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Clinical Study

Metabolic Syndrome in Italian Obese Children and Adolescents: Stronger Association with Central Fat Depot than with Insulin Sensitivity and Birth Weight

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Aim. To evaluate whether body fat distribution, birth weight, and family history for diabetes (FHD) were associated with metabolic syndrome (MetS) in children and adolescents. *Methods*. A total of 439 Italian obese children and adolescents (5–18 years) were enrolled. Subjects were divided into 2 groups: prepubertal and pubertal. MetS was diagnosed according to the adapted National Cholesterol Education Program criteria. Birth weight percentile, central obesity index (measured by dual-energy X-ray absorptiometry), insulin sensitivity (ISI), and disposition index were evaluated. Multivariate logistic regression models were used to determine variables associated with MetS. *Results*. The prevalence of MetS was 17%, with higher percentage in adolescents than in children (21 versus 12%). In the overall population, central obesity index was a stronger predictor of MetS than insulin sensitivity and low birth weight. When the two groups were considered, central fat depot remained the strongest predictor of MetS, with ISI similarly influencing the probability of MetS in the two groups and birth weight being negatively associated to MetS only in pubertal individuals. Neither FHD nor degree of fatness was a significant predictor of MetS. *Conclusion*. Simple clinical parameters like increased abdominal adiposity and low birth weight could be useful tools to identify European obese adolescents at risk for metabolic complications.

1. Introduction

In Western countries, the prevalence of paediatric obesity and comorbidities, which cluster together in the metabolic syndrome (MetS) [1], is going to reach epidemic proportions. Data from the National Heart Lung and Blood Institute Lipid Research Clinics and the Princeton Prevalence Study (1973–1976) and Princeton Follow-up Study (2000–2004) show that MetS in 5- to 19-year olds represents a risk factor for cardiovascular disease in adulthood [2]. This finding highlights the importance of early recognition of MetS in obese children as a strategy for primary prevention of cardiovascular disease later in life.

Clinical studies have shown that low birth weight increases the risk of MetS in adulthood [3]. The association between birth weight and MetS in childhood is far to be clear, and results are controversial, with studies showing a strong [4–6] or a weak [7–9] association between low or high birth weight and MetS.

Moreover, several reports indicate that family history of diabetes and increased abdominal fat adiposity are strong risk factors for MetS since childhood [5, 10–13].

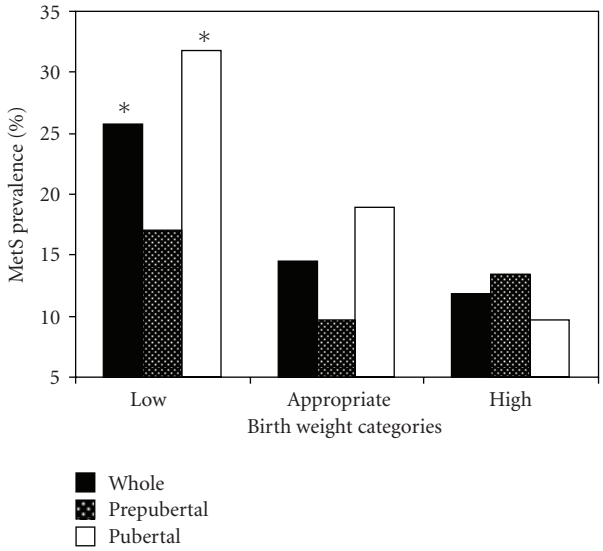

Figure 1: Prevalence of metabolic syndrome according to birth weight categories SGA, AGA, and LGA denoting small, appropriate, and large birth weight individuals, respectively. Symbols refer to comparison (Chi-square test) of prevalence of metabolic syndrome among birth weight categories, in the whole population, prepubertal subjects, and pubertal subjects. $^*P < .05$

Additionally, the marked decrease of insulin sensitivity associated with the onset of puberty in growing individuals [14, 15] may act as a further risk factor for the development of metabolic comorbidities, particularly in obese subjects. It is not clear if onset of puberty and its progression are characterized by different determinants of MetS in adolescents, compared to children.

