

**Title:** Early childhood BMI trajectories in relation to pre-clinical cardiovascular measurements in adolescence

**Short Title:** BMI trajectories and cardiovascular health

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**ABSTRACT** (225 words)

Cardiovascular diseases are the leading causes of morbidity and mortality. Overweight, obesity and accelerated growth during early childhood have been associated with adverse cardiovascular outcomes in later life. Few studies have assessed whether trajectories of accelerated growth in early childhood are associated with pre-clinical cardiovascular measurements. We aimed to evaluate the associations between childhood BMI growth trajectories and measures of macro- and microvascular function in early adolescence. Measurements of macrovascular function (systolic and diastolic blood pressure (SBP and DBP), pulse wave velocity (PWV)) and microvascular function (central retinal artery/vein equivalent) were assessed at 11 years old in a Spanish birth cohort study (n=489). BMI trajectories from birth to 9 years were identified using latent class growth analysis. Multiple linear regression assessed the associations between the BMI trajectories and macro- and microvascular function. Compared to children with average birth size and slower BMI gain (reference), children with a lower birth size and accelerated BMI gain had increased SBP [ $\beta=6.57$ ; (95%CI 4.00, 9.15)], DBP [ $\beta=3.65$ ; (95%CI 1.45, 5.86)], and PWV [ $\beta=0.14$ ; (95%CI 0.01, 0.27)]. Children with higher birth size and accelerated BMI gain had increased SBP [ $\beta=4.75$ ; (95%CI 1.79, 7.71)] compared to the reference. No significant associations between BMI trajectories and the microvascular measurements were observed. In conclusion, we found that childhood BMI trajectories characterized by accelerated growth are associated with pre-clinical macrovascular measurements in young adolescents.

**Keywords:** growth, growth trajectories, body mass index (BMI), blood pressure, cardiovascular health

## INTRODUCTION

Cardiovascular diseases are the leading causes of morbidity and mortality and a considerable part of their origin is likely to lie in fetal and childhood life. Recent research shows that cardiovascular risk in young and middle-aged adults can be traced back to higher risk in childhood and adolescence <sup>1,2</sup>. Measures of obesity and adiposity, blood pressure, and other markers of macro- and microvascular function during childhood have been associated with later cardiovascular morbidity and mortality <sup>2-5</sup>. For example, childhood blood pressure predicts adult blood pressure and other markers of cardiovascular disease <sup>6</sup>, and obesity during childhood has been shown to be associated with increased arterial stiffening, a potential precursor to atherosclerosis, during childhood and adulthood <sup>7,8</sup>. Further, structural changes in the microvasculature during childhood, as measured through retinal vein and artery diameters, have been linked to arterial hypertension, coronary heart disease, diabetes mellitus and obesity in adulthood <sup>9,10</sup>. Retinal venular widening is indicative of inflammation and atherosclerosis, while arterial narrowing is indicative of arterial damage <sup>10</sup>.

The developmental origins of health and disease hypothesis states that developmental programming during the pre- and early postnatal periods is sensitive to certain exposures that appear to play a critical role in future disease risk <sup>11</sup>. Accelerated growth during the postnatal period is one such exposure, suggested to play a role in adverse cardiovascular health over the life course, particularly among those with low birthweight. <sup>12,13</sup>. Studies examining the relationship between individual aspects of growth (e.g. birthweight, accelerated growth, obesity and adiposity status) have found that these different aspects are associated with risk factors for cardiovascular disease in later life such as, increased cholesterol, blood pressure, pulse wave velocity (PWV), and adverse changes to the retinal microvascular structure <sup>10,14-19</sup>. Fewer studies have utilized growth trajectories which integrate growth information over a period of time, thereby permitting a more accurate identification of children at a higher

disease risk than just growth assessed at a single time point<sup>20-24</sup>. These studies found associations between growth trajectories characterized by accelerated growth or early overweight/obesity and increased blood pressure, augmentation index (a measure of arterial stiffness), and cardiovascular risk during adolescence and early adulthood<sup>20-24</sup>.

