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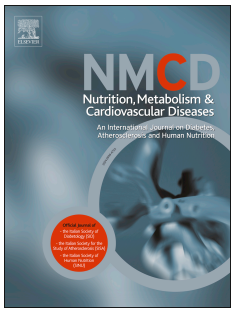

Associations between anthropometric indicators in early life and low-grade inflammation, insulin resistance and lipid profile in adolescence

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development of a series of cardiometabolic diseases [1], which ~~largely remain asymptomatic during youth. These risks~~ usually manifest themselves in adulthood yet may originate during infancy [2-4]. ~~, as~~ Higher levels of lipids and lipoproteins have been described in overweight or obese children and adolescents [5, 6], ~~. Previous data from the Bogalusa study [4] have shown that elevations of concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL), and triglycerides, as well as and lower concentrations of high-density lipoprotein cholesterol (HDL) in childhood~~, which have been significantly associated with later high prevalence ~~(≈70%)~~ of atherosclerotic lesions in young adulthood [4].

In addition to an unfavourable lipid profile [5], overweight and obese individuals usually ~~also~~ present impaired glucose metabolism [7] and higher levels of several inflammatory biomarkers [8] ~~than their normal weight counterparts~~. Although C-reactive protein (CRP) has been the most used marker of inflammation, other biomarkers such as the acute phase reactants fibrinogen and complement factors C3 (C3) and C4 (C4), cytokines as interleukin-6 (IL-6), adipokines as leptin and adiponectin, and non-specific systemic markers of inflammation such as erythrocyte sedimentation rate (ESR) and white blood cells (WBC), have been explored ~~as useful for assessing~~ to assess risk of cardiovascular diseases, and to more accurately characterize the low-grade inflammatory profile of an individual [9-11], ~~Further, these measures are valid in adults~~ also valid in children and adolescents [12-16].

grade inflammation, which seems to be a key component in the pathogenesis of insulin resistance, the best predictor of type 2 diabetes [10, 17], ~~. Insulin resistance is the best predictor of diabetes, and~~ which occurs several years before the onset of the disease [7], making early identification important for prevention and management of the disease. ~~The homeostatic model assessment of insulin resistance (HOMA-IR) [18] is used as a valid measure of insulin resistance in non-diabetic children and adolescents [19], and has been reported as being substantially increased in overweight/obese children compared with normal-weight [20].~~

Birth weight (BW) is commonly used as a proxy measure of intrauterine development, and both low and high BW have been explored as determinants for impaired future health related-outcomes, such as type 2 diabetes and the metabolic syndrome later in life [18, 19]. However, others studies suggest that growth patterns in infancy and childhood might have a more pronounced effect than with BW *per se* [20, 21].

Since there is strong evidence that overweight and obesity tracks from early childhood to adolescence and adulthood [22], and that body mass index (BMI) is the most commonly used anthropometric index to define weight status in large samples [23, 24], its close monitoring throughout early life could represent not only a procedure to identify an overweight condition, but also an easy, but useful way to prevent and detect a series of health-related parameters/diseases associated with that condition~~, such as diabetes and cardiovascular diseases~~.

knowledge, ~~those relations are not yet clear in the long-term. Further,~~ it is not well established ~~that~~ if a persistently high BMI during infancy and childhood can predict an unfavourable state of biomarkers in adolescence. Thus, the main objective of this study was to assess the associations between early life anthropometric indicators such as birth weight or BMI at several time points of age (6,12 and 18 months, and at 2, 3, 4, 5 and 6 years), with indicators of inflammation, insulin resistance and lipid profile ~~during~~ in adolescence.

METHODS

Study population, design and sampling

This study is based on data from the Longitudinal Analysis of Biomarkers and Environmental Determinants of Physical Activity Study (LabMed Physical Activity Study), a 3-year longitudinal cohort study started during the fall of 2011, and carried out in five schools in the north of Portugal, with the main aim of assessing the independent and combined associations of dietary intake and fitness levels on blood pressure levels of adolescents. The study protocol and procedures are described in detail elsewhere [25]. Briefly, from an initial sample of 1229 apparently healthy adolescents (12–18 years old) that agreed to participate in that study, 534 provided blood samples. Subsequently, 5 individuals were excluded due to high-sensitivity CRP values >10 mg/L, which were indicative of acute inflammation or illness [26]. Child Health Booklets records of 539 participants were also available for complete early life data

This study was conducted in accordance to the Helsinki Declaration for Human Studies of 1975, as revised in 2013 [27], and approved by the Portuguese Data Protection Authority (#1112434/2011) and the Portuguese Ministry of Science and Education (0246200001/2011). All participants were previously informed of this study aims, and written informed consent was obtained from participating adolescents and their parents/tutors.

