

PEDIATRIC ORIGINAL ARTICLE

Developmental trajectories of adiposity from birth until early adulthood and association with cardiometabolic risk factors

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OBJECTIVE: To identify developmental trajectories of adiposity from birth until early adulthood, and to investigate how they relate with cardiometabolic risk factors at 21 years of age.

METHODS: Participants' weight and height measurements were obtained using the EPITeen cohort protocol at 13, 17 and 21 years of age, and extracted from child health books as recorded during health routine evaluations since birth. Blood pressure, triglycerides, cholesterol and insulin resistance (HOMA-IR) were assessed at 21 years. Trajectories were defined using 719 participants contributing 11 459 measurements. The individual growth curves were modelled using mixed-effects fractional polynomial, and the trajectories were estimated using normal mixture modelling for model-based clustering. Differences in cardiometabolic risk factors at 21 years according to adiposity trajectories were estimated through analysis of covariance (ANCOVA), and adjusted means are presented.

RESULTS: Two trajectories—'Average body mass index (BMI) growth' (80.7%) and 'Higher BMI growth' (19.3%)—were identified. Compared with those in 'Average BMI growth', 'Higher BMI growth' participants were more frequently delivered by caesarean section, mothers were younger and had higher BMI, and parental education was lower; and at 21 years showed higher adjusted mean systolic (111.6 vs 108.3 mm Hg, $P < 0.001$) and diastolic blood pressure (71.9 vs 68.4 mm Hg, $P < 0.001$), and lower high-density lipoprotein cholesterol (53.3 vs 57.0 mg dl⁻¹, $P = 0.001$). As there was a significant interaction between trajectories and sex, triglycerides and HOMA-IR were stratified by sex and we found significantly higher triglycerides, in males, and higher HOMA-IR in both sexes in 'Higher BMI growth' trajectory. All the differences were attenuated after adjustment for BMI at 21 years.

CONCLUSIONS: In this long-term follow-up, we were able to identify two adiposity trajectories, statistically related to the BMI and cardiometabolic profile in adulthood. Our results also suggest that the impact of the adiposity trajectory on cardiometabolic profile is mediated by current BMI.

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INTRODUCTION

During the last decades, the prevalence of obesity reached an epidemic dimension worldwide. Although a levelling-off of obesity trends has been reported in some countries, such as in the US and in the UK adult population,¹ and in Sweden for pediatric ages,² the prevalence of obesity is still a major public health concern. According to a systematic analysis for the Global Burden of Disease Study 2013, the age-standardized regional prevalence estimates of overweight and obesity combined for Western Europe were 61.3% (60.5–62.2) in men and 47.6% (46.8–48.4) in women in 2013.³ For children and adolescents (< 20 years), the western region presents the highest prevalence of combined overweight and obesity in Europe, being the estimates 24.2% (23.1–25.2) for boys and 22.0% (21.0–23.0) for girls.³

It is well established that childhood obesity tends to track into adulthood: the risk of overweight children to become overweight adults is at least twice as high compared with normal-weight children.⁴ The prenatal period, the adiposity rebound in childhood and puberty are critical for the development of obesity,⁵ but less is known about their effects on obesity tracking. Most studies on tracking of obesity were based on few points in time (some studies using only two) and ignored the dynamics of body mass

index (BMI) across the pediatric age. The same occurred when addressing the association between childhood or adolescent obesity and future disease in adulthood.

Childhood obesity has been associated with increased risk of disease later in life, namely cardiometabolic morbidity, and increased overall mortality.⁶ However, trajectories of obesity across pediatric age and the independent effect of adult adiposity were not usually considered.⁷ As the same BMI at a given moment in two individuals might result from different accrual paces, different health outcomes can possibly result from apparently similar exposures at a certain moment. Therefore, approaches that take cumulative exposure to adiposity into account, beyond the information on the amount of adiposity at a specific moment, may overcome the limitations of using static analyses of adiposity/BMI. The identification of developmental trajectories of adiposity could add relevant information to describe how obesity evolves over time and to identify groups following similar developmental patterns across age.⁸

We aimed to identify trajectories of adiposity, from birth until early adulthood (21 years) in a Portuguese general population sample, and to investigate its association with cardiometabolic risk factors at 21 years of age.

