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# Fatty Acids in Childhood Obesity: A Link Between Nutrition, Metabolic Alterations and Cardiovascular Risk

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## ABSTRACT

**Objective:** Childhood obesity, affected by dietary choices, increases cardiovascular risk. Obesity is associated with inflammation and altered glucose, iron and lipid metabolism. This study explores connections between dietary habits, plasma fatty acid profile, cardiovascular risk factors and childhood obesity.

**Methods:** We conducted a case-control study including 20 children and adolescents with obesity and 20 controls. Anthropometric parameters and food frequency questionnaires were registered. Glucose metabolism, iron parameters, lipid profile, fatty acids profile, and lipoprotein-associated phospholipase $A_2$ (Lp-$PLA_2$), cholesteryl ester transfer protein and paraoxonase 1 (PON 1) activities were evaluated. Correlation, regression and mediation analyses were performed.

**Results:** The group with obesity consumed more bakery products and less cereals, and presented higher myristic, palmitoleic, margaric and gamma-linolenic acids, along with lower linoleic, arachidic, gadoleic, eicosatrienoic and eicosapentaenoic (EPA) acids ($p$<0.05). They also exhibited altered glucose metabolism, a more atherogenic lipid profile, higher Lp-$PLA_2$ and lower PON 1 activities ($p$<0.05). Consumption of several food groups correlated with metabolic alterations. Different correlations between pro-inflammatory, anti-inflammatory and obesity-related fatty acids, and cardiometabolic biomarkers were found, including: myristic acid with Lp-$PLA_2$ ($r$=0.32, $p$<0.05), EPA acid with hs-CRP ($r$=−0.36, $p$<0.05) and gadoleic acid with PON1 ($r$=0.39, $p$<0.05). Mediation analyses revealed fatty acids and cardiometabolic markers as mediators of the association between dietary habits and obesity.

**Conclusion:** Children and adolescents with obesity presented disrupted glucose and lipid metabolism, vascular inflammation, attenuated antioxidant function and altered fatty acid composition. Direct and indirect associations between dietary habits, fatty acids, cardiometabolic markers and the presence of obesity were found.

**Keywords:** Pediatric obesity; High density lipoprotein; Fatty acids; Paraoxonase; Lp-$PLA_2$

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**Conflict of Interest**

The authors have no conflicts of interest to declare.

**Data Availability Statement**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Author Contributions**

Conceptualization: Davico B, Martin M, Gaete L, Trifone L, Feliu MS, Brites F; Investigation: Davico B, Martin M, Impa Condori A, Lozano Chiappe E, Gaete L, Tetzlaff WF, Yanez A, Sáez MS, Bava A, Godoy MF, Palenque P; Methodology: Davico B, Martin M, Gaete L, Osta V, Sáez MS, Godoy MF, Palenque P, Feliu MS, Brites F; Writing - original draft: Davico B, Martin M, Impa Condori A, Lozano Chiappe E, Gaete L, Tetzlaff WF, Yanez A, Osta V, Sáez MS, Bava A, Godoy MF, Palenque P; Writing - review & editing: Ballerini MG, Trifone L, Gómez Rosso L, Feliu MS, Brites F.

## INTRODUCTION

Childhood obesity is now considered one of the most important health problems worldwide. Children and, particularly, adolescents with obesity are likely to become obese adults.[1] As a result, they are at increased risk of developing other diseases such as type 2 diabetes, cardiovascular disease and cancer, and, consequently, increased risk of premature morbidity and mortality.[1,2] Factors influencing pediatric obesity include parental weight status, family practices and stress, peer support for healthy lifestyle, weight stigma, media influence and school programs, among other socioeconomic aspects.[3] Importantly, parental eating behaviors shape the dietary choices and habits of their children, with the latter being a key determinant of childhood obesity.[4]

Atherogenic dyslipidemia and a proinflammatory state are among the comorbidities most frequently found closely linked to childhood obesity.[3] Alterations in lipid and lipoprotein spectrum are generally featured by increases in triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C), and a marked reduction in high-density lipoprotein cholesterol (HDL-C) levels, the unique cardioprotective marker.[5] Beyond traditional risk factors, novel ones have been also reported to be modified in obese children and adolescents. These include cholesterol efflux from macrophages, free cholesterol esterification by lecithin:cholesterol acyltransferase (LCAT) and TG-cholesteryl ester interchange between HDL and apoliprotein (apo) B-containing lipoproteins carried out by cholesteryl ester transfer protein (CETP), the three main steps of reverse cholesterol transport, which is the antiatherogenic pathway promoted by HDL particles.[6] In fact, past evidence showed that cholesterol efflux and LCAT activity were lower in childhood obesity, while CETP status still remains controversial.[7,8] Another HDL cardioprotective function is its antioxidative activity.[6] The activity of paraoxonase 1 (PON 1), an enzyme mainly transported by HDL, plays a central role in this function and has been also reported to be impaired in children and adolescents with obesity.[9] Regarding the pro-inflammatory state underlying childhood obesity, both a traditional marker of systemic inflammation, high-sensitivity C-reactive protein (hsCRP) concentration, and a specific biomarker of vascular inflammation, the activity of lipoprotein-associated phospholipase $A_2$ (Lp-$PLA_2$), were found to be significantly higher in obese children in comparison to normal weight controls.[8,10] Nevertheless, systemic inflammation can often be absent in childhood obesity.[8]

As is the case with glucose and lipid metabolisms, dysregulation of iron metabolism is now recognized as a potential comorbidity of obesity.[11] Evidence suggests that children with obesity present lower iron and transferrin saturation levels, probably as a consequence of low grade inflammation present in obesity.[11] Interestingly, a study conducted among Spanish children aged 9–10 years demonstrated that iron homeostasis is related not only to lipid and glycemic alterations, but also to fatty acid metabolism.[12] Furthermore, another study showed that the interplay between iron parameters and fatty acids changes with glucose tolerance in women with previous gestational diabetes mellitus.[13] As a result, iron metabolism is not only deeply associated with the development of obesity, but it also plays a role in the onset of metabolic comorbidities such as inflammation, insulin resistance (IR) and dyslipidemia. Therefore, iron associated parameters would represent targets of particular interest in the context of obesity.

