Journal of the Endocrine Society, 2023, **7**, 1–11
https://doi.org/10.1210/jendso/bvad014
Advance access publication 2 February 2023
Clinical Research Article

Cardiometabolic Risk and Its Relationship With Visceral Adiposity in Children With Cerebral Palsy

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Abstract

Context: Adults with cerebral palsy (CP) display a higher prevalence of cardiometabolic disease compared with the general population. Studies examining cardiometabolic disease risk in children with CP are limited.

Objective: The purpose of this study was to determine if children with CP exhibit higher cardiometabolic risk than typically developing children, and to examine its relationship with visceral adiposity and physical activity.

Methods: Thirty ambulatory children with CP and 30 age-, sex-, and race-matched typically developing control children were tested for blood lipids, glucose, and the homeostatic model assessment of insulin resistance (HOMA-IR). Visceral fat was assessed using dual-energy x-ray absorptiometry. Physical activity was assessed using accelerometer-based monitors.

Results: Children with CP had higher total cholesterol, low-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol (non-HDL-C), glucose, prevalence of dyslipidemia, prevalence of prediabetes, and visceral fat mass index (VFMI) and lower physical activity than controls (all $P < .05$). In the groups combined, non-HDL-C and glucose were positively related to VFMI ($r = 0.337$ and 0.313, respectively, $P < .05$), and non-HDL-C and HOMA-IR were negatively related to physical activity ($r = -0.411$ and -0.368, respectively, $P < .05$). HOMA-IR was positively related to VFMI in children with CP ($r = 0.698$, $P < .05$), but not in controls. Glucose was not related to physical activity in children with CP, but it was negatively related in controls ($r = -0.454$, $P < .05$).

Conclusion: Children with CP demonstrate early signs of cardiometabolic disease, which are more closely related to increased visceral adiposity than decreased physical activity.

Key Words: cerebral palsy, cardiometabolic disease, dyslipidemia, prediabetes, visceral fat

Abbreviations: BMI, body mass index; CMD, cardiometabolic disease; CP, cerebral palsy; DXA, dual-energy x-ray absorptiometry; FMI, fat mass index; FFMI, fat-free mass index; GMFCS, Gross Motor Function Classification System; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; VFMI, visceral fat mass index.

Cerebral palsy (CP) is the most common cause of physical disability among children, affecting about 1 in every 313 children in the United States [1]. It is the result of a nonprogressive insult to the brain during cerebral development and is characterized by deficits in motor control, posture, and muscle tone [2]. Those with CP often display decreased muscle quality [3, 4] and function [5, 6], smaller and more fragile bones [7], and up to 80% lower levels of physical activity [7] than those without CP. While the condition itself is defined as nonprogressive, motor function declines across their lifespan [8]. Concomitantly, adults with CP exhibit both a higher prevalence [9, 10] and an earlier onset [11] of cardiometabolic disease (CMD). While the pervasiveness of risk factors for CMD is documented in adults with CP [10, 11], less is known about children with CP. Due to the association between childhood cardiometabolic risk and CMD progression throughout adulthood in the general population [12, 13], it is paramount that the presence of associated risk factors is investigated and addressed early in life.

Increased accumulation of ectopic fat, which is strongly associated with the development of CMD [14], is observed intramuscularly [3, 15] and in the bone marrow [15] of children with CP. More recently, increased visceral adiposity has been reported in ambulatory children with CP, independent of body mass index (BMI) or body fat percentage [16]. Elevated levels of visceral adiposity are associated with increased inflammatory and decreased anti-inflammatory gene expression [17], as well as with serum biochemical marker profiles reflective of CMD progression, in typically developing children and adolescents with obesity [17, 18]. In addition,

Received: 24 August 2022. **Editorial Decision:** 24 January 2023. **Corrected and Typeset:** 17 February 2023

increased visceral adiposity has been included as a component of the metabolic syndrome [19]. Moreover, evidence of detriments in both vascular function and structure associated with the development of cardiovascular disease have recently been reported in a sample of children and adolescents with CP [20].

Despite the elevated visceral adiposity, decreased physical activity, vascular impairments, and increased prevalence of CMD in adulthood in individuals with CP, it is unclear whether biochemical markers of cardiometabolic risk are elevated in children with CP. Furthermore, a large proportion of research involving visceral adiposity and its contribution to cardiometabolic risk is focused on individuals with obesity, whereas children with CP display a unique phenotype of high visceral adiposity and low lean body mass, but total body fat levels and BMI comparable to those of typically developing children without obesity [16, 21]. Investigating the connection between visceral adipose tissue and biochemical markers of cardiometabolic risk could provide insight into the unique contribution of visceral adiposity to cardiometabolic risk in children with CP and other nonobese (as classified by BMI) populations with a similar phenotype.

Our primary aim was to determine whether children with CP display early signs of CMD development, as reflected by levels of biochemical markers, compared to their typically developing peers. The secondary aim was to determine the relationship of these markers with measures of visceral adiposity and physical activity.

Methods

We conducted a cross-sectional study using data collected from October 2012 to May 2021 and approved by the Institutional Review Boards at the University of Georgia and the University of Delaware. The same recruitment and data collection protocols were followed at each site. Ambulatory children with spastic CP (ie, level I, II, or III in the Gross Motor Function Classification System, GMFCS) [22] and typically developing children without CP who were similar in age, sex, and race to the children with CP were recruited from hospitals, public schools, and pediatric rehabilitation offices throughout the Southeast and Mid-Atlantic regions of the United States. Siblings of children with CP who enrolled in the study were also recruited. Recruitment was conducted via flyers, postcards, newspaper advertisements, social media posts, and word of mouth. Exclusion criteria included prior fracture in both femurs or tibias, currently taking bisphosphonates, unable to stand independently, unable to ambulate without assistance, orthopedic surgery within the last 6 months, currently taking baclofen, and botulinum toxin treatment within the last year. Additional exclusion criteria for typically developing children were participation in high-level sports, outside the 5th and 95th percentiles for age- and sex-based height or body mass, a history of a neurologic disorder, motor disorder, growth disorder, or chronic disease, and chronic use (> 6 months) of medications known to affect growth. Families who contacted our research team were provided an overview of the study using a standard script sent via e-mail or reviewed by a study coordinator via telephone. After the study was reviewed, the parent/guardian was offered to undergo a telephone screen to assess their child's eligibility. Families of eligible participants were offered to enroll in the study. Before any testing was conducted, a parent/guardian of an eligible child provided informed consent and the child provided assent, if able.

