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Gender-based differences in the clustering of metabolic syndrome factors in children and adolescents

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Abstract

Background: We depicted gender-differences in metabolic syndrome (MS) clustering before and after puberty in pediatrics, in order to develop gender specific preventive strategies for childhood obesity.

Methods: We considered 1079 children and adolescents (529 females and 550 males; mean age 11.5 ± 2.8 year). According to body mass index (BMI) percentiles the subjects were classified as normal weight BMI <75th, overweight BMI 75–95th and with obesity BMI >95th. MS was diagnosed when three of the following criteria for age and sex percentiles were met: BMI >95th, triglycerides (TGs) level >95th, high-density lipoprotein-cholesterol (HDL-c) level <5th, blood pressure (blood pressure) >95th percentile, fasting blood glucose (FBG) >100 mg/dL and/or homeostatic model assessment- insulin resistance (HOMA-IR) >97.5th percentile.

Results: The prevalence of dismetabolic factors was similar in both genders, except for pathological BP, which was higher in males ($p = 0.02$). MS was detected only in patients with obesity, with a higher prevalence in pubertal than late/post-pubertal subjects ($p < 0.001$), without any significant difference between gender. In pre-puberty, the most common MS combination was obesity (HBMI) + hypertension (HBP) + hyperglycemia/insulin resistance (HGLY/IR) followed by HBMI + low HDL-levels (LHDL) + HGLY/IR versus HBMI + HBP + HGLY/IR followed by HBMI + HBP + LHDL, respectively, in females and males. In the early and late/post-pubertal periods, the most prevalent combination remained similar to pre-puberty, additionally in both sexes other combinations, such as HBMI + HTG + HBP + HGLY/IR, HBMI + HBP + LHDL + HGLY/IR, HBMI + HTG + LHDL + HGLY/IR and HBMI + HTG + LHDL + HBP + HGLY/IR were also detected, differently distributed in males and females.

Conclusions: We confirm that MS is an important consequence related to obesity, particularly in the post-puberty stage. Some gender-based differences should be considered early in order to identify specific preventive and treatment strategies.

Keywords: adolescents; children; combination; gender; metabolic syndrome; sex.

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Introduction

Metabolic syndrome (MS) is defined as a cluster of several metabolic factors including obesity, abnormalities in glucose metabolism, hypertension and dyslipidemia, which increase the risk of diabetes mellitus and cardiovascular disease [1, 2]. The development of metabolic complication in the pediatric age is directly linked to both excessive weight gain and early onset of obesity [3–6].

There are key aspects of metabolic homeostasis that are regulated differently in males and females [7] and it has been reported that the prevalence of different combinations of MS factors are otherwise expressed by gender [8, 9].

The major contributors of gender dimorphisms in glucose, lipid and energy homeostasis are "activation" effects of estrogens and androgens acting on their receptors after the onset of puberty. There are several studies demonstrating differences in the incidence of cardio-metabolic risk factors in obese children according to their gender, as well as pubertal status [10–17], however, the combinations and interactions of the clustered MS risk factors, are not fully detailed in the pediatric age.

The aim of this cross-sectional study was to describe the gender differences in MS clustering before and after puberty in children and adolescents, in order to identify early childhood prevention intervention and treatments for at high risk children.

Subjects and methods

Subjects

From October 2016 to October 2018, 1079 Caucasian children and adolescents (529 females and 550 males) aged 2–18 years, referred to our outpatients' clinic for auxological evaluation (growth assessment, rapid weight changes) or for obesity by their general practitioner or primary care pediatrician, were consecutively included in the study.

According to the Italian Society for Pediatric Endocrinology and Diabetology (ISPED) criteria [18], the subjects were classified as normal weight, body mass index (BMI) <75th percentile; overweight, BMI 75–95th percentile; with obesity, BMI >95th percentile [19]. This classification was preferred since the ISPED and International Obesity Task Force (IOTF) systems of overweight and obesity assessment are similar and more specific in identifying obese children/adolescents with clustered cardiometabolic risk factors compared to the World Health Organization (WHO) criteria [18].

Exclusion criteria were: use of any medication, concomitant chronic or acute illnesses, known secondary obesity condition.

The study protocol was approved by the Ethical Committee of Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. The study was conducted in accordance with the 1975 Helsinki Declaration, as revised in 2008. All participants, or their responsible guardians, were asked to sign a written consent after being informed about the nature of the study.

Physical examination

Physical examination of the participants included evaluation of height, weight, waist circumference (WC), BMI (calculated as body weight in kilograms divided by height in meters squared), pubertal stage according to Marshall and Tanner (stage characteristics corresponding to Tanner stage 1) [20, 21], and blood pressure (BP) measurement. Waist to height ratio (WHtR) was also calculated to estimate adiposity distribution.

