Endocrine (2021) 73:580–587
https://doi.org/10.1007/s12020-021-02762-6

ORIGINAL ARTICLE

Children with metabolically healthy obesity have a worse metabolic profile compared to normal-weight peers: a cross-sectional study

Anastasios Serbis[1] · Vasilieios Giapros[1] · Stavroula A. Paschou[2] · Ekaterini Siomou[1]

Received: 19 January 2021 / Accepted: 10 May 2021 / Published online: 22 May 2021

Abstract

Purpose A phenotype of metabolically healthy obesity (MHO) has been described in youth with obesity, but data are still scarce in this age group. The aim of the current study was to describe and compare clinical and laboratory parameters related to obesity among three different groups of youth, namely youth with normal weight (NW), with MHO, and with metabolically unhealthy obesity (MUO).

Methods One hundred and three youngsters with obesity were divided according to 2018 consensus-based criteria into those with MHO [$n = 49$, age (±SD): 10.9 ± 2.9 years] and those with MUO [$n = 54$, 11.5 ± 2.7 years] and were compared to age-, sex- and Tanner-matched NW [$n = 69$, 11.3 ± 2.9 years]. Several obesity-related parameters were investigated for all three groups of children. Comparisons were made by analysis of variance (ANOVA) followed by the Fisher's PLSD test.

Results Youth with MHO had lower systolic ($p < 0.001$) and diastolic ($p < 0.01$) blood pressure z-score and triglycerides ($p < 0.01$), but higher HDL-C ($p < 0.001$), total cholesterol ($p < 0.05$), and apo-A1 ($p < 0.05$) compared to those with MUO. Compared to controls, both children with MHO and MUO showed higher fasting insulin ($p < 0.05$), HOMA-IR ($p < 0.05$), and QUICKI ($p < 0.001$). Similarly, both groups had higher hsCRP, fibrinogen, uric acid, and leptin compared to controls (for all, $p < 0.001$), while their adiponectin was lower ($p < 0.05$). Visfatin was higher in children with MUO compared to controls ($p < 0.01$), and it showed a trend to be lower in children with MHO compared to those with MUO ($p = 0.1$).

Conclusion This study provides evidence that children identified as having MHO by the consensus-based criteria had better metabolic profiles than youth with MUO, but worse than NW. Further research is needed in pediatric populations both regarding MHO criteria and the nature of the MHO phenotype per se.

Keywords Metabolically healthy obese · Consensus-based criteria · Children · Adolescents

Introduction

The worldwide prevalence of pediatric overweight and obesity has plateaued at high levels in many countries and continues to rise in others [1]. Robust evidence has shown that increased body weight in youth is associated with serious short- and long-term complications leading to increased risk of type 2 diabetes (T2D) and cardiovascular disease (CVD) in early adulthood [2]. Thus, childhood obesity remains one of the most alarming public health problems of our times, threatening to undermine both life expectancy and quality of life of generations to come [3].

However, it has been shown that not all individuals with obesity exhibit complications to the same severity and extent. In adult populations, for example, several reports have shown that there are men and women with obesity who, at a given time, do not demonstrate the traditional cardiometabolic risk factors linked to increased body fat. These individuals have been characterized as having metabolically healthy obesity (MHO) in contrast to those with metabolically unhealthy obesity (MUO) who exhibit obesity-related complications [4]. Depending on the criteria used to define the condition and the study population, adults with MHO represent up to 35% of the adult population with obesity, with dramatic differences in the prevalence among different studies [5].

✉ Anastasios Serbis
tasos_serbis@yahoo.com

[1] Child Health Department, School of Health Sciences, Faculty of Medicine, University of Ioannina, Ioannina, Greece

[2] Division of Endocrinology, Diabetes and Metabolism, Department of Clinical Therapeutics, Alexandra Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

Similar to the adult population, some evidence suggests that a percentage of children and adolescents with obesity can be characterized as having MHO at a given point in time [6, 7]. These kids seem to have a "favorable" metabolic profile with normal glucose metabolism, normal lipid, and blood pressure levels [8].

Several attempts have been made to define MHO in youth with obesity by using various diagnostic criteria related to insulin sensitivity and metabolic syndrome components, in various combinations and with diverse cut-off values [6, 9–13]. It is, thus, no wonder that the prevalence of pediatric MHO in youth with obesity varies between 3 and 80% depending on the definition used, the obesity criteria applied and the specific characteristics of the populations studied [8, 14]. In 2018, a scoping review was carried out in order to reach a consensus-based definition of pediatric MHO through experts' consultation and the application of a Delphi process [15]. However, the consensus was not reached for all criteria and some limitations were reported by the authors regarding the procedure.