Anthropometrics

Height was measured to the nearest 0.1 cm using a stadiometer (Seca 217; Seca GmbH & Co. KG., Hamburg, Germany). Because assessment of standing height can be challenging in some children with CP, height was also estimated using knee height and an equation from Stevenson et al [23]. Measured height and height estimated using knee height were not significantly different in the final sample ($P = .896$) and exhibited very strong agreement (intraclass correlation coefficient = 0.973); therefore, measured height is reported. Body mass was measured to the nearest 0.2 kg using a digital scale (Detecto, 6550, Cardinal Scale, Webb City, MO). Body mass index (BMI) was calculated based on height and body mass. Normative data published by the US Centers for Disease Control and Prevention [24] were used to determine age- and sex-based percentiles of height, body mass, and BMI.

Sexual Maturation

Sexual maturation was assessed by a healthcare professional (n = 19 children with CP and 16 controls) or by the child with assistance from a parent (n = 11 children with CP and 14 controls) using the Tanner staging technique [25, 26]. Signs of breast development were assessed in girls and pubic hair development in boys as recommended by Kuperminc et al [27]. Ratings range from I to V, with I indicating no signs of sexual development and V indicating full development. The reliability between healthcare professional and child/parent ratings was assessed in 20 children (15 children with CP and 5 typically developing children, 5-11 years). The Cronbach's alpha was .822, which indicates good reliability.

Gross Motor Function

Gross motor function was assessed by a trained healthcare professional using the GMFCS. The classification system ranges from I to V. The classifications of GMFCS I and II are independently ambulatory but have a reduced gait speed; people with GMFCS III achieve mobility through the use of assistive walking devices; and those with GMFCS IV and V achieve mobility through the use of a wheelchair.

Body Composition

Body composition was assessed using whole body dual-energy x-ray absorptiometry (DXA; Whole Body Analysis). For children with CP who were unable to remain still, a modified version of the BodyFIX (Medical Intelligence Inc, Schwabmunchen, Germany) procedure was used to secure them from the waist down, as previously described [28]. The procedure has no effect on fat mass and fat-free mass estimates from DXA in children [29]. Total body (excluding the head) fat mass index (FMI) and fat-free mass index (FFMI) were calculated:

$$\text{FMI} = \text{fat mass (kg)}/\text{height (m)}^2$$
$$\text{FFMI} = \text{fat-free mass (kg)}/\text{height (m)}^2$$

Visceral fat mass was determined using the manufacturer's instructions, as previously described [16]. Strong agreement between visceral adipose tissue estimates from DXA and

computed tomography, a gold standard method, has been reported suggesting that DXA provides valid estimates of visceral fat [30]. Visceral fat mass index (VFMI) was calculated:

$$\text{VFMI} = \text{visceral fat mass (kg)/height (m)}^2$$

The body composition data were collected using the Discovery W DXA model (n = 12 children with CP and n = 13 typically developing children) or the Horizon A DXA model (n = 18 children with CP and n = 17 typically developing children), which were both manufactured by the same company (Hologic Inc., Bedford, MA). To convert body composition data from the Discovery W DXA model to the Horizon A DXA, calibration equations were developed using data from 14 individuals who were tested on each instrument within a 1-week period (total body fat mass Horizon A DXA (kg) = 0.968×total body fat mass Discovery W DXA + 2.740, $r^2 = 0.991$; visceral fat mass Horizon A DXA (kg) = 0.812 × visceral fat mass Discovery W DXA + 0.047, $r^2 = 0.943$; total body fat-free mass Horizon A DXA (kg) = 0.941 × total body fat-free mass Discovery W DXA + 0457; $r^2 = 0.997$).

Physical Activity

Physical activity was assessed using physical activity monitors. Participants were asked to wear 2 monitors on the lateral aspect of the ankle of the more affected side in children with CP and on the nondominant side in typically developing children. Physical activity data was recorded for 4 days (3 weekdays and 1 weekend day) while the participants wore these monitors continuously for 24 hours. Participants and their families were asked to take the monitors off during bathing, showering, or swimming. This was confirmed by reviewing activity logs kept by the children with assistance from their parent and by visually examining the graphical output generated using software provided by the manufacturer. If participants did not wear the monitors on any of the days, they were asked to re-wear the monitors to make up for missed days. The total activity counts per day averaged from the 2 monitors are reported.

Physical activity data were collected using the Actigraph GT9X (Pensacola, FL; n = 12 children with CP and n = 13 typically developing children) or the Actical (Respironics Inc., Bend, OR; n = 18 children with CP and n = 17 typically developing children) accelerometer-based physical activity monitors. The Actigraph GT9X utilizes a gyroscope, magnetometer, a triaxial MEMS accelerometer, and measures acceleration between ±8*g* at a sampling rate of 30 to 100 Hz. The Actical activity monitors have an omnidirectional sensor that measures acceleration between 0.05 and 2 g at a sampling rate of 32 Hz. The raw data mode was in 15 second epochs which are used to register activity counts [31]. To convert total activity counts from the Actical to the Actigraph monitor, a calibration equation was developed using data from 7 ambulatory children with mild CP and 9 typically developing children 4 to 11 years of age who wore both monitors on the same ankle for 4 days (Actigraph total activity counts = 2.9681 × Actical activity counts + 199039, $r^2 = 0.961$).