Anthropometric measurements were performed as previously reported [22]. Blood pressure (BP) was measured using a mercury sphygmomanometer, after the participant sat comfortably for 5 min, with an appropriately sized cuff on the right arm, which was slightly flexed at heart level, for two consecutive times. The second BP measurement was used for analysis [22].

Pubertal maturation was assessed using the pubertal staging 1–5, for breast development, pubic hair and genitalia determined by visual inspection as described by Marshall and Tanner (Tanner staging). Clinical examination was performed by an experienced endocrinologist pediatrician (VC) to guarantee the quality assurance. Pubertal development was classified as: prepubertal: boys with genital Tanner stage 1, girls with breast Tanner stage I; early pubertal: boys with genital Tanner stage 2–3; girls with breast Tanner stage 2–3; late/post pubertal: boys with genital Tanner stage ≥4; girls with breast Tanner stage ≥4).

Elevated systolic blood pressure (SBP) or diastolic blood pressure (DBP) was defined when values exceeded the 95th percentile for age and sex [23].

Biochemical parameters and definitions

Blood samples were drawn in the morning, after an overnight fast. Metabolic blood assays included fasting blood glucose (FBG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), triglycerides (TGs), insulin, aspartase aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT).

Plasma glucose was measured using the hexokinase-G-6-phosphate dehydrogenase method (Siemens Healthcare Diagnostics, Camberley, UK) with a chemistry analyzer (Advia XPT, Siemens, Camberley, UK). The TC was determined by an enzymatic method (Advia XPT, Siemens Healthcare Diagnostics, Camberley, UK). HDL-c was measured by the selective detergent method followed by enzymatic reactions (Siemens Healthcare Diagnostics, Camberley, UK). TG concentration was measured by the glycerol phosphatase oxidase method (Siemens Healthcare Diagnostics, Camberley, UK). Serum insulin was determined by a solid-phase, two-site chemiluminescent immunometric assay with an immunochemistry analyzer (Immulite 2000, Siemens Healthcare Diagnostics, Camberley, UK). AST, ALT and GGT were measured with a chemistry analyzer (Advia XPT, Siemens Healthcare, Camberley, UK) equipped with dedicated reagents; the method for the transaminase assay is based on nicotinamide adenine dinucleotide phosphate (NADH) monitoring by ultraviolet (UV) detection without addition of P-5′-P. The method for the GGT assay is based on the transfer of the gamma-glutamyl group from L-gamma-glutamyl-3-carboxy-4-nitroaniline to the glycilglycine acceptor, to yield 3-carboxy-4-nitroaniline [22].

Elevated FBG was defined when values exceeded 100 mg/dL and impaired insulin sensitivity (ISI). Insulin resistance was determined by the homeostasis model assessment for insulin resistance (HOMA-IR) using the formula: insulin resistance = (insulin × glucose)/22.5. Impaired insulin sensitivity was defined with HOMA-IR whenever exceeding the 97.5th percentile for age and sex and for Italian children and adolescents [24].

Triglyceride-glucose index (TyG index) was evaluated using the formula (ln[fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2]), as a surrogate marker of IR and predictor of diabetes, TyG index was considered pathological with a cutoff exceeding 7.88, according to Vieira Ribeiro [25].

Abnormal hepatic function was defined with pathological increase of ALT and AST and/or GGT.

As previously reported [5, 6], we diagnosed MS according to the modified criteria from the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATPIII), the WHO and

the International Diabetes Federation. Patients were classified as having MS if they met three of the following criteria for age and sex: BMI >95th percentile, TG level >95th percentile, HDL-c level <5th percentile, SBP and/or DBP >95th percentile, FBG >100 mg/dL and/or HOMA-IR >97.5th percentile. As previously described [5], we used BMI as a criterion for MS as it correlates with visceral fat, blood pressure and dyslipidemia; furthermore, BMI percentiles for the Italian population are available [19]. Although WC in children is a good predictor of visceral adiposity, it might not detect differences in body proportions related to puberty. WC percentile nomograms in children have only recently become available for some ethnic groups but are not available for all and there is no internationally accepted classification of age-specific cut-off values [26, 27]. Pathological level of FBG and/or alteration of ISI were selected as markers of glucometabolic derangement, as impaired glucose tolerance and/or diabetes is rare in childhood and IR precedes glucose abnormalities playing an important role in the pathogenesis of normal glucose tolerance to impaired glucose tolerance transition [28]. The euglycemic-hyperinsulinemic clamp is the gold standard for measuring IR, but this study is invasive, time consuming and difficult to apply to children in a clinical setting. For these reasons, we used HOMA-IR as a surrogate marker of IR/sensitivity [29]. Finally, blood pressure and fasting lipid levels were compared with population norms adjusted for age and sex.