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SUBJECTS AND METHODS

Participants

Data were collected as part of the EPITeen study—Epidemiological Health Investigation of Teenagers in Porto, a population-based cohort that recruited 13-year-old adolescents born in 1990 and enrolled at public and private schools of Porto, Portugal, during 2003–2004, as previously described.⁹ A second evaluation took place in 2007–2008 and a third evaluation in 2011–2013.

The Ethic Committee of Hospital S. João approved this project and appropriate standard procedures were developed to guarantee data confidentiality and protection. Parents and adolescents received written and oral information explaining the purpose and design of the study and written informed consent was obtained from both.

In the first and second study waves, participants were evaluated at schools and information was collected through self-administered questionnaires. In the third study wave, participants were invited to complete the evaluation at our University department where face-to-face interviews and biological measurements took place, and self-administered questionnaires were completed. All procedures were standardized and performed by a team of trained health professionals. At the third study wave, participants were also asked to provide their child health book and data regarding all measurements of weight and length/height were extracted.

At the recruitment, 2786 eligible participants were identified and 2159 (77.5%) agreed to participate. In the second wave, we were able to reevaluate 1716 participants (79.5%) and a new group of 783 adolescents were integrated in the cohort as they moved to the area schools, and were evaluated for the first time. In the third study wave, 1764 participants were reevaluated and among these 764 have provided their child health books and were thus eligible for the analyses. We compared the characteristics of the participants included and those excluded from this study, and both groups were similar with regard to parental education, sex, practice of sports and BMI categories at 21 years of age. Regarding participants' education, a higher proportion of those included in the study presented higher education.

Measures

Anthropometrics. At the study site weight and height were obtained with the subject in light indoor clothes and no shoes. Weight was measured in kilograms, to the nearest tenth, using a digital scale and height was measured in centimetres, to the nearest tenth, using a stadiometer, according to standardized procedures.¹⁰ The weight and length/height extracted from the child health book records were performed and recorded by a pediatrician or a nurse as part of the medical routine following similar procedures.

Self-reported weight and height of the parents were collected in the first and second study waves and their BMI was categorized according to WHO (World Health Organization).¹¹ As some participants entered the study only in the second study wave, we created a single variable of mother's BMI, combining the data collected at both moments, to minimize missing data. For those with data at both study waves, we considered the highest category; when data was available only for one moment, we considered that information. For mothers with available data for both waves, we found a high correlation between the two evaluations ($r=0.842$) and when using the variable in categories (normal BMI or underweight; overweight; obese) the agreement was moderate (Kappa = 0.637).

Cardiometabolic risk factors. Cardiometabolic risk factors included in this analysis were assessed at 21 years of age. An overnight fast intravenous blood sample was taken from an antecubital vein. Routine chemistries, including glucose, triglycerides, total cholesterol and high-density lipoprotein cholesterol (HDL-C), were measured using conventional methods with an Olympus AU5400 automated clinical chemistry analyser (Beckman-Coulter, Brea, CA, USA). Insulin was measured by electrochemiluminescent immunoassay using a Cobas e411 automated analyser (Roche, Roche Diagnostics GmbH, Mannheim, Germany). All determinations took place in the Clinical Pathology Department of the São João Hospital Center, Porto.

Low-density lipoprotein cholesterol was calculated according to the Friedewald equation.¹² Insulin resistance was assessed by the homeostasis model method (HOMA-IR), based on fasting glucose and insulin concentrations: $\text{HOMA-IR} = \text{insulin} (\mu\text{U ml}^{-1}) \times \text{glucose} (\text{mg dl}^{-1}) / 405$.¹³

Blood pressure was measured on a single occasion, according to the guidelines from the American and International Societies of

Hypertension,¹⁴ using an oscillometric method (OMRON Blood Pressure Monitor). After 10 min of rest, two blood pressure measurements were taken, separately by at least 5 min, being a third measure taken when the difference between the first two was higher than 5 mm Hg. For analysis, the average of the two closest measurements was used.

