Original Contribution

Early Life Growth and Hemostatic Factors

The Barry Caerphilly Growth Study

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Associations between early life growth trajectories and a range of adult (aged ~25 years) hemostatic factors were assessed in the Barry Caerphilly Growth study (N = 517) in South Wales, 1974–1999. Associations of birth weight, birth length, and weight and height velocities during three periods (“immediate”: 0–<5 months, “infant”: 5 months–<1 year 9 months, and “childhood”: 1 year 9 months–5 years) with adult levels of hemostatic factors were assessed. Birth weight was inversely associated with fibrinogen (β per 1-unit change in z score = −0.08, 95% confidence interval (CI): −0.15, −0.02). Immediate weight velocity was inversely associated with factor VII (β = −1.88, 95% CI: −3.84, 0.09), factor VIII (β = −2.58, 95% CI: −4.07, −0.45), and von Willebrand factor antigen (β = −4.07, 95% CI: −7.25, −0.49). Birth length was inversely associated with fibrinogen (β = −0.07, 95% CI: −0.14, −0.01). Evidence was weaker for an inverse association of immediate height velocity with factor VIII (β = −2.16, 95% CI: −4.62, 0.29) and von Willebrand factor antigen (β = −2.85, 95% CI: −6.52, 0.81). Childhood height velocity was positively associated with D-dimer (ratio of geometric means = 1.11, 95% CI: 1.01, 1.23). Results support the view that the immediate postnatal period may be particularly important, possibly through impaired liver development and/or infection in early life, in determining cardiovascular disease risk.

factor VII; factor VIII; fibrin-fibrinogen degradation products; fibrinogen; growth and development; tissue plasminogen activator; von Willebrand factor

Abbreviations: CI, confidence interval; t-PA, tissue plasminogen activator; VWF, von Willebrand factor antigen.

Consistent evidence has demonstrated an inverse association between birth weight and adult risk of cardiovascular disease (1–5). Postnatal growth, predominantly in early infancy, may be of particular relevance in determining later-life risk of cardiovascular disease, and evidence suggests that this period may be critical in determining long-term cardiovascular risk (4, 6). There is also evidence that small size in infancy (at 2 years of age) combined with rapid weight gain in childhood increases the risk of cardiovascular disease in adulthood (7). One potential pathway that may mediate such an association is the hemostatic system through permanent alterations in the structure and function of the liver.

According to the programming hypothesis, fetal undernutrition results in maintaining the brain at the expense of the trunk, including the liver, which may cause permanent alterations to liver function (8). Support for this hypothesis comes from studies of rats that demonstrate structural and
Evidence of associations between postnatal and child-
hood growth and adult level of hemostatic factors is more
scarce. In the Hertfordshire study, weight at 1 year of age
was inversely associated with both fibrinogen and factor VII
for men but not for women. A formal test for interaction
between weight at 1 year and sex regarding their relation to
fibrinogen and factor VII was not reported (16, 17). In an-
other study of older British women, leg length, a biomarker
of prepubertal exposures affecting growth such as nutrition
and childhood infections, was inversely associated with lev-
el of liver enzymes (20). Therefore, intrauterine and early-
life exposures affecting birth size and growth may also
affect development of the liver because it remains plastic
in the first years of life (21).

Given that hemostatic markers may be implicated in the
etiology of coronary heart disease (22) and that existing ev-
cidence is scarce and conflicting, we studied the association
among birth weight, birth length, early-life growth trajecto-
ries, and a range of hemostatic factors (fibrinogen, factor VII,
factor VIII, von Willebrand factor antigen (VWF), tissue
plasminogen activator (t-PA), and D-dimer) in young adults.
Evidence also exists that birth weight is inversely associated
with liver enzymes in older women (13) and with increased
total cholesterol that is regulated by the liver (14).