Statistical analysis

Power consideration: considering about 50% of patients are males and about one third are prepuberal, about 1070 patients allows more than 80% power to find significant ($p < 0.05$) differences between groups in proportion of MS and its components of about 5–10%.

Qualitative variables were described as counts and percentage. The Shapiro-Wilk test was used to test the normal distribution of quantitative variables. As quantitative variables were normally distributed, the results were expressed as the mean value and standard deviation (SD). To study the association between clinical and metabolic data as independent variables and sex and pubertal stage (as explanatory variables) univariate linear regression models were fitted considering also an interaction term between gender and pubertal stage.

To study the association between pathological auxological and metabolic parameters and gender and pubertal stage (as explanatory variables) univariate binary logistic regression models were fitted considering also an interaction term between gender and pubertal stage.

All tests were two-sided and a p-value below 0.05 was considered statistically significant. The data analysis was performed with the STATA statistical package (release 15.1, 2017, Stata Corporation, College Station, TX, USA).

Results

Clinical and metabolic data

No statistical differences were found between males and females for age and pubertal stage.

In Tables 1 and 2, clinical and metabolic data of the enrolled subjects and regression analysis of the parameters are reported.

Compared to females, males showed higher WC ($p = 0.003$), glucose levels, (<0.001), SBP ($p < 0.01$), triglyceride glucose (TyG) index ($p = 0.04$) and WHtR ($p = 0.007$), Table 2.

Compared to prepubertal subjects, early pubertal patients showed significant differences in all parameters included in the evaluation except for BMI-standard deviation score (SDS), WHtR, HDL-c and TC, ALT and GGT and late/post-pubertal patients in all parameters except for HDL-c and TC, DBP, ALT and GGT, Table 2.

BMI-SDS ($p < 0.001$), insulin and HOMA-IR ($p < 0.001$), WHtR ($p < 0.01$), BP ($p < 0.001$) were higher in late/post-pubertal than in early pubertal patients.

The difference between genders is evident both before and during puberty for TyG ($p = 0.04$) and WHtR ($p = 0.04$) in early puberty and for insulin ($p = 0.01$), HOMA-IR ($p < 0.01$), HDL-c ($p = 0.01$), WHtR ($p = 0.02$) and ALT ($p = 0.04$) in late/post-puberty, Table 2.

Clustering of dismetabolic factors

Based on the BMI percentiles threshold, 190 out of 1079 patients (17.6%) were normal weight, 271 (25.11%) overweight and 618 (57.27%) affected by obesity. The distribution was not significantly different between gender and pubertal stages.

The percentage of patients with pathological auxological and metabolic parameters and the logistic analysis are reported in Tables 3–4.

The prevalence of dismetabolic factors was similar in males and females except for pathological BP that was higher in males ($p = 0.01$).

Compared to pre-pubertal children, early pubertal subjects showed a higher prevalence of pathological HOMA-IR ($p = 0.001$), TyG index ($p = 0.005$) and WHtR ($p = 0.01$) and late/post pubertal patients revealed a higher prevalence of pathological HOMA-IR ($p < 0.001$), HDL-c ($p = 0.05$), BP ($p = 0.01$) and TyG index ($p = 0.008$) without difference between gender, Table 4.

The prevalence of pathological parameters is not different in early and late/post-pubertal subjects, except for HOMA-IR ($p = 0.01$).

MS was detected only in patients with obesity (14.27%). The prevalence of MS was similar in prepubertal and early pubertal subjects (10.3% vs. 11.8%, $p = 0.1$) and higher in late/post-pubertal (27.6% vs. 10.3 $p < 0.001$ and 27.6% vs. 11.8%, $p < 0.01$), without any significant difference between males and females.

Table 1: Clinical and biochemical parameters of the enrolled patients according to gender and pubertal stage: descriptive statistic.

