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ORIGINAL PAPER

Exposure to Obesogenic Endocrine Disruptors in Childhood. Impact on Biomarkers of Metabolic Status

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Abstract

Childhood obesity is an escalating global health concern, partly driven by environmental factors such as endocrine disruptors (EDs), which can alter metabolism and promote adiposity. This cross-sectional study examined exploratory associations between exposure to obesogenic EDs (bisphenols, parabens and benzophenones) and body composition in 72 children aged 3 to 15 years (53 with obesity and 19 normal-weight controls) recruited from two hospitals in Spain. Metabolic status, body composition and urinary levels of EDs were evaluated using tandem mass spectrometry. The findings, which are pioneering in evaluating multiple exposure to chemicals, identify exploratory associations between the presence of EDs in 100% of the participants, with parabens the most frequently detected. Higher methylparaben levels were observed in the group with obesity. Correlational analyses revealed positive associations between specific EDs and adiposity parameters, including triponderal mass index and visceral fat percentage. These results suggest a potential link between exposure to EDs and the development of childhood obesity. The massive and early exposure to EDs underscores the urgent need for preventive policies and longitudinal studies to evaluate their effects. These preliminary findings provide exploratory insights for developing effective strategies to combat childhood obesity.

Keywords Childhood obesity · Endocrine disruptors · Metabolic risk · Chemical exposure

Introduction

Childhood obesity has become a serious public health issue, with its prevalence rising to pandemic proportions in recent years. In 2016, an estimated 650 million adults and 381 million children and adolescents worldwide were classified as overweight or obese (World Health Organization 2022). Notably, 41 million were children under the age of five (Ball et al. 2019). In Spain, the prevalence of childhood overweight is 23.3%, while childhood obesity affects 18.6% and continues to rise (World Health Organization 2022).

Obesity is also an important risk factor for numerous diseases such as diabetes, dyslipidemia, hypertension, metabolic syndrome and cardiovascular disease (Kumar and Kelly 2017). A high-calorie diet and lack of physical activity are primary contributors to the development and progression of obesity. In pediatric populations, therapeutic strategies are limited to lifestyle interventions, such as recommending healthy, low-calorie diets and regular physical exercise. While these approaches can help control obesity, the effectiveness is often limited, resulting in only modest and temporary weight loss (Vermeiren et al. 2021).

In this context, identifying novel factors involved in the regulation of energy metabolism is crucial for developing more effective strategies to combat obesity. Recent research has highlighted the potential role of exposure to chemicals that affect the endocrine system (Thoene et al. 2020). These compounds are known as endocrine disruptors (EDs),

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chemical substances foreign to the affected organism that can alter its hormonal balance or that of its offspring (Damstra et al. 2002). They can mimic the effect of natural hormones disrupting homeostasis and interfering with normal physiological functions. EDs are commonly found in pesticides, plastics, and cosmetic products, among other sources, leading to universal and often unnoticed human exposure (Velmurugan et al. 2017).

EDs are responsible for the increased incidence of certain metabolic diseases such as obesity, but their mechanisms of action are diverse and complex (Li et al. 2021). Many of these compounds are considered persistent organic pollutants, characterized by their long-lasting nature, bioaccumulation, toxicity at very low doses, and biomagnification through the food chain (Nadal et al. 2017).

Substances that have been clearly identified as EDs include the following:

Bisphenols are used in the production of polycarbonate plastics and epoxy resins, and primarily enter the body through the digestive tract. Common sources of exposure include tin cans, water bottles, kitchen utensils, paints, fabrics, car seats and various plastics. Among the most recognized bisphenols are bisphenol A (BPA) and bisphenol S (BPS) (Le Fol et al. 2017).

Phthalates and parabens are used to enhance the flexibility and durability of plastics. Similar to bisphenols, they are often present in food coatings and can be ingested through the diet. They are also found in products such as toys and cosmetics, where exposure can occur through inhalation (Xu et al. 2022).

Polybrominated diphenyl ethers have been used for several decades in industry for their flame-retardant properties. The peculiarity of these substances is that they do not bind chemically with the products to which they are added (such as furniture), facilitating their release and allowing their introduction into the human body by various routes: inhalation through the air, ingestion of contaminated water or oils or even food (especially those rich in fat) (Vuong et al. 2019).

Pesticides, **biocides and herbicides**, such as organophosphates, pyrethrins and pyrethroids can be found in both food and gardening products.

Polychlorinated biphenyls are used as coolants and lubricants in transformers, condensers, plasticizers, ink solvents and electrical equipment.

Metals and metalloids (lead, cadmium, nickel, mercury, arsenic, etc.) are present in food (fish and seafood) and in varnishes in construction materials, costume jewelry, batteries, toys, etc.

Perfluoroalkyl substances are one of the most widely used groups of chemicals in industry today. Their properties include stability at elevated temperatures and the ability to act as water and grease repellents. They are present in a multitude of everyday objects such as clothing, furniture, kitchen utensils, food packaging and non-stick surfaces.

Benzophenones are organic compounds of the ketone class, known for their ability to absorb ultraviolet radiation. They are widely used as ultraviolet filters in sunscreens, cosmetics, hair and nail care products, and are also found in plastic packaging, paints and coatings to protect against degradation caused by sunlight.

The effects of these substances depend on the hormonal system they impact and the timing of exposure, primarily affecting the estrogen or thyroid systems. Among their numerous metabolic effects, many of these substances have recently been identified as obesogenic, as they have been shown to interfere with how the body stores and processes fat, as well as with mechanisms regulating appetite and satiety (Nadal et al. 2017). The most common obesogenic EDs are parabens, bisphenols and benzophenones (Caporossi and Papaleo 2017). Nevertheless, there is limited information regarding exposure in infancy and childhood and its relationship with the development of obesity in children, whether occurring during gestation (Højsager et al. 2021) or in the postnatal stage (Aktağ et al. 2021).

80% of children with obesity will be adults with obesity and the metabolic complications of obesity begin in childhood (Ball et al. 2019). Therefore, understanding the impact of exposure to EDs as early as infancy is essential. The vast majority of studies investigating the interaction between EDs and the development of obesity have focused on exposure to individual chemicals. Research on the effects of simultaneous exposure to multiple chemicals in humans is scarce, and even more so in pediatric populations.