As mentioned above, dietary habits play a central role in the development of obesity.[4] Indeed, eating habits have been described as a major determinant of obesity, not only in adults,


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but also in children and adolescents.[14,15] In particular, consumption of sugar-sweetened beverages and candy can influence not only the development of obesity, but also the presence of associated metabolic comorbidities.[16-18] Similarly, among dietary habits, it is well-known that consumption of food rich in fatty acids is a nutritional factor affecting the development of obesity and IR.[19] Moreover, both, plasma fatty acid profile and fatty acid intake can affect lipid levels, having a direct impact on cardiovascular risk.[20-22] Hence, HDL-C levels can increase with the consumption of oleic acid,[23] and LDL-C levels are reported to decrease with stearic and linoleic acids.[24] Particularly, fatty acid profile in apolipoprotein B (apo B)-depleted plasma of children and adolescents with abdominal obesity was shown to affect the promotion of reverse cholesterol transport conducted by HDL.[25]

It is noteworthy that the novel markers of cardiometabolic risk mentioned above, including lipoprotein-associated enzymes and lipid transfer proteins, are of particular interest in pediatric populations in which evaluation of traditional indicators of subclinical atherosclerosis, such as intima media thickness, is hard to implement. Furthermore, traditional markers, such as LDL-C, have been shown to be insufficient to accurately predict atherogenic risk, making the evaluation of novel markers and potential associated modulators of high interest.[26] Plasma fatty acids could be among these potential modulators and their circulating levels would be susceptible to be modified by dietary habits.[20] Moreover, among novel atherogenic markers, those associated with HDL functionality have received most attention. Thus, given that HDL functions are generally evaluated in apo B-depleted plasma both by our group and by other authors, it would be worthy to characterize fatty acid profile in the same sample, where HDL is the only lipoprotein fraction present, and to further explore possible associations.[27,28] Therefore, the aim of the present study was to explore possible sequential connections between dietary habits, plasma fatty acid profile, cardiovascular risk factors and childhood obesity.

## MATERIALS AND METHODS

### 1. Study design and patients

Twenty children and adolescents with obesity and twenty normal weight controls matched by sex and age who attended the Nutrition and Diabetes Service of the Children's Hospital "Dr. Ricardo Gutiérrez" were included in a case-control observational study. All of them signed an informed consent and the study protocol was approved by the Ethics Committee of the Children Hospital "Dr. Ricardo Gutiérrez" according to the Helsinki declaration (Institutional Review Board: CEI 14.34). All children and adolescents were Argentinian and their ethnicity was Hispanic. Obesity was defined as body mass index (BMI) z-score >2.0. Both children and adolescents were included in the present study to better represent the full spectrum of pediatric individuals. Inclusion criteria for controls were: age between 8 and 17 years old (shared with the group with obesity), BMI z-score <1 and BMI <85th percentile according to World Health Organization (WHO) and presence of normal lipid levels.[29,30]

Subjects with presence of chronic or acute diseases other than obesity and subjects undergoing dietary or pharmacological treatment which could affect carbohydrate or lipid levels or metabolism were excluded. The study included a pediatric population with obesity and another of healthy controls, whose characteristics were previously described.[8]


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### 2. Anthropometric parameters and nutritional data

A trained physician examined all participants and recorded weight, height and Tanner score. Family history of obesity was also recorded. The WHO ANTHRO and ANTHRO plus programs were used to calculate BMI and BMI z-score. Food frequency questionnaires were carried out by a trained nutritionist who provided the necessary information and assisted participants in filling the questionnaire. All children and adolescents were accompanied by a parent or tutor while answering the questions. The frequency of consumption of each food included in the questionnaire was classified in 9 categories ranging from once per month to 7 or more times per week. Twenty-four food items were included in the questionnaire. Some of these items were excluded from analysis due to low consumption. The questionnaire was based on a prior work which validated a food frequency questionnaire for children and adolescents from Buenos Aires, Argentina.[31] Moreover, this same questionnaire was validated in other pediatric populations throughout South America.[31]

### 3. Fatty acid profile

Fatty acid profile in apo B-depleted plasma was determined by gas chromatography (GC). Fatty acid methyl esters (FAMEs) from plasma were prepared according to a modified method of Lepage. Briefly, 2 mL of a methanol:toluene (4:1, vol:vol) were added to 200 µL of plasma and then 0.2 mL of acetyl chloride were slowly incorporated. After heating at 100°C for 1 hour, 5 mL of a 6% $K_2CO_3$ solution was added to the tube, mixed on a vortex and centrifuged, and the clear toluene top layer containing FAMEs was obtained. FAMEs were analyzed using a Claurus 500 GC equipped with a Supelco SP 2560 100 m × 0.25 mm × 0.20 um column and FID detector at 280°C, using helium as carrier gas. The plasma fatty acid data were expressed as the percent (%) of total fatty acids (limit of quantification a value of 0.05%).[32]

### 4. Biochemical parameters related to glucose, iron and lipid metabolism

Plasma glucose and insulin concentrations as well as lipid profile plus Lp-$PLA_2$, CETP, and PON 1 activities were evaluated as previously described.[8] Abnormal lipid levels were defined following the recommendations of the National Health Institute.[33] Homeostatic Model Assessment for IR (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI) indexes were calculated. Hemoglobin (HB) and iron levels were quantified by standardized methods (Roche Diagnostics, Indianapolis, IN, USA). Ferritin concentration was determined by an electrochemiluminescence assay (VITROS® ECiQ; Ortho-Clinical Diagnostics, Raritan, NJ, USA). Plasma transferrin was measured by nephelometry (IMMAGE®; Beckman Coulter, Brea).

### 5. Plasma hsCRP and non-esterified fatty acids (NEFA)

Plasma hsCRP concentration was evaluated by a high sensitivity immunoturbidimetric assay (Roche Diagnostics) and plasma NEFA concentration was measured by a spectrophotometric method (FA 115 kit; Randox).

### 6. Sample calculation and statistical analysis

Sample calculation for 80% potency was performed employing Eppidata Software. Taking into account the fact that plasma fatty acids and novel markers of atherogenic risk represent the main targets of the current study, PON 1 activity and palmitoleic acid levels were employed as the selected variables and the calculation was performed with unpublished data from a preliminary study carried out by our group. PON 1 was chosen due to its central role in HDL function and palmitoleic acid has been previously associated with multiple alterations in childhood obesity.[25,34] The number of both patients and controls necessary to


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obtain 80% statistical power was estimated as 16 for PON 1 activity and 14 for palmitoleic acid levels. Variable distribution was assessed by the Shapiro Wilks test. The previous data (controls vs. subjects with obesity) was: 179±36 versus 140±41 nmol/mL.min for PON1 and 2.01%±0.68% versus 2.62%±0.41% for palmitoleic acid. Comparisons between populations were performed by Student's *t*-test for parametric variables and Mann Whitney *U* test for non-parametric ones. Data were displayed as mean ± standard deviation or median (interquartile range) depending on data distribution. Pearson (parametric) and Spearman (nonparametric) correlation coefficients were employed to analyze univariate associations employing data from the whole population. Multiple testing was corrected by adjusting individuals' *p*-values with the Benjamini-Hochberg Procedure. Linear regression was employed to explore the association between obesity and the different variables adjusting by age, sex and Tanner stage. Normality of residuals was checked by Shapiro-Wilks and homogeneity of variance by Levenne. Mediation analyses were carried out with the PROCESS package. All analyses were carried out with SPSS 25.0 statistical software (IBM Corp.).

