Fetal Growth and Preterm Birth Influence Cardiovascular Risk Factors and Arterial Health in Young Adults

The Cardiovascular Risk in Young Finns Study

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Objective—Impaired fetal growth is associated with cardiovascular disease in adulthood. The mechanisms of this association remain poorly described. We aimed to determine the associations of impaired fetal growth and preterm birth with cardiovascular risk factors and arterial health in a large cohort of young adults.

Methods and Results—Carotid intima-media thickness, brachial flow-mediated dilatation and cardiovascular risk factors were compared between young adults (24–45 years) born at term with impaired fetal growth (birth weight <10th percentile; n=207), born preterm (<37 weeks' gestation; n=253), and a control group born at term with normal fetal growth (birth weight 50–90th percentile; n=835), in the Cardiovascular Risk in Young Finns study. Compared with controls, those with impaired fetal growth had elevated triglycerides (P=0.006), C-reactive protein (P=0.004), low-density lipoprotein cholesterol, systolic blood pressure (both P=0.06), and intima-media thickness and impaired flow-mediated dilatation (both P=0.02), the latter partially mediated by systolic blood pressure, C-reactive protein, and triglycerides. Those born preterm had higher intima-media thickness (P=0.005) and lower flow-mediated dilatation (P=0.03) compared with controls, although this was restricted to those with concurrent fetal growth restriction.

Conclusion—Impaired fetal growth is associated with impaired endothelial function and elevated preclinical atherosclerosis in young adults, partly mediated by inflammation, blood pressure, and triglycerides. This association is most marked for those also born preterm. (Arterioscler Thromb Vasc Biol. 2011;31:2975-2981.)

Key Words: atherosclerosis ■ endothelial function ■ risk factors ■ fetal growth ■ fetal origins

There is now an established body of literature linking impaired fetal growth with adult cardiovascular disease. The exact pathophysiologic mechanisms that underlie this association and the specific timing underlying disease initiation remain only crudely determined in humans; however, early programming resulting in poor cardiometabolic risk profile and consequent endothelial dysfunction later in life, a perigestational increase in early atherosclerosis, or both may be involved.

Noninvasive methods for assessing vascular health predict clinical cardiovascular events beyond the influence of traditional risk factors, and their use for assessing the extent of atherosclerosis and arterial function may be particularly pertinent for determining the effects of fetal growth and the timing of vascular injury given the long time course separating the exposure from the onset of clinical symptoms. We have previously shown that reduced fetal growth is associated with increased aortic intima-media thickness (IMT) at birth when compared with average birth weight newborns. Studies in adults generally report no association between low birth weight and carotid IMT, although many of these studies do not have information on gestational age or are not appropriately powered to distinguish between preterm birth and reduced fetal growth as the cause of low birth weight. Furthermore, many of these prior studies rely on adult recall of birth weight and lack direct measurement of adult cardiovascular risk factors.

Accordingly, fetal growth, preterm birth, and indeed other maternal and fetal factors may have long-term influences on the risk of cardiovascular events. In this study, we sought to characterize the impact of reduced fetal growth and preterm birth on arterial structure, arterial function, and cardiovasc-
lar risk factors in early adulthood in participants in the Cardiovascular Risk in Young Finns study.

**Methods**

**Population**

The Cardiovascular Risk in Young Finns Study is an ongoing epidemiological study of atherosclerosis risk factors from childhood to adulthood. In 1980, children and adolescents aged 3 to 18 years were invited to participate (n=3596). The study was carried out in all 5 Finnish university cities with medical schools and their rural surroundings, with subjects chosen randomly from the national population register from these areas.7

At follow-up visits in 1983 and 1986, the subjects, together with their parents, completed a detailed questionnaire, including information on birth weight and preterm birth. The subjects were asked to bring with them their records from the well-baby clinics, and the information was checked by the study nurses.

The 21-year and 27-year follow-up visits were undertaken in 2001 and 2007 (n = 2265 and n = 2197, respectively). Data for birth weight, preterm birth, and carotid IMT or brachial artery flow-mediated dilatation (FMD) were available for 2281 nonpregnant subjects from 2001, or 2007 if missing from 2001.

