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Relationship between prenatal and postnatal conditions and accelerated postnatal growth. Impact on the rigidity of the arterial wall and obesity in childhood

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Original Article

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Abstract

Restricted growth *in utero* and accelerated postnatal growth (APG) in the postnatal period have been associated with the development of overweight, obesity and an increased cardiovascular risk in childhood. The objectives of this study were to evaluate the influence of prenatal and perinatal conditions on APG and to evaluate the influence of this APG on different cardiovascular risk factors such as body mass index (BMI), body fat mass index (FMI), blood pressure (BP) and arterial wall stiffness [carotid to femoral pulse wave velocity (cf-PWV)]. All measurements were performed in 355 children (185 boys and 170 girls; 8–11 years). Data on mother weight before and during pregnancy, gestational age (weeks), birth weight (g) and breastfeeding of children were obtained through interviews with families. Children who presented APG were born of mothers with lower BMIs before pregnancy and who gained less weight during the second trimester of pregnancy. They also have a lower gestational age and birth weight, a shorter duration of breastfeeding and a longer duration of artificial feeding (AF). Later in childhood, they had higher values of cf-PWV, BMI, FMI and higher prevalence of hypertension. Low maternal gestational weight gain, inadequate fetal development (low birth weight, shorter gestational age) and reduced breastfeeding duration favor APG. Infants with such APG had higher values of cf-PWV, BP, BMI and FMI later in childhood, along with a higher risk of hypertension and obesity. The interaction between APG and a longer duration of AF had a negative effect on cf-PWV (arterial stiffness) and FMI.

Introduction

Restricted growth *in utero* and accelerated postnatal growth (APG) in the postnatal period have been associated with the development of overweight and obesity[1–3] and an increase of cardiovascular risk factors (CVRFs) in later stages of life.[4,5] Although there is no uniform definition of APG in the literature,[6] it can be considered a rapid gain in height and weight along during the first 2 years of life.[5,7]

Among the fetal conditions considered as potential determinants of APG, the nutritional status of the mother during pregnancy and birth weight are the best known.[8–13] With regard to postnatal conditions, there is evidence of the effect on the APG of short breastfeeding.[6,14] Conversely, research conducted in recent decades shows that children fed formula milk have a greater weight gain for their age compared to those who receive breast milk in the same period.[6,7,14–16]

Despite an APG in the short term may be beneficial to the underweight child's health, as it reduces morbidity up to 5 years of age,[17,18] this 'catch-up' may increase the risk of cardiovascular disease (CVD) in childhood and adulthood.[3,15,19–27] Many published papers have focused on the influence of different prenatal, postnatal and maternal factors on childhood body mass index (BMI)[1–3,28] and hypertension,[26] but not much is known about the underlying mechanisms responsible for higher values of blood pressure (BP) in childhood. Some studies have focused on the importance of early arterial stiffness as a trigger for hypertension in adulthood[29] and finding an association between both inadequate fetal growth[30,31] and APG[32] with greater arterial wall thickness and a consequent increase in arterial stiffness.[33] Such rigidity is a risk factor for CVD in adulthood,[34] and is dependent on the amount and organization of collagen and elastin protein fibers.[33]

Arterial elastin fibers are synthesized from the earliest stages of fetal development, reaching a maximum at the end of the third trimester of pregnancy, gradually decreasing its synthesis until the end of the process of growth and development in adolescence.[35,36] If the environmental conditions during this key period are adverse (malnutrition, illness etc.), synthesis and

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organization of elastin and collagen in blood vessels are affected and may lead to permanent changes in their mechanical properties. Therefore, an arterial wall with less and/or disordered elastin is stiffer.[35–37]

The results of research on aspects related to growth and development during the fetal stage and during infancy and its contribution to the development of cardiovascular pathologies are fundamental for the promotion and prevention of health throughout the lifecycle.

Objectives

The aims of the present study were to evaluate in a sample of 8–11-year-old children the influence of their prenatal and perinatal conditions on APG in infancy and to evaluate the influence of this accelerate growth on different CVRFs such as BMI, body fat %, fat mass index (FMI), systolic and diastolic blood pressure (SBP, DBP) and carotid to femoral pulse wave velocity (cf-PWV) (a direct indicator of arterial wall stiffness).

Methods

Population and sample group characteristics

Data were gathered at schools in the Autonomous Community of Madrid after the approval of the school board. Earlier, observing the ethical standards for research on human beings set forth in the Helsinki Protocol[38] and Spanish Organic Law 15/1999 of 13 December on personal data protection, the project protocol was approved by the Ethics Committee of the Universidad Autónoma de Madrid. Participation in the study was voluntary, and the families signed informed consent documents allowing their children's inclusion before collection of any data. Only girls and boys with no previous history of arterial disease or hypertension and no current antihypertension medication were included in the study; girls with the onset of menarche were also excluded.

The sample consisted of 355 children (185 boys and 170 girls) with ages ranging from 8–11 years, with an average age of 10.2 years (SD = 1.07) for boys and 10.1 years (SD = 1.1) for girls ($t = 0.911$; $P = 0.363$).

The following variables were considered in the study:

Social demographic variables, parental phenotypes and peri- and postnatal factors.

