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Dietary antioxidant intake is inversely associated with 2,3-dinor oxylipin metabolites, the major excreted oxylipins in overweight and obese subjects

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ABSTRACT

Cardiometabolic disease risk factors, including obesity, insulin resistance, high blood pressure, and dyslipidemia, are associated with elevated oxidative stress biomarkers like oxylipins. Increased adiposity by itself induces various isomers of this oxidized lipid family, while dietary polyphenols show benefits in its regulation. Previously, we showed that specific co-abundant microorganisms characterized the gut microbiota of Colombians and associated differentially with diet, lifestyle, obesity, and cardiometabolic health status, which led us to hypothesize that urinary oxylipins would reflect the intensity of oxidative metabolism linked to gut microbiota dysbiosis. Thus, we selected a convenience sample of 105 participants (age: 40.2 ± 11.9 years, 47.6% women), grouped according to microbiota, cardiometabolic health status, and body mass index (BMI); and evaluated 33 urinary oxylipins by HPLC-QqQ-MS/MS (*e.g.*, isoprostanes, prostaglandins, and metabolites), paired with anthropometry and blood chemistry information and dietary antioxidants estimated from a 24-h food recall. In general, oxylipins did not show differences among individuals who differed in gut microbiota. While the unmetabolized oxylipin levels were not associated with BMI, the total content of oxylipin metabolites was highest in obese and cardiometabolically abnormal subjects (*e.g.*, insulin resistant), mainly by prostaglandin-D (2,3-dinor-11β-$PGF_{2\alpha}$) and 15-F_{2t}-IsoPs (2,3-dinor-15-F_{2t}-IsoP and 2,3-dinor-15-*epi*-15-F_{2t}-IsoP) metabolites. The total polyphenol intake in this cohort was 1070 ± 627 mg/day. After adjusting for body weight, the polyphenol intake was significantly higher in lean than overweight and showed an inverse association with dinor-oxylipin levels in principal component analysis. These results suggest that the 2,3-dinor-oxylipins could be more specific biomarkers associated with BMI than their parent oxylipins and that are sensitive to be regulated by dietary antioxidants.

1. Introduction

Oxidative stress and inflammation have been associated with the development of cardiometabolic disease and its independent risk factors, including obesity, glucose intolerance, insulin resistance, high blood pressure, smoking, and atherogenic dyslipidemia [1–3]. A common feature of these conditions is the enzymatic and non-enzymatic oxidation of polyunsaturated fatty acids (e.g., arachidonic acid) that produce oxylipins, including prostaglandins (PGs), prostanoid-like molecules, like isoprostanes (IsoPs) and thromboxanes [4]. The increased levels of oxylipins have been described in the regulation of numerous physiological processes, including inflammation, blood coagulation, leukocyte-endothelial interaction, vasoconstriction, platelet aggregation, and proteolysis [4,5]. In addition, the levels of

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15-F_{2t}-IsoP, a classical biomarker of oxidative stress, have been associated with a two-to three-fold increase in people at risk of cardiometabolic disease compared with healthy subjects [6–8].

In particular, obesity can induce systemic oxidative stress and several oxidized lipids, including oxidized LDL [9], oxidized phospholipids [10], oxysterols [11], and oxylipins [12,13]. They have been associated with increased adiposity and weight gain [14]. Oxylipins display a multiplicity of effects in adipocytes going from the control of cell differentiation to function [15]. Among PGs, the 15d-Δ 12,14-PGJ_2, a PGD_2-derived metabolite, has shown a pro-adipogenic effect [16]. Further cross-sectional studies have demonstrated that the F_2-IsoP metabolites, such as 2,3-dinor-5,6-dihydro-15-F_{2t}-IsoP, may be more sensitive markers of endogenous oxidative stress than the 15-F_2-IsoP on assessing the impact of obesity, age, antioxidant intake, as well as of diets with high glycemic index and glycemic load [17–19]. A cross-sectional analysis of urinary IsoPs paired with dietary intake information from the Shanghai Women's Health Study showed that a high concentration of urinary 2,3-dinor-5,6-dihydro-15-F_{2t}-IsoP was positively associated with increased body mass index (BMI) and negatively associated with the plasma concentrations of several lipophilic antioxidants, including vitamin E, *cis* and *trans*-β-carotenes, *cis*-lycopene and β-cryptoxanthin [20]. Thus, the dietary intake of antioxidants might effectively mitigate oxidative stress and oxylipins production.

Epidemiologic studies have shown that diets rich in plants and vegetables, including grains and legumes, fruits, seeds, coffee, cocoa, and tea, all foods rich in polyphenols, carotenoids, and antioxidant vitamins, reduce the risk of cardiovascular events, type-2 diabetes, and hypertension [21]. In addition, they are associated with health and well-being [22], directly associated with weight loss [23,24], and prevent obesity and obesity-related diseases [25]. Notably, the levels of several oxylipins detected in plasma are dramatically influenced postprandially by the nature of the diet [26,27]. Furthermore, short-term and long-term controlled dietary interventions have reported significant modulation of systemic cyclooxygenase and lipoxygenase-derived oxylipins after consuming polyphenol-rich foods in healthy humans [28,29]. Recently, using a method with both high sensitivity and accuracy for massive quantitation of oxylipins and metabolites by using ultra-high-performance liquid chromatography coupled to triple quadrupole mass spectrometry (UHPLC-QqQ-MS/MS) [30], we showed that concentrations of urinary 2,3-dinor-15-F_{2t}-IsoP, another F_2-IsoP metabolite, were significantly reduced in healthy adults consuming a filtered coffee with high content of polyphenols for eight weeks; this was not observed with 15-F_{2t}-IsoP [31]. Likewise, intake of red wine in healthy females reduced the urinary excretion of 2,3-dinor-15-F_{2t}-IsoP and the pro-inflammatory PG metabolite 2,3-dinor-11-β-$PGF_{2\alpha}$, as compared with the reduction of 15-F_{2t}-IsoP and 11β-$PGF_{2\alpha}$, respectively [32]. These findings suggest that dinor-oxylipin metabolites could be sensitive biomarkers of oxidative stress in age- and obesity-related disorders and under regulation by dietary antioxidants.

After intake, some polyphenols are directly absorbed through the small intestine [33–35]. However, dietary antioxidants are usually not completely assimilable, as they comprise a broad class of structurally complex molecules for which humans lack the enzymatic battery to cleave and make bioavailable; this is mainly achieved by the bacteria inhabiting the human gastrointestinal tract [36,37]. But the gut microbiome is not only a machine to cleave complex dietary molecules. It is central for physiologic and metabolic regulation and has been associated with cardiometabolic diseases, including type-2 diabetes, cardiovascular disease (CVD), and obesity [38,39]. We recently showed that the gut microbiota of a nonwestern population was described by five consortia of co-abundant microorganisms (CAGs) differentially associated with obesity, cardiometabolic disease risk, diet, and lifestyle [40–42]. This finding led us to hypothesize that urinary oxylipins, especially dinor-oxylipin metabolites, would reflect the intensity of the oxidative metabolism linked to obesity-associated with gut microbiota dysbiosis and the dietary intake of antioxidants.

2. Materials and methods

To understand the impact of diet and dietary antioxidants and micronutrients (phenolic compounds, vitamin A and vitamin C, Zn, Mn, Fe, and Cu) on oxylipins regulation, obesity, and cardiometabolic risk, we selected 105 subjects comprehensively grouped to an exclusive CAG and conducted a lipidomic study targeted to oxylipins, paired with complete 24-h dietary recall (24HDRs).

2.1. Study population

This study was conducted in a convenience sample of community-dwelling individuals previously characterized as having distinct gut microbiota dominated by one specific consortium of microorganisms and with varying cardiometabolic disease risks [40,43]. Details of this study and population were described previously [40]. In brief, between July and November 2014, we enrolled and thoroughly assessed demographic, gut microbiota, health-related and dietary parameters from 441 volunteers in approximately equal proportions of sex (men and women), age groups (18–40 and 41–62 years), BMI (lean, overweight and obese), and from Colombia's most important urban centers that make up to 30% of the Colombian population (Bogotá, Medellin, Cali, Barranquilla, and Bucaramanga).

2.2. Subjects

The 105 individuals were drawn from the study mentioned above in roughly similar proportions according to sex: male (n = 55) and female (n = 50); age ranges of 18–40 (n = 50) and 41–62 years (n = 55), the dominant gut microbiota: CAG-Prevotella (n = 19), CAG-Lachnospiraceae (n = 21), CAG-Pathogen (n = 23), CAG-Akkermansia (n = 23) and CAG-Ruminococcaceae (n = 19); BMI lean (n = 33, <25 kg/m^2), overweight (n = 45, 25–29.9 kg/m^2) and obese (n = 27, >30 kg/m^2); and cardiometabolic health status: healthy (n = 63) abnormal (n = 42). An abnormal cardiometabolic phenotype was assigned to individuals having two or more of the following conditions: systolic/diastolic blood pressure (BP) ≥ 130/85 mm Hg or consumption of antihypertensive medication, fasting blood sugar (FBS) ≥100 mg/dL, HOMA-IR > 3, and hs-CRP > 3 mg/L or consumption of antidiabetic medication, serum triglycerides ≥150 mg/dL, low-density lipoprotein (LDL) ≥ 130 mg/dL, and high-density lipoprotein (HDL) < 40 mg/dL (men) or <50 mg/dL (women) or consumption of lipid-lowering medication. Demographics, weight, height, waist circumference, body fat percentage, systolic (SBP) and diastolic (DBP) blood pressures, and blood chemistry parameters (HDL cholesterol, LDL cholesterol, very low-density lipoprotein (VLDL) cholesterol, triglycerides, fasting blood insulin and glucose, and urinary creatinine data were extracted from records of the original study [40,43]. This study analyzed plasma and urine samples kept at −80 °C since collection.