Based on these considerations, the main objective of this study was to characterize the levels of urinary exposure to various endocrine disruptors (bisphenols, parabens, and benzophenones) and explore their individual and grouped correlations with adiposity indicators and metabolic biomarkers in a pediatric population. Specifically, this work aims to describe the co-exposure profiles through hierarchical clustering and identify preliminary associations that could contribute to the development of childhood obesity. By focusing on these, we seek to provide a foundation for understanding how early-life exposure to multiple environmental chemicals relates to metabolic status in children.

Materials and Methods

Study Design and Participants

This cross-sectional observational study was conducted by the Pediatric Endocrinology service at two secondary-level

hospitals in Spain. The study population was selected using a convenience sampling approach, categorized into two groups for comparison: a group of children with obesity ($n=53$), identified based on a body mass index (BMI) > 2 standard deviations according to WHO criteria, and a group of normal-weight controls ($n=19$). The sample size was determined by the availability of patients during the study period at the participating hospitals. A post hoc power analysis was conducted to evaluate the robustness of the observed Spearman correlations. For the main associations identified between urinary EDs (such as BPA and parabens) and adiposity indices, with a total sample of 72 and observed correlation coefficients (rho) ranging from 0.32 to 0.55, the statistical power (1-β) was calculated to be between 0.82 and 0.99 ($\alpha=0.05$). This confirms that the study was sufficiently powered to detect the moderate-to-strong associations reported, despite the exploratory nature of the cross-sectional design. The study subjects were between 3 and 15 years of age, and voluntarily chose to participate in the study and their parents or legal guardians provided written informed consent. Patients were consecutively recruited from a childhood obesity clinic between October 2023 and October 2024. Nineteen healthy controls, with normal weight, were selected from routine health check-ups. Exclusion criteria included pre-existing metabolic diseases, endogenous obesity, or obesity secondary to other conditions.

Characterization of Metabolic Status

Obesity was defined using BMI percentiles, with values above the 95th percentile (age- and sex-specific) classified as obesity (Spanish Longitudinal Study of Growth 2017 (Carrascosa et al. 2018). Weight was recorded without clothes or shoes with a DC-430 scale (Tanita®: Middlesex, United Kingdom) (error +/±0.1 kg) and height with a 213 stadiometer, (Seca®: Birmingham, United Kingdom) (error +/±0.5 cm). BMI was calculated from anthropometric data and BMI Z-score was calculated using the Seinaptracker® program (Medicalsoft Intercath SL, University of Barcelona, Spain 2007–2008). Waist circumference was measured with a non-elastic tape at the midpoint between the lower costal margin and the iliac crest. Blood analysis included glucose, insulin, HOMA-IR, lipid profile, liver profile, uric acid, and HbA1c. Body composition was assessed via the InBody S10 (InBody Co., Ltd., South Korea), following manufacturer guidelines under controlled conditions.

Procedure

Exposure to obesogenic EDs was assessed via tandem mass spectrometry (UHPLC-MS/MS) to determine urinary phenol concentrations. Non-fasting urine samples were collected in 10 ml polypropylene tubes at the initial visit, between 9:00 and 11:00 a.m., and immediately stored at -80 °C. For analysis, the samples were thawed at room temperature, centrifuged, and an enzymatic solution of β-glucuronidase/sulfatase in 1 M ammonium acetate/acetic acid buffer solution (pH 5.0) was prepared. Each sample was enriched with 50 µL of enzyme solution to determine the total amounts (free and conjugated) of BPA, BPF, and BPS in urine and incubated for 24 h at 37◦C and supplemented with a standard replacement solution (5 mg/L EP-13C6, 2 mg/L BPA-D16 and 2 mg/L BP-d10) and 10% aqueous NaCl (pH 2.0, adjusted with 0.5 M HCl). Samples were mixed with acetone (dispersion solvent) and trichloromethane (extraction solvent), manually shaken and centrifuged. The sediment phase was transferred to a glass vial and the organic phase was evaporated under a stream of nitrogen. The residue was dissolved with acetonitrile/water and analyzed by UHPLC-MS/MS. The detection limit was defined as the minimum detectable amount of analyte with a signal-to-noise ratio ≥ 3 and was set at 0.1 ng/mL. The urinary concentrations of the phenolic compounds were expressed in µg/L. Due to the exploratory nature of this study and clinical constraints during sample collection, measurements were not normalized for urinary dilution. Consequently, raw concentrations were used for all subsequent statistical analyses.

To characterize the co-exposure profiles of the participants, a hierarchical cluster analysis was performed. This exploratory approach aimed to identify patterns or exposure profiles based on the concentrations of multiple EDs, rather than calculating a single mixture index. By using a dendrogram and a correlation matrix, we were able to describe how these substances group together in the pediatric population, providing a descriptive foundation for their potential combined presence in the organism.

Dietary quality was evaluated with the KidMed Mediterranean diet adherence scale (López-Gajardo et al. 2022). The index ranges from 0 to 12, based on a 16-question survey where positive dietary habits (e.g., fruit/vegetable consumption) add points and negative habits (e.g., skipping breakfast or consuming commercial baked goods) subtract points. Physical activity was estimated using the Krece Plus (Roman-Viñas et al. 2003) test, which evaluates weekly sports activity outside of school hours and daily screen time. Scores range from 0 to 5 points. The maximum test value is 10 and the minimum is 0. According to the overall test score, individuals are classified into three categories: Good (test value 9–10 for boys and 8–10 for girls), Fair (6 to 8 for boys and 5 to 7 for girls) and Poor (less than or equal to 5 for boys and less than or equal to 4 for girls) (Roman-Viñas et al. 2003).

Data Collection and Analysis

Data extraction was performed after obtaining informed consent. Variables were stored in a database, respecting confidentiality in accordance with the European General Data Protection Regulation (GDPR EU 2016/679).

A database was created to accurately capture the content of the data collection notebook. The data entry matrix was designed to include the possible ranges or values and to establish the various consistency rules between variables. Regarding the treatment of concentrations below the limit of detection (LOD) and detected but non-quantifiable values (LOQ), values were substituted with the LOD divided by the square root of 2 (LOD/√2) and with LOQ/√2, respectively. This method was chosen as it provides a more accurate estimation of the distribution parameters in environmental health studies when the proportion of non-detects is low-to-moderate. For compounds with high detection frequencies, such as parabens and bisphenol A, this approach ensured that all participants could be included in the correlational and clustering analyses.