Parental socioeconomic and anthropometric characteristics were obtained through interviews with families, including maternal/paternal education (higher education and others) and maternal/paternal smoking (yes/no). Parental phenotypic information comprised parental height (cm), weight (kg) and BMI) (kg/m^2). Antenatal factors included pre-pregnancy mother BMI (kg/m^2), maternal weight gain (kg) in the first, second and third trimesters of gestation and total maternal weight gain (kg) during the pregnancy. Values obtained for gestational weight gain were compared to the reference values from the subcommittee on nutritional status and weight gain during pregnancy of the USA National Academy of Sciences.[39] Weight gains were categorized as insufficient if the mothers had gained less weight than recommended, according to their pre-pregnancy BMI (kg/m^2). Peri- and postnatal factors included number of births in the delivery (one or more) and gestational age computed as the number of completed weeks of gestation from the date of the mother's last menstrual period to delivery.

This information was completed with the birth data that appear in the children's health booklets of each child, thus ensuring greater reliability in data collection. Information on gestational age, weight (g) and length (cm) at birth, at 1 year and at 2 years of age were collected from the health cards provided by the family. Retrospective information on duration of exclusive breastfeeding (EB), weaning age and total duration of breastfeeding (B) were also collected. Categories defined by the World Health Organization (WHO)[40] were used; EB: children who received only breast milk and no other liquid or solid except for vitamin drops or syrups, mineral supplements or medications; artificial feeding (AF): children who only received formula and children fed with breast milk and formula (B + F).

Measurement of body size and accelerated growth in infancy (birth to 2 years)

Subsequently, the weight at birth (g) was classified in a new variable with three categories: low birth weight (<2500 g), normal birth weight (2500–3999 g) and macrosomia (⩾4000 g). The American College of Obstetricians and Gynecologists (ACOG) defines macrosomia as birth weight over 4000 g irrespective of gestational age or >90th percentile for gestational age.[41] Intrauterine growth retardation (IUGR) was considered to be a birth weight <2500 g at a gestational age ⩾37 weeks.

Considering together the weight at birth and the weeks of gestation, another new variable was created in three categories:

- Normal; children born with >2500 g and 37 or more weeks of gestation
- Premature newborn; born with >2500 g and less of 37 weeks of gestation.
- IUGR; children born weighing <2500 g and with 37 weeks or more of gestation.

BMI was derived as body weight/(length or height)^2 (kg/m^2), and z-scores for body weight, length or height, and BMI for age were calculated using the WHO Growth Standard.[42,43]

APG in infancy was defined as a body weight z-score increase >0.67 SD between birth and 2 years,[6,7,14,15,25,28,44,45] the period hypothesized to be critical for the development of CVD.[21,22,27,46]

Anthropometric variables and indexes in childhood (8–11 years)

Weight (kg) and height (cm) were measured according to the International Biological Program guidelines.[47] All measurements were taken by trained specialized staff, using certified and approved instruments. Height was measured with a GPM anthropometer with a range of 0–2100 mm and a precision of 0.1 mm. Weight was measured on a digital scale with a range of 0–130 kg and a precision of 100 g. We also measured umbilical waist circumference (WC, cm) as an indicator of abdominal adiposity.[48,49]

The z-scores for weight, height and BMI were calculated using the 2007 WHO values as reference,[42] classifying the children as thin (< −2 SD), normal weight (between −2 and 1 SD), overweight (between 1 and 2 SD) and obese (⩾2 SD).

Biceps (mm), triceps (mm), subscapular (mm) and suprailiac (mm subcutaneous fat skinfolds) were measured using a 'Holtain'

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skinfold caliper with a range of 0–48 mm and precision of 0.2 mm. Body fat mass percentage (BFM%) was calculated from skinfold data after calculating body density (*D*) using Brook's equation:[50]

- Boys: D (kg/cm^3) = 1.1690–0.0788 × log (Σ skinfolds)
- Girls: D (kg/cm^3) = 1.2063–0.0999 × log (Σ skinfolds)

Having obtained *D*, calculations were made to find the BFM% using the expression proposed by Siri:[51]

$$\text{BFM}\,\% = [(4.95 / D) - 4.50] \times 100$$

Fat mass (FM, kg) was calculated as (BFM%/100) × body weight (kg). Fat mass index (FMI, kg/m^2) was FM (kg) divided by height squared (m^2), in order to adjust the body composition for height.[52]

Arterial pressure in childhood (8–11 years)

SBP and DBP (0–280 mmHg) were measured with a Diagnostec EW-BU30 automatic oscillometric tensiometer (Panasonic). All measurements were taken in the morning, with the child in a seated position with back supported and left arm uncovered and supported at heart level, legs uncrossed and feet flat on the floor after at least 5 min of rest. Arm circumference was measured at the midpoint between the acromion and olecranon for selecting the appropriate cuff (17–30 cm). Two consecutive measurements were registered, with the mean taken as the clinical SBP and DBP. In cases yielding high BP values, the family was informed and a visit to the pediatrician was recommended. The values obtained for each boy and girl were compared against the reference values for sex, age and height given in 'The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents'.[53] Subjects with BP values below the standard percentile 95 (p95) were placed in the 'normotensive' category, and children with SBP or DBP above the standard percentile 95 (⩾ p95) were considered 'hypertensive'. Mean arterial pressure (MAP) was calculated by the formula [SBP + (2 × DBP)]/3.

