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ARTICLE

Pediatrics

The bad rainbow of COVID-19 time: effects on glucose metabolism in children and adolescents with obesity and overweight

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BACKGROUND: COVID-19 restriction measurements have enhanced the obesity status in the pediatric population which might further contribute to obesity-related glucose-insulin metabolism alterations. Therefore, we retrospectively compared anthropometric and OGTT data on children with obesity during the 13 years before and during the COVID-19 pandemic.
SUBJECTS/METHODS: Data from 741 children with obesity and overweight were retrieved and clustered into seven groups starting from year 2008–2009 until 2020–2021. Differences in anthropometric measurements and glucose/insulin metabolism were evaluated between the different groups.
RESULTS: Children with overweight and obesity in the COVID-19 restriction group did not present increased values of SDSBody Mass Index (BMI). Significantly higher values for Waist Circumference (WC), SDS-WC, Waist/Height ratio (WHtR), and body mass fat were detected in these children (all $P < 0.01$). Fasting glycaemia, glucose, and insulin excursions were significantly higher compared to pre pandemic children (all $P < 0.01$). Insulin resistance was higher while insulin secretion was lower (all $P < 0.01$) determining a significantly higher percentage of impaired glucose tolerance in the COVID-19 restriction group ($P < 0.002$). Furthermore, High-Density Lipoprotein (HDL) cholesterol was significantly lower ($P < 0.01$) and SDS for systolic and diastolic blood pressure values were significantly higher ($P = 0.03$ and $P = 0.02$, respectively).
CONCLUSIONS: COVID-19 restriction measurements determined profound alterations in glucose and insulin metabolism in children with obesity and overweight. Urgent strategies are needed in order to reverse COVID-19 restriction measures' effects on glucose and insulin metabolism.

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INTRODUCTION

Obesity presents an alarming risk to both physical and psychological health. The epidemic of obesity in the pediatric population has become a major public health concern in Italy and worldwide [1]. Excessive weight gain early in life likely leads to lifelong overweight and obesity and is associated with greater risk and earlier onset of chronic disorders, such as cardiovascular (CV) and metabolic diseases [2, 3]. In recent years, insufficient outdoor physical activity has been recognized as a major risk factor for pediatric overweight or obesity development [4]. In fact, several reports on children have suggested that this unhealthy weight gain mainly occurs during the summer months, when children are out of school [5, 6], thus suggesting relevant effects of changes in daily life habits on the risk of obesity.

In order to contain and mitigate the spread of the novel SARS-CoV2 infection in March 2020, the Italian Government established more stringent containment measures leading to prompt and major modification in the habits and lifestyles of the population [7, 8]. Public activities were discouraged, and online courses were offered and delivered through TV broadcast and internet thus determining a drastic decline in any form of socialization. It has been estimated that more than 180 million school-aged children and adolescents were confined to their homes [8], thus disrupting unintentionally their lifestyles. Rundle et al. hypothesized that the COVID-19 pandemic would "exacerbate all of the risk factors for weight gain associated with summer recess" [9, 10]. Meanwhile, An et al. [11]. speculated that, compared with the pre-pandemic period in the United States, both Body Mass Index (BMI) -z-scores and childhood obesity prevalence under COVID-19 would rise, and the magnitude of the increase would be proportional to the length and severity of the pandemic. In fact, in a recent study, Vogel et al. have demonstrated a substantial weight gain across all age groups, reflected by a significant increase in the 3-month change in BMI-standard deviation scores (SDS) during this period, especially for children with obesity [12]. In addition, the rise in the incidence of obesity would be mirrored by an increasing number

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of cases of youth-onset type 2 diabetes (T2D), prediabetes, and early alteration of glucose metabolism-related to obesity [13, 14].

Therefore, an investigation into the progression of obesity development and its related consequences among children and adolescents during this dramatic period is urgently warranted. Thus, we aimed to comprehensively understand and analyze the impact of confinement due to the COVID-19 outbreak on obesity development and obesity-related complications in children and adolescents in our population. In detail, the objective of this study is to evaluate the possible effects on glucose metabolism and CV risk factors in children and adolescents with overweight and obesity during the 13 years before (from the year 2008 to 2019) and during the COVID-19 pandemic (years 2020/2021).

MATERIALS AND METHODS

Study population

The study was based on a retrospective review of the hard copy archive of the Pediatric Endocrinology Clinic of the Department of Pediatrics (University of Chieti, Chieti, Italy) for the period between March 2008 and July 2021.

The study population consisted of 741 Caucasian children and adolescents (349 boys and 392 girls, mean age 11.2 ± 2.6 years) diagnosed with overweight (BMI ≥ 85th and <97th percentiles for age and sex) or obesity (BMI ≥ 97th percentile for age and sex) who had undergone a complete physical examination, biochemical evaluation and had performed an Oral Glucose Tolerance Test (OGTT) after their first visit to the Pediatric Endocrinology Clinic [15]. In the data analysis, only subjects evaluated for the first time and who performed for the first time a complete evaluation with an OGTT and a complete blood work assessment were included. Therefore, no repeated OGTT data were included in the analysis. None of the patients had other chronic diseases (diabetes, thyroid or other endocrine disorders, genetic diseases, or systemic inflammation) and none were taking any medication. Data on family history of T2D and CV diseases were also available.

The study was conducted in compliance with ethical principles based on the Declaration of Helsinki. Formal consent for this study was not required, since it was confined to data collected as part of a routine assessment of children with obesity and data were entered into the study database in an anonymized and unidentifiable way.