Further to the pediatric MHO definition difficulties, there is accumulating evidence that MHO phenotype in adults is not a totally benign condition since the risk of developing T2D and CVD in MHO is lower than MUO but still higher than normal weight (NW) individuals [16–18]. Far less is known regarding health status and clinical implications associated with the MHO phenotype in pediatric populations.

We hypothesized that even children fulfilling the recently described MHO criteria may differ from peers with NW regarding other important metabolic parameters that are associated with obesity or its complications. We, therefore, compared several obesity-related clinical and metabolic parameters among three groups of age-, sex- and Tanner-matched youth, namely youth with NW, with MHO, and with MUO in order to evaluate the consensus-based pediatric MHO definition.

Materials and methods

The medical records of all Greek children and adolescents aged 5–16 years who attended the Outpatient Pediatric Clinic of the University Hospital of Ioannina, Ioannina, Greece between January and December 2016 were reviewed, in order to identify the ones with obesity. Among them, all children who fulfilled any of the following exclusion criteria were excluded from the study: recent (within prior 3 months) acute disease or use of medication; recent significant (>10%) change in body weight; clinical or laboratory evidence of any chronic cardiac, renal, hepatic, or endocrine (including thyroid) disease that could not be directly or indirectly related to obesity (for example, congenital heart disease, chronic viral hepatitis, etc.). Next, one of the authors contacted the parents of the eligible children, to ask if they are willing to participate in the study.

All children and adolescents enrolled in the study were Caucasian and were divided into those with MHO and those with MUO according to the first international consensus-based definition of pediatric MHO, published in 2018 by Damanhoury et al. [15]. More specifically, participants were classified as having MHO if they met all of the following criteria: HDL > 40 mg/dL (>103 mmol/L), triglycerides≤150 mg/dL (≤1.7 mmol/L), and systolic and diastolic blood pressure ≤ +1.28 standard deviation (SD) (≤90th percentile for age, sex, and height). Regarding glycemia, no consensus was achieved in the above definition, but we used fasting blood glucose (FPG) ≤ 100 mg/dL (≤5.6 mmol/L) as a euglycemia criterion since it was the one most commonly used in previous studies of MHO in children [8]. Children with obesity that did not meet one or more of the above criteria were classified as having MUO.

At the same time, NW age-, sex- and Tanner-matched children and adolescents that were examined during the same period of time at the same clinic for non-medical reasons (e.g., school certificates, scheduled vaccination, minor injuries, etc.) and who did not fulfill any of the above exclusion criteria were similarly asked if they are willing to participate in the study. These children comprised the NW group and were also Caucasian.

The study was reviewed and approved by the Institutional Scientific Review Board at Ioannina University Hospital and all parents and children of both groups (NW and with obesity) agreed to participate in the study.

An appointment was given for each child during which, weight, height, and waist circumference were measured and recorded by a single investigator. Bodyweight was measured to the nearest 0.1 kg on a medical scale with the child wearing only his/her underwear. Body height was measured with the child wearing no shoes, with a wall-mounted stadiometer, to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2) and obesity was defined as >+2 SD for age and sex according to the WHO growth charts. Waist circumference was measured to the nearest 1 mm at the midpoint between the lowest rib and the superior border of the iliac crest at minimal respiration, using an inelastic measuring tape with the participant standing still on both feet with arms hanging freely [19].

Systolic and diastolic blood pressure (SBP and DBP respectively) were measured three times on the right arm, in the seated position using a mercury sphygmomanometer with an appropriately sized cuff. The mean of the three measurements and subsequently the SBP and DBP z-scores for each child were calculated, according to the criteria established by the Fourth Report on the diagnosis,

evaluation, and treatment of high blood pressure in children and adolescents [20]. Pubertal development of each participant was assessed consistently by a single investigator and was recorded according to Tanner's stage [21, 22].

After a 12-h overnight fast, blood samples were drawn from all three groups and several laboratory parameters were measured using Siemens Advia 1650 Clinical Chemistry System (Siemens Medical Solutions, Erlangen, Germany). More specifically, regarding glucose metabolism, FPG (normal: 60–99 mg/dL), and fasting insulin (normal: 7–15 μU/mL) were measured. In addition, the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index and Quantitative Insulin Sensitivity Check Index (QUICKI) were calculated according to the following formulas: HOMA-IR = [FPG (mg/dL) × fasting insulin (mIU/mL)]/405 [23] and QUICKI = 1/[log(fasting insulin in μU/mL) + log (FPG in mg/dL)] [24].