Obesity and hypertension in childhood (8–11 years)

Children with obesity and arterial hypertension (AHT) were identified, and a new variable was created, CVRF, comprising two categories: 0 – absence of CVRF and 1 – presence of obesity and hypertension.

Arterial stiffness in childhood (8–11 years)

Measuring cf-PWV by tonometry is an appropriate method for determining arterial stiffness of large arteries and its use is recommended by the European Society of Hypertension and the European Society of Cardiology,[54–56] which is an important predictor of cardiovascular morbidity and mortality, independent of high BP.[55–58] Regardless, the cf-PWV reference values for healthy children and adolescents are still limited.[59–62]

cf-PWV was determined by means of the SphygmoCor® system.[63] Measurements were taken at a transcutaneous level by means of a tonometer which, through applanation, gathers pulse readings at two arterial points: between the carotid artery, a direct branch of the aorta and the right femoral artery, combining the two at a fixed point in the cardiac cycle by means of an electrocardiogram (ECG) reading. Monitoring the ECG during measurement ensured detection of the pulse wave initiation point. Measurements were taken at the right carotid artery, 1 cm below the carotid bulb, with the individual in supine decubitus 5 min before measurement, with the head turned 45° to the left.[54,63] The distance in millimeters between the two points (carotid and femoral) was measured on the body surface in order to establish a distance/time ratio based on the time lapse. The best distance estimate in adults (and probably also in children) is 80% of the full carotid–femoral distance.[64] Therefore, all cf-PWV values were adjusted to the standard distance to calculate the standard cf-PWV. To prevent any potential methodological bias, a single trained researcher performed all of the cf-PWV measurements.

Statistical analyses

Data analysis was performed using SPSS version 21.0 for Windows. The Kolmogorov–Smirnov test was used to test continuum variable normality. Comparisons of two means in normal data were analyzed with *t*-test, and in non-normal data were analyzed with Mann–Whitney *U*-test. χ^2-test was used to compare proportions.

Variables fitting normal distribution

Maternal height (cm), paternal height (cm), paternal BMI (kg/m^2), weight at 2 years (kg) and current characteristics of children: height (cm), weight (kg), BFM%, SBP (mmHg), DBP (mmHg), mean arterial pressure (MAP) (mmHg) and cf-PWV (m/s).

Generalized linear models were performed to analyze the contribution of different perinatal factors in the explanation of the variability observed in the main indicators of cardiovascular health used in the study, such as cf-PWV (arterial stiffness indicator), FMI (body fat accumulation indicator). Independent variables considered were pre-pregnancy mother BMI, maternal weight gain during the second trimester of pregnancy, duration of AF (main variables that influence the APG of growth) and infant weight gain between 0 and 2 years of age (AG). In order to control confounding factors such as birth weight and weeks of gestation, we performed the generalized models separately in children born with low weight, normal weight and macrosomia. The significance level for all tests set to $P < 0.05$.

Results

Socioeconomic characteristics, accelerated growth and indicators of cardiovascular health

Descriptions of socioeconomic characteristics of the sample as well as the pre- and postnatal factors considered to be possible risk factors and indicators of cardiovascular health in childhood are shown in Table 1.

Table 2 shows anthropometric characteristics of the sample at birth, at 2 years of age and at the time the study was carried out (8–11 years of age), including prevalence of APG. No differences were observed between sexes in terms of the *z*-scores for length/gestational age, weight/gestational age, BMI/gestational age and prevalence of APG from 0 to 2 years of age. No differences were found between boys and girls for WC, percentage of FM, total FM and fat index, though girls had lower values of height/age, weight/age and BMI/age. Values of cardiovascular health variables in childhood also appear in Table 2. No differences were found between boys and girls in SBP, DBP, MAP and cf-PWV. Therefore, subsequent analyzes were not performed by sex.

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Table 1. Socioeconomic characteristics, pre- and postnatal factors and indicators of cardiovascular health

