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Adiposity rebound and cardiometabolic health in childhood: results from the Generation XXI birth cohort

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Abstract

Background: We aimed to evaluate the association of adiposity rebound (AR) timing on cardiometabolic health in childhood.

Methods: Participants were part of the Generation XXI birth cohort, enrolled in 2005/2006 in Porto. All measurements of the child's weight and height performed by health professionals as part of routine healthcare were collected. Individual body mass index (BMI) curves were fitted for 3372 children, using mixed-effects models with smooth spline functions for age and random effects. The AR was categorized into very early (<42 months), early (42–59 months), normal (60–83 months) and late (≥84 months). At age 10 years, cardiometabolic traits were assessed and age- and sex-specific z-scores were generated. Adjusted regression coefficients and 95% confidence intervals [β (95% CI)] were computed.

Results: The mean age at AR was 61.9 months (standard deviations 15.7). Compared with children with normal AR, children with very early or early AR had higher z-scores for BMI [$\beta = 0.40$ (95% CI: 0.28; 0.53); $\beta = 0.21$ (95% CI: 0.12; 0.30)], waist circumference [$\beta = 0.33$ (95% CI: 0.23; 0.43); $\beta = 0.18$ (95% CI: 0.10; 0.25)], waist–height ratio [$\beta = 0.34$ (95% CI: 0.24; 0.44); $\beta = 0.14$ (95% CI: 0.07; 0.22)], fat mass index [$\beta = 0.24$ (95% CI: 0.15; 0.33); $\beta = 0.14$ (95% CI: 0.08; 0.21)], fat-free mass index [$\beta = 0.25$ (95% CI: 0.14; 0.35); $\beta = 0.11$ (95% CI: 0.03; 0.19)], systolic blood pressure [$\beta = 0.10$ (95% CI: 0.01; 0.20); $\beta = 0.08$ (95% CI: 0.01; 0.15)], insulin [$\beta = 0.16$ (95% CI: 0.04; 0.29); $\beta = 0.10$ (95% CI: 0.01; 0.19)], HOMA-IR [$\beta = 0.17$ (95% CI: 0.04; 0.29); $\beta = 0.10$ (95% CI: 0.03; 0.19)] and C-reactive protein [$\beta = 0.14$ (95% CI: 0.02; 0.26); $\beta = 0.10$ (95% CI: 0.01; 0.19)]. Children with very early AR also had worse levels of diastolic blood pressure [$\beta = 0.09$ (95% CI: 0.02; 0.16)], triglycerides [$\beta = 0.21$ (95% CI: 0.08; 0.34)] and high-density lipoprotein cholesterol [$\beta = -0.18$ (95% CI: −0.31; −0.04)]. When analysed continuously, each additional month of age at the AR was associated with healthier cardiometabolic traits.

Conclusion: The earlier the AR, the worse the cardiometabolic health in late childhood, which was consistently shown across a wide range of outcomes and in the categorical and continuous approach.

Key words: Growth, adiposity rebound, early rebounders, cardiometabolic health, birth cohort

Key Messages

- In a large sample of contemporary European children, adiposity rebound (AR) occurred at ~62 months of life.
- A very early AR (<42 months) was associated with higher adiposity, blood pressure, insulin, homeostatic model assessment-insulin resistance, triglycerides and C-reactive protein, and lower high-density lipoprotein cholesterol.
- Individual growth curves should be used to estimate the AR age and thus identify children at risk of impaired cardiometabolic health in a timely manner and invest in targeted preventive strategies.

Introduction

Overweight and obesity and associated cardiometabolic disorders are an important cause of morbidity and mortality.[1] Additionally, due to the advancement of the obesity epidemic t, these conditions are occurring at younger ages and tracking across the lifespan.[2–7] Thus, the identification of factors that can predict these disorders early in life is highly relevant.

In this sense, interest has turned to the detection of critical time periods for the development of such disorders. One of the identified critical windows is the adiposity rebound (AR) period.[8] After 1 year of age, body mass index (BMI) usually declines, reaching a minimum value (*nadir*) at ~6 years of age, and then increases throughout childhood. The time point at which BMI starts to increase, immediately after the *nadir*, is called the AR and was first identified as a critical window for the development of obesity by Rolland-Cachera *et al.* in 1984. These authors noticed that adolescents who had an early AR (<5.5 years) were more frequently obese than those who were later rebounders (>7 years).[8] Since then, other studies have confirmed that early AR is associated with a higher risk of overweight and obesity later in life.[9,10] Furthermore, early AR has been associated with impaired glucose tolerance, insulin resistance, type 2 diabetes, high blood pressure and metabolic syndrome in adulthood.[11–15] However, only recently has the effect of early AR on health during childhood/early adolescence been explored in five cohorts from different world regions.[16–21] In a cohort from Thailand, early AR was associated with insulin resistance at 8.5 years of age[16] and, in cohorts from Chile,[19] Japan,[20,21] the USA (Massachusetts)[17] and India,[18] it was associated with an adverse cardiometabolic profile at ages 7, 12, 13 and 13.5 years, respectively.

The limitations of previous studies on the deleterious medium- and long-term consequences of early AR include small sample sizes and a limited range of outcomes that were mainly focused on obesity risk.[10] To the best of our knowledge, we are not aware of any study performed in a contemporary European cohort evaluating outcomes other than overweight and obesity.

