± 11.4 years for women, and 45.1 ± 11.9 years for men. Obesity was revealed in 430 (26.9 %) people, according to the BMI criterion: 144 (25.0 %) men and 286 (27.9 %) women, without gender differences. The average BMI was 33.9 ± 3.6 kg / m².

Complete data were available for 416 obese people. After excluding people with CVD (52 people) and DM (48 people) at the time of examination, 116 (27.0 %) people showed metabolic health (according to the Meigs criterion): 79 women (61.8 %), 37 men (31.9 %). The status of MUHO was determined in 300 people (72.1 %): 195 women (65.0 %) and 105 men (35.0 %). There were no gender differences in both groups.

A comparative assessment of the indicators in individuals with MHO and MUHO phenotype was carried out using various statistical criteria after checking the parameters for the normality of distribution. The cardiometabolic profile of obese patients with different metabolic status according to the Meigs criterion is presented in Table 2 as mean and standard deviation (SD) with a normal distribution and as a median (Me) and quartiles (Q1-Q3) with a non-normal distribution.

Some of the participants were invited to the second stage of the survey in 2018–2019. The turnout was 288 people (18 % of the original sample). This analysis included obese patients who had a metabolic healthy status in 2012–2013 and had complete data to assess cardiometabolic status (Fig. 1). Figure 1 also shows the data on the dynamics of the metabolic health status of individuals with the initial MUHO phenotype.

Using methods for comparing related populations — paired t-test for indicators with a normal distribution and Wilcoxon's test for a distribution

Fig. 1. Dynamics of the status of MHO and MUHO of individuals through the time, the median of follow-up is 6.5 years

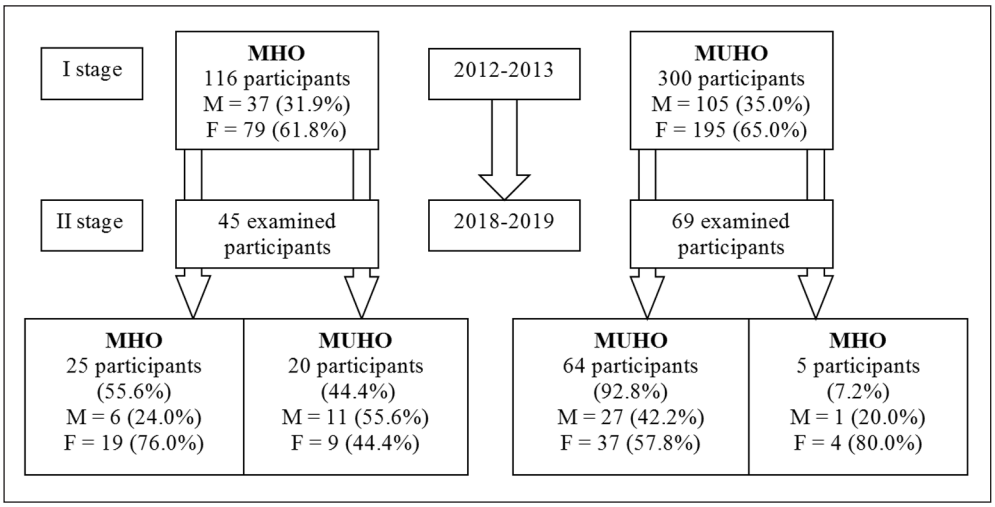

Table 3

CARDIOMETABOLIC PARAMETERS OF INDIVIDUALS WHO RETAINED THE MHO PHENOTYPE THROUGH THE TIME (n = 25)