	N	*N* (%) or Mean (95% CI)
Social demographic variables		
Sex of child (female)	355	170 (47.9%)
Current age of child (years)	355	10.1 (10.0/10.2)
Maternal age (years)	355	33.0 (31.0/36.0)
Maternal education (higher education)	355	193 (65.4%)
Paternal education (higher education)	355	182 (62.5%)
Maternal smoking during pregnancy (yes)	292	47 (16.1%)
Paternal smoking during pregnancy (yes)	286	105 (36.7%)
Current anthropometric characteristics of parents		
Maternal height (cm)	293	162.2 (161.4/162.9)
Maternal weight (kg)	292	63.0 (61.6/64.3)
Mother BMI (kg/m^2)	290	23.9 (23.4/24.4)
Paternal height (cm)	254	175.6 (174.7/176.5)
Paternal weight (kg)	259	79.7 (78.2/81.2)
Paternal BMI (kg/m^2)	252	25.8 (25.4/26.3)
Prenatal factors		
Mother BMI (kg/m^2) before pregnancy	275	22.19 (21.82/22.57)
Gestational weight gain (kg)	355	11.29 (10.62/11.95)
First trimester	355	2.88 (2.59/3.17)
Second trimester	355	4.32 (4.12/4.51)
Third trimester	355	3.86 (3.62/4.09)
Insufficient weight gained during the pregnancy (%)	273	149 (54.6%)
Perinatal and postnatal factors		
Type of delivery (simple)	355	281 (79.2%)
Birth weight (g)	355	3188.47 (3135.76/3241.19)
Length at birth (cm)	355	49.83 (49.47/50.20)
Gestational age (weeks)	289	39.13 (38.81/39.45)
Prevalence of low weight birth/ macrosomia (%)	355	22 (6.2)/ 11 (3.1)
Prevalence of IUGR (%)	289	9 (3.1)
Weight at 2.0 years (kg)	355	12.52 (12.33/12.71)
Length at 2.0 years (cm)	355	88.20 (87.63/88.77)
APG from 0 to 2.0 years (%)	354	165 (46.6)
Exclusive breastfeeding (EB) (weeks)	296	13.14 (11.94/14.34)
Formula feeding (AF) (weeks)	296	9.51 (8.40/10.61)
Mixed formula and breastfeeding (MxB) (weeks)	296	5.05 (4.08/6.02)
Total breastfeeding (TB) (weeks)	293	22.8 (20.4/25.1)
Prevalence of EB (%)	296	43 (14.5%)
Prevalence of AF (%)	296	220 (74.3%)
Prevalence of TB (%)	293	33 (11.1%)
Current characteristics of children		
Height (cm)	355	141.8 (140.6/142.9)
Weight (kg)	355	36.8 (35.8/37.9)
BMI (kg/m^2)	355	18.1 (17.8/18.5)
Waist circumference (cm)	352	65.88 (64.94/66.82)
Fat mass	355	9.3 (8.7/9.9)
Body fat mass (%)	355	24.0 (23.1/25.0)
Fat mass index (kg/m^2)	355	4.5 (4.3/4.8)
Systolic blood pressure (mmHg)	355	102.3 (100.4/104.3)
Diastolic blood pressure (mmHg)	355	62.2 (60.8/63.6)
Mean arterial pressure (mmHg)	355	75.6 (74.1/77.0)
Carotid-femoral pulse wave velocity (m/s)	354	5.00 (4.9/5.1)

BMI, Body mass index; IUGR, intrauterine growth rate; APG, accelerated postnatal growth.

Table 3 shows the characteristics in childhood of subjects with and without APG; as mentioned earlier, there were no differences between girls and boys. Regarding the prenatal factors, no differences were found in the sociodemographic and anthropometric characteristics of the parents of children with and without APG. Conversely, children who presented with APG during infancy were born of mothers with a lower BMIs at the beginning of pregnancy and gained less weight during pregnancy and during second trimester. The prevalence of multiple deliveries was higher in children with APG who had lower gestational age and birth weight. Table 3 also presents the prevalence of underweight, normal weight and macrosomia in children with and without APG. All children with low birth weight had APG during infancy, while not a single child born with macrosomia grew at an accelerated rate. Additionally, children with APG had a shorter duration of exclusive and total breastfeeding and a longer duration of formula feeding.

Impact of accelerated growth on the rigidity of the arterial wall and obesity in childhood

Table 4 shows the comparison between children with and without APG. Children who experienced APG had at birth lower length, weight and BMI when corrected for gestational age. At 2 years of age and later in childhood, those with APG had higher height, weight, BMI, WC, FM and FMI. Values of SBP, MAP and cf-PWV were also higher in 8–11-year-old children who exhibited APG in

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Table 2. Prevalence of accelerated growth and WHO standard *z*-scores for size at birth, 2 years and early school age, and current hemodynamic variables by sex

	Boys ($n = 185$)	Girls ($n = 170$)
	Mean (95% CI)/*N* (%)	Mean (95% CI)/*N* (%)
At birth		
LGZ	0.21 (−0.14/0.37)	0.01 (−0.42/0.14)
WGZ	−0.22 (−0.50/−0.06)	−0.30 (−0.48/0.07)
BMIGZ	−0.51 (−0.81/−0.28)	−0.45 (−0.59/0.01)
At 2.0 years		
HAZ	0.47 (0.09/0.53)	0.56 (−0.14/0.53)
WAZ	0.35 (−0.06/0.34)	0.50 (0.26/0.65)
BMIZ	0.08 (−0.29/0.14)	0.24 (0.26/0.71)
Prevalence of APG from 0 to 2 years	82 (44.6)	83 (48.8)
8–11 years		
HAZ	0.52 (0.35/0.74)*	0.23 (−0.04/0.33)
WAZ	0.83 (0.60/1.06)*	0.41 (0.18/0.64)
BMIZ	0.70 (0.49/0.97)*	0.46 (0.21/0.66)
WC (cm)	66.46 (65.14/67.77)	65.25 (63.89/66.61)
Fat mass (kg)	9.5 (7.4/4.8)	9.6(7.1/8.9)
BFM%	23.8 (21.3/24.4)	24.7(21.8/25.3)
FMI (kg/m2)	4.6 (3.9/4.8)	4.7(3.9/4.8)
SBP (mmHg)	103.2 (100.9/105.4)	102.8 (100.7/105.0)
DBP (mmHg)	62.6 (61.0/64.2)	63.1 (61.4/64.7)
MAP (mmHg)	76.16 (74.54/77.8)	76.3 (74.7/77.9)
cf-PWV (m/s)	5.0 (4.9/5.1)	5.0. (4.9/5.1)