The quality of the information received was controlled through an exploratory analysis to detect outliers, out-of-range values, or missing data. This analysis also provides insights into variable distributions and gives guidance on potential transformations.

A descriptive analysis was conducted based on BMI categorization (obese vs. non-obese), incorporating univariate regressions.

Data normality was assessed using the Shapiro-Wilk test. For the comparison of continuous variables between two groups (obesity vs. normal-weight), the Student's t-test was used for normally distributed data, while the Wilcoxon-Mann-Whitney U test was applied for non-normally distributed variables. Since the urinary concentrations of endocrine disruptors and several adiposity parameters did not follow a normal distribution, the Spearman rank correlation coefficient was used to evaluate the associations between variables and linear regressions with log-transformed variables for multivariate models.

For quantitative variables, results were presented as mean ± standard deviation, median with interquartile range, and minimum-maximum values. Hypothesis testing was performed using the Wilcoxon-Mann-Whitney or Kruskal-Wallis tests, depending on the number of grouping categories. In the latter case, post-hoc pairwise comparisons were conducted using the Wilcoxon-Mann-Whitney test, with *P*-values adjusted using the Benjamini-Hochberg method. For qualitative variables, frequency and proportions were calculated, with hypothesis testing performed using the χ^2 test with *P*-value simulation (2000 replicates). In all cases, statistical significance was set at $\alpha = 0.05$.

To evaluate the independent association between urinary ED concentrations and adiposity markers, multivariable linear regression models were constructed. These multivariable models were adjusted for potential confounding factors identified in the literature, including age, sex, physical activity, screen time, and adherence to the Mediterranean diet. This approach allowed us to estimate the relationship between ED exposure and metabolic status while controlling for lifestyle and demographic variables.

All analyses were performed in R (R Core Team, 2023). Similarly, STAMP® (Statistical Analysis of Metagenomic Profiles), a Python-based bioinformatics tool, was used statistical analysis and graph generation from large biological datasets.

Results

Anthropometric Characteristics

Between October 2023 and October 2024, 72 participants were included in the study (50% girls) with a mean age of 10.7 years (5.4–15.7 years). Of these, 53 had BMI compatible with obesity for their sex and age, and the remaining 19 were healthy children with normal weight. Their anthropometric characteristics are detailed in Table 1.

Mediterranean diet adherence scale scores showed no statistically significant differences between cases and controls. However, Krece Plus scores were lower in cases (3.93 vs. 6.21, $P = 0.002$), and screen time was higher (3.02 vs. 1.8 h, $P = 0.008$) (Table 1).

Body Composition

Body composition analysis was conducted for all participants (Table 2). The visceral fat area was significantly higher in cases than in controls ($P < 0.001$), as was the total body water/fat-free mass index (P 0.003).

The correlation between body fat, waist circumference and analytical markers of lipid and glycemic profile was analyzed using Sperman's test. A positive correlation was observed between waist circumference and total body fat, particularly perivisceral fat, while body fat showed a negative correlation with HDL levels (Table 3).

Endocrine Disruptors in Urine

Urine samples were analyzed for 10 phenolic EDs: BPA, BPS, bisphenol F (BPF), methylparaben (MPB), ethylparaben (EPB), propylparaben (PPB), butylparaben (BPB), benzophenone-1 (BP-1), benzophenone-3 (BP-3), and 4-hydroxy benzophenone (4-OH-BP).

Table 1 Anthropometric, lifestyle and analytical characteristics of the study participants

	Total participants ($N=72$)	Normal weight ($N=19$)	Obese ($N=53$)	P-value
Mean age (years)	10.76 (3.19)	10.31 (3.87)	10.93 (2.94)	0.5
Mean weight (kg)	61.62 (24.74)	41.31 (21.94)	68.90 (21.54)	**<0.001**
Mean height (cm)	148.68 (18.92)	142.31 (24.53)	150.96 (16.13)	0.091
Mean waist circumference (cm)	85.73 (16.65)	65.92 (12.69)	92.84 (11.30)	**0.001**
Mean waist circumference (SDS)	3.52 (2.19)	0.55 (1.37)	4.51 (1.36)	**<0.001**
Mean fat mass (kg)	22.16 (12.94)	8.26 (6.63)	26.97 (10.97)	**<0.001**
Mean fat-free mass (kg)	40.14 (15.10)	34.62 (16.67)	42.05 (14.19)	0.077
Skeletal muscle mass (kg)	21.95 (9.07)	18.57 (10.01)	23.12 (8.51)	0.071
Body fat percentage	33.63 (12.08)	17.93 (7.92)	39.06 (7.71)	**<0.001**
Mean BMI (kg/cm^2)	26.56 (6.37)	18.68 (4.02)	29.38 (4.36)	**0.003**
Mean TMI (kg/cm^3)	17.81 (3.50)	13.10 (1.33)	19.50 (2.25)	**0.016**
Mean percentile of SBP	74.76 (26.00)	65.83 (27.27)	77.79 (25.09)	0.1
Mean percentile of DBP	61.68 (20.54)	56.28 (21.81)	63.51 (19.98)	0.2
KIDMED score mean (SDS)	4.67 (2.80)	5.26 (2.28)	4.45 (2.95)	0.3
Krece-plus score mean (SDS)	4.64 (2.51)	6.21 (2.02)	3.93 (2.40)	**0.002**
Screen time (hours) (SDS)	2.66 (1.52)	1.84 (1.17)	3.02 (1.52)	**0.008**
Sports time (hours) (SDS)	2.75 (3.29)	3.74 (3.25)	2.31 (3.25)	0.14
TSH (µU/mL)	2.39 (1.05)	2.65 (0.91)	2.31 (1.08)	0.3
Total cholesterol (mg/dL)	145.82 (32.84)	154.31 (31.63)	143.21 (33.06)	0.2
HDL (mg/dL)	46.29 (9.18)	53.64 (9.15)	44.31 (8.20)	**0.002**
LDL (mg/dL)	88.91 (24.83)	94.43 (20.94)	87.36 (25.79)	0.3
Triglycerides (mg/dL)	76.82 (41.72)	66.88 (24.45)	79.88 (45.50)	0.3
Glucose (mg/dL)	88.30 (7.16)	86.88 (7.24)	88.75 (7.15)	0.3
Insulin (µU/dL)	12.61 (8.58)	8.05 (6.05)	13.90 (8.79)	**0.026**
HOMA	2.78 (1.95)	1.76 (1.49)	3.07 (1.98)	**0.031**
HbA1c (%)	5.29 (0.25)	5.28 (0.25)	5.29 (0.25)	0.9
GOT (U/L)	26.55 (10.29)	28.31 (12.19)	26.00 (9.70)	0.4
GPT (U/L)	21.87 (11.03)	17.31 (6.69)	23.27 (11.75)	0.075
GGT (U/L)	16.38 (11.02)	13.64 (2.31)	17.14 (12.30)	0.2
Uric acid (mg/dL)	5.26 (1.32)	4.61 (1.17)	5.40 (1.32)	0.08
Cortisol	10.49 (3.63)	10.82 (2.07)	10.45 (3.80)	0.8

