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ORIGINAL ARTICLE

Prevalence of overweight/obesity, abdominal obesity and metabolic syndrome and atypical cardiometabolic phenotypes in the adult Romanian population: PREDATORR study

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Abstract
Purpose The objectives were to assess the prevalence of overweight/obesity, abdominal obesity and metabolic syndrome (MetS), and to evaluate the characteristics of the metabolically unhealthy lean (MUHL) and metabolically healthy overweight/obese (MHO) phenotypes in a Romanian population-based sample from the PREDATORR study.
Methods PREDATORR was an epidemiological study with a stratified, cross-sectional, cluster random sampling design. Participants were classified into four cardiometabolic phenotypes based on the BMI, the cut-off value being 25 kg/m^2, and the presence of MetS (defined according to the Harmonization definition 2009): MUHL, MHO, metabolically healthy lean (MHL) and metabolically unhealthy overweight/obese (MUHO).
Results Overall, 2681 subjects aged 20–79 years were included in the analysis. The overall age and sex-adjusted prevalence of obesity was 31.90 %, overweight was 34.7 %, abdominal obesity was 73.90 % and MetS was 38.50 %. The age- and sex-adjusted prevalence of MHO phenotype was 31.60 %, while MUHL phenotype prevalence was 3.90 %. MUHL and MHO participants had a cardiometabolic profile, kidney function and CVD risk intermediary between MHL and MUHO. MUHL had higher odds of being associated with CVD risk (OR 5.8; $p < 0.001$), abdominal obesity, prediabetes, diabetes, hypertriglyceridemia and hypo-HDL cholesterolemia than MHL, while MHO phenotype was associated with hypo-HDL cholesterolemia (OR 3.1; $p = 0.002$), prediabetes (OR 2.9; $p < 0.001$) and abdominal obesity.
Conclusions PREDATORR study showed a high prevalence of obesity/overweight, abdominal obesity and MetS in the adult Romanian population, and their association with kidney function and several cardiometabolic factors.

Keywords PREDATORR study · Obesity/overweight · Metabolic syndrome · Metabolically unhealthy lean phenotype · Metabolically healthy overweight/obesity phenotype · Romania

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Introduction

Overweight/obesity represents a major challenge and a public health problem worldwide. According to the World Health Organization (WHO), 39 % of adults >18 years of age were overweight (Body mass index BMI ≥ 25 kg/m^2) and more than five hundred million had obesity

(BMI $\geq$ 30 kg/m^2) in 2014 [1]. Despite its recognition as a major contributor to the epidemic of diabetes and as a risk factor for other chronic diseases [2, 3], the prevalence of obesity has grown continuously. If in 1980 5 % of men and 8 % of women worldwide were reported to have obesity, these figures increased to 11 % of men and 15 % of women in 2014 [1, 4]. For Romania, the prevalence of obesity in the adult population, ranges between 7.9 [5] and 21.7 % [1], obesity rates being self-reported through estimates of anthropometric data. Two epidemiological studies performed in 2005 and 2006 [6, 7] indicated an obesity prevalence of 24 % and, respectively, 26.3 % (estimates derived from health examinations). It has been shown that obesity represents a major risk factor for diabetes, cardiovascular diseases and different types of cancer [2, 3, 8–10]. However, in the past years, a separate obesity phenotype has been described ('metabolically healthy overweight/obese', MHO) that is not associated with the usual obesity-related cardiometabolic profile [11]. MHO prevalence in the populations with obesity varied widely from 10 to 30 %, depending on the study population and definition criteria for MHO [12–14]. The data from the Whitehall II study (7122 participants aged 39–63 years) showed that 26.9 % of the participants were MHO and 9.1 % were metabolically unhealthy lean (MUHL) [15]. MHO and MUHL prevalence have been shown to vary according to the population enrolled in different studies, the prevalence of MHO and MUHL phenotype being 8.1 % and, respectively, 2.6 % for a population from the United States [16], and 34.9 % for MHO and 3.5 % for MUHL phenotype in a Swedish population 50 years of age [17]. This high variability in the MHO and MUHL prevalence has been shown to result from the lack of harmonized classification criteria for studies. Thus, "metabolically healthy" was defined based on insulin sensitivity (assessed by hyperinsulinemic-euglycemic clamp, HOMA-IR, Matsuda index) or absence of metabolic syndrome (MetS) with study specific MetS criteria, while obesity was defined based on BMI or waist circumference or body fat [12–17]. Available literature on the cardiovascular risk, diabetes risk and mortality associated with different phenotypes reported conflicting results, with studies showing the MHO phenotype to have both similar or higher risks when compared to the metabolically healthy lean (MHL) phenotype, and similar or lower risks when compared to the metabolically unhealthy overweight/obese (MUHO) phenotype [15, 18, 19].