We hypothesized that children with an earlier AR would be at higher risk of both higher adiposity and a more adverse profile of cardiometabolic indicators even as early as 10 years of age.

Thus, the objective of the present study was to estimate the timing of AR and to evaluate its association with adiposity and other cardiometabolic traits at 10 years of age.

Methods

Generation XXI

The participants of this study are part of the Generation XXI birth cohort,[22,23] assembled between April 2005 and August 2006, at the five public units providing obstetrical and neonatal care in the metropolitan area of Porto, Portugal. Of the 8647 initial cohort members, 7459 (86%), 6889 (80%) and 6397 (74%) were evaluated at the 4-, 7- and 10-year follow-up evaluations, respectively. At the 10-year-old evaluation, participants were evaluated in person but, when they were unable to visit our facilities, telephone or home interviews were performed (16%). At baseline, face-to-face interviews were conducted during the hospital stay by trained interviewers, 24–72 hours after

delivery. Data on socio-demographic characteristics, maternal pre-pregnancy anthropometrics and intrauterine exposures were collected. Information concerning the delivery and the newborn, including birthweight, was retrieved from clinical records by the same interviewers. In all subsequent Generation XXI follow-up evaluations, mothers were asked to bring their Child Health Book, in which every anthropometric measurement performed on the child as part of standard childcare in Portugal was recorded by health professionals. All data regarding children's weight and height measurements from birth to current age were abstracted from the Child Health Book and used to estimate BMI and its trajectories. For a total of 6685 children, the Child Health Book was available in at least one of the follow-ups.

Participant selection

Detailed information on the selection criteria is depicted in Figure 1. Multiple births and children with congenital anomalies were excluded due to non-independence of observations and expected differences in physical development. To guarantee the quality of the measurement information used to estimate the BMI trajectories, some criteria were applied. Children with up to three measurements, no measurements after 18 months of age or no measurements between 42 and 84 months of age were excluded. Additionally, for 1783 children, it was impossible to estimate the AR. This includes children whose BMI trajectories were always upwards or downwards or were very unstable, which means that they probably did not have an evident AR. These 1783 children were compared with those with estimable rebound ($n = 3793$) and the results are presented in Supplementary Table 1, available as Supplementary data at *IJE* online. For the 3793 children with an estimable rebound, a median of 23 (IQR 9) BMI measurements per child were available (the minimum was 5 measurements and the maximum was 75 measurements per child). As the outcomes analysed in this study demanded a physical examination and blood-sample collection at the 10-year follow-up evaluation, only data regarding participants who had face-to-face interviews were used. Differences between those included ($n = 3372$) and those not included ($n = 421$) regarding maternal,

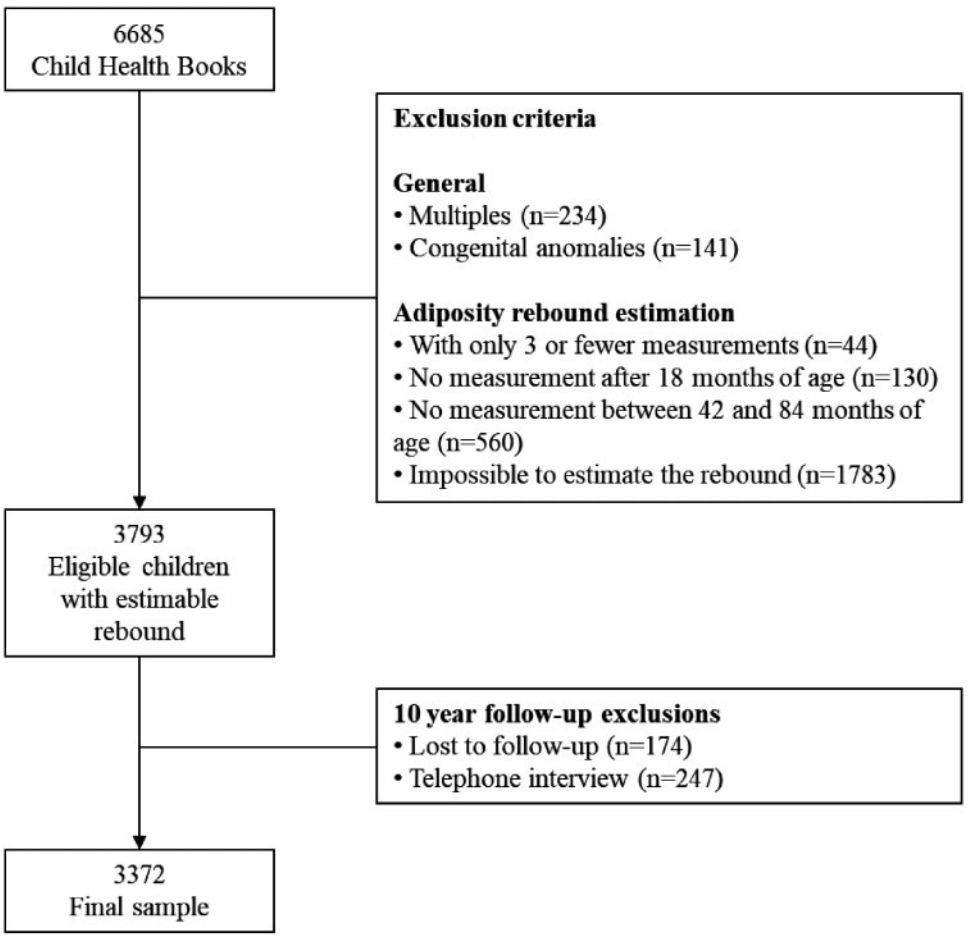

Figure 1 Study flow chart of participants

pregnancy, delivery and newborn characteristics are presented in Supplementary Table 1, available as Supplementary data at *IJE* online.