SDS, standard deviation; BMI, body mass index; TMI, triponderal mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TSH, thyroxine stimulating hormone; HDL, high-density lipoprotein; LDL, low density lipoprotein; HOMA, insulin resistance index; HbA1c, glycosylated hemoglobin; GOT, aspartate aminotransferase; GPT, glutamic-pyruvic transaminase; GGT, gamma-glutamyl transferase. Values in bold indicate statistical significance at $P < 0.05$.

Differences between BMI groups were assessed using the Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared using the Pearson's chi-squared test.

At least one ED was detected in 100% of the participants. Sex-specific differences in detection rates are shown in Fig. 1. Overall, levels were higher in girls, except for BPA and MPB, which were more elevated in boys.

The number of detected EDs per participant ranged from six to nine. The most commonly detected phenols were BPA, MPB, and BP3, which were present in 100% of the participants. The detection of BPB and 4-OH-BP was higher in children with excess weight. The mean urinary phenol blood levels were as follows: BPA, 2.78 ng/ml; BPS, 1 ng/ml; BPF, 0.68 ng/ml; MPB, 59.87 ng/ml; EPB, 2.11 ng/ml; PPB, 4.11 ng/ml; BP-1, 1.92 ng/ml; BP-3, 5.15 ng/ml; and 4-OH-BP, 0.88 ng/ml.

Box-plot diagrams were obtained for the ED concentrations studied revealed no significant differences between participants with normal weight and those with obesity, a finding confirmed by Student's t-test with a 95% confidence level.

For phenols, and many environmental pollutants, clinically significant levels or reference values have not been established. The phenol concentrations found in our urine samples were similar to those reported in other studies in children (Apel et al. 2017), except for MPB, which was notably elevated in the group with obesity (mean concentration 71.55 ng/ml, range 0.11-774.72 ng/ml) compared to controls (mean concentration 27.27 ng/ml, range 0.43-346.67 ng/ml). The relationship between ED levels and anthropometric characteristics is shown in Table 4.

Associations Between Endocrine Disruptors, Dietary Habits, and Physical Activity

Multivariable regression models revealed that lifestyle factors were significantly associated with specific endocrine disruptor (ED) levels (Table 4). Specifically, a significant negative association was found between BPF and KIDMED scores (β = -0.140, $p=0.02$), suggesting that lower adherence to the Mediterranean diet is linked to higher BPF exposure. Regarding physical activity, EPB concentrations were negatively associated with sports time (β = -0.109, $p=0.04$),

Table 2 Body composition characteristics of the study participants assessed by electrical bioimpedance

	Total participants (*N* = 72)	Normal weight (*N* = 19)	Obese (*N* = 53)	*P*-value
Intracellular water (L)	18.36 (6.95)	15.77 (7.68)	19.26 (6.53)	0.072
Extracellular water (L)	11.04 (4.11)	9.47 (4.48)	11.59 (3.87)	0.063
Total body water (L)	29.40 (11.05)	25.24 (12.15)	30.84 (10.38)	0.068
Extracellular water/ total body water (L)	0.38 (0.01)	0.38 (0.01)	0.38 (0.01)	0.6
Body cell mass (Kg)	26.30 (9.96)	22.58 (10.98)	27.58 (9.36)	0.071
Bone mineral content (Kg)	2.30 (0.91)	2.14 (1.02)	2.36 (0.87)	0.4
Arm circumference (cm)	30.31 (5.86)	23.76 (5.09)	32.58 (4.17)	**< 0.001**
Arm muscle circumference (cm)	23.38 (4.66)	20.04 (4.54)	24.54 (4.15)	**< 0.001**
Waist circumference (cm)	78.98 (17.40)	64.26 (13.54)	84.07 (15.67)	**< 0.001**
Visceral fat area (cm^2)	95.17 (57.25)	31.83 (28.03)	117.10 (47.60)	**< 0.001**
Basal metabolic rate (Kcal/d)	1,236.73 (326.19)	1,117.61 (360.10)	1,277.96 (306.58)	0.077
Total body water/fat free mass (L/kg)	73.32 (0.51)	72.97 (0.57)	73.44 (0.43)	**0.003**
Phase angle (º)	5.82 (1.27)	5.52 (0.67)	5.92 (1.42)	0.2

Data are expressed as mean ± SD. Differences between groups were evaluated using the Student's t-test or the Wilcoxon-Mann-Whitney U test, following the assessment of normality via the Shapiro-Wilk test. Values in bold indicate statistical significance at $P < 0.05$.

Table 3 Spearman correlation analysis between body composition and metabolic parameters

	Fat mass	Visceral fat area (cm^2)	Total body water/fat free mass (L/kg)
Waist circumference (cm)	**0.582 [0.446, 0.718]** *p*-value: <0.01	**2.306 [1.642, 2.970]** *p*-value: <0.01	**0.005[-0.005, 0.016]** *p*-value: 0.30
HDL (mg/dL)	**-0.198[-0.409, 0.013]** p-value: 0.07	**-0.919[-1.950, 0.112]** p-value: 0.08	-0.003 [-0.020, 0.013] p-value: 0.67
HOMA	-0.890 [-7.490, 5.709] p-value: 0.79	-2.523 [-34.737, 29.692 p-value: 0.88	0.086 [-0.421, 0.593] p-value: 0.73
Insulin (µU/dL)	0.389 [-1.104, 1.881] p-value: 0.60	1.750 [-5.536, 9.037] p-value: 0.63	-0.024 [-0.139, 0.090] p-value: 0.67
R^2 Adjusted	0.737	0.677	-0.031

HDL, high-density lipoprotein; HOMA, insulin resistance index.
Values in bold indicate statistical significance at $P < 0.05$.

while, conversely, BP-1 showed a positive association with weekly hours of sport (β = 0.141, $p = 0.01$). These results indicate that dietary habits and exercise frequency are relevant factors to consider when evaluating the exposure profiles of phenols and benzophenones in children.