LGZ, length for gestational age *z*-score; WGZ, weight for gestational age *z*-score; BMIGZ, body mass index for gestational age *z*-score; APG, accelerated postnatal growth; HAZ, height for age *z*-score; WAZ, weight for age *z*-score; BMIZ, body mass index for age *z*-score; WC: waist circumference (cm); BFM%, percentage of body fat mass; FMI, fat mass index; cf-PWV, carotid-femoral pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.
Data were analyzed with *t*-test for variables with normal distribution and Mann–Whitney *U*-test for variables without normal distribution.
*$P < 0.05$ indicates significant differences between girls and boys.

infancy. Also, children with APG were 2.5 times more likely to develop hypertension and twice as likely to develop CVRF (obesity and hypertension simultaneously) (Table 4).

The combined effect of pre- and postnatal factors on cardiovascular health in childhood was analyzed by two generalized lineal models in which cf-PWV (arterial stiffness indicator) and FMI (body fat accumulation indicator) were considered as dependent variables (Table 5). Independent variables considered were pre-pregnancy mother BMI, maternal weight gain during the second trimester of pregnancy, duration of AF (main variables that influence the APG) and infant weight gain between 0 and 2 years of age (APG).

Owing to the observed differences among children who experienced postnatal APG and those who did not in the prevalence of low birth weight and macrosomia (Table 4), we performed the generalized models separately in children born with low weight, normal weight and macrosomia.

In infants born with normal weight, the interaction between APG and longer duration of AF (weeks) had a significant effect on cf-PWV, and was associated with higher values of arterial stiffness. Conversely, the mother's BMI before pregnancy and the interaction between APG and longer duration of AF (weeks) had a significant effect on FMI, and also were associated with higher values of body FM.

In children with low birth weight, the variables that indicate worse nutritional status of the mother before and during pregnancy were predictors of a higher arterial stiffness. The mother's BMI before pregnancy and maternal weight gain in the second trimester had a negative coefficient, indicating that smaller weight gains by the mother were associated with higher values of cf-PWV of the child at 8–11 years of age. For the FMI, no statistically significant association was found.

Finally, in macrosomic children, the mother's BMI before pregnancy and duration of AF were associated with higher cf-PWV values. Conversely, maternal weight gain in the second trimester and the duration of AF were associated with lower FMI values.

Discussion

In this study, we analyzed the influence of fetal and perinatal conditions on APG and the impact of this acceleration on cardiovascular risk in childhood, as measured by cf-PWV, BP, obesity and body composition.

Previous research[44,45] have shown that the APG has been associated with a lower birth weight and a lower gestational age. Although this sample had good fetal conditions, as indicated by the low IUGR and low birth weight prevalences, a higher proportion of the children (46.6%) had APG, compared with other studies (30–35%).[7,14,20]

Children who experienced APG between birth and 2 years of age had different gestational characteristics from those that did not, including low maternal weight gain during the second trimester of pregnancy, shorter duration of gestation, lower birth weight and lower birth weight and length when corrected for gestational age.[2,3,14,25,65,66]

This apparent paradox could be explained by sociocultural factors, specifically the low weight gain of mothers during pregnancy, could be due to an exhaustive control of gestational weight gain that can have a negative effect on children's health. Our results are consistent with those observed in the general Spanish population, the average weight gained by Spanish women during pregnancy is low.[67–69] Nutritional restrictions at specific times during pregnancy, though slight, can have a negative impact on the growth of the fetus.[70] A low weight gain by the mother during pregnancy can compromise the supply of nutrients to the fetus, and has been associated with low birth weight, which is also related to cardiovascular risk later in life.[71–75] As the second trimester is when the fetus increases most in length and finishes the formation of the circulatory system, a lack of nutrients can drive structural deficiency in the arterial walls,[33] which is directly linked to high BP. The underlying mechanism may be that the lack of nutrients affects synthesis of elastin, decreasing its proportion

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Table 3. Socioeconomic characteristics, pre- and postnatal factors and indicators of cardiovascular health in childhood of subjects with and without accelerated growth