Compared with non-participants, participants presented higher maternal education and age, and a higher number of BMI measurements (Supplementary Table 1, available as Supplementary data at *IJE* online).

Outcome evaluation

At the 10-year follow-up evaluation, trained researchers performed anthropometric and blood-pressure measurements and obtained a fasting blood sample, according to standard procedures. While the child was barefooted and in underwear, the height was measured using a stadiometer to the nearest 0.1 cm and weight was measured using a digital scale to the nearest 0.1 kg; BMI was subsequently calculated. Waist circumference (WC) measurements were taken to the nearest 0.1 cm, at the umbilicus level, with the child in a standing position, with the abdomen relaxed, arms at the sides and feet positioned together. The waist-to-height (WHtR) ratio was calculated as waist (cm)/height (cm). Body composition was measured by a bioelectrical impedance analysis (BIA) generator, Akern's BIA Anniversary 101, with four surface electrodes placed on the right wrist and ankle while the child was lying horizontally. Every week, the device was calibrated and the participants were in their underwear without any jewellery or watches and were fasting. Before the exam, all were asked to empty their bladder. Fat mass index (FMI) and fat-free mass index (FFMI) were then calculated as total fat (kg)/height^2 (m) and total free fat (kg)/height^2 (m), respectively.

Two measurements of systolic (SBP) and diastolic (DBP) blood pressure, separated by at least 5 minutes, were taken after a 10-minute rest. If the difference between them was <5 mmHg for both SBP and DBP, the mean was calculated and, if the difference was >5 mmHg, a third measurement was taken and the mean of the two closest values was used.

After an overnight fast, a venous blood sample was collected before 11 a.m. Glucose was measured using ultraviolet (UV) enzymatic assay (hexokinase method), insulin was measured using electrochemiluminescence immunoassay, triglycerides (TG) and total and high-density lipoprotein cholesterol (HDL cholesterol) were measured using an enzymatic colorimetric assay and high-sensitivity C-reactive protein (hs-CRP) was measured using nephelometry. Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated as glucose (mg/dL) x insulin (μU/mL)/405 and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation.[24]

Pubertal development was also evaluated by trained nurses using the Tanner scale for pubic hair and breast development in girls and testicular development in boys.[25,26] The Tanner scale evaluates pubertal development by classifying each parameter into one of five stages: 1—prepubertal; 2, 3 and 4—pubertal; and 5—postpubertal.

Cardiometabolic health at 10 years of age was evaluated through different indicators: body-composition indicators (BMI, WC, WHtR, FMI and FFMI), blood pressure (SBP and DBP) and blood analytes (glucose, insulin, HOMA-IR, TG, HDL cholesterol, LDL cholesterol and hs-CRP). Cardiometabolic indicators are highly dependent on age and sex, and, to facilitate the comparison of the magnitude of the associations between them, age- and sex-specific z-scores were generated. As no consensual recommendation exists regarding most of the cardiometabolic indicators, age- (in 6-month categories) and sex-specific means and standard deviations (SDs) derived from the whole Generation XXI cohort were used. The exception was BMI and blood pressure, for which there are specific consensual recommendations for z-score calculations. For BMI, age- and sex-specific z-scores were established according to the World Health Organization.[27] For SBP and DBP, age-, sex- and height-specific z-scores were generated following the recommendations of the American Academy of Pediatrics.[28]

Ethics

All the phases of the study complied with the Ethical Principles for Medical Research Involving Human Subjects expressed in the Declaration of Helsinki. The study was approved by the Faculdade de Medicina da Universidade do Porto/Centro Hospitalar S. João Ethics Committee and parents or legal representatives signed an informed consent form in all the follow-up evaluations.

Statistical analysis

Individual BMI curves were fitted using mixed-effects models with cubic smoothing spline functions for age to capture the nonlinear trend in BMI.

These models are flexible for a population of individuals with individually varying parameters, i.e. allowing random intercepts and random variations of BMI along the time. The mixed-model framework also allows the average curve to be modelled while naturally accommodating non-independence and/or heterogeneity in the data.

The population of children was viewed as a set of regression splines that differ from the mean regression spline. The model was defined as: $Y_i = \eta(age_i, \beta, u_i) + \varepsilon_i$, $u_i \sim N(0, G)$ and $\varepsilon_i \sim N(0, R)$, where Y_i is the n_i-dimensional

response vector of BMI for the ith child ($i = 1, \ldots, s$) and age_i is the predictor vector. η is a regression spline (cubic smooth spline), with a column vector of population parameters β and a column vector of individual-specific parameters u_i (individual-level random effects); ε_i represents the n_i-dimensional error vector.

