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ORIGINAL CONTRIBUTION

# The dietary inflammatory index is associated with anti- and pro-inflammatory adipokines in Brazilian schoolchildren

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## Abstract

**Purpose** To investigate the relationship of Children's Dietary Inflammatory Index (C-DII™) scores with body fat distribution and serum adipokines in Brazilian schoolchildren.

**Methods** This population-based cross-sectional study enrolled 378 schoolchildren aged 8 and 9 years from Viçosa, Minas Gerais, Brazil. Food consumption was assessed using three 24-h dietary recalls from which C-DII scores were calculated. Serum adipokines [adiponectin, leptin, retinal-binding protein 4 (RBP4), and chemerin] were analyzed in blood samples. Sociodemographic characteristics and sedentary behavior were assessed using a semi-structured questionnaire. Total, truncal, android and gynoid body fat were evaluated by dual-energy X-ray absorptiometry (DXA). We compared the distributions of adiposity measures and serum adipokines by C-DII categories with linear regression, adjusting for potential confounders.

**Results** The mean sample C-DII was $0.59 \pm 0.94$ and ranged from − 2.16 to + 2.75. The C-DII was not associated with central and total body fat. However, the C-DII was modestly inversely associated with adiponectin and RBP4, and modestly directly associated with chemerin. These results remained significant after adjusting for body fat. Every 1 SD of C-DII was related, respectively, to a − 0.8 (− 1.5, − 0.03) and to a − 0.1 (− 0.2, − 0.05) units lower mean of adiponectin and RBP4, and to 7.2 (0.3, 14.1) units higher of chemerin.

**Conclusion** Higher C-DII score was modestly inversely and directly associated with anti- and pro-inflammatory adipokines, respectively, in Brazilian children. The development of public health policies is needed to promote healthy eating habits during childhood to prevent the early onset of systemic inflammation and ill health effects later in life.

**Keywords** Inflammation · Adiposity · Child · Food intake · Nutritional epidemiology

## Introduction

Obesity is considered a chronic low-grade inflammatory state, with excess adipose tissue leading to dysfunctional secretion of inflammatory signaling compounds, including the adipokines [1, 2]. Adipokines are circulating hormones that play a crucial role in energy homeostasis and modulation of several signaling cascades in target organs [1, 3]. Growing evidence indicates that the altered production and secretion of adipokines might mediate the relationship between obesity and several pathologies [3, 4].

Diet is an important modifiable risk factor in the etiology of obesity [5]. Moreover, an unhealthy diet may contribute to cardiometabolic risk [6–8], and a pro-inflammatory state [9–11] during childhood.

Recently, a new tool has been designed and validated to assess the quality and the inflammatory properties of the

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diet in pediatric populations: The Children's Dietary Inflammatory Index (C-DII™). The C-DII classifies the dietary patterns on a continuous scale from maximally anti- to maximally pro-inflammatory [12]. Higher C-DII scores have been associated with cardiometabolic risk and inflammation markers among children and adolescents; however, studies are still scarce [12, 13]. Furthermore, there is a gap in the literature on the relation between dietary inflammatory potential and adiposity-related inflammation in young ages.

Because eating habits are formed early in life and dietary choices may be related to the beginning of systemic inflammation and health outcomes later in life, we aimed to investigate the relationship of C-DII with (1) total and central body fat, (2) and serum adipokines in Brazilian schoolchildren. Our hypothesis is that the pro-inflammatory potential of diet is directly associated with adiposity and pro-inflammatory adipokines.

## Methods

### Participants and study design

This is a cross-sectional study based on a representative sample of children aged 8 and 9 years enrolled in all public ($n = 17$) and private ($n = 7$) schools in the urban area of Viçosa, Minas Gerais, Brazil. The participants were recruited from the Schoolchildren Health Assessment Survey (*Pesquisa de Avaliação da Saúde do Escolar*, PASE, in portuguese) carried out in 2015. All stages of data collection were performed at the *Universidade Federal de Viçosa* (UFV) by trained nutritionists.

The calculation of the sample size and the sampling process have been described previously [14, 15]. In brief, a random sample of 378 children aged 8–9 years was recruited. This sample was obtained from a population of 1464 eligible children of the same age range who were enrolled in the urban primary schools of the city of Viçosa. At the end of the data collection, we did not have any losses of participants due to the non-accomplishment of all stages of the study.

To be included, children could not regularly use medications or have some clinical diagnosis that could interfere with nutritional status, body composition, lipid profile, blood pressure, and/or glucose metabolism. Children whose parents or guardians were unavailable or unwilling to sign the informed consent form after three attempts also were not included.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Human Research Ethics Committee of the UFV (reference number 663.171/ 2014). Written informed consent was obtained from all parents or guardians of participants.

### Children's dietary inflammatory index (C-DII™)

The assessment of food consumption was performed over 3 non-consecutive days by 24-h dietary recalls (24HR), including a weekend day, and filled in according to the data reported by the parents/guardian and the child at the same time. Interviewers were trained to increase data reliability. During the interviews, household utensils and a photograph album with food serving sizes and beverages were used to help participants estimate the portion sizes [16].

Household measures were transformed into grams (g), milligrams (milligrams), or milliliters (mL) to assess the intake of energy (kcal) and nutrients, and then the average of the 3 days was calculated. The analysis of the food composition for the 24HR was performed with the software Dietpro® 5i, version 5.8, using the Brazilian Food Composition Table [17] and the USDA Food Composition Database [18].