Regarding lipid metabolism total cholesterol (TC) (normal: <170 mg/dL), triglycerides (TG) (normal: up to 9 years <75 mg/dL, older than 9 years <90 mg/dL), HDL-Cholesterol (HDL-C) (normal: >45 mg/dL), apolipoprotein A1 (apo-A1) (normal: >120 mg/dL) and B (apo-B) (normal: <90 mg/dL) were measured. In addition, LDL-Cholesterol (LDL-C) levels (normal: <110 mg/dl) were calculated using Friedewald's equation [25].

Pro-inflammatory and pro-thrombotic markers that were measured included high-sensitivity C-reactive protein (hsCRP) (normal: 0.22–1.15 mg/L), fibrinogen (normal: 200–400 mg/dL), and uric acid (UA) (normal: 2.6–6.6 mg/dL). In addition, aspartate transaminase (AST) (normal: 5–40 IU/L) and alanine transaminase (ALT) (normal: 5–40 IU/L) were measured to evaluate hepatic function.

Further, the adipokines that were measured included adiponectin, leptin, visfatin, and IL-6 all of which have reference values dependent on age and/or sex [26–29]. Adiponectin and visfatin were measured with enzyme immunoassay methods (EIA) (Phoenix Pharmaceuticals Inc., USA). Their sensitivities were 0.15 ng/mL and 2.3 ng/mL respectively and their intra- and inter-assay CVs 10 and 15%. Leptin was measured using an enzyme-linked immunosorbent assay (ELISA) kit (Diagnostic Systems Laboratories Inc, USA) with a sensitivity of 0.05 ng/mL, and intra- and inter-assay coefficients of variability (CVs), 6.2 and 5.3% respectively at the level of 12 ng/mL. Interleukin-6 (IL-6) was measured by a non-competitive assay (ImmunoTools GmbH, Germany) with sensitivity 4 pg/mL and intra- and inter-assay CVs 8.5 and 7.9% respectively.

Statistical analysis

After examination of parameters for normal distribution, comparisons between the two study groups of patients with obesity and the control group were made by analysis of variance (ANOVA) followed by the Fisher's PLSD test. To eliminate the effect of multiple comparisons the Benjamini–Hochberg procedure was utilized. ANCOVA analysis was also made to adjust for age. Moreover, a subgroup "sensitivity" analysis was made that included boys vs girls and prepubertal vs pubertal children. Values are expressed as mean plus/minus standard deviation (±SD). A level of significance of $p < 0.05$ was set. A power sample size estimation was performed which showed that a sample size of 170 children was sufficient for any parameter comparison between every two groups. This sample size is sufficient to demonstrate a 15% difference in all the parameters examined, with a power of >80% at a significance level of 0.05 [30]. Statistical analysis was performed using the Stat View software package of SAS Institute Inc. (Cary, USA).

Results

The medical records of 180 children and adolescents with obesity were retrieved, covering the 1-year search period, of which 122 were potentially eligible, and 103 agreed to participate in the study. Of these youth with obesity, 49 were identified as having MHO (21 boys) and 54 as having MUO (24 boys) giving an MHO phenotype prevalence of 47.6%. In addition, 69 children and adolescents (29 boys) with NW comprised the control group. It is worth mentioning that after applying the Damanhoury criteria on these NW children, 7/69 met one and 1/69 met two criteria.

Regarding age, sex, and Tanner stage, no statistically significant difference was observed among all three groups (Table 1). WC did not differ between the two groups of children with obesity (Table 1). The values of parameters used to characterize children as having either MHO or MUO differed significantly between the two obese groups except for BMI z-score (4.0 ± 1.6 vs 4.1 ± 1.8) and FPG levels (87.9 ± 7 vs 88.4 ± 10 mg/dL). In addition, all these parameters differed significantly between children with obesity and NW, except for FPG levels (Table 2).

Obesity related metabolic parameters such as fasting insulin levels, HOMA-IR and QUICKI, hsCRP, fibrinogen, and uric acid levels, as well as adipokine levels (adiponectin, leptin), were found to be affected in children with both MHO and MUO compared to controls (Table 3). Visfatin was higher only in children with MUO compared to NW while IL-6 showed no difference among the three groups. In addition, ALT was higher in both groups with obesity compared to controls while AST did not show a statistically significant difference (Table 3). Comparisons of the above parameters between the two groups with obesity showed no significant differences, apart from visfatin that showed a tendency to increase in children with MUO (Table 3).