In order to evaluate glucose metabolism during the 13 years before and especially, to explore the effects of COVID-19 lockdown, subjects were divided into seven groups based on the period when anthropometric measurements, OGTT, and biochemical assessment have been performed. In particular, we clustered the study population as follows:

group 1 (year 2008/2009), patients assessed between March 2008 and July 2009;
group 2 (year 2010/2011), patients assessed between March 2010 and July 2011;
group 3 (year 2012/2013), patients assessed between March 2012 and July 2013;
group 4 (year 2014/2015), patients assessed between March 2014 and July 2015;
group 5 (year 2016/2017), patients assessed between March 2016 and July 2017;
group 6 (year 2018/2019), patients assessed between March 2018 and July 2019;
group 7 (year 2020/2021 or COVID-19 restriction group), patients assessed between March 2020 and July 2021.

Clinical data

All children and adolescents affected by overweight and obesity were evaluated by the same Pediatric Endocrinology team (University of Chieti, Chieti, Italy), with the supervision of a senior physician, using standard methods. Height was measured to the nearest 0.1 cm with Harpenden stadiometer (Holtein, Wales, UK). For this measurement, patients stood straight, with feet placed together and flat on the ground; heels, buttock, and scapulae against the vertical backboard; arm loose and relaxed with palms facing medially and the head positioned in the Frankfurt plane. Body weight was measured to the nearest 0.1 kg with a calibrated scale. BMI, used as adiposity index, was calculated as the weight in kilograms divided by the square of the height in meters.

A spring-loaded, inelastic measuring tape was used to measure waist circumference to the nearest 0.1 cm at the mid-point between the lower ribs and the pelvic bone at the end of normal exhalation.

Height, weight, and BMI-SDS were calculated based on the age and sex reference values for the Italian population [14]. The waist-to-height ratio (WtHR) was also calculated in order to have an age- and sex-independent index [16, 17]. In all patients, pubertal stage was defined on the basis of breast development in girls and genital development in boys, based on Tanner's criteria [18]. Systolic (SBP) and diastolic (DBP) blood pressure were measured twice, after 10-min rest, using standard methods at the non-dominant arm, by using a calibrated sphygmomanometer. SBP and DBP standard deviation scores (SDS-SBP, SDS-DBP) were calculated according to the LMS method, using published reference data and a validated equation [19, 20].

Body composition was determined only for the last three groups using a Tanita scale, determining the percentage of body fat mass (BFM%) and total body water (TBW%).

Oral glucose tolerance test and biochemical assessments

All participants underwent a 2-h OGTT. All OGTT was performed at the Pediatric Endocrine Clinic by the same nurses, using a standard protocol. In details, after overnight fasting, an OGTT was performed between 07.00 and 8.00 in the morning after admission to the hospital. The day before the glucose tolerance test, all subjects received a normo-caloric, mixed diet.

Subsequently, subjects were given 1.75 g/kg body weight of oral glucose (up to a maximum of 75 g), and blood samples were drawn every 30 min up to 120 min for the measurement of glucose and insulin. Samples were transferred to the local laboratory soon after each collection to be processed.

Glucose tolerance status was classified according to the American Diabetes Association criteria [21]. In detail, impaired fasting glucose (IFG) was defined as glucose levels between 100 and 125 mg/dL [20], impaired glucose tolerance (IGT) as 2 h glucose levels between 140 and 199 mg/dL and T2D as 2 h glucose levels ≥200 mg/dL and/or fasting glucose levels ≥126 mg/dL.

At baseline were collected vein blood samples for determination of glucose, insulin, hemoglobin A1c (HbA1c) levels, and lipid profile [namely total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG)].

Lipid profile

Serum TC was measured by the colorimetric enzymatic CHOD-PAP method (%CV 134 intra assay: level 1: 0.8, level 2: 0.6; % CV inter assay: level 1: 0.4, level 2: 0.8). HDL-cholesterol was measured by accelerator selective detergent methodology (%CV intra assay: level 1: 1.7, level 136 2: 1; %CV inter assay: level 1: 1.1, level 2: 0.5). TG concentrations were measured by glycerol phosphate oxidase method (% CV intra assay: level 1: 0.7, level 2: 0.8; %CV inter assay: 138 level 1: 0.4, level 2: 0.6). LDL-cholesterol was determined by using Friedewald's equation: LDL cholesterol = [total cholesterol – (HDL-cholesterol + Triglycerides/5)]. Lipid profile was analyzed by Architect c16000 clinical chemistry analyzer (Abbott, Abbott Park, 130 Illinois, U.S.A.).

Glucose metabolism

Blood glucose was determined by the glucose oxidase methods. Serum insulin was measured with a two steps chemiluminescence enzyme immunoassay methodology (AIA CL Analyzer; 147 Tosoh, Tokyo, Japan) (% CV intra assay was for level 1: 1.7, for level 2: 1.7, for level 3: 2.7; %CV inter assay was for level 1: 2.9, for level 2: 3.5, for level 3: 4.4).

HbA1c concentrations were measured using a high-performance liquid chromatography method. The normal range was 4.2–6.0%, with an intra-assay %CV of 3%.

Indexes of insulin resistance and secretion

Area under the curve (AUC) values were determined using the trapezoidal rule and it was calculated for glucose and insulin levels during the OGTT from 0 to 120 min [22].

Insulin sensitivity was estimated by calculating the fasting glucose-insulin ratio (FGIR, G/I) [23].

The Homeostasis Model Assessment of Fasting insulin resistance (HOMA-IR), a measure of insulin resistance, was computed as follows: HOMA-IR = [fasting insulin (μIU/ml) × fasting glucose (mmol/ml)]/22.5 [24]. The Whole Body Insulin Sensitivity Index (WBISI) was calculated with the

Table 1. Anthropometric characteristics of studied population clustering for years.