Blood Analysis

Blood samples were collected between 7:00 and 8:30 AM by a trained phlebotomist after a 10-hour fast. Serum was separated using standard procedures and stored at −80 °C until analysis. All blood samples were batch analyzed for biochemical markers. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, and glucose (intra-assay CV% range = 1.1 to 6.1, inter-assay CV% range = 4.3 to 6.6) were measured on a Stanbio Sirus (Boerne, TX) analyzer, and low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald's formula [32]:

$$\text{LDL-C} = \text{total cholesterol—HDL-C—triglycerides/2.2.}$$

Non-HDL-C was calculated:

$$\text{Non-HDL-C} = \text{total cholesterol—HDL-C.}$$

Insulin (intra-assay CV% = 1.5, inter-assay CV% = 3.9) was measured on a TOSOH Bioscience AIA900 (South San Francisco, CA) using immunofluorescence. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated:

$$[\text{insulin (uU/mL)} \times \text{glucose (mg/dL)}]/405$$

Statistical Analysis

Data were analyzed using SPSS version 24.0 (IBM Corp., Armonk, NY). Matching of children in each group for age (±1.5 years), sex (male/female), and race (White/Black/Asian) was conducted using the case control matching option in SPSS. After participants were selected for inclusion in the study, variables were checked for normality by examining skewness, kurtosis, and the Shapiro-Wilk test. Group differences were determined using an independent *t* test if data were normally distributed and a Mann-Whitney U test if data were nonnormally distributed. Nonnormally distributed variables included height, height percentile, body mass, BMI, BMI percentile, total fat mass, FMI, FFMI, visceral fat mass, VFMI, HOMA-IR, triglycerides, and insulin. One-sample *t* tests were used to determine whether the height, body mass, and BMI percentiles were different from the 50th age- and sex-based percentile in each group. Group differences in Tanner stage were determined using a Mann-Whitney U test. Values are presented as mean ± SD unless stated otherwise. Alpha level was set at .05. Cohen's d (*d*) of 0.2, 0.5, and 0.8 were used to represent small, medium, and large effect sizes, respectively [33]. Chi-squared tests were used to compare the prevalence of borderline-high/low and high/low total cholesterol and lipoprotein levels as outlined by the National Heart, Lung, and Blood Institute [34], and the prevalence of prediabetes as indicated by fasting glucose ≥ 100 and ≤ 125 mg/dL and outlined by the American Diabetes Association [35], between groups. For dyslipidemia, chi-squared tests were conducted between values categorized as acceptable and borderline-high/low + high/low values pooled. Borderline-high and high values, as well as borderline-low and low values were pooled because some high categories and some low categories did not contain any values.

Linear regression was used to determine relationships between adiposity indices (ie, VFMI, visceral fat mass, and FMI) and biochemical markers associated with CMD (ie, non-HDL-C, glucose, and HOMA-IR) and then between physical activity and the same biochemical markers. For each analysis, we first tested the group by adiposity or group by physical activity interaction. If the interaction term was

significant then analyses were performed in the 2 groups separately and the group-specific relationships were reported. Linear regression was also used to determine if the relationships between adiposity indices and biochemical markers and between physical activity and biochemical markers remained when all variables (group, adiposity index, physical activity, biochemical marker) were included in the same regression models. Tests for interactions were performed and interactions were included in the models if statistically significant.

Results

A summary of the study interest and screening, enrollment, and matching procedure is reported in Fig. 1. There were 151 families with a child with CP who contacted the research team about the study and 109 children with CP who underwent screening. During the screening process, 31 declined participation, 28 were excluded, and 50 enrolled. There were 88 families of typically developing children who contacted the research team about the study details and 47 children who underwent screening. During the screening process, 1 declined participation, 6 were excluded, and 40 enrolled as controls. Of the 50 children with CP and 40 controls who enrolled, 41 children with CP and 32 control children completed all testing. We were able to match 30 children per group for age (±1.5 years), sex (male/female), and race (White/Black/Asian) and include them in the final analysis.

Physical Characteristics, Body Composition, and Physical Activity

Physical characteristics, body composition, and physical activity of the matched groups are reported in Table 1. As planned, there were no group differences in age, sex, or race. There were also no differences in Tanner stage, height, body mass, or BMI. Children with CP compared with controls had lower height percentile ($P = .012$). Children with CP were significantly lower than the 50th age- and sex-based percentile for height ($P = .001$) but were not different for body mass or BMI (both $P > .30$). Controls were not different from the 50th percentile for height, body mass, or BMI (all $P > .70$). Children with CP had significantly higher VFMI and FMI than controls ($P < .05$). Physical activity counts were 38% lower in children with CP than controls ($P < .001$).

Biochemical Markers

Results from the biochemical analysis are reported in Table 2. Significantly higher total cholesterol, LDL-C, non-HDL-C, and glucose were observed in children with CP compared with controls ($P < .05$). Occurrence of dyslipidemia and prediabetes in children with CP and controls is represented in Fig. 2. More than 2× as many children with CP had borderline-high or high total cholesterol ($P < .001$), 4.5× as many had borderline-high or high LDL-C (Con = 7%: $P = .020$), and 5.5× as many had borderline-high or high non-HDL-C ($P = .005$) compared with controls. The proportion of children with CP and controls with borderline-low or low HDL-C ($P = .640$) and borderline-high or high triglycerides ($P = .712$) was not significantly different. Compared with controls, 7× more children with CP presented with prediabetic levels of fasting glucose ($P = .011$).

Biochemical Markers: Relationship With Adiposity Indices and Physical Activity

Scatter plots demonstrating the bivariate relationships between adiposity indices (ie, VFMI and FMI) and biochemical markers (ie, non-HDL-C, glucose, and HOMA-IR) are presented in Fig. 3. Linear regression analysis detected no group interaction in the relationships between VFMI and the biochemical markers non-HDL-C and glucose. Therefore, the relationships for the combined group data are reported. Visceral fat mass index was positively related to non-HDL-C ($r = 0.337$, $P = .008$) and glucose ($r = 0.313$, $P = .015$). A significant group interaction was detected for the relationship between VFMI and HOMA-IR ($P = .015$). While VFMI was positively related to HOMA-IR in children with CP ($r = 0.698$, $P < .001$), there was no significant relationship in controls ($r = 0.125$, $P = .509$). Linear regression analysis detected no group interaction in the relationships between FMI and any of the biochemical markers. Therefore, the relationships for the combined group data are reported. Fat mass index was positively related to non-HDL-C ($r = 0.290$, $P = .025$), glucose ($r = 0.388$, $P = .002$), and HOMA-IR ($r = 0.671$, $P < .001$).