Table 1 Descriptive characteristics of children in normal weight (NW) group, in group of children with metabolically healthy obesity (MHO), and group of children with metabolically unhealthy obesity (MUO)

Parameters	NW	MHO	MUO	*P* (MHO vs NW, MUO vs NW)
Sex	29 boys, 40 girls	21 boys, 28 girls	24 boys, 30 girls	0.92, 0.93 NS
Age (years)	11.3 ± 2.9	10.9 ± 2.9	11.5 ± 2.7	0.56, 0.76 NS
Prepubertal/pubertal	23/46	22/27	19/35	0.28, 0.98 NS

Data are expressed as a number or as mean ± standard deviation (SD)

NS non-significant, statistical significance between each obese and control groups, *MHO* metabolically healthy obesity, *MUO* metabolically unhealthy obesity, *NW* normal weight

Table 2 Comparison of the mean values of parameters used as criteria to define metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO) among all three groups of youth

Parameters	NW	Youth with MHO	Youth with MUO
BMI z-score	0.59 ± 0.73	4.0 ± 1.6***	4.1 ± 1.8***
HDL-C (mg/dL)	50.7 ± 7.4	49.7 ± 7.9[b]	42.4 ± 9.6***
TG (mg/dL)	85 ± 32	89 ± 26[a]	106 ± 40***
Systolic blood pressure z -score	0.3 ± 0.6	0.89 ± 0.7***, [b]	1.9 ± 0.8***
Diastolic blood pressure z-score	0.56 ± 0.56	0.56 ± 0.59[a]	1.01 ± 0.92**
Fasting blood glucose (mg/dL)	88.1 ± 8	87.9 ± 7	88.4 ± 10

Data are expressed as mean ± standard deviation (SD)

BMI body mass index, *HDL-C* high-density lipoprotein-cholesterol, *MHO* metabolically healthy obesity, *MUO* metabolically unhealthy obesity, *NW* normal weight, *TG* triglycerides

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$: statistical significance between each group with obesity and control group

[a]$p < 0.01$, [b]$p < 0.001$: statistical significance between the two groups of youth with obesity

Regarding specifically insulin and insulin sensitivity indices, a comparison between prepubertal and pubertal youth showed no difference while both subgroups of MUO and MHO differed significantly compared to controls (Table 3). Further, an insulin cutoff value of >11.2 µU/mL showed a 75% specificity and a 47 and 66% sensitivity to diagnose µHO and MUO respectively. Regarding HOMA-IR, a value of >2.5 had a 77% specificity and a 43 and 67% sensitivity while a value <0.332 for QUICKI had a 76% specificity and 51 and 68% sensitivity in the 2 groups, respectively. At higher specificity values, sensitivity promptly declined.

The subgroup "sensitivity" analysis intending to define robustness across subgroups namely in boys vs girls and in prepubertal vs pubertal children (data not shown) yielded results in line with those of the main statistical analysis.

Discussion

In this cross-sectional study, 103 children and adolescents with obesity were divided according to the criteria proposed by Damanhoury et al. to either having MHO or MUO [15]. Several obesity-related clinical and laboratory parameters were compared between these two groups of youth with obesity and the third group of age-, sex-, and Tanner-matched NW children. As anticipated, most of the examined parameters were affected in children with MUO compared to NW, including the parameters used as criteria to differentiate MHO and MUO phenotypes (i.e., HDL-C, TG, SBP, DBP, and FBG) as well as indicators of visceral adiposity, insulin sensitivity, hepatic steatosis, thrombosis, immune system, and inflammation. What was not anticipated though, was the finding that several of the examined parameters were found to be affected also in children with MHO compared to NW.

Concerning glucose metabolism, no significant difference was observed regarding FPG levels among youth with NW, youth with MHO, and youth with MUO (88.1 ± 8 vs 87.9 ± 7 vs 88.4 ± 10 mg/dL). Such an observation could be explained by the fact that FBG usually remains within the normal range in children, despite obesity and changes in insulin sensitivity and secretion [31], especially in children with relatively short obesity duration such as our study participants [32]. In addition, possible differences in the genetic predisposition of each child to develop hyperglycemia could also play a role. Fasting insulin levels (8.4 ± 3.5 vs 12.4 ± 7.6 vs 14.7 ± 13.5 µU/mL) and HOMA-IR (1.85 ± 0.8 vs 2.7 ± 1.7 vs 3.3 ± 3.7) were lower and QUICKI (0.36 ± 0.032 vs 0.33 ± 0.05 vs 0.33 ± 0.03) was higher in NW compared to both children with MHO and MUO indicating that a state of insulin resistance and consequent hyperinsulinemia characterize both groups of children with obesity compared to NW peers. In addition, a relative overlapping was observed when cutoff values of

Table 3 Obesity-related somatometric and laboratory parameters examined in all three study groups, namely normal weight (NW) children, children with metabolically healthy obesity (MHO), and children with metabolically unhealthy obesity (MUO)