Early life data collection

Information on birth and postnatal periods was retrospectively collected from individual child health booklets records provided by the participants, called *Boletim de Saúde Infantil e Juvenil*. Anthropometric data regarding weight, length and height measurements, available from birth up until the age of 6 years, which were performed and recorded on the health booklets by the paediatricians during regular appointments with the participants, were extracted for the present analysis. Individuals were considered born with low BW (<2500g), adequate BW (2500–4000g), or high BW (>4000g), according WHO references [28]. BMI was calculated as weight divided by length squared (kg/m^2) from birth up until the age of 2 years, and from 2 years onward calculated as usual (weight divided by squared height [kg/m^2]). At the ages of 6, 12 and 18 months, and at 2, 3, 4, 5 and 6 years, the participants were classified according the BMI-for-age percentiles sex specific references provided by the World health Organization [29, 30], in one of two possible categories: normal weight (including underweight individuals) or overweight (including obese participants).

Anthropometric measures such as weight and height were collected according standardized procedures [31] and described elsewhere [25]. BMI was then calculated as previously described (kg/m^2), and all the adolescents were classified in two categories, normal weight (including underweight) or overweight (including obese), using the age and sex-specific BMI-for-age percentiles cut-off values proposed by the World Health Organization [30].

Pubertal stage assessment

Pubertal stages of sexual maturation (A - breast development in girls; genital development in boys; and B – pubic hair development, for both sexes) were self-assessed by the participants according to the classification by Tanner [32], in a private place, and then communicated in a closed envelope to a researcher of the same sex, with stage 1 being pre-pubertal and 5 being adult maturation. Given the low number of participants at Tanner stage 1, these were integrated with Tanner stage 2 and formed the pre-/early pubertal group.

Biochemical assessment

Blood samples were collected by venepuncture from the antecubital vein from each participant early in the morning, following a 10-hour overnight fast. The samples were stored in sterile blood collection tubes in refrigerated conditions (4° to 8°C) for no longer than 4 hours, during the morning of collection, and then delivered to an analytical laboratory for testing for a series of inflammatory markers, lipid profile (total cholesterol and fractions, triglycerides), and glucose and insulin determinations, according to standardized procedures, as follows: (i) high-sensitivity CRP, latex enhanced

adiponectin and leptin, ELISA (Plate Reader); (iv) complement factor C3 and complement factor C4, PEG enhanced immunoturbidimetric assay (Siemens ADVIA 1800, Erlangen, Germany); (v) ESR, Westergren method (Starrsed, RR Mechanotronics, Netherlands); (vi) IL-6, Chemiluminescence immunoassay (Siemens Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA); (vii) WBC, Cytometry (Siemens Advia 2120i); (viii) Glucose, Hexokinase method (Siemens Advia 1600/1800 Erlangen, Germany); (ix) Insulin, Chemiluminescence immunoassay (Siemens ACS Centaur System, Erlangen, Germany); (x) TC, HDL, LDL and triglycerides were measured by standard enzymatic methods (Siemens Advia 1600/1800, Erlangen, Germany). CRP, C3, C4, IL-6, adiponectin, leptin, glucose, insulin, TC, HDL, LDL and triglycerides were determined in serum, ESR and WBC were determined in whole blood, and fibrinogen was determined in plasma.

The homeostatic model assessment of insulin resistance (HOMA-IR) [as the product of fasting insulin (μIU/ml) and fasting glucose (mmol/l) divided by the constant 22.5] [33] was used as a surrogate measure of insulin resistance, and has been used as a valid measure in non-diabetic children and adolescents [34], reported as being substantially increased in overweight/obese children compared with normal-weight [35]. The ratio of TC to HDL (TC/HDL) was calculated, and used in the analyses as an index of an atherogenic lipid profile, as some studies have suggested that it provides a useful summary of the joint contribution of TC and HDL to cardiovascular disease risk [36-38].

Socioeconomic Status

regarding information on vehicles, home, lifestyle and access to technology, with a range of scores from 0 to 9 points, that allows adolescents to indirectly report their family income, with the highest score corresponding to the highest socioeconomic level.

KIDMED index

The KIDMED index [40] (Mediterranean Diet Quality Index for children and adolescents) was used to assess the degree of adherence to the Mediterranean diet, considered a healthy dietary model and associated to a lower occurrence of cardiometabolic diseases [41] and certain cancer types [42]. This index is based on a 16 questions self-administered, which sustain principles of Mediterranean dietary patterns as well as those that undermine it. Questions indicating a negative connotation with respect to the Mediterranean diet were assigned a value of -1 and those with a positive aspect +1. The sum of the values ranges from 0 to 12, where a higher index means good adherence to the Mediterranean diet.