Several retrospective cohort studies (15–19) have exam-
ined the association of birth dimensions (obtained from
medical records) with adult levels of hemostatic factors
(factor VII. Three articles that reported on the association of birth
size with factor VII found no evidence of such an associa-
tion (15, 16, 18). Studies that examined the association of
birth weight with fibrinogen yielded conflicting results. In
three of the retrospective cohort studies (16, 18, 19), no
evidence of an association was found, whereas Martyn
et al. (15) found that mean plasma fibrinogen decreased with
increasing birth weight and abdominal circumference (sepa-
ately) in men but not in women.

Materials and methods

The Barry Caerphilly Growth study is a follow-up of a
dietary-intervention, randomized controlled trial. The orig-
inal trial participants comprised pregnant mothers and their
offspring, who were followed up until 5 years of age. In the
late 1990s, the offspring were recontacted and were invited
to participate in a (follow-up) study when they were about
25 years of age.

Original study

Briefly, the original trial was undertaken from 1972 to
1974 in two small towns in South Wales: Barry, a seaside
town; and Caerphilly, a largely industrial town. Pregnant
mothers and their offspring were recruited through primary
care practices and were randomly assigned to the “supple-
mented” or control group. Women in the supplemented
group were provided with milk tokens throughout pregnancy
and, subsequently, for their child until the age of 5 years.

The women were visited twice during pregnancy, and data
on health behaviors were gathered by using a health visitor–
administered questionnaire. After birth, the infants were visited
at 10 days; 6 weeks; and 3, 6, 9, and 12 months. Thereafter,
they were visited at six monthly intervals—resulting in 14 home
visits—until their fifth birthday. Birth weight was obtained
from hospital records; thereafter, weight was measured on
a portable beam balance. Nine hundred fifty-one (82 percent)
singleton children completed the trial.

Follow-up study

From 1997 to 1999, an attempt was made to contact all
participants who had completed the original study (23). Of
the 951 subjects who completed the original study, 23 were
untraceable, had died (n = 4), or had emigrated, and 679
(71 percent) agreed to attend a follow-up clinic in which
standard anthropometric measures were recorded, informa-
tion on lifestyle and medical history was gathered by ques-
tionnaire, and blood samples were collected. Fibrinogen
was assayed by the automated von Clauss assay, and factors
VII and VIII by one-stage assays, in a Coag-A-Mate auto-
mated coagulometer (Organon Teknika, Cambridge, United
Kingdom). VWF (DAKO, Copenhagen, Denmark), t-PA
antigen, and fibrin D-dimer (Biopool, Umea, Sweden) were
measured by enzyme-linked immunoadsorbent assays (24),
as was insulin, which was measured after an overnight fast.
Participant smoking status was classified as nonsmoker,
former smoker, and current smoker. Maternal smoking status
was dichotomized. Childhood social class was derived from
reported father’s occupation and was classified according to
the Registrar General’s classification: I, II, III–nonmanual,
III–manual, IV, or V, with I being the highest (professionals)
and V the lowest (unskilled manual workers). Participants’
social class was classified by using the same categories. Self-
reported alcohol consumption was classified into abstainers
and quartiles of the distribution of nonabstainers. The Brof
Taf Local Research Ethics Committee (Bro Taf Health
Authority, South Wales) gave ethical approval for the study.

Statistical analysis

We utilized all 14 childhood measurements between birth
and 5 years in developing a linear-spline, random-effects
model with two knots (thus dividing follow-up into three
time periods, each with its own gradient). Spline models
with knots positioned at different time points were com-
pared with a third-order fractional polynomial model. The
positioning of the two knots was chosen by selecting the
spline model with the highest percentage of predicted values
within 5 percent of those of the fractional polynomial
model. With the use of the same procedure, three-knot
spline models were investigated. However, because the fit
of the three-knot model was comparable with that of the
two-knot model, the simpler two-knot model was chosen. The spline model was adjusted for sex, and the interaction terms between sex and each of the three time periods were considered. The random-effects model allowed the four coefficients, namely, the birth weight (or length) and the slopes for each of the three time periods, to vary between subjects. In addition, the model allowed for variation in measurement between occasions and within subjects, thereby capturing the change in the variance of measurements with age. The model was estimated by using Markov chain Monte Carlo methods with diffuse priors, which can be used to approximate maximum likelihood estimation.