## RESULTS

### 1. Anthropometric parameters

Both populations evaluated in the present study were similar in age, sex and Tanner stage, with *p*-values for all 3 parameters above 0.1 (**Supplementary Table 1**). Therefore, they were compared without adjustments. As expected, the group with obesity showed higher values of BMI and BMI z-score (**Supplementary Table 1**). Furthermore, this group also showed higher frequency of family history of obesity, reflecting the importance of family environment in the development of obesity (**Supplementary Table 1**).

### 2. Dietary information

The food frequency questionnaire exposed that children and adolescents with obesity consumed bakery products more often and cereals with less frequency than healthy controls (**Table 1**). These findings suggest healthier dietary habits for the control group given that cereal consumption is associated with beneficial effects in pediatric populations while bakery products consumption is a potential cause for metabolic alterations. There were no significant differences in the frequency of consumption for the rest of the food items evaluated (**Table 1**).

**Table 1.** Dietary habits in children and adolescents with obesity and controls

| Food group* | Controls with normal weight (n=20) | Patients with obesity (n=20) | *p*-value |
|---|---|---|---|
| Vegetables | 3 (2–5) | 3 (2–7) | 0.922 |
| Fruit | 3 (1–7) | 3.5 (2–5) | 0.475 |
| Dairy | 4 (2–7) | 7 (3–7) | 0.560 |
| Red meat | 7 (3–7) | 7 (7–7) | 0.114 |
| Charcuterie | 1.5 (1–2) | 1 (1–2) | 0.334 |
| Sugar-rich beverages | 7 (2–7) | 7 (2–7) | 0.624 |
| Candy | 4 (1–7) | 3 (3–5) | 0.623 |
| Dressing | 5 (2–7) | 4 (1–7) | 0.472 |
| Butter | 2 (1–3) | 1 (1–2) | 0.150 |
| Cereals | 7 (7–7) | 7 (6–7) | 0.021 |
| Bakery products | 1 (1–1) | 1 (1–2) | 0.038 |
| Cookies | 7 (7–7) | 7 (7–7) | 0.083 |
| Egg | 2 (1–3) | 2 (1–3) | 0.842 |

Ordinal variables presented as median (interquartile range). Benjamini-Hochberg method was implemented for multiple comparisons.
*Frequency score of consumption/times per week.


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## 3. Fatty acid profile

When analyzing the concentration of different fatty acids, patients with obesity revealed higher levels of myristic, palmitoleic, margaric and gamma-linolenic acids, as well as lower levels of linoleic, arachidic, gadoleic, eicosatrienoic acid and eicosapentaenoic acid (EPA) (**Table 2**). These findings reflect the presence of a more unfavorable fatty acid profile in the plasma of children and adolescents with obesity, characterized by lower levels of anti-inflammatory and cardioprotective components such as linoleic, eicosatrienoic acid and EPA and higher values of fatty acids associated with cardiometabolic disorders such as myristic and palmitoleic acids.

## 4. Biochemical parameters

The group with obesity showed higher insulin levels and HOMA-IR in addition to lower QUICKI (**Supplementary Table 2**). Regarding lipids and novel markers of cardiovascular disease, children and adolescents with obesity presented higher TG, LDL-C, and Lp-$PLA_2$ activity, plus lower HDL-C, apo A-I and ARE activity (**Supplementary Table 2**). There were no significant differences in HB, iron, ferritin, transferrin or transferrin saturation (**Supplementary Table 2**).

## 5. Correlations between fatty acids and dietary habits

The frequency of consumption of different food groups correlated with different fatty acids (**Table 3**). Frequency of consumption of vegetables correlated negatively with arachidonic acid and cookies consumption with margaric acid. Bakery products correlated with palmitoleic acid whilst cereals correlated with lauric, myristic, palmitoleic and arachidonic acids. Red meat consumption correlated with myristic, palmitoleic, eicosatrienoic acid and EPA; and charcuterie with linoleic and arachidonic acids. Frequency of consumption of dairy products only correlated with EPA. However, butter consumption correlated with docosahexaenoic acid. Sugary drinks correlated with arachidonic acid, as candy consumption correlated with stearic and linoleic acids.

**Table 2.** Fatty acid profile in children and adolescents with obesity and controls

| Parameter | Controls with normal weight (n=20) | Patients with obesity (n=20) | *p*-value |
|---|---|---|---|
| Lauric acid (C12:0) | 0.09 (0.08–0.13) | 0.13 (0.09–0.22) | 0.115 |
| Myristic acid (C14:0) | 0.76±0.26 | 1.12±0.28 | <0.001 |
| Palmitic acid (C16:0) | 20.05±2.42 | 21.39±2.66 | 0.139 |
| Palmitoleic acid (C16:1 n-7) | 1.99±0.67 | 2.59±0.42 | 0.005 |
| Margaric acid (C17:0) | 0.47 (0.42–0.56) | 0.68 (0.47–0.79) | 0.030 |
| Stearic acid (C18:0) | 8.63±0.88 | 8.92±1.44 | 0.514 |
| Oleic acid (C18:1 n-9) | 17.64±1.32 | 17.41±1.72 | 0.676 |
| Cis-vaccenic acid (C18:1 n-7) | 1.57±0.20 | 1.48±0.28 | 0.287 |
| Linoleic acid (C18:2 n-6) | 30.20 (29.09–31.11) | 27.25 (23.48–28.81) | 0.043 |
| Arachidic acid (C20:0) | 0.24 (0.22–0.36) | 0.18 (0.16–0.26) | 0.044 |
| Gamma-linolenic acid (C18:3 n-6) | 0.28 (0.25–0.31) | 0.33 (0.31–0.41) | 0.043 |
| Gadoleic acid (C20:1 n-11) | 0.14±0.03 | 0.13±0.03 | 0.042 |
| Alpha-linolenic acid (C18:3 n-3) | 0.22 (0.18–0.28) | 0.25 (0.19–0.32) | 0.176 |
| Eicosatrienoic acid (C20:3 n-9) | 0.75±0.14 | 0.65±0.15 | 0.045 |
| Arachidonic acid (C20:4 n-6) | 4.68 (3.80–5.12) | 5.16 (4.04–6.78) | 0.242 |
| Eicosapentaenoic acid (C20:5 n-3) | 0.33 (0.24–0.50) | 0.22 (0.14–0.34) | 0.042 |
| Lignoceric acid (C24:0) | 0.39±0.26 | 0.40±0.15 | 0.976 |
| Docosahexaenoic acid (C22:6 n-3) | 0.66 (0.54–0.82) | 0.84 (0.51–1.02) | 0.256 |
| Arachidonic acid/docosahexaenoic acid | 6.74 (6.04–7.89) | 6.76 (5.12–7.70) | 0.829 |

Results expressed as area %. Continuous variables presented as mean ± standard deviation or median (interquartile range) according to data distribution. Benjamini-Hochberg method was implemented for multiple comparisons.