Statistical analyses

Descriptive statistics are presented as means and standard deviations. Two-sided Student's t-test was used to compare groups for continuous variables.

As no marker alone seems to perfectly characterize the inflammatory profile of an individual, several studies in paediatric populations have been using a combined score of inflammatory biomarkers, since this approach seems to provide a more comprehensive assessment and characterization of the

dietary pattern (KIDMED index) and socioeconomic status, were used as a preliminary analysis to examine the associations between each inflammatory biomarker with BW and BMI at each age point during childhood (Supplemental Table 1). Significant correlations ($p \leq 0.05$) served as the criteria used to select 6 inflammatory biomarkers (C3, C4, CRP, ESR, fibrinogen, leptin) for the construction of a continuous inflammatory score. For each biomarker, a z-score was computed by sex, age and pubertal status, and all the z-scores of the individual factors were then summed to create a cluster of inflammatory biomarkers. A higher score is indicative of a worse inflammatory profile.

Linear regression analyses adjusted for age, pubertal stage, BMI, BF%, socioeconomic status and KIDMED index were performed to determine the associations between the clustered inflammatory biomarkers score, HOMA-IR and TC/HDL (as dependent variables), with BW and BMI at the ages of 6, 12 and 18 months, and at 2, 3, 4, 5 and 6 years of age (as predictor variables). Unstandardized regression coefficients were used to express the beta in the linear regression analyses, and the coefficient of determination was used to assess the variance explained in the model.

Analysis of Covariance with Bonferroni post-hoc multiple comparison tests were used to assess if children that were normal weight and overweight/obese at each time point of age analysed, presented differences in inflammatory, insulin resistance and lipid profiles during adolescence. Covariates included were age, pubertal stage, BMI, BF%, socioeconomic status and KIDMED index.

analyses did not yield different results, we included all the 415 participants in the final analyses.

Data were analysed using the Statistical Package for Social Sciences version 24.0 (SPSS, IBM Corp., NY, USA). A *p*-value of ≤0.05 was considered to denote statistical significance.

RESULTS

Tables 1 and 2 presents the descriptive characteristics of the participants at early life and adolescence periods. Boys were taller and heavier than girls, and presented significantly higher values of BW, birth length, and BMI at 6, 12 and 18 months of age ($p \leq 0.05$ for all). BF%, adiponectin, ESR, fibrinogen, leptin, insulin, HOMA-IR, TC, LDL, triglycerides and HDL values were significantly higher in girls, while fasting glucose and TC/HDL were significantly higher in boys ($p \leq 0.05$ for all).

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226 **Table 1.** Characteristics of the Participants at Early Life and Adolescence Periods

	All (*n* = 415)	**Girls (*n* = 220)**	**Boys (*n* = 195)**
Variables	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	14.1 (1.6)	14.1 (1.7)	14.0 (1.6)
Height (cm)	159.2 (9.2)	157.4 (6.7)	161.4 (10.9) **
Weight (kg)	54.5 (12.7)	52.9 (10.9)	56.3 (14.3) *
BMI (kg/m^2)	21.3 (3.8)	21.3 (3.9)	21.3 (3.8)
NW (n; %)	278; 67%	156; 70.9%	122; 62.6%
OW (n; %)	137; 33%	64; 29.1%	73; 37.4%
BF (%)	21.1 (8.0)	25.3 (6.9)	16.5 (6.5) **
Birth weight (g)	3 277 (492)	3 190 (490)	3 377 (476) **
Low (n; %)	27; 6.5%	19; 8.6%	8; 4.1%
Normal (n; %)	366; 88.2%	192; 87.3%	174; 89.2%
High (n; %)	22; 5.3%	9; 4.1%	13; 6.7%
Birth length (cm)	49.1 (2.2)	48.6 (2.2)	49.7 (2.0) **
BMI at 6 months (kg/m^2)	17.4 (1.5)	17.1 (1.4)	17.8 (1.6) **
BMI at 12 months (kg/m^2)	17.7 (1.5)	17.4 (1.4)	18.1 (1.6) **
BMI at 18 months (kg/m^2)	17.2 (1.4)	17.0 (1.4)	17.5 (1.5) *
BMI at 2 years (kg/m^2)	16.8 (1.5)	16.7 (1.4)	17.0 (1.6)
BMI at 3 years (kg/m^2)	16.6 (1.7)	16.4 (1.8)	16.7 (1.6)
BMI at 4 years (kg/m^2)	16.6 (1.9)	16.5 (1.9)	16.7 (1.9)
BMI at 5 years (kg/m^2)	16.9 (2.2)	16.8 (2.3)	16.9 (2.2)
BMI at 6 years (kg/m^2)	17.2 (2.6)	17.0 (2.5)	17.5 (2.7)
Pubertal stage A (%)			
Stage ≤ II	8.4	3.6	13.8
Stage III	34.2	31.4	37.4
Stage IV	43.9	52.3	34.4
Stage V	13.5	12.7	14.4
Pubertal stage B (%)			
Stage ≤ II	7.7	2.7	13.3
Stage III	23.9	25.5	22.1
Stage IV	46.7	44.1	49.7
Stage V	21.7	27.7	14.9
KIDMED index	7.2 (2.1)	7.3 (2.0)	7.0 (2.1)