Factor	Observation stages				p
	1 (2012–2013)		2 (2018–2019)		
	Mean ± SD\Me	Q1-Q3	Mean ± SD\Me	Q1-Q3	
Body weight, kg	91.4 ± 12.9		91.9 ± 14.2		0.588
BMI, kg / m^2	32.7	31.4–34.5	33.1	31.4–34.6	0.220
WC, cm	100.2 ± 10.0	–	103.9 ± 9.8	–	0.016*
WC\HC	0.9 ± 0.1	–	0.9 ± 0.1	–	0.164
SBP, mm Hg	122.0 ± 10.7	–	125.4 ± 12.4	–	0.158
DBP, mm Hg	77.5 ± 7.8	–	79.5 ± 7.8	–	0.211
Heart rate, beats per minute	70.1 ± 10.1	–	72.4 ± 9.2	–	0.254
Cholesterol, mmol / l	5.0	4.8–5.8	5.0	4.7–5.8	0.230
LDL, mmol / l	3.1	2.8–3.7	3.3	3.0–3.6	0.414
HDL, mmol / l	1.4	1.3–1.7	1.4	1.4–1.7	0.259
TG, mmol / l	1.0	0.8–1.2	1.0	0.7–1.2	0.732
Glucose, mmol / l	5.1	4.9–5.4	5.1	4.9–5.3	0.234
CRP, mg / ml	1.2	0.9–2.3	1.9	1.2–2.8	0.005*
Leptin, ng / ml	28.5	20.7–40.5	35.5	22.7–45.1	0.520
Adiponectin, μg / ml	10.5	6.1–16.4	9.4	7.9–16.8	0.434

Note: BP — blood pressure; SBP — systolic blood pressure; DBP — diastolic blood pressure; TG - triglycerides; Cholesterol — total cholesterol; HDL — high density lipoprotein; LDL — low density lipoprotein; WC — waist circumference; WC / HC — the ratio of the waist circumference to the hip circumference; BMI — body mass index; CRP — C reactive protein.

* — changes are statistically significant, $p < 0.05$.

Table 4

CARDIOMETABOLIC PARAMETERS OF INDIVIDUALS WHO SWITCHED TO MUHO PHENOTYPE THROUGH THE TIME (n = 20)

Factor	Observation stages				p
	1 (2012–2013)		2 (2018–2019)		
	Mean ± SD\Me	Q1-Q3	Mean ± SD\Me	Q1-Q3	
Body weight, kg	95.3 ± 14.4	–	100.2 ± 17.0	–	< 0.0001*
BMI, kg / m^2	33.2 ± 2.6	–	34.7 ± 3.0	–	0.003*
WC, cm	102.4 ± 10.6	–	110.2 ± 11.6	–	0.003*
WC\HC	0.9 ± 0.1	–	0.9 ± 0.1	–	0.326
SBP, mm Hg	137.6 ± 23.0	–	141.1 ± 19.3	–	0.457
DBP, mm Hg	85.0 ± 11.9	–	87.6 ± 10.3	–	0.350
Heart rate, beats per minute	70.3 ± 8.7	–	73.6 ± 11.4	–	0.170
Cholesterol, mmol / l	5.6 ± 0.9	–	5.5 ± 0.9	–	0.649
LDL, mmol / l	3.8 ± 0.75	–	3.5 ± 0.9	–	0.235
HDL, mmol / l	1.4 ± 0.2	–	1.3 ± 0.3	–	0.101
TG, mmol / l	1.0	0.8–1.6	1.2	1.0–2.0	0.157
Glucose, mmol / l	5.2	4.8–5.3	5.7	5.3–5.9	0.010*
CRP, mg / ml	1.8	1.2–2.7	3.0	1.9–4.3	0.169
Leptin, ng / ml	22.7	19.6–25.0	26.9	17.8–40.1	0.285
Adiponectin, μg / ml	10.1	7.6–14.8	7.5	6.2–13.0	0.169

Note: BP — blood pressure; SBP — systolic blood pressure; DBP — diastolic blood pressure; TG — triglycerides; Cholesterol — total cholesterol; HDL — high density lipoprotein; LDL — low density lipoprotein; WC — waist circumference; WC / HC — the ratio of the waist circumference to the hip circumference; BMI — body mass index; CRP — C reactive protein.

* — changes are statistically significant, $p < 0.05$

other than normal, the following data were obtained: cardiometabolic parameters of persons who retained the MHO phenotype through the time (n = 25) are presented in Table 3 in the mean and standard deviation (SD) for a normal distribution and as a median (Me) and quartiles (Q1-Q3) for a distribution other than normal.