In order to accommodate the variations between BMI growth across children, all coefficients were permitted to vary across children. Furthermore, due the differences in the growth of each child, each regression-spline term was specified to have a fixed and a random component with a flexible random-effects structure. The random effects were specified to be multivariate normal in all models that were also specified to have continuous AR[1] errors to accommodate temporal autocorrelation in the data.

Although cubic smoothing splines are mathematically more challenging, they are smoother and more flexible, and do not require the selection of the number of knots, as with the natural cubic splines.[29–33] The smoothing spline considers a knot at each unique age value and the fitting is carried out by least squares with a roughness penalty term that accounts for the fluctuations and controls the roughness of the function and variance of the model.

The aim when using smoothing splines is to minimize the error function that is modified by the addition of the roughness penalty that penalizes it for roughness and high variance. The model terms $\eta(age_i, \beta, u_i)$ were estimated using a penalized least-square method through the minimization of $H = \sum_{i=1}^{n} (Y_i - \eta(age_i, \beta, u_i))^2 + \lambda J(\eta)$, where the quadratic function $J(\eta)$ quantifies the roughness of η and λ controlled the trade-off between the goodness of fit and the smoothness of η. The smoothing parameter λ was automatically estimated using the cross-validation method.[31,33] We assessed model fit using a residual plot of observed and predicted BMI (Figure 2).

We estimated the age (in months) at the infant peak and at the AR by differentiation of the subject-specific BMI curve; the peak and the AR were located at the age at which the derivative of the curve equals zero. We estimated the magnitude of the BMI (kg/m^2) at the peak and at the AR as the highest and lowest points, respectively, of the child-specific BMI curve. Age at the AR was categorized using cut-off points described in the literature[10,19,34]: very early (<42 months), early (42–59 months), normal (60–83 months) and late (≥84 months). The median BMI curves according to the timing of the AR may be observed in Figure 3.

Proportions were compared using the chi-square test and the means or medians were compared using the Student's t-test, the Mann–Whitney test, one-way analysis of variance or the Kruskal–Wallis test, as appropriate. Regression coefficients (β) and 95% confidence intervals (CIs) were computed using generalized linear models and linear-regression models.

Maternal age, education, pre-pregnancy BMI, tobacco smoking during the third trimester of pregnancy, gestational diabetes, gestational weight gain, gestational age, type of delivery, birthweight and sex were tested as potential confounders. Only those that were associated with the age at the AR and with at least one of the outcomes were included in the final models, namely maternal education (years), pre-pregnancy BMI (kg/m^2), tobacco smoking during the third pregnancy trimester (yes/no) and child's birthweight (grams). The models were additionally adjusted for infant peak. The adjustment for BMI at the moment of the AR was tested, but the results remained similar; thus, it was not included in the final models.

Effect modification by the child's gender was investigated by running the models separately for girls and boys, and the results were similar. Thus, no effect modification was considered and, for that reason, the results presented represent the whole sample.

Analysis was performed using SPSS (version 23) and R.[35]

Results

The description of the AR and of the cardiometabolic indicators among the study participants are shown in Table 1. The mean age at AR was 61.9 months, which was similar for girls and boys (61.4 vs 62.3 months). Very early AR occurred in 12.7% of the children, early AR in 29.9% and late AR in 10.2%.

The mean (or median) values of the cardiometabolic indicators and of two potential mediators according to the timing of the AR are presented in Supplementary Table 2, available as Supplementary data at *IJE* online. A worse profile of cardiometabolic indicators was observed in children who presented very early or early AR, with the exception of glucose and LDL cholesterol levels. Children with an earlier timing of AR presented lower levels of BMI at the moment of AR. The timing of AR was not associated with pubertal stage at age 10 years (Supplementary Table 2, available as Supplementary data at *IJE* online).

The adjusted association of the timing of the AR with the age- and sex- z-scores of the cardiometabolic indicators [β (95%CI)] are depicted in Table 2. Compared with children with normal AR timing, children with very early or early AR had higher levels of adiposity, namely higher z-scores of BMI [0.40 (0.28; 0.53) and 0.21 (0.12; 0.30)], WC [0.33 (0.23; 0.43) and 0.18 (0.10; 0.25)], WHtR [0.34 (0.24; 0.44) and 0.14 (0.07; 0.22)], FMI [0.24 (0.15; 0.33) and 0.14 (0.08; 0.21)], FFMI [0.25 (0.14; 0.35) and 0.11 (0.03; 0.19)], SBP [0.10 (0.01; 0.20) and 0.08 (0.01;