development in girls, genital development in boys, and B = public hair development, for both sexes).

Table 2. Biochemical Characteristics of the Adolescents

	All (*n* = 415)	Girls (*n* = 220)	Boys (*n* = 195)
Variables	Mean (SD)	Mean (SD)	Mean (SD)
Adiponectin (mg/L)	12.0 (5.6)	13.2 (6.0)	10.7 (4.7) **
C-reactive protein (mg/L)	0.9 (1.7)	0.7 (1.6)	1.0 (1.8)
Complement C3 (mg/dL)	118.4 (16.1)	118.7 (16.2)	118.0 (16.1)
Complement C4 (mg/dL)	21.1 (6.4)	21.4 (6.6)	20.9 (6.2)
Erythrocyte sedimentation rate (mm/h)	6.5 (6.6)	7.6 (6.9)	5.3 (6.0) **
Fibrinogen (mg/dL)	265.4 (43.3)	269.5 (43.1)	260.8 (43.2) *
IL-6 (ng/L)	3.8 (4.8)	3.7 (4.3)	3.8 (5.3)
Leptin (ng/ml)	4.3 (5.0)	6.2 (5.6)	2.1 (3.1) **
White blood cells (10^9/L)	7.1 (1.7)	7.3 (1.6)	7.0 (1.7)
Fasting glucose (mmol/L)	4.9 (0.4)	4.8 (0.4)	5.0 (0.4) *
Insulin (μU/ml)	14.8 (7.56)	16.04 (7.42)	13.4 (7.5) **
HOMA-IR	3.3 (1.8)	3.5 (1.8)	3.0 (1.7) *
Total cholesterol (mg/dL)	154.1 (28.1)	159.4 (28.6)	148.3 (26.4) **
LDL (mg/dL)	85.1 (23.6)	87.8 (24.3)	82.1 (22.5) *
HDL (mg/dL)	54.9 (12.1)	57.9 (12.3)	51.5 (10.8) **
Triglycerides (mg/dL)	67.9 (32.2)	70.9 (32.6)	64.6 (31.5) *
TC/HDL ratio (mg/dL)	2.9 (0.6)	2.8 (0.6)	3.0 (0.6) *

$^{*}p \leq 0.05$; $^{**}p < 0.001$ for sex comparisons (two-tailed *t*-test)

Abbreviations: HOMA-IR, Homeostatic model assessment of insulin resistance index; IL-6, Interleukin 6; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SD, standard deviation; TC/HDL ratio, total cholesterol/high-density lipoprotein cholesterol ratio

Regression analyses in Tables 3 and 4 showed that, for both sexes, from the age of 2 years onwards BMI was significantly and positively associated with the inflammatory score and HOMA-IR in adolescence, after adjustments for age, pubertal stage, BMI, BF%, socioeconomic status and KIDMED index.

associated with the inflammatory score, HOMA-IR and TC/HDL.

Table 3. Linear Regression Coefficients, Significance Values and Coefficients of Determination, Examining the Associations Between Birth Weight and BMI at Several Time Points of Age, and Inflammatory Score, HOMA-IR and TC/HDL Ratio of Adolescent Girls, Adjusted for Age, Pubertal Stage, BMI, BF%, Socioeconomic Status and KIDMED Index