As previous studies primarily focused on measures of macrovascular health (e.g. blood pressure) or examined cross-sectional associations between infant growth or obesity and vascular health, there is need to examine the relationship between growth trajectories and a wider range of cardiovascular health measures. Therefore, in the present study, we aimed to evaluate the associations between childhood BMI growth trajectories from 0 to 9 years and pre-clinical cardiovascular measurements of macrovascular function (systolic and diastolic blood pressure, pulse wave velocity) and microvascular function (central retinal artery and vein equivalent) in young adolescents at 11 years old.

## **METHOD**

### **Study Population**

We studied children from the INMA (Infancia y Medio Ambiente, Environment and Childhood) birth cohort study from Sabadell, Spain. A total of 787 women were recruited at 10-13 weeks of gestation or at birth through regional hospitals from 2004 to 2007. The inclusion criteria were:  $\geq 16$  years of age, singleton pregnancy, intention to deliver at reference hospital, no assisted conception or communication issues<sup>25</sup>. Children and their families were followed up with at 28-32 weeks gestation, birth, and child's age 6 months, 1, 2, 4, 7, 9 and 11 years<sup>25</sup>. Information was collected through medical registries, interview-based questionnaires with the mothers, and physical examinations of the children conducted by specially trained personnel<sup>25</sup>. The present analysis was limited to children who participated in the 11 year follow-up and who had both a BMI trajectory and at least one

cardiovascular measurement available (N = 454-489, depending on outcome) (Figure 1). This study was approved by the Ethics Review Boards of the hospitals involved in the study. All mothers signed a written consent for themselves and their child's participation.

### **Growth Trajectories**

Repeated measurements of child's height and weight from birth to 9 years of age were extracted from medical records and measurements taken by trained INMA staff. Children were measured using standardized protocols, always without shoes and in lightweight clothing. BMI was calculated using the standard equation ( $\text{kg}/\text{m}^2$ ), and age and sex specific BMI z-scores were calculated using the WHO Child Growth Standards <sup>26,27</sup>.

BMI z-score trajectories (referred to as BMI trajectories hereafter) were previously estimated from 0 to 4 years using latent class growth analysis (LCGA) <sup>28,29</sup>. Following the same methods, the trajectories were extended to 9 years (mean=9.9 years) with an average of 14.3 measurement points per child. Five distinct BMI trajectories from birth to 9 years of age were identified as the best fit. Extending the trajectories to 9 years did not change the classes from the previously identified trajectories. The trajectories differed in birth size (defined as "lower", "average" or "higher") and in BMI gain velocity (defined as "slower" or "accelerated") (Figure 2). Based on these differences the five trajectories are: class 1, larger birth size with subsequent accelerated BMI gain; class 2, larger birth size with subsequent slower BMI gain; class 3, smaller birth size with subsequent accelerated BMI gain; class 4, average birth size with subsequent slower BMI gain; and class 5, smaller birth size with subsequent slower BMI gain. For analysis, we used class 4 as the reference category.

### **Cardiovascular Measurements**

INMA research nurses trained to use the necessary technology carried out the cardiovascular measurements. Children were visited during school time for the assessment.

### ***Blood Pressure***

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using an automated oscillometric device OMRON 705IT with brachial cuff attached. Children were asked to sit down in a chair and positioned with their arm and back supported and their legs uncrossed with both feet on the floor. The cuff was placed on the child's arm positing the artery index marker over the child's brachial artery. After 5 minutes of rest, 3 consecutive measurements were taken with one-minute intervals between. SBP and DBP measures were averaged using the 2<sup>nd</sup> and 3<sup>rd</sup> measures taken. Values are presented in millimeter of mercury (mmHg).

