

RESEARCH ARTICLE

# Pulse Wave Velocity at Early Adulthood: Breastfeeding and Nutrition during Pregnancy and Childhood

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## Abstract

### Background

Pulse wave velocity (PWV) is an early marker of arterial stiffness. Low birthweight, infant feeding and childhood nutrition have been associated with cardiovascular disease in adulthood. In this study, we evaluated the association of PWV at 30 years of age with birth condition and childhood nutrition, among participants of the 1982 Pelotas birth cohort.

### Methods

In 1982, the hospital births in Pelotas, southern Brazil, were identified just after delivery. Those liveborn infants whose family lived in the urban area of the city were examined and have been prospectively followed. At 30 years of age, we tried to follow the whole cohort and PWV was assessed in 1576 participants.

### Results

Relative weight gain from 2 to 4 years was positively associated with PWV. Regarding nutritional status in childhood, PWV was higher among those whose weight-for-age z-score at 4 years was >1 standard deviation above the mean. On the other hand, height gain, birthweight and duration of breastfeeding were not associated with PWV.

### Conclusion

Relative weight gain after 2 years of age is associated with increased PWV, while birthweight and growth in the first two years of life were not associated. These results suggest that the relative increase of weight later in childhood is associated with higher cardiovascular risk.

## Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. According to the World Health Organization (WHO), in 2008, 17.3 million deaths were due to CVD and it is estimated that this number will increase to 23.3 million by 2030 [1]. The traditional risk factors for CVD are hypertension, diabetes mellitus (DM), dyslipidemia, obesity and smoking. The occurrence of most cardiovascular diseases is closely related to atherosclerosis, which is characterized by the accumulation of fatty plaques (atheroma) within arteries [2].

Arterial stiffness increases with age and among young people may accelerate the atherosclerotic process, leading to several pathological conditions, such as decreased vascular compliance, increased systolic blood pressure, hypertrophy and fibrosis of the left ventricle, decreased coronary perfusion and endothelial dysfunction that leads to decreased production of nitric oxide, increasing smooth muscle tonus [3–8]. Pulse wave velocity (PWV) has been used to assess arterial stiffness. Each ventricular ejection generates a pulse pressure, which is propagated throughout the arterial tree. Pulse wave velocity is determined by the geometric and elastic properties of the arterial wall and increases with arterial stiffness [9]. Therefore, PWV is considered as an early marker of atherosclerosis and risk of CVD [10–11]. Indeed, PWV is higher among subjects who have experienced cardiovascular events [12–13]. With regard to the development of atherosclerosis, autopsy studies of children and young adults have identified fatty streaks in the coronary arteries, suggesting that the atherosclerotic process starts in early life [14–16].

With respect to the risk factors of cardiovascular diseases, evidence suggests that early exposures, such as intrauterine growth, birthweight, nutrition status in childhood and infant feeding, may program the development of metabolic cardiovascular risk factors [17–18]. On the other hand, few studies have evaluated the effect of early exposures on early markers of atherosclerosis, such as PWV [19–25]. In 1995, Martyn et al. evaluated the relationship between PWV in adulthood and measures of body size at birth. The PWV was higher among those with lower birthweight and smaller head and abdominal circumferences [19]. Mzayek et al. observed, in the Bogalusa study, that low birthweight was associated with higher PWV at 35 years of age [20]. On the other hand, Montgomery and colleagues found no association between low birth size and PWV [21], whereas Murray et al. reported that birthweight was positively associated with PWV in men and negatively in women in aorto-iliac and aorto-dorsalis pedis segments, but that in the aorto-radial segment the association was negative in both sexes [22].

In relation to breastfeeding and timing of introduction of solid foods, Jonge et al. reported that those children who had never been breastfed had higher PWV at 6 years of age, smaller left atrial diameter (LAD) and less left ventricular mass, whereas breastfeeding was not associated with blood pressure [23]. Tauzin et al. reported that PWV in early adulthood was higher among those subjects who were born at less than 32 weeks of gestational age [24]. In relation to nutrition, Tennant et al. found that adults who presented severe malnutrition in childhood (marasmus, kwashiorkor) had decreased cardiac output, PWV, increased diastolic pressure and increased systemic vascular resistance [25].

This study was aimed at assessing the association between PWV at 30 years of age and infant feeding and nutritional status during pregnancy and early childhood.

## Methods

In 1982, the maternity hospitals located in Pelotas were visited daily and all births identified. The 5914 liveborn infants whose families lived in the urban area were examined and their mothers interviewed. These individuals have been followed several times at different ages. Details of the methods of this cohort are available elsewhere [26,27]. Between June 2012 and

February 2013, we tried to follow the entire cohort, using multiple search strategies and 3701 subjects were interviewed and examined in the research clinic.