In Romania, scarce data are available regarding the obesity and metabolic syndrome prevalence and the association of obesity with chronic kidney disease. No data on the prevalence of different phenotypes is available for Romania.

In this context, a study that would evaluate the prevalence of cardiometabolic diseases in Romania is needed. The PREvalence of DiAbeTes mellitus, prediabetes, overweight, Obesity, dyslipidemia, hyperuricemia and chRonic kidney disease in Romania (PREDATORR) study was a population-based study coordinated by the Romanian Society of Diabetes, Nutrition and Metabolic Diseases, and the Romanian Society of Nephrology which investigated the prevalence of cardiometabolic diseases, chronic kidney disease (CKD) and cardiovascular disease (CVD) risk in Romanian participants aged 20–79 years [20]. Here, we present the results on the prevalence of overweight (BMI = 25–29.9 kg/m^2), obesity (BMI $\geq$ 30 kg/m^2), abdominal obesity (waist circumference $\geq$80 cm in women and $\geq$94 cm in men), and MetS (Harmonization definition 2009). We also investigate the prevalence of MUHL and MHO phenotypes, and their association with kidney function, cardiometabolic, socio-demographic and lifestyle risk factors.

Materials and methods

Study design and participants

The PREDATORR study (EudraCT number:2012-004803-12) was a cross-sectional, population-based study conducted between 2012 and 2014. The study design was described elsewhere [20]. Briefly, participants were enrolled through an automated random computer decision from the databases of 101 general practitioners (GPs) affiliated with the National Health Insurance House. Enrollment was based on the following inclusion criteria: age between 20 and 79 years, born in Romania, living for the past 10 years mainly in Romania, included on the list of a GP, no pregnancy or lactation. To have representativeness of the sample for the adult Romanian population, 2728 participants aged 20–79 years were enrolled based on the 2002 Romanian Census.

Socio-demographic and lifestyle data

Information regarding socio-demographic (sex, age, marital status, education level), lifestyle characteristics (physical activity, alcohol drinking, sleep duration), and personal medical history were collected using an interviewer-administered questionnaire. The education level was categorized as low (secondary/primary school) or high (university, high school, college). Low sleep duration was considered in participants with an average amount of sleep of less than 7 h per night. Participants who declared no alcohol consumption during the past month were considered non-drinkers. A sedentary lifestyle was considered when participants underwent physical activity (at least 30 min of brisk walking daily) less than 4 days per week.

Clinical and biochemical data

The physical examination consisted in the measurement of the height, weight, waist circumference, systolic (SBP) and diastolic blood pressure (DBP) using standard procedures. The participants with a BMI = 25–29.9 kg/m^2 were considered as having overweight and those with BMI ≥30 kg/m^2 were categorized as having obesity. Abdominal obesity was defined as a waist circumference ≥80 cm in women and ≥94 cm in men [21].

Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg and/or personal history of hypertension and/or taking antihypertensive therapy.

All samples were collected in a fasting state, and the biochemical assays were performed at the Synevo Romania SRL laboratories according to standardized procedures. Fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, uric acid, creatinine and urinary creatinine levels were determined using enzymatic methods. The low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedwald formula (LDL = TC–HDL–TG/5.0) if total TG levels were <400 mg/dL. Albuminuria and HbA1c were determined using the immunoturbidimetric method, and serum insulin was assessed with a chemiluminiscent immunoassay. Insulin resistance (HOMA-IR) was estimated using the equations proposed by Matthews DR et al. [22].

The impaired glucose regulation (IGR)—previously known and unknown diabetes, prediabetes—was defined according to the 2012 American Diabetes Association guidelines [23], based on FPG, HbA1c and 2 h plasma glucose during oral glucose tolerance test or self-reported diagnosis.

Hypertriglyceridemia was considered when TG ≥150 mg/dL or drug treatment for hypertriglyceridemia, and hypo-HDL cholesterolemia was considered when HDL levels were <40 mg/dL in men or <50 mg/dL in women or drug treatment for reduced HDL [21]. Hypercholesterolemia was considered when TC ≥200 mg/dL and/or statin therapy was used, and hyper-LDL cholesterolemia was considered when LDL ≥100 mg/dL and/or statin therapy was used [24]. CKD was defined according to the KDIGO 2012 guidelines [25] using as criteria estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (CKD-EPI equation) and/or urinary albumin to creatinine ratio ≥30 mg/g.

The risk of developing CVD was estimated with the Framingham 10–year CVD risk score [26]. The CVD risk was stratified into low (Framingham CVD risk score <10 %) and moderate/high (Framingham CVD risk score ≥10 %).