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**Table 3.** Statistically significant correlations between food group consumption and fatty acid levels

| Acid | Vegetables | Dairy | Red meat | Charcuterie | SRB | Candy | Butter | Cereals | Bakery products | Cookies |
|---|---|---|---|---|---|---|---|---|---|---|
| Lauric | - | - | - | - | - | - | - | −0.49 (0.02) | - | - |
| Myristic | - | - | 0.33 (0.04) | - | - | - | - | −0.32 (0.04) | - | - |
| Palmitoleic | - | - | 0.39 (0.02) | - | - | - | - | −0.35 (0.04) | 0.52 (0.01) | - |
| Margaric | - | - | - | - | - | - | - | - | - | −0.34 (0.04) |
| Stearic | - | - | - | - | - | 0.43 (0.03) | - | - | - | - |
| Linoleic | - | - | - | −0.55 (0.02) | - | −0.48 (0.01) | - | - | - | - |
| Eicosatrienoic | - | - | −0.43 (0.01) | - | - | - | - | - | - | - |
| Arachidonic | −0.43 (0.02) | - | - | 0.52 (0.04) | −0.40 (0.04) | - | - | −0.41 (0.02) | - | - |
| Eicosapentaenoic | - | −0.50 (0.01) | −0.34 (0.04) | - | - | - | - | - | - | - |
| Docosahexaenoic | - | - | - | - | - | - | −0.47 (0.04) | - | - | - |

Data are shown as *r* (*p*-value). Benjamini-Hochberg method was implemented for multiple comparisons.
SRB, sugar-rich beverages.

## 6. Correlations between fatty acids and biochemical parameters

**Table 4** shows the correlations between fatty acids and both anthropometric and biochemical parameters. Interestingly, myristic acid correlated with BMI z-score, HDL-C, insulin, HOMA index, QUICKI index and NEFA. Margaric acid also correlated with NEFA, while lignoceric acid correlated with NEFA, glucose and transferrin. Arachidic acid correlated with glucose levels as well. Palmitoleic acid correlated with HDL-C, apo A-I, insulin, HOMA index, QUICKI index and NEFA. Furthermore, linoleic acid correlated with HDL-C, BMI z-score, iron and NEFA. Gamma-linolenic acid correlated with BMI z-score and alpha-linolenic acid with TG. Cis-vaccenic acid correlated negatively with ferritin. Finally, EPA correlated with HDL-C, transferrin, HOMA index and NEFA.

**Table 4.** Statistically significant correlations between fatty acid levels and anthropometric and biochemical parameters

| Acid | BMI-z | IR biomarkers | | | | | Iron metabolism indicators | | | Lipid and inflammation-related parameters | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Glu | Insulin | HOMA-IR | QUICKI | NEFA | Iron | Fer | Transf | TG | HDL-C | Apo A-I | hsCRP | Lp-$PLA_2$ | CETP | PON 1 | ARE |
| Myristic | 0.46 (<0.01) | - | 0.41 (0.02) | 0.40 (0.03) | −0.41 (0.02) | 0.36 (0.04) | - | - | - | - | −0.38 (0.03) | - | - | 0.32 (0.04) | - | - | - |
| Palmitoleic | - | - | 0.43 (0.01) | 0.34 (0.04) | −0.39 (0.03) | 0.44 (0.02) | - | - | - | - | −0.51 (<0.01) | −0.34 (0.04) | 0.44 (0.02) | - | - | - | - |
| Margaric | - | - | - | - | - | 0.33 (0.04) | - | - | - | - | - | - | - | - | - | - | - |
| Cis-vaccenic | - | - | - | - | - | - | - | −0.34 (0.04) | - | - | - | - | - | - | - | 0.42 (<0.01) | - |
| Linoleic | −0.41 (<0.01) | - | - | - | - | −0.36 (0.04) | −0.35 (0.04) | - | - | - | 0.32 (0.04) | - | −0.37 (0.04) | - | - | - | - |
| Alpha-linoleic | - | - | - | - | - | - | - | - | - | 0.47 (<0.01) | - | - | - | - | - | - | - |
| Gamma-linoleic | 0.38 (0.03) | - | - | - | - | - | - | - | - | - | - | - | 0.33 (0.04) | - | - | - | - |
| Arachidic | - | 0.35 (0.04) | - | - | - | - | - | - | - | - | - | - | - | - | 0.36 (0.04) | - | - |
| Gadoleic | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 0.39 (0.02) | - |
| Arachidonic | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | −0.50 (<0.01) |
| Eicosapentaenoic | - | - | - | −0.34 (0.04) | - | −0.36 (0.04) | - | - | −0.54 (0.01) | - | 0.35 (0.04) | - | −0.36 (0.04) | - | - | - | - |
| Lignoceric | - | 0.39 (0.04) | - | - | - | 0.48 (0.02) | - | - | 0.40 (0.04) | - | - | - | - | - | 0.38 (0.04) | - | - |

Data arer shown as *r* (*p*-value). Benjamini-Hochberg method was implemented for multiple comparisons.
BMI, body mass index; IR, insulin resistance; Glu, glucose; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; QUICKI, Quantitative Insulin Sensitivity Check Index; NEFA, non-esterified fatty acids; Fer, ferritin; Transf, transferrin; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; Apo, apolipoprotein; hsCRP, high-sensitivity C-reactive protein; Lp-$PLA_2$, lipoprotein-associated phospholipase $A_2$; CETP, cholesteryl ester transfer protein; PON 1, paraoxonase 1; ARE, arylesterase.


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As regards markers of cardiovascular risk, hsCRP correlated with palmitoleic acid, linoleic acid, gamma-linolenic acid and EPA (**Table 4**). Lp-$PLA_2$ correlated with myristic acid (**Table 3**). CETP activity correlated with arachidic and lignoceric acids, while PON activity correlated with cis-vaccenic and gadoleic acids, and ARE activity with arachidonic acid (**Table 4**).

## 7. Association of the presence of obesity with dietary habits, fatty acids and cardiometabolic markers

Linear regression was explored to analyze the association between obesity and dietary habits, fatty acids and cardiometabolic markers after adjusting by age, sex and Tanner stage. The association remained significant for cereal consumption, plus myristic, palmitoleic, margaric, linoleic and gadoleic acids in addition to Lp-$PLA_2$ and ARE activities (**Table 5**).

