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Article

Severe Obesity Defined by Percentiles of WHO and Cardiometabolic Risk in Youth with Obesity

Giuliana Valerio ^{1,*†}, Procolo Di Bonito ^{2,†}, Anna Di Sessa ³, Giada Ballarin ¹, Valeria Calcaterra ⁴, Domenico Corica ⁵, Maria Felicia Faienza ⁶, Francesca Franco ⁷, Maria Rosaria Licenziati ⁸, Claudio Maffeis ⁹, Giulio Maltoni ¹⁰, Emanuele Miraglia del Giudice ³, Anita Morandi ⁹, Enza Mozzillo ¹¹ and Malgorzata Wasniewska ¹²

¹ Department of Medical, Movement Sciences and Wellbeing, University of Napoli "Parthenope", 80133 Napoli, Italy; giada.ballarin@uniparthenope.it

² Department of Internal Medicine, "S. Maria delle Grazie" Hospital, 80078 Pozzuoli, Italy; procolodibonito53@gmail.com

³ Department of Woman, Child and of General and Specialized Surgery, University of Campania "Luigi Vanvitelli", 80138 Napoli, Italy; anna.disessa@unicampania.it (A.D.S.); emanuele.miraglia@unicampania.it (E.M.d.G.)

⁴ Pediatric Department, "V. Buzzi" Children's Hospital, 20154 Milano, Italy; Department of Internal Medicine, 27100 University of Pavia, Pavia, Italy; valeria.calcaterra@unipv.it

⁵ Department of Human Pathology in Adulthood and Childhood, University of Messina, 98122 Messina, Italy; domenico.corica@unime.it

⁶ Pediatric Unit, Department of Precision and Regenerative Medicine and Ionian Area, University of Bari "Aldo Moro", 70124 Bari, Italy; mariafelicia.faienza@uniba.it

⁷ Pediatric Department, Azienda Sanitaria Universitaria Friuli Centrale, Hospital of Udine, 33100 Udine, Italy; francesca.franco@asufc.sanita.fvg.it

⁸ Neuro-Endocrine Diseases and Obesity Unit, Department of Neurosciences, Santobono-Pausilipon Children's Hospital, 80129 Napoli, Italy; mrlizenziati@gmail.com

⁹ Department of Surgery, Dentistry, Pediatrics and Gynecology, Section of Pediatric Diabetes and Metabolism, University and Azienda Ospedaliera Universitaria Integrata of Verona, 37126 Verona, Italy; claudio.maffeis@univr.it (C.M.); anita.morandi@univr.it (A.M.)

¹⁰ Pediatric Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, 40138 Bologna, Italy; giulio.maltoni@aosp.bo.it

¹¹ Section of Pediatrics, Department of Translational Medical Science, Regional Center of Pediatric Diabetes, University of Naples "Federico II", 80131 Napoli, Italy; mozzilloenza@gmail.com

¹² Department of Human Pathology in Adulthood and Childhood, University of Messina, 98122 Messina, Italy; malgorzata.wasniewska@unime.it

* Correspondence: giuliana.valerio@uniparthenope.it

† These authors contributed equally to this work.

Abstract: Background/Objectives: The pediatric definition of severe obesity (OB) depends on the body mass index (BMI) references. We evaluated different BMI derived metrics of the World Health Organization (WHO) system to define which cut-off is associated with the highest cardiometabolic risk (CMR); **Methods:** In this multicentric study data were obtained by 3727 youths (1937 boys; 2225 children, 1502 adolescents. severe OB was defined as BMI >99th percentile (BMI₉₉), BMI₉₇ ≥120% or BMI Z-score > 3 (WHO tables). The continuous CMR Z-score (sum of residual standardized for age and sex of waist-to-height ratio, systolic and diastolic blood pressure, triglycerides, and HDL-Cholesterol x -1) and the cluster of at least two CMR factors (hypertension, high triglycerides, low HDL-Cholesterol and high waist-to-height ratio) were calculated; **Results:** Continuous CMR Z-score was significantly higher both in children or adolescents with severe OB defined by 120% BMI₉₇ compared to BMI >99th ($p < 0.0001$), while it was lower only in adolescents with severe OB defined by 120% BMI₉₇ compared to BMI Z-score >3 ($p < 0.0001$). Compared to BMI₉₇ ≥120%, BMI Z-score >3 had higher specificity, but lower sensitivity in identifying children and adolescents with clustered CMR factors; **Conclusions:** The definition of severe OB based on BMI₉₇ ≥120% is superior to BMI₉₉ but it is inferior to BMI Z score >3 as far as the association between severe OB and CMR factors is