	Groups for years							
Variables	**2008/2009**	**2010/2011**	**2012/2013**	**2014/2015**	**2016/2017**	**2018/2019**	**2020/2021**	***P***
Number	167	102	80	101	98	103	78	
Age (years)	10.7 (±2.4)	10.7 (±2.7)	10.9 (±3.0)	11.2 (±3.0)	11.5 (±2.9)	11.7 (±2.5)	11.7 (±2.7)	0.07
Sex (M/F)	83/84	49/53	29/51	49/52	42/56	45/58	46/32	0.12
Puberty (Pre/Pubertal)	68/99	49/53	45/35	40/61	40/58	34/69	35/43	0.62
Auxological parameters								
SDS-Weight	2.1 (±0.6)	2.1 (±0.6)	2.2 (±0.7)	2.2 (±0.7)	2.2 (±0.6)	2.3 (±0.8)	2.3 (±0.8)	0.15
SDS-Height	0.6 (±0.9)	0.7 (±1.0)	0.6 (±1.2)	0.6 (±1.0)	0.8 (±1.0)	0.5 (±1.2)	0.8 (±1.3)	0.26
Obesity index								
SDS-BMI	2.2 (±0.4)	2.2 (±0.4)	2.3 (±0.4)	2.4 (±0.6)	2.2 (±0.4)	2.4 (±0.5)	2.3 (±0.6)	0.39
WC (cm)	80.1 (±8.4)	83.9 (±8.5)	82.2 (±10.2)	87.6 (±9.4)	89.5 (±5.9)	93.9 (±11.2)	96.7 (±10.7)	**<0.01**[abcdef]
SDS-WC	2.5 (±0.26)	3.1 (±0.31)	2.8 (±0.34)	3.2 (±0.34)	3.5 (±0.23)	4.2 (±0.50)	4.6 (±0.50)	**<0.01**[abcdef]
WHtR	0.57 (±0.06)	0.58 (±0.05)	0.58 (±0.05)	0.57 (±0.04)	0.61 (±0.03)	0.61 (±0.06)	0.64 (±0.06)	**<0.01**[abcd]
Body composition								
BFM (%)	-	-	-	-	33.2 ± 7.1	34.2 ± 8.3	**40.3 ± 12.6**	**<0.01**[ab]
TBW (%)	-	-	-	-	53.8 ± 2.5	53.2 ± 2.7	**51.0 ± 3.3**	**<0.01**[ab]

Data presented as media ± SD.
M Male, *F* Female, *SDS* Standard Deviation, *BMI* Body Mass Index, *WC* Waist Circumference, *SBD* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *WHtR* Waist to Height ratio, *BFM* Body Fat Mass, *TBW* Total Body Water.
[a]group 7 vs group 1.
[b]group 7 vs group 2.
[c]group 7 vs group 3.
[d]group 7 vs group 4.
[e]group 7 vs group 5.
[f]group 7 vs group 6.
Bold values indicate *P* values with significant differences between the groups.

formula: WBISI = [10.000/(fasting glucose × fasting insulin × mean glucose × mean insulin concentration)$^{1/2}$], where mean glucose and mean insulin are the averaged glucose and insulin concentrations during the OGTT; glucose and insulin are expressed in mg/dl and μIU/ml, respectively [25]. The insulin secretion was estimated by means of the Insulinogenic Index (IGI), defined as: IGI = [insulin (t30) − insulin (t0)/glucose (t30) − glucose (t0)], where glucose is expressed in mg/dl and insulin is expressed in μIU/ml [24, 26]. The Disposition Index (DI), a measure of insulin secretion relative to insulin sensitivity, was calculated as: DI = IGI × WBISI [27].

The shape of the curve

The shape of OGTT curve, in line with previous studies, was classified into three categories. A monophasic curve was defined as an increase in blood glucose between 30 and 90 min until a peak followed by a subsequent decline of more than 4.5 mg/dL. A biphasic curve was defined as a rise of blood glucose to a peak followed by a fall (as in the monophasic curve), but then followed by a second rise of ≥4.5 mg/dL; and an incessant increase curve, defined as a continuing increase in blood glucose during the 2-h OGTT without a fall of ≥4.5 mg/dL [28–30].

Statistical analysis

All calculations are made with the computer program Statistical Package for the Social Science (SPSS) version 23.0 (SPSS Inc., Chicago, IL, USA). All data were analyzed with Kolmorgorov-Smirnov test and the data not normally distributed were log-transformed when requested.

All data are expressed as mean ± standard deviation. Differences across the seven groups were analyzed with analysis of variance (ANOVA) in order to define a *P* for trend in the study population. In addition, Bonferroni analysis was used for post-hoc analysis in order to characterize differences between group 7 and all the other seven groups. Furthermore, in order to define differences in terms of overall glucose and insulin excursion during OGTT (Time 0, +30, +60, +90, +120) ANOVA for repeated measurements was used. In addition, Bonferroni analysis was used for post-hoc analysis in order to characterize which curve was different across the groups. Finally, in order to attempt to evaluate differences mainly related to COVID restriction compared to all the previous years, in terms of overall glucose and insulin excursion during OGTT (Time 0, +30, +60, +90, +120) ANOVA for repeated measurements was used including in the analysis OGTT data of group 7 compared to the mean values of all the previous years (2008–2019). As well differences for each time point of OGTT data between these two groups were analyzed by *t*-testing. Differences in categorical variables were assessed with χ^2 test repeating the test for each pairwise comparison by Bonferroni correction and $P < 0.0025$ were taken as statistically significant in order to adjust for the multiple conducted comparisons [31]. In order to explore factors related to WC a Pearson correlation analysis was performed for variables of interest.

RESULTS

Anthropometric and metabolic characteristics of all participants categorized into the seven groups are presented in Tables 1, 2, and 3.