## 8. Analysis to explore the possible mediation of fatty acids and cardiometabolic markers in the association between dietary habits and obesity

We tested 4 mediation models: 1) Fatty acid → cardiometabolic marker → obesity; 2) Dietary habits → fatty acid → obesity; 3) Dietary habits → cardiometabolic marker → obesity; and 4) Dietary habits → fatty acid → cardiometabolic marker → obesity. **Fig. 1** shows the models where we found significant mediation. **Fig. 2** presents a general diagram showing all the direct and indirect interactions between dietary habits, fatty acids and cardiometabolic markers with obesity found in our study.

In summary: In one model, NEFA acted as a mediator between myristic acid and obesity (**Fig. 1A**), suggesting that IR could be the link between myristic acid and obesity. Nevertheless, in the model, myristic acid also showed a direct association with obesity independently of NEFA (**Fig. 1A**). Similarly, in another model, NEFA was a significant mediator of the relation between bakery consumption and obesity (**Fig. 1B**). Furthermore, in a serial mediation model that included linoleic acid and NEFA as mediators, these parameters were significant mediators in the association between candy consumption and obesity (**Fig. 1C**). There was no direct association between candy consumption and obesity in the model. Based on our results, candy consumption would have a negative effect on linoleic acid which would in turn increase NEFA and explain its association with the presence of obesity. Consistently, in another serial mediation model that included anti-inflammatory EPA and NEFA, both parameters were significant mediators of the association between dairy consumption and obesity (**Fig. 1D**). In this model dairy consumption decreases EPA levels with a resulting increase in NEFA linking it to obesity. In another model, we found HDL-C as a mediator of the association between myristic acid and obesity (**Fig. 1E**). In agreement with the model that used NEFA as mediator, myristic acid displayed a direct association with obesity. Moreover,

**Table 5.** Linear regression analysis to assess associations of different parameters with obesity, adjusted by age, sex and Tanner stage

| Parameter | $R^2$ | B | *p*-value |
|---|---|---|---|
| Myristic acid | 0.43 | 0.34 | 0.002 |
| Palmitoleic acid | 0.43 | 0.18 | 0.013 |
| Margaric acid | 0.21 | 0.06 | 0.031 |
| Linoleic acid | 0.28 | −2.48 | 0.044 |
| Gadoleic acid | 0.15 | −0.02 | 0.043 |
| Lp-$PLA_2$ | 0.16 | 1.31 | 0.044 |
| ARE | 0.09 | −9.57 | 0.043 |
| Cereal consumption | 0.35 | −1.37 | 0.002 |

$R^2$, adjusted $R^2$ (a measure of the proportion of variance in the dependent variable explained by the independent variables included in the regression model); B, coefficient B (a measure of the slope of the regression line); Lp-$PLA_2$, lipoprotein-associated phospholipase $A_2$; ARE, arylesterase.


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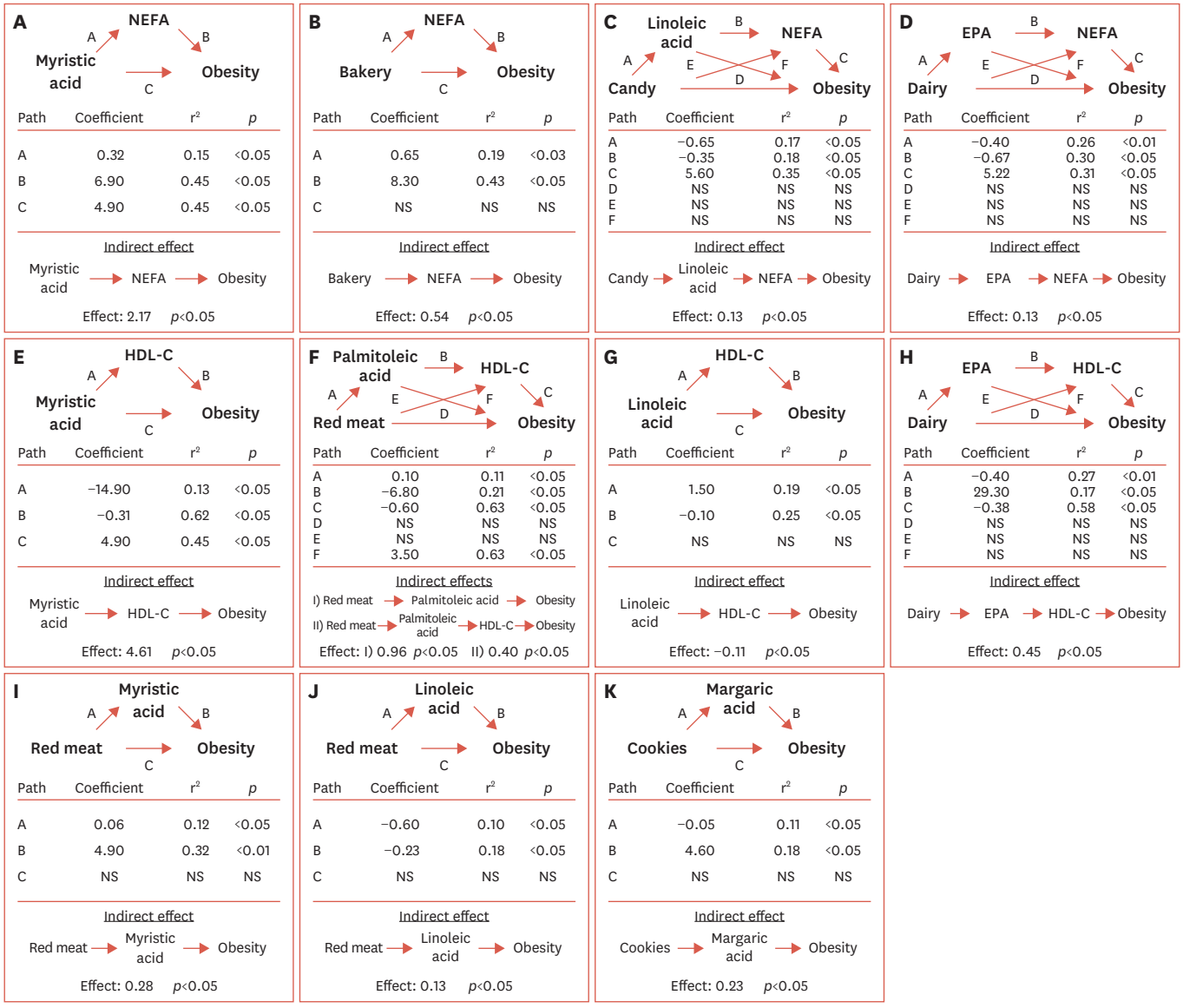