Associations Between ED Exposure and Adiposity Markers

Initial bivariate analysis using Spearman correlations showed several significant positive associations between urinary ED levels and markers of adiposity. To confirm these findings, multivariable linear regression models were applied, adjusting for age, sex, and lifestyle factors. In these adjusted models, ED concentrations were log-transformed to ensure the normality of residuals. The associations remained significant for specific compounds; notably, BPA and BP-1 showed significant positive associations with fat mass percentage, but significant negative associations with visceral fat area (Table 4). This indicates that these relationships are independent of key potential confounders. For other compounds, although initial crude correlations were observed, the associations were attenuated in the multivariable models, and the adjusted R^2 values indicated a modest overall contribution to the variance (Table 4).

Correlational and Cluster Analysis of Urinary ED Concentrations

An analysis of correlations between all possible ED pairs was performed (Fig. 2). Figure 2A shows Spearman's correlation coefficients, indicating the strength of the monotonic relationships between the variables. Strong correlations were observed between MPB and PPB, MPB and BPB, EPB and BPB, and BP-1 and BP-3, suggesting related exposure patterns or shared metabolic pathways. The dendrogram further supports these correlations, particularly highlighting the clusters between MPB and PPB, and BP-1 and BP-3 (Fig. 2B).

The associations between urinary ED levels and anthropometric and body composition parameters were evaluated using multivariable linear regression models (Table 4). After adjusting for potential confounders, a statistically significant positive association was identified between BPA and BP-1 and fat mass percentage. Conversely, a statistically significant negative association was observed between BPA and BP-1 and visceral fat area.

	t	*P*-value
BPA	-0.737	0.464
BPS	0.476	0.636
BPF	-0.162	0.872
MPB	-0.634	0.528
EPB	0.616	0.540
PPB	-0.080	0.936
BPB	-0.949	0.346
BP-1	1.165	0.248
BP-3	0.528	0.599
4-OH-BP	-0.984	0.328

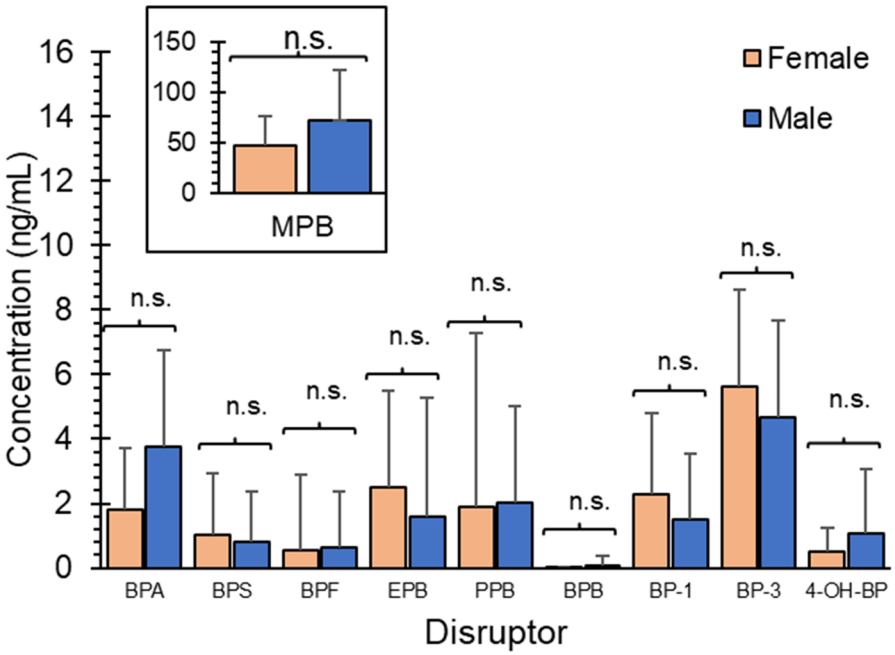


Fig. 1 Phenol levels detected in urine (ng/ml), classified according to gender. Student's *t*-test results. n.s. = no significant differences observed across groups (*P*-value > 0.05)

Discussion

Our study is the first to investigate the presence of obesogenic EDs in a population of children, revealing the presence of EDs in all the participants. Paraben levels were particularly high and have been linked to excess weight in cases of prenatal exposure (Starling 2020).

Childhood obesity is a growing public health concern due to its many short- and long-term consequences for children's physical, emotional, and social well-being. Obesity is associated with an increased risk of chronic diseases such as type 2 diabetes, hypertension, and cardiovascular disorders, as well as psychological and self-esteem issues. Understanding the role of ED exposure in obesity is critical for developing targeted interventions and public health strategies. Environmental health encompasses all external physical, chemical, and biological factors affecting an individual. According to the World Health Organization, environmental factors contribute to 24% of the global disease burden and 23% of mortality (Tardón 2022).

Exposure to EDs during childhood is common yet often unnoticed. The potential effects are multifaceted, including weight gain. In 2015, the Parma consensus broadened the term obesogen to include EDs that influence metabolic conditions associated with obesity, such as insulin resistance, hypertension, dyslipidemia, and hyperglycemia, ultimately contributing to the development of metabolic syndrome (Heindel et al. 2015).

Our study includes participants spanning a broad range of childhood ages, which is particularly valuable given the limited research analyzing how the early-life environment influences obesity development. The similar proportion of boys and girls in our cohort ensures that the results are representative of both sexes. Furthermore, by comparing data from children both with normal weight and with overweight, our study provides more robust evidence regarding metabolic changes and their association with BMI. The classification into cases (children with obesity) and controls (normal-weight children) was appropriate, as both groups exhibited significantly different characteristics, not only in anthropometric parameters but also in body composition.

No significant differences were found in Mediterranean diet adherence, likely due to the study population residing in the Mediterranean basin. However, daily screen time was significantly higher in children with overweight, indicating a more sedentary lifestyle.