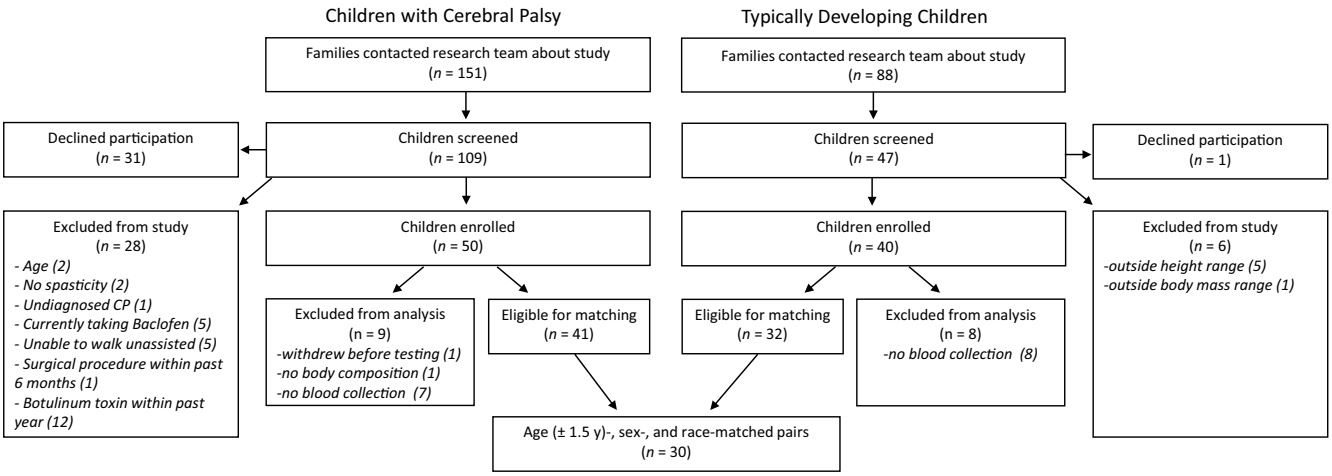

Figure 1. Flowchart demonstrating study interest and the participant screening, enrollment, and matching procedure.

Table 1. Physical characteristics, body composition, and physical activity in children with cerebral palsy (CP) and typically developing children (Con)

	CP (n = 30)	Con (n = 30)	*d*	*P*
Age (y)	8.7 ± 2.3	8.7 ± 2.0	<0.001	.919
Sex (M/F)	22/8	22/8		1.000
Race (White/Black/Asian)	25/3/2	25/3/2		1.000
Tanner stage (I/II/III/IV/V)	21/6/3/0/0	25/4/1/0/0		.521
Height (m)	1.27 ± 0.15	1.31 ± 0.13	0.285	.239
Height (%)	29.8 ± 31.0[a]	50.5 ± 30.4	0.674	.009
Body mass (kg)	29.3 ± 9.7	29.4 ± 9.2	0.011	.963
Body mass (%)	44.0 ± 34.6	50.0 ± 31.7	0.181	.491
BMI (kg/m^2)	17.8 ± 3.8	16.7 ± 2.8	0.330	.201
BMI (%)	56.8 ± 36.0	48.1 ± 32.9	0.252	.335
GMFCS (I/II/III)	19/9/2			
Visceral fat mass (kg)	0.22 ± 0.14	0.16 ± 0.08	0.526	.076
VFMI (kg/m^2)	0.14 ± 0.08	0.09 ± 0.05	0.750	.018
Total fat mass (kg)	8.88 ± 5.47	7.13 ± 4.00	0.369	.249
FMI (kg/m^2)	5.32 ± 2.72	4.03 ± 1.82	0.557	.049
Total fat-free mass (kg)	19.5 ± 6.1	21.0 ± 5.9	0.250	.442
FFMI (kg/m^2)	11.9 ± 1.9	11.9 ± 1.4	0.010	.355
Physical activity (counts/day)	1 280 151 ± 649 378	2 062 677 ± 589 832	1.261	> .001

Values are mean ± SD; % for height, body mass, and body mass index (BMI) reflect the percentile relative to age- and sex-based norms.
Abbreviations: FFMI, total body (minus head) fat-free mass index; FMI, total body (minus head) fat mass index; GMFCS, Gross Motor Function Classification system; VFMI, visceral fat mass index.
[a]Different from age- and sex-based 50th percentile.

Scatter plots demonstrating the bivariate relationships between physical activity and biochemical markers (ie, non-HDL-C, glucose, and HOMA-IR) are presented in Fig. 4. Linear regression analysis detected no group interaction in the relationships between physical activity and the biochemical markers non-HDL-C and HOMA-IR. Therefore, the relationships for the combined group data are reported. Physical activity was significantly and inversely related to non-HDL-C ($r = -0.411$; $P = .001$) and HOMA-IR ($r = -0.368$, $P = .004$). A significant group interaction was detected in the relationship between physical activity and glucose ($P = .033$). Whereas physical activity was not significantly related to glucose in children with CP ($r = 0.055$, $P = .764$), it was significantly and inversely related to glucose in controls ($r = 0.454$, $P = .012$).

Linear regression models including group, both indices of adiposity, physical activity, and significant interaction terms to predict biochemical markers are presented in Table 3. A significant interaction was again observed between group and VFMI in relation to HOMA-IR ($P = .013$) and between group and physical activity in relation to glucose ($P = .020$).