Parameters	NW	Youth with MHO	Youth with MUO	trends
Somatometric parameters				
Waist circumference z-score [19]	−0.3 ± 0.7	1.85 ± 1***	2.04 ± 1.2***	
Glucose metabolism				
Fasting Insulin (μU/mL)	8.4 ± 3.5	12.4 ± 7.6*	14.7 ± 13.5**	
Prepubertal	7.5 ± 2.9	10.8 ± 6.2*	11.9 ± 3.7**	
Pubertal	8.9 ± 3.6	13.5 ± 8.5*	16.2 ± 14**	
HOMA-IR	1.85 ± 0.8	2.7 ± 1.7*	3.3 ± 3.7***	
Prepubertal	1.64 ± 0.7	2.4 ± 1.4*	2.7 ± 0.8**	
Pubertal	1.95 ± 0.9	2.98 ± 1.8*	3.7 ± 4.1**	
QUICKI	0.36 ± 0.032	0.33 ± 0.05***	0.33 ± 0.03***	
Prepubertal	0.38 ± 0.034	0.34 ± 0.05**	0.34 ± 0.05**	
Pubertal	0.35 ± 0.030	0.32 ± 0.05**	0.31 ± 0.05**	
Lipid metabolism				
T-Chol (mg/dL)	172 ± 17	178 ± 26[a]	167 ± 28	
LDL-C (mg/dL)	104 ± 16	111 ± 22[t]	103 ± 23	$p = 0.055$
Apo-A1 (mg/dL)	145 ± 19	139 ± 20[a]	128 ± 23***	
Apo-B (mg/dL)	71 ± 15	79 ± 18**	81 ± 16**	
Apo-B/Apo-A1	0.50 ± 0.13	0.58 ± 0.16**, [t]	0.65 ± 0.16***	$p = 0.06$
Pro-inflammatory and pro-thrombotic markers				
hsCRP (mg/L)	2.1 ± 1.2	4.7 ± 3.8***	5.4 ± 3.9***	
Fibrinogen (mg/dL)	296 ± 50	361 ± 109***	381 ± 76***	
Uric Acid (mg/dL)	4.4 ± 0.9	5.4 ± 2***	5.02 ± 1.4***	
Adipokines				
Adiponectin (μg/mL)	11.9 ± 5.8	9.8 ± 5.8*	9.4 ± 5*	
Leptin (ng/mL)	10.5 ± 7	31 ± 19***	34 ± 15***	
Visfatin (ng/mL)	9.8 ± 5	11.7 ± 6[t]	12.9 ± 7**	$p = 0.10$
IL-6 (pg/mL)	9.4 ± 10	8.3 ± 6.4	9.9 ± 9.5	
NAFLD				
AST (U/L)	24 ± 6.8	24.4 ± 6.4	25.9 ± 8.3	
ALT (U/L)	18.7 ± 8	23.6 ± 13***	26.5 ± 15***	

Data are expressed as mean ± standard deviation (SD)

ALT alanine transaminase, *Apo-A1* apoliporoptein-A1, *Apo-B* apolipoprotein-B, *AST* aspartate transaminase, *HOMA-IR* homeostasis model assessment of insulin resistance, *hsCRP* high sensitivity C-reactive protein, *IL-6* interleukin-6, *LDL-C* low-density lipoprotein-cholesterol, *MHO* metabolically healthy obesity, *MUO* metabolically unhealthy obesity, *NAFLD* non-alcoholic fatty liver disease, *NW* normal weight, *QUICKI* quantitative insulin sensitivity check index, *T-Chol* total cholesterol

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$: statistical significance between each group with obesity and control group

[t]trend, [a]$p < 0.05$: statistical significance between the two groups of youth with obesity

[¶]no differences were found comparing between prepubertal and pubertal groups for any of glucose metabolism parameters

insulin, HOMA-IR, and QUICKI were calculated to differentiate between groups of children.

Regarding subclinical inflammation and atherogenesis, hsCRP (2.1 ± 1.2 vs 4.7 ± 3.8 vs 5.4 ± 3.9 mg/L), fibrinogen (296 ± 50 vs 361 ± 109 vs 381 ± 76 mg/dL), and UA (4.4 ± 0.9 vs 5.4 ± 2 vs 5.02 ± 1.4 mg/dL) were found to be lower in NW compared to both children with MHO and MUO while they did not differ significantly between the latter two groups. A recent study in adults showed that pro-inflammatory monocyte subsets were lower in adults with MHO compared to those with MUO but higher than NW suggesting a sub-clinical inflammation in individuals with MHO [33]. To the best of our knowledge, no studies have been published linking hsCRP or fibrinogen levels with MHO phenotype in children, while increased UA levels have recently been linked to MUO in youth [34]. Our results

show that obesity is associated with subclinical inflammation and a pro-atherogenic milieu, even in children with the MHO phenotype.

