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# Is Slower Early Growth Beneficial for Long-Term Cardiovascular Health?

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**Background**—Accelerated neonatal growth increases the later propensity to cardiovascular disease (CVD) in animals, whereas slower growth is thought to have a beneficial effect. To test this hypothesis in humans, we measured flow-mediated endothelium-dependent dilation (FMD) in a population subject to slower early growth and in healthy controls.

**Methods and Results**—High-resolution vascular ultrasound was used to measure the change in brachial artery diameter in response to reactive hyperemia in adolescents age 13 to 16 years who were either part of a cohort born preterm and followed up prospectively (n=216) or controls born at term (n=61). Greater weight gain or linear growth in the first 2 weeks postnatally was associated with lower FMD at adolescence (regression coefficient,  $-0.026$ -mm change in mean arterial diameter per 100-g increase in weight; 95% CI,  $-0.040$  to  $-0.012$  mm;  $P=0.0003$ ) independent of birthweight and potential confounding factors. Mean FMD in the half of the preterm population with the lowest rates of early growth was higher than in both the half with the greatest growth ( $P=0.001$ ) and subjects born at term ( $P=0.03$ ).

**Conclusions**—FMD was 4% lower in adolescents with the highest compared with the lowest rate of weight gain in the first 2 weeks after birth, a substantial negative effect similar to that for insulin-dependent diabetes mellitus or smoking in adults. Our findings are consistent with the adverse effects of accelerated neonatal growth on long-term cardiovascular health and suggest that postnatal growth patterns could explain the previously reported association between birthweight and later CVD. (*Circulation*. 2004;109:1108-1113.)

**Key Words:** infants ■ vasodilation ■ atherosclerosis ■ cardiovascular diseases

Developing organisms have compensatory growth after a period of nutritional deficit.<sup>1</sup> Although of potential short-term benefit,<sup>1</sup> such accelerated growth has important adverse consequences that are not evident until much later in life.<sup>1</sup> For instance, accelerated or “catch-up” growth during crucial periods in development has been shown to adversely affect glucose tolerance, obesity, and lifespan in rats, fat deposition in salmon, and resistance to starvation in butterflies.<sup>1</sup> In humans, growth acceleration in childhood increases the propensity to later cardiovascular disease (CVD)<sup>2</sup> and its risk factors, such as insulin resistance,<sup>3</sup> obesity,<sup>4</sup> and higher blood pressure.<sup>5</sup>

The most rapid acceleration in growth occurs in the first weeks after birth.<sup>6,7</sup> Factors that promote such growth, such as enhanced neonatal nutrition, could therefore permanently affect, or program,<sup>8</sup> long-term health. Several lines of evidence support this hypothesis. In rats, fetal growth impairment followed by catch-up growth is associated with reduced lifespan.<sup>9</sup> Even in rats without intrauterine growth retardation, overfeeding during the brief suckling period (which accelerates growth) permanently increases later plasma insulin and cholesterol concentrations,<sup>10,11</sup> obesity, blood pres-

sure, and tendency to diabetes and syndrome X.<sup>11,12</sup> Recently, we found similar adverse effects of accelerated neonatal growth for markers for non-insulin-dependent diabetes mellitus in adolescents born prematurely.<sup>13</sup> We postulated that such growth could explain associations between low birthweight and later cardiovascular risk (“fetal origins” hypothesis<sup>14</sup>), because infants born after fetal growth retardation often show postnatal catch-up growth, which might be deleterious.

In the present study, we tested the hypothesis that slower neonatal growth reduces the changes in vascular biology that might contribute to the later development of atherosclerotic CVD. We measured endothelial function, because we have shown previously,<sup>15,16</sup> like others,<sup>17</sup> that this early stage in the atherosclerotic process is affected by factors early in life. We studied premature infants, because this is one human population that shows slow early postnatal growth, and a group of healthy subjects of similar age born at term. Our study provided a unique opportunity to investigate the influence of early growth on long-term cardiovascular health in controlled comparison groups in a human population.