Table 2. Biochemical analysis of children with cerebral palsy (CP) and typically developing children (Con)

	CP (n = 30)	Con (n = 30)	*d*	*P*
Total cholesterol (mg/dL)	174.4 ± 31.5	154.5 ± 21.5	0.728	.006
HDL-C (mg/dL)	60.8 ± 10.2	61.0 ± 11.1	0.019	.933
LDL-C (mg/dL)	96.1 ± 25.8	78.2 ± 18.4	0.799	.003
Non-HDL-C (mg/dL)	113.6 ± 29.6	93.5 ± 17.6	0.825	.002
Triglycerides (mg/dL)	87.1 ± 85.2	76.4 ± 42.5	0.159	.684
Glucose (mg/dL)	93.7 ± 6.9	89.8 ± 7.6	0.537	.042
Insulin (μU/mL)	10.5 ± 10.1	7.4 ± 5.7	0.378	.148
HOMA-IR	2.5 ± 2.5	1.7 ± 1.4	0.404	.171

Values are mean ± SD.
Abbreviations: HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol.

Discussion

This is the first study to report evidence of dyslipidemia or prediabetes in children with CP using a typically developing control group, which is a major strength of the study. Signs of dyslipidemia in children with CP included higher total cholesterol, LDL-C, and non-HDL-C than observed in typically developing controls, with no group difference in HDL-C. Furthermore, compared with controls, 2, 4.5, and 5.5 times more children with CP showed borderline-high and high levels of total cholesterol, LDL-C, and non-HDL-C, respectively. The strongest indicator of dyslipidemia in children with CP was their higher levels of non-HDL-C. There is evidence that non-HDL-C, which is an estimate of all apolipoprotein B containing lipoproteins, is a more robust measure of cardiovascular disease risk than LDL-C alone [36]. The observations in children with CP are consistent with reports of dyslipidemia in young adults with CP [11, 37]. The increased occurrence of dyslipidemia in this study also provides context regarding recent observations of vascular impairments in older children and adolescents with CP [17], although further investigation is needed to infer a direct relationship. Signs of prediabetes in children with CP were reflected by higher levels of fasting

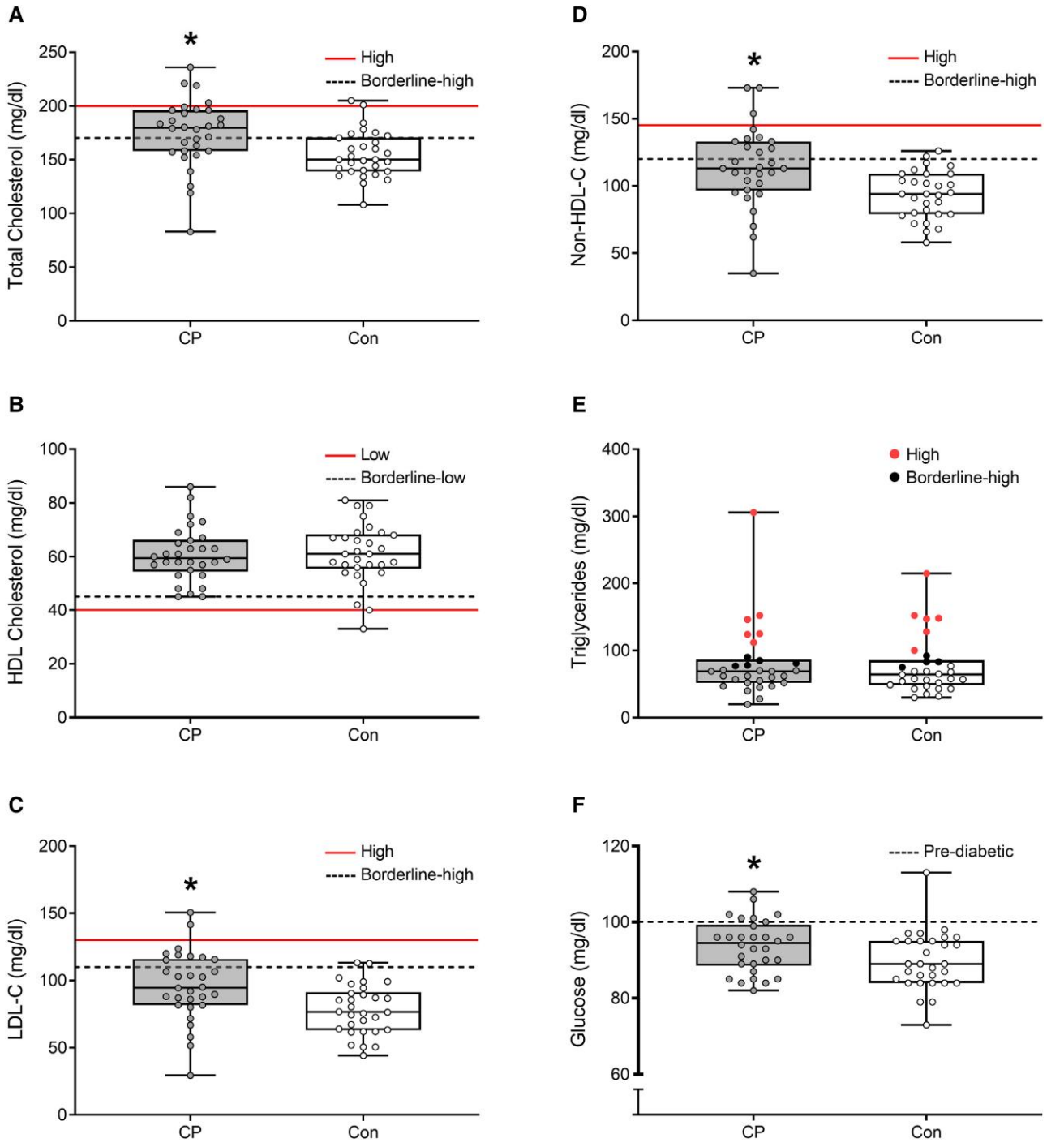

Figure 2. Occurrence of dyslipidemia in CP and Con as determined by total cholesterol, HDL-C, LDL-C, non-HDL-C, and triglycerides (A-E), and occurrence of prediabetes in CP and Con as determined by fasting glucose levels (F). Values are mg/dL in consistency with borderline-high/low and high/low lipid and lipoprotein levels established by the Expert Panel on Integrated Cardiovascular Health and Risk Reduction in Children and Adolescents [34] and prediabetic glucose levels based on the American Diabetes Association "Standards of Medical Care in Diabetes" [35]. Values for borderline-high and high triglycerides are age-dependent, and therefore are depicted by red (high) and black (borderline-high) circles. Abbreviations: Con, typically developing control children; CP, cerebral palsy; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. *Different from controls, $P < .05$.

blood glucose compared with controls. Moreover, using the fasting glucose cutoff of ≥100 mg/dL, 7 times more children with CP were classified as prediabetic than controls. Previous studies had not detected glucose dysregulation in adults with CP [11, 37]. Some limitations of these previous studies include the lack of a control group [37] or the use of data collected from medical records [11].