The study followed the principles of the Declaration of Helsinki as revised in 2008 and had minimal risk, according to the Colombian Ministry of Health (Resolution 8430 of 1993). Cryopreserved plasmas from participants that donated their samples for future studies were used. The Bioethics Committee of CES university reviewed the protocol and the consent forms and approved the procedures described here (approval act 768-149-2, July 31, 2020).

2.3. OxLDL

The concentration of oxLDL in plasma was determined by the oxidized LDL ELISA (OxLDL) from Mercodia (Mercodia, Uppsala, Sweden) according to the manufacturer's instructions, readings were performed at 450 nm using a Synergy HT Multi-Mode Microplate Reader (BioTek Instruments Inc., Winooski, USA) and the results are reported as U/L.

2.4. Oxylipin determination

2.4.1. Chemicals and materials

The LC-MS grade solvents were purchased from J.T. Baker (Phillipsburg, New Jersey, USA). Formic acid was obtained from Panreac (Castellar Del Vallés, Barcelona, SPA). The β glucuronidase from *Helix pomatia* (type H-2) was provided by Sigma–Aldrich (St. Louis, Missouri, USA). Solid-phase extraction (SPE) cartridges (Strata X and X-AW, 100 mg, 3 mL) were purchased from Phenomenex (Torrance, CA, USA).

2.4.2. Oxylipins

Six isoprostanes (15-F_{2t}-IsoP, 15-keto-15-F_{2t}-IsoP, 9-*epi*-15-F_{2t}-IsoP, 15-keto-15-E_{2t}-IsoP, 15-E_{1t}-IsoP, and 15-F_{1t}-IsoP), seventeen prostaglandins (PGE_2, tetranor-PGEM (a tetranor-PGE-metabolite), tetranor-PGAM (a tetranor-PGA-metabolite), 20-OH-PGE_2, 15-keto $PGF_{2\alpha}$, tetranor PGFM (a tetranor-PGF-metabolite), 20-OH-$PGF_{2\alpha}$, 19(*R*)–OH–$PGF_{2\alpha}$, PGD_2, 11β-$PGF_{2\alpha}$, 2,3-dinor-11β-$PGF_{2\alpha}$, PGDM (a PGD-metabolite), tetranor-PGDM (a tetranor-PGD-metabolite), tetranor-PGDM lactone, tetranor-PGJM (a tetranor-PGJ-metabolite), PGE_1 and $PGF_{1\alpha}$), 2,3-dinor-6-keto $PGF_{1\alpha}$, 6-keto $PGF_{1\alpha}$ and one thromboxane (11-dehydrothromboxane B_2 (TXB_2)) were from Cayman Chemical (Ann Arbor, Michigan, USA). Seven additional isoprostanes (2,3-dinor-15-F_{2t}-IsoP, 2,3-dinor-15-*epi*-15-F_{2t}-IsoP, 5-F_{2t}-IsoP, 5-*epi*-F_{2t}-IsoP, 15-*epi*-15-E_{2t}-IsoP, 8-F_{3t}-IsoP, and 8-*epi*-8-F_{3t}-IsoP) were synthesized by Dr. Thierry Durand's team at the Institut des Biomolécules Max Mousseron (Montpellier, France) according to previously published procedures [44–48].

2.4.3. Sample preparation

To assess the excretion of oxylipins (IsoPs, TXB_2, and PGs), urine samples were thawed at room temperature and centrifuged (11,000×*g*, 5 min). Next, all samples were hydrolyzed using ~5000 UE/mL β-glucuronidase from *Helix pomatia,* type H2, and 0.1 M acetate buffer (pH 4.9) for 2 h at 37 °C. Then, 500 μL of methanol/200 mM HCl were added to the mix, followed by centrifugation at 10,000×*g* for 5 min to precipitate proteins. One milliliter of supernatant was mixed with 1250 μL of methanol and 2 mL of Bis-Tris buffer with 0.02 M HCl (pH 7.0) and subjected to SPE with a Strata X-AW cartridge. Target compounds were eluted with 1 mL of methanol and dried using a SpeedVac concentrator (Savant SPD121P; Thermo Scientific, MA, USA). The extracts were reconstituted in 200 μL of solvent A/B (90:10, *v/v*) and filtered through a 0.45 μm PVDF (polyvinyl difluoride) filter (Millipore, MA, USA) [30,49,50] *UHPLC-QqQ-MS/MS analyses*: The separation of oxylipins was performed using a UHPLC coupled with a 6460 QqQ-MS/MS (Agilent Technologies, Waldbronn, Germany), using the setup described by Medina et al. [30,31] with modifications. The chromatographic separation was performed on an Acquity UPLC BEH C18 column (2.1 × 150 mm, 1.7 μm; Waters; Milford, MA, USA), the column temperature was 6 °C, and the sample volume injected was 20 μL. The mobile phases employed were solvent A (H_2O/acetic acid; 99.99:0.01, *v/v*) and B (MeOH/acetic acid; 99.99:0.01, *v/v*). The flow rate was 0.15 mL/min using a linear gradient scheme (minutes; %B): (0.00; 60), (7.00; 60), (7.01; 73), (10.00; 73), (10.01; 80), (18.00; 100), (19.00; 100), and (19.01; 60). The MS analysis was performed in MRM (multiple reaction monitoring) quantification mode, using negative ESI. The operating conditions for the MS parameters were as follows: gas flow: 8 L/min, nebulizer: 30 psi, capillary voltage: 4000 V, nozzle voltage: 2750 V, gas temperature: 325 °C, sheath gas temperature: 350 °C, and jet-stream gas flow: 12 L/min. The MS fragmentor parameters (ion optics; capillary exit voltage) and collision energy of the new analytes were optimized for each compound to generate the most abundant product ions. The MS parameter (fragmentor voltage) ranged from 50 to 160 V, and the collision energy ranged from 0 to 24 V. Data acquisition and processing were performed using the Mass Hunter software version B.08.00 (Agilent Technologies). The quantification of oxylipins detected was performed using authentic markers calculated from the area ratio of the ion peak of each compound to that of the corresponding standard. Stock solutions of oxylipins were diluted with methanol-water (1:1, *v/v*) to obtain the appropriate working solutions at 1000 nmol/L. For the calibration curve, twelve successive dilutions were prepared. All solutions were stored at −80 °C. The oxylipin concentrations were calculated from standard curves freshly prepared each day.

2.5. Diet assessment, food data analysis, and polyphenol intake

We retrieved 24HDRs interviews performed by trained nutritionists using validated forms, food models, geometric figures, and full-size pictures to assess portion sizes and improve accuracy, as reported by García-Vega et al. [42]. The recovered data included the nutritional composition and the estimations of total dietary fiber, as well as vitamins, and micronutrients involved directly and indirectly in antioxidant processes (vitamins A and C, Zn, Mn, Fe, and Cu) from foods consumed by the respondent in the past 24 h from interviews randomly distributed on different days of the week. In addition, the dietary intake of each food and beverage record was directly entered into a local 24HDRs database, including the types of food and the way they were consumed.

The local 24HDRs database was crossed and complemented using the information provided in the *USDA's Food and Nutrient Database* for *Dietary Studies* (FNDDS)- Foods and Beverages 2017–2018) as the food codes and the main food descriptions [51]. For foods that were not available in the USDA's FNDDS database but consumed in high frequency (*e.g.*, tropical fruits and typical local meals from Colombia), new food codes and main food descriptions were created and assigned by us using criteria defined in the FNDDS –*guide* [52]. In addition, the food codes and main food descriptions from the FNDDS database were assigned to all *Phenol-Explorer* foods and beverages to facilitate their searching and matching to our local 24HDRs database. New food codes were neither supervised nor authorized by the USDA. Food groups were categorized according to their FNDDS food code as follows: 1. milk and milk products; 2. meat, poultry, fish, and mixtures; 3. eggs; 4. dry beans, peas, other legumes, nuts, and seeds; 5. grain products; 6. fruits; 7. vegetables; 8. fats, oils, and salad dressings; and 9. sugars, sweets, and beverages. The gram weight or milliliters of consumed foods and drinks and their contribution of fiber and phenol compounds were calculated using the individual food record file from the local 24HDRs database.