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## Methods

### Subjects

Participants were part of a cohort of 926 children who had been born preterm and participated in studies that investigated the effect of early diet and growth on later cognitive function and CVD.<sup>18–21</sup> These children had been randomized at birth to receive either a nutrient-enhanced diet (preterm formula) or 1 of the 2 standard diets (breast milk donated by unrelated lactating women or a standard term formula).<sup>18–21</sup> A representative subset (n=216) of this cohort was reviewed at age 13 to 16 years.<sup>21</sup> Controls (n=61) of the same age but born at term and above the 10th centile of birthweight for gestation, were recruited from schools in the same communities<sup>22</sup> and were closely matched to those born preterm in terms of demographic, anthropometric, and socioeconomic factors.<sup>22</sup> All participants were nonsmokers, clinically well at the time of study, and free of chronic disease or disability. Ethical approval for the follow-up study was obtained from national and local research ethics committees, and written consent was obtained from all children and their guardians.

Extensive demographic, social, anthropometric, and clinical data were collected in preterm infants throughout their hospital admission as previously described.<sup>18–20</sup> Infants were weighed daily by trained staff, and a mean weight was calculated for each week after birth to reduce inaccuracies arising from daily fluctuations in weight.<sup>18</sup> Weights were also available at discharge from the neonatal unit and at age 18 months, 9 to 12 years, and 13 to 16 years. Body length (to the next succeeding millimeter) was obtained close to birth and then twice weekly with a stadiometer.<sup>18</sup>

### Flow-Mediated Arterial Dilation

Our primary outcome was brachial artery flow-mediated endothelium-dependent dilation (FMD).<sup>15</sup> This was determined by researchers who were unaware of the subject's gestational age. Subjects were rested supine for 10 minutes before the ultrasound scan, which was conducted by a single observer in a temperature-controlled (22°C to 24°C), darkened room, between 9:00 AM and 1:00 PM. The brachial artery was imaged in longitudinal section, 5 to 10 cm above the elbow, with a 7-MHz linear array transducer and an Accuson 128XP/10 system. The transducer was then fixed with a stereotactic clamp, and fine position adjustments were made when necessary with micrometer screws. A pneumatic cuff was inflated around the forearm to 300 mm Hg for 5 minutes, followed by rapid deflation, causing a large increase in blood flow (reactive hyperemia). The resting and posthyperemic blood flow velocities in the center of the imaged artery were determined with pulsed Doppler. End-diastolic B-mode images were digitized and stored offline sequentially every 3 seconds throughout the scan procedure to allow arterial diameter measurements immediately after the scan procedure (for 1 minute resting, 5 minutes cuff inflation, and 3 minutes after cuff deflation). Blood pressure was monitored with an automated oscillometric device (Accutorr, Datascope Corp) and heart rate recorded with a 3-lead ECG linked to the ultrasound machine. The reproducibility and detailed methodology for measuring FMD has been described previously.<sup>23,24</sup> FMD was expressed as the absolute maximal change between prehyperemic and posthyperemic brachial artery diameter adjusted for prehyperemic diameter (using regression analysis<sup>15</sup>) and as the absolute change in diameter expressed as a percentage of prehyperemic diameter (FMD%).<sup>23,24</sup>

### Anthropometry and Biochemistry at Follow-Up

Height was measured with a portable stadiometer accurate to 1 mm (Holtain Instruments Ltd) and weight with electronic scales accurate to 0.1 kg (Seca). Measurements were made according to standard protocols by 1 of 2 observers trained in the techniques involved. Tanner staging was performed in private by self-assessment using standard Tanner-stage photographs. Social class was based on the occupation of the parent providing the main financial support for the family (or if both parents worked, the father's occupation) according to the Registrar General's classification.<sup>19</sup>

Blood was obtained by venipuncture between 9:00 and 11:00 AM after an overnight fast. Plasma was separated immediately, stored initially at -20°C and then at -80°C, and thawed only once immediately before analysis. Plasma concentrations of LDL cholesterol were determined by standard laboratory methods.