Table 1 Cardiometabolic phenotypes of obesity

	BMI <25 kg/m^2	BMI ≥25 kg/m^2
MetS absent	MHL	MHO
MetS present	MUHL	MUHO

MHL metabolically healthy lean (MetS absent and BMI < 25 kg/m^2), *MUHL* metabolically unhealthy lean (MetS present and BMI < 25 kg/m^2), *MHO* metabolically healthy obese (MetS absent and BMI ≥ 25 kg/m^2), *MUHO* metabolically unhealthy obese (MetS present and BMI ≥ 25 kg/m^2), *BMI* body mass index , *MetS* metabolic syndrome (Harmonization definition 2009)

MetS was defined according to the Harmonization definition 2009 [21].

Participants were classified into four cardiometabolic phenotypes based on the BMI, the cut-off value being 25 kg/m^2, and the presence of MetS, MUHL, MHO, MUHO and MHL (Table 1).

Statistical analysis

The PREDATORR study used a cluster sampling design to select participants. Sample size calculations were performed only for the primary objective of PREDATORR (IGR prevalence).

The global age- and sex-adjusted prevalence of overweight/obesity, abdominal obesity, MetS and cardiometabolic phenotypes of obesity was calculated using data from 2011 Census of Romania.

Kruskal–Wallis and Chi-squared tests were used for comparisons between cardiometabolic obesity phenotypes of continuous and categorical variables. Multivariate analysis by multinomial logistic regression was performed to assess the association of renal and cardiometabolic parameters (independent variables) with MUHL and MHO phenotypes (dependent variable). The analysis was adjusted for covariates (age, sex, educational level, marital status, alcohol drinking, sedentariness, sleep duration), and MHL was considered reference category. $p < 0.05$ (two-tailed) was considered significant. Analyses were performed using SPSS software v19.0.

Results

Of the 2728 participants enrolled in the PREDATORR study, 11 participants were lost to follow-up and 36 participants had incomplete data and were not included in the analyses. Overall, 2681 (55.8 ± 13.9 years, 47.4 % males) were included in the analysis by cardiometabolic phenotypes of obesity.

Table 2 Prevalence of metabolic syndrome, overweight/obesity and abdominal obesity in Romanian population aged 20–79 years

	Age groups			Overall
	20–39 years	40–59 years	60–79 years	
Total population				
MetS	20.00 (18.54–21.46)	45.20 (43.74–46.66)	56.60 (55.14–58.06)	38.50 (37.04–39.96)
Men				
MetS	26.50 (25.04–27.96)	52.00 (50.54–53.46)	56.70 (55.24–58.16)	43.20 (41.74–44.66)
Women				
MetS	13.80 (12.34–15.26)	39.40 (37.94–40.86)	56.40 (54.94–57.86)	34.20 (32.74–35.66)
Total population				
Underweight	4.40 (2.94–5.86)	1.59 (0.13–3.05)	1.47 (0.01–2.93)	2.20 (0.74–3.66)
Overweight	27.20 (25.74–28.66)	36.60 (35.14–38.06)	43.10 (41.64–44.56)	34.70 (33.24–36.16)
Obesity	20.90 (19.44–22.36)	39.40 (37.94–40.86)	37.40 (35.94–38.86)	31.90 (30.44–33.36)
Men				
Underweight	1.49 (0.03–2.95)	1.47 (0.01–2.93)	1.53 (0.07–2.99)	1.51 (0.05–2.97)
Overweight	40.20 (38.74–41.66)	45.00 (43.54–46.46)	47.50 (46.04–48.96)	43.70 (42.24–45.16)
Obesity	20.70 (19.24–22.16)	37.70 (36.24–39.16)	31.10 (29.64–32.56)	29.40 (27.94–30.86)
Women				
Underweight	7.60 (6.14–9.06)	1.70 (0.24–3.16)	1.54 (0.08–3.00)	3.50 (2.04–4.96)
Overweight	14.80 (13.34–16.26)	29.40 (27.94–30.86)	39.20 (37.74–40.66)	26.40 (24.94–27.86)
Obesity	21.10 (19.64–22.56)	40.90 (39.44–42.36)	43.10 (41.64–44.56)	34.10 (32.64–35.56)
Total population				
Abdominal obesity	52.10 (50.64–53.56)	84.10 (82.64–85.56)	91.00 (89.54–92.46)	73.90 (72.44–75.36)
Men				
Abdominal obesity	47.30 (45.84–48.76)	82.80 (81.34–84.26)	82.60 (81.14–84.06)	68.90 (67.44–70.36)
Women				
Abdominal obesity	52.10 (50.64–53.56)	84.10 (82.64–85.56)	91.00 (89.54–92.46)	73.90 (72.44–75.36)

Data show adjusted percentages, with 95 % CI in parentheses

MetS, metabolic syndrome (Harmonization definition 2009). Abdominal obesity: waist circumference ≥80 cm in women and ≥94 cm in men. Underweight: BMI < 25 kg/m^2 , Overweight: BMI = 25–29.99 kg/m^2 , Obesity: BMI ≥ 30 kg/m^2

The age- and sex-adjusted overall prevalence of MetS in Romanian adult population was 38.50 % (95 % CI 37.04–39.96 %), and prevalence of abdominal obesity was 73.90 % (95 % CI 72.44–75.36 %), with the highest percentage in the 60–79 age group (Table 2). There was a higher prevalence of MetS in men than in women, whereas abdominal obesity was predominant in women (Table 2).