In the 2012–13 visit, pulse wave velocity (PWV) was assessed using the Sphygmocor® system (Atcor Medical, Version 9.0, Sydney, Australia), a noninvasive device, which measures the PWV with a tonometric transducer. Participants were asked to refrain from smoking, drinking alcohol, caffeine, eating or physical activity at least 30 minutes before exams. A trained technician took the measurements, after 5 minutes of rest with the participants in the supine position in a quiet environment with controlled temperature (22–24°C). The tonometer was lightly pressed on the participant's skin, after palpation of the right carotid and femoral pulses, with simultaneous recording of the electrocardiogram for synchronization of carotid and femoral pulse wave times.

The PWV was calculated from measurements of pulse transit time and distance traveled by the pulse wave. Pulse transit time was estimated using the intersecting tangent foot-to-foot algorithm. The distance traveled by the pulse wave was measured using a flexible tape as the distance from the suprasternal notch to the femoral site of the pulse wave recording and the distance from the carotid site of the pulse wave recording and the suprasternal notch. The PWV was estimated as the distance between the measurement sites divided by the transit time delay between the femoral and carotid pulse wave [10].

In the 2012–13 visit, weight was measured using an electronic scale with a maximum capacity of 150 kg (Tanita®). Height was measured with a portable stadiometer with an accuracy of 0.1 cm.

Birthweight was assessed by the hospital staff using pediatric scales that were calibrated weekly by the research team. Gestational age was estimated from the last menstrual period. Birthweight according to gestational age z-score was calculated from the mean and standard deviation of birthweight based on gestational age and sex of the Williams's reference population [28]. Detailed information about the duration of breastfeeding was collected in childhood (1984 and 1986). In the present analyses, we used the information obtained closest to the time of weaning.

Weight and length/height measures were transformed into weight-for-age or length/height-for-age z-scores using the WHO growth curves [29]. Conditional weight and length/height gain were used to estimate childhood growth; this measure indicates how much an individual measurement moves away from its previous path and from the population. The conditional growth is the residual of a linear regression. Conditional variables were generated by regressing current size (weight or length/height) on birthweight and earlier measures of weight and length/height, and standardized residuals were derived. To estimate conditional height, current length or height was regressed on previous weight and length. Therefore, conditional height at 2 years was estimated by regressing length-for-age z-scores at 2 years on birthweight. On the other hand, conditional relative weight was estimated from current length/height and previous measures of length/height and weight. Therefore, conditional relative weight at 2 years was derived by regressing weight at 2 years on birthweight and length at 2 years. Positive values indicate that the child grew faster than expected based on their previous growth and its population. Conditional growth in length is considered as the increase in length that is not predicted by previous length measurements; conditional growth in weight is considered as the increase in weight that is not predicted by previous weight or length measurements. Conditional variables were expressed in z-scores.

The analyses were performed using Stata 12® statistical package. Sex, race, maternal schooling, income, smoking during pregnancy and birthweight were considered as possible confounders. Analysis of variance (ANOVA) was used to compare means and multiple linear regression to adjust for confounding factors. In the linear regression, we estimated the p-value

comparing the differences among the categories of the variable. Furthermore, we also assessed the p-value using the continuous exposure variable.

This study was approved by the research ethics committee of the Faculty of Medicine, Federal University of Pelotas, affiliated with the National Council on Ethics in Research of the Ministry of Health. All participants signed an informed consent.

## Results

In the 2012–13 visit, 3701 individuals were interviewed, and PWV was assessed in 1576 participants (27% of the original cohort). We were not able to measure the PWV in the remaining 2125 subjects due to operational problems. [Table 1](#) shows that the proportion of subjects who had the PWV measured was independent of socioeconomic and demographic characteristics, breastfeeding duration and maternal smoking during pregnancy.

PWV was lower among white individuals ( $P = 0.01$ ). On the other hand, no association was observed for family income and education. ([Table 2](#))

[Table 3](#) shows that PWV was independent of birthweight and birthweight according to the gestational age z-score. Additionally, breastfeeding duration was not related to PWV. On the

**Table 1. Proportion of all subjects followed up to 30 years and those with pulse wave velocity measurement.** The 1982 Pelotas (Brazil) Birth Cohort Study.

Variables	% subjects followed at 30 years with PWV data	% subjects followed at 30 years without PWV data
<b>Gender</b>		
Male	51.1	46.0
Female	48.9	54.0
<b>Skin colour</b>		
White	75.3	76.9
Non-white	24.7	23.1
<b>Family income (minimum wage)</b>		
≤1	19.0	20.2
1.1–3	50.6	48.4
3.1–6	19.1	20.0
6.1–10	5.9	6.1
>10	5.4	5.3
<b>Education (years)</b>		
0–4	6.7	5.7
5–8	19.9	20.0
9–11	29.4	30.5
≥12	44.0	43.8
<b>Breastfeeding duration (months)</b>		
<1	20.2	22.1
1–2.9	25.7	25.6
3–5.9	24.4	22.1
6–8.9	9.1	9.9
9–11.9	4.2	3.8
≥12	16.4	16.5
<b>Maternal smoking during pregnancy</b>		
Yes	37.9	32.8
No	62.1	67.2

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**Table 2. Pulse wave velocity according to socioeconomic and demographic variables at 30 years of age.** The 1982 Pelotas (Brazil) Birth Cohort Study.