C-DII scores were calculated according to the validated method employed in pediatric populations, as previously described [12]. Briefly, the C-DII was calculated by linking the PASE dietary data to a regionally representative world database that provides a robust global estimate mean and standard deviation for each parameter in the C-DII calculation. First, a $z$ score was created by subtracting the 'standard mean' from the reported amount and dividing this value by the global standard deviation. Second, these $z$ scores were converted to proportions to minimize the effect of "right skewing". Then, the result was centered on 0 (null) and bounded between − 1 (maximum anti-inflammatory) and + 1 (maximum pro-inflammatory), by doubling each proportion and subtracting 1. Next, this centered proportion score was multiplied by the respective food parameter effect score, derived from the literature review to obtain the food parameter-specific C-DII score for an individual. Finally, all the food parameter-specific C-DII scores were then summed to create the overall C-DII score for each child. Moreover, C-DII was adjusted per 1000 kcal consumed to take into account differing amounts of energy intake between people. Of 25 possible food parameters to C-DII calculation [12], we use the following: carbohydrate, protein, total fat, saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid, fiber, iron, zinc, magnesium, vitamin C, vitamin B1, vitamin B2, vitamin B3, vitamin B6, and vitamin D. A higher C-DII score indicates a pro-inflammatory diet.

### Adipokines

Blood samples were collected at the Laboratory of Clinical Analysis of the Health Division of the UFV, after 12-h of fasting, by venipuncture in the antecubital area of the arm.

Aliquots of this biological material were packed in 1.5 ml microtubes, encoded and stored at − 80 °C. We evaluated adiponectin, leptin, retinol-binding protein 4 (RBP4), and chemerin.

Plasma adiponectin, RBP4 and chemerin were measured using commercials ELISA sandwich kits (human adiponectin: SEA605Hu; human chemerin: SEA945Hu; human RBP4: SEA929Hu, Cloud Clone Corp.®, Houston, TX, USA; standardized protocols from *Laboratório Especializado em Análises Científicas*—LEAC) (intra-assay precision CV < 10% and inter-assay CV < 12%). Serum leptin was assessed using commercials ELISA kits by enzyme immunoassay method (KAP2281, DIAsource®, Louvain-la-Neuve, Belgium; standardized protocols from *Diagnósticos do Brasil*) (intra-assay precision CV < 13.3% and inter-assay CV < 10.2%).

### Sociodemographic and behavioral data

The sociodemographic characteristics were collected through a semi-structured questionnaire applied to parents or guardians. Data obtained included: sex, age (years) and race (White, Brown, Black), type of school (public and private), and household's *per capita* income (US$).

Sedentary behavior was evaluated by time engaged in screen-based recreation, including video games, computer, television, mobile phone, or tablet. The child was categorized as sedentary when he or she exceeded 2 h/day of screen time [19].

### Adiposity measures

Body fat distribution (total, truncal, android and gynoid) was assessed by dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy Advance, GE Medical Systems Lunar, Milwaukee, WI, USA). During the examination, children were fasted and wore light clothing without any metal objects. They remained in supine position on the scanning bed until the equipment reading was completed. Excessive body fat was assessed according to Lohman [20] cutoff points.

### Statistical analyses

The inflammatory potential of diet, evaluated by C-DII scores expressed in quintiles, was considered the exposure in the analysis. The outcome variables were the adiposity measures (% total, truncal, android and gynoid body fat) and serum adipokines (adiponectin, leptin, RBP4, and chemerin), all fit as continuous variables. Covariates included the child's age, sex, race, type of school enrolled, screen time, and the household's *per capita* income (categorized into quartiles).

First, the distributions of C-DII were compared by categories of covariates. Next, the distribution of energy and nutrient intakes were evaluated using mean ± standard deviation (SD) according to C-DII categories from multivariable linear regression adjusted by age, sex, race, screen time, *per capita* income, and % body fat. Then, the distributions of outcomes (adiposity measures and serum adipokines) were compared according to the C-DII categories (exposure), using mean differences and 95% confidence intervals (CI) from unadjusted and multivariable linear regression models adjusted for age, sex, screen time, and per capita income. Finally, the multivariable models were additionally adjusted for body fat. All potential confounders included in the analysis were chosen after a literature review.

Robust estimates of the variance were specified in all models and partial $R^2$ were used to all significant associations. Analyses were carried out in Stata® version 14 (StataCorp LP, CollegeStation, TX, USA). The significance level was 5% for all hypothesis tests.

## Results

The children's mean ± SD age was 8.5 ± 0.5 years; 52.1% were girls; 68.5% were non-White; and 70.9% were enrolled in public schools. The prevalence of excess body fat was 50% in the sample. The mean ± SD of C-DII was 0.59 ± 0.94 and ranged from − 2.16 (maximum anti-inflammatory profile) to 2.75 (maximum pro-inflammatory profile). The means ± SD of adiponectin, leptin, RBP4, and chemerin were, respectively, 13.6 ± 7.4 µg/mL, 5.7 ± 9.5 ng/mL, 4.0 ± 0.7 µg/mL, and 83.6 ± 64.8 ng/mL.

Non-White children and students from public schools were more likely to have a pro-inflammatory diet. Additionally, the C-DII was inversely associated with per capita income (Table 1).

Table 2 shows the association of energy and nutrient intakes with C-DII. The C-DII was inversely associated with antioxidant nutrients such as fiber, zinc, magnesium, vitamins B and C.

The C-DII was not associated with central and total body fat (Table 3). However, it was inversely associated with adiponectin ($R^2 = 2.7\%$) and RBP4 ($R^2 = 5.3\%$), and directly associated with chemerin ($R^2 = 4.0\%$), regardless of child's age, sex, race, *per capita* income, screen time and body fat. Compared with first, the fifth quintile of C-DII was related to lower adiponectin [− 1.9 (− 4.4, 0.6)] and lower RBP4 [ − 0.4 (− 0.7, − 0.2)]. Every 1 SD of C-DII was associated with − 0.8 (− 1.5, − 0.03) and to a − 0.1 (− 0.2, − 0.05) units lower mean of adiponectin and RBP4, respectively. Children with the most pro-inflammatory diet (fifth quintile) had, 17.6 ng/mL (− 4.2, 37.8) higher chemerin than children with the most anti-inflammatory diet (referent, first quintile).