The age- and sex-adjusted overall prevalence of obesity (BMI ≥30 kg/m^2), in Romanian adult population was 31.90 % (95 % CI 30.44–33.36 %) and that of overweight (BMI = 25–29.9 kg/m^2), was 34.70 % (95 % CI 33.24–36.16 %). The highest percentage of obesity was in the 40–59 age group and in men, whereas, overweight was predominant in the 60–79 age group and in women (Table 2).

Only 2.20 % (95 % CI 0.74–3.66 %) of participants had underweight (BMI <18.5 kg/m^2), most of them being young women (Table 2).

In the Romanian population aged 20–79 years, the age- and sex-adjusted overall prevalence of MHO phenotype was 31.60 % (95 % CI 30.14–33.06 %), with the highest percentage observed in the 60–79 year age group, while only 3.90 % (95 % CI 2.44–5.36 %) of participants had MUHL phenotype (Table 3).

Both MUHL and MHO participants had a higher Framingham 10–year CVD risk, worse kidney function and cardiometabolic profile (FPG, HbA1c, HOMA-IR, lipid profile, uric acid, blood pressure) than MHL participants (Table 4).

MUHL participants had significantly higher actual BMI ($p < 0.001$) and maximum reported BMI ($p < 0.001$), higher waist circumference ($p < 0.001$) and higher IGR prevalence compared to MHL participants (Table 4). Despite a lower BMI, lower maximum BMI and waist circumference compared to MHO participants, MUHL participants had

Table 3 Prevalence of cardiometabolic phenotypes of obesity in Romanian population aged 20–79 years

	Age groups			Overall
	20–39 years	40–59 years	60–79 years	
Total population				
MUHL	3.00 (1.54–4.46)	3.90 (2.44–5.36)	5.40 (3.94–6.86)	3.90 (2.44–5.36)
MUHO	17.00 (15.54–18.46)	41.40 (39.94–42.86)	51.10 (49.64–52.56)	34.60 (33.14–36.06)
MHO	30.30 (28.84–31.76)	34.70 (33.24–36.16)	29.20 (27.74–30.66)	31.60 (30.14–33.06)
Men				
MUHL	4.00 (2.54–5.46)	3.10 (1.64–4.56)	6.00 (4.54–7.46)	4.20 (2.74–5.66)
MUHO	22.40 (20.94–23.86)	49.00 (47.54–50.46)	50.60 (49.14–52.06)	39.00 (37.54–40.46)
MHO	36.80 (35.34–38.26)	34.70 (33.24–36.16)	28.00 (26.54–29.46)	33.80 (32.34–35.26)
Women				
MUHL	1.90 (0.44–3.36)	4.50 (3.04–5.96)	4.90 (3.44–6.36)	3.60 (2.14–5.06)
MUHO	11.80 (10.34–13.26)	34.90 (33.44–36.36)	51.60 (50.14–53.06)	30.50 (29.04–31.96)
MHO	24.00 (22.54–25.46)	34.70 (33.24–36.16)	30.40 (28.94–31.86)	29.70 (28.24–31.16)

Data show adjusted percentages, with 95 % CI in parentheses

MHL metabolically healthy lean (MetS absent and BMI < 25 kg/m^2), *MUHL* metabolically unhealthy lean (MetS present and BMI < 25 kg/m^2), *MHO* metabolically healthy obese (MetS absent and BMI ≥25 kg/m^2), *MUHO* metabolically unhealthy obese (MetS present and BMI ≥ 25 kg/m^2)

a higher Framingham 10–year CVD risk ($p < 0.001$) and lower eGFR ($p = 0.023$) (Table 4).

Compared to MUHO participants, MUHL individuals had higher HbA1c and a similar Framingham 10–year CVD risk.

MHO participants had better kidney function ($p < 0.001$), cardiometabolic profile (except for LDL-cholesterol which was higher for the MHO participants), and had a lower Framingham 10–year CVD risk ($p < 0.001$) than MUHO participants.

The frequency of CKD was higher in the metabolically unhealthy phenotypes (MUHL and MUHO) compared to the metabolically healthy phenotypes (MHL and MHO); however, the difference between MHO and MUHL phenotypes was not statistically significant (Table 4).