Our findings highlight a complex interplay between lifestyle habits and ED exposure. The negative association between BPF and KIDMED scores suggests that children with poorer dietary quality may be more exposed to certain phenols, possibly through a higher intake of ultra-processed foods and plastic-packaged products. Furthermore, the diverging associations between physical activity and different compounds—where EPB was linked to lower sports time but BP-1 was associated with higher sports time — underscore the variety of exposure routes. While some compounds may be related to sedentary indoor environments,

Table 4 Multivariable linear regression analysis between body composition parameters and log-transformed urinary concentrations of endocrine disruptors

	BMI (kg/cm2)	TMI (kg/cm^3)	Waist circumference (cm)	Fat mass (%)	Visceral fat area (cm^2)	KIDMED score mean	Sports time (h)	R2 Adjusted
BPA	-0.770 [-1.869, 0.328] *p*-value = 0.17	0.781 [-0.782, 2.344] *p*-value = 0.32	0.159 [-0.158, 0.477] *p*-value = 0.32	0.204 [0.071, 0.337] *p* value = < 0.01	-0.021 [-0.041, -0.001] *p*-value = 0.04	0.008 [-0.092, 0.107] *p*-value = 0.88	0.008 [-0.072, 0.088] *p*-value = 0.85	0.051
BPS	0.551 [-0.812, 1.914] p-value = 0.42	-0.723 [-2.662, 1.217] p-value = 0.46	-0.153 [-0.547, 0.241] p-value = 0.44	-0.047 [-0.211, 0.117] p-value = 0.57	0.004 [-0.020, 0.029] p-value = 0.73	-0.046 [-0.169, 0.078] p-value = 0.46	0.002 [-0.097, 0.101] p-value = 0.97	-0.100
BPF	-0.920 [-2.195, 0.354] p-value = 0.15	1.241 [-0.573, 3.055] p-value = 0.18	0.195 [-0.173, 0.564] p-value = 0.29	0.132 [-0.022, 0.286] p-value = 0.09	-0.011 [-0.034, 0.012] p-value = 0.35	-0.140 [-0.255, -0.024] **p-value = 0.02**	-0.020 [-0.113, 0.073] p-value = 0.67	0.115
MPB	0.382 [-2.293, 3.057] p-value = 0.78	-0.676 [-4.483, 3.131] p-value = 0.72	-0.183 [-0.957, 0.590] p-value = 0.64	0.149 [-0.174, 0.472] p-value = 0.36	-0.012 [-0.060, 0.035] p-value = 0.61	0.100 [-0.143, 0.343] p-value = 0.41	-0.121 [-0.316, 0.074] p-value = 0.22	-0.060
EPB	-0.819 [-2.242, 0.605] p-value = 0.25	1.245 [-0.780, 3.271] p-value = 0.22	0.251 [-0.161, 0.662] p-value = 0.23	0.119 [-0.052, 0.291] p-value = 0.17	-0.016 [-0.042, 0.009] p-value = 0.21	-0.076 [-0.205, 0.053] p-value = 0.24	-0.109 [-0.213, -0.006] **p-value = 0.04**	0.160
PPB	-0.603 [-2.589, 1.383] p-value = 0.54	0.808 [-2.019, 3.634] p-value = 0.57	0.219 [-0.355, 0.794] p-value = 0.45	-0.012 [-0.252, 0.227] p-value = 0.92	0.005 [-0.030, 0.041] p-value = 0.76	0.071 [-0.109, 0.251] p-value = 0.43	-0.140 [-0.285, 0.004] p-value = 0.06	-0.004
BP-1	-1.151 [-2.614, 0.313] p-value = 0.12	1.542 [-0.541, 3.625] p-value = 0.14	0.289 [-0.134, 0.712] p-value = 0.18	0.186 [-0.010, 0.363] **p-value = 0.04**	-0.029 [-0.055, -0.002] **p-value = 0.03**	-0.066 [-0.199, 0.067] p-value = 0.32	0.141 [0.035, 0.248] p-value = 0.01	0.062
BP-3	-0.982 [-2.429, 0.465] p-value = 0.18	1.413 [-0.646, 3.471] p-value = 0.17	0.273 [-0.146, 0.691] p-value = 0.20	0.129 [-0.045, 0.304] p-value = 0.14	-0.024 [-0.050, 0.002] p-value = 0.07	-0.040 [-0.171, 0.092] p-value = 0.55	0.048 [-0.057, 0.154] p-value = 0.36	-0.059
4-OH-BP	-0.003 [-1.398, 1.391] p-value = 1.00	-0.065 [-2.050, 1.919] p-value = 0.95	-0.010 [-0.413, 0.393] p-value = 0.96	0.002 [-0.166, 0.170] p-value = 0.98	-0.003 [-0.027, 0.022] p-value = 0.84	-0.033 [-0.159, 0.094] p-value = 0.61	-0.009 [-0.111, 0.092] p-value = 0.86	-0.133

BPA, bisphenol A; BPS, bisphenol S; BPF, bisphenol F; MPB, methylparaben; EPB, ethylparaben; PPB, propylparaben; BP-1, benzophenone 1; BP-3, benzophenone 3; 4-OH-BP, 4-hydroxybenzophenone.

Data in bold represent those with statistical significance ($P < 0.05$).

others, like benzophenones (BP-1), could be linked to outdoor activities and the subsequent use of personal care products such as sunscreens. These observations reinforce the necessity of including lifestyle variables as key covariates in environmental health studies to avoid confounding bias.