The aim of the study was to evaluate whether family history of type 2 diabetes (FHD) in first-degree relatives, either low or high birth weight, and increased central body fat depot are independent risk factors for the development of MetS in Italian obese children and adolescents.

2. Methods

2.1. Study Population. The children who participated in the present cross-sectional investigation are a subsample of an ongoing longitudinal study exploring risk factors for the development of type 2 diabetes in young Italian subjects.

Obese children and adolescents, referred to the Endocrinology and Diabetes Unit of Bambino Gesù Children's Hospital for obesity from January 2003 to January 2010, were included in the present investigation if they met the following criteria: (1) being overweight or obese according to the International Obesity Task Force [16]; (2) absence of underlying diseases; (3) Italian origin (all four grandparents of Italian descent); (4) availability of data relative to gestation, birth, and FHD among first-degree relatives. Moreover, as we were interested in the role of fetal factor in the development of metabolic comorbidities [17], low and high birth weights (as defined below) were additional selection factors. Participants were not following a weight-reducing diet, taking any medication, or carrying a previous clinical diagnosis known to influence body composition, glucose metabolism, physical activity, or dietary intake.

Information on birth weight, FHD, and gestational diabetes was obtained. Birth weight was based on information recorded at the time of birth. The gestational age was determined by ultrasound in the first trimester, if available, and otherwise calculated from the date of the last menstruation. Weight at birth was converted into percentiles for gestational age and sex, according to the Italian birth weight curves [18]. Participants were defined on the basis of their birth weight percentile as small for gestational age (SGA) (birth weight $\leq$10th percentile), appropriate for gestational age (AGA) (birth weight >10th and <90th percentile), and large for gestational age (LGA) (birth weight $\geq$90th percentile). FHD was defined by the presence of type 2 diabetes in at least one parent. FHD, maternal gestational, and pre-existing diabetes were ascertained by a self-administered parents' questionnaire.

Written informed consent and assent were obtained from parents before any testing procedure. Approval of the protocol was obtained by the Local Scientific Committee. The study was conducted in accordance with The Declaration of Helsinki.

After a 12-hour overnight fast, at approximately 8:00 Am, all subjects were admitted in the clinic for one-day inpatient visit. Height was measured without shoes to the nearest 0.1 cm using a wall Stadiometer, and weight was measured in underwear to the nearest 0.1 kg using a medical balance beam scale. To compare body mass index (BMI) across different ages and between genders, values of BMI were expressed as standard deviation score (SDS) [16]. Blood pressure (BP) was measured using a standard mercury sphygmomanometer two times in the supine position, at the beginning and at the end of the visit, using the right arm after the subject had rested quietly for 5 minutes. On each occasion, three readings of blood pressure were obtained, and the average was recorded. Physical maturation was assessed on the basis of breast development in girls and genitalia development in boys according to Tanner [19]. Due to the well-known relationship between pubertal development and decrease in insulin sensitivity [14, 15], subjects were divided into two groups according to the pubertal stage: prepubertal (Tanner stage 1), pubertal (Tanner stage from 2 to 5).

2.2. Metabolic Evaluation. Fasting blood samples were taken via antecubital vein catheter for measurement of glucose, insulin, C peptide, high density lipoprotein (HDL), cholesterol, and triglycerides. Then subjects ingested 1.75 g of glucose solution per kilogram of body weight (to a maximum of 75 g). Plasma samples were drawn for determination of glucose, insulin, and C peptide concentration every 30 minutes, until 2 hours after glucose load.

Insulin sensitivity index (ISI) [20] was calculated from oral glucose tolerance test (OGTT). It has been demonstrated to strongly correlate with the euglycemic-hyperinsulinemic clamp in obese children and adolescents [21].

To asses beta cell function, we used the insulinogenic index, calculated as the ratio of the increment in the plasma C peptide level to that in the plasma glucose level during the first 30 minutes after the ingestion of glucose.