### ***Pulse Wave Velocity***

Pulse wave velocity (PWV) was recorded using VICORDER®, an arterial stiffness testing system with neck cuff and femoral thigh cuff attached in combination with the VICORDER® vascular diagnostic program package. To do this, the child laid in the supine position with a support to raise their head and shoulders 30° above their heart level. The thigh cuff was placed on their upper right thigh as high as possible, and the neck cuff was placed after palpating the pulse of the right common carotid artery. The 80% method was used (80% of the measured direct distance between the carotid and femoral recording sites) to ensure the smallest possible measurement error. With the child relaxed and still, three waveform measurements were recorded with the nurse observing a stable wave pattern. PWV measures were averaged using the three initial measurements. Values are given in meter per second (m/s).

### ***Central Retinal Artery/Vein Equivalent***

Retinal images were photographed using a Canon CR2-Plus Non Mydriatic retinal camera which provides information on retina changes not visible with standard photography. The child was seated behind the camera with their chin on the chin rest and their forehead pressed to the overhead bar (glasses were removed if needed). The child was asked to look straight into the camera lens while the operator used software guides to properly align the child's eye using the joystick, finally taking the retina image. Photos were taken from both the left and right eyes and saved in high resolution for later analysis with the IFlexis software (version 2.1.1, VITO Health, Mol, Belgium). This software calculates the Central Retinal Vein Equivalent (CRVE) and Central Retinal Artery Equivalent (CRAE) using the Parr-Hubbard-Knudtson formula<sup>30</sup>. Average CRVE and CRAE were calculated using the big 6 methodology; an average of the six widest arterioles and venules running through a zone between 0.5 and 1 disc diameter from the optic disc margin<sup>31</sup>. Processing of these measurements was carried out by one trained researcher to limit observer variability. CRAE and CRVE measures were averaged between the right and left eyes. Values are denoted in micrometer ( $\mu\text{m}$ ).

### **Statistical Analysis**

Our analysis included a maximum of 489 children. After confirming normality of residuals, homoscedasticity and outliers, associations between child BMI trajectories and cardiovascular measurements were assessed using multiple linear regression. Covariates were selected using directed acyclic graphs (DAGs). Models were adjusted for child age at cardiovascular measurement (years), child sex (male/ female), gestational age (weeks), family socioeconomic status (SES) (low/middle/high) based on occupation using the Goldthorpe model, maternal smoking during pregnancy (none/until 1<sup>st</sup> trimester/until 3<sup>rd</sup>

trimester), maternal prepregnancy BMI ( $\text{kg}/\text{m}^2$ ), paternal BMI ( $\text{kg}/\text{m}^2$ ), and parental cardiovascular history (neither parent has diagnosis/1 parent has at least one diagnosis/both parents have at least one diagnosis) based on questionnaire data from parents on previous cardiovascular events: heart attack, angina, hemorrhage or stroke, atherosclerosis in legs, high cholesterol, high blood sugar, and high blood pressure. SBP, DBP and PWV were additionally adjusted for child's height (cm) at cardiovascular measurement. BMI was not included in the models because the DAG indicated that it was a mediator rather than a covariate. Further variable descriptions can be found in Supplemental Material Table S1.

In order to maximize sample size, multiple imputation generating 20 datasets was performed to handle missing covariate observations (missing values between 1-13%). Imputation was carried out using the multiple imputation by chained equations (MICE) approach using the *ice* command in STATA 14. This approach assumes that data is missing at random, thus additional covariates were added to the predictive models for more accurate imputation. The imputed data were used for our main analyses and results were combined using Rubin's combination rules.

To assess any differences by sex, we stratified the associations. Further, we conducted the following sensitivity analyses: a) not adjusting for height for associations with SBP, DBP and PWV; b) removing those children with incomplete measures (less than 2 measures for SBP and DBP or less than 3 measures for PWV) or less than good quality measures (as assessed by a trained researcher and computer software) for CRAE and CRVE; c) a complete case analysis using the non-imputed dataset; and d) cross-sectional analysis of zBMI and cardiovascular measurements.



Statistical significance was defined at p-value <0.05. LCGA analysis for determining the BMI z-score trajectories was performed using the “lcm” function in Rstudio. All other analyses were conducted using STATA version 14 (College Station, TX).