Parameters	All patients (n=1079)			Females (n=529)			Males (n=550)		
	Pre-pubertal (n=329)	Early pubertal (n=547)	Late pubertal (n=203)	Pre-pubertal (n=172)	Early pubertal (n=265)	Late pubertal (n=92)	Pre-pubertal (n=157)	Early pubertal (n=282)	Late pubertal (n=111)
Age, years	8.5±2.2	11.88±1.31	15.45±1.42	8.1±2.0	11.71±1.37	15.48±1.21	9.0±2.2	12.04±1.24	15.42±1.58
BMI-SDS	1.42±1.08	1.34±1.18	1.82±1.29	1.39±0.95	1.40±1.10	1.96±1.31	1.44±1.21	1.29±1.25	1.70±1.27
WC, cm	74.2±11.7	82.09±13.27	92.96±15.24	71.4±9.6	81.15±12.56	90.75±15.69	77.5±13.0	82.98±13.87	94.56±14.79
FBG, mg/dL	79.3±9.8	80.51±9.34	82.34±9.8	77.3±10.5	79.44±10.18	81.58±13.77	81.6±8.4	81.54±8.34	82.98±10.38
Insulin (mU/mL)	8.80±6.0	14.24±12.99	19.93±26.58	9.1±6.5	14.68±10.60	13.82±14.92	8.5±5.4	14.24±12.99	16.47±13.48
HOMA-IR	1.76±1.37	2.83±2.72	4.25±6.74	1.8±1.5	1.80±1.49	2.91±2.19	1.7±1.2	1.72±1.22	2.75±3.14
HDL-c, mg/dL	47.45±10.1	47.52±10.85	43.58±10.45	47.40±9.9	47.36±11.16	46.22±10.40	47.5±10.2	47.51±10.22	47.68±10.53
TC, mg/dL	160.6±26.8	157.47±30.10	158.59±10.85	158.5±27.4	156.91±28.92	161.63±33.49	162.8±26.1	158.0±31.23	156.02±28.02
TGs, mg/dL	70.5±40.5	75.92±38.11	85.21±48.63	68.4±35.4	77.84±36.86	86.31±55.46	72.8±45.5	74.07±39.26	84.30±42.38
SBP, mmHg	104.1±11.7	109.92±11.92	118.89±12.48	102.3±10.2	109.28±11.79	117.13±12.88	106.0±12.7	110.52±12.03	120.32±12.01
DBP, mmHg	64.7±8.7	67.72±8.63	73.77±7.98	64.2±8.8	67.31±8.98	73.02±8.62	65.3±8.6	68.09±8.28	74.39±7.41
TGs index	7.80±0.50	7.92±0.47	8.02±0.52	7.7±0.4	7.93±0.46	8.0±0.55	7.8±0.5	7.90±0.49	8.03±0.50
WHtR	0.50±0.10	0.53±0.07	0.55±0.08	0.5±0.1	0.53±0.07	0.56±0.09	0.6±0.1	0.53±0.08	0.55±0.08
AST, mU/mL	24.12±8.77	21.75±6.68	21.53±7.96	24.1±10.7	21.26±7.51	20.46±7.51	24.1±5.7	22.26±4.80	22.40±8.25
ALT, mU/mL	21.3±17.0	19.90±13.60	23.43±16.05	21.7±21.0	19.66±16.43	20.69±13.60	20.7±10.0	20.13±10.01	25.74±17.59
GGT, mU/mL	17.0±12.3	16.19±8.81	18.35±9.21	16.9±10.2	15.36±6.16	16.15±6.82	17.2±14.4	17.04±10.81	20.18±10.49

AST, aspartate transaminase; ALT, alanine aminotransferase; BMI-SDS, body mass index-standard deviation score; DBP, diastolic blood pressure; FBG, fasting blood glucose; GGT, gamma glutamyl transpeptidase; HDL-c, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment- insulin resistance; SBP, systolic blood pressure TC, total cholesterol; TGs, triglycerides; WC, waist circumference; WtHR, waist to height ratio.

Table 2: Clinical and biochemical parameters of the enrolled patients according to gender and pubertal stage: regression analysis.