### Statistical Analysis

We tested the hypothesis that accelerated growth affected later FMD by assessing early postnatal growth as both a continuous and dichotomous variable.

To investigate the effect of growth acceleration as a continuous variable, multiple linear regression analyses were used to assess associations between the rate of neonatal growth (weight gain) and later FMD. Neonatal weight gain was expressed as the change in absolute weight and as the change in weight *z* score between birth and age 2 weeks and between age 2 weeks and discharge (median age, 4 weeks).<sup>13</sup> Growth beyond the neonatal period was calculated as the change in *z* score for weight between discharge and age 18 months, between 18 months and 9 to 12 years, and between 9 to 12 years and 13 to 16 years. All regression analyses were adjusted for potential confounding factors (age, sex, neonatal morbidity [number of days in >30% oxygen and number of days of ventilation], and social class at birth, and for height, weight, serum LDL cholesterol concentration at follow-up, and room temperature).

To assess the influence of early growth as a dichotomous variable, the preterm population was divided into 2 groups by their early growth (median for weight gain in the first 2 weeks after birth). Mean FMD in these 2 groups was compared with that of control subjects born at term by ANOVA, and probability values were adjusted for multiple comparisons using Bonferroni corrections. Statistical significance was taken as  $P < 0.05$  for all analyses, which were all 2 tailed.

## Results

Some background characteristics of the participants are given in Table 1. Background characteristics of the subjects according to their randomized dietary assignments have been described previously.<sup>21</sup> There were no statistically significant differences in mean FMD between adolescents born preterm and given different diets at birth (mean, SD, trial 1: preterm formula versus banked breast milk: 6.0%, 3.0 vs 6.4%, 3.4, respectively; trial 2: preterm formula versus term formula: 7.2%, 3.4 vs 7.1%, 3.7, respectively). This justifies combining all feed groups in the analyses below.

### Neonatal Growth and Later FMD

Assessing growth as a continuous variable, both weight gain and change in weight *z* score between birth and the second week (but, notably, not between the second week and discharge) were associated with lower FMD in adolescence (Table 2, Figure 1). These associations were independent of birthweight, gestation, and potential confounding factors (see above) (Table 2). Taking neonatal growth as a dichotomous variable, FMD in participants with weight gain in the first 2 weeks above the sample median (-51.0 g) (mean, 5.7%; SD, 2.9%) was lower than in those with weight gain below the median (mean, 7.4%; SD, 3.4%;  $P = 0.0003$ ). This association was independent of birthweight, gestation, and potential confounding factors (as above) ( $P = 0.001$ ) and independent of a family history of diabetes or CVD ( $P < 0.0005$  for both).

To exclude the possibility that postnatal weight change because of fluid shifts explained the association between neonatal weight gain and later FMD, 2 further analyses were conducted. First, we considered weight gain from time of