The disposition index (DI) [22] was defined as the product of ISI and insulinogenic index. It reflects the capacity of pancreatic islets to compensate for lower insulin sensitivity.

2.3. Body Composition Evaluation. At least 10 days after the first inpatient visit children were admitted again for body composition evaluation. Body composition was measured by dual-energy X-ray absorptiometry (DEXA) using Hologic QDR Delphi (Hologic Inc., Bedford, MA), as previously described [15]. Fat and lean mass were corrected for differences in height as follow fat mass/height^2 (fat BMI) and lean mass/height^2 (lean BMI), expressed as kg/m^2 [23]. Body fat distribution was evaluated by the central obesity index calculated as the ratio of the amount of fat tissue in the trunk region to the amount of fat tissue in the leg region [24].

2.4. Definition of Metabolic Syndrome. Identification of MetS among children was based on the adult criteria defined by the National Cholesterol Education Program [1]. In the adult definition, a minimum of three of five major criteria (obesity determined by waist circumference, hypertension, low HDL cholesterol levels, elevated triglycerides, and glucose intolerance) should be fulfilled. These criteria have been modified for children [6]. Overweight and obesity were defined according to the Obesity Task Force [16]: hypertriglyceridaemia as triglycerides >95th percentile for age and sex [25]; low HDL cholesterol as concentrations <5th percentile for age and sex [25]; elevated BP as systolic or diastolic BP >95th for age and sex [26]; glucose intolerance as fasting glucose ≥100 mg/dL and/or 2-hour post-OGTT glucose ≥140 [27]. Therefore, we defined MetS as the presence of at least 2 other findings out of overweight/obesity.

2.5. Assays. Serum insulin and C peptide were measured by chemiluminescence on ADVIA Centaur analyzer (Kyowa, Medex Co., Tokyo, Japan); both assays are two-site sandwich immunoassays using direct chemiluminescent technology [intra- and interassay coefficient of variation (CV) 3.3–4.6 and 2.6–5.9%; 3.7–4.1 and 1.0–3.3%, resp.].

Quantitative determination of blood glucose, HDL cholesterol, and triglycerides was measured by enzymatic method on Roche automated clinical chemistry analyser (Roche/Hitachi 904 analyzer, Roche Diagnostics, Mannheim, Germany).

Intra- and interassay, CV for glucose, HDL cholesterol, and triglycerides were 0.9 and 1.8%; 0.6–0.95 and 1.2-1.3%; 1.5% and 1.8%, respectively.

2.6. Statistical Analysis. Numerical values are reported as mean ± standard deviation and categorical variables as proportions. The Kolmogorov-Smirnov goodness-of-fit test was used for determining whether sample data are likely to derive from a normal distributed population. Variables that diverged significantly from normal distribution were logarithmically transformed before analysis.

Between-group differences were examined using independent sample t-test and Chi-square test for numerical and categorical variables, respectively.

First, bivariate logistic regression was used to determine the associations between MetS and gender, age, FHD, diabetes during pregnancy, birth weight percentile, BMI SDS, fat and lean BMI, central obesity index, ISI, insulinogenic index, and DI. Then, variables significantly associated with MetS were inserted into multivariate logistic regression analyses, with MetS as dependent variable. We performed the multivariate logistic regression analysis in successive steps. In the first step, variables influencing MetS were evaluated in the overall population. In the second step, the population was stratified according to the pubertal development.

Significance level for all tests was set at $P < .05$. SPSS software version 13.0 (SPSS Inc., Chicago, IL) was used for all analyses.

3. Results

Study participants included 439 obese subjects (213 boys, 226 girls), aging 5.2–17.9 years (mean age 11.3 ± 2.6) with a mean BMI SDS of 2.2 ± 0.3. Twohundred and one subjects were prepubertal and 238 were pubertal.

MetS was present in 17.1% of individuals with higher prevalence in pubertal than prepubertal subjects (21.4 versus 11.9%, $P = .008$).

Clinical and metabolic characteristics of subjects with and without MetS, divided according to pubertal development, are reported in Table 1.