The total polyphenol intake was estimated using the *Phenol-Explorer* database 3.6 [53] by matching food consumption data records (24HDR). Retention factors reflecting polyphenol losses or gains due to food processing were used to adjust polyphenol content values; relevant cooking and processing methods were equivalently assigned to facilitate the application of retention factors. For our analysis of dietary polyphenol intake, we only used the total values of phenolic compounds estimated by the Folin-Ciocalteu method and expressed in gallic acid equivalents (GAE/day). For foods and beverages not available in the *Phenol-Explorer* database (*e.g.*, tropical fruits), the polyphenol composition was searched and calculated from scientific reports and included in the analysis. These new reports were critically evaluated before inclusion in the local 24HDRs database. Vitamins and polyphenols are known to target [54–58] and distribute to adipose tissue [56,59,60], thus to adjust for the volumetric dilution that would result from the increased adiposity, the intake of vitamins, micronutrients, and phenolic compounds for each food per subject were also adjusted by the subjects body weight (in kg).

2.6. Tree-based analysis of food and phenolic compounds contribution

A phenetic and hierarchical food tree in which all distances between tree levels are the same for each food was created from the USDA's food code numbering system, using R scripts previously reported [61]. Briefly, the three first levels of the tree structure were inferred from the FNDDS Food Code labeling scheme. Then, additional levels were given to each food by manual curation and review of the FNDDS Food Code, and logical grouping levels were added to the food tree taxonomy. As an

example, the levels of the tree for a typical food, such as decaffeinated coffee, were denoted as L1_Sugars_Sweets_and_Beverages; L2_Non-alcoholic_beverages; L3_Coffee; L4_Coffee_decaffeinated; L5_Coffee_N-S_as_to_brewed_or_instant_decaffeinated. In addition, the adjusted-average amount of phenolic compounds (in mg GAE/kg of body weight) for each food reported by participants were included for assessing the contribution of polyphenol sources. Finally, visualizations of the tree of foods were generated using Graphlan [62] as implemented in the galaxyproject.org [63].

2.7. Statistical analysis

For subjects grouped by gut microbiota composition, BMI (lean, overweight, obese), and cardiometabolic health status (healthy, abnormal), data are reported as the mean ± SD and 95% CIs. The normality of the continuous variables in each group was evaluated with the Shapiro-Wilks test. Finally, an unsupervised exploratory multivariate data analysis was performed by principal component analysis (PCA). All analyses were performed with the R-statistical open-source software (Rx64 version 4.0.5, R Foundation for Statistical Computing, Vienna, Austria; URL http://www.R-project.org/). The employed code and the database for statistical analyses are available on Github (https://github.com/vidarium/FoodPhenolTree). The changes in oxylipin levels and dietary antioxidants were assessed using Kruskal Wallis tests. $p < 0.05$ were considered statistically significant. When an interaction was significant, Dunn's post hoc tests were applied. Before multiple linear model analysis, a constant was added to variables with zero values (less than 5% of all variables analyzed) to avoid infinite values in the transformation. Then a logarithmic transformation of oxylipin levels and dietary antioxidant values was performed to approximate the data to the normal distribution). We performed both unadjusted analyses as well as analyses adjusted by potential confounders, including age (categorical; 18–40 yrs and 41–62 yrs), sex (categorical; male, female), and city (categorical; Bogotá, Medellin, Cali, Barranquilla, Bucaramanga). Tests for trends were performed by entering the continuous variable in the model using ANOVA. Diet diversity was estimated from the 24HDRs database by calculating alpha diversity (Shannon index, Simpson index, and the number of different items) to the items consumed by each participant. The alpha diversity index was included as an explanatory variable in multivariable models to test whether the foods' diversity correlated with the amount of excreted oxylipins.

3. Results

3.1. Dinor-oxylipin metabolites are the major urinary oxylipins in obese subjects

The present study was conducted on 105 participants from a previous Colombian Gut microbiota and cardiometabolic risk study [40]. Participants had roughly similar proportions of the dominant gut microbiota (CAG-Prevotella n = 19; CAG-Lachnospiraceae n = 21; CAG-Pathogen n = 23; CAG-Akkermansia n = 23; and CAG-Ruminococcaceae n = 19), sex (50 females and 55 male), age range (18–40 years (n = 50) and 41–60 years (n = 55)) and the city of origin (Bogota n = 15; Medellin n = 21; Cali n = 28; Barranquilla n = 21; and Bucaramanga n = 20). The mean age and BMI were 40.3 ± 11.9 years and 27.7 ± 5.0 kg/m^2, respectively.

Participants' demographics, gut microbiota, health-related and dietary parameters according to BMI are shown in Table 1. We observed that participants included in the lean group (<25 kg/m^2) were mainly the higher in HDL and insulin sensitivity, as well as the lower in VLDL, TG, %body fat, SBP, DBP, insulin, β-cell function, and insulin resistance than the obese group (>30 kg/m^2) ($q < 0.001$, Kruskal-Wallis test). We also observed the highest abundance of CAG-Ruminococcaceae in lean subjects compared to subjects classified as overweight or obese ($q = 0.003$, Kruskal-Wallis test). The analysis by BMI also indicated that obese subjects were more likely to have higher overall and central obesity, hypertension, and metabolic dysregulation ($q < 0.01$, Kruskal-Wallis test) (Table 1), to have a gut microbiota with a high representation of pathobionts, and to excrete the higher levels of several urinary oxylipins (15-F_{1t}-IsoP, total PGs and 2,3-dinor-oxylipin metabolites) (Table 2) when compared with lean subjects. Likewise, the total levels of dinor-oxylipin metabolites were also higher in overweight than lean individuals ($p < 0.01$, Dunn's multiple comparisons test) and correlated positively with BMI and body fat (Fig. S1). In general, after adjustment for age, sex, and city, lean subjects had lower concentrations of all (log-transformed) dinor-oxylipins ($p < 0.05$, multiple linear regression). In contrast, oxylipins such as 15-F_{2t}-IsoP (classical oxidative stress marker) and other F- and E− IsoPs were similar across BMI categories and did not correlate with BMI and body fat and, dinor oxylipin metabolites were marginally associated with other oxylipins (Fig. S1). Importantly, subjects with two or more cardiometabolic abnormalities (Table S2), which had higher BMI, waist circumference, and % body fat than subjects classified with a normal cardiometabolic status ($q < 0.01$, Mann Whitney test), had increased levels of 2,3-dinor-11β-$PGF_{2\alpha}$ and the total 2,3-dinor-oxylipins metabolites ($p < 0.05$, multiple linear regression). The same behavior was observed when subjects were categorized by HOMA-IR (Fig. S2) but not under other cardiometabolic dysfunctions (e.g., levels of TGs or blood pressure; data not shown). Finally, although the levels of oxLDL were increased by 22.5% in obese subjects, no significant differences were detected compared to the lean group (Table 2).

Obesity has been associated with dysbiosis in gut microbiota and is one of the pathologies clustered by the cardiometabolic syndrome. Thus participants' demographics, health-related and dietary parameters were also categorized according to gut microbiota composition and cardiometabolic health status, as shown in Table S1 and Table S2, respectively. We did not find significant differences ($p > 0.05$, Kruskal-Wallis test) in the levels of excreted oxylipins or the overall intake of dietary antioxidants adjusted by kg of body weight as per the participants' gut microbiota composition. However, the intake of micronutrients Fe, Zn, and Mn from the diet, adjusted by kg of body weight, were higher in subjects with a microbiota dominated by the consortium CAG-Akkermansia, as compared to subjects with a microbiota dominated by the consortium CAG-Pathogen ($p < 0.05$, Dunn's multiple comparisons test) that were significantly lower.

3.2. The intake of dietary antioxidants is lower in subjects with overweight and obesity

To test our hypothesis that dietary antioxidant intake was associated with oxylipins excretion and obesity, we analyzed the 24 HDRs to extract the dietary contribution of phenolic compounds for each BMI group, represented by FNDDS categories (Table 3 and Supplementary data 2), as well as the total contribution vitamins A and C, and micronutrients Cu, Fe, Mn, Zn (Table 4).

Unadjusted daily consumption of polyphenols from each FNDDS group in the 105 subjects analyzed is presented in Supplementary data 2. Mean ± SD, 25%, 50%, and 75% percentiles of polyphenol intakes for the whole population were 1070 ± 627.5, 598.4, 867.4, and 14,757 mg/day, respectively. Sugars, sweets, and beverages (mainly coffee beverage) represented the main food groups from which dietary polyphenols were obtained; together, they provided 378.3 ± 383.5 mg/day of polyphenols (corresponding to 35.4% of the total polyphenol intake). Fruits (283.6 ± 391.6 mg/day, 26.5%), vegetables (169.2 ± 190.4 mg/day, 15.8%), legumes (90.0 ± 273.0 mg/day, 8.4%), chocolate drinks (83.2 ± 244.2 mg/day, 7.8%), grains (65.7 ± 55.5 mg/day, 6.1%), fats (0.32 ± 0.92 mg/day, 0.03%) and meats (0.04 ± 0.40 mg/day, 0.004%) also contributed with dietary polyphenols. The foods that represented sources of dietary polyphenols in this population were coffee beverages, chocolate drinks, non-citric fruits (*e.g.*, apple, banana, mango, and blackberry), grains (*e.g.*, lentils and beans), and high-starch vegetables (*e.g.*, potato and plantains) which contributed two to three-folds more

Table 1

Health information, anthropometry, blood biochemistry, and gut microbiota of individuals grouped according to BMI categories. Data presented as the mean ± SD. BMI: body mass index, TC: total cholesterol, TG: triglycerides, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, VLDL: very low-density lipoprotein cholesterol, HOMA-IR: homeostatic model assessment–insulin resistance. BP: blood pressure. All groups were compared using a Kruskal Wallis test. * ($p < 0.05$) was adjusted using the Dunn's test for multiple comparisons in post hoc analyses between overweight or obese *vs.* lean subjects. The q-value shows a p-value that has been adjusted for the false discovery rate on all variables. Additionally, ANOVA estimates from a multiple linear regression (MLR) in which levels of variables were log-transformed and adjusted for potential confounding: age range, city of origin of the participants, and sex at birth ($p < 0.05$) are also shown.