**Fig. 1.** Significant associations obtained in separate mediation analyses.
NEFA, non-esterified fatty acids; NS, not significant; EPA, eicosapentaenoic; HDL-C, high density lipoprotein cholesterol.

in another serial mediation model, both palmitoleic acid and HDL-C were mediators of the association between red meat consumption and obesity (**Fig. 1F**). In this model, red meat consumption would increase palmitoleic acid, causing a decrease in HDL-C, explaining its association with obesity. Nevertheless, it is important to note that, similar to myristic acid, palmitoleic acid also displayed an independent association with obesity in the model. Consistently, in another model, HDL-C was also a mediator of the association between anti-inflammatory linoleic acid and obesity (**Fig. 1G**). Furthermore, in a serial mediation model, both EPA and HDL-C explained the association between dairy consumption and obesity (**Fig. 1H**). In the model, dairy consumption would decrease EPA levels with a consequent negative effect on HDL-C levels leading to a positive association between dairy consumption and obesity. Interestingly, mediation analysis also revealed that some fatty acids could mediate the association between dietary habits and obesity without the involvement of cardiovascular markers. In this regard, in separate models, red meat consumption was found to have a


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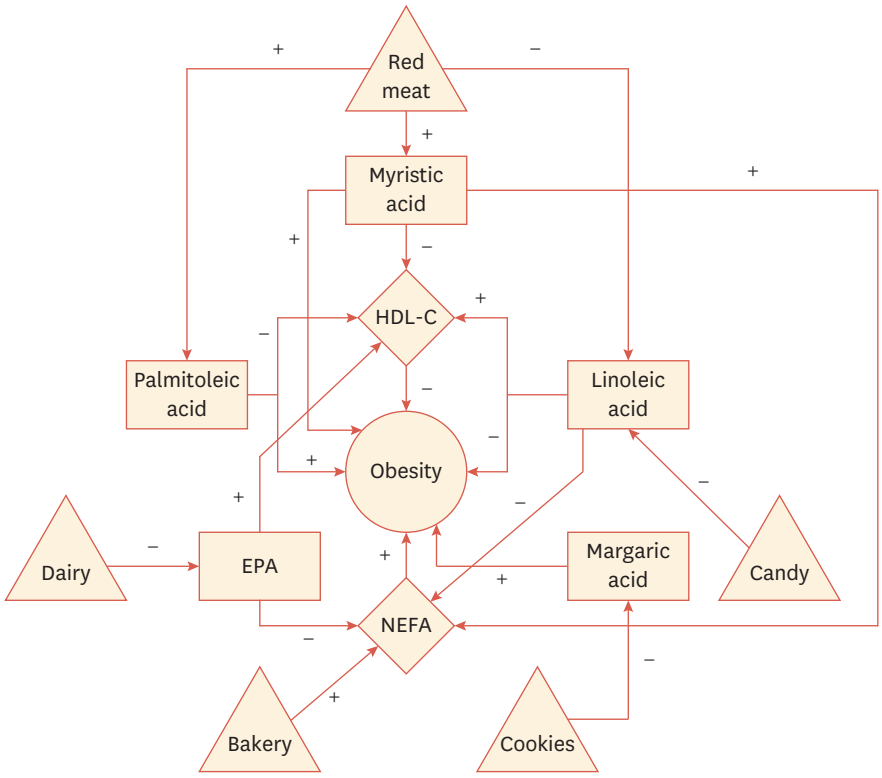


**Fig. 2.** Direct and indirect interactions between dietary habits (triangles), fatty acids (rectangles), cardiometabolic markers (diamonds) and childhood obesity (circle).
HDL-C, high density lipoprotein cholesterol; EPA, eicosapentaenoic; NEFA, non-esterified fatty acids.

positive effect on proatherogenic myristic acid and a negative effect on linoleic acid, with these two fatty acids mediating its association with the presence of obesity (**Fig. 1I and J**). Furthermore, cookie consumption was negatively associated with cardioprotective margaric acid, which mediated its link with obesity (**Fig. 1K**).

## DISCUSSION

The group with obesity showed higher consumption of bakery products and lower of cereals. Moreover, the group of children and adolescents with obesity displayed higher plasma levels of myristic, palmitoleic, margaric and gamma-linoleic acids, as well as lower concentrations of linoleic, arachidic, gadoleic, eicosatrienoic acid and EPA. Notably, the significant differences in cereal consumption, plus myristic, palmitoleic, margaric, linoleic and gadoleic acids remained even after adjusting by age, sex and Tanner stage. Importantly, individual fatty acids exhibited correlations with both traditional and novel markers of cardiovascular risk. Moreover, individual fatty acids also correlated with dietary habits. Finally, mediation analysis suggested that specific fatty acids and cardiometabolic markers could act as links that connect dietary habits and the presence of obesity.

Interestingly, in the present study, the group with obesity also showed a major history of family obesity than the control group. Growing up in an obesogenic environment promotes a sedentary lifestyle, food overconsumption and unhealthy weight status.[35] In fact, family functioning including aspects such as poor communication, poor behavior control and high


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levels of family conflict are associated with an increased risk of child and adolescent obesity.[36] All these factors can affect dietary habits, which were proved to be different between the two groups in our study. The group with obesity consumed bakery products more often and cereals with less frequency than healthy controls. In accordance, high grain intake in children and adolescents was reported to be protective against obesity.[37]