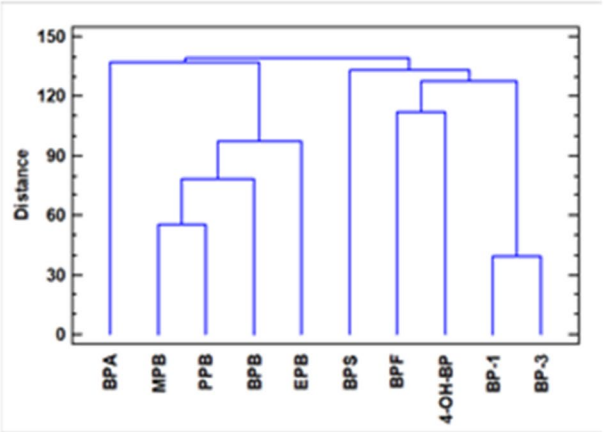
Prolonged screen use is linked to weight gain through reduced physical activity, increased consumption of unhealthy foods, and exposure to high-calorie food advertising. Excessive screen time can also disrupt sleep patterns, increasing obesity risk. The American Academy of Pediatrics and the WHO recommend complete avoidance of screen use in children under 2 years of age, limiting screen time to less than 1 h in children aged 2 to 5 years and to less than 2 h between the ages of 5 and 17 years. However, most children, especially children with obesity, do not adhere to these guidelines (Cartanyà-Hueso et al. 2022). Similar findings were described by Wolf (Wolf et al. 2018) and Kolovos (Kolovos et al. 2021), who found an overall daily average of 2 h and 19 min of screen exposure in children aged 0 to 8 years and 3 h in children aged 10 to 18 years.

The children with overweight had moderate obesity and exhibited metabolic alterations, including elevated insulin levels, higher HOMA index, and worse lipid profiles, indicating increased susceptibility to metabolic disorders. These findings underscore the seriousness of childhood obesity and the need for early interventions.

Body composition also differed between groups, with the obese group showing greater perivisceral fat accumulation. This central fat distribution was significantly associated

	BPA	BPS	BPF	MPB	EPB	PPB	BPB	BP-1	BP-3	4-OH-BP
BPA		0.08	0.11	0.13	0.02	0.02	-0.03	0.32	0.33	0.11
BPS	0.08		0.25	0.18	0.08	0.20	0.06	0.13	0.17	0.35
BPF	0.11	0.25		0.06	0.17	0.02	0.16	0.10	0.20	0.23
MPB	0.13	0.18	0.06		0.47	0.55	0.24	0.03	0.09	0.06
EPB	0.02	0.08	0.17	0.47		0.44	0.06	-0.07	0.11	0.11
PPB	0.02	0.20	0.02	0.55	0.44		0.16	-0.15	-0.19	0.24
BPB	-0.03	0.06	0.16	0.24	0.06	0.16		0.00	-0.06	-0.18
BP-1	0.32	0.13	0.10	0.03	-0.07	-0.15	0.00		0.83	0.21
BP-3	0.33	0.17	0.20	0.09	0.11	-0.19	-0.06	0.83		0.18
4-OH-BP	0.11	0.35	0.23	0.06	0.11	0.24	-0.18	0.21	0.18	

(a)



(b)

Fig. 2 **a** Spearman's product moment correlations between each pair of variables. Data: raw concentrations without transformations. **b** Dendrogram obtained from the concentrations of endocrine disruptors. Patients = 72

with waist circumference, reinforcing its value as an anthropometric measure of fat mass in children.

Our study's strength lies in the simultaneous analysis of a wide range of EDs commonly encountered through ingestion, inhalation, and skin absorption. Assessing multiple EDs helps understand the effects of co-exposure, particularly in childhood obesity, and identifies potential synergistic interactions that may amplify adverse health outcomes. This comprehensive approach is essential for designing more effective prevention strategies and public health policies to protect vulnerable populations, including children, from the risks associated with ED exposure.

All the participants in our study had at least one detectable disruptor in urine, with most showing a combination of bisphenols and parabens, reflecting findings from previous research (Nadal et al. 2017). This widespread exposure, even at early ages, underscores the importance of studies like ours that assess the effect of these chemicals on children's health.

Few publications have analyzed exposure to multiple EDs during childhood and/or adolescence and their association with various obesity markers (Heindel et al. 2022). Research on BPA has identified a positive association between BPA levels and obesity (Mustieles et al. 2019). Studies such as Menale et al. (Menale et al. 2017) comparing patients with obesity with and without metabolic syndrome, have demonstrated significantly higher urinary BPA levels in patients with metabolic syndrome or insulin resistance. Various mechanisms have been described by which bisphenols alter energy storage and metabolism such as dysregulation of messenger RNA and microRNA (Verbanck et al. 2017), alterations in the hypothalamic-pituitary-gonadal

axis (Yang et al. 2017), disruption of adiponectin synthesis and secretion (Liu et al. 2019), promotion of preadipocyte differentiation, inhibiting the peroxisome proliferator-activated receptor gamma (PPARγ) (Zheng et al. 2016), and downregulating of uncoupling protein 1 expression (Verbanck et al. 2017), among others (Nadal et al. 2017).

The maximum urinary BPA levels in our sample were close to the safe limit established by the Commission on Human Biomonitoring (Apel et al. 2017). While BPA concentrations were higher in the case group than in controls, the difference was not statistically significant. This may be due to lower exposure levels compared to previous studies, likely due to BPA use restrictions (Liu et al. 2019). As BPA is replaced by BPF and BPS, both of which have been linked to increased obesity risk in children and adolescents (Liu et al. 2019; Thoene et al. 2020), a critical question remains regarding the cumulative effects of these bisphenols. Notably, some studies have reported adverse effects even at exposure levels lower than those detected in our study (Verbanck et al. 2017). Indeed, many scientists have advocated a "zero threshold" approach to ED exposure (Rochester and Bolden 2015), as the in vitro effects of high doses do not always reliably predict the safety of low doses (Apel et al. 2017).

Regarding parabens, the levels in our participants with excess weight were higher than the limits described by other authors (Apel et al. 2017) and established as safe. The literature supports a positive association between paraben levels and the increase in childhood obesity (Højsager et al. 2021), particularly with increased BMI and body fat percentage. This is in agreement with previous studies (Højsager et al. 2021), and is explained through the action of parabens on leptin and proopiomelanocortin. An epigenetic modification is produced that reduces proopiomelanocortin levels, altering some of its usual functions such as the induction of satiety in the hypothalamus (Leppert et al. 2020). Additionally, parabens promote adipocyte differentiation through the PPARγ pathway, increasing adiposity, especially butylparaben, as reported by Hu et al. (Hu et al. 2017).