	Lean n = 33; Female = 16				**Overweight** n = 45; Female = 25				**Obese** n = 27; female = 14				**Kruskal-Wallis test**		**MLR**
	Mean	**SD**	**CI 95%**		**Mean**	**SD**	**CI 95%**		**Mean**	**SD**	**CI 95%**		**p-value**	**q-value**	**p-value**
Age (Years)	39.48	11.76			40.38	11.93			41.22	12.52					
BMI (kg/m^2)	22.43	1.61	21.86	23.00	27.67*	1.21	27.30	28.03	34.06*	4.06	32.46	35.67	**<0.001**	**<0.001**	**<0.0001**
Weight (kg)	59.53	8.44	56.54	62.53	74.40*	9.20	71.64	77.16	91.97*	13.55	86.61	97.33	**<0.001**	**<0.001**	**<0.0001**
Body size (m)	1.63	0.09	1.59	1.66	1.64	0.09	1.61	1.66	1.64	0.10	1.60	1.68	0.668	0.318	0.3395
Waist Circumference (cm)	79.55	7.13	77.02	82.07	93.59*	6.73	91.57	95.62	109.03*	10.28	104.96	113.09	**<0.001**	**<0.001**	**<0.0001**
ApoB	96.19	27.90	86.30	106.09	107.24	94.56	78.83	135.65	94.74	24.85	84.91	104.57	0.978	0.392	0.9319
HDL (mg/dL)	51.30	10.50	47.58	55.03	42.47*	8.85	39.81	45.13	40.93*	11.52	36.37	45.48	**<0.001**	**<0.001**	**<0.0001**
VLDL (mg/dL)	21.70	9.38	18.37	25.02	30.90	19.57	25.02	36.77	39.61*	34.02	26.15	53.07	**0.010**	**0.014**	**0.0006**
LDL (mg/dL)	125.00	38.73	111.27	138.73	113.29	32.38	103.56	123.02	114.48	32.87	101.48	127.49	0.470	0.289	0.4134
TC (mg/dL)	195.85	43.52	180.42	211.28	183.60	37.62	172.30	194.90	189.15	41.58	172.70	205.60	0.611	0.308	0.4813
HbA1c (%)	5.38	0.29	5.28	5.48	5.42	0.34	5.32	5.52	5.73*	0.61	5.49	5.97	**0.034**	**0.043**	**0.0003**
TG (mg/dL)	108.39	46.90	91.76	125.02	156.33*	97.42	127.07	185.60	197.78*	170.19	130.45	265.10	**0.008**	**0.011**	**0.0006**
Body Fat (%)	33.20	5.04	31.41	34.99	37.26*	4.08	36.04	38.49	41.71*	4.18	40.05	43.36	**<0.001**	**<0.001**	**<0.0001**
Systolic BP (mm Hg)	115.85	11.86	111.64	120.05	130.20*	20.37	124.08	136.32	128.96*	17.47	122.05	135.87	**0.001**	**<0.001**	**0.0003**
Diastolic BP (mm Hg)	73.18	9.24	69.90	76.46	82.80*	13.14	78.85	86.75	83.44*	11.99	78.70	88.19	**0.001**	**0.001**	**0.0001**
Glucose (mmol/L)	4.76	0.60	4.55	4.97	4.82	0.44	4.69	4.96	5.23	1.23	4.74	5.71	**0.151**	**0.132**	**0.0433**
Insulin (μU/ml)	8.82	4.49	7.23	10.41	11.93*	5.48	10.28	13.57	21.60*	11.71	16.97	26.24	**<0.001**	**<0.001**	**<0.0001**
β-cell function	115.51	43.25	100.18	130.85	137.42	44.31	124.10	150.73	183.78*	74.86	154.16	213.39	**<0.001**	**<0.001**	**<0.0001**
Insulin Sensibility	108.98	45.53	92.84	125.13	78.43*	33.20	68.45	88.40	49.37*	33.47	36.13	62.62	**<0.001**	**<0.001**	**<0.0001**
HOMA-IR	1.88	1.00	1.53	2.24	2.57*	1.27	2.19	2.95	5.08*	3.09	3.86	6.31	**<0.001**	**<0.001**	**<0.0001**
hs-CRP (mg/dL)	1.40	1.02	1.04	1.76	3.44*	6.61	1.45	5.42	3.97*	3.24	2.69	5.25	**<0.001**	**<0.001**	**<0.0001**
Prevotella	0.14	0.19	0.07	0.20	0.22	0.27	0.14	0.30	0.11	0.19	0.04	0.19	0.225	0.170	0.8762
Lachnospiraceae	0.20	0.23	0.12	0.28	0.21	0.21	0.15	0.28	0.26	0.26	0.16	0.37	0.699	0.322	0.5472
Pathogen	0.10	0.20	0.03	0.17	0.20	0.27	0.12	0.29	0.29*	0.32	0.16	0.41	**0.013**	**0.018**	**0.0195**
Akkermansia	0.24	0.27	0.14	0.34	0.16	0.24	0.09	0.23	0.16	0.22	0.07	0.25	0.257	0.181	0.2275
Ruminococcaceae	0.17	0.16	0.11	0.22	0.09*	0.13	0.05	0.13	0.07*	0.12	0.02	0.12	**0.001**	**0.002**	**0.0047**

Table 2
Oxylipins, total 2,3-dinor oxylipins (2,3-dinor-15-F_{2t}-IsoP, 2,3-dinor-15-*epi*-15-F_{2t}-IsoP, and 2,3-dinor-11β-PGF2α) and oxidized LDL (oxLDL) levels according to the BMI classification. All groups were compared through a Kruskal Wallis test. P values were adjusted using the Dunn's test for multiple comparisons in post hoc analyses between overweight or obese *vs.* lean subjects, *$p < 0.05$. Additionally, ANOVA estimates from a multiple linear regression (MLR) in which levels of oxylipins were log-transformed and adjusted for potential confounding: age range, city of origin of the participants, and sex at birth ($p < 0.05$) are also shown.