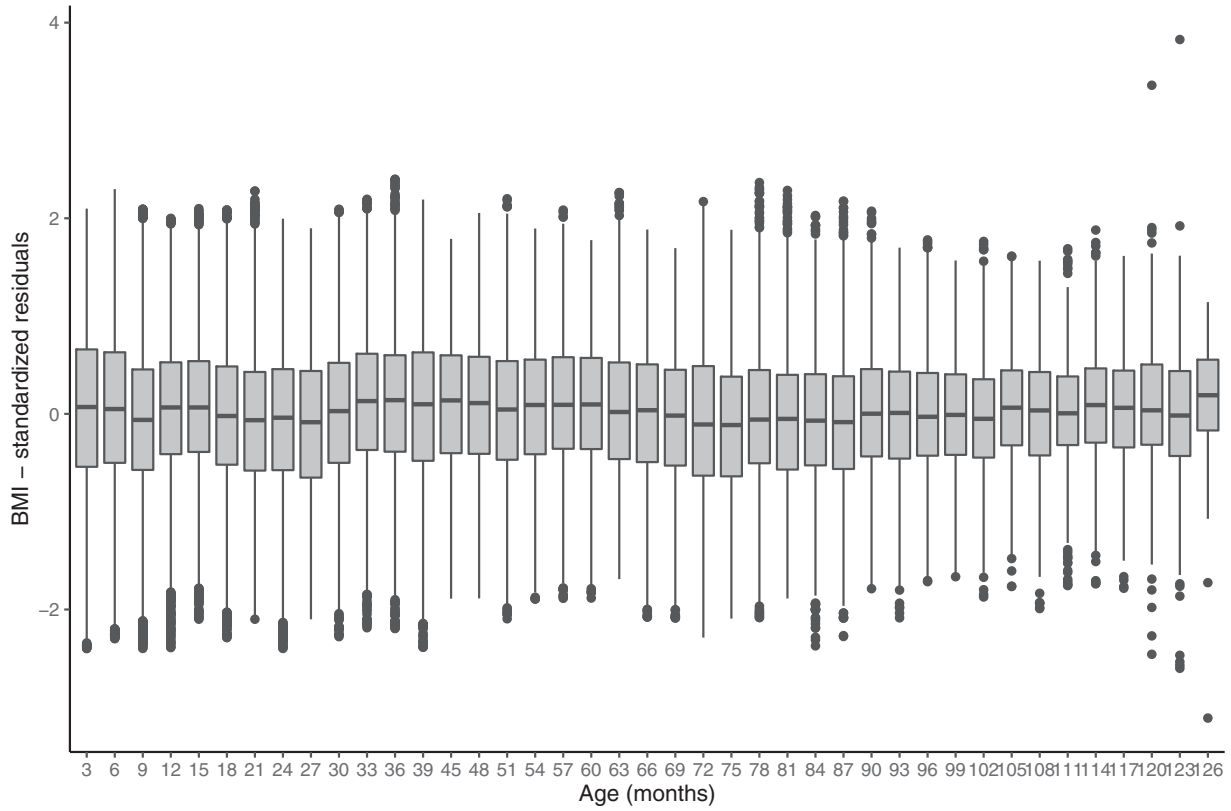

Figure 2 Plot of residual body mass index (BMI) values (observed – predicted BMI values) over age in months

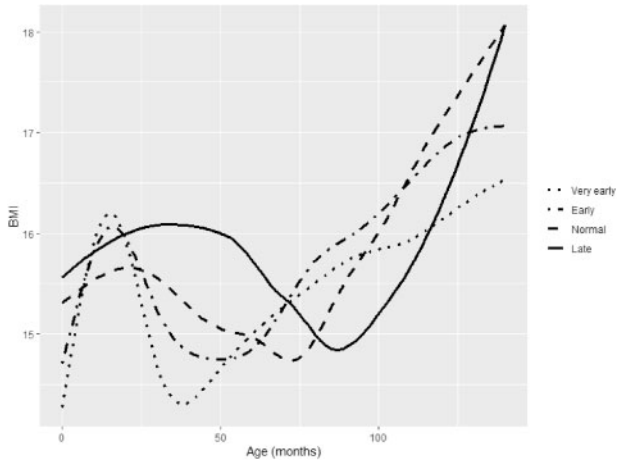

Figure 3 Median body mass index curves according to the timing of adiposity rebound

0.15)], insulin [0.16 (0.04; 0.29) and 0.10 (0.01; 0.19)], HOMA-IR [0.17 (0.04; 0.29) and 0.10 (0.03; 0.19)] and hs-CRP [0.14 (0.02; 0.26) and 0.10 (0.01; 0.19)]. Children with very early AR also had higher z-scores for DBP [0.09 (0.02; 0.16)] and TG [0.21 (0.08; 0.34)] and lower z-scores for HDL cholesterol [−0.18 (−0.31; −0.04)].

The results presented in Table 2 regarding BMI are different from those in Figure 3. In the unadjusted analyses in Figure 3, the group with very early AR has a lower median BMI by almost 1.5 kg/m^2 (about 1 SD) than the group with normal timing of AR at 10 years of age. On the other hand, in results presented in Table 2, which are adjusted for confounders (sex, maternal education, pre-pregnancy BMI, tobacco smoking during the third pregnancy trimester, birthweight, an infant peak), the group with very early AR has a higher mean BMI z-score (∼0.4 SD) than the group with normal time of AR. This inconsistency seems to be related to unadjusted vs adjusted analyses. Also, Figure 3 represents a prospective model that predicts children's median BMI according to their age, taking into account the children's measurements during their lifetime, included in the Child Health Book, whereas Table 2 represents the associations between the timing of the AR and the BMI z-scores.

When age at the AR was analysed in a continuous way, it was observed that, for each additional month of age at the AR, the lower the adiposity (BMI, WC, WHtR and FMI), blood pressure and analyte levels were (although the values for HDL cholesterol were higher) (Figure 4).