concerned. Pediatricians should take into consideration the implication of the use of different BMI metrics in those countries that recommend the WHO system.

Keywords: body mass index Z-score; cardiometabolic risk; severe obesity; World Health Organization

1. Introduction

Severe obesity (OB) in adults is defined by a body mass index (BMI) value ≥ 40 kg/m². It has been associated with a high risk of developing type 2 diabetes, hypertension, congestive heart failure, and poor therapeutic success. In such cases, bariatric surgery currently represents the main therapeutic option able to induce significant weight loss and mitigation of cardiometabolic comorbidities including type 2 diabetes [1].

The definition of severe OB in children and adolescents is still a matter of debate and depends on the BMI reference values used. In Canada and several European countries, including Italy, the World Health Organization (WHO) cut-offs [2] are used. According to this system, the definition is based either on BMI Z-score >3 standard deviations (which corresponds to 99.9th percentile) [3] or BMI ≥ 99 th percentile (as a rounded percentile of the 99.9th) [3,4]. On the contrary, the recent guideline for the treatment of obesity released by the American Academy of Pediatrics recommends using percentages of the 95th percentile of BMI-for-age and sex (BMI₉₅) to indicate different levels of severe OB [5]. In fact, the extreme values of BMI Z-score released by the Centers for Disease Control (CDC) are considered less reliable due to sparse reference data and compression >97 th percentile. Namely, the limit of BMI₉₅ $\geq 120\%$ of CDC has been proposed to classify children and adolescents with severe OB [6,7].

The discrepancy in the categorization of severe OB may have consequences either in public health or in clinical practice. For instance, by using different definitions the classification of severe OB in children is heterogeneous, as shown by a recent systematic review with meta-analysis [8]. Therefore, a unified cut-off would provide a better comparison at international level and understanding of the clinical implications. Of note, the indication of bariatric surgery in adolescents is based on percentages of BMI₉₅ (namely BMI₉₅ $\geq 140\%$, or BMI₉₅ $\geq 120\%$ with a comorbidity), or on absolute values of 40 and 35 kg/m² [5], which does not have the equivalent in those countries using BMI Z-scores.

It is well known that cardiometabolic risk factors worsen with increasing severity of OB [9]. As far as we know, the empirical evidence for comparing the cardiometabolic risk across different BMI derived metrics of the WHO tables, namely extended values of BMI over the 97th percentile (BMI₉₇) and BMI Z-scores is lacking. Therefore, we compared individual and clustered cardiometabolic risk factors among different metrics of OB and severe OB, namely 97th percentile, 99th percentile, BMI₉₇ $\geq 120\%$ of the WHO tables in children and adolescents with OB. Furthermore, a comparison of the cardiometabolic variables between youths with BMI Z-score >3 and BMI₉₇ $\geq 120\%$ was evaluated.