The four between-subject random effects from the spline model thus summarize an individual’s growth curve from birth to age 5 years, denoting the deviation from the average predicted birth weight or length and the deviation from the average predicted growth rate (kilograms/year, centimeters/year) for each of the three time periods. These periods are defined as “immediate” weight (or height) velocity (between birth and <5 months), “infant” weight (or height) velocity (between 5 months and <1 year 9 months), and “childhood” weight (or height) velocity (between 1 year 9 months and 5 years). We converted birth weight and length and the weight and height velocity variables into z scores so that the sizes of the coefficients were directly comparable.

The adult hemostatic factors—fibrinogen, factor VII, factor VIII, VWF, t-PA, and natural logged D-dimer (due to a positively skewed distribution)—were analyzed by using linear regression with the four random effects (deviance from the average predicted birth weight or length and deviance from the average predicted growth rate (kilograms/year, centimeters/year) for each of the three time periods) as exposures. To account for the varying precision of the four estimated exposures, a weighted linear regression analysis was conducted, weighting each subject by the average of the four standard deviations of these random effects. We also ran models again to obtain results using actual weight (kilograms) and height (centimeters). These results are reported in the text.

We examined the effects of early growth with three different models: 1) incorporating the growth exposures separately while adjusting for allocation to intervention or control in the original trial, adult age, sex, and gestational age; 2) the same as model 1 but including all four growth exposures together; 3) the same as model 2 but adding social class in childhood and adulthood, maternal smoking during pregnancy, smoking, and alcohol consumption. We considered childhood social class and maternal smoking during pregnancy potential confounders because they are associated with birth weight and nutrition, which in turn affects childhood growth, and with cardiovascular risk factors and disease. Adult social class, smoking, and alcohol consumption were also considered potential confounders because of their association with childhood social class and cardiovascular risk factors and disease.

We hypothesized that adult obesity and height mediate associations of early life growth with hemostatic factors and that insulin resistance may share a causal pathway with hemostatic markers in relation to early life growth; adult body size is determined by childhood growth and is associated with levels of hemostatic factors (25). Evidence is also robust that insulin resistance is affected by both prenatal and postnatal growth (6, 26) and is associated with levels of hemostatic factors (27). We therefore studied the effect of including a term for each of these factors (separately) in our final models (model 3). Doing so enabled us to examine whether these pathways explain associations of early life growth with hemostatic factors, in which case associations would be attenuated toward the null. Waist circumference was used as a measure of adult obesity because it was the measure most strongly associated with outcomes (compared with waist-to-hip ratio and body mass index). Homeostasis model assessment (HOMA) was used as a measure of insulin resistance (28).

Multicollinearity between exposures was also assessed. The correlations between the four standardized weight measures ranged from 0.06 to 0.51 and between the four standardized height measures from 0.003 to 0.67. Growth was not expressed as ponderal index because this measure reaches a peak at 2 months so that the gradient of the first slope is based on only two measurements, resulting in poor model fit.

RESULTS

Of the 679 original trial participants who agreed to participate in the follow-up study, 633 provided a blood sample and complete data on exposures, and covariables and at least one outcome were available for 517 participants. Characteristics of participants are displayed in table 1. Only a selection of the weight and height measures are shown because they are reported elsewhere (29). Participants included in this analysis had a greater probability of having a mother who smoked during pregnancy and of being a current smoker themselves, they were of a higher mean gestational age and had a higher homeostasis model assessment score than participants in the follow-up study who were not included in this analysis, and they had a lower probability of abstaining from alcohol as well as lower t-PA levels. They did not differ regarding any other of the measures listed in table 1.