TABLE 1. Subject Characteristics

	Term Controls† (n=61)	Preterm† (n=216)	Preterm Subjects With Early Weight Gain*	
			On or Below Median (n=102)	Above Median (n=101)
At follow-up				
Male sex, n (%)	29 (47)	97 (45)	49 (48)	40 (40)
Age, y	14.7±0.8	15.0±0.9	15.0±0.9	15.1±0.9
Body mass index, kg/m <sup>2</sup>	21.6±4.1	21.2±3.7	21.0±3.2	21.3±3.7
Social code	3.3±1.5	3.2±1.3	3.3±1.3	3.2±1.4
Tanner stage‡	4 (4–5)	4 (4–5)	4 (4–5)	4 (4–5)
Blood pressure, mm Hg				
Diastolic	64.2±8.2	63.7±7.4	62.8±8.0	64.7±6.8
Systolic	115.8±8.9	115.8±8.4	115.3±8.9	116.3±8.0
Cholesterol, mmol/L				
Low-density lipoprotein	2.5±0.8	2.7±0.7	2.6±0.6	2.7±0.7
High-density lipoprotein	1.2±0.3	1.2±0.3	1.2±0.3	1.2±0.2
Family history (first degree relative)				
Cardiovascular disease, %	26	32	32	33
Diabetes mellitus, %	11	11	15	8
Neonatal				
Birthweight, kg	3.5±0.6	1.4±0.3	1.3±0.3	1.4±0.3
Gestation, wk	40.0±1.2	31.0±2.7	30.0±2.2	32.0±2.6
z score birthweight	0.04±0.8	−0.9±1.2	−0.3±0.9	−1.5±1.0
z score discharge weight	...	−2.1±0.9	−2.0±0.9	−2.2±0.9
Days ventilation‡	...	0 (0–4)	3 (0–7)	0 (0–1)
Days in 30% O <sub>2</sub> ‡	...	2 (0–8)	6 (2–18)	1 (0–2)
Neonatal growth				
Weight change between				
Birth and 2 weeks, g	...	−41.5±102.6	−121.9±56.1	39.8±69.2
Minimum weight and 2 weeks, g	...	97.6±52.5	68.5±32.7	127.0±52.4
Change in weight z score between				
Birth and discharge	...	−1.2±0.8	−1.7±0.7	−0.7±0.5
Birth and 2 weeks	...	−1.0±0.5	−1.4±2.9	−0.7±2.8
Endothelial function				
Arterial diameter	3.7±0.6	3.5±0.5	3.5±0.5	3.5±0.5
FMD%§	6.1±2.8	6.6±3.3	7.4±3.4	5.8±2.9
Reactive hyperemia, %	683±362	682±314	651±295	691±325

\*Preterm subjects with weight gain in the first 2 weeks after birth above and below the median for the population.

†Small loss of n for some variables.

Data are mean±SD except ‡median (interquartile range).

§FMD% = (Change in arterial diameter/prehyperaemic diameter)×100.

minimum weight after birth to the second week. Greater weight gain during this period was associated with lower FMD in adolescence independent of birthweight, gestation, and potential confounding factors (see above) (Table 2). Second, greater length gain between birth and the second week, unlikely to be related to postnatal fluid loss, was associated with lower FMD in adolescence independent of birthweight, gestation, and potential confounding factors (Table 2).

In contrast to the effect of neonatal growth, growth expressed as the change in z score for weight between

discharge and age 18 months, 18 months and 9 to 12 years, or between 9 to 12 years and 13 to 16 years was not significantly related to later FMD (data not presented).

### Birthweight, Neonatal Growth, and Later FMD

Because infants born small for gestation show postnatal catch-up<sup>6,7</sup> growth and lower FMD later in life,<sup>15</sup> we tested the hypothesis that the association between accelerated neonatal growth and later FMD was explained by intrauterine growth retardation (as measured by a low birthweight z score). As expected, a low birthweight z score was associated

**TABLE 2. Regression Analyses of Endothelial Function in 216\* Subjects (Posthyperemic Change in Brachial Artery Diameter, mm)**

Variable	Unadjusted				Adjusted			
	Regression Coefficient, mm	95% CI	100(R <sup>2</sup> )	P	Regression Coefficient, mm	95% CI	100(R <sup>2</sup> )	P
Birthweight z score†	0.013	0.001 to 0.026	2	0.03	0.016	0.002 to 0.029	6	0.02
Change in weight z score between‡								
Birth and 2 weeks	-0.057	-0.087 to -0.024	5	0.001	-0.063	-0.113 to -0.012	10	0.01
2 weeks and discharge	-0.025	-0.056 to 0.005	1	0.1	0.004	-0.043 to 0.035	7	0.8
Weight change between‡								
Birth and 2 weeks, 100 g	-0.026	-0.040 to -0.012	6	0.0003	-0.024	-0.043 to -0.006	10	0.009
Minimum weight and 2 weeks, 100 g	-0.037	-0.065 to -0.009	3	0.01	-0.035	-0.069 to 0.000	9	0.05
Length change between birth and 2 weeks, cm‡§	-0.002	-0.004 to -0.0002	3	0.03	-0.002	-0.004 to -0.0001	12	0.04

Each line represents a separate regression model. All analyses adjusted for prehyperemic brachial artery diameter.