2. Materials and Methods

Study Design and Participants

We retrospectively analysed the data of children and adolescents (age range 6-17 years) retrieved from the database of the CARITALY (CARDiometabolic risk factors in overweight and obese children in ITALY) study, a multicentre cross-sectional study on the behalf of the Obesity study group of the Italian Society for Pediatric Endocrinology and Diabetology [10]. Participants were observed between 2003-2020 in ten Italian centers for the management of paediatric obesity distributed across different regions. We selected youths with OB as defined by the 97th percentile of BMI from the WHO tables, in whom anthropometric, clinical, and biochemical variables were available. Youths with type 1 or

type 2 diabetes, LDL-C ≥ 190 mg/dL, TG ≥ 400 mg/dL, secondary obesity or under pharmacological treatment were excluded.

Anthropometric Assessment

In each centre, physical examinations were performed by trained pediatricians and puberal maturation was evaluated according to Tanner staging. Anthropometric parameters were measured following standard procedures [10]. BMI was calculated as weight (Kg)/height (m)², BMI Z-scores were calculated using the WHO AnthroPlus software (<https://www.who.int/tools/growth-reference-data-for-5to19-years/application-tools>). Waist circumference was measured at the midpoint between the last rib and the iliac crest at minimal respiration when the participant was in a standing position. The waist to height ratio (WHtR) was calculated by dividing waist circumference (cm) by height (cm).

Clinical and Laboratory Evaluations

Blood pressure (BP) was measured three times within two minutes in the sitting position after 5-minute rest through an aneroid sphygmomanometer with an appropriately sized cuff as elsewhere described [10].

Blood samples for glucose, insulin, triglycerides (TG), cholesterol, and high-density lipoprotein-cholesterol (HDL-C) were drawn after an overnight fast. These biochemical parameters were analysed in the centralized laboratory of each center, as elsewhere described [10].

All laboratories belonged to the Italian National Health System and are certified according to International Standards ISO 9000 (www.iso9000.it/) with semi-annual quality controls and inter-lab comparisons.

Definition of Severe Obesity

Obesity was defined as BMI >97 th percentile (BMI₉₇). Severe OB was defined according to the following thresholds: BMI >99 th percentile (BMI₉₉), BMI₉₇ $\geq 120\%$ or BMI Z-score > 3 of the WHO tables.

Definitions of Cardiometabolic Risk

The continuous metabolic risk score (cCMR) was expressed as Z-score and calculated by linear regression analysis. The cCMR was obtained using the sum of residual standardized for age and sex of WHtR, systolic BP, diastolic BP, TG (Ln) and HDL-C $\times -1$.

In addition, the cardiometabolic risk was analysed as a categorical variable, based on a cluster of at least two factors among hypertension, high TG, low HDL-C and high WHtR. Hypertension was defined according to the criteria of European Society of Cardiology based on 95th percentile of systolic and/or diastolic BP for age, sex, and height [11]. High TG was defined by a value above 100 mg/dL in children and 130 mg/dL in adolescents. Low HDL-C was defined by HDL-C levels < 40 mg/dL. High WHtR was defined by a value ≥ 0.65 [12].

Statistical Analyses

The normal distribution of the variables was assessed by using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as mean $\pm$ standard deviation. Variables with skewed distribution were log transformed using natural log (Ln) for statistical analyses, but they were presented as median and interquartile range for a better understanding. The sample was stratified into three mutually exclusive groups according to the following BMI cut-offs: BMI₉₇, BMI₉₉ and BMI₉₇ $\geq 120\%$. Between group comparison for continuous variables was assessed by t-test or ANOVA. Qualitative variables were presented as number and percentage (%) and compared using χ^2 test.

The diagnostic accuracy of either BMI Z-score >3 or BMI₉₇ $\geq 120\%$ to discriminate the presence of clustered cardiometabolic risk factors was assessed. Receiver operating characteristic (ROC) curve

analysis was used to evaluate accuracy (area under the curve), specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV), using 2x2 tables.

A *p* value <0.05 was considered for statistical significance. Statistical analyses were conducted using IBM SPSS Statistics software, Version 20.0 (IBM, Armonk, NY).