		Dependent Variables		
		Inflammatory Score	**HOMA–IR**	**TC/HDL**
Birth weight	B (*p* value)	0.00 (0.71)	0.00 (0.10)	-4.90 (0.95)
	r^2	-0.00	0.10	0.05
BMI at 6 months	B (*p* value)	0.51 (0.28)	0.09 (0.35)	-0.02 (0.58)
	r^2	0.03	0.07	0.06
BMI at 12 months	B (*p* value)	0.51 (0.48)	0.09 (0.42)	-0.01 (0.71)
	r^2	0.02	0.08	0.00
BMI at 18 months	B (*p* value)	0.56 (0.15)	0.14 (0.12)	-0.01 (0.78)
	r^2	0.02	0.09	0.05
BMI at 2 years	B (*p* value)	**0.82 (<0.01)**	**0.21 (0.02)**	0.05 (0.12)
	r^2	**0.06**	**0.12**	0.02
BMI at 3 years	B (*p* value)	**0.79 (<0.01)**	**0.23 (<0.01)**	0.07 (0.09)
	r^2	**0.09**	**0.18**	0.07
BMI at 4 years	B (*p* value)	**0.93 (<0.01)**	**0.21 (<0.01)**	0.03 (0.34)
	r^2	**0.15**	**0.16**	0.00
BMI at 5 years	B (*p* value)	**0.92 (<0.01)**	**0.35 (<0.01)**	**0.07 (<0.01)**
	r^2	**0.22**	**0.23**	**0.13**
BMI at 6 years	B (*p* value)	**0.77 (<0.01)**	**0.17 (<0.01)**	**0.04 (0.03)**
	r^2	**0.19**	**0.14**	**0.06**
Current BMI	B (*p* value)	**0.51 (<0.01)**	**0.15 (<0.01)**	**0.04 (<0.01)**
	r^2	**0.22**	**0.15**	**0.11**

Abbreviations: BMI, body mass index; B, linear regression coefficient; *p*, significance value; r^2, coefficient of determination; HOMA–IR, homeostatic model assessment of insulin resistance index; TC/HDL, total cholesterol to high-density lipoprotein cholesterol ratio.

Table 4. Linear Regression Coefficients, Significance Values and Coefficients of Determination, Examining the Associations Between Birth Weight and BMI at Several Time Points of Age, and Inflammatory Score, HOMA-IR and TC/HDL Ratio of adolescent boys, Adjusted for Age, Pubertal Stage, BMI, BF%, Socioeconomic Status and KIDMED Index

		Dependent Variables		
		Inflammatory Score	**HOMA–IR**	**TC/HDL**
Birth weight	B (*p* value)	1.37 (0.98)	-3.73 (0.89)	-6.87 (0.47)
	r^2	0.00	0.01	0.00
BMI at 6 months	B (*p* value)	-0.19 (0.36)	0.02 (0.82)	0.02 (0.45)
	r^2	0.06	0.03	0.01
BMI at 12 months	B (*p* value)	-0.01 (0.96)	0.09 (0.44)	0.02 (0.58)
	r^2	0.12	0.02	0.02
BMI at 18 months	B (*p* value)	-0.02 (0.95)	0.19 (0.05)	-0.01 (0.78)
	r^2	0.06	0.03	0.00
BMI at 2 years	B (*p* value)	**0.04 (0.01)**	**0.16 (0.02)**	0.03 (0.31)
	r^2	**0.03**	**0.07**	0.02
BMI at 3 years	B (*p* value)	**0.15 (<0.05)**	**0.20 (0.03)**	0.03 (0.38)
	r^2	**0.05**	**0.04**	0.14
BMI at 4 years	B (*p* value)	**0.33 (<0.01)**	**0.27 (<0.01)**	0.05 (0.10)
	r^2	**0.11**	**0.07**	0.03
BMI at 5 years	B (*p* value)	**0.29 (<0.01)**	**0.23 (<0.01)**	**0.04 (<0.01)**
	r^2	**0.11**	**0.08**	**0.03**
BMI at 6 years	B (*p* value)	**0.36 (0.02)**	**0.32 (<0.01)**	**0.05 (<0.01)**
	r^2	**0.10**	**0.25**	**0.03**
Current BMI	B (*p* value)	**0.44 (<0.01)**	**0.23 (<0.01)**	**0.04 (<0.01)**
	r^2	**0.17**	**0.24**	**0.07**

Abbreviations: BMI, body mass index; B, linear regression coefficient; *p*, significance value; r^2, coefficient of determination; HOMA–IR, homeostatic model assessment of insulin resistance index; TC/HDL, total cholesterol to high-density lipoprotein cholesterol ratio.

ANCOVA adjusted for age, pubertal stage, BMI, BF%, socioeconomic status and KIDMED index confirmed the results of the linear regressions, as

inflammatory score and HOMA-IR later in adolescence ($p \leq 0.05$). From the age of 5, those who were overweight also presented a higher TC/HDL ratio. In adolescence, obese individuals also had higher inflammatory score, HOMA-IR and TC/HDL ratio than their normal weight counterparts.