Out of the records of 741 children and adolescents with overweight or obesity twelve subjects were excluded due to incomplete data for OGTT. Out of the remaining 729 patients, 343 were males (47%) and 311 subjects (43%) were prepubertal.

The seven groups were not different in terms of age, gender, and Tanner stage status (all $P > 0.05$). No differences were found between the seven groups for weight-SDS, height -SDS, and BMI-SDS.

In contrast, WC, SDS-WC, and WHtR were significantly different between the seven groups ($P < 0.01$). In detail, values of WC and SDS-WC increased steadily over time reaching significant differences across the seven groups ($P < 0.01$). In addition, in group 7 WC and SDS-WC were significantly larger compared to all other groups (all $P < 0.01$). Similarly, WHtR index was significantly higher in group 7 compared to groups 1, 2, 3, and 4 (all $P < 0.01$). Although WHtR index was higher compared to group 5 and 6 it did not reach a statistical significance. In addition, significantly

Table 2. Metabolic profile of childhood population clustering for years.

Groups for years								
Variables	**2008/2009**	**2010/2011**	**2012/2013**	**2014/2015**	**2016/2017**	**2018/2019**	**2020/2021**	***p***
FBG (mg/dL)	89.9 (±10.2)	88.4 (±9.0)	92.9 (±9.2)	89.9 (±9.5)	92.2 (±7.2)	96.7 (±8.8)	98.3 (±9.4)	**<0.01**[abcdef]
HbA1c (mmol/L)	34.5 (±3.0)	35.5 (±6.5)	35.4 (±3.8)	35.0 (±3.5)	35.7 (±2.9)	35.6 (±3.6)	35.6 (±3.2)	0.41
IFG (%)	15.0	9.0	21,0	12.0	14.0	39.0	47.0	**<0.01**[abcde]
% high 1-h (>132.5 mg/dL)	16	21	25	25	25	27	34	**0.03**[a]
% high 1-h (>155 mg/dL)	6	8	5	7	4	6	13	0.1
IGT (%)	1.5	3.3	8.0	3.4	5.3	6.5	12.2	**<0.01**[ab]
Shape of OGTT curve (%):								
Monophasic	49.6	61.3	38.2	49.5	48.9	47.3	50.0	**<0.01**[abcef]
Biphasic	48.2	37	60	47	48.9	50.5	38.8	
Incessant increase	2.2	1.7	1.8	3.5	2.1	2.1	12.5	
Insulin resistance and secretion index								
Fasting insulinemia (μU/mL)	14.5 (±6.9)	17.5 (±9.1)	16.9 (±9.9)	17.1 (±12.4)	18.5 (±11.6)	18.3 (±10.7)	23.0 (±14.7)	**<0.01**[abcd]
HOMA-IR	3.3 (±1.7)	3.8 (±2.1)	3.9 (±2.6)	3.7 (±2.7)	4.2 (±2.7)	4.4 (±2.7)	5.6 (±3.8)	**<0.01**[abcde]
Insulin AUC $_{0-120}$	68 (±41)	127 (±171)	83 (±47)	89 (±79)	83 (±54)	86 (±63)	107 (±70)	**<0.01**[a]
IGI	2.38 (±3.3)	2.22 (±3.0)	2.00 (±2.43)	2.19 (±2.60)	2.69 (±2.44)	3.02 (±3.17)	2.73 (±2.54)	**<0.01** [abcd]
WBISI	6.5 (±7.8)	6.2 (±5.5)	5.2 (±4.5)	5.1 (±4.1)	3.9 (±3.0)	3.4 (±1.9)	3.0[ab] (±2.2)	**<0.01**[ab]
DI	7.8 (±8.3)	6.4 (±6.8)	7.2 (±8.7)	6.6 (±6.8)	9.4 (±8.2)	10.9 (±11.0)	5.8 (±4.0)	**<0.01**[f]
FGIR	1.9 (±0.4)	1.7 (±0.5)	1.8 (±0.5)	1.8 (±0.5)	1.7 (±0.6)	1.8 (±0.5)	1.6 (±0.5)	**<0.01**[a]

Data presented as media ± SD.
FBG fasting blood glucose, *IFG* impaired fasting glucose, *IGT* impaired glucose tolerance, *HOMA-IR* Homeostasis Model Assessment Insulin Resistance, *WBISI* Whole-Body Insulin Sensitivity Index, *IGI* insulinogenic index, *DI* disposition index, *FGIR* fasting glucose-insulin ratio.
[a]group 7 vs group 1.
[b]group 7 vs group 2.
[c]group 7 vs group 3.
[d]group 7 vs group 4.
[e]group 7 vs group 5.
[f]group 7 vs group 6.
Bold values indicate *P* values with significant differences between the groups.

Table 3. Cardiometabolic risk factors of childhood population clustering for years.

	Groups for years							
Variables	**2008/2009**	**2010/2011**	**2012/2013**	**2014/2015**	**2016/2017**	**2018/2019**	**2020/2021**	***P***
Lipidic profile								
Total cholesterol (mg/dL)	157 (±23)	165 (±21)	161 (±27)	160 (±30)	152 (±27)	157 (±28)	159 (±25)	0.40
HDL (mg/dL)	47 (±9)	48[a] (±9)	47 (±9)	44 (±10)	48 (±11)	43 (±9)	**43 (±7)**	**<0.01**[a]
LDL cholesterol (mg/dL)	92 (±24)	97 (±22)	96 (±27)	94 (±28)	85 (±22)	94 (±25)	99 (±24)	0.37
Triglycerides (mg/dL)	91 (±49)	96 (±42)	88 (±43)	98 (±47)	89 (±38)	96 (±41)	99 (±46)	0.20
Blood pressure								
SDS_SBP	0.73 (±1.19)	0.59 (±1.35)	0.76 (±0.91)	0.94 (±0.84)	0.27 (±0.71)	0.37 (±1.84)	**1.05 (±0.92)**	**0.03**
SDS_DBP	0.59 (±0.84)	0.58 (±0.65)	0.67 (±0.74)	0.69 (±0.64)	0.52 (±0.25)	0.24 (±1.12)	**0.53 (±0.71)**	**0.02**

SBP systolic blood pressure, *DBP* diastolic blood pressure.
[a]group 7 vs group 2.
Bold values indicate *P* values with significant differences between the groups.

higher values of BFM% and lower values of TBW% in group 7 was documented compared to groups 6 and 5 (all $P < 0.01$).