\*Slight loss of n in some models.

†Adjusted for age, sex, height, weight, fasting serum LDL cholesterol concentration, room temperature, social class, and indices of neonatal morbidity (No. of days of ventilation or days in >30% oxygen).

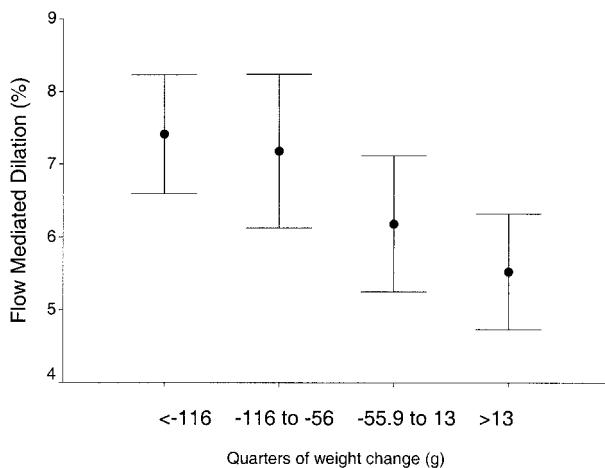
‡Adjusted for confounding variables (as above) and birthweight and gestation.

§n=100.

with greater weight gain from birth to the second week (regression coefficient, -51.6 g per z score increase in birthweight; 95% CI, -61.6 to -41.5 g;  $P<0.0001$ ). A low birthweight z score was also associated with lower FMD later in life independent of potential confounding factors (Table 2). However, 2 analyses suggested that the effect of accelerated neonatal growth on later FMD was independent of size at birth. First, FMD in adolescence was significantly related to early growth acceleration even after adjustment for birthweight z score (regression coefficient, -0.06-mm change per z score increase in weight between birth and 2 weeks;  $P=0.01$ ). Second, the interaction between birthweight z score and weight change from birth to the second week on later FMD was not statistically significant ( $P=0.6$ ).

### Comparison With Participants Born at Term

Mean FMD was greater in adolescents born preterm with weight gain in the first 2 weeks below the population median

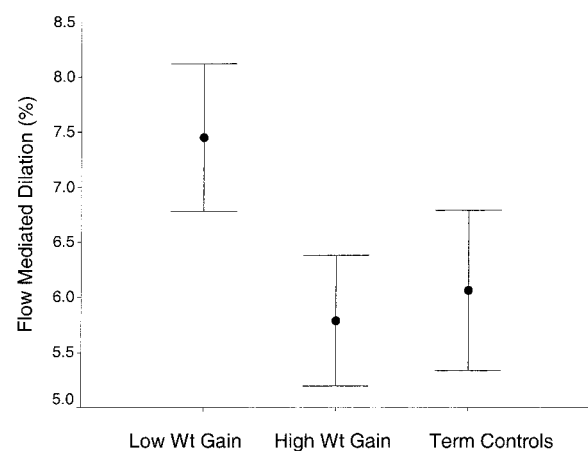


**Figure 1.** Flow-mediated endothelium-dependent dilation in adolescence according to quarters of weight change in first 2 postnatal weeks. Analyzed by linear regression.

than in those with weight gain above the median ( $P=0.001$ ) or control subjects born at term (mean, 6.1%; SD, 2.8%;  $P=0.027$ ) (Figure 2). However, mean FMD in preterm subjects with early weight gain above the population median did not differ significantly from control subjects born at term ( $P=0.9$ ).