3. Results

The sample was represented by 3727 youths (1937 boys and 1790 girls), divided into 2225 children (age <12 years) and 1502 adolescents (age ≥12 years). Mean age was 11.2±2.4 years (range 6-17 years).

The characteristics of the three mutually exclusive categories based on different BMI derived metrics are described in Table 1. Anthropometric, clinical, and biochemical variables progressively increased from the lowest to the highest BMI category, while HDL-C levels decreased (*p* <0.0001 for all). No difference among groups was observed only for fasting glucose and total cholesterol.

Table 1. Anthropometric, clinical, and biochemical variables by different BMI derived metrics among children and adolescents with obesity and severe obesity.

	BMI ₉₇	BMI ₉₉	BMI ₉₇ ≥120%	<i>p</i> value
<i>n</i> =3727	337	757	2633	
Male gender, n (%)	124 (36.8)	339 (44.8)	1474 (56.0)	<0.0001
Prepubertal stage, n (%)	42 (12.5)	188 (24.8)	828 (31.4)	<0.0001
Age (years)	12.4±2.4	11.4±2.5	11.0±2.4	<0.0001
BMI, Kg/m ²	25.5±2.7	26.5±3.0	31.1±4.6	<0.0001
BMI Z-score	2.1±0.1	2.6±0.2	3.5±0.6	<0.0001
WHtR	0.57±0.06	0.59±0.05	0.64±0.06	<0.0001
Glucose, (mg/dL)	87.3±7.8	86.5±8.4	86.7±9.1	0.594
Insulin, (μUI/ml)	13.4 (9.5-19.1)	13.0 (9.1-18.6)	16.4 (11.7-24.1)	<0.0001
Cholesterol, (mg/dL)	160.1±33.7	156.5±30.6	157.3±30.0	0.492
HDL-C (mg/dL)	50.7±12.7	49.3±11.1	47.1±10.6	<0.0001
Triglycerides (mg/dL)	75.0 (55.0-103.0)	73.0 (55.0-98.0)	83.0 (62.0-112.0)	<0.0001
Systolic BP (mmHg)	109.8±13.7	109.6±13.0	112.7±14.1	<0.0001
Diastolic BP (mmHg)	65.5±10.0	65.2±9.3	67.3±10.0	<0.0001

Data are expressed as mean±standard deviation, median (IQ range), n (%). Abbreviations: BMI₉₇, BMI >97th percentile; BMI₉₉, BMI >99th percentile; BMI₉₇ ≥120%, BMI >120% BMI₉₇; BP, blood pressure; HDL-C, high density lipoprotein-cholesterol; WHtR, waist-to-height ratio.

Mean values of cCMR Z-score stratified in the three BMI categories are shown in Figure 1 separately by age group (children, panel a; adolescents, panel b). Differences between categories were significant for all groups (*p* <0.0001), either in children or adolescents.