Girls and boys were equally distributed among individuals with and without MetS in both groups. Surprisingly, rates of FHD were similar between subjects with and without MetS. As expected ISI and central obesity index were significantly different, with subjects with MetS being more insulin resistant (prepubertal: 3.0 ± 1.9 versus 4.1 ± 2.3, $P = .010$; pubertal: 2.5 ± 1.9 versus 3.6 ± 2.5, $P < .0001$) and having more central fat depot (prepubertal: 1.32 ± 0.20 versus 1.19 ± 0.39, $P = .017$; pubertal: 1.30 ± 0.29 versus 1.19 ± 0.24, $P = .024$) compared to individuals without MetS. Mean birth weight percentile and DI were lower in individuals with MetS compared to individuals without MetS, but differences were statistically significant only in the pubertal group (birth weight percentile prepubertal: 38.2 ± 34.0 versus 47.0 ± 32.2, $P = .117$; pubertal 33.5 ± 30.7 versus 45.0 ± 31.8, $P = .011$; DI prepubertal: 0.36 ± 0.22 versus 0.46 ± 0.38, $P = .204$; pubertal: 0.33 ± 0.31 versus 0.41 ± 0.28, $P = .012$).

3.1. Role of Birth Weight. To further analyze the relation between birth weight and MetS, we evaluated the prevalence of MetS into the three birth weight categories. Because low and high birth weights were selection factors, we had 22.3% of SGA ($n = 98$), 62.2% of AGA ($n = 273$), and 15.5% of LGA ($n = 68$).

Table 1: Clinical and metabolic characteristics of obese children and adolescents.

	Prepubertal (n.201)			Pubertal (n.238)		
	MetS	No MetS	*P*	MetS	No MetS	*P*
Number	24	177		51	187	
Male/female	10/14	92/85	.343	23/28	88/99	.804
Age (years)	9.4 ± 1.1	9.3 ± 1.7	.763	13.2 ± 1.9	13.1 ± 2.0	.835
Family history of diabetes (%)	15.0	20.5	.397	7.7	13.3	.399
Birth weight (kg)	3.1 ± 0.7	3.3 ± 0.7	.362	3.2 ± 0.6	3.3 ± 0.6	.098
Birth weight (percentile)	38.2 ± 34.0	47.0 ± 32.2	.117	33.5 ± 30.7	45.0 ± 31.8	.011
BMI (kg/m^2)	28.5 ± 3.9	27.8 ± 3.6	.379	32.7 ± 5.9	31.4 ± 4.9	.115
BMI SDS	2.3 ± 0.3	2.3 ± 0.3	.845	2.3 ± 0.3	2.2 ± 0.3	.077
Fat BMI (kg/m^2)	11.7 ± 2.7	11.4 ± 2.3	.531	12.2 ± 3.5	12.3 ± 3.1	.717
Lean BMI (kg/m^2)	15.7 ± 1.5	15.2 ± 1.5	.182	18.2 ± 2.7	17.6 ± 2.4	.613
Central obesity index	1.32 ± 0.20	1.19 ± 0.39	.017	1.30 ± 0.29	1.19 ± 0.24	.024
HDL cholesterol (mg/dL)	35.7 ± 6.5	49.3 ± 9.6	<.0001	37.0 ± 6.8	46.0 ± 8.9	<.0001
Triglycerides (mg/dL)	141.1 ± 45.6	78.3 ± 38.6	<.0001	177.5 ± 93.0	82.3 ± 40.3	<.0001
PAs (mmHg)	107.1 ± 12.0	106.9 ± 9.6	.961	124.2 ± 14.3	114.9 ± 12.8	<.0001
PAd (mmHg)	67.9 ± 8.4	66.9 ± 9.7	.916	72.1 ± 12.1	69.3 ± 10.0	.139
Fasting glucose (mg/dL)	83.3 ± 9.4	80.1 ± 6.3	.046	83.4 ± 11.8	81.4 ± 7.6	.192
2-hour glucose (mg/dL)	113.2 ± 32.1	108.2 ± 16.2	.671	125.7 ± 23.3	110.5 ± 20.4	<.0001
ISI	3.0 ± 1.9	4.1 ± 2.3	.010	2.5 ± 1.9	3.6 ± 2.5	<.0001
Insulinogenic index$_{(C\ peptide\ 30-0)}$	0.13 ± 0.06	0.11 ± 0.07	.094	0.27 ± 0.98	0.13 ± 0.14	.199
DI$_{(C\ peptide\ 30-0)}$	0.36 ± 0.22	0.46 ± 0.38	.204	0.33 ± 0.31	0.41 ± 0.28	.012