Covariates. Perinatal information, such as weight and length at birth, gestational age and type of delivery, was extracted from child health book records. Mother's smoking and smoking during pregnancy, breastfeeding and complementary feeding were assessed at the baseline evaluation of the cohort using self-reported questionnaires administered to the mothers. Exclusive breastfeeding (including water intake), total breastfeeding and timing of introduction of complementary foods were also assessed in the mothers' questionnaire. Smoking status of the mother was asked regarding the current situation and also for the pregnancy period, and classified as: no smoker; smoker, but not during pregnancy; smoker during pregnancy.

Self-perceived social class was evaluated using the options: lower, lower middle, upper middle, upper and does not know/answer. For the present analysis, the categories upper middle and upper were combined. The parental educational level was measured as the number of successfully completed years of formal schooling and we considered the information from the parent with the highest education.

Family history of a medical diagnosis of diabetes, dyslipidaemia and hypertension was asked separately to the mother and the father. For each of these conditions, we calculated the variable family history combining information of both mother and father, classified as: positive, when at least one of the adolescent's parents had the diagnosis; negative, when both parents reported no diagnosis; or non-classifiable, when the available information showed no diagnosis, but, at least, one of the parents reported to 'be unaware' or did not answer.

Statistical analysis

Developmental trajectories of adiposity. For the analyses of developmental trajectories, we used measurements extracted from the child health books and measurements obtained during the EPITeen cohort evaluations (at 13, 17 and 21 years of age). We excluded participants presenting less than five measurements from birth until 21 years of age ($n=45$). The measurements varied considerably between participants, and were more frequent at earlier ages. Therefore, instead of using all single measurements, a 3-month average was computed for each participant to decrease the effect of auto-correlation of the errors. The final analyses included 719 participants with 11 459 measurements of weight and length/height (average of 16 measurements per subject).

Developmental trajectories were identified using growth mixture modelling, estimated in two steps. In the first step, the growth modelling, random effects were used to capture individual differences in development through a mixed-effect fractional polynomial;¹⁵ in the second step, the mixture modelling, we used normal mixture modelling for model-based clustering.¹⁶

Regarding the first step, instead of modelling BMI or BMI z-score, which leaves residual confounding of height, we used a mixed-effect fractional polynomial to linearize the effect of age and height on the weight. The quality of different models was compared using Bayesian Information Criterion, the correlation between the predicted and observed values and the Relative Squared Error.¹⁷ The Relative Squared Error is the error associated with the model prediction, relative to what it would have been if a simple predictor, such as the average of the actual values, had been used instead. The best fit was found for the model that can be written as:

$$\begin{aligned} \ln(\text{weight}_{ij}) \sim & \beta_0 + \beta_1 \text{height}_{ij}^{-3} + \beta_2 \text{height}_{ij}^3 + \beta_3 \text{height}_{ij}^3 \ln(\text{height}_{ij}) + \\ & \beta_4 (\text{age}_{ij} + 1)^{-1} + \beta_5 (\text{age}_{ij} + 1)^{-0.5} + \beta_6 (\text{age}_{ij} + 1)^{-0.5} \ln(\text{age}_{ij} + 1) + \\ & b_{0i} + b_{4i} (\text{age}_{ij} + 1)^{-1} + b_{5i} (\text{age}_{ij} + 1)^{-0.5} + b_{6i} (\text{age}_{ij} + 1)^{-0.5} \ln(\text{age}_{ij} + 1) \end{aligned} \quad (1)$$

where $\ln(\text{weight}_{ij})$ is the logarithm of weight for individual i at age j ; β are the estimated fixed coefficients, representing the average regression coefficients for the population; and b are the random coefficients, representing the deviation from the average estimates for individual i .

In the second step, the individual random effects estimated in the mixed effects model (b in the formula (1)) were used as response variables in the normal mixture modelling for model-based clustering to identify the patterns in the growth trajectories. The most appropriate models were considered those allowing for the most homogeneous grouping of the

individual patterns of growth selected among those with the lowest Bayesian Information Criterion.

These analyses were run in R language and software environment for statistical computation (version 3.0.1, R Foundation for Statistical Computing, Austria, 2013), using the packages nlme¹⁸ and mclust,¹⁹ for mixed-model analysis and model-based clustering, respectively.

Trajectories characterization and association with cardiometabolic risk factors. For the characterization of the trajectories according to social and early life factors and the association with cardiometabolic risk factors, data are presented as counts and proportions for categorical variables, and median (25th–75th percentiles) for continuous variables, and comparisons were performed using Chi-square and Mann–Whitney test, respectively.