Urine oxylipins (ng/mg creatinine)	**Lean** n = 33; Female = 16				**Overweight** n = 45; Female = 25				**Obese** n = 27; female = 14				**Kruskal Wallis test**		**MLR**
	Mean	**SD**	**CI 95%**		**Mean**	**SD**	**CI 95%**		**Mean**	**SD**	**CI 95%**		**p-value**	**q-value**	**p-value**
Isoprostanes															
15-F_{2t}-IsoPs															
15-F_{2t}-IsoP	2.33	2.03	1.62	3.05	2.10	1.48	1.66	2.55	2.29	1.68	1.62	2.96	0.945	0.385	0.7060
15-*epi*-15-F_{2t}-IsoP	2.01	1.52	1.47	2.55	2.06	1.41	1.63	2.48	2.52	2.00	1.73	3.31	0.562	0.303	0.6067
2,3-dinor-15-F_{2t}-IsoP	3.33	1.72	2.72	3.94	4.27	2.34	3.57	4.97	4.72	3.06	3.51	5.93	0.161	0.137	0.0533
2,3-dinor-15-*epi*-15-F_{2t}-IsoP	2.51	1.39	2.02	3.01	3.28	1.83	2.73	3.83	3.48	2.32	2.56	4.39	0.144	0.132	0.0665
15-keto-15-F_{2t}-IsoP	0.46	0.56	0.26	0.66	0.64	0.64	0.44	0.83	0.65	0.57	0.42	0.87	0.216	0.167	0.0682
Total 15-F_{2t}-IsoP	10.64	4.93	8.89	12.39	12.35	5.32	10.75	13.95	13.65	7.63	10.63	16.67	0.180	0.147	0.1659
5-F_{2t}-IsoPs															
5-F_{2t}-IsoP	1.20	0.91	0.88	1.52	1.12	0.70	0.91	1.33	1.15	0.93	0.78	1.52	0.949	0.385	0.6505
5-*epi*-5-F_{2t}-IsoP	1.75	1.50	1.22	2.28	1.67	1.19	1.32	2.03	1.77	1.06	1.36	2.19	0.682	0.318	0.5404
Total 5-F_{2t}-IsoP	2.95	2.37	2.11	3.79	2.80	1.80	2.26	3.34	2.92	1.92	2.16	3.68	0.897	0.382	0.9216
Other IsoPs															
15-*epi*-15-E_{2t}-IsoP	2.22	1.62	1.64	2.79	2.05	1.21	1.69	2.41	2.31	1.75	1.62	3.00	0.824	0.360	0.3921
15-F_{1t}-IsoP	0.33	0.55	0.13	0.52	0.76	1.99	0.16	1.36	0.52	0.51	0.31	0.72	**0.041**	**0.048**	**0.0032**
Total IsoPs	16.13	8.31	13.18	19.08	17.96	8.08	15.53	20.38	19.40	10.92	15.08	23.72	0.321	0.215	0.3012
Prostaglandins															
PGE_2	0.46	0.39	0.32	0.59	0.51	0.38	0.39	0.62	0.54	0.41	0.38	0.70	0.583	0.303	0.6613
Tetranor-PGFM	0.76	0.85	0.46	1.06	0.57	0.46	0.44	0.71	0.48	0.42	0.31	0.64	0.576	0.303	0.8189
PGD metabolites															
11β-$PGF_{2\alpha}$	1.26	1.06	0.89	1.64	1.56	0.95	1.27	1.84	1.57	1.33	1.05	2.10	0.457	0.288	0.1354
2,3-dinor-11β-$PGF_{2\alpha}$	9.55	5.33	7.66	11.44	12.27	6.32	10.37	14.17	13.27*	6.44	10.72	15.82	**0.036**	**0.044**	**0.0090**
Total PGD	10.82	5.66	8.81	12.82	13.83	6.68	11.82	15.84	14.84*	7.22	11.99	17.70	**0.030**	**0.040**	**0.0173**
Total PGs	12.03	5.77	9.99	14.08	14.91	6.89	12.84	16.98	15.86	7.43	12.92	18.80	0.053	0.055	**0.0500**
Total 2,3-dinor oxylipins	15.39	8.07	12.53	18.25	19.83	10.10	16.79	22.86	21.47	11.53	16.90	26.03	0.057	0.055	**0.0173**
Thromboxanes															
11-DH-TXB_2	0.47	0.29	0.37	0.57	0.55	0.72	0.34	0.77	0.57	0.29	0.46	0.68	0.151	0.132	0.3325
Plasma oxLDL (U/L)	160.40	116.50	119.09	201.71	158.65	81.42	134.19	183.11	196.04	162.73	131.67	260.42	0.673	0.318	0.8491

bioactive compounds in lean than overweight or obese subjects (Fig. 1 and Supplementary data 2).

We additionally produced comparative phenetic, hierarchical trees of foods for the 24HDRs analysis on subjects from each BMI phenotype classification (Fig. 1). This approach visualized information across related foods, enabling us to measure the overall tree-based diversity of foods consumed by a person and the tree-based diversity of food sources for a particular nutrient, including polyphenols (Fig. 1) and fiber (Table S3). The polyphenols sources of the diet in this study correspond mainly to fruits (apple, mango, pineapple, banana, guava, and blackberries), high-starch vegetables (plantains, potatoes, tomatoes, carrots, and onions), beverages (coffee, chocolate, and brown sugarloaf), legumes (lentils and beans) and grains (rice, corn, and white bread). In addition, comparable to the global reports for adults, common polyphenols in the diet were flavanols from apples, mango, banana, pineapple, blackberries, lentils, beans, cocoa, potato, plantains, tomatoes, carrots, onions, corn, and white bread; hydroxycinnamates from coffee, blackberries, apples, plantains, tomatoes, carrots, lentils, beans, rice, corn), flavonols (blackberries, cocoa, plantains, lentils, and beans), flavones (lentils and potato), anthocyanins (blackberries, beans, and purple tomatoes) and lignanes (potatoes and white bread) (**Supplementary data 2**). We evaluated whether the diversity of polyphenol sources in the diet affected the total 2,3-dinor-oxylipin excretion but found no correlation between the total excreted levels and the alpha diversity of food items.

While polyphenol intake (mg of GAE/day) was highly variable among BMI groups, fiber intake was relatively similar. Although the trend was not statistically significant, in raw data, overweight and obese individuals tended to obtain lower amounts of phenolic compounds from the diet than lean individuals (Table 3); this difference became statistically significant after adjusting the intake of phenolic compounds per kg of body weight ($p < 0.05$, Dunn's multiple comparisons test), with obese individuals eating lower amounts of grains, vegetables, and sweets and beverages rich in these compounds. After further adjustment by potential confounders, including age range, participants' city of origin, and sex at birth, the difference remained statistically significant (Table 3).

Differences per BMI category of other dietary antioxidants and micronutrients with antioxidant function (Zn, Mn, Cu, and Fe) are presented in Table 4. Similar to the results obtained with dietary polyphenols, consumption of micronutrients and vitamins A and C per kg of body weight were significantly higher in lean than obese subjects (all $p < 0.0001$, Dunn's multiple comparisons test). Furthermore, these associations remained significant after adjustment for potential confounders (Table 4).

Table 3
Dietary intake of phenolic compounds raw and adjusted by kg of body weight from the nine FNDDS food groups (Level 1). All groups were compared using a Kruskal Wallis test. P values were adjusted using the Dunn's test for multiple comparisons between overweight or obese *vs.* lean subjects, *p < 0.05. ANOVA estimates from a multiple linear regression (MLR): values of selected variables were log-transformed and adjusted for potential confounding: age range, city of origin of the participants, and sex at birth.

Sources of dietary phenolic compounds	**Lean** n = 33; Female = 16				**Overweight** n = 45; Female = 25				**Obese** n = 27; female = 14				**Kruskal Wallis test**		**MLR**
FNNDS category	**Mean**	**SD**	**CI 95%**		**Mean**	**SD**	**CI 95%**		**Mean**	**SD**	**CI 95%**		**p-value**	**q-value**	**p-value**
Raw intake in mg GAE															
Milk	120.33	289.06	17.83	222.83	82.21	267.50	1.84	162.57	36.36	92.75	−0.33	73.05	0.721	0.323	0.9076
Meats	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.16	0.81	−0.16	0.48	0.236	0.171	0.2333
Eggs	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00			
Legumes	115.23	390.21	−23.13	253.60	69.45	180.45	15.23	123.66	93.60	232.45	1.64	185.56	0.495	0.289	0.5156
Grains	71.43	56.06	51.55	91.31	64.68	54.50	48.31	81.05	60.74	58.15	37.74	83.75	0.432	0.277	0.0980
Fruits	201.06	208.05	127.29	274.83	329.32	461.67	190.62	468.02	308.17	431.95	137.29	479.04	0.500	0.289	0.7509
Vegetables	184.04	187.14	117.69	250.40	163.91	200.55	103.66	224.16	160.02	183.02	87.62	232.42	0.576	0.303	0.5115
Fats	0.15	0.16	0.09	0.20	0.39	1.09	0.06	0.72	0.40	1.13	−0.05	0.85	0.936	0.385	0.7013
Sweets and beverages	487.22	422.57	337.39	637.06	375.10	394.63	256.54	493.66	250.54*	269.92	143.76	357.31	0.046	0.050	0.1572
Total intake/BMI	1145.92	589.20	937.00	1354.84	1050.16	617.49	864.64	1235.67	1009.16	700.57	732.03	1286.30	0.307	0.209	0.5369
mg GAE/kg bw per day															
Milk	1.49	3.52	0.24	2.74	0.75	3.01	−0.16	1.65	1.46	3.89	−0.08	3.00	0.181	0.147	0.2923
Meats	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.01	0.236	0.171	0.2333
Eggs	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00			
Legumes	2.15	7.49	−0.50	4.81	0.92	2.34	0.22	1.63	1.08	2.79	−0.02	2.19	0.500	0.289	0.6476
Grains	1.21	0.92	0.88	1.53	0.88	0.83	0.64	1.13	0.67*	0.66	0.41	0.93	**0.008**	**0.011**	**0.0052**
Fruits	3.46	3.63	2.17	4.75	4.49	6.29	2.60	6.38	3.40	4.80	1.51	5.30	0.476	0.289	0.5145
Vegetables	3.08	3.06	1.99	4.16	2.25	2.77	1.41	3.08	1.64	1.74	0.95	2.33	**0.045**	**0.050**	0.1605
Fats	0.00	0.00	0.00	0.00	0.01	0.01	0.00	0.01	0.00	0.02	0.00	0.01	0.587	0.303	0.7013
Sweets and beverages	8.24	6.96	5.77	10.71	4.99	5.10	3.46	6.52	2.73*	3.09	1.51	3.96	**0.001**	**0.002**	**0.0163**
Total intake/kg	19.63	10.45	15.92	23.33	14.28	8.40	11.76	16.80	11.00*	7.76	7.93	14.07	**0.001**	**0.001**	**0.0011**

Table 4
Additional dietary antioxidants and micronutrients with antioxidant functions. Raw and adjusted by kg of body weight intake of vitamins A and C and micronutrients. All groups were compared using a Kruskal Wallis test. P-values were adjusted using the Dunn's test for multiple comparisons between overweight or obese *vs.* lean subjects, *p < 0.05. ANOVA estimates from multiple linear regression (MLR) values of selected variables were log-transformed and adjusted for potential confounders: age range, participants' city of origin, and sex at birth.