Parameters	p Coefficient (95%CI)				
	Females vs. males	Pre-pubertal vs. early pubertal	Pre-pubertal vs. late pubertal	Gender and early puberty interaction	Gender and late puberty interaction
BMI-SDS	0.71	0.95	<0.001	0.34	0.14
	0.05 (−0.21 to 0.30)	0.01 (−0.22 to 0.23)	0.56 (0.27− 0.86)	−0.15 (−0.48 to 0.17)	−2.36 (−8.24 to 3.51)
WC, cm	0.003	<0.001	<0.001	0.06	0.43
	6.18 (2.10–10.25)	9.77 (6.61–13.93)	19.37 (15.11–23.63)	−4.34 (−8.94 to 0.25)	−4.34 (−8.94 to 0.25)
FBG, mg/dL	<0.001	0.03	0.001	0.11	0.10
	4.29 (2.12–6.46)	2.13 (0.21–4.05)	4.28 (1.75–6.81)	−2.19 (−4.94 to 0.55)	−2.89 (−6.40 to 0.60)
Insulin, mU/mL	0.72	<0.001	<0.001	0.90	0.01
	−0.59 (−3.92 to 2.74)	5.60 (2.68–8.52)	15.05 (11.18–18.85)	−0.26 (−4.43 to 3.90)	−7.03 (−12.35 to 1.70)
HOMA-IR	0.83	0.002	<0.001	0.87	<0.01
	−0.08 (−0.86 to 0.70)	1.10 (0.42–1.79)	3.48 (2.58–4.39)	−0.77 (−1.05 to 0.55)	−1.81 (−3.06 to 2.34)
HDL-c, mg/dL	0.93	0.97	0.40	0.89	0.01
	0.10 (−2.33 to 2.54)	−0.36 (−2.13 to 2.06)	−1.17 (−3.93 to 1.58)	0.21 (−2.82 to 3.24)	−5.0 (−8.86 to 1.15)
TC, mg/dL	0.18	0.57	0.41	0.43	0.06
	4.30 (−2.10 to 10.73)	−1.61 (−7.31 to 4.09)	3.11 (−4.37 to 10.60)	−3.21 (−11.34 to 4.91)	−9.91 (−20.30 to 0.47)
TGs, mg/dL	0.34	0.02	0.001	0.16	0.38
	4.37 (−4.65 to 13.39)	9.45 (1.50–13.37)	17.92 (7.47–28.37)	−8.14 (−19.50 to 3.22)	−6.38 (−20.87 to 8.11)
SBP, mmHg	0.01	<0.001	<0.001	0.15	0.80
	3.72 (−0.87 to 6.56)	6.98 (4.56–9.40)	14.84 (11.68–17.99)	−2.48 (−5.89 to 0.93)	−0.53 (−4.88 to 3.81)
DBP, mmHg	0.3	<0.001	0.15	0.79	0.86
	1.09 (−0.93 to 3.12)	3.09 (1.36–4.82)	8.80 (6.53–11.06)	−0.31 (−2.76 to 2.12)	0.27 (−2.84 to 3.38)
TG index	0.04	<0.001	<0.001	0.04	0.36
	0.10 (0.00–0.21)	0.18 (0.08–2.27)	0.25 (0.13–0.37)	−0.13 (−0.26 to 0.008)	−0.07 (−0.25 to 0.09)
WHtR	0.006	0.74	<0.001	0.04	0.02
	0.03 (0.00–0.05)	0.18 (0.08–2.27)	−0.003 (−0.02 to 0.37)	−0.13 (−0.26 to 0.01)	−0.04 (−0.07 to 0.005)
AST, mU/mL	0.95	<0.001	0.001	0.37	0.18
	−0.05 (−1.95 to 1.84)	−2.88 (−4.47 to 1.28)	−3.68 (−5.78 to 1.57)	1.05 (−1.28 to 3.38)	1.99 (−0.95 to 4.94)
ALT, mU/mL	0.59	0.19	0.62	0.52	0.04
	−1.03 (−4.81 to 2.74)	−2.08 (−4.80 to 2.72)	−1.05 (−5.23 to 3.12)	1.50 (−3.12 to 6.13)	6.08 (0.20–11.96)
GGT, mU/mL	0.79	0.15	0.59	0.39	0.06
	0.33 (−2.16 to 2.83)	−1.54 (−3.63 to 0.54)	−0.74 (−3.51 to 2.01)	1.34 (−1.72 to 4.40)	3.68 (−0.19 to 7.57)

Abbreviations as for Table 1.

Table 3: Prevalence of the pathological parameters in the enrolled patients according to gender and pubertal stage.

Parameters	Females			Males		
	Prepubertal	Early pubertal	Late pubertal	Prepubertal	Early pubertal	Late pubertal
BMI >95° centile	50.58%	53.21%	78.26%	60.51%	53.55%	64.86%
FBG >100 mg/dL	1.74%	1.51%	5.43%	1.27%	1.06%	1.80%
HOMA-IR >97° centile	20.93%	20.93%	31.32%	14.65%	15.29%	24.82%
HDL-c < 5° centile	9.88%	14.34%	18.48%	11.46%	12.77%	26.13%
TC >95° centile	11.63%	7.17%	13.04%	13.38%	10.28%	9.01%
TGs >95° centile	5.23%	4.15%	5.32%	2.55%	10.87%	8.11%
BP >95° centile	9.88%	13.96%	20.65%	19.75%	17.73%	25.23%
TG index >7.88	37.21%	50.94%	54.35%	51.82%	49.65%	63.06%
WHtR >0.5	41.86%	54.34%	47.83%	41.40%	56.03%	54.05%
Pathological liver enzymes	5.23%	4.53%	8.70%	3.18%	3.90%	9.01%

Abbreviations as for Table 1.