There was a statistically significant increase in WC (without an increase in weight and BMI) and an increase in the level of CRP in individuals who retained the MHO phenotype through the time. Cardiometabolic parameters of individuals who switched to MUHO phenotype through the time (n = 20) are presented in Table 4, as mean and standard deviation (SD) with a normal distribution and as a median (Me) and quartiles (Q1-Q3) with a distribution other than normal.

A statistically significant increase in body weight, BMI, and waist circumference was revealed in obese individuals who demonstrated the transformation of a healthy metabolic status into an unhealthy one. There was a significant increase in WC as a marker of visceral obesity, accompanied by a general increase in BMI. We carried out a comparative analysis of the cardiometabolic profile of the MHO of individuals at stage 1, depending on whether the healthy phenotype was transformed into an unhealthy one (n = 20) in the future or remained intact (n = 25). Data are presented in Table 5 as mean and standard deviation (SD) for normal distribution and as median (Me) and quartiles (Q1-Q3) for non-normal distribution.

Individuals, who retained a metabolically healthy obesity phenotype through the time, had a significantly lower baseline SBP and DBP, a more favorable lipid profile — a significantly lower level of atherogenic lipids (LDL and TG), without a significant difference in the HDL level, a significantly lower uric acid level, insulin and HOMA-IR. Caution should be exercised in interpreting the revealed higher level of leptin in persons who retained the MHO status, due to the small number of observations.

When performing logistic regression analysis, there was no statistically significant change in the probability of transformation of the MHO phenotype into the MUHO with an increase in the dynamics of such cardiometabolic indicators as SBP, DBP, total cholesterol, LDL, HDL, triglycerides, insulin, adiponectin, leptin, CRP. However, with an increase in glucose levels of 0.5 mmol / L and higher, the probability of transformation of the MHO into MUHO phenotype increased by 10.9 times, adjusted for gender and age, 95% CI [2.0; 58.3], p = 0.005. An increase in glucose by less than 0.5 mmol / L did not lead to a statistically significant increase in the likelihood of the transformation of the MHO into an unhealthy phenotype.

Discussion

The phenomenon of metabolically healthy obesity has been actively studied for more than twenty years. In addition to the fact that either the metabolic syndrome components are totally absent, or only 1–2 of them are present, the MHO status is characterized by a lower amount of visceral fat (waist circumference as a marker of visceral obesity is smaller) [18], lower markers of subclinical inflammation and insulin resistance [3, 19] as well as a lower level of uric acid [20] and higher levels of the protective adipokine adiponectin compared to the unhealthy obesity phenotype [21], which is consistent with the given description of cardiometabolic indices of the examined group of MHO individuals. Despite the favorable cardiometabolic profile, many researchers still raise the question of the appropriateness of viewing the MHO group as predictively favorable, based on epidemiological studies demonstrating an increased risk of cardiovascular events and type 2 diabetes in this cohort of patients. In this relation, the analysis of 22 prospective studies revealed a 1.45 times higher risk of MHO individuals developing cardiovascular disease as compared to healthy participants without obesity. [22]. Another large meta-analysis examined the risk of diabetes mellitus depending on the stability of metabolically healthy phenotype in 3,479,514 healthy individuals over the age of 20 years in the course of the National Health Screening Program (NHSP) in Korea. Upon 4 years of observation in the MHO group, the obesity phenotype of 31.5% of patients transformed into the unhealthy one. In the adjusted multivariate model this “unstable” group with the MHO phenotype showed a high risk of developing type 2 diabetes (OR 4.67 [4.58; 4.77]) as compared to the stable MHO group (OR 1.81 [CI 1.76; 1.85]) [23]. One can assume that the cardiometabolic risk is higher precisely in those MHO individuals, whose metabolic status transforms into the unhealthy one over time. Various studies