When the data from the children with CP were compared with the average values reported for children and adolescents who participated in the National Health and Nutrition Examination Survey (NHANES), the overall pattern is generally consistent with the comparison to typically developing controls in the present study. Specifically, compared to NHANES data from children aged 6 to 11 years [38], a higher

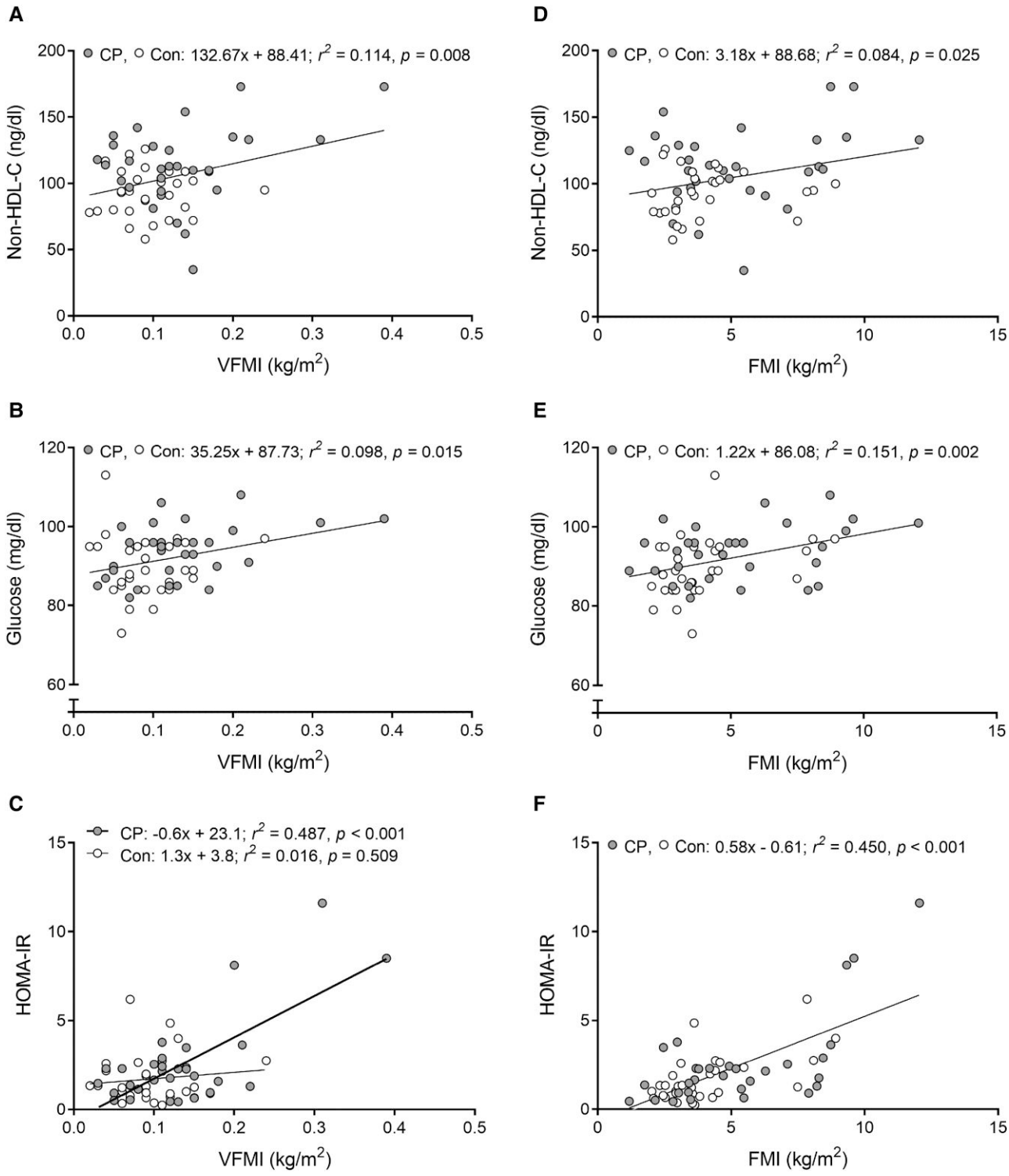

Figure 3. Relationships between VFMI (A-C), FMI (D-F), and biochemical markers. Separate regression lines are plotted for CP and Con for relationships in which a group by adiposity index interaction was significant. Abbreviations: Con, typically developing control children; CP, cerebral palsy; FMI, total body (minus head) fat mass index; HOMA-IR, homeostatic model assessment of insulin resistance; Non-HDL-C, non-high-density lipoprotein cholesterol; VFMI, visceral fat mass index.

proportion of children with CP in the present study (5-11 years) had high total cholesterol (13.3% vs 6.7%) and non-HDL-C (10% vs 6.7%). Moreover, compared to NHANES data from adolescents 12 to 18 years of age [39], children with CP in the present study were twice as likely to be classified as prediabetic using the fasting blood glucose cutoff ≥100 ng/dL (23.3% vs 11.1%). Not all results from the 2 comparisons are consistent, however. Specifically, none of the children with CP in the present study had low HDL-C, whereas 9% of the 6- to 11-year-old children in the NHANES study had low HDL-C [38]. The reason for the lack of children with CP with low HDL-C is unclear, but it