The separate associations of birth weight, birth length, and weight and height growth velocities with hemostatic factors are presented in table 2. Coefficients are mean differences (ratios of geometric means for D-dimer) per increase in a z-score unit. There was evidence of inverse associations of birth weight with fibrinogen, of immediate weight and height velocities with factor VIII, and of immediate weight velocity with VWF. In contrast, childhood height velocity was positively associated with VWF.

Multivariable associations of birth weight and weight velocities with fibrinogen, factor VII, factor VIII, and VWF are presented in table 3 and were similar to those observed when each growth exposure was studied in separate models (table 2). Because there was no evidence of associations between growth and D-dimer or t-PA, results for D-dimer and t-PA are not presented here (available upon request from the authors). Birth weight continued to be inversely associated with fibrinogen, and this association was unaffected by further adjustments for potential lifestyle confounders.
(model 2: $\beta = -0.08$, 95 percent confidence interval (CI): $-0.15$, $-0.02$; $p < 0.01$). This finding is equivalent to a decrease of 0.1 pg/ml (95 percent CI: 0.02, 0.17) in fibrinogen per 500-g (1 standard deviation) increase in birth weight.

Immediate weight velocity was inversely associated with factor VII (model 2: $\beta = -1.88$, 95 percent CI: $-3.84$, 0.09; $p = 0.06$), factor VIII ($\beta = -2.58$, 95 percent CI: $-4.07$, $-0.45$; $p = 0.02$), and VWF ($\beta = -4.07$, 95 percent CI: $-7.25$, $-0.89$; $p = 0.01$). In other words, an increase in 1 kg/month in the first 5 months of life was associated with a 13.5-IU/dl (95 percent CI: 0.7, 27.6) decrease in factor VII, a 17.8-IU/dl (95 percent CI: 2.5, 33.2) decrease in factor VIII, and a 28.2-IU/dl (95 percent CI: 5.4, 51.0) decrease in VWF fibrinogen at the age of 25 years. Adjustment for potential confounders, if anything, slightly strengthened associations. There was no strong evidence of associations of infant and childhood growth with fibrinogen, factor VII, factor VIII, or VWF.

Multivariable associations of birth height and height velocities with fibrinogen, factor VIII, VWF, and D-dimer are presented in table 4. Because there was no evidence of associations between growth and factor VII or t-PA, these results are not presented. Birth length, similar to birth weight, was inversely associated with fibrinogen, and this finding was robust to further adjustment (table 4, model 2: $\beta = -0.07$, 95 percent CI: $-0.14$, $-0.01$; $p = 0.03$). This result is equivalent to a decrease of 0.02 pg/ml (95 percent CI: 0.00, 0.03) in fibrinogen per 500-g (1 standard deviation) increase in birth length.

Greater immediate height velocity—similarly to immediate weight velocity—was associated with decreasing levels of factor VIII and VWF (model 2: $\beta = -2.16$, 95 percent CI: $-4.62$, 0.29; $p = 0.08$ and $\beta = -2.85$, 95 percent CI: $-6.52$, 0.81; $p = 0.13$, respectively); however, these associations did not reach conventional statistical significance and are compatible with chance, particularly because we conducted multiple comparisons. For factor VIII, it is equivalent to a decrease of 8.5 IU/dl (95 percent CI: 1.3, 18.2) per 1-cm increase in height in the first 5 months of life.

Childhood height velocity was positively associated with D-dimer levels (ratio of geometric means $= 1.11$, 95 percent CI: 1.01, 1.23; $p = 0.03$). Associations of childhood height velocity with VWF ($\beta = 3.99$, 95 percent CI: $-0.69$, 8.66; $p = 0.10$) and factor VIII ($\beta = 2.48$, 95 percent CI: $-0.65$, 5.62; $p = 0.12$) were in the same direction as that for childhood height velocity and D-dimer, but 95 percent confidence intervals included the null value.