The study complies with the Declaration of Helsinki and was approved by local ethics committees, and subjects gave written informed consent.

**Carotid IMT and Brachial FMD**

Ultrasound studies to measure carotid IMT were performed as previously reported.8,9 This technique has previously been demonstrated to have a high degree of reproducibility in our laboratory.8

FMD was measured as previously described.10,11 This technique has previously been demonstrated to have a 2-hour between-study coefficient of variation of 9% and a 3-month between-visit coefficient of variation of 26% in our laboratory.11,12

**Assessment of Socioeconomic, Lifestyle, and Cardiovascular Risk Factors**

Blood pressure was measured using a random zero sphygmomanometer (Hawksley & Sons); the average of 3 measurements was used in the analysis. Fasting venous blood samples were drawn, and serum was stored at −70°C until analysis. Serum lipids were measured in duplicate as described previously.13 Low-density lipoprotein cholesterol (LDL-c) concentration was calculated,14 high-sensitivity C-reactive protein (hsCRP) was analyzed by latex turbidimetric immunoassay (Wako Chemicals), and plasma glucose concentrations were analyzed enzymatically (Olympus).13

A self-administered questionnaire was used to determine current medication use (including antihypertensives, lipid-lowering medication, and oral contraception), prior diagnosis of diabetes, employment, marital status, and smoking status.

**Fetal Growth and Preterm Birth**

Preterm birth status was defined as birth before 37 weeks’ gestation, and number of weeks preterm was ascertained in those who reported preterm birth. Birth weight was averaged between values recorded in 1983 and 1986. Individuals born preterm were categorized as either appropriate birth weight for gestational age (AGA) or with fetal growth restriction (FGR) based on gender-stratified birth weight adjusted for gestational age (AGA: second, third, and fourth quartiles; FGR: first quartile). Gender-specific birth weight percentiles were calculated based on all 2667 subjects born at term and with birth weight data in the Young Finns study (females: 10th percentile 2975 g, 50th percentile 3500 g, 90th percentile 4100 g; males: 10th percentile 3050 g, 50th percentile 3640 g, 90th percentile 4300 g). Term births were classified as small for gestational age (SGA) (birth weight <10th percentile), AGA (birth weight 50–90th percentile), or large for gestational age (birth weight >90th percentile). SGA was used to identify those born at term with impaired fetal growth. Those born large for gestational age at term were excluded from these analyses, leaving 2110 nonpregnant subjects, including 253 born preterm.

**Statistical Analyses**

The primary analysis consisted of a comparison of those born AGA at term, with (1) those born SGA at term and (2) those born preterm. Statistical analyses were performed using SPSS software (version 17.0, SPSS). Statistical significance was inferred as a 2-sided probability value <0.05.

Differences in carotid IMT and brachial artery FMD associated with reduced fetal growth and preterm birth were determined by independent-samples t-tests and multivariable linear regression. FMD is expressed as percentage change from resting arterial diameter. Logistic regression was used to examine the associations of birth weight and preterm birth with high-risk IMT (defined as focal thickening or mean IMT ≥90th gender-specific percentile) and endothelial dysfunction (defined as FMD ≤10th gender-specific percentile).

Models were adjusted for age, gender, socioeconomic factors (marital and employment status), and smoking, with a subsequent model further adjusted for cardiovascular risk factors (LDL-c, high-density lipoprotein cholesterol, triglycerides [Ln transformed], systolic blood pressure [SBP], glucose [Ln transformed], hsCRP [Ln transformed], diabetes), and current medication use (antihypertensives, lipid-lowering medication, and oral contraceptive use for women). All FMD models were adjusted for resting brachial diameter. Additional models were adjusted for adult body mass index (BMI), and the interaction of adult BMI with birth weight was assessed to distinguish between the influences of fetal and postnatal growth.15

**Results**

**Fetal Growth, Preterm Birth, and Cardiovascular Risk Factors**

Participant characteristics and cardiovascular risk factor levels stratified by fetal growth and preterm birth are shown in Table 1. For term births, those born SGA had markedly greater triglycerides and hsCRP than those born AGA, and there was also some evidence that they had higher LDL-c and SBP. Those born preterm had similar characteristics to those born AGA at term. For those born preterm, the average gestational age was 33.5 weeks (SD 1.8).