Multivariate multinomial logistic regression analysis showed that the MUHL phenotype had higher odds of being associated with CVD risk ($p < 0.001$), prediabetes, diabetes, hypertriglyceridemia and hypo-HDL cholesterolemia than the MHL phenotype (Table 5). The MHO phenotype was associated with prediabetes ($p < 0.001$) and hypo-HDL cholesterolemia ($p = 0.002$), but interestingly unrelated with moderate/high Framingham 10–year CVD risk. Abdominal obesity was an independent predictor for the presence of the MUHL and MHO phenotypes, while previous overweight/obesity (maximum reported BMI ≥25 kg/m^2) was not a predictor for the MUHL phenotype (Table 5).

Discussion

The PREDATORR study was the first national study to systematically assess the prevalence of cardiometabolic diseases in the Romanian adult population. In this population-based study, we found an increased prevalence of overweight and obesity (31.90 % and, respectively, 34.70 %). The overall age adjusted prevalence of obesity in the Romanian adult population in our study was higher than worldwide estimates (13 %) [1] and higher than the global European (16.7 %) obesity prevalence [5], but lower than the obesity prevalence in the United States (34.9 %) [27]. For the Romanian adult population, the prevalence of obesity (evaluated based on measured height and weight), was reported to be 24 % in SEPHAR study and 26.3 % in CARDIO-Zone study [6, 7].

PREDATORR study found a central obesity prevalence comparable with the results reported in the international IDEA Study which used the same definition criteria in 18 to 80 years old participants from 63 countries (overall prevalence 56 % in men and 71 % in women) [28].

The differences between our study and the previous reports may be due to the fact that for most studies, overweight/obesity rates are self-reported through estimates of anthropometric data from population-based health interview surveys. In our study, BMI was calculated using anthropometric data measured during the physical examination.

Table 4 Clinical and biological characteristics by metabolic phenotypes

Variables	MHL	MUHL	MUHO	MHO
No. participants	802	105	927	847
High educational level, %	88.0	86.0	82.7[f]	85.6
Marital status, % (overall [a,c,e,f])				
Married	70.9	75.4	74.5	75.7
Single	15.3	4.1	3.4	7.2
Divorced	6.7	5.7	5.8	5.6
Widowed	7.1	14.8	16.4	11.6
Alcohol drinking (yes), %	51.5	61.2	54.5	59.0[c,e]
Sedentarism, %	19.4	16.7	20.0	16.5
Low sleep duration, %	25.1	39.3[a]	35.3[f]	35.2[c]
BMI (kg/m^2), mean (SD)	22.1 (2.1)	23.5 (1.4)[a,b,d]	31.4 (4.7)[f]	29.8 (4.0)[c,e]
Maximum BMI (kg/m^2), mean (SD)	24.4 (3)	25.8 (2.8)[a,b,d]	33.2 (5.4)[f]	31.4 (4.6)[c,e]
Waist (cm), mean (SD)	81.2 (9.8)	90.5 (9.1)[a,b,d]	106.3 (11.7)[f]	100.1 (12.1)[c,e]
FPG (mmol/l), mean (SD)	4.4 (1)	5.9 (2.9)[a,b,d]	5.9 (2.1)[f]	4.6 (0.6)[c,e]
HbA1c (%), mean (SD)	5.3 (0.4)	6.6 (7.1)[a,b,d]	6.1 (1.1)[f]	5.5 (0.4)[c,e]
HOMA–IR, mean (SD)	1.5 (1.4)	3.8 (2.5)[a,b,d]	4.4 (4.1)[f]	2.2 (1.8)[c,e]
Impaired glucose regulation, %	12.1	36.9[a,b,d]	59.5[f]	26.1[c,e]
Prediabetes, %	9.1	17.2	26.0	24.6
Known diabetes, %	2.7	16.4	26.2	1.3
Unknown diabetes, %	0.3	3.3	7.3	0.2
Uric acid (μmol/l), mean (SD)	261.7 (77.3)	315.2 (166.5)[a,b]	339 (89.2)[f]	303.3 (83.3)[c,e]
SBP (mmHg), mean (SD)	125.2 (24.5)	140.7 (18.5)[a,d]	142.4 (19.1)[f]	134.6 (18.6)[c,e]
DBP (mmHg), mean (SD)	74.3 (10.1)	81.0 (11.4)[a]	82.1 (12.9)[f]	79.7 (11.4)[c,e]
TC (mmol/l), mean (SD)	5.2 (1.3)	5.6 (1.5)[a]	5.5 (2)[f]	5.4 (1.2)[c,e]
TG (mmol/l), mean (SD)	1.1 (0.6)	2.3 (1.8)[a,d]	2.2 (1.2)[f]	1.2 (0.5)[c,e]
HDL (mmol/l), mean (SD)	1.7 (0.4)	1.3 (0.7)[a,d]	1.2 (0.3)[f]	1.5 (0.3)[c,e]
LDL (mmol/l), mean (SD)	3.1 (1.1)	3.5 (1.2)[a]	3.3 (1.1)[f]	3.4 (1.1)[c,e]
Framingham 10–year CVD risk (%), mean (SD)	9.6 (9.5)	19.6 (9.4)[a,d]	21.3 (9.1)[f]	14.3 (10)[c,e]
eGFR (ml/min/1.73 m^2), mean (SD)	99.5 (18.4)	88.2 (20.6)[a,d]	87.4 (18.1)[f]	92.9 (17.4)[c,e]
CKD %	5.3	12.3[a]	12.4[f]	7.7[e]