	APG		Nonaccelerated postnatal growth	
	N	*N* (%)/Mean (95% CI)	*N*	*N* (%)/Mean (95% CI)
Sociodemographic variables				
Sex (female)	165	83 (50.3)	189	87 (46.0)
Current age (years)	165	10.2 (10.1/10.5)	189	10.1 (9.9/10.4)
Maternal age (years)	165	34.0 (31.0/36.0)	189	33.0 (30.0/35.0)
Maternal education (higher)	165	86 (64.7)	163	107 (66.5)
Paternal education (higher)	165	80 (61.1)	163	102 (64.2)
Maternal smoking (yes)	135	25 (18.5)	165	24 (14.5)
Paternal smoking (yes)	132	54 (35.0)	163	57 (40.9)
Parental anthropometric characteristics				
Mother height (cm)	131	162.0 (161.2/163.6)	160	162.4 (161.1/163.0)
Mother weight (kg)	131	62.4 (59.7/63.6)	160	64.5 (62.4/66.4)
Mother BMI (kg/m^2)	131	23.7 (22.7/24.1)	160	24.45 (23.8/25.2)
Paternal height (cm)	117	176.0 (174.8/177.2)	140	175.2 (173.9/176.4)
Paternal weight (kg)	117	81.3 (78.1/83.4)	140	78.8 (77.0/80.6)
Paternal BMI (kg/m^2)	117	26.2(25.3/26.8)	140	25.7 (25.2/26.2)
Antenatal factors				
Mother BMI (kg/m^2) before pregnancy	123	21.8 (21.2/22.5)*	151	22.6 (22.0/23.0)
Mother gestational weight gain (kg)	165	10.7 (9.7/11.7)	189	11.6 (10.7/12.7)
First trimester	165	2.6 (2.1/2.9)	189	3.0 (2.7/3.6)
Second trimester	165	4.1 (3.8/4.4)*	189	4.4 (4.2/4.8)
Third trimester	165	3.8 (3.5/4.2)	189	3.9 (3.5/4.2)
Insufficient weight gained during the pregnancy	123	72 (58.5)	151	76 (51.0)
Perinatal and postnatal factors				
Type of delivery (simple)	131	120 (73.0)*	161	160 (84.7)
Gestational age (weeks)	131	38.4 (38.0/39.1)**	157	39.7 (39.4/40.0)
Birth weight (g)	165	2956.0 (2853.3/3058.6)**	189	3438.0 (3364.6/3511.4)
Prevalence of NW		144 (44.7)**		178 (55.3)
Prevalence of LW		21 (100.0)**		0 (0.0)
Prevalence of M		0 (0.0)**		11 (100.0)
Duration of EB (weeks)	133	11.5 (10.0/13.7)*	162	13.7 (12.6/15.8)
Duration of AF (weeks)	133	43.3 (36.6/52.1)	162	38.1 (33.2/44.1)
Duration of B + F (weeks)	133	4.7 (3.6/6.3)	162	5.5 (3.8/6.6)
Duration of TB (weeks)	132	21.2 (16.2/21.7)*	160	25.1 (22.0/28.4)
Prevalence of EB (%)		10 (7.6)*		32 (19.8)
Prevalence of AF (%)		102 (77.3)*		118 (72.8)
Prevalence of TB (%)		20 (16.2)*		12 (7.4)

BMI, body mass index (kg/m^2); EB, exclusive breastfeeding; AF, artificial feeding; B + F, breast milk and formula; TB, total breastfeeding; NW, normal weight; LW, low weight; M: macrosomia. *$P < 0.05$; **$P < 0.001$. Continuous data were analyzed with *t*-test and χ^2 and discontinuous data were analyzed with Mann-Whitney *U*-test. Difference between subjects with and without accelerated growth.

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Table 4. Differences in anthropometric and hemodynamic characteristics between subjects with or without accelerated weight gain during infancy and likely to develop obesity and hypertension (odds ratio)

	APG		Nonaccelerated postnatal growth	
	N	*N* (%)/Mean (95% CI)	*N*	*N* (%)/Mean (95% CI)
Birth				
LGZ	165	−0.20 (−0.81/−0.01)**	189	0.38 (0.12/0.49)
WGZ	165	−0.77 (−1.01/−0.50)**	189	0.18 (−0.10/0.21)
BMIGZ	165	−1.02 (−1.19/−0.44)**	189	−0.02 (−0.34/0.06)
2.0 years				
HAZ	165	1.00 (0.52/1.19)**	189	0.09 (−0.38/0.05)
WAZ	165	0.89 (0.65/1.05)**	189	0.03 (−0.25/0.06)
BMIZ	165	0.43 (0.30/0.69)**	189	−0.06 (−0.24/0.22)
8–11 years				
HAZ	165	0.64 (0.38/0.81)**	189	0.16 (0.00/0.35)
WAZ	77	0.92 (0.65/1.20)*	108	0.42 (0.22/0.62)
BMIZ	165	0.45(0.56/1.09)*	189	0.41 (0.22/0.62)
WC (cm)	165	67.23 (65.74/68.72)*	186	64.74 (63.57/65.91)
Fat mass (kg)	165	10.3 (8.0/10.6)*	189	8.90 (6.7/8.1)
BFM%	165	24.9 (22.3/26.2)	189	23.6(21.0/23.9)
FMI (kg/m^2)	165	4.9 (4.2/5.3)*	189	4.0 (3.7/4.4)
SBP (mmHg)	165	106.5 (103.6/109.2)**	189	100.7 (96.8/101.8)
DBP (mmHg)	165	63.7 (61.6/65.2)	189	62.4 (60.9/63.7)
MAP (mmHg)	165	77.94 (75.82/79.26)*	189	75.2 (73.5/76.5)
cf-PWV (m/s)	165	5.0 (5.0/5.1)*	189	5.0 (4.9/5.1)
Presence of hypertension	165	34 (20.6%)*	189	18 (9.5%)
Presence of obesity	165	24 (14.5%)	189	17 (9.0%)
Presence of CVRF	165	46 (27.9%)*	189	31 (16.4%)
		OR (ref: nonaccelerated growth)		95%CI
Presence of hypertension		2.47		1.33–4.56*
Presence of obesity		1.72		0.89–3.33
Presence of CVRF		1.97		1.18–3.29*