To test the differences of cardiometabolic risk factors at 21 years of age according to developmental trajectories of adiposity we used analysis of covariance (ANCOVA) to estimate adjusted means. The best transformation for skewed variables (HOMA-IR and triglycerides) was performed, and adjusted means were then retransformed to the original scale to improve data interpretation. For each cardiometabolic risk, an adjusted model was computed (including sex and family history of disease) and then a second model with additional adjustment for BMI at 21 years of age was performed to test the effect of the trajectories on cardiometabolic outcomes, independently of current BMI. For HOMA-IR and triglycerides, a statistically significant interaction was found between sex and developmental trajectory, and analyses were stratified by sex.

Statistical analysis was conducted using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 21.0; IBM Corp., Armonk, NY, USA) and the significance level was set at 0.05 for two-sided tests.

RESULTS

Using a total of 11 459 measurements from 719 subjects, two developmental trajectories of adiposity were identified: 'Average BMI growth' that comprised 580 (80.7%) participants and 'Higher BMI growth' that included 139 (19.3%) participants.

Characterization of weight and BMI velocity

Figure 1 presents the mean values of predicted weight and predicted BMI, and respective velocities throughout age, for each trajectory identified. The weight gain presents velocity inflection points at similar ages for both trajectories (approximately at 4.5 years starts the increasing period and at 11 years the decreasing period). However, velocity in the trajectory 'Higher BMI growth' is higher than in the 'Average BMI growth' group (velocity of 3.0 vs 2.1 kg per year at 4.5 years; and of 5.4 vs 4.2 kg per year at 11 years, respectively, for the trajectories).

BMI velocity is affected by the rate of weight gain and of height gain, presenting the first inflection at the same age in both trajectories (about 4.5 years of age). At this inflection point, the trajectory 'Average BMI growth' reaches negative values (approximately -0.4 kg m^{-2} per year), which represents a decrease in BMI values, while trajectory 'Higher BMI growth' always presents a positive velocity with a minimum of 0.2 kg m^{-2} per year. The second inflexion point in BMI velocity happens earlier in the 'Higher BMI growth' (9.8 years vs 11.7 years), and with a higher velocity (0.9 kg m^{-2} per year vs 0.6 kg m^{-2} per year). These differences in BMI gain velocity result in increasing values of BMI across age and in higher adulthood mean BMI in 'Higher BMI growth', compared with the 'Average BMI growth' group. At 21 years of age, the prevalence of overweight and obesity combined is 71.8% in 'Higher BMI growth' and 12.1% in 'Average BMI growth'.

Participants and family characteristics and trajectories

The 'Higher BMI growth' trajectory presented a lower proportion of participants reporting upper or upper middle self-perceived social class and a lower proportion of parents with higher education, although differences were not statistically significant (Table 1). Birth weight was similar between the two trajectories;