**Fetal Growth, Birth Weight, and Carotid IMT**

Carotid IMT was significantly higher in those born SGA than in those born AGA (Figure 1). This was weakened by adjustment for cardiovascular risk factors and current medication use (AGA: 0.578 mm [95% CI 0.573, 0.584], versus SGA: 0.588 mm [95% CI 0.577, 0.599]; P=0.11, for subjects with complete data for all cardiovascular risk factors). Despite the higher carotid IMT in those born SGA, they did not have a significantly increased prevalence of high-risk IMT (focal thickening or mean IMT ≥90th gender-specific percentile; Figure 2).

In those born at term, there was an inverse linear association between birth weight and carotid IMT during adulthood (mean IMT: −0.007 mm [SD 0.003] per 500 g birth weight, P=0.007). This association did not differ by gender (P interaction=0.13) or age (P interaction=0.51). Adjustment for cardiovascular risk factors and current medication use weakened the association (mean IMT: −0.005 mm [SD 0.003] per 500 g birth weight, P=0.05), which was weakened further by adjustment for brachial FMD (P=0.09). Adjustment for adult BMI did not alter the association (Table 2), and a BMI×birth weight interaction term was not significant.
When BMI from an earlier study visit during childhood/adolescence (1980 or, if missing, 1983 or 1986) was introduced to this model, only birth weight and adult BMI were significantly associated with IMT (Table 2).

The inverse association of birth weight with carotid IMT during adulthood was of similar magnitude for those born preterm (mean IMT: \(0.008 \text{ mm} \pm 0.005\) per 500 g birth weight, \(P=0.10\)). When those born preterm and those born at term were pooled for analysis, there was a significant association of birth weight with carotid IMT (mean IMT: \(-0.008 \text{ mm} (SD 0.002)\) per 500 g birth weight, \(P=0.0001\)), which remained after adjustment for cardiovascular risk factors and current medication use (\(P=0.002\)).

**Fetal Growth, Birth Weight, and Brachial Artery FMD**

FMD was lower in those born SGA than in those born AGA (Figure 1). This persisted when adjusted for cardiovascular...
risk factors and current medication use ($P=0.02$). However, the prevalence of endothelial dysfunction ($\text{FMD} < 10\text{th}$ gender-specific percentile) did not differ between those born SGA and AGA (Figure 2).

In those born at term, there was a direct linear relationship between birth weight and FMD (0.432% [SD 0.096] per 500 g birth weight, $P=0.0001$). This association did not differ by gender ($P$ interaction=0.08) and was independent of cardiovascular risk factors and current medication use (0.452% [SD 0.129] per 500 g birth weight, $P=0.0005$). Adjustment for adult BMI did not alter the association (Table 2), and a BMI×birth weight interaction term was not significant ($P=0.90$). When BMI from an earlier study visit during childhood/adolescence (1980 or, if missing, 1983 or 1986) was introduced to this model, birth weight and adult BMI, but not the intermediate BMI, were significantly associated with FMD (Table 2).

The inverse association of birth weight with FMD was weaker for those born preterm (0.277% [SD 0.209] per 500 g birth weight, $P=0.19$). When those born at term and those born preterm were analyzed together, there was a significant association of birth weight with FMD (0.369% [SD 0.096] per 500 g birth weight, $P=0.0001$), which was similar after adjustment for cardiovascular risk factors and current medication use ($P<0.0001$).