MetS, BMI, PAs, PAd, ISI, and DI denote metabolic syndrome, body mass index, systolic blood pressure, diastolic blood pressure, insulin sensitivity index, and disposition index, respectively.

Table 2: Variables significantly associated to metabolic syndrome.

Dependent variable: MetS		
Independent variables[a]	Beta[b] ± SE	*P*
Entire population		
Log central obesity index	2.815 ± 0.947	.003
Log ISI	−1.257 ± 0.306	<.001
Log birth weight	−0.411 ± 0.128	.001
Prepubertal group		
Log central obesity index	4.804 ± 1.587	.002
Log ISI	−1.1290.564	.045
Pubertal group		
Log central obesity index	2.491 ± 1.170	.033
Log ISI	−1.013 ± 0.371	.006
Log birth weight	−0.3850.167	.021

[a]All values are log-transformed to approximate normal distribution.
[b]Generalized equation estimation method regression coefficient.
MetS and ISI denote metabolic syndrome and insulin sensitivity index, respectively.

Prevalence of subjects with MetS was significantly higher in the SGA category (25.7%), with LGA having the lowest (11.8%) and AGA the intermediate (14.5%) prevalence (P = .015). This trend was maintained in the pubertal group (P = .027) but not in the prepubertal one (P = .423) (Figure 1).

As gestational diabetes is associated with large size at birth and is known to strongly influence the risk of developing MetS in the offspring [6, 28], we evaluated the prevalence of MetS in the different birth weight categories after excluding offspring of diabetic mothers. Diabetes during pregnancy (either gestational diabetes or pre-existing type 1 or 2 diabetes) was present in 28 cases (6.3%). Most cases of offspring of diabetic mothers were in the LGA group (18 out of 28). Prevalence of MetS in the different birth weight categories, after excluding offspring of mother with diabetes during pregnancy, did not change substantially (in the whole population 26.1, 13.7, and 10.9% in SGA, AGA, and LGA, resp., P = .007).

3.2. Logistic Regression Analysis. Bivariate logistic regression analysis revealed age, lean BMI, insulinogenic index, and central obesity index to be positively associated with MetS (P = .033, .004, .027, and .001, resp.) and birth weight, ISI, and DI to be negatively associated with MetS (P = .003, < .001, and = .002, resp.). Gender, FHD, diabetes during pregnancy, and degree of obesity expressed either as BMI SDS or fat BMI did not influence the dependent variable.

In the entire population, the multivariate logistic regression analysis revealed central obesity index to be positively and independently associated with MetS and ISI and birth weight to be negatively associated with MetS, with central obesity index being the strongest predictor of MetS (Table 2).

When the prepubertal and pubertal subjects were analysed separately, central obesity index remained the most powerful variable influencing MetS in both groups, with ISI similarly influencing MetS in the two populations and birth

weight being negatively associated to MetS only in pubertal individuals (Table 2).

4. Discussion

In the present study of Italian growing obese individuals, our findings revealed that increased central fat depot is the strongest determinant of MetS, no matter if subjects were children or adolescents, with central obesity index being more predictive of MetS than insulin sensitivity. Moreover, low birth weight appeared to be a less powerful risk factor for MetS with significant association only in pubertal individuals. Surprisingly, FHD, age, insulinogenic index, DI, and degree of obesity, expressed either as BMI SDS or total fat amount, were not significant determinants of MetS in this cohort of obese subjects.