Table 4: Pathological parameters according to gender and pubertal stage: logistic regression.

Parameters	p-Value OR (95%CI)				
	Females vs. males	Pre-pubertal vs. early pubertal	Pre-pubertal vs. late pubertal	Gender and early puberty interaction	Gender and late puberty interaction
BMI >95° centile	0.75	0.43	0.21	0.29	0.68
	1.09 (0.62–1.91)	1.23 (0.74–2.02)	1.58 (0.77–3.24)	0.68 (0.34–1.39)	0.81 (0.31–2.17)
FBG > 100 mg/dL	0.73	0.84	0.11	0.29	0.1
	0.72 (0.11–4.40)	0.86 (0.19–3.90)	3.23 (0.75–313.86)	0.97 (0.09–10.11)	0.43 (0.03–5.10)
HOMA-IR >97° centile	0.14	0.01	<0.001	0.86	0.95
	0.64 (0.36–1.15)	1.72 (0.01–1.09)	3.17 (1.82–5.50)	1.06 (0.53–2.09)	1.02 (0.45–2.27)
HDL-c <5° centile	0.64	0.17	0.05	0.47	0.59
	1.10 (0.58–2.38)	1.52 (0.83–2.80)	2.06 (0.99–4.27)	0.72 (0.31–1.71)	1.30 (0.49–3.44)
TC >95° centile	0.63	0.11	0.73	0.60	0.30
	1.17 (0.60–2.25)	0.58 (0.30–1.13)	1.14 (0.53–2.45)	1.26 (0.51–3.08)	0.56 (0.18–1.69)
TGs >95° centile	0.22	0.59	0.09	0.17	0.58
	0.47 (0.14–1.56)	0.78 (0.31–1.93)	2.20 (0.86–5.64)	2.73 (0.64–11.55)	1.52 (0.33–7.03)
BP >95° centile	0.01	0.20	0.01	0.18	0.23
	2.24 (1.18–4.23)	1.47 (0.80–2.72)	2.37 (1.16–4.38)	0.58 (0.26–1.29)	0.57 (0.22–1.43)
TG index >7.88	0.08	0.005	0.008	0.12	0.95
	1.46 (0.94–2.27)	1.75 (1.18–2.59)	2.00 (1.20–3.35)	0.64 (0.37–1.99)	0.97 (0.47–1.99)
WHtR >0.5	0.93	0.01	0.35	0.31	0.74
	0.98 (0.63–1.52)	1.65 (1.12–2.43)	1.27 (0.76–2.11)	1.09 (0.62–1.89)	1.30 (0.64–2.65)
Pathological liver enzymes	0.36	0.73	0.28	0.61	0.46
	0.59 (0.19–1.81)	0.85 (0.35–2.08)	1.72 (0.64–4.63)	1.43 (0.35–5.78)	1.74 (0.39–7.66)

Abbreviations as for Table 1.

Combination of MS components

As reported in Figure 1 and Table 5, dismetabolic factors presented alone or associated with one to four other parameters, with different combinations according to gender and puberty.

In pre-puberty, the most common combination was obesity (HBMI) + hypertension (HBP) + hyperglycemia/insulin resistance (HGLY/IR) followed by HBMI + low HDL-levels (LHDL) + HGLY/IR in females and HBMI + HBP + HGLY/IR followed by HBMI + HBP + LHDL in males (Table 5).

As reported in Table 5, in the early and late/post-pubertal period, the most prevalent combination remained similar to pre-puberty, additionally in both sexes other combinations, such as HBMI + HTG + HBP + HGLY/IR, HBMI + HBP + LHDL + HGLY/IR, HBMI + HTG + LHDL + HGLY/