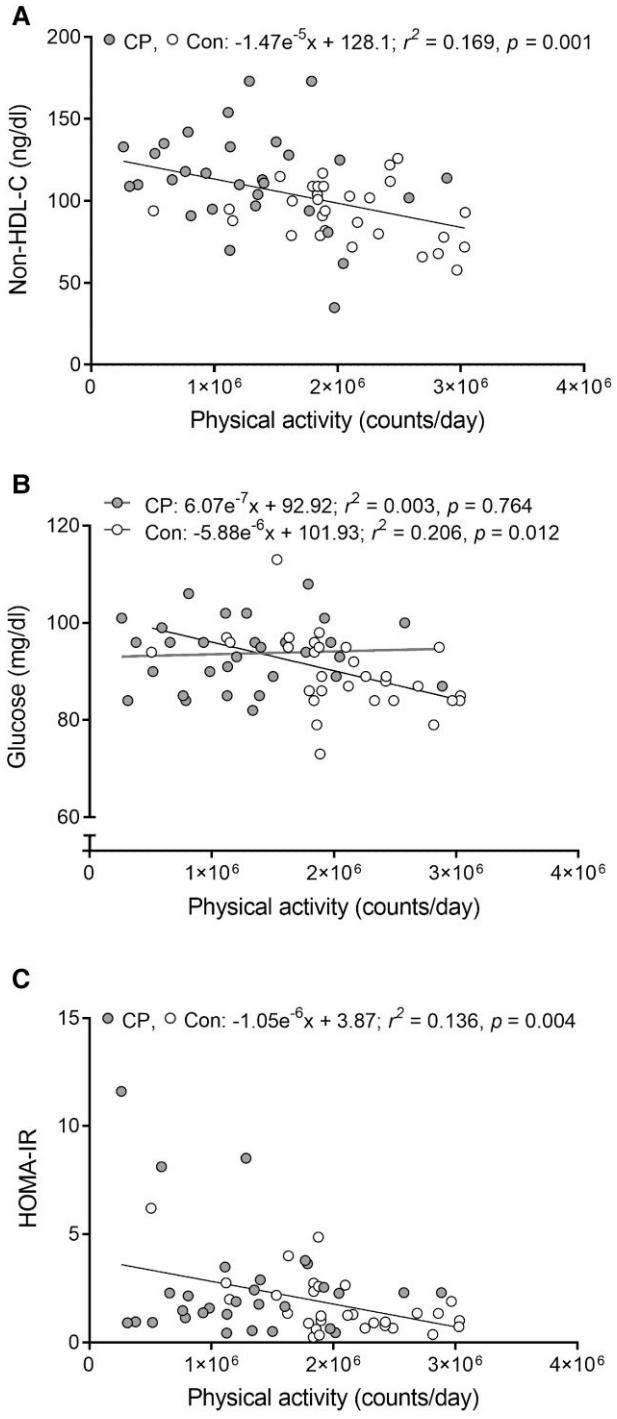

Figure 4. Relationships between physical activity and the biochemical markers non-HDL-C (A), glucose (B), and HOMA-IR (C). Separate regression lines are plotted for CP and Con for relationships in which a group by physical activity interaction was significant. Abbreviations: Con, typically developing control children; CP, cerebral palsy; HOMA-IR, homeostatic model assessment of insulin resistance; Non-HDL-C, non-high-density lipoprotein cholesterol.

is worth noting that 2 of the children with CP (6.7%) had borderline-low HDL-C (40 to 45 ng/mL). Furthermore, only 1 of the controls in the present study (3.3%) had low HDL-C and 2 had borderline-low HDL-C.

Signs of dyslipidemia and prediabetes in children with CP may be tied to the high level of relative adiposity, especially in the viscera. This notion is supported by the observation that higher LDL-C and non-HDL-C in children with CP were accompanied by higher VFMI and FMI. Additionally, non-HDL-C, a robust biochemical marker of dyslipidemia, was positively related to VFMI ($r = 0.338$, $P = .008$), and to a slightly lesser extent, FMI ($r = 0.290$, $P = .025$), a marker of total body adiposity, in children with CP. In addition to elevated fasting glucose and a higher occurrence of prediabetes in children with CP, a significant group interaction effect between measures of visceral adiposity and insulin resistance was observed. For instance, VFMI was positively related to HOMA-IR in children with CP ($r = 0.698$, $P < .001$), but not in controls, suggesting that visceral adiposity may be more predictive of prediabetes and insulin resistance in children with CP than in typically developing children. Moreover, this interaction persisted when physical activity was statistically controlled. We speculate that this is a function of the greater visceral adiposity observed in children with CP, as there is evidence that visceral adiposity above average displays stronger positive relationships with HOMA-IR than those at or below the mean [40]. If visceral adiposity has a different relationship with insulin resistance in children with CP compared to typically children, it is plausible that the underlying mechanism is an increased deposition of visceral fat in and around the liver, pancreas, and other important organs in those with CP, which is strongly related to both dyslipidemia and insulin resistance [41]. Further, previous studies have shown increased ectopic fat intramuscularly and in the bone marrow of children with CP [3, 15]. The relationship between these fat depots and cardiometabolic risk factors in children with CP warrants further exploration.

A significant group interaction was also detected in the relationship between physical activity and glucose. While there was a significant negative relationship between physical activity and glucose in controls, there was not a significant relationship in children with CP. The interaction persisted even when visceral adiposity was statistically controlled. This finding is not out of line with previous research. There is conflicting evidence regarding the relationship between physical activity levels and cardiometabolic risk in those with CP [42, 43]. However, in line with our observations, a more consistent relationship between decreased activity/increased sedentary behavior and elevated cardiometabolic risk is found in the general population [44-46]. We hypothesize that physical activity participation in children with CP may be too low, on average, to elicit measurable protective effects against the development and progression of CMD. Moreover, even without a direct relationship observed in the current study, we believe it is likely that increased physical activity would lower the elevated cardiometabolic risk factors observed in children with CP.