Regarding adipokines, adiponectin was higher (11.9 ± 5.8 vs 9.8 ± 5.8 vs 9.4 ± 5 μg/mL), and leptin was lower (10.5 ± 7 vs 31 ± 19 vs 34 ± 15 ng/mL) in controls compared to both children with MHO and MUO. Visfatin was higher in children with MUO compared to NW (12.9 ± 7 vs 9.8 ± 5 ng/mL, $p < 0.01$) but showed no difference between children with MHO and NW (11.7 ± 6 vs 9.8 ± 5 ng/mL). IL-6 did not differ between the three groups of children (9.4 ± 10 vs 8.3 ± 6.4 vs 9.9 ± 9.5 pg/mL). Visfatin showed a tendency to increase between patients with MHO and MUO (11.7 ± 6 vs 12.9 ± 7, $p = 0.10$) while the other three adipokines did not differ between the two groups of children with obesity. Similar to our results, studies have shown that children with MHO may present with lower adiponectin levels compared to NW, and higher leptin levels [35, 36]. Regarding visfatin and the MHO phenotype, data have been conflicting thus far [37, 38], while, to the best of our knowledge, there have been no studies investigating IL-6 levels in children with MHO and MUO. These results point toward a pro-inflammatory milieu that could gradually lead to metabolic derangements not only in children with MUO but also in those with MHO compared to NW.

Regarding liver transaminases, ALT, which is considered to be the best screening tool to detect NAFLD in children [39], was higher in youth with both MHO and MUO compared to NW [(23.6 ± 13) vs (26.5 ± 15) vs (18.7 ± 8) U/L respectively, $p < 0.001$]. In addition, children with MUO had mean ALT values (26.5 ± 15 U/L) above the upper limit of normal in children (22 U/L for girls and 26 U/L for boys) according to the latest NASPGHAN Clinical Practice Guideline [39]. These findings imply that mainly children with MUO but also those with MHO are at increased risk of developing liver dysfunction and possibly NAFLD, in agreement with other studies in both adolescents and adults with obesity [40–42]. Fortunately, only one of all youth included in the study, a prepubertal child with MUO, had ALT > 80 U/L, a finding that has been linked with increased risk of fibrosis in children with non-alcoholic steatohepatitis [39].

The uncertainties that still exist regarding pediatric MHO definition may imply that MHO does not represent a biologically defined distinct subgroup of individuals with obesity and that it might not be a totally benign condition after all [16, 43]. Indeed, evidence is gradually accumulating, both in adults and children, that individuals with MHO have a worse metabolic profile compared to their lean counterparts and are at increased risk of obesity complications. In a recent study, for example, Caleyachetty et al. showed that adults with MHO had a higher risk of coronary heart disease, CVD, and heart failure than NW counterparts [17]. In youth, individuals with MHO have shown an increased risk of hepatic steatosis, a higher degree of visceral fat accumulation, higher inflammatory biomarkers, and higher carotid intima-media thickness, a proxy of CVD, compared to NW [35, 41, 44, 45]. The findings of our study corroborate the notion that MHO is not a totally benign condition that can be clearly differentiated from MUO but rather, obesity represents a continuum-increased risk for complications and CVD.

This study has some limitations, namely the relatively small sample size from an epidemiological point of view, and the lack of information regarding long-term outcomes (e.g., obesity complications and related morbidities) due to the study's cross-sectional design. In addition, it could be speculated that there may have been subtle differences in fat composition or fat distribution between the study groups since reference methods of adiposity estimation were not used. Further, information on children's birth, diet, lifestyle habits, and family history is lacking. The strengths of this study were that all three groups were age-, sex- and Tanner-matched as well as of the same ethnicity, that several obesity-related biochemical parameters were measured and that the differences observed were statistically strong making the results more reliable.

In conclusion, it was shown that children and adolescents with obesity diagnosed as having MHO show a better metabolic profile than their peers with MUO, but a worse profile compared to NW. These findings question the benign nature of the pediatric MHO. More comprehensive and stringent criteria could possibly better define children and adolescents with obesity that are metabolically healthy, but still, the clinical significance and the long-term outcome of such a phenotype are highly debatable. Until more data are gathered, children with MHO should be considered as having a vaguely defined and possibly unstable phenotype and should therefore be treated as all children with obesity.

Author contributions VG and AS contributed to the study conception and design. Material preparation and data collection were performed by AS and ES. Data analysis was performed by VG and SP. The first draft of the manuscript was written by AS and VG. ES and SP made substantial contributions to the final version of the manuscript. All authors read and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethics approval (include appropriate approvals or waivers) Approved by the Institutional Scientific Review Board at Ioannina University Hospital.

Consent to participate (include appropriate statements) Written informed consent and each child's assent were obtained from all participants and their parents of all groups for participating in the study.