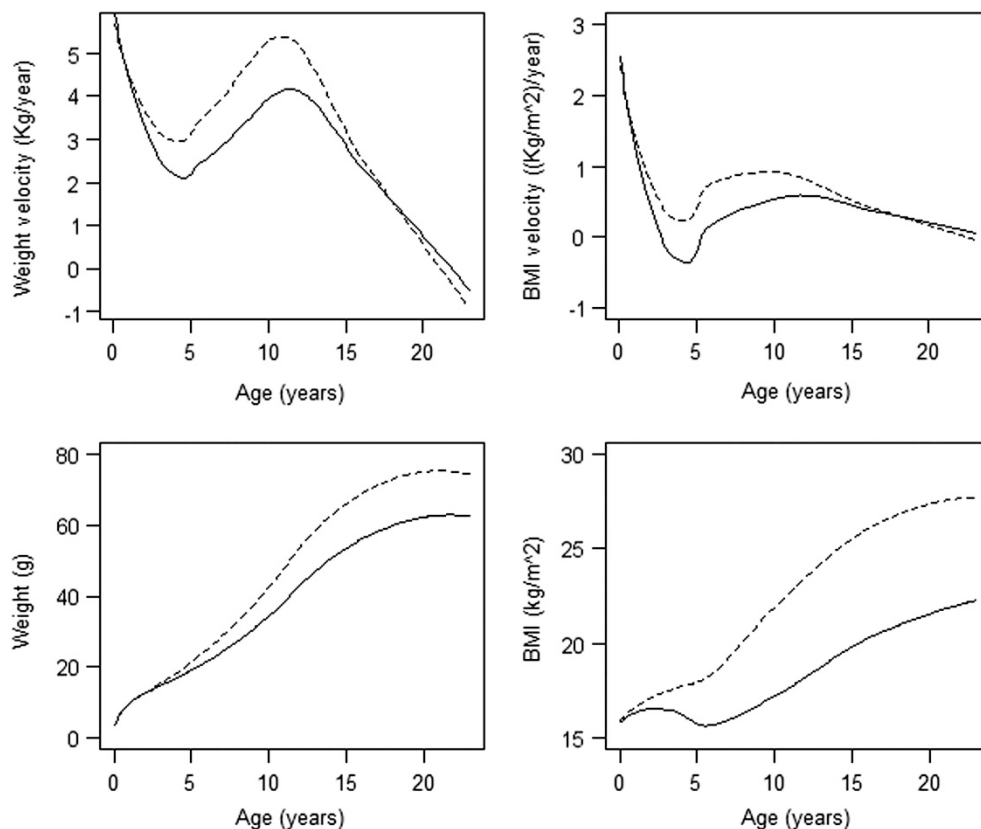


Figure 1. Weight velocity (top left), BMI velocity (top right), mean values of predicted weight (bottom left) and predicted BMI (bottom right) throughout age, according to the two trajectories identified. Solid line: 'Average BMI growth'; dashed line: 'Higher BMI growth'.

Table 1. Descriptive data on social and early life factors, according to developmental trajectories of adiposity

	'Higher BMI growth' n = 139	'Average BMI growth' n = 580	P-value	Missing (n)
Sex^a				
Female	81 (58.3)	308 (53.1)	0.315	0
Male	58 (41.7)	272 (46.9)		
Self-perceived social class^a				
Lower	8 (6.1)	26 (4.6)	0.660	22
Lower middle	72 (55.0)	293 (51.8)		
Upper/upper middle	43 (32.8)	216 (38.2)		
Does not know/answer	8 (6.1)	31 (5.5)		
Parental education (years)^a				
0–6	25 (18.2)	111 (19.2)	0.072	3
7–9	33 (24.1)	92 (15.9)		
10–12	42 (30.7)	168 (29.0)		
> 12	37 (27.0)	208 (35.9)		
Mother's age at child birth (years)^b	27 (24–30)	28 (25–31)	0.005	17
Delivery^a				
Vaginal	82 (62.6)	387 (72.9)	0.027	57
Caesarean	49 (37.4)	144 (27.1)		
Gestational age (weeks)^b	39 (38–40)	40 (38–40)	0.347	55
Birth weight (g)^b	3250 (3007–3592)	3350 (3100–3600)	0.259	11
Birth length (cm)^b	49 (48–50)	50 (48–51)	0.049	20
Mother's smoking^a				
No smoker	77 (61.1)	336 (61.7)	0.706	48
Smoker, but not during pregnancy	34 (27.0)	157 (28.8)		
Smoker during pregnancy	15 (11.9)	52 (9.5)		
Exclusive breastfeeding^a				
Never or < 1 week	16 (17.4)	67 (17.4)	0.655	242
≥ 1 week and < 3 months	26 (28.3)	127 (33.0)		
≥ 3 months	50 (54.3)	191 (49.6)		
Total breastfeeding (months)^b	4 (1–10)	4 (2–8)	0.573	287
Timing of complementary feeding (months)^b	4 (4–6)	4 (4–6)	0.458	225
Mother's BMI (kg m⁻²)^a				
< 25.0	56 (45.2)	338 (62.5)	< 0.001	54
25.0–29.9	38 (30.6)	151 (27.9)		
≥ 30.0	30 (24.2)	52 (9.6)		

Abbreviation: BMI, body mass index. Values are presented as ^an (%); ^bmedian (25th–75th percentiles).

however, participants from the 'Higher BMI growth' presented lower length at birth (49 vs 50 cm, $P=0.049$), and caesarean delivery was more frequent. Mothers of participants in the 'Higher BMI growth' trajectory were younger, and more frequently overweight (30.6 vs 27.9%) or obese (24.2 vs 9.6%; $P<0.001$).