Table 5. Analyses of Covariance of Values of the Inflammatory Score, HOMA-IR and TC/HDL Ratio of Adolescent Girls, Accordingly Their Birth Weight Category and BMI Status at Several Time Points of Age, Adjusted for Age, Pubertal Stage, BMI, BF%, Socioeconomic Status and KIDMED Index

		Inflammatory Score		HOMA–IR		TC/HDL	
		Mean (SE)		Mean (SE)		Mean (SE)	
Birth weight	LOW (8.6%)	-0.49 (0.97)		3.53 (0.39)		2.82 (0.13)	
	NORMAL (87.3%)	0.11 (0.31)		3.46 (0.12)		2.84 (0.04)	
	HIGH (4.1%)	-1.28 (1.43)		4.53 (0.57)		2.73 (0.19)	
BMI at 6 months	NW (85.4%)	-0.15 (0.34)		3.41 (0.14)		2.82 (0.04)	
	OW (14.6%)	0.86 (0.83)		3.78 (0.34)		2.81 (0.11)	
BMI at 12 months	NW (68.7%)	-0.19 (0.44)		3.69 (0.20)		2.83 (0.06)	
	OW (31.3%)	0.42 (0.65)		3.63 (0.29)		2.77 (0.09)	
BMI at 18 months	NW (61.1%)	-0.32 (0.40)		3.34 (0.16)		2.82 (0.06)	
	OW (38.9%)	0.50 (0.50)		3.78 (0.20)		2.80 (0.07)	
BMI at 2 years	NW (55.9%)	**-0.85 (0.44)**	**	**3.20 (0.16)**	*	2.73 (0.06)	
	OW (44.1%)	**1.06 (0.49)**		**3.78 (0.18)**		2.89 (0.07)	
BMI at 3 years	NW (63.0%)	**-0.81 (0.41)**	**	**3.14 (0.16)**	**	2.78 (0.06)	
	OW (37.0%)	**1.39 (0.54)**		**3.92 (0.21)**		2.92 (0.07)	
BMI at 4 years	NW (63.6%)	**-1.05 (0.43)**	***	**3.39 (0.18)**	*	2.80 (0.06)	
	OW (36.4%)	**1.87 (0.58)**		**4.03 (0.24)**		2.90 (0.08)	
BMI at 5 years	NW (61.8%)	**-1.12 (0.46)**	***	**3.25 (0.20)**	***	**2.72 (0.06)**	**
	OW (38.2%)	**1.79 (0.58)**		**4.41 (0.25)**		**3.06 (0.08)**	
BMI at 6 years	NW (56.4%)	**-1.17 (0.48)**	***	**3.30 (0.20)**	*	**2.74 (0.06)**	*
	OW (43.6%)	**1.49 (0.54)**		**3.93 (0.23)**		**2.93 (0.07)**	
Current BMI	NW (71.5%)	**-1.05 (0.28)**	***	**3.19 (0.12)**	***	**2.77 (0.04)**	**
	OW (28.5%)	**2.63 (0.45)**		**4.34 (0.20)**		**3.01 (0.07)**	

*$p \leq 0.05$; **$p < 0.01$; ***$p < 0.001$

Abbreviations: BMI, body mass index; HOMA–IR, homeostatic model assessment of insulin resistance index; TC/HDL, total cholesterol to high-density lipoprotein cholesterol ratio. NW, normal weight; OW, overweight; SEM, standard error of the mean.

Table 6. Analyses of Covariance of Values of the Inflammatory Score, HOMA-IR and TC/HDL Ratio of Adolescent Boys, Accordingly Their Birth Weight Category and BMI Status at Several Time Points of Age, Adjusted for Age, Pubertal Stage, BMI, BF%, Socioeconomic Status and KIDMED Index