Table 5

CARDIOMETABOLIC PROFILE OF MHO INDIVIDUALS AT STAGE 1, DEPENDING ON THE FURTHER PHENOTYPE TRANSFORMATION

Parameter	Maintain MHO		Transformation to MUHO		p
	Mean±SD	95%CI	Mean±SD	95%CI	
Age, years	49.5 ± 9.3	45.8–53.2	50.4 ± 10.0	45.5–55.4	0.743
Body weight, kg	91.4 ± 12.9	86.2–96.5	95.3 ± 14.4	88.2–102.5	0.340
WC, cm	100.2 ± 10.0	96.2–104.2	102.4 ± 10.6	97.1–107.7	0.483
WC\HC	0.9 ± 0.1	0.86–0.93	0.9 ± 0.1	0.9–1.0	0.257
SBP, mm Hg	122.0 ± 10.7	117.8–126.2	137.6 ± 22.9	126.2–149.0	0.013*
DBP, mm Hg	77.5 ± 7.8	74.4–80.6	85.0 ± 11.9	79.1–90.9	0.026*
Heart rate, beats per minute	70.1 ± 10.1	66.1–74.1	70.3 ± 8.7	66.0–74.6	0.947
Cholesterol, mmol / l	5.3 ± 1.0	4.9–5.7	5.8 ± 1.1	5.3–6.4	0.090
LDL, mmol / l	3.4 ± 0.9	3.1–3.7	4.0 ± 1.0	3.5–4.5	0.034*
HDL, mmol / l	1.4 ± 0.3	1.3–1.5	1.3 ± 0.2	1.2–1.4	0.227
	Me	Q1-Q3	Me	Q1-Q3	
BMI, kg / m^2	32.7	31.4–34.5	32.7	30.8–34.6	0.982
TG, mmol / l	1.0	0.8–1.2	1.3	0.9–1.6	0.028*
Glucose, mmol / l	5.1	4.9–5.3	5.2	4.9–5.3	0.354
Uric acid, μmol / l	293.0	269.0–321.5	367.0	270.0–401.0	0.009*
CRP, mg / ml	1.2	0.9–2.3	1.4	1.1–2.9	0.261
Insulin, pmol / l	77.9	53.1–90.6	112.8	69.9–136.8	0.012*
HOMA-IR	2.4	1.8–2.8	3.5	2.2–4.5	0.009*
Cortisol, nmol / l	442.3	344.8–473.4	433.3	364.3–531.0	0.711
Leptin, ng / ml	28.5	21.2–40.6	20.8	10.9–24.9	0.039*
Adiponectin, μg / ml	10.3	5.8–14.4	8.3	4.1–12.7	0.502

Note: MHO — metabolically healthy obesity; MUHO — metabolically unhealthy obesity; BP - blood pressure; SBP — systolic blood pressure; DBP - diastolic blood pressure; TG — triglycerides; Cholesterol — total cholesterol; HDL — high density lipoprotein; LDL — low density lipoprotein; WC — waist circumference; WC / HC - the ratio of the waist circumference to the hip circumference; BMI — body mass index; CRP — C reactive protein; HOMA-IR — index of insulin resistance Homeostasis Model Assessment of Insulin Resistance.

* — differences in indicators are statistically significant ($p < 0.05$).

have shown that the portion of individuals demonstrating transformation of the healthy phenotype (MHO) into the unhealthy one (MUHO) is determined by time interval. Thus, in a 20-year cohort study, out of 66 patients with the MHO phenotype 21 (31.8%), 27 (40.9%) and 34 (51.5%) participants acquired the MUHO status in 5, 10 and 20 years of observation, respectively [24]. In another study 2422 participants in 8 years of observation showed transformation of the MHO status into the MUHO status in 44.2% of these persons [8]. According to our data, 44.4% of individuals with the MHO phenotype moved to the MUHO category after an average of 6.5 years of observation, which is consistent with the data of foreign studies. In a situation where this kind of natural transformation is inevitable over time, it is reasonable to identify predictors of metabolic status transition in obese individuals and prevent its development at the personal level. In various studies the "progression" of the healthy status to the unhealthy one in obese individuals is linked to a significant increase in waist circumference (aggravation of visceral obesity) occurring dynamically: there was a 2.7 times growth of probability of phenotype transformation with an increase in waist circumference of MHO individuals after 8 years of observation [8]. In the Tehran study of 916 MHO individuals, baseline low HDL levels, baseline hypertriglyceridemia, or insulin resistance were classified as significant predictors of metabolic disorders [12]. In another 10-year-long observation, dyslipidemia (low HDL level) (OR 0.24 [0.11–0.53], $p < 0.001$), increased fasting plasma insulin (OR 2.45 [1.07–5.62], $p =$