**Table 1** Distribution of Children's Dietary Inflammatory Index (C-DII) according to sociodemographic and behavior characteristics in schoolchildren from Viçosa, Minas Gerais, Brazil, 2015

| Characteristics | *n* | C-DII | | *P* -value[b] |
|---|---|---|---|---|
| | | Mean ± SD | Mean difference (95% CI) | |
| Sex | | | | |
| Boys | 181 | 0.6 ± 0.9 | Reference | 0.47 |
| Girls | 197 | 0.5 ± 0.9 | − 0.1 (− 0.3, 0.1) | |
| Age (years) | | | | |
| 8 | 183 | 0.5 ± 0.9 | Reference | 0.58 |
| 9 | 195 | 0.6 ± 0.9 | 0.1 (− 0.1, 0.2) | |
| Race | | | | |
| White | 119 | 0.3 ± 0.9 | Reference | 0.001* |
| Non-white | 259 | 0.7 ± 0.9 | 0.3 (0.1, 0.5) | |
| School | | | | |
| Private | 110 | 0.3 ± 1.0 | Reference | < 0.001* |
| Public | 268 | 0.7 ± 0.9 | 0.3 (0.1, 0.5) | |
| Per capita income (US$)[a] | | | | |
| < 96.9 (1st quartile) | 93 | 0.7 ± 0.9 | Reference | 0.001* |
| 97.0 < 155.3 (2nd quartile) | 94 | 0.7 ± 0.9 | − 0.0 (− 0.3, 0.2) | |
| 155.4 < 262.2 (3rd quartile) | 97 | 0.6 ± 0.9 | − 0.1 (− 0.3, 0.2) | |
| > 262.3 (4th quartile) | 94 | 0.3 ± 1.0 | − 0.4 (− 0.6, − 0.1) | |
| Screen time (hours/day) | | | | |
| ≤ 2 | 198 | 0.5 ± 0.9 | Reference | 0.22 |
| > 2 (sedentary behavior) | 180 | 0.6 ± 1.0 | 0.1 (− 0.1, 0.3) | |

*SD* standard deviation, *95% IC* 95% confidence interval

[a]Approximate exchange rates of real (R$) to dollar (US$) at the time of this study (US$1.00 = R$ 3.22)

[b]Adjusted by child's sex, age, race, school, and screen time, Cochran-Armitage test. For variables with three or more categories, *P* value was from Wald test for linear trend representing ordinal categories as continuous

$P < 0.05$*

Every 1 SD of C-DII was associated with 7.2 (0.3, 14.1) units higher chemerin concentration (Table 4).

## Discussion

Results from this cross-sectional study supported the hypothesis that C-DII score was inversely and directly related with anti- and pro-inflammatory adipokines in children, respectively. A pro-inflammatory diet has been related to obesity [21–24] in childhood, in young adults [25], and in individuals with cardiometabolic risk [26]. However, no association was found between higher C-DII and adiposity measures as hypothesized. A possible explanation for this is the elevated prevalence of excess of body fat (50%) among children in our sample that could interfere in the association. It is worth noting that, in the current study, body fat distribution was assessed using DXA, the gold standard method, differing from previous results that evaluated adiposity by skinfold thickness [23] or other anthropometric indices [21, 22, 24]. Hence, further studies conducted in children are necessary to elucidate the influence of pro-inflammatory diet on adiposity measures.

Our findings showed an inverse association between C-DII and serum adiponectin. This adipokine is considered an anti-inflammatory marker [27] and lower adiponectin concentration has been recently associated with cardiometabolic comorbidities in children [28]. Furthermore, a cross-sectional study of 1992 adults from Ireland observed that the habitual intake of a more pro-inflammatory diet is negatively associated with adiponectin, corroborating our results [29]. The interaction among dietary imbalances and inflammation should be explored in greater detail in order to clarify its possible contribution to cardiometabolic risk, especially in young ages.

Surprisingly, C-DII was inversely associated with serum RBP4. This pro-inflammatory adipokine [30] is the main protein transporter of vitamin A (retinol) into the circulation [31]. Although the studies are limited, RBP4 has been inversely related to antioxidant nutrients consumption [32, 33]. This unexpected result possibly can be explained by vitamin A intake, which could increase RBP4 expression [34] due to the need to transport, store, and metabolize this

**Table 2** Distribution of energy and nutrients intake according to Children's Dietary Inflammatory Index (C-DII) in schoolchildren from Viçosa, Minas Gerais, Brazil, 2015

| Nutrients[a] | C-DII (quintiles) | | | | | *P* trend[b] |
|---|---|---|---|---|---|---|
| | Q1 (− 2.16 to − 0.19) (*n* = 75) | Q2 (− 0.20–0.41) (*n* = 76) | Q3 (0.42–0.86) (*n* = 76) | Q4 (0.87–1.41) (*n* = 76) | Q5 (1.42–2.75) (*n* = 75) | |
| Energy (kcal) | 1500.5 ± 356.7 | 1481.1 ± 438.6 | 1424.7 ± 520.0 | 1304.22 ± 467.6 | 1275.3 ± 398.4 | < 0.001* |
| Carbohydrate (g) | 152.0 ± 15.7 | 149.4 ± 15.7 | 148.0 ± 15.2 | 145.3 ± 14.7 | 143.9 ± 14.1 | < 0.001* |
| Protein (g) | 38.1 ± 7.3 | 36.5 ± 6.7 | 33.8 ± 6.9 | 32.3 ± 6.6 | 32.6 ± 7.3 | < 0.001* |
| Lipids (g) | 29.6 ± 6.1 | 29.4 ± 5.5 | 30.9 ± 5.3 | 32.6 ± 5.3 | 32.8 ± 5.5 | < 0.001* |
| MUFA (g) | 9.1 ± 2.0 | 9.2 ± 2.1 | 9.6 ± 2.3 | 10.3 ± 2.1 | 10.8 ± 2.4 | < 0.001* |
| PUFA (g) | 6.7 ± 2.1 | 6.1 ± 1.9 | 6.5 ± 2.3 | 6.1 ± 2.2 | 5.2 ± 2.0 | < 0.001* |
| Saturated fat (g) | 9.9 ± 2.4 | 9.9 ± 2.5 | 10.2 ± 2.3 | 10.9 ± 2.7 | 11.1 ± 2.4 | 0.001* |
| Fiber (g) | 13.5 ± 3.5 | 11.2 ± 3.2 | 9.6 ± 2.4 | 8.2 ± 2.2 | 6.9 ± 1.5 | < 0.001* |
| Iron (mg) | 5.6 ± 3.2 | 5.1 ± 1.7 | 4.8 ± 1.6 | 4.2 ± 1.4 | 4.3 ± 1.2 | < 0.001* |
| Zinc (mg) | 5.2 ± 2.0 | 4.5 ± 1.3 | 4.3 ± 1.3 | 4.1 ± 1.1 | 3.9 ± 0.8 | < 0.001* |
| Magnesium (mg) | 137.7 ± 29.0 | 125.4 ± 39.4 | 106.0 ± 14.6 | 96.8 ± 16.2 | 84.7 ± 14.2 | < 0.001* |
| B1 (mg) | 0.8 ± 0.2 | 0.7 ± 0.2 | 0.7 ± 0.2 | 0.6 ± 0.2 | 0.6 ± 0.2 | < 0.001* |
| B2 (mg) | 0.8 ± 0.3 | 0.8 ± 0.3 | 0.8 ± 0.2 | 0.7 ± 0.3 | 0.7 ± 0.2 | 0.02* |
| B3 (mg) | 8.1 ± 4.1 | 7.2 ± 3.2 | 6.8 ± 2.7 | 6.4 ± 2.6 | 6.3 ± 2.8 | < 0.001* |
| B6 (mg) | 0.7 ± 0.3 | 0.6 ± 0.2 | 0.6 ± 0.2 | 0.6 ± 0.2 | 0.5 ± 0.1 | < 0.001* |
| C (mg) | 93.8 ± 118.4 | 91.0 ± 223.8 | 41.2 ± 97.2 | 29.2 ± 32.6 | 13.6 ± 11.0 | 0.03* |
| D (µg) | 1.3 ± 0.9 | 1.1 ± 0.7 | 1.4 ± 1.1 | 1.4 ± 1.2 | 1.2 ± 1.0 | 0.24 |