LGZ, length for gestational age *z*-score. WGZ, weight for gestational age *z*-score. BMIGZ, body mass index for gestational age *z*-score. HAZ, length for age *z*-score. WAZ, weight for age *z*-score. BMIZ, body mass index for age *z*-score. WC, waist circumference (cm); BFM%: percentage of body fat mass; FMI, fat mass index; cf-PWV, carotid–femoral pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; *N* indicates the number of subjects; OR, odds ratio; CI, confidence interval; CVRF, cardiovascular risk factors (presence of obesity and hypertension, simultaneous).
*$P < 0.05$; **$P < 0.001$; continuous data were analyzed with *t*-test and nonparametric data were analyzed with Mann–Whitney *U*-test. Difference between subjects with or without accelerated weight gain, mean values.

relative to collagen in the arterial walls, which would increase their rigidity.[76,77] Such poor arterial wall structure is irreversible, lasting throughout the person's life.[35–37] This is an important question to take into account in the development of health promotion programs since in Western culture women are concerned about their body image and they may control what they eat in order to limit their weight gain throughout pregnancy.[78–80]

Duration of breastfeeding also depends on social factors.[81] In Spain, the duration of breastfeeding does not meet the recommendations of the WHO,[82] the maternity leave in Spain is 16 weeks and the most common reason for stopping breastfeeding is mother's return to work after maternity leave.[81] As in other studies, our results show a higher prevalence of APG in babies with short duration of breastfeeding and those fed with formula.[14,16,23,25,65,83,84] In other words, a low maternal gestational weight gain, inadequate development of the fetus (low birth weight, shorter gestational age) and reduced breastfeeding favors APG.

In turn, in our study and consistent with other studies,[19,22,24,85–87] individuals who exhibited APG in infancy had higher mean values of BMI, WC, FMI, SBP, MAP and cf-PWV in childhood. APG from 0 to 2 years, in itself, did not have a significant effect on cf-PWV and FMI in childhood, but it did have the interaction between AF and APG. Children who were born with a normal weight but had APG and a longer duration of formula milk showed higher arterial rigidity and greater fat accumulation in childhood.

The mechanisms of the interactions between the duration of AF and the APG and its impact on overweight and arterial wall stiffness in later stages of life are not yet well known. It has been postulated that the highest protein content of formula milk with respect to human milk is associated with an increase in the secretion of growth factor similar to insulin type I (IFG-1), whose synthesis is stimulated by the hormone growth (GH).[5,88] Children fed with AF would have a higher protein intake that would constitute a significant load of solutes for the kidneys (high renal load) and increase the secretion of IFG-1, which in turn promotes protein synthesis and cell proliferation, increasing the APG. Rolland-Cachera *et al.*[89] and Michaelsen[88] concluded that a higher protein intake at 2 years was associated with a higher BFM at 8 years and an early adipose rebound.

Elastin is a macropolymer of a precursor protein called Tropoelastin, which in the arteries is synthesized mostly by smooth muscle cells. Tropoelastin is encoded by a single gene located on human chromosome 7 and the modulation of its expression is not yet known, although it has been shown that the gene can be regulated by IFG-1.[33,90,91] Greater expression of GH induces a greater excretion of IFG-1 and would be increasing the synthesis of elastin but in a disorganized and dysfunctional way.[33,91] As in the case of pathologies such as HTA,[33] in syndromes such as those of Marfan[92–94] or acromegaly,[95,96] individuals have a higher cf-PWV than the control despite having a higher elastin content. This approach could explain the results obtained in our study on the relationship between APG with a longer duration of AF, greater presence of overweight and greater rigidity of the arteries in childhood.

In those born with macrosomia, maternal pre-pregnancy BMI and duration of AF were the variables that affected cf-PWV. Some studies have suggested that a mother BMI above 26 kg/m^2 and gain >15 kg during pregnancy are factors leading to macrosomia.[97,98] However, other studies have shown that it is not gestational weight gain, but mother's obesity before pregnancy

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Table 5. Predictive models for different indicators of cardiovascular health