Variables	N	Mean Pulse Wave Velocity in m/s (sd)
<b>Sex</b>		P = 0.06
Male	805	6.47(1.10)
Female	771	6.37 (1.08)
<b>Skin colour</b>		P = 0.01
White	1185	6.38 (1.07)
Non-white	389	6.54 (1.15)
<b>Family income (minimum wage)</b>		P = 0.21
≤1	299	6.36 (1.0)
1.1–3	794	6.46 (1.07)
3.1–6	299	6.42 (1.20)
6.1–10	93	6.53 (1.05)
>10	84	6.21(1.31)
<b>Achieved schooling (years)</b>		P = 0.07
0–4	104	6.20 (0.85)
5–8	309	6.48 (1.12)
9–11	458	6.48 (1.02)
≥12	684	6.39 (1.16)

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other hand, PWV was higher among those subjects whose weight-for-age z-score at 4 years of age was > 1 standard deviation above the mean. With regards to growth in childhood, relative weight gain from 2 to 4 years was positively associated with PWV, whereas there was no clear pattern for relative weight gain in the first two years, and the confidence intervals for each of the categories of relative weight gain included the null value. Length/height gain in the first 4 years was not associated with PWV.

## Discussion

In this cohort that has been prospectively followed since birth, in a southern Brazilian city, we observed that relative weight gain from 2 to 4 years of age was associated with increased PWV, whereas birthweight, relative weight gain in the first two years of life, and linear growth (length/height gain) in childhood were not associated with PWV. Furthermore we did not observe any programming effect of breastfeeding on PWV at 30 years of age.

Information on birthweight, gestational age, breastfeeding duration and nutritional status was collected close to the time of its occurrence, reducing the possibility of misclassification. In addition, the absence of any trend in the association between breastfeeding and PWV suggests that it is unlikely that measurement error underestimated an association. By the same token, confounding variables were measured in early childhood, reducing the chance of residual confounding. On the other hand, PWV was not assessed for all subjects who were followed at the age of 30, but PWV examination was independent of socioeconomic status, breastfeeding duration and nutritional status, suggesting that selection bias is unlikely. On the other hand, we were not able to adjust the conditional growth estimates to birth length because information on this variable had not been collected in the perinatal study.

With regard to the long-term effects of breastfeeding on the risk of cardiovascular disease, some studies have observed that breastfeeding is inversely associated with cardiovascular risk factors [23,30], whereas others have not observed such an association [31–36]. Most studies that observed a protective effect of breastfeeding had been carried out in high-income

**Table 3. Pulse wave velocity according to pregnancy variables, breastfeeding, weight and height at 2 and 4 years of age.**