## RESULTS

Study population characteristics are presented in Table 1. There was virtually no difference between socioeconomic status (SES) categories. On average both parent’s had a normal prepregnancy BMI, and the majority of mother’s (73%) did not smoke during pregnancy. Approximately 40% of children had one parent with at least one diagnosed cardiovascular condition (Table 1). At the time of cardiovascular measurement, on average children were 11 years old, weighed 42 kilograms (kg) and were 146 centimeters (cm) tall. Imputed study population data can be found in Supplementary Material Table S2.

Children were most likely to belong the reference trajectory, class 4, characterized by average birth size and slower BMI gain (35%). Subsequently; class 1, higher birth size and accelerated BMI gain (9.8%); class 2, higher birth size and slower BMI gain (27%); class 3, lower birth size and accelerated BMI gain (13.7%); and class 5, lower birth size and slower BMI gain (14.5%) (Table 1 and Figure 1).

Average SBP and DBP were 101.6mmHg and 59.5mmHg, respectively (Table 1). Average PWV was 4.4 m/s, and average CRAE and CRVE measures were 180.6µm and 252.0µm, respectively. Averages and standard deviations for each cardiovascular measurement by BMI trajectory can be found in Table 2. Correlation coefficients between cardiovascular measurements can be found in Supplementary Material Table S3 and Figure S1.

In covariate only analyses, boys had higher SBP and PWV, and smaller CRAE and CRVE measurements than girls (Supplementary Material Table S4). Those children with lower

family SES had higher SBP and DBP than those with higher SES. Height and maternal prepregnancy BMI were positively correlated with SBP and PWV, while gestational age was positively correlated with CRAE. Children of mothers who smoked through the 3<sup>rd</sup> trimester had higher SBP and PWV compared to those whose mothers did not smoke, and children with one parent with a cardiovascular event in their history had higher PWV compared to those with parents with no history.

Table 3 shows the adjusted associations between BMI trajectories and cardiovascular measurements. Compared to children with average birth and slower BMI gain (class 4, reference trajectory), children with a lower birth size and accelerated BMI gain (class 3) had a higher SBP [ $\beta=6.57$ ; (95%CI 4.00, 9.15)], DBP [ $\beta=3.65$ ; (95%CI 1.45, 5.86)], and PWV [ $\beta=0.14$ ; (95%CI 0.01, 0.27)]. The BMI trajectory with children with higher birth size and accelerated BMI gain (class 1) showed an increase in SBP [ $\beta=4.75$ ; (95%CI 1.79, 7.71)] compared to the reference trajectory. We found no significant associations between BMI trajectories and the retinal measurements, CRAE or CRVE. Crude associations were similar although higher, and all significant associations remained the same (Supplementary Material Table S5).

Overall, results were similar to main analyses when stratifying by sex. We found that both boys and girls with accelerated BMI gain (class 1 and 3) had a higher SBP (Supplementary Material S5). However, we found that the observed associations for children with a lower birth size and accelerated BMI gain (class 3) with DBP and PWV were only significant for boys. Furthermore, girls from class 2 characterized by higher birth size and slower BMI gain had a decreased PWV when compared to the reference.

In sensitivity analyses, not adjusting for height strengthened all associations (Supplemental Material Table S7). No significant differences were found between children with complete

measures and those with incomplete measures for DBP, PWV, or those with less than good measures for CRAE and CRVE (Supplemental Material Table S8-S9). Complete case analyses showed similar results to analysis with imputed data (Supplementary Material Table S10). Cross-sectional analysis showed similar significant relationships between zBMI and the cardiovascular measurements, however associations were stronger with the BMI trajectories (Supplementary Material Table S11).

## **DISCUSSION**

In this prospective population-based study in Spain we found that BMI trajectories from birth to 9 years were associated with preclinical macrovascular measurements in young adolescents at 11 years. Specifically, we found that children with a lower birth size and accelerated BMI gain (class 3) had increased SBP, DBP and PWV, when compared to the reference class. Children with a higher birth size and accelerated BMI gain (class 1) had increased SBP. We found no associations between BMI trajectories and retinal microvascular measurements.