The relationship between chemical levels and body composition showed that at least one compound from each phenol group (bisphenols, parabens, benzophenones) was associated with adiposity. Interestingly, our multivariable models showed that BPA and BP-1 were positively associated with fat mass percentage, while a negative association was observed with visceral fat area. These findings suggest a complex role of EDs in adipose tissue distribution during childhood. The negative correlation between the ED levels and BMI may stem from the limitations of BMI in estimating body composition, as it does not account for body mass distribution. TMI, in contrast, has been proposed as a more accurate adiposity predictor in children and adolescents because it is less affected by height and has a more linear relationship with body fat (De Lorenzo et al. 2019). Furthermore, the observed negative association with visceral fat in our study—despite a positive association with total fat mass percentage—could indicate that certain EDs alter metabolism in ways that promote peripheral rather than visceral fat accumulation in this specific age group, or it may reflect differences in chemical storage within different fat depots (Amato et al. 2021). Moreover, in pediatric populations, a child with a lower BMI but a higher TMI may have a lower relative weight due to lower lean mass, but a higher proportion of body fat (Niu et al. 2023).

The benzophenone group, specifically BP-1, suggested a potential association with higher body fat percentage. While these chemicals have been more commonly associated with neurodevelopmental disorders, male infertility, and intrauterine growth restriction (Long et al. 2019), they have also been linked to potential obesogenic effects (Thoene et al. 2020). Our findings suggest an association with specific adiposity markers, such as fat mass percentage, although these relationships were not consistently observed across all anthropometric parameters, such as TMI or waist circumference, in the multivariable models. These results highlight the importance of using detailed body composition markers alongside traditional metrics to better understand the role of benzophenones in pediatric metabolic health.

The individual analysis of endocrine disruptors has several limitations, particularly as it does not account for interactions between different molecules in the body, which may amplify or mitigate biological effects. Therefore, simultaneously measuring multiple EDs provides a comprehensive exposure profiling, better reflecting real-world conditions and detecting interactions that may influence biological outcomes. This allows for the evaluation of both synergistic and inhibitory effects, providing a more accurate picture of their consequences on health.

Our findings emphasize the growing concern about obesogenic substance exposure, especially in children and adolescents. These stages involve the maturation of key endocrine systems that are vulnerable to chemical exposure. This increased susceptibility calls for enhanced surveillance and prevention efforts to reduce exposure to EDs and their health effects. The strong link between ED exposure and obesity prevalence underscores the need to assess these chemicals in patient samples during obesity consultations, as such exposure is often overlooked in medical history assessments. Studies are also needed to evaluate the impact of industrial, governmental, and domestic measures aimed at reducing exposure to environmental pollutants, particularly in vulnerable populations like children.

Despite the relevance of our findings, several limitations must be addressed. First, the cross-sectional design

prevents us from establishing causal relationships. Second, although we employed multivariable GLMs, the potential residual confounding remains, as other unmeasured factors (e.g., total caloric intake or specific chemical co-exposures) could influence the observed associations. Third, the use of a single spot urine sample may not fully reflect long-term exposure to these rapidly metabolized compounds; however, this is a common challenge in large-scale pediatric studies. Regarding the urine dilution, although we did not apply a formal creatinine or specific gravity correction, we adjusted for age and sex, which are primary determinants of urinary flow. Furthermore, we acknowledge the risk of type I error due to multiple statistical comparisons; therefore, our results should be considered exploratory. Finally, while we characterized exposure profiles through clustering, the absence of complex mixture models means that the cumulative or synergistic effects of these substances could not be fully quantified. However, it is more likely to underestimate rather than overestimate exposure. Approaches such as Weighted Quantile Sum regression (Carrico et al. 2015) and Bayesian Kernel Machine Regression (Bobb et al. 2015) allow for the estimation of joint effects and the identification of key contributors within a mixture. These methodologies have been successfully applied in cohorts such as INMA to evaluate the impact of metal or phenol mixtures on child development (García-Villarino et al. 2022; Güil-Oumrait et al. 2022). Given our exploratory design and sample size, we prioritized a descriptive profiling approach; however, applying these multivariable mixture models in larger longitudinal cohorts will be essential to confirm the cumulative impact of EDs on pediatric metabolic health. Another limitation of our study is the small sample size, which, while comparable to previous studies, may reduce the statistical power to detect significant differences.

Despite these limitations, our study is valuable as it provides data on exposure to multiple disruptors, reflecting real-world environmental exposure. Although specific mixture modeling was not performed, the identification of co-exposure patterns through hierarchical clustering highlights the complexity of environmental chemical mixtures and their potential link to obesity. We also analyzed body composition, rather than relying solely on anthropometric data, adding value to the findings. To our knowledge, this is the first study in our setting to focus on the pediatric population and the effects of ED exposure during this critical stage of development.

The presence of EDs affected all the participants in our study, highlighting the ubiquity of these compounds and the need to evaluate their effects in the pediatric population. A deeper understanding of the interactions between obesogenic EDs and metabolism can undoubtedly guide the design of strategies to minimize exposure to these chemicals, optimizing health outcomes. Additionally, it may contribute to the identification of new biomarkers for the early diagnosis of complications associated with the disease and its prognosis in adulthood. This knowledge will enable the development of more targeted and effective preventive and therapeutic strategies, ultimately improving the quality of life for future generations.

In conclusion, exposure to EDs in childhood is massive and universal, with indications of potential association between exposure to certain EDs and adiposity markers in the pediatric age group. Given the ubiquitous and universal nature of ED exposure, as well as the challenges regulatory authorities face in controlling it, investigating the interactions between environmental factors and health is essential. For condition such as childhood obesity—characterized by severe medium- and long-term consequences and limited therapeutic options—reducing exposure to EDs presents a promising avenue for innovative therapeutic strategies.

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Author Contributions APNR: Study concept and design; study supervision; statistical analysis; interpretation of results; drafting and critical revision of the manuscript. LATG: laboratory analyses; data analysis and quality control; input on the discussion section. NPF: data visualization; literature search; interpretation of findings; review and revision of the manuscript for important intellectual content. FSF: participant recruitment and clinical data collection; coordination of hospital collaborations; review of the manuscript for accuracy and coherence.

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Data Availability The data that support the findings of this study are available on request from the corresponding author.

Materials Availability The authors declare that all material included in this manuscript is original and does not require permission for reproduction from other sources.

Declarations

Conflict of Interest The authors declare no conflicts of interest.

Ethical Approval The study was approved by the Research Ethics Committee (approval code: 21/039) and conducted in accordance with the Declaration of Helsinki. It also complies with the ethical policies of Public Health Challenges.

Consent to Participate Informed consent was obtained from the parents or legal guardians.

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