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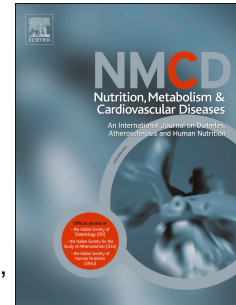
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Associations between anthropometric indicators in early life and low-grade inflammation, insulin resistance and lipid profile in adolescence

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KEYWORDS: Early life anthropometry, cardiometabolic biomarkers, overweight, adolescents

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

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

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

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

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

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

59

60 **METHODS**

61 **Study population, design and sampling**

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

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

82 **Early life data collection**

83 Information on birth and postnatal periods was retrospectively collected
84 from individual child health booklets records provided by the participants, called
85 *Boletim de Saúde Infantil e Juvenil*. Anthropometric data regarding weight,
86 length and height measurements, available from birth up until the age of 6
87 years, which were performed and recorded on the health booklets by the
88 paediatricians during regular appointments with the participants, were extracted
89 for the present analysis. Individuals were considered born with low BW
90 (<2500g), adequate BW (2500–4000g), or high BW (>4000g), according WHO
91 references [28]. BMI was calculated as weight divided by length squared
92 (kg/m^2) from birth up until the age of 2 years, and from 2 years onward
93 calculated as usual (weight divided by squared height [kg/m^2]). At the ages of 6,
94 12 and 18 months, and at 2, 3, 4, 5 and 6 years, the participants were classified
95 according the BMI-for-age percentiles sex specific references provided by the
96 World health Organization [29, 30], in one of two possible categories: normal
97 weight (including underweight individuals) or overweight (including obese
98 participants).

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

107 **Pubertal stage assessment**

108 Pubertal stages of sexual maturation (A - breast development in girls;
109 genital development in boys; and B – pubic hair development, for both sexes)
110 were self-assessed by the participants according to the classification by Tanner
111 [32], in a private place, and then communicated in a closed envelope to a
112 researcher of the same sex, with stage 1 being pre-pubertal and 5 being adult
113 maturation. Given the low number of participants at Tanner stage 1, these were
114 integrated with Tanner stage 2 and formed the pre-/early pubertal group.

115 **Biochemical assessment**

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

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

139 The homeostatic model assessment of insulin resistance (HOMA-IR) [as
140 the product of fasting insulin ($\mu\text{IU/ml}$) and fasting glucose (mmol/l) divided by
141 the constant 22.5] [33] was used as a surrogate measure of insulin resistance,
142 and has been used as a valid measure in non-diabetic children and adolescents
143 [34], reported as being substantially increased in overweight/obese children
144 compared with normal-weight [35]. The ratio of TC to HDL (TC/HDL) was
145 calculated, and used in the analyses as an index of an atherogenic lipid profile,
146 as some studies have suggested that it provides a useful summary of the joint
147 contribution of TC and HDL to cardiovascular disease risk [36-38].

148 **Socioeconomic Status**

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

155 **KIDMED index**

156 The KIDMED index [40] (Mediterranean Diet Quality Index for children
157 and adolescents) was used to assess the degree of adherence to the
158 Mediterranean diet, considered a healthy dietary model and associated to a
159 lower occurrence of cardiometabolic diseases [41] and certain cancer types
160 [42]. This index is based on a 16 questions self-administered, which sustain
161 principles of Mediterranean dietary patterns as well as those that undermine it.
162 Questions indicating a negative connotation with respect to the Mediterranean
163 diet were assigned a value of -1 and those with a positive aspect +1. The sum
164 of the values ranges from 0 to 12, where a higher index means good adherence
165 to the Mediterranean diet.

166 **Statistical analyses**

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

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

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

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

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

201 analyses did not yield different results, we included all the 415 participants in
202 the final analyses.
203 Data were analysed using the Statistical Package for Social Sciences
204 version 24.0 (SPSS, IBM Corp., NY, USA). A p -value of ≤ 0.05 was considered
205 to denote statistical significance.

206

207 **RESULTS**

208 Tables 1 and 2 presents the descriptive characteristics of the participants
209 at early life and adolescence periods. Boys were taller and heavier than girls,
210 and presented significantly higher values of BW, birth length, and BMI at 6, 12
211 and 18 months of age ($p \leq 0.05$ for all). BF%, adiponectin, ESR, fibrinogen,
212 leptin, insulin, HOMA-IR, TC, LDL, triglycerides and HDL values were
213 significantly higher in girls, while fasting glucose and TC/HDL were significantly
214 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

Variables	All (n = 415)	Girls (n = 220)	Boys (n = 195)
	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)

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Table 2. Biochemical Characteristics of the Adolescents

Variables	All (n = 415)	Girls (n = 220)	Boys (n = 195)
	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) *

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

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

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254 **Table 3.** Linear Regression Coefficients, Significance Values and Coefficients of Determination,
 255 Examining the Associations Between Birth Weight and BMI at Several Time Points of Age, and
 256 Inflammatory Score, HOMA-IR and TC/HDL Ratio of Adolescent Girls, Adjusted for Age,
 257 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

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

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269 **Table 4.** Linear Regression Coefficients, Significance Values and Coefficients of Determination,
 270 Examining the Associations Between Birth Weight and BMI at Several Time Points of Age, and
 271 Inflammatory Score, HOMA-IR and TC/HDL Ratio of adolescent boys, Adjusted for Age,
 272 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

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

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

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

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286 **Table 5.** Analyses of Covariance of Values of the Inflammatory Score, HOMA-IR and TC/HDL
 287 Ratio of Adolescent Girls, Accordingly Their Birth Weight Category and BMI Status at Several
 288 Time Points of Age, Adjusted for Age, Pubertal Stage, BMI, BF%, Socioeconomic Status and
 289 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) **

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

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

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DISCUSSION

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

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

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

350 According to World Health Organization reference values [28], 6.5% of
351 the participants in this study had low BW (<2500g) and 5.3% high BW
352 (>4000g). However, when the same participants were assessed during the
353 adolescence period, one third of the sample was classified as being overweight
354 or obese. This seems to support the need for a greater emphasis that should be
355 given on the monitoring of BMI status and its development during infancy and
356 childhood, even more so because overweight and obesity appear to track
357 throughout life from early ages [22, 56]. In addition, it seems that the longer an
358 individual is overweight during adolescence and adulthood, the more adverse
359 their level of adipokines and inflammatory markers will be later in life [57].

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

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

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

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

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

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

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425

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	BW	CRP	FIBRIN	ESR	C3	C4	LEPTIN	ADIPO	IL-6	WBC
Birth weight	1	-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

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

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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.

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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;

ACCEPTED MANUSCRIPT