0.034) and visceral obesity (OR 2.04 [1.11–3.72], p = 0.021) [25] were also included in the list of phenotype conversion predictors. Our study also demonstrated a baseline higher level of triglycerides and insulin (as well as a baseline higher insulin resistance HOMA-IR) in individuals that moved to the MUHO phenotype over time; no significant baseline differences in HDL were obtained. An increase in waist circumference over time was marked in all the participants with baseline MHO status. Against the background of an increase in waist circumference as a marker of visceral obesity, the processes associated with subclinical inflammation are possibly aggravated (a significant dynamic increase in CRP was revealed), which, in its turn, may lead to further transformation of the phenotype into the MUHO group in some individuals in the future.

It can be assumed that if the increase in waist circumference as a marker of visceral obesity reaches a certain critical value with a significant BMI growth (which was observed only in the group of persons who moved to the MUHO phenotype), then the functional state of visceral adipose tissue may change, which is reflected in carbohydrate metabolism (a significant increase in fasting glucose) as well as in markers of subclinical inflammation. Simultaneously, the carbohydrate metabolism disorder in metabolically healthy patients viewed dynamically, according to our data, predetermines their transition to the MUHO category with more than tenfold probability.

So an increase in waist circumference and BMI and impaired carbohydrate metabolism in the form of an increase in glucose levels can be linked to the transformation from the MHO into the MUHO phenotype over time.

A considerably higher level of uric acid both in individuals with the MUHO phenotype and in those MHO individuals, whose phenotype has transformed into MUHO one, is consistent with the data of foreign studies — the level of uric acid is an important predictor of unhealthy obesity. In a study of 354 individuals aged 18 to 60 years, a complex logistic regression model identified uric acid as the best predictor of MUHO with an OR of 3.4 [1.4–8.0] per unit increase in serum uric acid (per 1 mg/dL). [26]. A large epidemiological study demonstrated that hyperuricemia often precedes the development of insulin resistance, and that serum uric acid levels are an independent risk factor for metabolic syndrome, including insulin resistance [27]. It is possible that an increase in the level of uric acid is among the initial disorders that predetermine the transition from a healthy cardiometabolic status to an unhealthy one. Experimental studies have suggested that uric acid inhibits the release of nitric oxide from endothelial cells, activates the renin-angiotensin system, and increases oxidative stress, which damages endothelial cells and causes vasoconstriction, leading to the development of hypertension [28] and contributing to subclinical atherosclerosis. Therefore, assessment and regulation of uric acid levels in individuals with MHO status may also become a therapeutic goal.

Our study is limited by small sample size, which can be the reason for a wide confidence interval when conducting regression analysis. Another limitation is the undetermined duration of the MHO status presence at the time of the initial examination. There is data evidence that the onset of obesity (in a person's childhood/adolescence, among postmenopausal women, etc.) is important in relation to the MHO status [29]. We will take this fact into account in the subsequent data analysis. This work does not include an assessment of behavioral factors that can also be associated with the transition of the healthy phenotype to the unhealthy one [30, 31]. Besides, it is possible that genetic determinants have a protective effect on the maintenance of metabolic health over time: at present this topic is not among those fully explored, and it has not been studied by us within the framework of this research.

Conclusions

Initially higher levels of blood pressure, insulin resistance, low-density lipoproteins, and uric acid were associated with the transformation of a metabolically healthy phenotype into an unhealthy phenotype in obese individuals.

All persons with metabolically healthy obesity had a significant increase in waist circumference over time, accompanied by an increase in body mass index only in those who passed into the category of metabolic ill health.

In obese individuals in whom the transformation of a healthy phenotype into an unhealthy one was registered, a significant increase in blood glucose was noted, with a more than tenfold increase in the

probability of conversion of the phenotype to an unhealthy one with an increase in glucose level of more than 0.5 mmol / L.

The prevention of visceral adipose tissue increase and the correction of glucose metabolism have a priority direction in order to preserve the status of the MHO.