Association between trajectories and cardiometabolic risk factors at 21 years of age

In the model adjusted for sex and family history of disease, higher mean systolic blood pressure (111.6 vs 108.3 mm Hg, $P<0.001$) and diastolic blood pressure (71.9 vs 68.4 mm Hg, $P=0.001$) were found in 'Higher BMI growth' group. On the contrary, lower HDL-C was found in the group 'Higher BMI growth' (53.3 vs 57.0 mg dl⁻¹, $P=0.001$) (Table 2). However, differences in blood pressure and in HDL-C were no longer significant after adjustment for BMI at 21 years of age. As there was a significant interaction between trajectories and sex, triglycerides and HOMA-IR were stratified by sex (Table 3). In comparison with trajectory 'Average BMI growth',

we found higher levels of triglycerides in participants from the trajectory 'Higher BMI growth', but only among males (89.0 vs 70.2 mg dl⁻¹, $P<0.001$). Differences in adjusted means of HOMA-IR were also found when comparing trajectories, significant both in females and in males, but larger in males (2.41 vs 1.49, $P<0.001$) than in females (2.07 vs 1.67, $P<0.001$). After adjustment for BMI at 21 years of age, differences in triglycerides and HOMA-IR between trajectories were also attenuated and were no longer statistically significant.

We additionally computed the association between the trajectories and cardiometabolic factors at 13 years (Supplementary Table 1), and the results were similar to those found with the outcomes at 21 years, supporting that the associations are already present at 13 years of age.

DISCUSSION

Using data from birth until early adulthood, we identified two developmental trajectories of adiposity. The 'Average BMI growth'

Table 2. Crude and adjusted means of blood pressure and cholesterol at 21 years of age, according to developmental trajectories of adiposity

Cardiometabolic risk factors at 21 years	Developmental trajectory		P-value
	'Higher BMI growth'	'Average BMI growth'	
Mean (95% CI)			
SBP (mm Hg)			
Crude	110.5 (108.6–112.5)	107.9 (106.9–108.9)	0.017
Adjusted ^a	111.6 (110.0–113.1)	108.3 (107.5–109.0)	< 0.001
Adjusted ^a + BMI 21 years	107.7 (105.8–109.6)	109.1 (108.3–109.9)	0.186
DBP (mm Hg)			
Crude	71.7 (70.5–73.0)	68.3 (67.7–68.9)	< 0.001
Adjusted ^a	71.9 (70.6–73.1)	68.4 (67.8–69.0)	< 0.001
Adjusted ^a + BMI 21 years	69.5 (68.0–71.0)	69.0 (68.3–69.6)	0.543
LDL-C (mg dl⁻¹)			
Crude	103.5 (99.0–108.1)	103.1 (100.8–105.4)	0.860
Adjusted ^b	103.0 (98.4–107.6)	102.4 (100.1–104.7)	0.821
Adjusted ^b + BMI 21 years	95.0 (89.3–101.7)	104.3 (101.9–106.7)	0.005
HDL-C (mg dl⁻¹)			
Crude	54.6 (52.3–56.8)	57.6 (56.5–58.7)	0.017
Adjusted ^b	53.3 (51.4–55.3)	57.0 (56.0–58.0)	0.001
Adjusted ^b + BMI 21 years	54.6 (52.1–58.0)	56.7 (55.7–57.7)	0.130

Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure. ^aAdjusted for sex and family history of hypertension. ^bAdjusted for sex and family history of dyslipidaemia.