Discussion

In this large contemporary European birth cohort, the mean age at AR was ∼62 months, similar for boys and girls. Younger children at AR presented worse

Table 1 Description of the adiposity rebound and the cardiometabolic indicators in the study participants

	Girls $n = 1622$	Boys $n = 1750$
Age at adiposity rebound (months)[a]	61.4 (15.9)	62.3 (15.4)
Timing of the adiposity rebound[b]		
Very early (<42 months)	242 (14.9)	187 (10.7)
Early (42–59.9 months)	468 (28.9)	540 (30.9)
Normal (60–83.9 months)	747 (46.1)	845 (48.3)
Late (≥84 months)	165 (10.2)	178 (10.2)
Cardiometabolic indicators at age 10 years		
BMI (kg/m^2)[a]	18.8 (3.3)	18.5 (3.2)[d]
Body composition		
Waist circumference (cm)[a]	68.0 (9.5)	67.2 (9.3)[d]
Waist-to-height ratio[a]	0.481 (0.060)	0.477 (0.057)[d]
Fat mass index (kg/m^2)[a]	3.5 (2.2)	2.9 (2.2)[d]
Fat-free mass index (kg/m^2) [a]	15.3 (1.9)	15.6 (1.8) [d]
Blood pressure		
Systolic blood pressure (mmHg)[a]	109.3 (9.6)	109.3 (9.1)
Diastolic blood pressure (mmHg)[a]	68.8 (6.9)	69.1 (7.1)
Blood analytes		
Glucose (mg/dL)[a]	86.1 (6.1)	87.9 (10.2)[d]
Insulin (μU/mL)[c]	9.2 (7.1)	6.8 (5.0)[d]
HOMA-IR[c]	2.0 (1.6)	1.5 (1.1)[d]
Triglycerides (mg/dL)[c]	62.0 (32.0)	55.0 (30.0)[d]
HDL cholesterol (mg/dL)[a]	54.9 (10.6)	56.8 (10.6)[d]
LDL cholesterol (mg/dL)[a]	95.3 (23.1)	93.2 (22.7)[d]
C-reactive protein (mg/L)[c]	0.50 (1.20)	0.40 (0.90)[d]

[a]Mean (SD).
[b]*n* (%).
[c]Median (IQR).
[d]$P < 0.05$ compared with girls, using independent-samples *t*-test.
BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; LDL, low-density lipoprotein.

cardiometabolic profiles at 10 years of age, including higher total and central adiposity, blood pressure, levels of insulin, HOMA-IR, TG and hs-CRP, and lower levels of HDL cholesterol. Children with a very early AR, occurring before the age of 42 months, were those at the highest risk of an impaired cardiometabolic profile.

Since Rolland-Cachera *et al.*[8] first described the AR and the association between an early AR and obesity later in life, a discussion emerged on whether AR represents a critical window of development or whether it is simply an epiphenomenon, resulting from the fact that an earlier AR occurs in children who are already in higher BMI percentiles.[36–38] Later, Cole stated that an early AR corresponded to a high BMI percentile and/or upward percentile crossing, also defending the notion that this association occurred at any age and, given that a critical window of development should have a distinct beginning and end, the period of the AR should not be considered a critical window.[36] However, previous studies have examined the BMI pattern of the percentile curves constructed cross-sectionally, whereas studies using longitudinal data have shown that many children who had an early AR had a normal or even low BMI at or before the AR, followed by an increased BMI after the AR.[21,34,39–41] This was confirmed in the present study, as younger children at AR had a lower BMI at AR but an increased BMI after AR, specifically at 10 years of age. These data refute the idea that AR is merely an epiphenomenon, as previously described, and add to the importance of the timing of AR as a predictor of later BMI and cardiometabolic health. Nevertheless, we must note that, for ~30% of our sample, we could not estimate a rebound in the BMI trajectory. This may reflect the trajectory of children who either have a very late BMI rebound, after the 10 years of age, or, on the other hand, those who never experience a rebound in their BMI trajectory. Thus, for those for whom a BMI rebound could be in fact estimated, it seems that our study hypothesis was verified, as the earlier the AR, the worse the cardiometabolic profile was.

Whether the later higher BMI in early rebounders reflects higher fat or higher fat-free mass has also been a

Table 2 Association between the timing of the adiposity rebound and the z-scores of the cardiometabolic indicators at 10 years of age

	β (95% CI)[a,b]		
	Very early	Early	Late
BMI	0.40 (0.28; 0.53)[c]	0.21 (0.12; 0.30)[c]	−0.21 (−0.35; −0.08)[c]
Body composition			
Waist circumference	0.33 (0.23; 0.43)[c]	0.18 (0.10; 0.25)[c]	−0.12 (−0.23; −0.01)[c]
Waist-to-height ratio	0.34 (0.24; 0.44)[c]	0.14 (0.07; 0.22)[c]	−0.13 (−0.24; −0.02)[c]
Fat mass index	0.24 (0.15; 0.33)[c]	0.14 (0.08; 0.21)[c]	−0.06 (−0.15; 0.04)
Fat-free mass index	0.25 (0.14; 0.35)[c]	0.11 (0.03; 0.19)[c]	−0.16 (−0.27; −0.04)[c]
Blood pressure			
Systolic blood pressure	0.10 (0.01; 0.20)[c]	0.08 (0.01; 0.15)[c]	−0.08 (−0.19; 0.02)
Diastolic blood pressure	0.09 (0.02; 0.16)[c]	0.03 (−0.02; 0.08)	−0.02 (−0.10; 0.06)
Blood analytes			
Glucose	0.02 (−0.13; 0.16)	0.04 (−0.07; 0.15)	0.05 (−0.11; 0.21)
Insulin	0.16 (0.04; 0.29)[c]	0.10 (0.01; 0.19)[c]	0.02 (−0.12; 0.16)
HOMA-IR	0.17 (0.04; 0.29)[c]	0.10 (0.03; 0.19)[c]	0.03 (−0.11; 0.17)
Triglycerides	0.21 (0.08; 0.34)[c]	0.08 (−0.02; 0.17)	0.17 (0.03; 0.31)[c]
HDL cholesterol	−0.18 (−0.31; -−0.04)[c]	−0.04 (−0.14; 0.06)	−0.01 (−0.16; 0.14)
LDL cholesterol	0.03 (−0.10; 0.16)	−0.01 (−0.11; 0.08)	−0.03 (−0.17; 0.12)
C-reactive protein	0.14 (0.02; 0.26)[c]	0.10 (0.01; 0.19)[c]	−0.08 (−0.21; 0.06)