*MUFA* monounsaturated fat, *PUFA* polyunsaturated fat, *Q* quintiles

Values are mean ± SD

[a]Nutrients adjusted for 1000 kcal

[b]From linear regression models with a variable representing ordinal C-DII categories introduced as continuous. Robust estimates of variance were specified in all models. Adjusted for child's age, sex, race, per capita income, screen time, % body fat

$P < 0.05$*

vitamin [35]. The greatest sources of vitamin A and beta-carotene include liver, dairy products, eggs, fishes, fruits and vegetables [36]. These foods are frequently consumed in healthy and anti-inflammatory dietary patterns [6, 7, 37, 38], suggesting that vitamin A intake and, consequently, RBP4 are probably inversely related to C-DII as we observed. However, future studies with vitamin A adjustment should be carried out to confirm this association.

Also, we observed a positive association between C-DII and serum chemerin. This pro-inflammatory adipokine [39] has potential role on the obesity [40] and metabolic syndrome [41] pathogenesis in children. Similar to our results, Mirmajidi et al. [42] showed a positive association between DII score and chemerin in healthy obese Iranian subjects (18–60 years old).

Altogether, our findings are consistent with other investigations that have reported the relationship between a pro-inflammatory diet and inflammation [43, 44]. In fact, certain foods rich in sugar and saturated fat (e.g. ultra-processed foods) are pro-inflammatory stimulants [45, 46], triggering an innate immune response with higher pro-inflammatory cytokines secretion [47]. In contrast, the adherence to an anti-inflammatory diet, plant-based food and rich in antioxidants properties, can beneficially affect inflammatory status [37, 38, 48], protecting against the development of chronic diseases [49, 50]. Taken together, diet plays a key role in the modulation of inflammation reinforcing that healthy eating habits should be encouraged since childhood.

This study has some limitations. Respondents to the 24HR may show memory bias; however, some strategies were used to minimize this factor and to increase data reliability such as the interviewers' training, use of a food photo album, and standard measurement tools. The C-DII score was calculated based on 16 of the total 25 food parameters in the original C-DII. Nevertheless, most of the nutrients were included (64%) and our mean C-DII score was comparable to a previous study [21]. Another limitation is that the vitamin A intake was not included in the adjustments of the association between C-DII and RBP4 concentrations. Moreover, all associations were modest in magnitude, with partial $R^2$ values ≤ 5% upon adjustment. Finally, due to its

**Table 3** Crude and adjusted analyses of the association between Children's Dietary Inflammatory Index (C-DII) and adiposity measures in schoolchildren from Viçosa, Minas Gerais, Brazil, 2015