Funding

The research was supported by the State assignment "Development of a new technology for targeted correction of the intestinal microbiome and the development of a personalized approach to primary prevention and treatment of atherosclerosis in cardiovascular diseases".

Conflict of interest

The authors declare no conflict of interest.

References

1. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377(1):13–27. doi:10.1056/NEJMoa1614362

2. World Health Organization Obesity and Overweight (6 December 2019). Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

3. Phillips CM. Metabolically healthy obesity: definitions, determinants and clinical implications. Rev Endocr Metab Disord. 2013;14(3):219–227. doi:10.1007/s11154-013-9252-x

4. Primeau V, Coderre L, Karelis AD, Brochu M, Lavoie ME, Messier V et al. Characterizing the profile of obese patients who are metabolically healthy. Int J Obes (Lond). 2011;35(7):971–981. doi:10.1038/ijo.2010.216

5. Mustafina SV, Shcherbakova LV, Kozupeeva DA, Malyutina SK, Ragino YuI, Rymar OD. The prevalence of metabolically healthy obesity: data from the epidemiological survey in of Novosibirsk. Obes Metab. 2018;15(4):31–37. doi:10.14341/omet 9615. In Russian.

6. Boyarinova MA, Orlov AV, Rotar OP, Alieva AS, Moguchaya EV, Vasilieva EU. Adipokines level in metabolically healthy obese Saint-Petersburg inhabitants (ESSE-RF). Kardiologiia. 2016;56(8):40–45. doi:10.18565/cardio.2016.8.40-45. In Russian.

7. Korduner J, Bachus E, Jujic A, Magnusson M, Nilsson PM. Metabolically healthy obesity (MHO) in the Malmö diet cancer study — epidemiology and prospective risks. Obes Res Clin Pract. 2019;13(6):548–554. doi:10.1016/j.orcp.2019.10.002

8. Hamer M, Bell JA, Sabia S, Batty GD, Kivimäki M. Stability of metabolically healthy obesity over 8 years: the English Longitudinal Study of Aging. Eur J Endocrinol. 2015;173(5):703–708. doi:10.1530/EJE-15-0449

9. Gonçalves CG, Glade MJ, Meguid MM. Metabolically healthy obese individuals: Key protective factors. Nutrition. 2016;32(1):14–20. doi:10.1016/j.nut.2015.07.010

10. Sethi JK, Vidal-Puig AJ. Thematic review series: adipocyte biology. Adipose tissue function and plasticity orchestrate nutritional adaptation. J Lipid Res. 2007;48(6):1253–1262. doi:10.1194/jlr.R 700005-JLR 200

11. Kilpeläinen TO, Zillikens MC, Stančákova A, Finucane FM, Ried JS, Langenberg C et al. Genetic variation near IRS 1 associates with reduced adiposity and an impaired metabolic profile. Nat Genet. 2011;43(8):753–760. doi:10.1038/ng.866

12. Eshtiaghi R, Keihani S, Hosseinpanah F, Barzin M, Azizi F. Natural course of metabolically healthy abdominal obese adults after 10 years of follow-up: the Tehran Lipid and Glucose Study. Int J Obes (Lond). 2015;39(3):514–519. doi:10.1038/ijo.2014.176

13. Schröder H, Ramos R, Baena-Díez JM, Mendez MA, Canal DJ, Fíto M et al. Determinants of the transition from a cardiometabolic normal to abnormal overweight/obese phenotype in a Spanish population. Eur J Nutr. 2014;53(6):1345–1353. doi:10.1007/s00394-013-0635-2

14. Dalleck LC, Van Guilder GP, Richardson TB, Bredle DL, Janot JM. A community-based exercise intervention transitions metabolically abnormal obese adults to a metabolically healthy obese phenotype. Diabetes Metab Syndr Obes. 2014;7:369–380. doi:10.2147/DMSO.S 67441

15. Orlov AV, Rotar OP, Boyarinova MA, Alieva AS, Dudorova EA, Kolesova EP et al. Gender characteristics of the prevalence of behavioral risk factors among residents of St Petersburg. Bull Russ Acad Med Sci. 2015;70(5):585–591. In Russian.