[a]Adjusted for maternal education, pre-pregnancy BMI, tobacco smoking during the third pregnancy trimester, birthweight and infant peak.
[b]Effect estimates and 95% confidence intervals are compared with those of children with normal timing of adiposity rebound.
[c]$P < 0.05$.
BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; LDL, low-density lipoprotein.

matter of discussion. However, evidence indicated that it is mainly attributed to higher fat[8,10,39,41–43] and our results showed that early rebounders had higher fat mass after AR, at 10 years of age. The Taylor *et al*. review[10] concluded that changes in BMI during AR occur due to a high velocity of weight gain, which in turn is due to a rapid deposition of fat rather than fat-free mass, with early rebounders gaining fat mass at approximately three times the rate as late rebounders. Nevertheless, in our study, we also found that early rebounders had higher fat-free mass, which means that the increase in BMI in our sample was due to both fat and fat-free mass.

It has been described that pubertal development could explain the association between earlier AR and worse cardiometabolic profile, as an earlier AR timing could lead to advanced pubertal development,[44] which in turn has been associated with a worse cardiometabolic profile.[45] Only two out of the five cohort studies that analysed the effect of AR timing on cardiometabolic profile in childhood/early adolescence were adjusted for pubertal development and, when the adjustment was performed, the results remained similar.[17,18] In the present study, the timing of AR was not associated with pubertal development, which adds to the evidence against the mediating role of pubertal development on the association between the earlier timing of AR and a worse cardiometabolic profile. However, we have previously found in this cohort that, independently of the BMI prior to the onset of puberty, children with more advanced pubertal development at 10 years of age had already higher adiposity and worse cardiometabolic health.[45]

Another contribution of the present study was the description of the AR in this large European cohort of children born in 2005/2006. The mean age at e AR was 61.9 months, which was very similar to the age of 60.9 months found in a US cohort (Massachusetts)[17] (born in 1999/2002); however, our BMI at rebound was lower (14.5 vs 15.9 kg/m^2). In the cohort from Japan[21] (born in 1995/1996), the age at the AR was ∼57 months, to some extent lower than in our study, and, in the Indian cohort[18] (born in 1997/1998), it was >70 months, which was considerably higher than in our study and the previously mentioned studies. Among our children, 12.7% had a very early AR (<42 months) and 29.9% had an early AR (42–59 months), which was similar to the combined proportion found in the cohort of Chile[19] (born in 2002/2003), in which 46.6% of girls and 40.9% of boys had an early AR (<60 months), whereas the proportion of late AR was 10.2% in our study and it was >20% in the Chilean cohort (>84 months). In a sample of children from the Avon