| Body fat (%) | C-DII (quintiles) | | | | | Per 1 SD | *P* trend[c] |
|---|---|---|---|---|---|---|---|
| | Q1 (− 2.16 to − 0.19) (*n* = 75) | Q2 (− 0.20–0.41) (*n* = 76) | Q3 (0.42–0.86) (*n* = 76) | Q4 (0.87–1.41) (*n* = 76) | Q5 (1.42–2.75) (*n* = 75) | | |
| Total | | | | | | | |
| Mean ± SD | 23.5 ± 10.2 | 25.0 ± 10.2 | 24.5 ± 9.4 | 25.0 ± 10.5 | 22.9 ± 10.0 | | |
| Unadjusted difference (95% CI)[a] | Reference | 1.6 (− 1.7, 4.8) | 1.0 (− 2.1, 4.2) | 1.5 (− 1.8, 4.9) | − 0.6 (− 3.1, 2.7) | − 0.0 (− 1.1, 1.0) | 0.93 |
| Adjusted difference (95% CI)[b] | Reference | 1.7 (− 1.4, 4.8) | 1.5 (− 1.6, 4.6) | 2.1 (− 1.2, 5.3) | − 0.3 (− 3.6, 2.9) | 0.1 (− 1.0, 1.2) | 0.84 |
| Truncal | | | | | | | |
| Mean ± SD | 19.4 ± 11.3 | 21.0 ± 11.7 | 20.7 ± 10.3 | 21.2 ± 11.4 | 19.5 ± 11.3 | | |
| Unadjusted difference (95% CI)[a] | Reference | 1.5 (2.1, 5.2) | 1.2 (− 2.2, 4.7) | 1.8 (− 1.9, 5.4) | 0.1 (− 3.5, 3.7) | 0.2 (− 0.9, 1.3) | 0.77 |
| Adjusted difference (95% CI)[b] | Reference | 1.6 (− 1.9, 5.2) | 1.7 (− 1.7, 5.2) | 2.2 (− 1.4, 5.9) | 0.2 (− 3.4, 3.9) | 0.3 (− 0.9, 1.5) | 0.61 |
| Android | | | | | | | |
| Mean ± SD | 16.5 ± 12.2 | 18.0 ± 12.7 | 17.9 ± 11.3 | 18.7 ± 12.5 | 17.0 ± 12.5 | | |
| Unadjusted difference (95% CI)[a] | Reference | 1.5 (− 2.5, 5.5) | 1.4 (− 2.3, 5.2) | 2.2 (− 1.7, 6.2) | 0.5 (− 3.5, 4.5) | 0.4 (− 0.8, 1.6) | 0.53 |
| Adjusted difference (95% CI)[b] | Reference | 1.6 (− 2.2, 5.5) | 1.9 (− 1.9, 5.7) | 2.7 (− 1.3, 6.7) | 0.7 (− 3.4, 4.7) | 0.5 (− 0.7, 1.8) | 0.42 |
| Gynoid | | | | | | | |
| Mean ± SD | 30.5 ± 11.7 | 32.2 ± 11.2 | 32.3 ± 10.6 | 32.3 ± 12.1 | 29.5 ± 11.6 | | |
| Unadjusted difference (95% CI)[a] | Reference | 1.6 (− 2.0, 5.3) | 1.7 (− 1.8, 5.3) | 1.8 (− 2.0, 5.6) | − 1.0 (− 4.7, 2.3) | − 0.2 (− 1.4, 1.0) | 0.77 |
| Adjusted difference (95% CI)[b] | Reference | 1.8 (− 1.6, 5.3) | 2.4 (− 1.1, 5.8) | 2.5 (− 1.2, 6.2) | − 0.6 (− 4.3, 3.1) | 0.0 (− 1.2, 1.3) | 0.93 |

*95% IC* 95% confidence interval, *Q* quintiles

[a]From linear regression models with each adiposity marker as a continuous outcome and C-DII as predictor. Robust estimates of variance were specified in all models

[b]From linear regression adjusted for child's age, sex, race, per capita income and screen time

[c]For a variable representing ordinal C-DII categories introduced as a continuous predictor

$P < 0.05$*

cross-sectional design, lack of temporal specification limits causal inference.

Despite these weaknesses, our work has several strengths. To the best of our knowledge, this is the first epidemiological study to evaluate the relationship of C-DII with serum adipokines in children, providing relevant data to public health and a better understanding on the role of dietary factors in childhood obesity and low-grade inflammation. In addition, body composition was assessed by DXA (reference method), and the statistical analyses were adjusted for body fat.

In conclusion, a pro-inflammatory diet was modestly inverse and directly associated to anti- and pro-inflammatory adipokines, respectively, in Brazilian schoolchildren. The development of public health policies and actions of food and nutritional education, especially in school and family environments, are needed to promote healthy eating habits since the first stages of life and to prevent the early inflammation and the cardiometabolic risk.

**Table 4** Crude and adjusted analyses of the association between Children's Dietary Inflammatory Index (C-DII) and adipokines in schoolchildren from Viçosa, Minas Gerais, Brazil, 2015