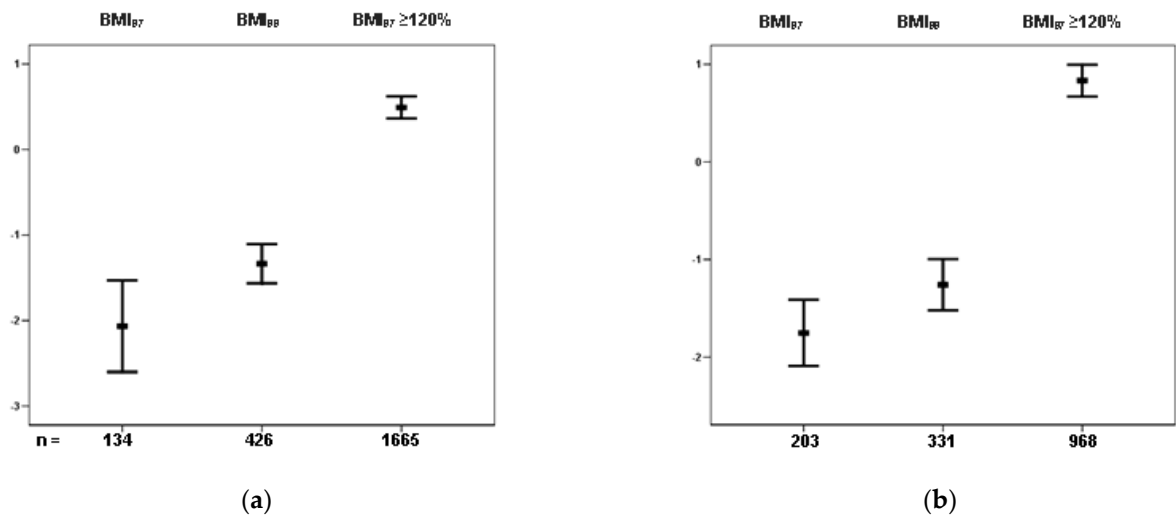


Figure 1. Continuous cardiometabolic risk Z-score in children (left panel) and adolescents (right panel) by different BMI derived metrics. Abbreviations: BMI₉₇, BMI >97th percentile; BMI₉₉, BMI >99th percentile; BMI₉₇ ≥ 120%, BMI ≥ 120% BMI₉₇.

Comparisons between groups with severe OB classified by BMI Z-score >3 or BMI₉₇ ≥ 120% are shown separately by age group in Table 2. The prevalence of severe OB as defined by the cut-off of BMI₉₇ ≥ 120%, was significantly higher than that observed by using BMI Z-score >3, both in children (74.8% vs 60.5%) and adolescents (64.4% vs 37.7%), *p* < 0.0001.

Table 2. Comparison between children or adolescents with severe obesity classified by 1.2 times BMI₉₇ or BMI Z-score >3.

n =	Children (n =2225)			Adolescents (n =1502)		
	BMI ₉₇ ≥120%	BMI Z-score >3	p value	BMI ₉₇ ≥120%,	BMI Z-score >3	p value
	1665 (74.8%)	1346 (60.5%)		968 (64.4%)	567 (37.7%)	
Male gender, n (%)	882 (53.0)	765 (56.8)	0.038	592 (61.2)	334 (58.9)	0.384
Age (years)	9.5±1.5	9.3±1.5	0.002	13.5±1.4	13.6±1.3	0.999
BMI, Kg/m ²	29.1±3.4	29.5±3.6	0.002	34.5±4.4	37.0±3.9	<0.0001
BMI Z-score	3.6±0.6	3.8±0.5	<0.0001	3.3±0.53	3.6±0.50	<0.0001
WHtR	0.64±0.06	0.65±0.06	<0.0001	0.65±0.07	0.67±0.07	<0.0001
Glucose, (mg/dL)	86.0±8.6	85.8±8.6	0.527	87.9±9.8	87.5±10.2	0.554
Insulin, (μUI/ml)	2.71±0.56	2.71±0.57	0.999	3.02±0.57	3.10±0.58	0.008
Cholesterol, (mg/dL)	158.4±29.2	158.2±29.1	0.854	154.9±30.0	155.9±31.2	0.499
HDL-C (mg/dL)	48.1±10.7	47.9±10.7	0.611	45.5±10.1	44.7±10.0	0.187
Triglycerides (mg/dL)	4.41±0.42	4.41±0.42	0.997	4.46±0.41	4.47±0.41	0.644
Systolic BP (mmHg)	109.1±13.1	108.9±13.4	0.679	118.9±13.5	120.1±13.8	0.09
Diastolic BP (mmHg)	65.4±9.5	65.4±9.6	0.999	70.6±10.2	71.4±10.4	0.143
cCMR Z-score	0.49±2.65	0.66±2.70	0.08	0.83±2.59	1.47±2.60	<0.0001

Data are expressed as mean±standard deviation, median (IQ range), n (%). Abbreviations: BMI₉₇ ≥ 120%, BMI ≥ 120% BMI₉₇; BP, blood pressure; cCMR, continuous cardiometabolic risk; HDL-C, high density lipoprotein-cholesterol; WHtR, waist-to-height ratio.