### **Macrovasculature**

We found that a trajectory characterized by lower birth size and accelerated BMI gain during infancy and early childhood was associated with increased measurements of macrovascular function. Previous longitudinal studies using growth trajectories have found similar results<sup>21-24</sup>. One study that analyzed pre-/postnatal growth trajectories found that those with decreased or normal fetal growth and accelerated infant growth had higher blood pressure<sup>24</sup>. Other studies found that rapid weight gain from the first year onward and early persistent obesity were positively associated with SBP and DBP in young adults of 18 years old<sup>20,22</sup>. While an Australian birth cohort that identified growth trajectories from birth to 14 years did not find associations between growth trajectories and blood pressure or PWV, they did find

that augmentation index was higher in consistently overweight children <sup>21</sup>. Augmentation index is an independent measure to PWV, but they are both measures of macrovascular structure function and specifically arterial stiffness. Lycett et al. found that those in an “always very high” zBMI trajectory from 2-11 years had higher PWV at 11-12 years old <sup>32</sup>. Additionally, in our study we observed that those with a higher birth size followed by accelerated BMI gain had higher SBP. Likewise, Boyer et al. calculated trajectories from 15 months to 10.5 years of age and found that higher BMI at 15 months coupled with slower declines before adiposity rebound and faster BMI rebound after adiposity rebound, predicted higher adolescent cardiovascular risk as calculated using waist to height ratio, skinfold thickness, SBP and BMI <sup>23</sup>.

Blood pressure and PWV are closely related measures of the macrovascular system. Young people with hypertension have been shown to have similar heart damage as the elderly <sup>33</sup>, and hypertension, once developed early in life, is irreversible <sup>34</sup>. Further, PWV is an indicator of early vascular alterations and is considered the most precise noninvasive measurement of arterial stiffness related to cardiovascular events and mortality in adults <sup>5</sup>. From the aforementioned studies, including our own there is a pattern of higher blood pressure and PWV (or other arterial stiffness marker) associated with accelerated growth during infancy or afterward. Given that childhood blood pressure tracks into adulthood and hypertension is a risk factor for cardiovascular disease <sup>6</sup> identifying early risk factors should be a priority to avoid adverse health outcomes in later life. Identification of children and/or adolescents at high-risk through the use of growth trajectories may be helpful for preventative strategies targeting the reduction of cardiovascular events. One of the most important modifiable risk factors for cardiovascular health is overweight and obesity. Juonala et al. observed that children who had overweight or obesity but achieved normal weight status by adulthood had a similar cardiovascular risk to those who never had overweight or obesity <sup>2</sup>. These results

show that children's bodies are still flexible and developing, which may imply that their cardiovascular system is more adaptable than during adulthood indicating a point of reversibility during childhood.

### **Microvasculature**

There are a limited number of studies that have used retinal measurements to assess cardiovascular outcomes in healthy children and adolescents. In our study, childhood growth trajectories were not associated with microvasculature measured through retinal imaging. Comparably, an Australian study did not observe an association between their calculated growth trajectories and microvasculature measured by the arteriole-to-venule ratio (AVR= $\text{CRAE}/\text{CRVE}$ )<sup>21</sup>. To our knowledge this is the only other study to have assessed retinal microvascular measurements with growth trajectories. However, a systematic review of cross-sectional studies found that adverse retinal vascular changes were associated with childhood overweight and obesity<sup>10</sup>. This cross-sectional relationship was not found in our study.

Given that we took measures of both micro and macrovasculature, we had initially hypothesized to find changes in the microvasculature structure associated with the child growth trajectories if changes in the macrovasculature were observed. In diabetic individuals it has been shown that microvascular disease plays a causative role in the development of macrovascular disease, and the two diseases being highly intertwined<sup>35</sup>. However, in many instances, changes in the micro and macrovascular structures are observed together, and it remains unclear whether microvascular changes precede macrovascular changes or occur concurrently. This is even less clear in the case of healthy children. The small body of research in this area does seem to indicate a relationship between overweight and obesity and adverse changes in the retinal microvasculature, however we did not find this in our study.