A key strength of this study in relation to similar previous studies is the inclusion of a typically developing control group. Controls were carefully matched to children with CP for age, sex, and race, and they were not different from the 50th age- and sex-based percentiles for height, body mass, and BMI. This provides evidence that the controls were reasonable representatives of the general population of children. The observation of both elevated cardiometabolic risk and a relationship between this elevated risk and visceral adiposity in a sample of ambulatory children with a mild form of CP (and on average, without traditional obesity) is especially novel because most pediatric research on cardiometabolic risk and visceral adiposity involves children with obesity [17, 18]. Another

Table 3. Statistical models for predicting biochemical markers of cardiometabolic risk using physical activity counts, indices of adiposity, and group

Outcome measure	Coefficients	β	t-value	SE	*P*	Std β	Model R^2, adj R^2
Non-HDL-C							0.236, 0.195[a]
	Intercept	103.84	7.79	13.33	<.001		
	Group	10.49	1.44	7.283	.155	0.20	
	VFMI	73.19	1.46	50.13	.150	0.19	
	Physical activity (counts/day)	−8.32e⁻6	−1.62	<0.01	.111	−0.23	
							0.219, 0.177[a]
	Intercept	105.19	6.98	15.08	<.001		
	Group	11.82	1.62	7.29	.110	0.23	
	FMI	1.36	0.93	1.45	.355	0.12	
	Physical activity (counts/day)	−8.32e⁻6	−1.53	<0.01	.131	−0.23	
Glucose							0.227, 0.171[a]
	Intercept	98.42	19.88	4.95	<.001		
	Group	−10.45	−1.93	5.42	.059	−0.71	
	VFMI	27.71	1.90	14.59	.063	0.25	
	Physical activity (counts/day)	−5.43e⁻6	−2.52	<0.01	.015[a]	−0.52	
	Group by physical activity interaction	6.98e⁻6	2.40	<0.01	.020[a]	0.74	
							0.183, 0.139[a]
	Intercept	87.85	19.94	4.41	<.001		
	Group	1.90	0.89	2.13	.376	0.13	
	FMI	0.97	2.30	0.42	.025[a]	0.31	
	Physical activity (counts/day)	−9.56e⁻7	−0.60	<0.01	.549	−0.09	
HOMA-IR							0.438, 0.397[b]
	Intercept	2.81	2.65	1.06	.011		
	Group	−2.39	−2.55	0.94	.014[a]	−0.58	
	VFMI	2.07	0.31	6.60	.755	0.07	
	Physical activity (counts/day)	−6.27e⁻7	−1.78	<0.01	.081	−0.21	
	Group by VFMI interaction	19.51	−2.57	7.59	.013[a]	0.82	
							0.456, 0.427[b]
	Intercept	0.04	0.04	1.00	.972		
	Group	−0.10	−0.21	0.48	.838	−0.02	
	FMI	0.55	5.75	0.10	<.001[b]	0.64	
	Physical activity (counts/day)	−2.69e⁻7	−0.75	<0.01	.458	−0.10	

For group: CP = 1, Controls = 0.
Abbreviations: FMI, total body (minus head) fat mass index; HOMA-IR, homeostatic model assessment of insulin resistance; Non-HDL-C, non-high-density lipoprotein; VFMI, visceral fat mass index.
[a]$P < .05$.
[b]$P \leq .001$.

strength of the study is that all biochemical samples were collected and processed using the same rigorous protocol, and batch analyzed. Therefore, error associated with measurement variation was minimized.

Regarding limitations, first, only relationships were examined due to the cross-sectional design of the study. Further research is needed to establish causality. In addition, only a limited number of explanatory variables were included in the linear regression models. Larger samples are needed to determine the potential influence of other factors, like nutrition, on biochemical markers of dyslipidemia and prediabetes in children with CP. It is plausible that nutritional factors, such as nutritional supplementation used to offset reduced intake due to oral motor issues in children with CP, can contribute to the elevated markers of dyslipidemia and prediabetes. However, the influence of altered nutrition is much more likely in children who have more severe forms of CP and require enteral feeding [47]. In the present study, only one child received nutritional supplementation (ie, gastrostomy tube), and it was limited to breakfast. Furthermore, the results of the study remained when that participant was excluded from the statistical analysis. Another limitation was restricting the inclusion to ambulatory children with CP which limits the application of the results to children with milder forms of CP. It is plausible that the degree of dyslipidemia and prediabetes is even greater in nonambulatory children due to even lower levels of physical activity, and possibly excessive energy intake if they receive nutritional supplementation [47]; thus, the magnitude of the cardiometabolic risk in children with CP may be underestimated by the results of the present study. In addition, the measurement of physical activity in the current study was limited to total activity counts. The use of

intensity cut-points to delineate between light and moderate-to-vigorous activity may yield more specific relationships between physical activity and biochemical markers of cardiometabolic risk in children with CP. Another limitation of the study is that DXA was used to assess visceral fat, which does not provide the same level of accuracy as other methods, such as magnetic resonance imaging and computed tomography. Nonetheless, studies have demonstrated that DXA provides valid estimates of visceral adiposity [30]. Moreover, a group difference in visceral adiposity was detected and statistically significant relationships between visceral adiposity and biochemical markers of cardiometabolic risk were observed despite these methodological limitations.

In this cross-sectional study, we found that ambulatory children with CP, relative to typically developing children, display higher levels of cardiometabolic risk factors, namely dyslipidemia and prediabetes, and that these risk factors are related to visceral adiposity. To better assess cardiometabolic risk in children with CP, an assessment protocol that includes biochemical markers in addition to more extensive measures of body composition may be warranted. However, larger studies that control for other factors related to cardiometabolic risk, such as intensity of physical activity and nutritional status, are needed to gain a clearer understanding of the relationship between visceral adiposity and cardiometabolic risk. Moreover, studies that identify clinical, exercise, and nutritional strategies to improve cardiometabolic health and suppress the early development of CMD in children with CP are needed.

Acknowledgments

We thank all participants and their families.

Funding

All phases of this study were supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development [RO1 HD090126 and R15 HD071397 to C.M.M.]. Funding was also received from the University of Georgia Athletic Association to C.M.M.

Disclosures

The authors have nothing to disclose.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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