Table 3. Crude and adjusted means of HOMA-IR and triglycerides at 21 years of age, according to developmental trajectories of adiposity and stratified by sex

Cardiometabolic risk factors at 21 years	Developmental trajectory		P-value
	'Higher BMI growth'	'Average BMI growth'	
Mean (95% CI)			
Triglycerides (mg dl⁻¹)			
Females			
Crude	84.8 (77.4–92.9)	85.8 (81.8–89.9)	0.821
Adjusted ^a	83.3 (76.0–91.4)	84.5 (80.5–88.8)	0.788
Adjusted ^a + BMI 21 years	81.4 (72.5–91.3)	85.1 (80.7–89.7)	0.512
Males			
Crude	85.3 (76.6–94.9)	69.5 (66.1–73.0)	0.001
Adjusted ^a	89.0 (80.1–99.1)	70.2 (66.8–73.8)	< 0.001
Adjusted ^a + BMI 21 years	77.2 (68.0–87.6)	72.6 (68.9–76.4)	0.402
HOMA-IR			
Females			
Crude	2.06 (1.84–2.30)	1.66 (1.56–1.75)	0.001
Adjusted ^b	2.07 (1.84–2.32)	1.67 (1.55–1.79)	0.001
Adjusted ^b + BMI 21 years	1.60 (1.40–1.84)	1.81 (1.68–1.94)	0.147
Males			
Crude	2.33 (2.01–2.71)	1.43 (1.34–1.54)	< 0.001
Adjusted ^b	2.41 (2.06–2.82)	1.49 (1.36–1.63)	< 0.001
Adjusted ^b + BMI 21 years	1.75 (1.46–2.10)	1.58 (1.45–1.73)	0.317

Abbreviations: BMI, body mass index; CI, confidence interval; HOMA-IR, homeostasis model assessment. ^aAdjusted for family history of dyslipidaemia. ^bAdjusted for family history of diabetes.

trajectory was the most prevalent, presenting on average a BMI within normal ranges. The 'Higher BMI growth' trajectory is characterized by higher BMI mean values since birth, being the difference between the trajectories more pronounced since the period of adiposity rebound. At 21 years of age, almost three quarters of the individuals from this trajectory present overweight or obesity.

Developmental trajectories in children and adolescents were described in different settings but study comparisons are inappropriate due to differences in statistical solutions, growth modelling^{20,21} versus growth mixture modelling (a group-based approach);^{22–27} great heterogeneity in age ranges and differences in the outcome modelled, mostly using BMI^{25–27} or BMI z-score.^{20,22–24}

Adiposity differences between trajectories appeared in the first years of life and there was a low probability (about 10%) of changing trajectory from adolescence onwards (data not shown). These results suggest that the determinants of the two different trajectories are related to early events. We found that participants from trajectory 'Higher BMI growth' were born more frequently by caesarean section and their mothers were younger and more frequently overweight or obese. The direct association between parental BMI and childhood obesity have been extensively addressed and have been also found when analysing the association with BMI trajectories in childhood or youth.^{22–24,26–28} The association between caesarean section and offspring overweight and obesity have been previously described,²⁹ although some authors have argued that it is not causal, and may be due to

uncontrolled confounding.^{30,31} Maternal smoking during pregnancy, breastfeeding and complementary feeding was not different according to developmental trajectories. Limited accuracy of the information self-reported by the mothers when adolescents were 13 years of age without additional information from the second study wave, and no information for participants enrolled at that wave make inferences less reliable.

Parental education is often used as a proxy for socioeconomic status of the child or adolescent, influencing exposures since early stages of life. In our study, a higher proportion of participants in the trajectory 'Higher BMI growth' had parents with lower educational level. This finding is in accordance with other previous studies analysing developmental trajectories,^{27,28} although some studies have reported non-significant associations.^{22,26}

Regarding the association between developmental trajectories and cardiometabolic risk factors in early adulthood, we found that participants from 'Higher BMI growth' trajectory presented a worse cardiometabolic profile, with higher levels of blood pressure, HOMA-IR and triglycerides, and lower levels of HDL-C. To our knowledge, few studies have evaluated the effect of pediatric adiposity trajectories on adult cardiometabolic outcomes, since the majority of studies are limited to childhood or adolescence. Ziyab *et al.*²³ have studied BMI trajectories from 1 to 18 years in the Isle of Wight birth cohort, UK, and found that an early persistent obesity trajectory was associated with higher blood pressure at 18 years of age. The West Australian Pregnancy cohort showed three trajectories (birth to age 14) characterized by accelerating adiposity associated with increased risk of prehypertension or hypertension at 17 years of age.³² In a previous study, these trajectories were also related to higher insulin resistance at 14 years.³³