Variables	N	Mean PWV m/s (sd)	Adjusted regression coefficient (95% CI)
<b>Birthweight (g)</b>		P = 0.98	P = 0.26 <sup>#</sup> * P = 0.94 <sup>##</sup> **
≥3500	499	6.43 (1.14)	0 (Reference)
3000–3499	583	6.42 (1.10)	-0.02 (-0.15;0.11)
2500–2999	375	6.43 (1.07)	-0.03 (-0.18;0.12)
<2500	119	6.38 (0.98)	-0.07 (-0.29;0.16)
<b>Birthweight for gestational age (z-score)</b>		P = 0.64	P = 0.37 <sup>#</sup> * P = 0.59 <sup>##</sup> **
< -1.28	177	6.36 (1.06)	0 (Reference)
-1.28–0	543	6.45 (1.05)	0.10 (-0.09;0.29)
>0	531	6.42 (1.16)	0.08 (-0.11;0.27)
<b>Breastfeeding duration (months)</b>		P = 0.52	P = 0.19 <sup>##</sup> ** P = 0.56 <sup>###</sup> ***
<1	311	6.46 (1.12)	0 (Reference)
1–2.9	393	6.35 (1.12)	-0.11(-0.28;0.05)
3–5.9	374	6.39 (1.05)	-0.07(-0.24;0.10)
6–8.9	139	6.52 (0.98)	0.06(-0.16;0.29)
9–11.9	64	6.48 (1.08)	-0.01(-0.29;0.36)
≥12	252	6.47 (1.17)	-0.01(-0.19;0.18)
<b>Weight for age (z-score) age of 2</b>		P = 0.13	P = 0.14 <sup>#</sup> * P = 0.07 <sup>##</sup> **
<-1	216	6.43 (1.04)	0 (Reference)
-1–0.99	955	6.40 (1.12)	-0.02(-0.19;0.15)
≥1	288	6.54 (1.08)	0.15(-0.05;0.35)
<b>Weight for age (z-score) age of 4</b>		P = 0.001	P = 0.005 <sup>#</sup> * P = 0.001 <sup>##</sup> **
<-1	241	6.40 (1.05)	0 (Reference)
-1–0.99	958	6.38 (1.07)	-0.003(-0.16;0.16)
≥1	227	6.67 (1.26)	0.31(0.11;0.52)
<b>Length for age (z-score) age of 2</b>		P = 0.09	P = 0.10 <sup>#</sup> * P = 0.04 <sup>##</sup> **
<-1	565	6.42 (1.05)	0 (Reference)
-1–0.99	786	6.41 (1.14)	0.03(-0.09;0.16)
≥1	108	6.65 (0.99)	0.29(0.06;0.53)
<b>Length for age (z-score) age of 4</b>		P = 0.006	P = 0.05 <sup>#</sup> * P = 0.003 <sup>##</sup> **
<-1	539	6.39 (1.03)	0 (Reference)
-1–0.99	795	6.42 (1.14)	0.04(-0.08;0.16)
≥1	89	6.78 (1.08)	0.43(0.18;0.68)
<b>Conditional height (age of 2)</b>		P = 0.47	P = 0.56 <sup>#</sup> * P = 0.25 <sup>##</sup> **
<0	535	6.41(1.11)	0 (Reference)
0.0001–1	358	6.43(1.08)	0.03(-0.12;0.19)
> 1	177	6.52(1.15)	0.16(-0.04;0.35)
<b>Conditional height (age of 4)</b>		P = 0.19	P = 0.13 <sup>#</sup> * P = 0.22 <sup>##</sup> **
<0	550	6.43(1.11)	0 (Reference)
0.0001–1	347	6.38(1.05)	-0.07(-0.22;0.08)
> 1	173	6.56(1.19)	0.11(-0.08;0.30)
<b>Conditional weight (age of 2)</b>		P = 0.03	P = 0.19 <sup>#</sup> * P = 0.02 <sup>##</sup> **
<0	561	6.44(1.12)	0 (Reference)
0.0001–1	335	6.33(0.99)	-0.12(-0.27;0.04)
> 1	174	6.61(1.25)	0.16(-0.03;0.35)
<b>Conditional weight (age of 4)</b>		P = 0.03	P = 0.02 <sup>#</sup> * P = 0.01 <sup>##</sup> **
<0	567	6.37(1.12)	0 (Reference)
0.0001–1	353	6.44(1.04)	0.06(-0.09;0.21)

(Continued)

Table 3. (Continued)

Variables	N	Mean PWV m/s (sd)	Adjusted regression coefficient (95% CI)
> 1	150	6.65(1.21)	0.27(0.07;0.47)

#Adjustment for sex, skin colour, education, family income and smoking during pregnancy.

## Adjustment for sex, skin colour, education, family income, smoking during pregnancy and birth weight.

\* P-value based on continuous variables.

\*\* P-value based on categorical variables.

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countries, where breastfeeding is more common among wealthier subjects. Therefore, the observed associations could be due to residual confounding. Brion et al. found in the Pelotas (Brazil) birth cohort, where breastfeeding is not associated with socioeconomic status, that breastfeeding was not associated with prevalence of obesity and blood pressure [37], whereas in the ALSPAC cohort [38], where breastfeeding is positively associated with socioeconomic status, an association was observed. Similarly, in the PROBIT study, blood pressure was similar in the both intervention and control groups [39]. A recently published meta-analysis, found that breastfeeding protects against overweight/obesity and type-2 diabetes, but was not associated with blood pressure and total cholesterol [40]. As our study evaluated young adults without chronic diseases, it is not surprising that we have not found an association between breastfeeding and PWV.

With respect to childhood growth, it has been reported that growth in early childhood is not associated with an increased risk, whereas weight gain in late childhood is positively associated with cardiovascular risk factors [41–47]. Furthermore, Menezes et al. observed that relative weight gain and not linear growth is associated with higher risk [48]. Therefore, our findings reinforce the evidence that a relative increase in weight gain later in childhood is positively associated with a marker of atherosclerosis in early adulthood. Therefore, only early weight gain should be promoted.

### Author Contributions

Conceived and designed the experiments: CAV BLH DPG FCLFB. Performed the experiments: CAV BLH DPG FCLFB. Analyzed the data: CAV BLH DPG FCLFB. Contributed reagents/materials/analysis tools: CAV BLH DPG FCLFB. Wrote the paper: CAV BLH DPG FCLFB.

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