### Table 2. Association of Birth Weight, BMI in Childhood/Adolescence, and BMI in Adulthood With Carotid IMT and Brachial FMD in Term Births

<table>
<thead>
<tr>
<th></th>
<th>Mean IMT</th>
<th>P</th>
<th>Maximum IMT</th>
<th>P</th>
<th>FMD</th>
<th>P</th>
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<tr>
<td><strong>Early size model</strong></td>
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<tr>
<td>Birth weight</td>
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<td>0.007</td>
<td>-0.064</td>
<td>0.004</td>
<td>0.077</td>
<td>0.0005</td>
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<tr>
<td><strong>Combined early and adult size model</strong></td>
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<tr>
<td>Birth weight</td>
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<td>0.002</td>
<td>-0.073</td>
<td>0.001</td>
<td>0.070</td>
<td>0.001</td>
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<tr>
<td>BMI, adulthood</td>
<td>0.170</td>
<td>&lt;0.0001</td>
<td>0.175</td>
<td>&lt;0.0001</td>
<td>0.172</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Combined early, intermediate &amp; adult size model</strong></td>
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<tr>
<td>Birth weight</td>
<td>-0.071</td>
<td>0.001</td>
<td>-0.076</td>
<td>0.0007</td>
<td>0.074</td>
<td>0.0007</td>
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<tr>
<td>BMI, childhood/adolescence</td>
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<td>0.46</td>
<td>0.031</td>
<td>0.32</td>
<td>-0.046</td>
<td>0.13</td>
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<tr>
<td>BMI, adulthood</td>
<td>0.162</td>
<td>&lt;0.0001</td>
<td>0.164</td>
<td>&lt;0.0001</td>
<td>0.188</td>
<td>&lt;0.0001</td>
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Standardized $\beta$-regression coefficients for carotid IMT and brachial artery FMD. All models were adjusted for age, gender, employment status, marital status, and smoking status. FMD models further adjusted for arterial diameter. IMT models, n=1845; FMD models, n=1821. BMI indicates body mass index; IMT, intima-media thickness; FMD, flow-mediated dilatation.
versus AGA at term; preterm and AGA: FMD β-coefficient −0.468 [SE 0.351], *P*=0.18 versus AGA at term; adjusted for socioeconomic factors and smoking). These associations were similar after further adjustment for cardiovascular risk factors and current medication use (results not shown).

Those born preterm with FGR had a higher prevalence of high-risk IMT compared with those born AGA at term, and there was also some evidence for endothelial dysfunction in this group (Figure 2). In contrast, the prevalence of these arterial abnormalities was not increased in those born preterm who were AGA.

**Correlates of IMT and FMD: Birth Characteristics and Cardiovascular Risk Factors in Adulthood**

The strength of associations of birth weight, preterm birth, and cardiovascular risk factors with carotid IMT and brachial artery FMD are shown in Table 3. With regards to carotid atherosclerosis, the magnitude of the effect of birth weight was such that a difference in birth weight of 500 g influenced carotid IMT by the same amount as 7 mm Hg SBP, 1.3 mmol/L LDL-c, 1.0 mmol/L high-density lipoprotein cholesterol, and 2.3 kg/m² BMI and was similar to the effect of daily smoking. Conversely, the influence on carotid IMT for each year of age was equivalent to the influence of reduced fetal growth, and adjustment for cardiovascular risk factors, particularly hsCRP, triglycerides, SBP, and LDL-c in those with reduced fetal growth, and adjustment for cardiovascular risk factors, particularly hsCRP, triglycerides, and SBP, partially mitigated the influence of reduced fetal growth on carotid atherosclerosis. Further statistical modeling designed to differentiate between the influences of adult BMI and birth weight¹⁵ indicated that our results are consistent with the “fetal origins” hypothesis. Along with prior findings by ourselves and others,²⁵ our results support a model in which an adverse intrauterine environment promotes the initiation and marked progression of early atherosclerosis in utero, with further enhanced postnatal progression due to a poor cardiovascular risk profile. Genetic and epigenetic mechanisms may be involved in this conceptual model²⁶,²⁷; however, our results do not provide information on this, nor do they provide information to support or exclude a role for other putative mechanistic links between early life influences and adult cardiovascular disease, such as an endothelial-mediated predisposition toward thrombosis.²⁸