16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412–429. doi:10.1007/BF00280883

17. Meigs JB, Wilson PW, Fox CS, Vasan RS, Nathan DM, Sullivan LM et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. J Clin Endocrinol Metab. 2006;91(8):2906–2912. doi:10.1210/jc.2006-0594

18. Kang EY, Yim JE. Differences in dietary intakes, body compositions, and biochemical indices between metabolically healthy and metabolically abnormal obese Korean women. Nutr Res Pract. 2019;13(6):488–497. doi:10.4162/nrp.2019.13.6.488

19. Stefan N, Häring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol. 2013;1(2):152–162. doi:10.1016/S 2213–8587(13)70062–7

20. Chen HH, Tseng YJ, Wang SY, Tsai YS, Chang CS, Kuo TC et al. The metabolome profiling and pathway analysis in metabolic healthy and abnormal obesity. Int J Obes (Lond). 2015;39(8):1241–1248. doi:10.1038/ijo.2015.65

21. Ahl S, Guenther M, Zhao S, James R, Marks J, Szabo A et al. Adiponectin levels differentiate metabolically healthy vs unhealthy among obese and nonobese white individuals. J Clin Endocrinol Metab. 2015;100(11):4172–4180. doi:10.1210/jc.2015–2765

22. Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB. Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. Eur J Prev Cardiol. 2016;23(9):956–966. doi:10.1177/2047487315623884

23. Kim JA, Kim DH, Kim SM, Park YG, Kim NH, Baik SH et al. Impact of the dynamic change of metabolic health status on the incident type 2 diabetes: a Nationwide Population-Based Cohort Study. Endocrinol Metab (Seoul). 2019;34(4):406–414. doi:10.3803/EnM.2019.34.4.406

24. Bell JA, Hamer M, Sabia S, Singh-Manoux A, Batty GD, Kivimaki M. The natural course of healthy obesity over 20 years. J Am Coll Cardiol. 2015;65(1):101–102. doi:10.1016/j.jacc.2014.09.077

25. Hwang YC, Hayashi T, Fujimoto WY, Kahn SE, Leonetti DL, McNeely MJ et al. Visceral abdominal fat accumulation predicts the conversion of metabolically healthy obese subjects to an unhealthy phenotype. Int J Obes (Lond). 2015;39(9):1365–1370. doi:10.1038/ijo.2015.75

26. Mangge H, Zelzer S, Puerstner P, Schnedl WJ, Reeves G, Postolache TT et al. Uric acid best predicts metabolically unhealthy

obesity with increased cardiovascular risk in youth and adults. Obesity (Silver Spring). 2013;21(1): E 71–E 77. doi:10.1002/oby.20061

27. Yoo TW, Sung KC, Shin HS, Kim BJ, Kim BS, Kang JH et al. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. Circ J. 2005;69(8):928–933. doi:10.1253/circj.69.928

28. Lee SJ, Oh BK, Sung KC. Uric acid and cardiometabolic diseases. Clin Hypertens. 2020;26:13. doi:10.1186/s40885–020–00146-y

29. Velho S, Paccaud F, Waeber G, Vollenweider P, Marques-Vidal P. Metabolically healthy obesity: different prevalences using different criteria. Eur J Clin Nutr. 2010;64(10):1043–1051. doi:10.1038/ejcn.2010.114

30. Konieczna J, Yañez A, Moñino M, Babio N, Toledo E, Martínez-González MA et al. Longitudinal changes in Mediterranean diet and transition between different obesity phenotypes. Clin Nutr. 2020;39(3):966–975. doi:10.1016/j.clnu.2019.04.002

31. Dalleck LC, Van Guilder GP, Richardson TB, Bredle DL, Janot JM. A community-based exercise intervention transitions metabolically abnormal obese adults to a metabolically healthy obese phenotype. Diabetes Metab Syndr Obes. 2014;7:369–380. doi:10.2147/DMSO.S 67441.eCollection 2014

Author information

Maria A. Boyarinova, MD, Junior Researcher, Scientific Research Laboratory of Epidemiology of Noncommunicable Diseases, Almazov National Medical Research Centre, e-mail: boyarinova@almazovcentre.ru;