### Discussion

A greater rate of weight gain during a critical window in the first 2 weeks after birth was associated with endothelial dysfunction up to 16 years later. Therefore, consistent with data from several animal species,<sup>1</sup> our findings suggest that accelerated growth immediately after birth has adverse effects on later cardiovascular health in humans. Preterm infants who had slower growth had greater FMD than those with faster growth or control subjects born at term. Consequently, as shown previously for cardiovascular risk factors in animals<sup>9-12</sup> and in our study of insulin resistance in the



**Figure 2.** Flow-mediated endothelium-dependent dilation in adolescents born preterm with weight gain above and below median and in control subjects born at term.

same preterm population,<sup>13</sup> this supports the hypothesis that slower growth in early life is beneficial for long-term cardiovascular outcomes. The first 2 weeks after birth seem to be a sensitive period. Adolescents with the greatest weight gain during this period had 4.0% lower FMD than those with the lowest weight gain, a substantial effect on FMD similar to that of insulin-dependent diabetes (4%)<sup>24</sup> and smoking (6%)<sup>25</sup> in adults.

Our findings have 2 potential consequences. First, our data suggest that factors that promote postnatal growth early in infancy (for example, formula feeding compared with breast-feeding<sup>26</sup>) might adversely affect later cardiovascular health. Second, as accelerated early growth displaced the influence of birthweight for gestation on later endothelial function, our data support a role for postnatal growth, rather than intrauterine factors, in adversely programming later cardiovascular outcomes. This supports a shift in focus from the so-called "fetal origins" hypothesis of CVD to an accelerated postnatal growth hypothesis,<sup>13</sup> with important clinical implications.

We chose as our end point endothelial dysfunction, which has a central role in the transduction of abnormal vascular biology involved in early atherosclerosis<sup>27</sup> and is one mechanism that has been suggested to link early factors (such as birthweight) with later CVD.<sup>15–17</sup> Endothelial dysfunction measured by lower FMD of the brachial artery is closely related to dysfunction in the coronary vessels<sup>28</sup> and shows a dose-response relation with classic cardiovascular risk factors.<sup>29</sup> Furthermore, there is a spatial relation between endothelial function and sites of atheroma in coronary arteries and evidence in older subjects that coronary endothelial dysfunction<sup>30</sup> or brachial artery FMD<sup>31</sup> is linked to later development of adverse clinical cardiovascular events. Also, unlike other cardiovascular outcomes, FMD measures early stages of arterial dysfunction relevant to the atherosclerotic process in adolescents, thereby avoiding some of the confounding effects of classic cardiovascular risk factors on the relation between early factors and later CVD in adults.

The effect of accelerated neonatal growth on later FMD in the present study was similar to that on later insulin resistance, which we have shown recently in the same population.<sup>13</sup> Data from both reports now suggest that the promotion of early growth, a fundamental tenet of public health policy, needs careful risk-benefit analysis. In preterm infants, any potential advantageous effect of slower growth in early life, for instance, as a consequence of a lower nutrition, must be tempered against the adverse effects of undernutrition on the brain.<sup>20</sup> Consequently, it might be beneficial to promote early growth in preterm infants.<sup>20</sup> Whether risk-benefit analysis would lead to the same conclusions in individuals born at full term, when the brain is likely to be less vulnerable to poor nutrition, requires further research. Nonetheless, growth is highly sensitive to nutrition even in infants born at term and is slower in breast-fed compared with formula-fed babies.<sup>26</sup> Our findings, therefore, support the hypothesis that the relative undernutrition and slower growth associated with breast-feeding early in infancy<sup>13</sup> could reduce the development of later CVD.<sup>32</sup>