		Inflammatory Score		HOMA–IR		TC/HDL	
		Mean (SE)		Mean (SE)		Mean (SE)	
Birth weight	LOW (4.1%)	-0.28 (0.82)		3.30 (0.33)		2.91 (0.12)	
	NORMAL (89.2%)	0.10 (0.22)		3.25 (0.09)		2.90 (0.03)	
	HIGH (6.7%)	-1.37 (0.91)		3.36 (0.37)		2.73 (0.13)	
BMI at 6 months	NW (75.3%)	-0.04 (0.26)		3.20 (0.11)		2.87 (0.04)	
	OW (24.7%)	0.17 (0.54)		3.56 (0.23)		2.94 (0.08)	
BMI at 12 months	NW (54.9%)	-0.12 (0.33)		3.28 (0.15)		2.88 (0.05)	
	OW (45.1%)	0.20 (0.43)		3.50 (0.19)		2.93 (0.06)	
BMI at 18 months	NW (55.8%)	-0.11 (0.30)		3.13 (0.12)		2.90 (0.04)	
	OW (44.2%)	0.16 (0.35)		3.48 (0.15)		2.87 (0.05)	
BMI at 2 years	NW (58.8%)	**-0.57 (0.32)**	**	**3.03 (0.12)**	*	2.85 (0.05)	
	OW (41.2%)	**0.76 (0.36)**		**3.47 (0.14)**		2.93 (0.05)	
BMI at 3 years	NW (64.4%)	**-0.46 (0.30)**	*	**2.96 (0.12)**	**	2.87 (0.04)	
	OW (35.6%)	**0.81 (0.40)**		**3.63 (0.16)**		2.98 (0.06)	
BMI at 4 years	NW (60.5%)	**-0.65 (0.31)**	**	**3.02 (0.14)**	**	2.89 (0.05)	
	OW (39.5%)	**1.07 (0.41)**		**3.81 (0.18)**		2.97 (0.06)	
BMI at 5 years	NW (54.4%)	**-0.82 (0.34)**	***	**2.91 (0.14)**	***	**2.83 (0.05)**	*
	OW (45.6%)	**1.15 (0.40)**		**3.86 (0.17)**		**3.00 (0.06)**	
BMI at 6 years	NW (45.0%)	**-0.96 (0.38)**	***	**2.94 (0.15)**	***	**2.85 (0.05)**	*
	OW (55.0%)	**1.00 (0.38)**		**3.75 (0.16)**		**3.02 (0.06)**	
Current BMI	NW (67.6%)	**-1.08 (0.20)**	***	**2.86 (0.09)**	***	**2.81 (0.03)**	***
	OW (32.4%)	**2.48 (0.31)**		**4.09 (0.13)**		**3.08 (0.05)**	

$^{*}p \leq 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

Abbreviations: BMI, body mass index; HOMA–IR, homeostatic model assessment of insulin resistance index; TC/HDL, total cholesterol to high-density lipoprotein cholesterol ratio. NW, normal weight; OW, overweight; SEM, standard error of the mean.

DISCUSSION

differences in those outcomes regardless of BW; (ii) The main findings of this study showed that from 2 years onwards, overweight was positively associated with higher inflammatory scores and HOMA-IR in adolescence, ; (iii) and that positive associations between BMI and TC/HDL became statistically significant from the age of 5 years.

Regardless of BW status, we observed no differences in the levels of inflammatory scores, insulin resistance or unfavourable lipid profiles later in adolescence. Our results are in agreement agree with other reports [43-45], suggesting that BW is not as relevant as other anthropometric measures during childhood in the prediction of future cardiometabolic outcomes, and with previous studies with children and adolescents that have also reported no associations between BW and several inflammatory biomarkers [45-49]. However, the relatively small number of participants in the low BW category (27 participants) and in the high BW category (22 participants) advises some caution in inferring solid conclusions about these associations. For example, Labayen *et al.* [15] found mixed results, reporting associations between BW and some biomarkers such as (C3, C4 and fibrinogen), but not with CRP, as well as other studies suggesting that, at least low BW, may be associated with increased systemic inflammation during adolescence [50] and adulthood [51]. Instead of an individualized analysis of each biomarker, we used an inflammatory score, as it provided a more comprehensive characterization of the inflammatory state in adolescence [10, 12]. In addition to low-grade inflammation, our data concurs with other studies that have reported no

As suggested by Jeffery *et al.* [44], demographic changes may be one of the reasons for the apparent decrease in the importance of BW in the development of later cardiometabolic diseases [21]. It must be ~~taken into account~~ considered that the concept of foetal programming, and its pathophysiologic consequences later in life, emerged from the pioneer works of Barker *et al.* [54] and Hales *et al.* [55], which were conducted on populations born in the early 20th century, who were born and grew up in the pre–World War II period, but matured in another. Moreover, socioeconomic and health conditions were totally different from those of today.

According to World Health Organization reference values [28], 6.5% of the participants in this study had low BW (<2500g) and 5.3% high BW (>4000g). However, when the same participants were assessed during the adolescence period, one third of the sample was classified as being overweight or obese. This seems to support the need for a greater emphasis that should be given on the monitoring of BMI status and its development during infancy and childhood, even more so because overweight and obesity appear to track throughout life from early ages [22, 56]. In addition, it seems that the longer an individual is overweight during adolescence and adulthood, the more adverse their level of adipokines and inflammatory markers will be later in life [57].

Skinner *et al.* [58] showed that multiple inflammatory markers are strongly and positively associated with increasing weight status in children as young as age 3. Although in the present study we did not have inflammatory biomarkers data at those early ages, we observed that being overweight from

have shown that rapid weight gain throughout life (particularly after 2 years of age) was positively related with increased leptin concentrations during childhood [59], and with increased leptin and CRP levels in young adulthood in males and females [60]. We are not aware of other studies that have measured cardiometabolic outcomes during adolescence using BMI at various time points of age as predictor variable, as we did in the present study.