Micronutrient	**Lean** n = 33; Female = 16				**Overweight** n = 45; Female = 25				**Obese** n = 27; female = 14				**Kruskal Wallis test**		**MLR**
	Mean	**SD**	**CI 95%**		**Mean**	**SD**	**CI 95%**		**Mean**	**SD**	**CI 95%**		**p-value**	**q-value**	**p-value**
Raw intake mg/day															
Fe (mg)	14.22	2.30	13.40	15.03	12.88*	1.86	12.32	13.43	13.26	1.86	12.53	14.00	**0.048**	0.051	**<0.0001**
Zn (mg)	10.57	0.64	10.34	10.79	10.37	0.83	10.12	10.62	10.27	0.65	10.01	10.53	0.106	0.100	0.2789
Cu (mg)	1.74	0.78	1.47	2.02	1.51	0.70	1.30	1.72	1.50	0.60	1.26	1.74	0.261	0.181	0.1640
Mn (mg)	3.20	0.67	2.96	3.44	3.13	0.59	2.95	3.30	3.07	0.50	2.87	3.26	0.737	0.326	0.7191
Vitamin A (IU)	856.42	212.25	781.17	931.68	785.31	157.86	737.88	832.74	787.59	157.66	725.22	849.96	0.400	0.262	0.2135
Vitamin C (mg)	163.12	55.01	143.62	182.63	164.91	56.50	147.94	181.89	160.74	58.77	137.49	183.99	0.918	0.385	0.9989
Intake/kg bw per day															
Fe (mg)	0.24	0.04	0.23	0.26	0.18*	0.03	0.17	0.19	0.15*	0.03	0.14	0.16	**<0.001**	**<0.001**	**<0.0001**
Zn (mg)	0.18	0.02	0.17	0.19	0.14*	0.02	0.14	0.15	0.11*	0.01	0.11	0.12	**<0.001**	**<0.001**	**<0.0001**
Cu (mg)	0.03	0.01	0.02	0.03	0.02*	0.01	0.02	0.02	0.02*	0.01	0.01	0.02	**<0.001**	**<0.001**	**<0.0001**
Mn (mg)	0.05	0.01	0.05	0.06	0.04*	0.01	0.04	0.05	0.03*	0.01	0.03	0.04	**<0.001**	**<0.001**	**<0.0001**
Vitamin A (IU)	14.65	4.00	13.23	16.07	10.72*	2.63	9.93	11.51	8.68*	1.78	7.97	9.38	**<0.001**	**<0.001**	**<0.0001**
Vitamin C (mg)	2.76	0.93	2.43	3.09	2.23*	0.77	2.00	2.47	1.77*	0.69	1.50	2.05	**<0.001**	**<0.001**	**0.0001**

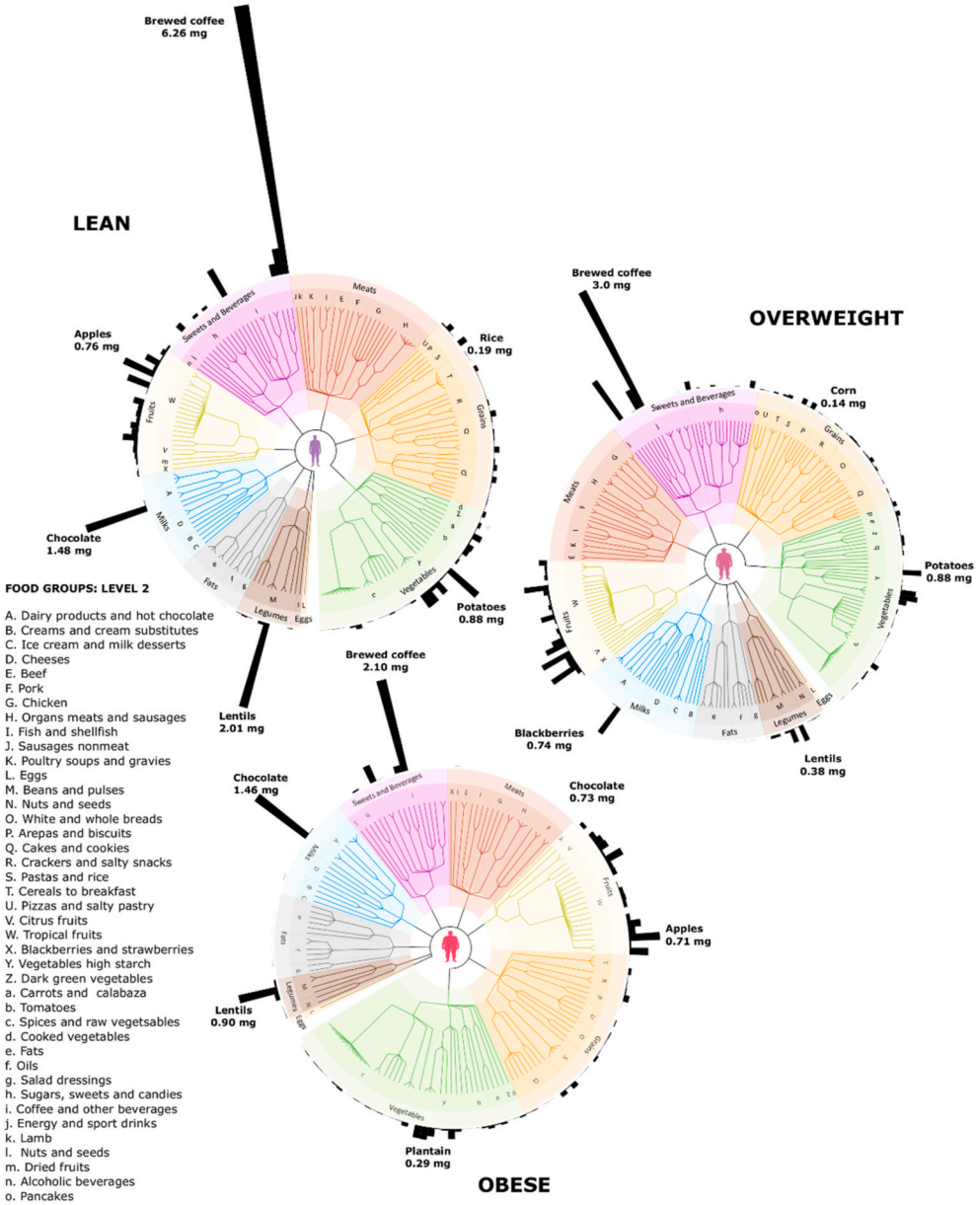

Fig. 1. Dietary diversity and food contribution to polyphenol intake according to the tree-based analysis of the 24HRDs. The food-tree representation of food groups is a hierarchical, phenetic tree built from the local 24HRDs database using the FNDDS as the reference database. Colored branches are grouped according to the nine FNDDS food groups (Level 1). Specific food groups within each Level 1 food group (i.e., Level 2) are additionally highlighted (see legend inset). The leaves of the tree represent unique foods. The black bars extending beyond the leaves correspond to the average intake (mg) of phenolic compounds per kg of body weight reported by subjects.

3.3. Dietary antioxidants are inversely associated with obesity and cardiometabolic risk

We performed a PCA with all variables quantified in the 105 subjects analyzed in this study (Fig. 2). The first and second PCs accounted for 18.2% and 15.2% of the variance, respectively. The correlations of variables with PC1 or PC2 and *p*-values are described in Table S4. Oxylipins were positively correlated with PC1, while most cardiometabolic risk factors, dinor-oxylipin metabolites, and gut microbiota dominated by the CAG-Pathogen correlated positively with PC2 (Fig. 2). In contrast, dietary antioxidants and micronutrients, a microbiota dominated by the CAG-Ruminococcaceae, HDL, and insulin sensitivity, showed a negative correlation with PC2. Lean, overweight, and obese individuals spread across the PC2. As expected, obesity was associated with clinical variables contributing to cardiometabolic risk (*e.g.*, dyslipidemia, glucose dysregulation, hypertension), greater production/excretion of dinor-oxylipin metabolites, and a lower intake of dietary antioxidants.

4. Discussion

Even though previous studies have extensively investigated the relation between F_2-IsoPs and disease [64–66], very few human studies have comprehensively assessed the relationship between F_2-IsoPs, body weight, and dietary antioxidants. The current study evaluated the association of 33 urinary oxylipins (including several PGs, F- and E-IsoPs, and metabolites) with obesity, cardiometabolic status, gut microbiota composition, food diversity, and dietary antioxidants intake. Although oxylipins were not significantly associated with cardiometabolic status or the gut microbiota composition, BMI was positively correlated to urinary excretion of oxylipins. Although, as expected, not all isoprostanes had the same response to an increased body mass and adiposity, of all, 2,3-dinor-oxylipin metabolites were the compounds with greater excretion levels, more than their parent compounds and were more strongly associated with obesity and insulin resistance than 15-F_{2t}-IsoPs, the classical biomarker of oxidative stress.