OGTT and glucose metabolism

Figure 1 shows the plasma glucose and insulin excursions during OGTT for the seven groups (upper panel) and the excursion in group 7 compared to the mean values of all the other groups (mean of years 2008–2019, lower panel). As shown in Fig. 1 (upper panel), the seven groups differed significantly for blood glucose levels in fasting and post-load state (*all P for trend for each time point* < 0.01, Fig. 1 upper panel*)* and this was further documented after comparing group 7 with the mean values (mean of years 2008–2019, Fig. 1 lower panel) of all the other groups (*all P for each time point* < 0.01). In detail, fasting glycaemia was

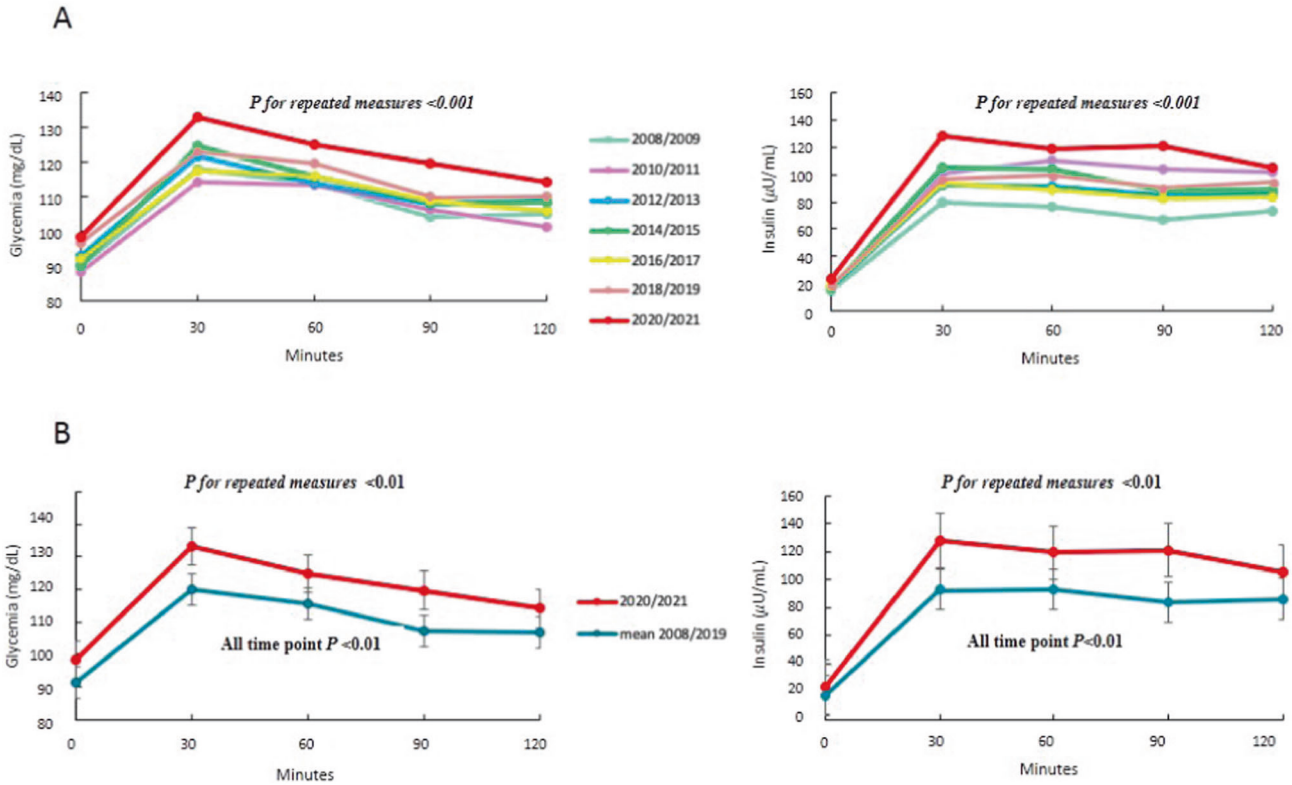

Fig. 1 Glucose and insulin excursions during OGTT. A Glucose and insulin levels following the oral glucose load in children and adolescents with obesity and overweight in the seven groups. **B** Glucose and insulin levels following the oral glucose load in children and adolescents with obesity and overweight in the COVID-19 restriction group compared to the mean of all other groups.