Children with severe OB defined by BMI Z-score >3 showed higher values of BMI, BMI Z-score, and WHtR than those defined by BMI₉₇ ≥ 120%, while they showed no difference with respect to individual cardiometabolic risk factors, except for a borderline difference for cCMRF (*p* = 0.08). Similar findings were found in adolescents, except for significantly higher levels of insulin and cCMR Z-score (Table 2).

Similarly, the prevalence of clustered cardiometabolic risk factors was higher in adolescents with severe Ob classified by BMI Z-score >3 ($p < 0.001$), while no substantial difference was found between the two classification methods in children (Figure 2).

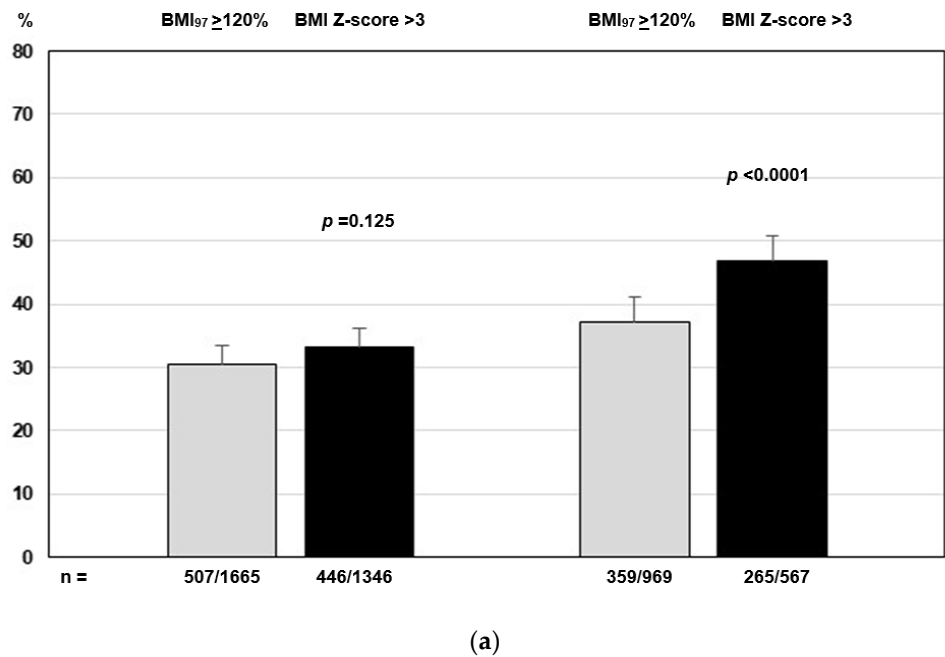


Figure 2. Proportion of youths with a cluster of cardiometabolic risk factors by BMI₉₇ ≥120% (grey bars) and BMI Z-score >3 (black bars) in children and adolescents. Abbreviations: BMI₉₇ ≥120%, BMI ≥120% BMI₉₇.

AUC, sensitivity, specificity, PPV, NPV of BMI Z-score >3 or BMI₉₇ ≥120% defined categories of severe OB for predicting clustered cardiometabolic risk are synthesized in Table 3. The AUC values were 0.60 for BMI₉₇ ≥120%, and 0.63 for BMI Z-score >3 in children, and 0.62 and 0.66 respectively in adolescents. Compared to BMI₉₇ ≥120%, BMI Z-score >3 had higher specificity and PPV, but lower sensitivity and PPN in identifying children and adolescents with clustered cardiometabolic risk factors.