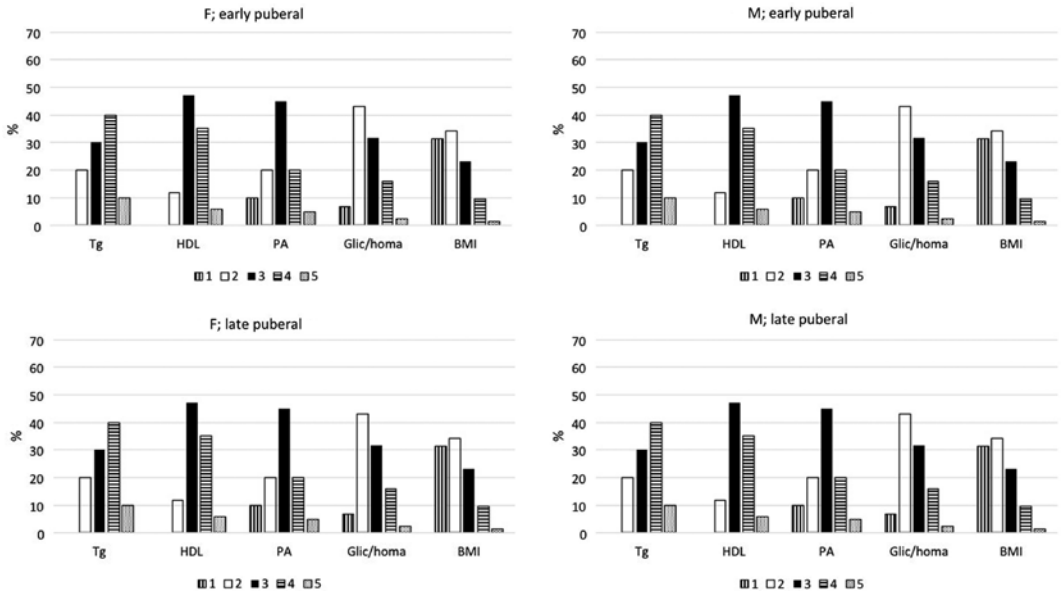

Figure 1: Distribution of combination of 1–5 pathological metabolic syndrome components according to pubertal stage and gender. (BMI, body mass index; Glyc, glycemia; HOMA-IR, homeostasis model assessment for insulin resistance; HDL-Chol, HDL-cholesterol; BP, blood pressure).

Table 5: Combination of metabolic syndrome components according to pubertal stage and gender.

Combinations	Prepubertal		Early pubertal		Late pubertal	
	Females	Males	Females	Males	Females	Males
Three components						
HBMI + HTG + HGLY/IR	6.67%	0%	5.56%	0%	8%	0%
HBMI + HTG + HBP	6.67%	0%	2.78%	0%	0%	3.03%
HBMI + HTG + LHDL	1.33%	5.56%	2.78%	0%	0%	3.03%
HBMI + LHDL + HBP	0%	33.3%	0%	6.9%	8%	12.12%
HBMI + LHDL + HGLY/IR	26.67%	16.67%	36.11%	20.69%	20%	24.24%
HBMI + HBP + HGLY/IR	40%	38.89%	30.56%	17.24%	28%	24.24%
Four components						
HBMI + HTG + LHDL + HGLY/IR	0%	0%	2.78%	10.34%	12%	6.06%
HBMI + HTG + HBP + HGLY/IR	0%	0%	2.78%	6.9%	4%	3.03%
HBMI + LHDL + HBP + HGLY/IR	6.67%	5.56%	13.89%	27.59%	12%	18.18%
Five components						
HBMI + HTG + LHDL + HBP + HGLY/IR	0%	0%	2.78%	10.34%	4%	6.06%

HBMI, obesity (BMI >95° centile); HTG, hypertriglyceridemia (TG >95° centile); LHDL-c, low levels of high density lipoprotein cholesterol (HDL-c <5th centile); HBP, hypertension (Blood pressure >95th centile); HGLY/IR, hyperglycemia (FBG >100 mg/dL) and/or insulin resistance (HOMA-IR > 97th centile).

IR and HBMI + HTG + LHDL + HBP + HGLY/IR were also detected, differently distributed in males and females.

Discussion

The present study focused on the prevalence and characteristics of MS in a pediatric population according to gender and pubertal status. We confirmed a higher prevalence of MS in children with obesity compared to normal weight ones as well as in late/post-pubertal than in pre-pubertal subjects, without any significant gender difference. Though the most common combination of MS components does not differ by gender, some sex-based differences and an increased number of MS components at early and late/post-puberty were detected.

MS is defined by a constellation of physiological, biochemical, clinical and metabolic factors that directly increase the risk of atherosclerosis, type 2 diabetes mellitus (T2DM), and all-cause mortality [1–6].

In the pediatric age, it is difficult to estimate MS prevalence as many different criteria have been used in multiple definitions. The literature reports prevalence ranging from 0.2% to 38.9%, with a median prevalence of 11.9% (range 2.8–29.3%) and 29.2% (range 10–66%), respectively, in overweight children and in those with obesity; for non-obese, non-overweight populations, the range was 0–1% [2].