Recently, we suggested that faster postnatal growth could explain, in part, what up to now has been regarded as the fetal

origins of adult CVD.<sup>13</sup> The findings from our present study are consistent with this hypothesis. Not only was later endothelial function explained by early postnatal rather than fetal growth but, notably, postnatal growth was related to later vascular function regardless of whether or not the fetus was growth retarded. Nevertheless, previous observations are entirely consistent with our new data. Because the growth-retarded fetus is one category of individual that shows catch-up growth after birth,<sup>6,7,33</sup> it is not surprising that intrauterine growth retardation appeared from our present and previous studies,<sup>15,16</sup> and from those of others,<sup>17,34</sup> to be a risk factor for impaired vascular health. From as early as 4 days of age, this catch-up growth is associated with hormonal changes (such as increased insulin-like growth factor-1 concentrations<sup>35</sup>) that are likely to be permanent<sup>33</sup> and could influence the later risk of CVD.<sup>36</sup> This focus on the importance of early postnatal growth is consistent with previous<sup>10</sup> and new emerging evidence in animals that early postnatal overnutrition is important in adversely programming long-term risk factors for CVD quite independently of fetal growth.<sup>11,12</sup> Moreover, similar adverse effects of overnutrition in infancy have recently been described in a large study in humans.<sup>37</sup> Nevertheless, an observational analysis such as ours cannot prove causation and we cannot exclude other explanations such as a genetic predisposition to both postnatal weight gain and later CVD.

### Potential Limitations

Ascertainment bias is unlikely to account for our observations, because subjects reviewed at age 13 to 16 years were representative of those recruited at birth,<sup>21</sup> and the relation between early factors and later FMD is unlikely to differ systematically between adolescents who were and were not reviewed. The lack of an association between early diet and later FMD was not unexpected, because enteral feeding usually makes only a small contribution to the early nutrient intake and growth of preterm infants, who are intolerant to oral feeds and are fed primarily intravenously in the early neonatal period.

We chose to study preterm infants because this is one human population subject to early undernutrition and consequently marked variation in early postnatal growth. Whether our results can be generalized to the full-term infant requires further research, although preliminary evidence for cardiovascular risk factors suggests that this is likely.<sup>37</sup> We recognize that preterm infants are different from those born at term in many respects: most notably, that they have medical problems related to prematurity per se. Nevertheless, even if our findings are not generalizable, they could still apply to the 6% of the population born preterm. However, substantial data support the hypothesis that our findings are generalizable. First, the adverse long-term consequence of early growth acceleration appears to be a fundamental biological phenomenon seen in many animals.<sup>1</sup> Second, infants small for gestation, whether born at term or preterm, have increased later risk factors for CVD disease<sup>3,13</sup> (including endothelial dysfunction, as shown here), and both populations show similar early postnatal catch-up growth.<sup>7</sup> Therefore, it seems unlikely that the mechanisms for the programming of vascu-

lar function differ between infants born preterm or at term. Finally, prematurity itself does not seem to influence later FMD,<sup>22</sup> and, as with previous observations of early growth and later cardiovascular risk factors,<sup>3,13</sup> our findings are independent of gestation or neonatal morbidity.

### Conclusions

Regardless of prematurity, our data suggest, for the first time, a beneficial effect of slower growth in the first 2 weeks of life for the atherosclerotic process. That growth during such a brief window in postnatal life should have such a strong influence on later vascular health is remarkable but entirely consistent with the general biological evidence on programming.<sup>8</sup> Furthermore, our observations are irrespective of size at birth and consistent with the hypothesis that factors acting early in infancy rather than antenatally could explain, in part, what has up to now has been regarded as fetal programming.<sup>13</sup> Because postnatal factors may be more amenable to intervention, the distinction between antenatal and postnatal programming of risk factors for CVD, in addition to being of scientific importance, is likely to have important public health implications. For instance, our data support the benefit of relative undernutrition associated with colostrum and breast-feeding very early in infancy in reducing the development of atherosclerotic CVD. Furthermore, our data suggest that public health interventions that aim to reduce the risk of coronary heart disease by the promotion of weight gain in infancy, as suggested recently,<sup>2,38</sup> may even be deleterious.

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