| Adipokines | C-DII (quintiles) | | | | | *P* trend[d] | Per 1 SD *P* trend[d] |
|---|---|---|---|---|---|---|---|
| | Q1 (− 2.16 to − 0.19) (*n* = 75) | Q2 (− 0.20–0.41) (*n* = 76) | Q3 (0.42–0.86) (n = 76) | Q4 (0.87–1.41) (*n* = 76) | Q5 (1.42–2.75) (*n* = 75) | | |
| Adiponectin (µg/mL) | | | | | | | |
| Mean ± SD | 14.5 ± 7.7 | 14.6 ± 7.8 | 12.4 ± 6.3 | 13.6 ± 7.5 | 12.6 ± 7.5 | | |
| Unadjusted difference (95% CI)[a] | Reference | 0.2 (− 2.3, 2.6) | − 2.0 (− 4.3, 0.2) | − 0.8 (− 3.3, 1.6) | − 1.8 (− 4.3, 0.6) | − 0.7 (− 1.5, − 0.04) | 0.04* |
| Adjusted difference (95% CI)[b] | Reference | 0.1 (− 2.4, 2.6) | − 2.2 (− 4.5, 0.1) | − 1.0 (− 3.5, 1.5) | − 1.9 (− 4.4, 0.6) | − 0.8 (− 1.6, − 0.1) | 0.04* |
| Adjusted difference (95% CI)[c] | Reference | 0.2 (− 2.2, 2.7) | − 2.0 (− 4.3, 0.2) | − 0.8 (− 3.2, 1.7) | − 1.9 (− 4.4, 0.6) | − 0.8 (− 1.5, − 0.03) | 0.04* |
| Leptin (ng/mL) | | | | | | | |
| Mean ± SD | 6.0 ± 11.3 | 5.7 ± 8.9 | 5.0 ± 7.7 | 6.8 ± 10.6 | 5.0 ± 8.5 | | |
| Unadjusted difference (95% CI)[a] | Reference | − 0.3 (− 3.6, 2.9) | − 1.0 (− 4.1, 2.0) | 0.8 (-2.7, 4.3) | 1.0 (4.2, 2.2) | − 0.0 (− 0.9, 0.9) | 0.91 |
| Adjusted difference (95% CI)[b] | Reference | − 0.3 (3.6, 3.0) | − 0.8 (− 4.1, 2.5) | 1.0 (-2.6, 4.6) | 0.9 (− 4.3, 2.5) | 0.0 (− 0.9, 1.1) | 0.90 |
| Adjusted difference (95% CI)[c] | Reference | − 1.3 (− 4.1, 1.4) | − 1.7 (− 4.3, 1.0) | -0.5 (-3.4, 2.4) | − 0.7 (− 3.3, 1.9) | − 0.1 (− 0.8, 0.6) | 0.90 |
| RBP4 (µg/mL) | | | | | | | |
| Mean ± SD | 4.2 ± 0.9 | 4.2 ± 0.7 | 3.9 ± 0.5 | 4.0 ± 0.6 | 3.8 ± 0.5 | | |
| Unadjusted difference (95% CI)[a] | Reference | 0.0 (− 0.3, 0.2) | − 0.3 (− 0.6, − 0.1) | -0.2 (-0.5, -0.1) | − 0.4 (− 0.7, − 0.2) | − 0.1 (− 0.2, − 0.1) | < 0.001* |
| Adjusted difference (95% CI)[b] | Reference | 0.0 (− 0.3, 0.3) | − 0.3 (− 0.6, 0.0) | -0.2 (-0.5, 0.0) | − 0.4 (− 0.7, − 0.2) | − 0.1 (− 0.2, − 0.05) | 0.001* |
| Adjusted difference (95% CI)[c] | Reference | 0.0 (− 0.3, 0.2) | − 0.3 (− 0.6, − 0.1) | -0.2 (-0.5, 0.0) | − 0.4 (− 0.7, − 0.2) | − 0.1 (− 0.2, − 0.05) | 0.001* |
| Chemerin (ng/mL) | | | | | | | |
| Mean ± SD | 75.0 ± 65.4 | 74.6 ± 58.2 | 89.7 ± 68.9 | 89.3 ± 71.1 | 89.2 ± 58.9 | | |
| Unadjusted difference (95% CI)[a] | Reference | − 0.4 (− 20.3, 19.4) | 14.6 (− 6.8, 36.1) | 14.3 (-7.5, 36.1) | 14.2 (− 5.7, 34.2) | 6.1 (− 0.5, 12.7) | 0.07 |
| Adjusted difference (95% CI)[b] | Reference | 1.1 (− 19.1, 21.2) | 18.4 (− 3.1, 39.9) | 17.3 (-5.2, 39.7) | 16.6 (− 4.6, 37.8) | 7.4 (0.4, 14.4) | 0.04* |
| Adjusted difference (95% CI)[c] | Reference | − 0.1 (− 20.4, 20.2) | 17.3 (− 4.1, 38.8) | 16.3 (-6.5, 38.1) | 17.6 (− 4.2, 37.8) | 7.2 (0.3, 14.1) | 0.04* |

*95% IC* 95% confidence interval, *Q* quintiles

[a]From linear regression models with each adipokine as a continuous outcome and C-DII as predictor. Robust estimates of variance were specified in all models

[b]From linear regression adjusted for child's age, sex, race, per capita income and screen time

[c]From linear regression adjusted for child's age, sex, race, per capita income, screen time and % body fat

[d]For a variable representing ordinal C-DII categories introduced as a continuous predictor

$P < 0.05$*

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## Compliance with ethical standards

**Conflict of interest** We declare no conflicts of interest. Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI. The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project.