As regards fatty acid profile of apo B-depleted plasma, according to our results, children and adolescents with obesity exhibited higher levels of myristic, palmitoleic, margaric and gamma-linolenic acids, as well as lower levels of linoleic, arachidic, gadoleic, eicosatrienoic acid and EPA. Consistent with our results, a prior study reported higher levels of palmitoleic acid in children with obesity,[38] adding to the fact that the same acid was associated with markers of adiposity.[39] Nevertheless, it is important to note that the above-mentioned study employed whole plasma to evaluate fatty acid profile, while apo B-depleted plasma was examined in our study. Regarding the correlations between fatty acids and dietary habits, arachidonic acid, which was previously reported to have an impact on oxidative and inflammatory processes,[40,41] was positively related to the frequency of consumption of charcuterie, and negatively with the frequency of consumption of vegetables and cereals, even though its levels were not found to be higher in the group with obesity as in another study.[37] In line with our findings, vegetables are known for their antioxidant properties,[42] and higher intakes of cereal fiber could have a role in reducing systemic inflammation.[43] These reports offer a possible explanation to their negative correlation with pro-inflammatory arachidonic acid, as observed in our study. Consistently, other fatty acids related to inflammation, namely lauric and myristic acids,[44,45] also correlated negatively with cereal consumption. Moreover, palmitoleic acid also correlated negatively with cereal consumption in this study. Palmitoleic acid represents a fatty acid of particular interest in the context of obesity. Indeed, previous studies have linked it to anti-inflammatory properties.[46] Nevertheless, it has also been linked with obesity and insulin resistance.[38,39,47] Consistent with the latter, its levels were higher in our group with obesity, who, in addition, consumed less cereals than the control group. Contrary to vegetables and cereals, red meat consumption has been previously related to higher inflammatory markers.[48] In agreement, our findings indicate that meat consumption correlated negatively with anti-inflammatory fatty acids such as EPA and eicosatrienoic acid, whilst it correlated positively with myristic and palmitoleic acids, both commonly found in red meat.[49] Similarly, palmitoleic acid also correlated with the consumption of bakery products, in which it is also present, though in smaller amounts than other fatty acids.[50] Interestingly, cookie consumption, associated with the development of IR and diabetes, correlated negatively with margaric acid, a saturated fatty acid which is tied to a lower risk of type 2 diabetes.[51] Moreover, dairy consumption, which is also tied to reduced insulin sensitivity,[52] correlated negatively with EPA, a fatty acid that improves glycemic control.[53] However, it should be noted that other studies have suggested a moderate beneficial anti-inflammatory effect for dairy consumption.[54] As expected, stearic acid, known to be used as an additive for chewing gum and sweets,[55] correlated positively with candy consumption.

As previously reported,[8] the group with obesity not only presented higher BMI than a healthy control group, but also exhibited altered lipid and glucose metabolism. These alterations were characterized by higher insulin levels, as well as higher HOMA-IR and lower QUICKI indexes. In the present study, we confirmed the alterations in glucose metabolism with the observation of higher NEFA levels in the group with obesity. In fact, in individuals with obesity, NEFA are released together with glycerol, different hormones and pro-inflammatory cytokines by adipose tissue into the circulation where they play a major role in the development of IR.[56,57]


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Remarkably, palmitoleic acid, along with palmitic and myristic acids, are the main products of *de novo* lipogenesis, previously associated with obesity and diabetes mellitus, and thus the concentration of these fatty acids are commonly used as biomarkers of obesity-related metabolic abnormalities.[47] Consistently, in our study, palmitoleic acid levels correlated positively with markers of carbohydrate metabolism like HOMA-IR and NEFA and negatively with a marker of insulin sensitivity such as QUICKI. Similarly, myristic acid was positively related to HOMA-IR and negatively to QUICKI. In contrast, EPA has been associated with the prevention of metabolic alterations and chronic diseases such as obesity.[53] Nevertheless, in the same study, palmitoleic acid also showed to have the same benefits.[53] In our study, EPA showed a negative correlation with HOMA-IR and positive with NEFA, in accordance with its protective role. Moreover, n-3 polyunsaturated acids (PUFA), including EPA, and n-9 PUFAs such as eicosatrienoic acid, are considered to have anti–inflammatory effects, while n-6 PUFAs are generally pro-inflammatory.[58,59] In fact, gamma-linolenic acid, a n-6 PUFA, was found to be higher in our population with obesity, in line with another study.[38] On the contrary, linoleic acid, another n-6 PUFA, has anti-inflammatory properties,[37] and its level was lower in the group with obesity. Thus, the role of different fatty acids and the interaction between n-3 and n-6 PUFAs are controversial and need further research.[60] As regards saturated fatty acids, myristic acid, whose levels were higher in children and adolescents with obesity according to our results, have been widely related to inflammation and have been reported to stimulate it in adipose tissue through the involvement of toll-like receptor 4.[44,61] Other saturated fatty acids, namely stearic and palmitic acids, have been related to the presence or development of obesity and IR,[39] but were not found to be altered in our study. However, it is important to note that these studies investigated their role in different populations and only a few, including our own,[25] in childhood and incorporating adolescents as well. Moreover, our study analyzed apo B-depleted plasma, different to other studies that evaluated fatty acid profile in different samples such as serum. The evidence suggests that lifestyle, including dietary habits, modulates not only inflammatory and cardiometabolic biomarkers but also influences serum fatty acid profile,[62] which should be considered to assess patients' risk of developing further complications.

Regarding lipid metabolism, the group with obesity showed higher TG and LDL-C levels, and lower HDL-C and apo A-I concentrations, which represents a more atherogenic lipid profile consistent with the presence of obesity and IR.[63] Furthermore, the group with obesity showed higher Lp-$PLA_2$ and lower ARE activities. There were no differences in CETP or PON activities. The presence of lower HDL-C without differences in CETP activity observed in the group with obesity is interesting, given the well-known inverse association between both parameters.[8] Nevertheless, in the context of obesity, there are multiple possible causes for a decrease in HDL-C that are not related to CETP activity such as lower cholesterol efflux and shifts in HDL-subclass distribution.[64,65] Indeed, we previously reported lower cholesterol efflux in obese children and adolescents.[8] These results suggest that the decrease in HDL-C levels observed in these children and adolescents would be independent of CETP activity. Furthermore, consistent with the lower HDL-C and apo A-I levels observed in the group with obesity, these children and adolescents also displayed lower ARE activity, with a reflection of PON 1 enzyme concentration.[66] This alteration was not detected in PON activity. This finding is not uncommon; in fact, a previous study reported lower ARE activity without changes in PON activity in childhood obesity.[67] Moreover, previous studies have shown different behaviors for PON and ARE in pediatric populations.[68,69] Importantly, in our study, the differences in Lp-$PLA_2$ and ARE activities remained significant even after adjusting by age, sex and Tanner stage.


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It is noteworthy that fatty acid profile was determined in apo B-depleted plasma where the only lipoprotein fraction that can be found is HDL, the unique cardioprotective lipoprotein. This allows exploring the possible associations between fatty acid levels and the activities of HDL-bound enzymes and lipid transfer proteins, better than with fatty acid profile measured in whole plasma, which contains both atherogenic lipoproteins with apo B and antiatherogenic HDL. Then, PON activity correlated with cis-vaccenic and gadoleic acids, which help to protect against cardiovascular disease,[70,71] while ARE activity correlated negatively with arachidonic acid, whose metabolites are involved in oxidative and inflammatory processes,[40,41] and, therefore, confirms the previously reported negative effect of inflammation and fatty acid concentrations on the antiatherogenic role of HDL particles.[72,73] The correlations of ARE and PON activities with different fatty acids are not surprising given that, as previously mentioned, ARE is usually considered a marker of concentration whilst PON represents a better reflection of the enzyme intrinsic activity.[8,66,69,74]