In our study, we computed an additional model controlling for current BMI (at 21 years of age), and differences in the cardiometabolic outcomes were attenuated, or in some cases reverted. The adjustment for current BMI might be inappropriate, since it can be an intermediate step between the adiposity trajectory and the cardiometabolic outcome. This question has been discussed mainly with regard to analysis investigating the association between childhood obesity on adult disease, independently of adult BMI. Some authors argue that this adjustment may introduce over-adjustment biases,³⁴ while others raise some questions about the interpretation of the results, because this adjustment controls for change in adiposity between measurements, not only for adult body size.³⁵ Considering this difficulties, Lucas *et al.*³⁵ recommend the presentation of different models, with and without adjustment for later adiposity, to make studies in this area comparable. In our study, we computed a model with additional adjustment for current BMI, and the attenuation of the results indicates that the association between adiposity trajectory and adult outcomes is mediated by current BMI. However, we are not able to fully disentangle this complex association with our analysis. Future studies using more sophisticated statistical techniques, such as structural equation modelling, are needed to clarify whether the effect of the adiposity trajectory is totally mediated by current BMI or not, and to quantify the direct and indirect effects of the trajectories on adult cardiometabolic outcomes.

Strengths and limitations

In addition to the anthropometric data assessed under the strict cohort exams, we also used data extracted from child health books, measured routinely by health professionals. Although we could not test the accuracy of the recorded information, weight and height extracted from child health individual books have been shown to present no systematic bias, supporting their use for research.³⁶

Regarding the identification of the trajectories, we excluded participants having less than five measurements during the period under studied, to ensure a number of measurements higher than the number of random parameters in the model (four). We did not stratify the analysis of the trajectories by sex, but we tested a model including interaction terms between sex and all the other terms. Although the interaction terms were statistically significant, the goodness-of-fit of the model remained similar and the trajectories obtained from this analysis were similar to those obtained from the model without interaction for sex. Therefore, we chose the simplest model, without interaction for sex. This option was then supported by a similar sex distribution of the two trajectories identified. We also performed other sensitive analysis, such as the exclusion of the participants born pre-term ($n=41$). Trajectories identified without pre-terms were also similar to those identified in the total sample, and therefore we decided to use all the participants to enhance statistical power of the analysis, and to improve external validity of our results. The number of participants identified in the 'Higher BMI growth' trajectory was lower than in the other trajectory, but it was in accordance to the BMI distribution in a population setting. Despite this unbalanced sample size between trajectories, we were able to detect statistically significant differences on most of the cardiometabolic risk factors analysed.

The current analysis was performed in a sub-sample of the participants of the third study wave of the cohort. Participants included in the study presented higher education than those excluded and this difference may have led to an underestimation of the prevalence of the 'Higher BMI growth' trajectory, but it is not expected that it had influenced the definition of the trajectories.

Regarding the analysis of the association between the trajectories and the cardiometabolic outcomes, we also tested the effect of other potential confounders, such as parental and participants' education, practice of sports and diet (total energy intake), but they were not considered in the final models, since they did not significantly changed the estimates.

The study is strengthened by using multiple anthropometric measures across the pediatric age (16 per subject, on average), which increases the accuracy of the trajectories identification. We have also tested different models, with different outcomes using either BMI or weight and height. When using BMI, a worse goodness-of-fit of the model was found suggesting it is a measure not equally adequate across the whole pediatric period. We also tested the use of different covariates in the model, as height and age. Our final model was the one presenting the best goodness-of-fit, using the logarithm of weight as outcome, and including height and age as covariates. Finally, our analysis covers the whole pediatric period and the early adulthood, and we were able to study the association of the adiposity trajectories on adult cardiometabolic outcomes, such as blood pressure, insulin resistance, cholesterol and triglycerides.

In this population-based cohort, we identified two trajectories of adiposity from birth until early adulthood. The trajectory 'Higher BMI growth' found in 19% of the population presented higher values of BMI in adulthood and led to a worse cardiometabolic profile. Our results also suggest that the impact of the adiposity trajectory on cardiometabolic profile is mediated by the effect on current BMI, but future studies are needed to clarify the direct and indirect effects of the adiposity trajectories on adult cardiometabolic outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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