Adding terms for adult height, waist circumference (or body mass index; results not shown), and homeostasis model assessment did not substantially change the associations between birth weight and height, weight and height velocities, and hemostatic factors. (This information is described in two supplementary tables (tables 4 and 5), which are posted on the Journal’s website (http://aje.oupjournals.org/).)

**DISCUSSION**

In this study of a contemporary birth cohort, we found strong evidence of inverse associations of birth weight and birth length with fibrinogen and of immediate weight velocity with factor VII, factor VIII, and VWF. Weaker evidence ($p > 0.05$) of inverse associations of immediate height velocity with factor VIII and VWF was also found.

These associations are in line with the hypothesis that smaller birth dimension may adversely affect the liver, resulting in higher levels of hemostatic factors. There was also
TABLE 2. Association of birth weight and birth length and of immediate, infant, and childhood weight and height velocities† with hemostatic factors, Barry Caerphilly Growth study, South Wales, 1974–1999‡

<table>
<thead>
<tr>
<th></th>
<th>Fibrinogen (g/liter), n = 515</th>
<th>Factor VII (IU/dl), n = 516</th>
<th>Factor VIII (IU/dl), n = 517</th>
<th>VWF§ (IU/dl), n = 510</th>
<th>D-dimer (ng/ml), n = 493</th>
<th>t-PA§ (ng/ml), n = 509</th>
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<tbody>
<tr>
<td></td>
<td>Mean difference 95% CI‡</td>
<td>Mean difference 95% CI</td>
<td>Mean difference 95% CI</td>
<td>Mean difference 95% CI</td>
<td>Ratio of geometric means 95% CI</td>
<td>Mean difference 95% CI</td>
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<td><strong>Weight</strong></td>
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<td>Birth</td>
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<tr>
<td>Immediate (0–&lt;5 months)</td>
<td>-0.07* (-0.13, -0.01)</td>
<td>-1.05 (-3.19, 1.09)</td>
<td>-1.71 (-4.07, 0.64)</td>
<td>-2.00 (-5.49, 1.49)</td>
<td>0.96 0.89, 1.03</td>
<td>-0.03 -0.28, 0.22</td>
</tr>
<tr>
<td>Infant (5 months–&lt;1 year 9 months)</td>
<td>0.00 (-0.05, 0.06)</td>
<td>-1.80 (-3.70, 0.10)</td>
<td>-2.31* (-4.39, -0.22)</td>
<td>-3.72* (-6.81, -0.63)</td>
<td>0.98 0.92, 1.05</td>
<td>0.05 -0.17, 0.27</td>
</tr>
<tr>
<td>Childhood (1 year 9 months–5 years)</td>
<td>0.02 (-0.03, 0.07)</td>
<td>0.46 (-1.42, 2.33)</td>
<td>-1.14 (-3.21, 0.93)</td>
<td>0.07 -3.00, 3.14</td>
<td>1.05 0.98, 1.11</td>
<td>-0.05 -0.27, 0.17</td>
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<tr>
<td><strong>Height</strong></td>
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<td>Birth</td>
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<td>Immediate (0–&lt;5 months)</td>
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<td>0.75 (-1.69, 3.19)</td>
<td>1.14 -2.48, 4.76</td>
<td>0.95 0.88, 1.02</td>
<td>-0.08 -0.33, 0.18</td>
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<tr>
<td>Infant (5 months–&lt;1 year 9 months)</td>
<td>-0.02 (-0.08, 0.03)</td>
<td>-0.52 (-2.51, 1.48)</td>
<td>-2.35* (-4.54, -0.16)</td>
<td>-2.67 -5.92, 0.58</td>
<td>1.03 0.96, 1.10</td>
<td>-0.02 -0.25, 0.20</td>
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<tr>
<td>Childhood (1 year 9 months–5 years)</td>
<td>0.01 (-0.04, 0.07)</td>
<td>1.09 (-0.82, 3.00)</td>
<td>0.19 -1.92, 2.30</td>
<td>1.59 -1.54, 4.73</td>
<td>1.02 0.96, 1.09</td>
<td>0.05 -0.17, 0.27</td>
</tr>
</tbody>
</table>