The central role of abdominal adiposity and particularly of visceral adiposity in the development of MetS has been widely demonstrated in adulthood [29, 30]. Similar findings have been described in children, where waist circumference and increased visceral fat depot have been confirmed to be strong and independent predictors of metabolic alterations [12, 13]. In the present study, by directly measuring with the DEXA technique the total fat amount and the body fat distribution, we showed that in, obese Italian growing subjects, the preponderance of fat in the abdomen is the real determinant of MetS, rather than the total body fat amount. As a matter of fact, neither BMI SDS nor fat BMI appeared to be risk factors for MetS. Similar findings were reported by an Italian study, where waist-to-height ratio was the only clinical parameter directly related to MetS, with the same predictive power of insulin resistance [31].

In our study, SGA individuals showed a significant higher incidence of MetS, with subjects born LGA apparently protected from the development of MetS. However, small size at birth was not an important predictor of MetS as was central obesity index. The present data of increased metabolic risk in subjects born SGA confirm a large body of the literature in adulthood and also in childhood [3]. Moreover, our findings on apparently protective role of large size at birth are in contrast with other studies conducted in different ethnic groups, like Pima Indians [28] and Mexican children [5], that have showed an increased risk for metabolic alterations in children born LGA.

We have previously showed that obese children and adolescents born SGA manifest reduced insulin secretion in the context of increased insulin resistance milieu and more evident central repartition of fat than AGA and LGA, with LGA presenting the highest insulinogenic index, despite comparable degree of insulin resistance [17]. Similar to our findings, a study conducted in French obese children has showed a favourable metabolic profile in children born LGA, with obese children and adolescents born with high birth weight displaying approximately 60% higher insulin sensitivity and lower central fat distribution compared with those born eutrophic [9]. One could hypothesize that the role of large size at birth is different in the different ethnic groups, with European obese children being protected from metabolic complications if born LGA.

As the Pima Indian study has showed that the increased risk of metabolic alterations among Pima with high birth weight was largely explained by maternal diabetes during pregnancy [28], we evaluated the role of diabetes during pregnancy in our sample of obese children and adolescents. We found no association with diabetes during pregnancy, probably because cases of either gestational diabetes or pre-existing type 1 or 2 diabetes were only 28 and we had no statistical power to show any relation with MetS.

Surprisingly, FHD was not associated with MetS. Different findings have been reported by other authors, who described FHD to be a risk factor for MetS [5] and hyperinsulinemia [6] in children and adolescents. One explanation for this discrepancy could be due to the fact that type 2 diabetes in adults is age dependent. Additionally, we did not measure directly blood glucose in the parents. It is likely that in our study some currently healthy parents have silent diabetes or will develop diabetes in the future. This could be a potential source of bias in the classification of positive FHD. The specific role of FHD in the development of MetS could not be determined with certainty, and follow-up studies are needed to confirm our results.

Although our study has strengths, including the use of imaging technique to evaluate body fat portioning and a large representative sample of exclusively Italian obese children and adolescents, we acknowledge some limitations. First, we did not distinguish visceral from subcutaneous abdominal fat; secondly, we did not study insulin sensitivity with the gold standard hyperinsulinaemic euglycemic clamp technique for its complexity in pediatric patients; thirdly, because this was a cross-sectional analysis, causation could not be inferred.

In conclusion, simple clinical parameters like increased abdominal adiposity, eventually estimated by waist circumference and low birth weight, could be useful tools to identify obese growing European individuals at risk for metabolic complications.

As not all obese adults display the clustering of metabolic and cardiovascular risk factors, with some of them being metabolically healthy but obese individuals [32], one could speculate that obese adolescents born LGA, with predominantly peripheral fat portioning, could be healthy obese adolescents, having a favourable metabolic profile.

Prospective studies with serial measurements of cardiovascular risk factors are needed to confirm our findings.

Conflict of Interests

There is no conflict of interests that could be perceived as prejudicing the impartiality of the research reported. This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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