MHL metabolically healthy lean (MetS absent and BMI < 25 kg/m^2), *MUHL* metabolically unhealthy lean (MetS present and BMI < 25 kg/m^2), *MHO* metabolically healthy obese (MetS absent and BMI ≥ 25 kg/m^2), *MUHO* metabolically unhealthy obese (MetS present and BMI ≥ 25 kg/m^2), *FPG* fasting plasma glucose , *HOMA-IR* , homeostasis model assessment for insulin resistance., *SBP* systolic blood pressure , *DBP* diastolic blood pressure , *TC* total cholesterol , *TG* triglycerides , *HDL* high-density lipoprotein , *LDL* low-density lipoprotein , *CVD* cardiovascular diseases , *eGFR* estimated glomerular filtration rate , *CKD* chronic kidney disease

[a] $p < 0.05$ for MUHL vs MHL

[b] $p < 0.05$ for MUHL vs MUHO

[c] $p < 0.05$ for MHO vs MHL

[d] $p < 0.05$ for MHO vs MUHL

[e] $p < 0.05$ for MHO vs MUHO

[f] $p < 0.05$ for MHL vs MUHO

The discrepancies in the prevalence pattern may be also explained by the different time period when the studies were conducted, diagnostic criteria for overweight/obesity, or different prevalence of risk factors for excess weight in different populations (specific age groups) included in the evaluations.

The prevalence of the MetS in the adult Romanian population reported in PREDATORR study is higher

Table 5 Factors associated with MUHL and MHO phenotypes (Multivariate multinomial logistic regression)

Variables	MUHL (105 participants) OR (95 %CI)	MHO (847 participants) OR (95 %CI)
Framingham 10–year CVD risk ≥ 10 %	5.8 (2.3–14.9)*	1.3 (0.8–2.1)
Maximum BMI ≥ 25 kg/m^2	1.5 (0.6–3.6)	77.1 (29.9–198.7)*
Abdominal obesity	94.7 (35.9–249.5)*	16.8 (10.6–26.6)*
Prediabetes	2.8 (1.2–6.4)*	2.9 (1.7–5.2)*
Known diabetes	26 (2.4–279.9)*	0.4 (0.1–4.2)
Unknown diabetes	44.7 (12.7–157.3)*	0.9 (0.3–2.8)
Hypertension	0.9 (0.5–1.7)	1.2 (0.8–1.7)
Hypercholesterolemia	2.4 (0.9–6)	1.3 (0.8–2)
Hypertriglyceridemia	59.6 (26.9–132)*	1.3 (0.7–2.3)
Hypo–HDL cholesterolemia	43.2 (18.3–59.5)*	3.1 (1.5–6.5)*
Hyper–LDL cholesterolemia	0.4 (0.2–1.1)	1.2 (0.6–2.1)
Hyperuricemia	0.9 (0.4–2.3)	1.3 (0.7–2.3)
CKD	0.8 (0.2–2.4)	0.8 (0.4–1.7)

The regression analysis was adjusted for covariates (age, sex, educational level, marital status, alcohol drinking, sedentariness, sleep duration). MHL was considered reference category

MUHL metabolically unhealthy lean (MetS present and BMI < 25 kg/m^2), *MHO* metabolically healthy obese (MetS absent and BMI ≥ 25 kg/m^2), *OR* odds ratio, *CI* confidence interval, *BMI* body mass index, *CVD* cardiovascular disease, *CKD* chronic kidney disease, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

* $p < 0.05$

than the prevalence reported for Europe, where approximately one-fourth of the adult population has MetS [29], but similar with the reports from US where the prevalence was 38.5 % [30] (by Harmonization definition 2009).

The MHO phenotype prevalence in PREDATORR study was 31.60 % (95 % CI 30.14–33.06 %), but as there is no currently harmonized definition of metabolic health, it is difficult to compare these results with the prevalence ranging between 3 and 43 % reported in other studies [12, 31]. The prevalence of the MUHL phenotype in the PREDATORR study was 3.90 % (95 % CI 2.44–5.36 %), which is lower compared to that reported in National Health and Nutrition Examination Survey (5 %) [32] and in the Finnish type 2 diabetes survey (7.2 %) [14], but higher than that reported in the Framingham Offspring Study (2.6 %) [16].