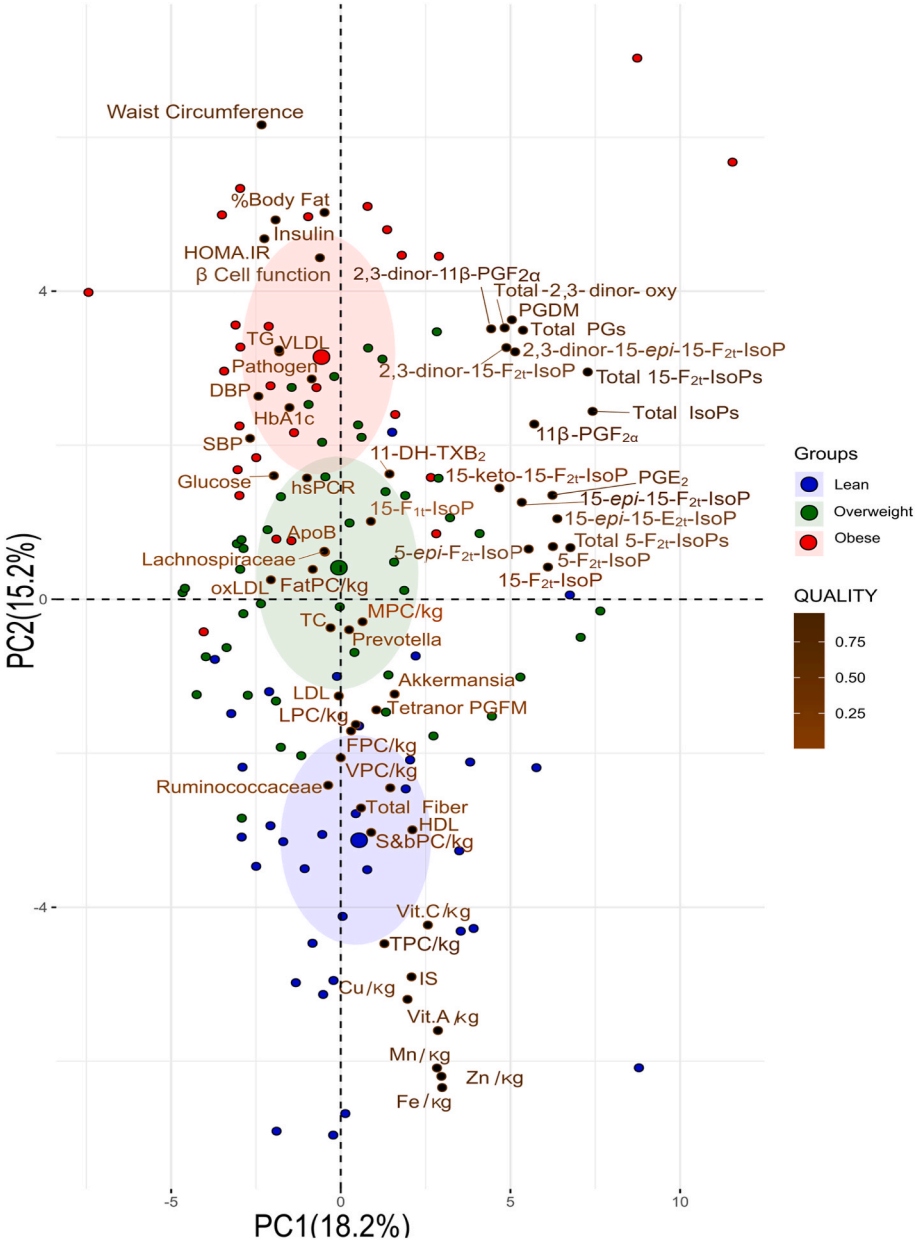

Fig. 2. PCA of variables informing cardiometabolic status, oxylipin excretion, and dietary intake of antioxidants in subjects classified by BMI. PC1 and PC2 explained 33.4% of the total variance. The intensity of the brown in variable names indicates a high quality of representation. TC: total cholesterol, TG: triglycerides, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, VLDL: very low-density lipoprotein cholesterol, HOMA-IR: homeostatic model assessment–insulin resistance, HbA1c: Glycated hemoglobin, DBP: diastolic blood pressure, SBP: systolic blood pressure, oxLDL: oxidized LDL. The phenolic compounds intake adjusted by weight is abbreviated as total values of consumption (TPC/kg) and total consumption by sources according to the FNDDS food category: fruits (FPC/kg), vegetables (VPC/kg), grains (GPC/kg), Milk (MPC/kg), Fats (FatPC/kg), sweets and beverages (S&bPC/kg), and legumes (LPC/kg). The micronutrients intake adjusted by weight is abbreviated as total values for manganese (Mn/kg), zinc (Zn/kg), iron (Fe/kg), copper (Cu/kg), vitamin A (Vit. A/kg), and vitamin C (Vit. C/kg). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4.1. 2,3-Dinor oxylipin metabolites are sensitive biomarkers of oxidative modification of lipids in obesity

Obesity and insulin resistance has been associated with increased F_{2t}-IsoP levels cross-sectionally [14,18,19,67]. In a pilot case-control study (n = 299) nested within the Insulin Resistance Atherosclerosis Study, Il'yasova et al. found strong and significant associations for 2,3 dinor-15-F_{2t}-IsoP and 5-F_{2t}-IsoP and weak and non-significant associations for the 15-F_{2t} -IsoP and 5-F_{2t}-IsoP with BMI, suggesting that the ability of F_{2t}-IsoPs to detect the association with obesity vary, and that 2,3-dinor-15-F_{2t}-IsoP as biomarker is the most sensitive in detecting the link between urinary F_2-IsoPs and obesity [14]. Furthermore, dietary interventions have proven useful in reducing the excretion of dinor metabolites; Dorjgochoo et al. found that a major downstream dinor-oxylipin metabolite in the oxidation pathway of 15-F_{2t}-IsoP (30%), the 2,3-dinor-5,6-dihydro-15-F_{2t}-IsoP, increased in women according to BMI and decreased in habitual consumers of multivitamin and vitamin E supplements, in contrast to 15-F_{2t}-IsoP that did not show any difference among the participants [20]. Similarly, two years of caloric restriction in healthy, young, and lean middle-aged individuals significantly reduced urinary excretion of 2,3-dinor-15-F_{2t}-IsoP and F_{2t}-IsoPs; however, only changes in 2,3-dinor-15-F_{2t}-IsoP significantly correlated with changes in leptin and insulin sensitivity [68]. Additionally, it has been suggested that the 2,3-dinor-15-F_{2t}-IsoP is a metabolite of 15-F_{2t} -IsoP that has greater urinary excretion in humans than the parent compound and that it would be useful as a biomarker for the overall formation of 15-F_{2t}-IsoP and, by extension, lipid peroxidation *in vivo* [69]. Our analysis confirms the previous reports on the positive cross-sectional associations between some urinary F_{2t}-IsoP metabolites and overall obesity. In contrast, other F- or E-IsoPs and metabolites did not increase with BMI, or the statistical significance was lost after adjusting by confounding factors (sex, city, and age), except for 15-F_{1t}-IsoP in overweight subjects. In addition, during obesity, the limited expandability of the subcutaneous adipose tissue leads to the accumulation of visceral and ectopic fat deposition, associated with macrophage infiltration and subsequent insulin resistance [70]. Recently, it has been reported that 15-F_{2t}-IsoP signal to the β-cells in a compensatory mechanism to overcome insulin resistance in obesity

through a crosstalk between adipose tissue and β-cells in rats [13]. Here, we observed increased levels of 2,3-dinor-oxylipins associated with insulin resistance; however, whether dinor-oxylipins metabolites like 15-F_{2t}-IsoP also contribute to β-cells compensation to overcome insulin resistance has not been yet evaluated.

The 15-F_{2t}-IsoP was the first isomer used as an index of lipid peroxidation *in vivo* and, therefore, is the classical biomarker frequently used to measure oxidative stress [14,64,71]; however, because renal tissue may contribute disproportionally to the total production of 15-F_{2t}-IsoP, the abundant β-oxidation metabolite that occurs predominantly in the extra-renal tissues 2,3-dinor-15-F_{2t}-IsoP has also been used in human studies as an index of oxidative status and is proposed as a better indicator to reflect the entire body production of the parent compound 15-F_{2t}-IsoP [14,65,68]. Furthermore, urinary concentrations of 2,3-dinor-15-F_{2t}-IsoP are several folds higher than its precursor 15-F_{2t}-IsoP, thus reducing measurement error [64,68,72].

Urinary 2,3-dinor-oxylipins (2,3-dinor-11β-$PGF_{2\alpha}$ and 2,3 dinor-15-*epi*-15-F_{2t}-IsoP) had been recognized as markers of inflammation in mice and humans [73,74]. However, it is still of considerable interest to understand the biological activity of these metabolites both in the mediation and resolution of inflammation. PGD_2 may play a role in the evolution of atherosclerosis and inflamed arterial intima [75]. Among PGD_2 metabolites evaluated, only 2,3-dinor-11β-$PGF_{2\alpha}$ was increased in obesity, but not products derived upstream from PGD metabolism (tetranor PGDM, tetranor PGJM, and tetranor PGDM lactone) [74,76]. Thus, it is plausible that 2,3-dinor-11β-$PGF_{2\alpha}$ could also interact with PGD_2 receptors (e.g., DP2). In the same way, 2,3 dinor-15--*epi*-15-F_{2t}-IsoP may display the inflammatory and vasoconstrictor effects found for 15-F_{2t}-IsoPs in vascular tissue, mediated by prostanoid receptors, including the thromboxane, PGE and PGF receptors [77].