Given that the observed differences in previous studies were small, perhaps our study lacks sufficient variability and/or sample size to observe such changes.

### **Strengths and limitations**

Major strengths of this study were the longitudinal study design that permitted the collection of repeated weight and height measurements to be able to calculate the distinct BMI trajectories, and the detailed measures of micro- and macrovasculature structure utilized.

Further, the strong follow-up in the INMA study permitted us to measure micro- and macrovascular function in a pediatric population, that is otherwise infrequently measured.

This study also had some limitations. Our small sample size was prohibitive in that we were not able to stratify groups further by potentially important modifying factors like SES.

Although we controlled for SES in our regression models there may still be some residual confounding given that SES was based solely on occupation. In initial models we tested SES based on occupation and maternal education as potential markers of SES and found similar results with both variables. Nevertheless, we cannot exclude residual confounding by unmeasured social factors related to cardiovascular measures in young adolescents. Further, longitudinal studies are prone to selection bias and our study is no exception. Those with an interest in research and of higher SES tend to agree to participate and continue. However, follow-ups were done in the school setting, making it more easily accessible for children to participate. Lastly, there was little variation for all cardiovascular measurements. This is most likely due to the fact that these measurements were taken in healthy children during early adolescence. Nevertheless, we still found significant differences with macrovascular measurements across BMI trajectories.

### **Implications**

Our study offers an important contribution to the current literature, as we were able to demonstrate two distinct patterns of accelerated BMI gain (departing from higher and lower birth size) and show that both patterns of accelerated growth are associated with measures of preclinical macrovascular health. A study by Barker et al. previously found that the risk of coronary events in later life is more related to tempo (i.e. rate or speed) of childhood BMI gain rather than BMI at any particular age<sup>12</sup>. Like Barker's findings, other studies concluded that chronic diseases were most common in children who experienced weight gain after infancy, and weight gain during infancy (0-2 years old) had less impact on cardiovascular risk than weight gained during later childhood years<sup>13,19</sup>. While these findings relate to participants of lower birth size and accelerated growth after infancy our study shows that the same may in part be true for those born at higher birth size and experience accelerated BMI gain during infancy. One potential explanation for the reported differences could be the income level of the study population country. The aforementioned studies reported results from low to middle income countries where rapid/catch-up growth during the first two years in otherwise small infants may be protective<sup>36</sup>. This may not be the case in high income countries like Spain where our study population is from.

To further quantify our results on the population level, knowing that blood pressure tracks from childhood to adulthood<sup>6</sup>, a reduction of SBP as little as 2 mmHg could result in a 10% decrease in stroke and a 7% decrease in coronary heart disease during middle age<sup>37</sup>. Being able to identify those at the highest risk for coronary events at the earliest age possible may be possible through BMI trajectories. BMI trajectories are non-invasive and easily calculated measures. Additionally, using blood pressure and PWV screening in those children with higher risk growth trajectories (i.e. those who have an accelerated growth trajectory pattern) may be a novel way to identify those at greatest risk for cardiovascular disease during

adulthood, early in life, while damage may be reversible and set the child on a healthier trajectory.

## **Conclusion**

We conclude that BMI trajectories from birth to 9 years are associated with preclinical macrovascular measurements in young adolescents at 11 years. This study provides evidence that accelerated growth, especially in those of lower birth size, during infancy is a risk factor for higher systolic and diastolic blood pressure, and pulse wave velocity in early adolescence. This subset of the population that may be at greater risk for cardiovascular disease later in life. This knowledge could be used to help prevent future cardiovascular disease by targeting individuals at need for extra monitoring and lifestyle interventions. Prevention strategies for future mothers and throughout infancy and childhood should be a priority to avoid adverse health outcomes in later life.

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### **CONFLICTS OF INTEREST**

None.

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