The association of preterm birth with increased prevalence of high-risk IMT and reduced FMD was limited to those born preterm with FGR. This is consistent with an association with ischemic heart disease observed in a retrospective cohort of subjects born in 1925 to 1949.²⁹ In contrast, studies of vascular health in younger populations, including vascular

<table>
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<tr>
<th>Table 3. Strength of the Associations of Birth Characteristics and Cardiovascular Risk Factors With Carotid IMT and Brachial FMD</th>
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<tbody>
<tr>
<td><strong>Carotid IMT, mm</strong></td>
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<tr>
<td><strong>BMI, per kg/m²</strong></td>
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<td><strong>SBP, per mm Hg</strong></td>
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<td><strong>Male gender</strong></td>
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<tr>
<td><strong>Birth weight, per 500 g</strong></td>
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<td><strong>Glucose†</strong></td>
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<td><strong>hsCRP†</strong></td>
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<td><strong>Triglycerides†</strong></td>
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<td><strong>LDL-c, per mmol/L</strong></td>
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<td><strong>Daily smoker</strong></td>
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<td><strong>HDL-c, per mmol/L</strong></td>
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<td><strong>Preterm birth†</strong></td>
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<tr>
<td><strong>Brachial FMD, %</strong></td>
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<tr>
<td><strong>Male gender</strong></td>
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<tr>
<td><strong>Age, per y</strong></td>
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<tr>
<td><strong>Birth weight, per 500 g</strong></td>
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<tr>
<td><strong>hsCRP†</strong></td>
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</table>

Each variable was modeled separately except as noted (*). Variation in IMT or FMD is the unstandardized β-coefficient, and the regression coefficient is the standardized β-coefficient. Variables ordered by strength of regression coefficient. All models adjusted for age, gender, employment status, marital status, and smoking status. Mean carotid IMT was used for analysis. FMD models were further adjusted for arterial diameter. IMT indicates intima-media thickness; FMD, flow-mediated dilatation; BMI, body mass index; SBP, systolic blood pressure; hsCRP, high-sensitivity C-reactive protein; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol.

*Birth weight and preterm birth were modeled concurrently.
†Ln transformed.
function, aortic narrowing, and arterial stiffness, have predominantly shown no evidence of poor vascular health in those born preterm either with or without FGR. These differences may be due to changes in the treatment and survival of preterm infants over time; however, we found no evidence of heterogeneity by year of birth. A number of studies now indicate that preterm birth is associated with an increase in SBP in young adults of approximately 5 mm Hg, which may translate to an increased risk of cardiovascular events. Our findings were independent of cardiovascular risk factors including SBP, suggesting that preterm birth accompanied by FGR may have an impact on cardiovascular health and disease beyond its effects on blood pressure alone.

Strengths of this study include the assessment of both carotid IMT and brachial artery FMD, allowing for the comparison of both the structural and functional health of the vasculature in the same subjects; the large sample size; the ascertainment of birth weight during childhood (from parents and childhood health records, at study visits in 1983 and 1986), which should increase the accuracy of the measure compared with recall during adulthood; the availability of BMI from childhood, adolescence, and adulthood; and the population-representative nature of the cohort at the time of initial recruitment in 1980. Our findings are limited by the lack of data concerning cardiovascular events, which will require longer follow-up; potential confounders, such as fetal exposure to maternal smoking and maternal nutrition during pregnancy, information concerning growth during infancy, particularly the period from birth to 3 years of age; and arterial health during childhood.

Our findings indicate that impaired fetal growth is associated with the extent of preclinical atherosclerosis in young adults, largely independently of concurrent endothelial impairment; however, it was partly mediated by parallel associations of fetal growth with inflammation, SBP, and triglycerides. This association is markedly greater in those also born preterm, in whom there is an increased prevalence of high-risk IMT and endothelial dysfunction. When considered along with our prior finding that aortic IMT is increased in newborns with impaired fetal growth, these findings suggest that those with impaired fetal growth may be a potential target for early intervention strategies aimed at preventing early atherosclerosis, followed by later strategies targeting altered components of their cardiovascular risk profile.

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Disclosures
None.

References


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