Table 3. Performance of BMI₉₇ ≥120% and BMI Z-score >3 in relation to cluster of cardiometabolic risk factors.

	AUC	Sensitivity	Specificity	PPV	NPV
Children					
BMI ₉₇ ≥120%	0.60 (0.58-0.63)	0.90 (0.89-0.92)	0.30 (0.29-0.32)	0.31 (0.29-0.32)	0.90 (0.89-0.92)
BMI Z-score >3	0.63 (0.60-0.65)	0.80 (0.78-0.81)	0.46 (0.44-0.48)	0.33 (0.31-0.35)	0.87 (0.85-0.88)
Adolescents					
BMI ₉₇ ≥120%,	0.62 (0.59-0.65)	0.81 (0.79-0.83)	0.43 (0.40-0.45)	0.37 (0.35-0.40)	0.85 (0.83-0.86)
BMI Z-score >3	0.66 (0.63-0.69)	0.60 (0.57-0.62)	0.72 (0.69-0.74)	0.47 (0.44-0.49)	0.81 (0.79-0.83)

Abbreviations: BMI₉₇ ≥120%, BMI ≥120% BMI₉₇, AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value.

4. Discussion

The present study provided the empirical evidence that cardiometabolic risk factors increased with rising degrees of OB, as defined by BMI-derived metrics from the WHO system; specifically, the threshold of 120% BMI₉₇ had a stronger association with clustered risk factors compared to BMI₉₉ in children and adolescents. Furthermore, compared to BMI₉₇ ≥120%, BMI Z-score >3 was associated with worse adiposity measures either in children and adolescents, although neither definition was

significantly associated with individual cardiometabolic risk factors. On the contrary, adolescents with severe OB defined by BMI Z-score >3 had worse cCMR score and higher prevalence of clustered cardiometabolic risk factors than those defined by BMI₉₇ $\geq 120\%$.

Severe OB affects a large number of children in Europe [13]. Between 2007-2013 the prevalence of severe OB in 6- to 9-year-old school children from 21 countries of the WHO European Region ranged from 1.0% to 5.5% (WHO definition), with the highest levels (above 4%) in Southern Europe, including Italy.

As it emerged by a recent systematic review on the global prevalence of severe OB in childhood, several definitions have been used in children and adolescents [8]. In particular, BMI₉₅ $\geq 120\%$, as proposed by the CDC and endorsed by the American Academy of Pediatrics [5] and BMI ≥ 35 kg/m² were the most frequently used. Other definitions relied upon the cut-off of age- and gender-specific 99th percentile from the CDC or WHO standards, or BMI >3 SDS from the WHO system.

The drawbacks of using BMI Z-score for very high BMIs from the CDC system led to adopt the BMI₉₅ $\geq 120\%$. On the contrary, the BMI Z-score is still in use in those countries that adhered to the WHO definition, since it does not suffer from limitation associated to CDC [2]. In fact, despite both CDC and WHO used the same database from the US National Center for Health Statistics [14], some manipulations were done to build the WHO standards: measurements taken after 1973 were truncated to avoid the obesity epidemic and 3% of children with 'unhealthy' weights for heights were excluded. In addition, the SD23 restriction of the LMS (Lambda Mu and Sigma) method (i.e., the standard deviation at each age was fixed to the distance between ± 2 SD and ± 3 SD) was applied for data beyond the limits of the observed values (i.e., between -3 SD and 3 SD) [2].

Previous cross-sectional studies reported that the prevalence of several cardiometabolic risk factors, such as dyslipidemia, hypertension, type 2 diabetes and fatty liver disease was higher in individuals with severe OB compared to mild OB with any of the definition used [9,15–17]. In agreement with previous studies, anthropometric, clinical, and individual cardiometabolic risk factors (except for fasting glucose and total cholesterol) progressively worsened from the lowest to the highest BMI category, as represented by BMI₉₇ $\geq 120\%$. In particular, the cCMR score was greatly higher both in children and adolescents with severe OB defined by BMI₉₇ $\geq 120\%$ compared to BMI₉₉. These results confirm a previous study conducted by our group in a different cohort of youths with OB, where the definition of severe OB slightly varied from the definition adopted in the present study (respectively, BMI₉₅ $\geq 120\%$ instead of BMI₉₇ $\geq 120\%$) [18].