In a 9–year longitudinal study with children, Gardner *et al.* [43] reported that weight alone at 5 years of age presented little relation to BW, but closely predicted weight at 9 years of age. In addition, the authors composed a metabolic score based on insulin resistance, blood pressure, triglycerides, and TC/HDL ratio, and found that it was also poorly predicted by BW, but was associated with weight at 5 years, and even more at 9 years. Our results showed that children who were overweight from the age of 5 presented a higher TC/HDL ratio in adolescence. Another study [61] have also reported that the time period at around 5 years of age was a critical period for the development of overweight and obesity, as well as obesity-related factors, supporting the suggestion that a single measure of weight at 5 years of age could provide an indicator to future health for the individual [43].

Our data shows that, during adolescence, BMI maintained a positive association with inflammatory score, HOMA-IR and TC/HDL ratio. Given that the pro-inflammatory state seems to track from adolescence to adulthood [62], the findings of this report seem to be of interest, because they support and emphasize the potential value of an early screening for unhealthy BMI. A timely

ages [2, 20].

Our study is not without limitations. First, from the age of 6 years onwards, the routine appointments to the paediatrician become more irregular than in the first years of life, and consequently, anthropometric records were sparse, and due to the loss of data it was impossible to run analyses for later ages. Second, we have no information about the pregnancy, and the evolution of the pregnant (weight gain, maternal BMI, risk factors, e.g. smoking). However, we have information on the duration of the pregnancy, which allowed us to identify pre- or post-term babies. Last, the use of a single measure of each inflammatory biomarker may eventually not reflect a long-term pattern of that specific biomarker. Nevertheless, to somewhat overcome this limitation, we have analyzed several inflammatory biomarkers, which provided us with better global picture of the inflammatory status of the adolescents, and this constitutes one of the strengths of this study. Another strong point of this report is the direct extraction from the written records of data relative to birth and growth until the age of 6 years old, as we did not rely on parent reports.

In conclusion, our results suggest that the maintenance of a high BMI from very early ages was consistently associated with worse inflammatory and lipid profiles, and increased insulin resistance in adolescence. On the other hand, no associations were found between BW and the same analysed outcomes.

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several ages, and birth weight and inflammatory biomarkers.

	BW	CRP	FIBRIN	ESR	C3	C4	LEPTIN	ADIPO	IL-6	WBC
Birth weight	-	-0.05	-0.05	0.02	-0.07	-0.03	0.02	0.03	-0.06	-0.1
Birth length	**0,74*** **	-0.02	-0.05	0.00	-0.06	0.01	0.01	-0.02	-0.05	-0.08
BMI at 6 months	0,11	-0.02	0.03	0.00	0.01	-0.04	0.15	0.11	-0.02	-0.08
BMI at 12 months	0,03	-0.06	0.07	0.05	0.08	-0.02	0.09	0.08	-0.02	-0.00
BMI at 18 months	0,12	-0.01	0.05	0.04	0.05	0.03	**0.19*** **	0.06	-0.05	-0.06
BMI at 2 years	0,04	-0.01	0.09	**0.14***	**0.12***	0.09	**0.17****	0.06	0.00	-0.03
BMI at 3 years	-0,02	0.08	**0.11***	**0.12***	**0.15****	0.06	**0.32*****	-0.03	-0.11	-0.02
BMI at 4 years	-0.04	0.06	**0.17****	0.11	**0.14***	**0.12***	**0.44*****	-0.04	-0.05	-0.06
BMI at 5 years	-0,09	0.12	**0.22*****	**0.12***	**0.23*****	**0.17****	**0.49*****	-0.01	-0.09	-0.05
BMI at 6 years	-0.07	**0.18 ****	**0.22****	**0.13***	**0.29*****	**0.17****	**0.53*****	-0.09	-0.06	0.05
Current BMI	0,06	**0.19 *****	**0.26*****	**0.13****	**0.39*****	**0.20*****	**0.62*****	-0.18	0,05	0,09

$^{*}p \leq 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

Abbreviations: BMI, body mass index; BW, birth weight; CRP, C-reactive protein; FIBRIN, fibrinogen; ESR, erythrocyte sedimentation rate; C3, complement C3; C4, complement C4; ADIPO, adiponectin; IL-6, interleukin 6; WBC, white blood cells.

1. ~~Birth weight show no associations with any cardiometabolic outcome in adolescence;~~

2. Overweight at 2 years was associated with inflammation and HOMA-IR in adolescence;

3. Overweight at 5 years was associated with worse lipid profiles in adolescence;

4. A persistently high BMI during infancy and childhood is associated with an unfavourable state of biomarkers in adolescence;