As previously stated, CETP activity was similar in both groups, which is in agreement with other results in pediatric population with obesity from our group.[25] CETP activity in our study correlated positively with arachidic and lignoceric saturated acids, whose roles in IR and inflammation are controversial.[75,76] In this regard, in our study, both arachidic and lignoceric acids were positively related to markers of carbohydrate metabolism like glucose and NEFA. Furthermore, Lp-$PLA_2$ activity was higher in the pediatric group with obesity, reflecting the presence of vascular inflammation that cannot be detected, in this case, with the traditional marker of systemic inflammation, hsCRP.[77,78] In accordance, Lp-$PLA_2$ activity correlated with myristic acid which, as previously mentioned, stimulates inflammation. Moreover, palmitoleic and gamma linolenic acids correlated positively with hsCRP, suggesting that these acids could play a role in the inflammatory process of these patients, while linoleic acid and EPA correlated negatively with the same biomarker. These findings align with the previously discussed anti-inflammatory role of linoleic acid and EPA.[37,39]

Regarding iron metabolism, our study shows similar levels of the analysed parameters in both groups, but different correlations with the fatty acid profile were detected. Cis-vaccenic acid showed a negative correlation with ferritin levels, which are elevated during ferroptosis.[79] Accordingly, cis-monounsaturated fatty acids were recently reported to inhibit ferroptosis.[80] Transferrin level correlated negatively with EPA and positively with lignoceric acid. Notably, a previous study carried out in animal models reported that EPA can downregulate transferrin expression.[81] Moreover, iron levels correlated negatively with linoleic acid. Interestingly, a study shows that plasma of rats fed with a lower intake of iron had higher levels of linoleic acid, among other alterations, suggesting that iron regulation could affect fatty acid metabolism.[82] As previously mentioned, iron metabolism can affect fatty acid levels and *vice versa*; in fact, unsaturated and saturated fatty acids show different effects on iron metabolism.[13] This could explain the contrasting correlations observed for PUFAs such as EPA and saturated acids like lignoceric. Nevertheless, these findings highlight the importance of understanding the interaction between fatty acid concentration and iron metabolism in childhood obesity, given that both can affect the development of cardiovascular complications.[12,83]

Finally, mediation analysis revealed interesting indirect associations between dietary habits, fatty acids, cardiovascular markers and the presence of obesity. In one model, NEFA acted as a mediator between myristic acid and obesity. As previously mentioned, evidence suggests that myristic acid is associated with the development of cardiometabolic complications such


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as IR.[47] Our finding suggests that IR could be the link between myristic acid and obesity. However, the same model also showed a direct association between myristic acid and obesity independently of NEFA. Moreover, in another model, NEFA acted as a mediator between bakery consumption and the presence of obesity. Interestingly, in a separate model, both linoleic acid and NEFA were serial mediators of the association between candy consumption and obesity. Based on our results, candy consumption would have a negative effect on anti-inflammatory linoleic acid[37] which would in turn increase NEFA and explain its association with the presence of obesity. It is important to note, however, that the mediator effect of NEFA, was not found for other parameters related with IR such as HOMA-IR. Notably, NEFA are known to enhance inflammatory response independently of their role in IR, which could explain their role as mediators in our study.[84,85] Consistently, in a different serial mediation model, both anti-inflammatory EPA and NEFA mediated the association between dairy consumption and obesity. In this model dairy consumption decreases EPA levels with a resulting increase in NEFA linking it to obesity. Furthermore, in another model, we found HDL-C as a mediator between myristic acid and obesity. As previously mentioned, myristic acid would be involved in the development of cardiometabolic conditions, including dyslipemia.[47] Similar to the model that used NEFA as mediator, myristic acid displayed a direct association with obesity independently of HDL-C. Moreover, both palmitoleic acid and HDL-C were mediators between red meat consumption and obesity in another serial mediation model. In this model, red meat consumption would increase palmitoleic acid, causing a decrease in HDL-C, explaining its association with obesity. Indeed, red meat is known to contain palmitoleic acid[49] and this fatty acid has been associated with cardiometabolic complications.[47] As was the case with myristic acid, palmitoleic acid was also independently associated with obesity in the model. In agreement, in a separate model, HDL-C also mediated the association between anti-inflammatory linoleic acid and obesity. Moreover, in a serial mediation model, both EPA and HDL-C explained the association between dairy consumption and obesity. In this model, dairy consumption would decrease EPA levels with a consequent negative effect on HDL-C levels leading to a positive association between dairy consumption and obesity. Indeed, dairy consumption has previously been linked with cardiometabolic complications,[52] and a negative effect on EPA levels could, at least in part, explain such association. Lastly, as mentioned in the results section, some fatty acids could mediate the association between dietary habits and obesity without the involvement of cardiovascular markers. In this regard, in separate models, red meat consumption was found to have a positive effect on proatherogenic myristic acid and a negative effect on linoleic acid, with these two fatty acids mediating its association with the presence of obesity. Furthermore, cookie consumption was negatively associated with cardioprotective margaric acid, which mediated its link with obesity. In summary, mediation analysis revealed both positive and negative involvement for individual fatty acids in the association between dietary habits, cardiometabolic markers and obesity.

Some limitations must be acknowledged. Despite achieving an 80% power with the sample size, results must be cautiously interpreted and there could be lack of power to detect differences in parameters that were not the primary endpoints of the study. Furthermore, the food frequency questionnaire employed was semiquantitative; so, information regarding portion size is missing for each food item. Data on physical activity could not be obtained and its influence on the results cannot be ruled out. Finally, in the present study, glucose metabolism was evaluated employing HOMA-IR and QUICKI indexes, so other assays, such as the hyperinsulinemic-euglycemic clamp, would be useful in future studies.


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Altogether, our results suggest the presence of alterations in glucose and lipid metabolisms, as well as modified fatty acid composition of apo B-depleted plasma, in a group of children and adolescents with obesity. These findings would highlight the importance of analyzing the interaction between different metabolic pathways when assessing cardiometabolic risk. Additionally, the presence of vascular inflammation and attenuated antioxidant ARE activity of the PON 1 enzyme also correlated with individual fatty acids, suggesting a role for the latter in the status of not only traditional atherogenic markers, but also in novel ones with the potential to be better surrogates in pediatric populations. Importantly, all these findings were related to dietary habits that children and adolescents have and differ from the ones of a control group with normal weight, highlighting the importance of reversible habits in the development of metabolic alterations. Furthermore, mediation analyses revealed both direct and indirect associations between dietary habits, fatty acids, cardiometabolic markers and the presence of obesity, revealing possible causal pathways in the development of this pathology and associated complications. Nevertheless, the present study was limited in size, so results should be interpreted with caution. Future studies should include larger cohorts and longitudinal designs to allow a better extrapolation of the results.

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Anthropometric data in children and adolescents with obesity and controls

### Supplementary Table 2

Biochemical parameters in children and adolescents with obesity and controls

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