Our study showed that MUHL participants had higher maximum reported BMI and waist circumference compared to MHL. Therefore, it is plausible that previous overweight/obesity and excess visceral adipose tissue may explain, at least partially, the presence of metabolically unhealthy characteristics and also the impaired kidney function in lean participants [33].

In our study, CKD prevalence and Framingham 10–year CVD risk score were higher in participants with unhealthy metabolic profile, rather than in those with overweight/obesity. These results are consistent with previous findings from prospective and longitudinal observational studies [15, 18, 34–36], and indicate that the metabolic changes rather than excess weight may confer increased CKD and CVD risk.

Taking into consideration the findings of Eshtiaghi et al. who showed that over half of MHO subjects progress to the MUHO phenotype during a 10–year follow-up period [37], the concept of the MHO phenotype should be interpreted with caution due to its potential of becoming MUHO phenotype.

The main strengths of the PREDATORR study are the representativeness of the sample for the adult Romanian population, and the comprehensive diagnosis criteria of obesity, overweight and MetS used. Additionally, sociodemographic, lifestyle and anamnestic data were collected using an interviewer–administered questionnaire, and all laboratory measurements were performed in the same certified laboratory.

Concerning limitations, our study was cross-sectional, thereby, we cannot explore the future evolution of the cardiometabolic profile, kidney function and cardiovascular risk, related to the MUHL and MHO phenotypes. Another limitation would be the low number of the MUHL subjects in different subgroups, which may explain the wide confidence intervals in regression analysis. In conclusion, the PREDATORR study shows an unexpectedly high prevalence of obesity/overweight, abdominal obesity and MetS, in the adult Romanian population.

These results are valuable for the health authorities by indicating the necessity to initiate the implementation of prevention programs that may reduce the economic burden of obesity in Romania.

MUHL phenotype should be actively identified to intervene on the cardiometabolic and cardiovascular risk of lean subjects.