significantly higher in group 7 compared to the all other groups (all $P < 0.01$). Thus, compared to groups 1 to 5, a significantly higher percentage of subjects presented with IFG (all $P < 0.0025$) in group 7. In addition, although a higher percentage of subjects in group 7 presented with IFG when compared to group 6, it did not reach a statistical significance. The blood glucose excursion (AUC) curve was significantly different across all the groups showing group 7 the higher values (all $P < 0.01$). Particularly, post hoc analysis showed that blood glucose excursion was significantly different in group 7 when compare to all other groups. In order to attempt to evaluate differences mainly related to COVID restriction compared to all the previous years, in terms of overall glucose excursion during OGTT (Time 0, +30, +60, +90, +120), analysis of variance for repeated measurements (ANOVA) showed significant differences between group 7 compared to the mean values of all the previous years (2008–2019) (Fig. 1 lower panel). As well statistically significant differences for all time points of glucose OGTT data were documented between these two groups (Fig. 1 lower panel). More importantly, group 7 presented significantly higher levels at timepoint 60 minutes compared to group 1 ($P = 0.026$) associated with a significantly higher percentage of subjects with 1-h post-load plasma glucose level >132.5 mg/d ($P < 0.01$). In addition, although the percentage of subjects with 1-h post-load plasma glucose level >132.5 mg/d ($P < 0.01$) in group 7 was higher compared to all the other group it did reach a statistical significance. Significant differences were documented in terms of IGT occurrence across the seven groups ($P < 0.01$). In detail, group 1 and 2 presented significantly lower blood glucose levels at timepoint 120 min when compared to group 7 ($P = 0.03$ and $P < 0.01$, respectively). In addition, 12% of subjects presented with IGT in group 7, thus significantly higher compared to 1.5% ($P < 0.002$) and to 3.3% of subjects in group 1 and group 2 ($P < 0.01$), respectively. Although IGT% was higher in group 7 compared to all the other groups, it did not reach a statistical significance. As expected, AUC of the glycaemia during OGTT was significantly different in the seven groups ($P < 0.01$). In particular, significantly higher AUC glucose levels were found between group 7 and groups 1, 2, 3, and 4 (all $P < 0.01$) (Fig. 2). In addition, although AUC glucose levels were higher group 7 compared to groups 5 and 6, it did not reach a statistical significance.

As shown in Fig. 1, the seven groups differed significantly for blood insulin levels in fasting and post-load state (Fig. 1 upper panel, *P for repeated measures* < 0.001) and this was further documented after comparing group 7 with the mean values (mean of years 2008–2019, Fig. 1 lower panel) of all the other groups (*P for repeated measures* < 0.01). In detail, fasting insulinemia was significantly higher in group 7 compared to groups 1–4 (all $P < 0.01$). In addition, although fasting insulin was higher in group 7 compared to group 5 and group 6, it did not reach a statistical significance. Furthermore, blood insulin excursion curve was significantly higher in group 7 compared to group 1 (post-hoc analysis). In order to attempt to evaluate differences mainly related to COVID restriction compared to all the previous years, in term of overall insulin excursion during OGTT (Time 0, +30, +60, +90, +120), ANOVA for repeated measurements showed significant differences between group 7 compared to the mean values of all the previous years (2008–2019) (Fig. 1 lower panel). As well statistically significant differences for all time points of insulin OGTT data were documented between these two groups (Fig. 1 lower panel). AUC insulinemia values were statistically different across the seven groups ($P < 0.01$). In particular, group 7 showed significantly higher levels when compared to group 1 ($P = 0.02$), while although higher in group 7 compared to all the other groups (2-3-4-5 and 6), it did not reach a statistical significance.

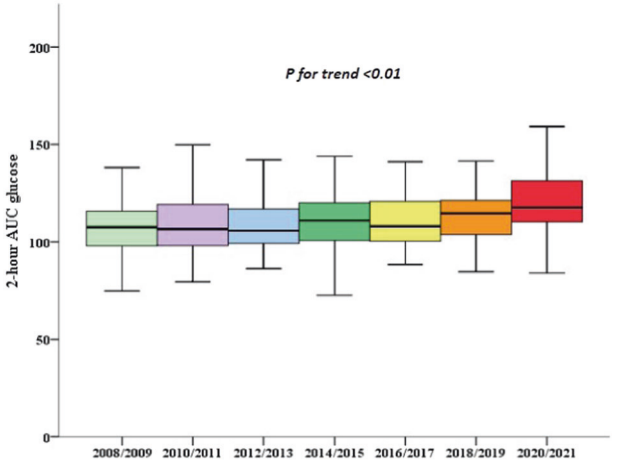

Fig. 2 AUC of the glycemia during OGTT in the seven groups.

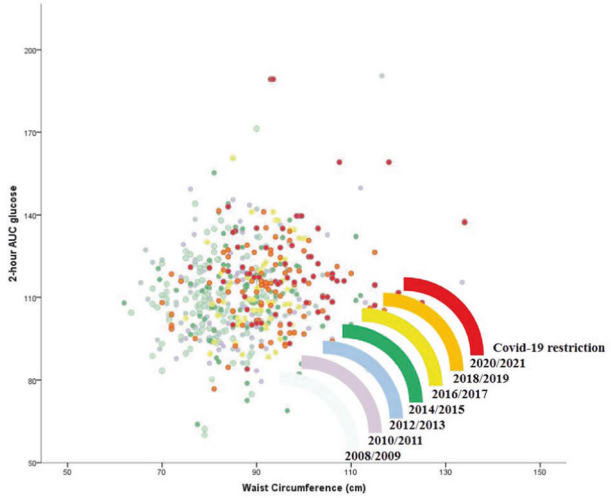

Fig. 3 The bad rainbow of COVID-19 time. The correlation between waist circumference and 2-h AUC glucose during OGTT that shows a progressive increase overtime.