In our study, 2,3-dinor-oxylipin metabolites had greater excretion levels than their parent compounds and were more strongly associated with obesity and insulin resistance than 15-F_{2t}-IsoP. In summary, data suggest that 2,3-dinor-oxylipin metabolites are plausibly more sensitive markers of endogenous oxidative stress linking urinary 15-F_{2t}-IsoPs and obesity than 15-F_{2t}-IsoP.

4.2. Total phenolic compounds intake in Colombian adults

Particular attention has been paid to the antioxidant role of polyphenols in the human diet, and evidence supports the contribution of polyphenols in preventing obesity. Oxidative stress has been observed as key to its development [78]. There is substantial evidence that a long-term polyphenol-rich diet contributes to body-weight loss, protecting from several chronic diseases. Several clinical trials, *in vitro* evaluations, and epidemiological studies support a role for phenolic compounds subclasses (phenolic acids, anthocyanidins, flavones, flavonols, flavan-3-ols, and flavanones) against the development of cardiometabolic diseases [21,79,80]. However, dietary interventions conducted in this area have important inconsistencies related to the anti-obesity impact of dietary antioxidants, mainly because studies vary in terms of designs, lengths, subjects (age, gender, ethnicity), and chemical forms of the dietary polyphenols used, among other confounding factors [25]. Moreover, differences in total polyphenols intake among cohort studies appear both by the obvious difference in dietary patterns of the populations assessed but also by methodological differences in the use of phenol composition databases, such as not using retention factors to correct for weight gains or losses after food processing and using chromatography or Folin-Ciocalteau (FC) results to report total polyphenols. The FC method is widely used to quantify total polyphenols in foods. Although less specific than chromatography, it includes other antioxidant compounds that could better reflect the total antioxidant potential of foods [81]. Ours is the first report of dietary polyphenol intake for Colombian adults, averaging 1070 ± 627.5 mg GAE/day, which reasonably agrees with global reports on adults. The prospective Nutrinet-Santé French Cohort study [82] and a Greek retrospective study [83] used FC and reported polyphenol intake in adults of 2083 and 1905 mg of mg GAE/day, respectively, which doubles the polyphenol intake of our cohort. The Nutrinet-Santé French Cohort study also reported a polyphenol intake of 999 mg/day based on the sum of individual compounds by chromatography and compared the association with risk of CVD and all-cause mortality; however, it only showed an inverse association with the total intake of polyphenols estimated by Folin-Ciocalteau; while the total polyphenol intake estimated by FC in healthy Greek adults also show that an increased polyphenol intake was associated with decreased waist-to-hip circumference [83]. Other studies worldwide of phenolic compound intake in adults using the *Phenol explorer* database, by estimation with chromatography data, reported inverse associations with cardiometabolic risk. For example, in Europe, polyphenol intakes ranging between 300 and 1756 mg/day showed positive effects on diabetes, BMI, hypertension, dyslipidemia, metabolic syndrome, and CVD risk [84–89]; in Asians, 220–1422 mg of polyphenols/day associated with improved insulin sensitivity and metabolic syndrome [90] while in South America had been reported a polyphenol intake range of 100–377 mg/day with a positive impact on hypertension and cardiovascular risk [91–93].

4.3. Dietary antioxidants are negatively associated with 2,3-dinor oxylipin metabolites in Colombian adults

We found that a high polyphenol intake from vegetables, legumes, beverages such as coffee and chocolate, as well as vitamins C and E, were associated with lower levels of excreted dinor metabolites of oxylipins. Similarly, it has also been reported that high intakes of fruit, vegetables, vitamin C and carotenes were related to lower dinor-oxylipin concentrations but not to F_2-IsoP concentrations in unadjusted models. None of these associations remained significant after adjustment for potential confounding factors [20]. An inverse association between urinary F_2-IsoPs and intakes of total fruit, vegetables, vitamin C, and β-carotene in adolescents aged 13–17 has been reported [94]. 2,3-dinor-oxylipin levels were modulated after intervention with dietary antioxidants. For example, the chronic intervention with a coffee beverage in healthy adults reduced 2,3-dinor-15-F_{2t}-IsoP [31], while the acute intake of red wine reduced 2,3-dinor-5,6-dihydro-15-F_{2t}-IsoP and the pro-inflammatory prostaglandin metabolite 2,3-dinor-11-β-$PGF_{2\alpha}$. This regulation was not observed in both cases for the parent compounds 15-F_{2t}-IsoP or 11β-$PGF_{2\alpha}$ [32]. On the other hand, since the food diversity is recognized as an important component of a good diet quality and is accompanied by positive health outcomes [95,96], we evaluated the alpha diversity for different foods or food groups as dietary sources of polyphenolic compounds. The alpha diversity index of diet did not explain changes in 2,3-dinor-oxylipins for each BMI category, indicating that the quantities of polyphenol consumed but not the diversity of food sources is key for reducing these oxidative stress biomarkers.

Even though dietary polyphenols have been linked to a reduced risk of chronic disease in humans, there is no recommended dietary allowance as there are for many other nutrients. For this reason, the current recommendation is based on the number of foods with high polyphenol content [97]. In addition, improvements in blood pressure, lipid profile, insulin sensitivity, and endothelial function, and the alleviation of systemic inflammation, thrombosis, and the decrease in urinary IsoPs [21,80,98,99] have been reported for flavanols and flavonols, two of the phenolic compound subgroups with the highest consumption in this study (*e.g.*, by intake of cocoa, fruits, and vegetables). Furthermore, consumption of phenolic acids, *e.g.*, hydroxycinnamic acids from coffee, have been proven to increase the plasmatic antioxidant capacity and reduce oxylipin levels [31,100], reducing the risk of developing type-2 diabetes [101].

The strengths of this work include the comprehensive assessments of body composition, cardiometabolic abnormalities (e.g., obesity, body fat, and insulin resistance), and oxidative stress markers. However, our study is not without limitations. Our findings are based on observational

data that cannot provide causal inference. Nevertheless, models were adjusted by the potential confounders: age range, participants' city of origin, and sex at birth. In addition, dietary data rely on self-reported data; thus, misreporting of food intake may distort relationships between diet and objectively measured outcomes. Finally, we did not estimate de intake of bioactive forms of vitamin E, which have been demonstrated to protect PUFAs from oxidation [102] and impact the intestinal permeability and the gut microbiota [103].

5. Conclusions

In conclusion, data from this cohort of Colombian adults showed that high dinor-oxylipin metabolites highly correlated with obesity, and were consistently related to BMI and cardiometabolic health status independently of socio-demographic parameters. In addition, we reported the total polyphenol intake in Colombian adults for the first time and observed that diets with higher polyphenols intakes are associated with lower excretion of dinor-oxylipins, suggesting that increasing the intake of dietary antioxidants might provide benefits in reducing markers of oxidative stress. However, more studies are needed to understand the implications of reducing the production of oxylipins in nutritional interventions with polyphenols and physiological-aging associated chronic diseases.

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Author contributions

Study conception and design: Juan S. Escobar, Ángel Gil-Izquierdo, Katalina Muñoz-Durango and Jelver A. Sierra. Methodology, Ángel Gil-Izquierdo, Thierry Durand, Sonia Medina, Camille Oger, Thierry Durand, Jean-Marie Galano and Katalina Muñoz-Durango. Food intake analysis: Vanessa Corrales-Agudelo, Laura Salazar-Jaramillo, Jelver A. Sierra and Óscar J. Lara-Guzmán. Processing of samples and analyses of urinary oxylipins Diego A. Rivera and Sonia Medina. Formal analysis, Óscar J. Lara-Guzmán and Jelver A. Sierra. Writing—original draft preparation, Óscar J. Lara-Guzmán, Juan S. Escobar, Katalina Muñoz-Durango and Jelver A. Sierra. Writing—review and editing, Ángel Gil-Izquierdo, Sonia Medina, Camille Oger, Thierry Durand, and Jean-Marie Galano. Project supervision and administration, Katalina Muñoz-Durango and Jelver A. Sierra. Funding acquisition, Jelver A. Sierra. All authors read and approved the final version of the manuscript.

Author disclosure statement

While engaged in this study, Óscar J. Lara-Guzmán., Diego A. Rivera, Vanessa Corrales-Agudelo, Laura Salazar-Jaramillo, Juan S. Escobar, Katalina Muñoz-Durango and Jelver A. Sierra were employed by a research center belonging to a food company (Grupo Empresarial Nutresa). Ángel Gil-Izquierdo, Sonia Medina, Camille Oger, Thierry Durand, and Jean-Marie Galano had no conflict of interest.

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Appendix A. Supplementary data

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