## References

1. Cao H (2014) Adipocytokines in obesity and metabolic disease. J Endocrinol 220:T47. https://doi.org/10.1530/JOE-13-0339
2. Hotamisligil GS (2006) Inflammation and metabolic disorders. Nature 444:860–867. https://doi.org/10.1038/nature05485
3. Ouchi N, Parker JL, Lugus JJ, Walsh K (2011) Adipokines in inflammation and metabolic disease. Nat Rev Immunol 11:85. https://doi.org/10.1038/nri2921
4. Su X, Peng D (2020) Adipokines as novel biomarkers of cardiometabolic disorders. Clin Chim Acta. https://doi.org/10.1016/j.cca.2020.04.009
5. WHO (2003) Diet, nutrition, and the prevention of chronic diseases: report of a joint WHO/FAO expert Consultation. World Health Organization, Geneva
6. Vieira-Ribeiro SA, Andreoli CS, Fonseca PC, Hermsdorff HM, Pereira PF, Ribeiro AQ, Priore SE, Franceschini SC (2019) Dietary patterns and body adiposity in children in Brazil: a cross-sectional study. Public Health 166:140–147. https://doi.org/10.1016/j.puhe.2018.10.00
7. Rocha NP, Milagres LC, Filgueiras MD, Suhett LG, Silva MA, Albuquerque FM, Ribeiro AQ, Vieira SA, Novaes JF (2019) Associação dos Padrões Alimentares com Excesso de Peso e Adiposidade Corporal em Crianças Brasileiras: Estudo Pase-Brasil. Arquivos Brasil Cardiol (AHEAD). https://doi.org/10.5935/abc.20190113
8. Rocha NP, Milagres LC, Longo GZ, Ribeiro AQ, de Novaes JF (2017) Association between dietary pattern and cardiometabolic risk in children and adolescents: a systematic review. J Pediat (Versão Português) 93:214–222. https://doi.org/10.1016/j.jped.2017.01.002
9. Wisnuwardani RW, De Henauw S, Ferrari M, Forsner M, Gottrand F, Huybrechts I, Kafatos AG, Kersting M, Knaze V, Manios Y, Marcos A (2020) Total polyphenol intake is inversely associated with a pro/anti-inflammatory biomarker ratio in European adolescents of the HELENA study. J Nutr. https://doi.org/10.1093/jn/nxaa064
10. Suhett LG, Silveira BK, Filgueiras MD, Peluzio MD, Hermsdorff HH, de Novaes JF (2018) Inverse association of calcium intake with abdominal adiposity and C-reactive protein in Brazilian children. Public Health Nutr 21:1912–1920. https://doi.org/10.1017/S136898001800023X
11. González-Gil EM, Tognon G, Lissner L, Intemann T, Pala V, Galli C, Wolters M, Siani A, Veidebaum T, Michels N, Molnar D (2018) Prospective associations between dietary patterns and high sensitivity C-reactive protein in European children: the IDEFICS study. Eur J Nutr 57:1397–1407. https://doi.org/10.1007/s00394-017-1419-x
12. Khan S, Wirth MD, Ortaglia A, Alvarado CR, Shivappa N, Hurley TG, Hebert JR (2018) Design, development and construct validation of the children's dietary inflammatory index. Nutrients 10:993. https://doi.org/10.3390/nu10080993
13. Suhett LG, Hermsdorff HH, Cota BC, Ribeiro SA, Shivappa N, Hébert JR, Franceschini SD, de Novaes JF (2020) Dietary inflammatory potential, cardiometabolic risk and inflammation in children and adolescents: a systematic review. Crit Rev Food Sci Nutr 10:1. https://doi.org/10.1080/10408398.2020.1734911
14. Filgueiras MD, Suhett LG, Silva MA, Rocha NP, de Novaes JF (2018) Lower vitamin D intake is associated with low HDL cholesterol and vitamin D insufficiency/deficiency in Brazilian children. Public Health Nutr 21:2004–2012. https://doi.org/10.1017/S1368980018000204
15. Milagres LC, Rocha NP, Filgueiras MS, Albuquerque FM, Castro APP, Pessoa MC et al (2017) Vitamin D insufficiency/deficiency is associated with insulin resistance in Brazilian children, regardless of body fat distribution. Public Health Nutr 20:2878–2886. https://doi.org/10.1017/S136898001700194X
16. Zabotto CB, Vianna RPT, Gil MF (1996) Registro Fotográfico Para Inquéritos Dietéticos: Utensílios e Porções. Goiânia: Nepa-Unicamp; available at http://www.fcm.unicamp.br/fcm/sites/default/files/2016/page/manual_ fotografico.pdf Accessed 22 May 2020
17. Núcleo de Estudos e Pesquisas em Alimentação, Universidade Estadual de Campinas (2011) Tabela Brasileira de Composição de Alimentos – TACO, 4ª ed. rev. e ampl. Campinas: Nepa–Unicamp, p 161
18. US Department of agriculture, agricultural research service (2016) USDA national nutrient database for standard reference (Release 28). http://www.fnic.nal.usda.gov/food-composition/usda-nutrient-data-laboratory Accessed 22 May 2020
19. American Academy of Pediatrics, Council on Communications and Media (2013) Children, adolescents, and the media. Pediatrics 132:958–961. https://doi.org/10.1542/peds.2013-2656
20. Lohman TG (1992) Advances in body composition assessment. Hum Kinet 1–23
21. Navarro P, Shivappa N, Hébert JR, Mehegan J, Murrin CM, Kelleher CC, Phillips CM (2019) Predictors of the dietary inflammatory index in children and associations with childhood weight status: a longitudinal analysis in the Lifeways Cross-Generation Cohort Study. Clin Nutr. https://doi.org/10.1016/j.clnu.2019.09.004
22. Aslani Z, Qorbani M, Hébert JR, Shivappa N, Motlagh ME, Asayesh H, Mahdavi-Gorabi A, Kelishadi R (2019) Association of dietary inflammatory index with anthropometric indices in children and adolescents: the weight disorder survey of the childhood and adolescence surveillance and prevention of adult non-communicable disease (CASPIAN)-IV study. Br J Nutr 121:340–350. https://doi.org/10.1017/S0007114518003240
23. Sen S, Rifas-Shiman SL, Shivappa N, Wirth MD, Hebert JR, Gold DR, Gillman MW, Oken E (2018) Associations of prenatal and early life dietary inflammatory potential with childhood adiposity