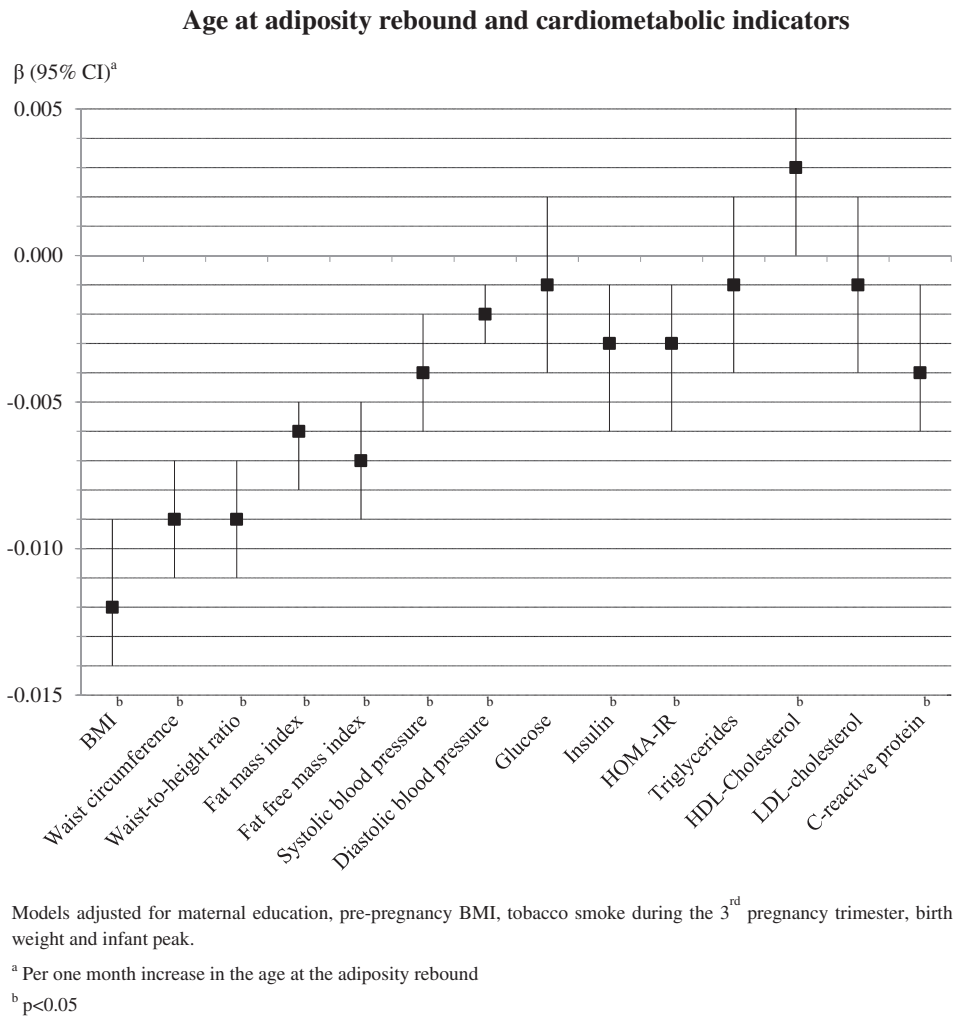

Figure 4 Linear association between the age at adiposity rebound (per 1-month increase) and the z-scores of the cardiometabolic indicators at 10 years of age. Models adjusted for maternal education, pre-pregnancy BMI, tobacco smoking during the third pregnancy trimester, birthweight and infant peak. [a]Per 1-month increase in the age at the adiposity rebound. [b]$P < 0.05$.

Longitudinal Study of Parents and Children (ALSPAC) cohort (born in 1991/1992),[34] 6.9% had a very early AR—a much lower proportion than in the present study—and 20.3% had an early AR. These figures illustrate the differences across populations regarding the age at the AR.

There is also evidence showing that AR now occurs earlier than in the past[10,39,46,47] and it has been argued whether this shift is due to the obesity epidemic or to the secular trend of accelerated growth and pubertal development. Against that former hypothesis is the fact that the shift in the timing of the AR has occurred in different BMI strata[46,48]—among normal and overweight children, but also among underweight ones—adding also to the fact that, in most recent and longitudinal studies such as ours, the BMI before or at the AR is lower among those with early AR.[21,34,40,41]

Currently, both Rolland-Cachera and Cole agree that, independently of whether it is considered a critical window of development, AR is an important phenomenon, predictive of later adiposity and cardiometabolic health.[38] This has been demonstrated in previous studies[16–21] and now, in the present study, using an even larger sample size and contemporary data. The present study also adds to the literature the fact that this association is independent of BMI at the AR, which was lower in early rebounders, and of pubertal development, which was not associated with the timing of the AR.

Hence, importance must be given to the period before the AR, such as the early programming occurring during the first 1000 days of life, in which environmental factors may modify future BMI trajectories. Thus, research on the identification of factors that can influence the timing of AR should help to clarify the early pathways for the development of obesity and impaired cardiometabolic health.[38] For now, in clinical settings, individual growth curves may help to define the age at the AR and thus identify children

at risk of impaired cardiometabolic health in a timely manner and invest in targeted preventive strategies. For the future, the challenge is to identify actions able to delay the age of the AR, which would allow the prevention of early AR and the consequent promotion of a healthier cardiometabolic profile.

Strengths and limitations

The use of data from a large birth cohort of contemporary European children is one of the greatest strengths of the present study. The availability of numerous measures of early-life growth collected in a prospective manner, the long-term follow-up and the wide range of cardiometabolic indicators measured by trained examiner using standardized protocols are also important strengths of this study. Additionally, a well-fitting growth curve was used to estimate the AR.

Weight and height measurements used to calculate BMI were based on routine recordings in a clinical setting, where measurement errors are believed to be random and thus tend to attenuate the associations between age at the AR and cardiometabolic indicators. Moreover, it was previously shown by Howe *et al.*[49] that such measurements are accurate for research purposes and are not systematically biased.

The multiple cardiometabolic indicators explored as outcomes increased the risk of false-positive results, which could be a limitation. However, we decided not to adjust for multiple comparisons and instead base the 'significance' of our conclusions on the strength and consistency of the associations observed across the outcomes.[50]

Another potential limitation of this study was the differences observed between the included and excluded participants. Compared with non-participants, participants presented higher maternal education and age, and a higher number of BMI measurements (Supplementary Table 1, available as Supplementary data at *IJE* online).

Conclusion

The present study concluded that, in contemporary European children, the mean age at AR was ~62 months. For each month decrease in the age at AR, the cardiometabolic profile worsened at 10 years of age. Children with a very early AR are those at the highest risk of impaired cardiometabolic health.

Supplementary Data

Supplementary data are available at *IJE* online.

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Conflict of interest

None declared.

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