Insulin resistance and secretion indices

Data on insulin resistance and secretion indices are reported in Table 2. HOMA-IR levels increased steadily and WBISI levels decreased steadily over time (all $P < 0.01$). In details, significant differences between group 7 compared to group 1, 2, 3, 4, and 5 (all $P < 0.01$) were documented. Although, group 7 showed higher levels when compared to group 6 it did not reach a statistical significance. Furthermore, values of WBISI were significantly different between group 7 compared to group 1 and 2 (all $P <$ 0.01). Although, group 7 showed lower values compared to group 3, 4, 5 and 6, it did not reach a statistical significance. FGIR index was different between the seven groups (P for trend $P < 0.01$) being significantly lower in group 7 compared to group 1 ($P <$ 0.01); while it did not reach a statistical significance when group 2-3-4-5 and 6 were compared to group 7. The DI index was significantly different between the seven groups (P for trend $P <$ 0.01) being significantly lower in group 7 when compared to group 6 ($P = 0.04$). While, although lower in group 7 compared to all the other groups (1-2-3-4 and 5), it did not reach a statistical significance. Finally, the IGI index was significantly different between the seven groups ($P < 0.01$). In details, a significant difference was documented between group 7 and group 1, 2, 3, and 4 ($P = 0.04$, $P = 0.02$, $P = 0.01$ and $P = 0.02$, respectively), while it did not reach a statistical significance when compared to group 5 and group 6.

Shape of OGTT curve

The distribution of shape of the OGTT curve, monophasic, biphasic and incessant increase was significantly different between the seven groups ($P < 0.01$). In particular, group 7 had a significant different distribution of the three shapes when compared to group 1 ($P < 0.0025$). In addition, although in group 7 the shape of OGTT curve respectively showed a lower and higher percentage of biphasic and incessant increase curves compared to all the other groups (2-3-4-5 and 6), it did not reach a statistical significance.

CV risk factors

CV risk factors of all participants are presented in Table 3. No significant differences were found between the seven groups for TC, LDL-C and TG values. In contrast, significant differences were identified for HDL-C between the seven groups ($P < 0.01$). In particular, subjects of group 7 showed lower HDL-C values compared to group 2 ($P < 0.01$), while it did not reach a statistical significance when compared to all the other groups. Significant differences between the seven groups were found for SDS-SBP and SDS-DBP (all $P < 0.03$), however without reaching significance during post-hoc analysis.

Correlations between WC and variables of interest

Pearson correlation documented a statistically significant correlation between WC and particularly the 2-h AUC Glucose ($\beta = 0.160$; $P < 0.001$, Fig. 3). In fact, as shown in Fig. 3, a progressive and significant increase of 2-h AUC Glucose values and of WC was documented over time, thus showing subjects in the group 7 (year 2020/2021 or COVID restriction group) the highest values in terms of AUC glucose and WC. Similarly, a significant correlation was documented between WC and fasting glucose ($\beta = 0.239$; $P < 0.001$), fasting insulin ($\beta = 0.385$; $P < 0.001$), 2-h AUC Insulin ($\beta = 0.261$; $P < 0.001$), HOMA-IR ($\beta = 0.414$; $P < 0.001$), WBISI ($\beta = -0.344$; $P < 0.001$), IGI ($\beta = 0.223$; $P < 0.001$), and HDL-C ($\beta = -0.180$; $P < 0.001$).

DISCUSSION

In order to contain and mitigate the spread of the novel Coronavirus and the large number of infections and deaths stringent containment measures were established in different countries [7]. Although the lockdown had the positive effect of flattening the epidemic curve, these mandatory measures also has disastrous effects on lifestyle changes [8, 10, 32–34]. Our database represents an important opportunity to explore and compare overall metabolic alterations in the pediatric population affected by overweight and obesity in a long observation period of 13 years starting in 2008. The second decade of the 21th century is associated with important social modifications related to both, alimentation and physical activity [13, 35]. COVID-19 restriction represents a further unexpected, speedy and radical modification in habits of the overall population imposing a stay-at-home lifestyle. The impact of the lockdown on adults has well been described but alarming data are also emerging for the pediatric population. In this respect, children and adolescent with overweight and obesity might represent one of most penalized categories during the lockdown. In a recent study, authors provide a description of the eating habits and lifestyle of Italian children and adolescent with overweight and obesity during the COVID-19 lockdown [34]. They showed increased consumption of carbohydrate, reduction in the consumption of fresh food, accompanied by a deficiency of vitamins and minerals [34]. In fact, more than half of the subjects increased the consumption of homemade desserts, bread, pasta, and pizza, cooked to fill the time [34]. However, the most relevant effect of lockdown was the imposed and justified sedentary lifestyle [36]. The practice of physical

activity among children decreased drastically due to time and space limitations and the lack of social stimuli related to its practice [37–39]. In addition, the increased exposure to television and electronic devices including time spent on the computer for education or entertainment, increased the time children spent on sedentary activities. More importantly, changes in children's habits are difficult to reverse once adopted and represent an increasing risk for obesity and non-communicable diseases both in the short and long term [4, 5].

Physical inactivity and sedentary behavior lead to reduced energy expenditure and are responsible for diminished AMPK activation and skeletal muscle glucose uptake providing increased substrate for de novo lipogenesis in adipose tissue and liver. Consequently, there is an expansion of adipose tissue mass, intrahepatic lipid accumulation, and increased lipid export from the liver as VLDL triacylglycerol particles and serum triacylglycerol with induction of systemic insulin resistance [40].

In addition, the transition to physical inactivity causes a brusque reduction in skeletal muscle insulin sensitivity, due to altered insulin signaling, contributing to a repartitioning of energy substrates into alternative tissues, increasing thereby central fat accumulation and ectopic storage within the liver and other organs, exacerbating insulin resistance [41–43]. As peripheral insulin resistance progresses, continued ectopic fat accumulation within the liver and pancreas precipitates development of the metabolic syndrome, a progressive decline in beta-cell function and, ultimately, T2D [40].