Oxana P. Rotar, MD, PhD, DSc, Chief Researcher, Scientific Research Laboratory of Epidemiology of Noncommunicable Diseases, Almazov National Medical Research Centre, e-mail: rotar'_op@almazovcentre.ru;

Anastasia M. Erina, MD, Researcher, Scientific Research Laboratory of Epidemiology of Noncommunicable Diseases, Almazov National Medical Research Centre, e-mail: erina_am@almazovcentre.ru;

Nadezhda A. Paskar, MD, PhD, Head, Research Laboratory of Health Care System, Almazov National Medical Research Centre, e-mail: paskar'_na@almazovcentre.ru;

Asiiat S. Alieva, MD, PhD, Head, Laboratory of Lipid Disorders and Atherosclerosis, World-Class Research Center for Personalized Medicine, Head, Centre of Atherosclerosis, Almazov National Medical Research Centre, e-mail: alieva_as@almazovcentre.ru;

Ekaterina V. Moguchaia, MD, Junior Researcher, Scientific Research Laboratory of Epidemiology of Noncommunicable Diseases, Almazov National Medical Research Centre, e-mail: moguchaya_ev@almazovcentre.ru;

Ekaterina P. Kolesova, MD, PhD, Researcher, Scientific Research Laboratory of Epidemiology of Noncommunicable Diseases, Almazov National Medical Research Centre, e-mail: kolesova_ep@almazovcentre.ru;

Aleksandra O. Konradi, MD, PhD, DSc, Professor, Corresponding Member of RAS, Head, Research Laboratory of Pathogenesis and Treatment of Hypertension, Research Department of Hypertension, Deputy General Director on Research, Almazov National Medical Research Centre, Director, Translational Medicine Institute, ITMO University, ORCID: 0000–0001–8169–7812, e-mail: konradi_ao@almazovcentre.ru.

Информация об авторах

Бояринова Мария Анатольевна — младший научный сотрудник научно-исследовательской лаборатории эпидемиологии неинфекционных заболеваний Института сердца и сосудов ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, e-mail: boyarinova@almazovcentre.ru;

Ротарь Оксана Петровна — доктор медицинских наук, главный научный сотрудник научно-исследовательской лаборатории эпидемиологии неинфекционных заболеваний Института сердца и сосудов ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, e-mail: rotar'_op@almazovcentre.ru;

Ерина Анастасия Максимовна — научный сотрудник научно-исследовательской лаборатории эпидемиологии неинфекционных заболеваний Института сердца и сосудов ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, e-mail: erina_am@almazovcentre.ru;

Паскарь Надежда Андреевна — кандидат медицинских наук, заведующая научно-исследовательской лабораторией организации медицинской помощи научно-исследовательского отдела стандартизации и организации медицинской помощи ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, e-mail: paskar'_na@almazovcentre.ru;

Алиева Асият Сайгидовна — кандидат медицинских наук, заведующая научно-исследовательской лабораторией нарушений липидного обмена и атеросклероза Научного центра мирового уровня «Персонализированная медицина», руководитель центра атеросклероза ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, e-mail: alieva_as@almazovcentre.ru;

Могучая Екатерина Викторовна — младший научный сотрудник научно-исследовательской лаборатории эпидемиологии неинфекционных заболеваний Института сердца и сосудов ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, e-mail: moguchaya_ev@almazovcentre.ru;

Колесова Екатерина Павловна — кандидат медицинских наук, научный сотрудник научно-исследовательской лаборатории эпидемиологии неинфекционных заболеваний Института сердца и сосудов ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, e-mail: kolesova_ep@almazovcentre.ru;

Конради Александра Олеговна — доктор медицинских наук, профессор, член-корреспондент Российской академии наук, заместитель генерального директора по научной работе, заведующая научно-исследовательской лабораторией патогенеза и терапии артериальной гипертензии научно-исследовательского отдела артериальной гипертензии ФГБУ «НМИЦ им. В. А. Алмазова» Минздрава России, директор Института трансляционной медицины Университета ИТМО, ORCID: 0000–0001–8169–7812, e-mail: konradi_ao@almazovcentre.ru.