Future research should focus on a harmonizing definition and the risks of these two atypical cardimetabolic phenotypes of obesity, so that physicians can effectively identify individuals with increased cardiometabolic risk for tailored therapeutic and preventive interventions.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest. The sponsors had no role in the design of the study, in the execution, interpretation of the data or the decision to submit the results.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the Romanian National Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. World Health Organization (2014) Global status report on noncommunicable diseases Attaining the nine global noncommunicable diseases targets; a shared responsibility. http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf. Accessed 05 Jan 2016
2. World Health Organization (2002) The world health report 2002: Reducing risks, promoting healthy life. Geneva http://www.who.int/whr/2002/en/whr02_en.pdf?ua=1. Accessed 05 Jan 2016
3. World Cancer Research Fund/American Institute for Cancer Research (2009) Policy and action for cancer prevention. Food, nutrition, and physical activity: a global perspective. AICR. Washington DC http://www.dietandcancerreport.org/cancer_resource_center/downloads/chapters/pr/Introductory%20pages.pdf. Accessed 05 Jan 2016
4. World Health Organization.(2010) Global Status Report on noncommunicable diseases Chapter 1. Burden: mortality, morbidity and risk factors. http://www.who.int/nmh/publications/ncd_report_chapter1.pdf. Accessed 20 Dec 2015
5. OECD (2014) Health at a Glance: Europe 2014 completed with Eurostat Statistics Database. OECD Publishing. doi:10.1787/health_glance_eur-2014-en. Accessed 20 Dec 2015
6. Cinteza M, Pana B, Cochino E et al (2007) Prevalence and control of cardiovascular risk factors in Romania cardio-zone national study. Mædica J Clin Med 2(4):277–282
7. Dorobantu M, Badila E, Ghiorghe S et al (2008) Total cardiovascular risk estimation in Romania. Data from the SEPHAR study. Rom J Intern Med 46(1):29–37
8. Motamed N, Razmjou S, Hemmasi G, et al (2015) Lipid accumulation product and metabolic syndrome: a population-based study in northern Iran, Amol. J Endocrinol Invest **[Epub ahead of print]**
9. Macut D, Antić IB, Bjekić-Macut J (2015) Cardiovascular risk factors and events in women with androgen excess. J Endocrinol Invest 38(3):295–301. doi:10.1007/s40618-014-0215-1
10. de Luis DA, Aller R, Izaola O et al (2014) Cardiovascular risk factors and adipocytokines levels after two hypocaloric diets with different fat distribution in obese subjects and rs6923761 gene variant of glucagon-like peptide 1 receptor. J Endocrinol Invest 37(9):853–859. doi:10.1007/s40618-014-0116-3
11. Primeau V, Coderre L, Karelis AD et al (2011) Characterizing the profile of obese patients who are metabolically healthy. Int J Obes (Lond) 35(7):971–981. doi:10.1038/ijo.2010.216
12. Van Vliet-Ostaptchouk JV, Nuotio ML, Slagter SN et al (2014) The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. BMC Endocr Disord 14:9–21. doi:10.1186/1472-6823-14-9
13. Wildman RP, Muntner P, Reynolds K et al (2008) The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). Arch Intern Med 168(15):1617–1624. doi:10.1001/archinte.168.15.1617
14. Pajunen P, Kotronen A, Korpi-Hyövälti E et al (2011) Metabolically healthy and unhealthy obesity phenotypes in the general population: the FIN-D2D Survey. BMC Public Health 11:754. doi:10.1186/1471-2458-11-754
15. Hinnouho GM, Czernichow S, Dugravot A et al (2015) Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: the Whitehall II cohort study. Eur Heart J 36(9):551–559. doi:10.1093/eurheartj/ehu123
16. Meigs JB, Wilson PW, Fox CS et al (2006) Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. J Clin Endocrinol Metab 91(8):2906–2912
17. Ärnlöv J, Sundström J, Ingelsson E et al (2011) Impact of BMI and the metabolic syndrome on the risk of diabetes in middle-aged men. Diabetes Care 34(1):61–65. doi:10.2337/dc10-0955
18. Hamer M, Stamatakis E (2012) Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. J Clin Endocrinol Metab 97(7):2482–2488. doi:10.1210/jc.2011-3475
19. Kuk JL, Ardern CI (2009) Are metabolically normal but obese individuals at lower risk for all-cause mortality? Diabetes Care 32(12):2297–2299. doi:10.2337/dc09-0574
20. Mota M, Popa SG, Mota E et al (2015) Prevalence of Diabetes Mellitus and Prediabetes in the Adult Romanian Population: PREDATORR Study. J Diabetes. doi:10.1111/1753-0407.12297
21. Alberti KG, Eckel RH, Grundy SM et al (2009) Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120(16):1640–1645. doi:10.1161/CIRCULATIONAHA.109.192644
22. Matthews D, Hosker J, Rudenski A et al (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28(7):412–419
23. American Diabetes Association (2012) Standards of medical care in diabetes -2012. Diabetes Care 35(1):S11–S63. doi:10.2337/dc12-s011
24. Cleeman J, Grundy S, Becker D et al (2001) Expert panel on detection, evaluation and treatment of high blood cholesterol in adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III). JAMA 285:2486–2497
25. Kdigo, CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3(1):1–150
26. D'Agostino RB Sr, Vasan RS et al (2008) General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 117(6):743–753. doi:10.1161/CIRCULATIONAHA.107.699579
27. Ogden CL, Carroll MD, Kit BK, et al (2013) Prevalence of Obesity among Adults: United States, 2011-2012. NCHS data brief. http://www.cdc.gov/nchs/data/databriefs/db131.pdf. Accessed 20 Dec 2015
28. Balkau B, Deanfield JE, Després JP et al (2007) International Day for the Evaluation of Abdominal Obesity (IDEA): a study of

waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. Circulation 116(17):1942–1951
29. Grundy SM (2008) Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol 28(4):629–636. doi:10.1161/ATVBAHA.107.151092
30. Ford ES, Li C, Zhao G (2010) Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US. J Diabetes 2(3):180–193. doi:10.1111/j.1753-0407.2010.00078.x
31. Roberson LL, Aneni EC, Maziak W et al (2014) Beyond BMI: The "Metabolically healthy obese" phenotype & its association with clinical/subclinical cardiovascular disease and all-cause mortality – a systematic review. BMC Public Health 14:14. doi:10.1186/1471-2458-14-14
32. Kaur J (2014) A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014:943162. doi:10.1155/2014/943162
33. Kramer H, Shoham D, McClure LA et al (2011) Association of waist circumference and body mass index with all-cause mortality in CKD: The REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. Am J Kidney Dis 58(2):177–185. doi:10.1053/j.ajkd.2011.02.390
34. Chen S, Zhou S, Wu B et al (2014) Association between metabolically unhealthy overweight/obesity and chronic kidney disease: the role of inflammation. Diabetes Metab 40(6):423–430
35. Seo MH, Rhee EJ (2014) Metabolic and cardiovascular implications of a metabolically healthy obesity phenotype. Endocrinol Metab (Seoul) 29(4):427–434. doi:10.3803/EnM.2014.29.4.427
36. Park J, Kim SH, Cho GY et al (2011) Obesity phenotype and cardiovascular changes. J Hypertens 29(9):1765–1772. doi:10.1097/HJH.0b013e32834a50f3
37. Eshtiaghi R, Keihani S, Hosseinpanah F et al (2015) Natural course of metabolically healthy abdominal obese adults after 10 years of follow-up: the Tehran Lipid and Glucose Study. Int J Obes (Lond) 39(3):514–519. doi:10.1038/ijo.2014.176