Consent for publication (include appropriate statements) Written informed consent and each child's assent were obtained from all participants and their parents of all groups for publishing the study's results.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. J. Bentham, M. Di Cesare, V. Bilano, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet. **390**: 2627–2642 (2017)
2. R. Lakshman, C.E. Elks, K.K. Ong, Childhood obesity. Circulation **126**, 1770–1779 (2012)
3. S.J. Olshansky, D.J. Passaro, R.C. Hershow et al. A potential decline in life expectancy in the united states in the 21st century. N. Engl. J. Med. **352**, 1138–1145 (2005)
4. A. Tsatsoulis, S.A. Paschou, Metabolically healthy obesity: criteria, epidemiology, controversies, and consequences. Curr. Obes. Rep. **9**, 109–120 (2020)
5. H. Lin, L. Zhang, R. Zheng et al. The prevalence, metabolic risk and effects of lifestyle intervention for metabolically healthy obesity: a systematic review and meta-analysis. Medicine **96**, e8838 (2017)
6. R.L. Prince, J.L. Kuk, K.A. Ambler et al. Predictors of metabolically healthy obesity in children. Diabetes Care **37**, 1462–1468 (2014)
7. D.Y. Yoon, Y.A. Lee, J. Lee et al. Prevalence and clinical characteristics of metabolically healthy obesity in Korean children and adolescents: data from the Korea National Health and Nutrition Examination Survey. J. Korean Med. Sci. **32**, 1840–1847 (2017)
8. R. Vukovic, T.J. Dos Santos, M. Ybarra et al. Children with metabolically healthy obesity: a review. Front. Endocrinol. **10**, 865 (2019)
9. R. Weiss, S.E. Taksali, S. Dufour et al. The "Obese insulin-sensitive" adolescent: Importance of adiponectin and lipid partitioning. J. Clin. Endocrinol. Metab. **90**, 3731–3737 (2005)
10. R. Vukovic, T. Milenkovic, K. Mitrovic et al. Preserved insulin sensitivity predicts metabolically healthy obese phenotype in children and adolescents. Eur. J. Pediatr. **174**, 1649–1655 (2015)
11. D. Weghuber, S. Zelzer, I. Stelzer et al. High risk vs "metabolically healthy" phenotype in juvenile obesity—neck subcutaneous adipose tissue and serum uric acid are clinically relevant. Exp. Clin. Endocrinol. Diabetes **121**, 384–390 (2013)
12. L. Bervoets, G. Massa, Classification and clinical characterization of metabolically "healthy" obese children and adolescents. J. Pediatr. Endocrinol. Metab. **29**, 553–560 (2016)
13. C. Cadenas-Sanchez, J.R. Ruiz, I. Labayen et al. Prevalence of metabolically healthy but overweight/obese phenotype and its association with sedentary time, physical activity, and fitness. J. Adolesc. Heal. **61**, 107–114 (2017)
14. M.L. Evia-Viscarra, R. Guardado-Mendoza. Comparison between metabolically healthy obesity and metabolically unhealthy obesity by different definitions among Mexican children. J. Pediatr. Endocrinol. Metab. **33**, 215–222 (2020)
15. S. Damanhoury, A.S. Newton, M. Rashid et al. Defining metabolically healthy obesity in children: a scoping review. Obes. Rev. **19**, 1476–1491 (2018)
16. F. Magkos, Metabolically healthy obesity: what's in a name? Am. J. Clin. Nutr. **110**, 533–537 (2019)
17. R. Caleyachetty, G.N. Thomas, K.A. Toulis et al. Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. J. Am. Coll. Cardiol. **70**, 1429–1437 (2017)
18. M. Blüher, Obesity: the myth of innocent obesity. Nat. Rev. Endocrinol. **13**, 691–692 (2017)
19. K.D. Tambalis, D.B. Panagiotakos, G. Arnaoutis et al. Establishing cross-sectional curves for height, weight, body mass index and waist circumference for 4- to 18-year-old Greek children, using the Lambda Mu and Sigma (LMS) statistical method. Hippokratia **19**, 239–248 (2015)
20. B. Falkner, S.R. Daniels. Summary of the fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Hypertension **44**, 387–388 (2004)
21. W.A. Marshall, J.M. Tanner, Variations in the pattern of pubertal changes in boys. Arch. Dis. Child **45**, 13–23 (1970)
22. W.A. Marshall, J.M. Tanner, Variations in pattern of pubertal changes in girls. Arch. Dis. Child **44**, 291–303 (1969)
23. D.R. Matthews, J.P. Hosker, A.S. Rudenski et al. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia **28**, 412–419 (1985)
24. A. Katz, S.S. Nambi, K. Mather et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J. Clin. Endocrinol. Metab. **85**, 2402–2410 (2000)
25. W.T. Friedewald, R.I. Levy, D.S. Fredrickson. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin. Chem. **18**, 499–502 (1972)
26. U. Lausten-Thomsen, M. Christiansen, C.E. Fonvig et al. Reference values for serum total adiponectin in healthy non-obese children and adolescents. Clin. Chim. Acta **450**, 11–14 (2015)
27. M.B. Horlick, M. Rosenbaum, M. Nicolson et al. Effect of puberty on the relationship between circulating leptin and body composition. J. Clin. Endocrinol. Metab. **85**, 2509–2518 (2000)
28. D. Taşkesen, B. Kirel, T. Us. Serum visfatin levels, adiposity and glucose metabolism in obese adolescents. J. Clin. Res. Pediatr. Endocrinol. **4**, 76–81 (2012)
29. U. Sack, U. Burkhardt, M. Borte et al. Age-dependent levels of select immunological mediators in sera of healthy children. Clin. Diagn. Lab. Immunol. **5**, 28–32 (1998)
30. D. Altman, Sample size, in *Practical Statistics for Medical Research* (Chapman & Hall, London, 1994), pp. 456–60
31. G. O'Malley, N. Santoro, V. Northrup et al. High normal fasting glucose level in obese youth: a marker for insulin resistance and beta cell dysregulation. Diabetologia **53**, 1199–1209 (2010)
32. E. Hagman, T. Reinehr, J. Kowalski et al. Impaired fasting glucose prevalence in two nationwide cohorts of obese children and adolescents. Int. J. Obes. **38**, 40–45 (2014)
33. K.A. Christou, G.A. Christou, A. Karamoutsios et al. Metabolically healthy obesity is characterized by a proinflammatory phenotype of circulating monocyte subsets. Metab. Syndr. Relat. Disord. **17**, 259–265 (2019)
34. S. Genovesi, L. Antolini, A. Orlando, et al. Cardiovascular risk factors associated with the metabolically healthy obese (MHO) phenotype compared to the metabolically unhealthy obese (MUO) phenotype in children. Front. Endocrinol. (Lausanne) **11**, 27–35 (2020)
35. J. Fu, Y. Li, I.C. Esangbedo et al. Circulating osteonectin and adipokine profiles in relation to metabolically healthy obesity in Chinese children: Findings from BCAMS. J. Am. Heart Assoc. **7**, e009169 (2018)
36. W. Ding, H. Cheng, F. Chen et al. Adipokines are associated with hypertension in metabolically healthy obese (MHO) children and adolescents: a prospective population-based cohort study. J. Epidemiol. **28**, 19–26 (2018)