		Models					
		cf-PWV			FMI		
		β	95% CI	*P*	β	95% CI	*P*
Low birth weight	(intercept)	5.978	4718/5168	0.000	−1.535	−10.295/7.224	0.731
	Mother BMI (kg/m^2) before pregnancy	−0.043	−0.084/ −0.002	0.041	0.260	− 0.011/0.632	0.166
	Mother weight (kg) gain in the second trimester of pregnancy	−0.060	−0.111/ −0.009	0.021	0.176	−0.305/0.657	0.474
	Duration of AF (weeks)	0.014	−0.006/0.035	0.175	−0.141	−0.339/0.058	0.166
	Accelerated weight gain, birth-2 years	0	–	–	0	–	–
	APG* Duration of AF (weeks)	0	–	–	0	–	–
Normal birth weight	(intercept)	4.943	4.718/5.168	0.000	−2.303	−4.422/ −0.185	0.033
	Mother BMI (kg/m^2) before pregnancy	0.001	−0.007/0.010	0.770		0.202/0.365	
	Mother weight (kg) gain in the second trimester of pregnancy	0.007	−0.010/0.023	0.458	0.282	−0.076/0.2032	0.000
	Duration of AF (weeks)	−0.004	−0.009/ −1.113E −005	0.049	0.078	−0.057/0.027	0.319
	Accelerated weight gain, birth-2 years	0.028	−0.046/0.102	0.458	0.321	−0.378/1.020	0.368
	APG* Duration of AF (weeks)	0.008	0.002/0.014	0.08	0.070	0.014/0.126	0.015
Macrosomia	(intercept)	3.946	3.355/4.537	0.000	14.943	7.113/22.774	0.000
	Mother BMI (kg/m^2) before pregnancy	0.049	0.029/0.070	0.000	−0.065	−0.334/0.205	0.638
	Mother weight (kg) gain in the second trimester of pregnancy	−0.009	−0.072/0.055	0.792	−1.350	−2.186/ −0.513	0.002
	Duration of AF (weeks)	0.016	0.003/0.029	0.018	−0.277	−0.449/ −0.105	0.002
	Accelerated weight gain, birth-2 years	0	–	–	0	–	–
	APG* Duration of AF (weeks)	0	–	–	0	–	–

APG, accelerated postnatal growth; cf-PWF, carotid–femoral pulse wave velocity; AF, artificial feeding; BMI, body mass index.
Dependent variable: pulse wave velocity (cf-PWV); fat mass index (FMI).
Predictors considered in each model: Mother weight gain during the second trimester of pregnancy (kg); mother BMI before pregnancy; duration of AF (weeks); APG 0–2 years and interaction between APG 0–2 years and duration of AF.

that best determines the incidence of macrosomia in the offspring.[97] The mechanism responsible for the high cf-PWV in macrosomic children is different than for those with low birth weight; autopsies have revealed fatty streaks in the arterial walls of fetuses from overweight/obese mothers. This is likely due to the fact that the mothers also have more cholesterol in their bloodstream, which passes through the placenta to be deposited in the arteries of the fetus.[99]

On the other hand, in newborns with low birth weight, a lower maternal weight gain in the second trimester and lower maternal pre-pregnancy BMI were associated with higher cf-PWV values. As already mentioned, the second trimester is when the fetus increases most in length and finishes the formation of the circulatory system, and a lack of nutrients can drive for structural affect synthesis of elastin, decreasing its proportion relative to collagen in the arterial walls, which would increase their rigidity.[76,77] Such poor arterial wall structure is irreversible, lasting throughout the person's life.[35–37]

The results of this study supply valuable information from a lifecycle perspective about the multifactorial origin of obesity and cardiovascular problems in the most developed countries.

Prevention and promotion of cardiovascular health requires a broad perspective, with action from the very early stages throughout the life of every individual. The social environment in which human beings are immersed influences certain factors such as dietary habits of pregnant women and social support for breastfeeding, duration of maternity leave etc. These sociocultural factors have an important effect on the biological processes of growth and development that influence cardiovascular health throughout life.

Strengths of the study

The information obtained from health records and family interviews are considered to be quite valuable. Regardless, a strong point of the study is the direct measurement of arterial stiffness via cf-PWV, a new method that provides more rigorous data than that obtained from measurement of BP alone.

Study limitations

This study was partially longitudinal, with observations from birth to 2 years of age, however, the children were not followed

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from that point through childhood. It would have been interesting to continue measurements of body size and composition from 3 years of age through adolescence, which would have allowed the study of adiposity rebound and its effect on cardiovascular health. These circumstances could be considered a weakness of the study, which we will try to mitigate with the follow-up of the sample.

Conclusions

This sample had good fetal conditions, as indicated by the low IUGR and low birth weight prevalences, but a higher proportion of the children had AGP. Low maternal gestational weight gain, inadequate fetal development (low birth weight), shorter gestational age and reduced breastfeeding duration favor APG.

Infants with such APG had higher values of cf-PWV, SBP, WC, BMI and BFM later in childhood, along with a higher risk of hypertension and obesity. In infants born with normal weight the interaction of a longer duration of AF and APG between birth and 2 years increases the values of arterial stiffness and body fat in childhood. All children with low birth weight had APG during infancy, while children born with macrosomia grew at an accelerated rate.

In children with low birth weight, a lower maternal weight gain in the second trimester and lower maternal pre-pregnancy BMI were associated with higher cf-PWV values. Meanwhile, in the macrosomic children, increase in maternal pre-pregnancy BMI values and duration of AF determine a greater arterial rigidity and corporal fatty accumulation.

Prevention of disease and promotion of cardiovascular health requires a broad perspective, with action from the very early stages throughout the life of every individual.

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