and cardiometabolic risk in Project Viva. Pediat Obesity 13:292–300. https://doi.org/10.1111/ijpo.12221
24. Correa-Rodríguez M, González-Jiménez E, Rueda-Medina B, Tovar-Gálvez MI, Ramírez-Vélez R, Correa-Bautista JE, Schmidt-RioValle J (2018) Dietary inflammatory index and cardiovascular risk factors in Spanish children and adolescents. Res Nurs Health 41:448–458. https://doi.org/10.1002/nur.21904
25. Oliveira TM, Bressan J, Pimenta AM, Martínez-González MÁ, Shivappa N, Hébert JR, Hermsdorff HH (2020) Dietary inflammatory index and prevalence of overweight and obesity in Brazilian graduates from the Cohort of Universities of Minas Gerais (CUME project). Nutrition 71:110635. https://doi.org/10.1016/j.nut.2019.110635
26. Meneguelli TS, Hinkelmann JV, de Novaes JF, Rosa CD, Filgueiras MD, Silveira B (2019) Dietary inflammatory index is associated with excessive body weight and dietary patterns in subjects with cardiometabolic risk. J Food Nutr Res 7:491–499. https://doi.org/10.12691/jfnr-7-7-2
27. Wolf AM, Wolf D, Rumpold H, Enrich B, Tilg H (2004) Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. Biochem Biophys Res Commun 323:630–635. https://doi.org/10.1016/j.bbrc.2004.08.145
28. Frithioff-Bøjsøe C, Lund MAV, Lausten-Thomsen U, Hedley PL, Pedersen O, Christiansen M et al (2020) Leptin, adiponectin, and their ratio as markers of insulin resistance and cardiometabolic risk in childhood obesity. Pediatr Diabetes 21:194–202. https://doi.org/10.1111/pedi.12964
29. Phillips CM, Shivappa N, Hébert JR, Perry IJ (2018) Dietary inflammatory index and biomarkers of lipoprotein metabolism, inflammation and glucose homeostasis in adults. Nutrients 10:1033. https://doi.org/10.3390/nu10081033
30. Farjo KM, Farjo RA, Halsey S, Moiseyev G, Ma J-X (2012) Retinol-Binding protein 4 induces inflammation in human endothelial cells by an NADPH oxidase- and nuclear factor kappa B-dependent and retinol-independent mechanism. Mol Cell Biol 32:5103–5115. https://doi.org/10.1128/MCB.00820-12
31. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM et al (2005) Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature 436:356–362. https://doi.org/10.1038/nature03711
32. Jing L, Xiao M, Dong H, Lin J, Chen G, Ling W, Chen Y (2018) Serum carotenoids are inversely associated with RBP4 and other inflammatory markers in middle-aged and elderly adults. Nutrients 10:260. https://doi.org/10.3390/nu10030260
33. Hermsdorff HH, Zulet MÁ, Puchau B, Bressan J, Martínez JA (2009) Association of retinol-binding protein-4 with dietary selenium intake and other lifestyle features in young healthy women. Nutrition 25:392–399. https://doi.org/10.1016/j.nut.2008.09.015
34. Daneshzad E, Farsad-Naeimi A, Heshmati J, Mirzaei K, Maghbooli Z, Keshavarz SA (2019) The association between dietary antioxidants and adipokines level among obese women. Diabetes Metab Synd Clin Res Rev 13:1369–1373. https://doi.org/10.1016/j.dsx.2019.02.022
35. Quadro L, Blaner WS, Salchow DJ, Vogel S, Piantedosi R, Gouras P, Freeman S, Cosma MP, Colantuoni V, Gottesman ME (1999) Impaired retinal function and vitamin a availability in mice lacking retinol-binding protein. EMBO J 18:4633–4644. https://doi.org/10.1093/emboj/18.17.4633
36. Bates CJ (1995) Vitamin A. Lancet 345:31–35. https://doi.org/10.1016/s0140-6736(95)91157-x
37. Sureda A, Bibiloni MD, Julibert A, Bouzas C, Argelich E, Llompart I, Pons A, Tur JA (2018) Adherence to the mediterranean diet and inflammatory markers. Nutrients 10:62. https://doi.org/10.3390/nu10010062
38. Arouca A, Moreno LA, Gonzalez-Gil EM, Marcos A, Widhalm K, Molnár D, Manios Y, Gottrand F, Kafatos A, Kersting M, Sjöström M (2019) Diet as moderator in the association of adiposity with inflammatory biomarkers among adolescents in the HELENA study. Eur J Nutr 58:1947–1960. https://doi.org/10.1007/s00394-018-1749-3
39. Dimitriadis GK, Kaur J, Adya R, Miras AD, Mattu HS, Hattersley JG, Kaltsas G, Tan BK, Randeva HS (2018) Chemerin induces endothelial cell inflammation: activation of nuclear factor-kappa beta and monocyte-endothelial adhesion. Oncotarget 9:16678. https://doi.org/10.18632/oncotarget.24659
40. Landgraf K, Friebe D, Ullrich T, Kratzsch J, Dittrich K, Herberth G, Adams V, Kiess W, Erbs S, Körner A (2012) Chemerin as a mediator between obesity and vascular inflammation in children. J Clin Endocrinol Metab 97:E556–E564. https://doi.org/10.1210/jc.2011-2937
41. Niklowitz P, Rothermel J, Lass N, Barth A, Reinehr T (2018) Link between chemerin, central obesity, and parameters of the Metabolic Syndrome: findings from a longitudinal study in obese children participating in a lifestyle intervention. Int J Obesity 42:1743–1752. https://doi.org/10.1038/s41366-018-0157-3
42. Mirmajidi S, Izadi A, Saghafi-Asl M, Vahid F, Karamzad N, Amiri P, Shivappa N, Hébert JR (2019) Inflammatory potential of diet: association with chemerin, omentin, lipopolysaccharide-binding protein, and insulin resistance in the apparently healthy obese. J Am Coll Nutr 38:302–310. https://doi.org/10.1080/07315724.2018.1504348
43. Almeida-de-Souza J, Santos R, Barros R, Abreu S, Moreira C, Lopes L, Mota J, Moreira P (2018) Dietary inflammatory index and inflammatory biomarkers in adolescents from LabMed physical activity study. Eur J Clin Nutr 72:710–719. https://doi.org/10.1038/s41430-017-0013-x
44. Shivappa N, Hebert JR, Marcos A, Diaz LE, Gomez S, Nova E, Michels N, Arouca A, González-Gil E, Frederic G, González-Gross M (2017) Association between dietary inflammatory index and inflammatory markers in the HELENA study. Mol Nutr Food Res 61:1600707. https://doi.org/10.1002/mnfr.201600707
45. Lopes AE, Araújo LF, Levy RB, Barreto SM, Giatti L (2019) Association between consumption of ultra-processed foods and serum C-reactive protein levels: cross-sectional results from the ELSA-Brasil study. Sao Paulo Med J 137:169–176. https://doi.org/10.1590/1516-3180.2018.0363070219
46. Koebnick C, Black MH, Wu J, Shu YH, MacKay AW, Watanabe RM, Buchanan TA, Xiang AH (2018) A diet high in sugar-sweetened beverage and low in fruits and vegetables is associated with adiposity and a pro-inflammatory adipokine profile. Br J Nutr 120:1230–1239. https://doi.org/10.1017/S0007114518002726
47. Galland L (2010) Diet and inflammation. Nutr Clin Pract 25:634–640. https://doi.org/10.1177/0884533610385703
48. Ambroszkiewicz J, Chełchowska M, Rowicka G, Klemarczyk W, Strucińska M, Gajewska J (2018) Anti-inflammatory and pro-inflammatory adipokine profiles in children on vegetarian and omnivorous diets. Nutrients 10:1241. https://doi.org/10.3390/nu10091241
49. Notario-Barandiaran L, Valera-Gran D, Gonzalez-Palacios S, Garcia-de-la-Hera M, Fernández-Barrés S, Pereda-Pereda E, Fernández-Somoano A, Guxens M, Iñiguez C, Romaguera D, Vrijheid M (2020) High adherence to a mediterranean diet at age 4 reduces overweight, obesity and abdominal obesity incidence in children at the age of 8. Int J Obesity 9:1–2. https://doi.org/10.1038/s41366-020-0557-z
50. Widmer RJ, Flammer AJ, Lerman LO, Lerman A (2015) The Mediterranean diet, its components, and cardiovascular disease. Am J Med 128:229–238. https://doi.org/10.1016/j.amjmed.2014.10.014