37. G. Labruna, F. Pasanisi, C. Nardelli, et al. High leptin/adiponectin ratio and serum triglycerides are associated with an at-risk phenotype in young severely obese patients. Obesity (Silver Spring) **19**, 1492–1496 (2011)
38. I. Aldhoon-Hainerová, H. Zamrazilová, M. Hill et al. Insulin sensitivity and its relation to hormones in adolescent boys and girls. Metabolism **67**, 90–98 (2017)
39. M.B. Vos, S.H. Abrams, S.E. Barlow et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the expert committee on NAFLD (ECON) and the North American society of pediatric gastroenterology, hepatology and nutrition (NASPGHAN). J. Pediatr. Gastroenterol. Nutr. **64**, 319–334 (2017)
40. Y. Kim, Y. Chang, Y.K. Cho, et al. Metabolically healthy versus unhealthy obesity and risk of fibrosis progression in non-alcoholic fatty liver disease. Liver Int. **39**, 1884–1894 (2019)
41. P.K.C. Selvakumar, M.N. Kabbany, R. Lopez et al. Prevalence and risk factors of nonalcoholic fatty liver disease in metabolically healthy obese adolescents in the United States: an analysis of national health and nutrition examination survey data. J. Hepatol. **66**, S587–S588 (2017)
42. A. Lonardo, A. Mantovani, S. Lugari et al. Epidemiology and pathophysiology of the association between NAFLD and metabolically healthy or metabolically unhealthy obesity. Ann. Hepatol. **19**, 359–366 (2020)
43. M. Blüher, Metabolically healthy obesity. Endocr. Rev. **41**, 405–420 (2020)
44. G. Farello, A. Antenucci, S. Stagi et al. Metabolically healthy and metabolically unhealthy obese children both have increased carotid intima-media thickness: a case control study. BMC Cardiovasc. Disord. **18**, 140–146 (2018)
45. M. Zhao, A. López-Bermejo, C.A. Caserta et al. Metabolically healthy obesity and high carotid intima-media thickness in children and adolescents: international childhood vascular structure evaluation Consortium. Diabetes Care **42**, 119–125 (2019)