We noted a higher prevalence of MS in prepubertal than late/post-pubertal children with obesity. Although the pathogenesis of MS is not completely understood, recent data suggest that interaction between obesity, IR and inflammation play a key-role in the development [15]. Notably, puberty is associated with a progressive marked decrease in insulin sensitivity and this normal tendency for IR during puberty may be considered a natural cofactor for the development of MS [30].

As far as gender distribution, published reports showed interesting differences in adults [31, 32]. Results are mixed showing, on the one hand, a higher MS incidence in males [31, 32] and on the other hand, a higher MS incidence in females [33, 34]. These conflicting results are probably due to an intrinsic sexual dimorphism in MS susceptibility, which probably relates to various factors, including the influence of androgens and estrogens on a multitude of metabolic and vascular biological processes [35]. Besides, although androgens and estrogens are the main sex hormones, respectively, for males and females, we should not forget that they are present in both genders, albeit in different concentrations, exerting different effects. Additionally, gender differences on gene expression (especially genes located on the X chromosome) may predispose to different cardio-metabolic risks [35]. Yet environmental factors and lifestyle behaviors have been shown to be implicated.

In children and adolescents, only a limited number of studies reports gender differences on metabolic risk factors for MS [10–13]. Our results confirm data previously published, showing no significant gender differences in MS prevalence [11, 12], however, the prevalence of some MS components, such as high SBP, was higher in males than in females. In our population, children with obesity did not exhibit a higher impaired fasting glucose in males nor a higher predominance of IR in females [36]. Despite sex hormone levels, androgen/estrogen balance may play an important role in the development of MS; also in children and adolescents [37, 38], the different impact of gender on MS in the pediatric age, supports the hypothesis that polygenic contribution is probably of utmost importance, along with hormonal factors. Collection of data on genomics, metabolomics, gut microbiota besides deep phenotyping and environmental variables, including diet and lifestyle, may better explain inter- and intra-individual differences, upgrading a stratified level of diagnosis and intervention by means of conventional guidelines for population subgroups to a precision individual approach level of diagnosis and tailored prevention/treatment interventions.

As reported in adults [39], different combination patterns of MS components are detected according to gender, moreover the most frequent combination pattern of MS is obesity + hypertension + hyperglycemia/IR both in females and males. These data confirm that IR and compensatory hyperinsulinemia is frequent in the pediatric age and support the hypothesis that IR could be a key factor linking obesity to the onset of the metabolic comorbidities also in the pediatric age. Additionally, the results identify hypertension as a common manifestation of the metabolic disturbances associated with IR and hyperinsulinemia. The causative role of insulin in hypertension development is still questioned [5, 6]; hypertension could be secondary to a combination of IR, autonomic dysfunction, abnormal vascular structure and function related to a dysregulated production of specific adipokines in subjects with obesity.

At puberty, in our population a rising number of MS components was observed, with different percentages at early and late/post-pubertal stage, supporting a higher risk for persistence throughout adult life and confirming that a prompt identification and treatment of metabolic complications in pediatric obesity is recommended both for the present and future health of the child [5, 6]. However, the authors acknowledge some limitations of the study, including the possible confounders for MS development such as physical activity, dietary habits and socioeconomic status, that should be considered in future research for a deeper and more comprehensive understanding. Secondly, it should be clear that this cross-sectional study may not provide definite information but can offer a hook for future investigations with longitudinal studies that are more likely to suggest cause and effect as for MS medical complications development. The study was performed on a clinical population and not on a general one. This is a study limitation as far as prevalence is concerned, as we acknowledge that it is not representative for the whole pediatric population. On the other hand, it is necessary to recognize the difficulty to recruit subjects from the general population for studies with invasive measurements such as blood draw, that, among

other things, are expensive and not supported by the health care system. Finally, the concept of cardiovascular risk factors stability during puberty progression remains unsolved. Reinehr et al. [14, 16] described that changing from mid- to late-puberty is associated with improvement of these factors; on the other hand, it has been reported that metabolic alterations do not revert to prepubertal values [40, 41]. We noted some differences in the distribution of the dismetabolic parameters between early and late/post-puberty, moreover in our pediatric population it is not possible to define the evolution of these factors. However, our study provides an analysis of a considerable sample size useful to provide important information for future longitudinal cohort studies. In addition it delivers evidence on occurrence and exposure, useful for assessment and interventions tailored for children with obesity at high risk of metabolic and cardiovascular disease.

Our results indeed confirm that MS is an important consequence related to obesity, particularly in the post-puberty period. No significant difference in the prevalence of MS was noted between females and males, however, some gender-based differences observed in our sample should be investigated more and considered in order to develop gender specific preventive strategies, particularly when puberty begins.

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