Extended time spent in sedentary behaviors is directly linked to poor metabolic outcomes including abnormalities in glucose homeostasis [44]. In our population we could not detect a worsening of SDS-BMI over time. In fact, we did not document statistically significant differences in SDS-BMI across the seven groups, thus evidencing contrasting data compare to other studies, showing significant increases during COVID-19 restriction. In contrast, in our study a progressive increase over the years has been documented for SDS-WC starting in 2014, reflecting the ongoing social modifications. However, SDS-WC worsened considerable in the COVID-19 restriction group being higher compared to all previous years. This important increase of SDS-WC reflects a progressive worsening of visceral fat distribution confirmed by the finding of increased body fat percentage and a reduction of muscle tissue percentage in the COVID-19 restriction group. Therefore, a redistribution of body composition in these children has occurred, certainly and strongly influenced by changes in habits and in particular by sedentary lifestyle. The role of abdominal obesity in the adult population has been comprehensively studied over the last years, but in the pediatric population is far from being completely clarified [45, 46]. Visceral fat contributes to distorted metabolism to a much greater amount than subcutaneous fat due to its location and metabolic characteristics. Recent study indicated that central body fat deposition in children increases the probability of cardiometabolic risk factors [35]. However, as known, visceral obesity is also a leading cause of altered glucose/insulin homeostasis. Thus, WC represents a clinical predictor on insulin resistance and incipient T2D [47] characterized by the combination of both insulin resistance and development of β-cell dysfunction [48]. Recent studies have shown that glucose levels rise already before the clinical diagnosis of diabetes, allowing diagnosis of prediabetes defined by IFG or IGT well before the onset of diabetes [49, 50]. It is therefore of crucial importance to explore possible alterations of glucose homeostasis in relation to the detected increased WC in our study population. In fact, to the best of our knowledge, this is the first study evaluating not only significant differences in body composition during the lockdown period but looking also to detailed glucose metabolism alterations including indices of insulin resistance and secretion. Glucose excursions during OGTT in the COVID-19 restriction group demonstrated profound differences. Not only fasting glycaemia was significantly high and a higher percentage of children presented with IGT, but also the glucose levels at each single timepoint were alarming elevated. This was tightly correlated to the increased values of WC. A recent study suggests that in children and adolescents with overweight and obesity a 1-h plasma glucose response during OGTT exceeding 132.5 mg/dL, was able to identify those with a worse metabolic profile due to impaired insulin sensitivity and secretion [51]. For adults 155 mg/dl has been proposed to be a good predictor for the progression to diabetes [52, 53]. In our study population a worrying high number of subjects had glucose levels at 60 min higher than the proposed values which thus result in a higher percentage of children (12%) finishing the OGTT with IGT and in an high number of subjects presenting the shape compatible with incessant increase curve. These overall blood glucose excursions represent profound modifications when compared to pre-pandemic findings. The previous findings were not surprisingly associated with a trend of increasing insulin resistance over time. HOMA-IR was higher in the COVID-19 restriction group compared to almost all others thus showing a lower hepatic and peripheric insulin sensitivity induced reasonable by redistribution of adipose tissue. Not only fasting insulin levels reflect insulin resistance but the entire insulin excursion curve during OGTT might be defined as a severe hyperinsulinemic status. These data are compatible with the pathophysiological compensatory process of high blood glucose levels that leads to increased insulin production, secondary to resistance to insulin action in the target organs. Not only insulin resistance, but also deterioration of β-cell function is fundamental to the initial development and progression to impaired glucose regulation. For assessing insulin secretion several indices have been proposed defining β-cell function trajectory in the transition from normal glucose tolerance to overt diabetes [54]. The most used surrogate index is Disposition Index which reflects the ability of β-cell to compensate insulin resistance status. In fact, with increasing insulin resistance over time, the DI index increased in our study population. One possible explanation for this finding might be that it reflects the capacity of the beta-cell to respond to increasing glucose levels with increased insulin production in the lower states of glucose intolerance, whereas the capacity starts to decline in the more advanced states of glucose intolerance. In fact, in the pre-pandemic period an appropriated response in insulin secretion was guaranteed whereas in the COVID-19 restriction group the drastic burden of glucose levels was not compensated by adequate insulin secretion. These alterations might be compatible with a condition of "pre-prediabetes" which has been previously proposed by different authors in order to contain further expansion of true glucose derangements. However, with time this compensatory increase in insulin is completely lost, resulting in hyperglycemia, glucose intolerance, and eventually, T2D.

It might therefore be speculated that where lifestyle modifications are not urgently implemented, progression to TD2 might be not be avoidable for our subjects.

In terms of CV risk factors COVID-19 restriction children presented higher values of systolic and diastolic blood pressure combined with lower HDL cholesterol values. This is in line with previous findings and tightly related to WC.

Some limitations of this study need to be acknowledged. In particular the assessment of a single OGTT, given the known variable reproducibility of this test. However, the study reflects what generally happens in the clinical setting, where the OGTT is a test, which can be easily performed, but it is repeated only when abnormal findings are detected. Due to the retrospective design no detailed anamnestic data for physical and dietic parameters are available. Therefore, further studies evaluating also these important issues are needed. More importantly, the data cannot fully show in an unequivocal way that the profound alterations are attributable to COVID-19 time or to a trend of increasing prevalence of overweight Italian children. Therefore, it is of paramount importance to compare our results to further subsequent researches in order to completely and undoubtedly elucidate this relevant issue.

In conclusion, our data demonstrate an alarming increase of unfavorable adipose tissue distribution, overtime, that are further worsened during COVID-19 restriction. This is associated with profound modifications in glucose/insulin homeostasis laying the grounds to an increased risk of a second hit of COVID-19 era related to a spread of new onset T2D pandemia. It is therefore mandatory to stimulate worldwide appropriate strategies that could diminish the impact of COVID-19 related lockdown on children's lifestyle.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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AUTHOR CONTRIBUTIONS

AM and NP drafted the manuscript. AM and NP devised the study and the main conceptual ideas. NP collected the data. NP and CG performed the statistical analysis. CG and FC provided critical feedback. All authors contributed to the manuscript and approved the submitted version.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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