To make the situation more complicated, the definition of severe OB can be alternatively based on BMI₉₉ or BMI_{99.9} (equivalent to 3 standard deviations). Therefore, we also compared anthropometric, clinical, and individual cardiometabolic risk factors between BMI₉₇ $\geq 120\%$ to the BMI Z-score >3 . Although the prevalence of severe OB was significantly higher when the cut-off of BMI₉₇ $\geq 120\%$ was compared to BMI Z-score >3 both in children (69.7% vs 56.4%) and adolescents (63.9% vs 37.4%), both systems appeared to be interchangeable in children, without a particular superiority one to another in stratifying individuals at cardiometabolic risk. Instead, in adolescents worse cCMR scores and higher prevalence of clustered cardiometabolic risk factors were found in individuals with severe OB defined by BMI Z-score >3 compared to BMI₉₇ $\geq 120\%$. The ability to discriminate the cluster of at least two cardiometabolic risk factors between the two definitions of severe OB was modest with both definitions (AUCs ranging from 0.60 for BMI₉₇ $\geq 120\%$ in children to 0.66 for BMI Z-score in adolescents) (Table 3). Remarkably, it was quite similar to that reported by Ball et al. in a large sample of children and adolescents enrolled in the CANadian Pediatric Weight management Registry (AUC 0.62 for BMI Z-score and 0.64 for BMI₉₇ $\geq 120\%$) [19]. In our sample BMI Z-score >3 had higher specificity and PPV, but lower sensitivity and PPN in identifying individuals with clustered cardiometabolic risk factors, especially in adolescents.

Our study is not exempt of having some limitations. Youths with OB were recruited in pediatric obesity services, therefore findings cannot be extended to the general population. Moreover, BMI is not the only factor influencing the cardiometabolic risk: genetics, perinatal and early life determinants, lifestyle habits and fat distribution can also modulate the risk in children. In addition, the investigation was limited to cardiometabolic risk factors, without considering the respiratory,

musculoskeletal, or psychosocial complications associated with severe OB. Lastly, the cross sectional design of the study does not allow to assess the ability of the BMI derived metrics to predict cardiometabolic outcomes in adulthood.

5. Conclusions

Our results show that within the WHO system, the definition of severe OB based on BMI₉₇ ≥120% is superior to BMI₉₉ but it is inferior to BMI Z score >3 as far as the association between severe OB and cardiometabolic risk factors is concerned. The definition based on BMI Z-score >3 has a discriminatory advantage over of the BMI₉₇ ≥120% for identifying severely obese children at increased cardiometabolic risk, particularly in adolescents. However, the higher sensitivity of the BMI₉₇ ≥120% definition in identifying a higher number of children and adolescents with severe OB at expense of lower specificity may provide advantages in terms of early cardiovascular prevention. Pediatricians should take into consideration the implication of the use of BMI₉₉ or BMI Z-score >3 in those countries that recommend using the WHO growth reference.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the University of Campania ‘Luigi Vanvitelli’ (reference number 834/2016) for youths observed from 2003–2013 and by the Ethics Committee of the AORN Santobono-Pausilipon (reference number 22877/2020) for youths observed from 2016 to 2020.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: We encourage all authors of articles published in MDPI journals to share their research data. In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Where no new data were created, or where data is unavailable due to privacy or ethical restrictions, a statement is still required. Suggested Data Availability Statements are available in section “MDPI Research Data Policies” at <https://www.mdpi.com/ethics>.

Conflicts of Interest: The authors declare no conflicts of interest.

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