* p < 0.05.
† The birth weight standard deviation (SD) was 0.43; the immediate, infant, and childhood weight velocity SDs were 1.67, 0.67, and 0.40, respectively. The birth length SD was 1.92; the immediate, infant, and childhood height velocity SDs were 2.98, 1.18, and 0.59, respectively.
‡ All models were adjusted for allocation to the intervention or control arm in the original trial, adult age, sex, and gestational age.
§ VWF, von Willebrand factor antigen; t-PA, tissue plasminogen activator; CI, confidence interval.
strong evidence of a positive association of childhood height velocity with adult D-dimer levels, and we found weaker evidence of association of childhood height velocity with VWF and factor VIII. The magnitude and strength of these associations were not substantially changed when controlling for potential confounders.

We found no evidence supporting the hypothesis that insulin resistance may explain the observed associations of growth with adult levels of clotting factors, even though fasting insulin itself was associated with fibrinogen, factor VII, factor VIII, and t-PA. We also hypothesized that adult waist circumference or height may mediate the positive association between childhood growth and hemostatic factors because we have previously shown in this cohort that body size tracks from childhood to adulthood (29). However, adjusting for height and waist circumference (separately) did not attenuate the associations observed between birth weight and length, height and weight velocities, and some of the hemostatic factors.

Multiple exposures and outcomes were examined in this study. For some hemostatic markers (t-PA and D-dimer, for example), there was no or very little evidence of associations with early life growth, whereas, for other factors, such as factor VIII, associations with several exposures were noted. Despite these findings, we propose that a pattern can be discerned. Lower birth weight and shorter birth length were associated with higher fibrinogen levels in our study, as in others (15). Reduced immediate weight velocity was associated with greater levels of several hemostatic factors. By the age of 1 year 9 months, the direction of

### TABLE 3. Association of birth weight and of immediate, infancy, and childhood weight velocities* with hemostatic factors, Barry Caerphilly Growth study, South Wales, 1974–1999

<table>
<thead>
<tr>
<th>Outcome/variable</th>
<th>Model 1†</th>
<th>Model 2‡</th>
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<tbody>
<tr>
<td></td>
<td>Mean difference</td>
<td>95% CI</td>
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<tr>
<td>Fibrinogen (g/liter), n = 515</td>
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<tr>
<td>Birth weight</td>
<td>−0.08</td>
<td>−0.15, −0.02</td>
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<tr>
<td>Immediate (0–&lt;5 months)</td>
<td>0.01</td>
<td>−0.05, 0.06</td>
</tr>
<tr>
<td>Infant (5 months–&lt;1 year 9 months)</td>
<td>−0.00</td>
<td>−0.06, 0.06</td>
</tr>
<tr>
<td>Childhood (1 year 9 months–5 years)</td>
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<tr>
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<td>−3.71, 0.15</td>
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<tr>
<td>Infant (5 months–&lt;1 year 9 months)</td>
<td>0.42</td>
<td>−1.76, 2.60</td>
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<tr>
<td>Childhood (1 year 9 months–5 years)</td>
<td>0.41</td>
<td>−1.82, 2.64</td>
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<td>Factor VIII (IU/dl), n = 517</td>
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<tr>
<td>Birth weight</td>
<td>−1.70</td>
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<td>Immediate (0–&lt;5 months)</td>
<td>−2.16</td>
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<td>−1.61</td>
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<tr>
<td>Childhood (1 year 9 months–5 years)</td>
<td>1.37</td>
<td>−1.08, 3.81</td>
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<td>VWF§ (IU/dl), n = 510</td>
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* The birth weight standard deviation (SD) was 0.43; the immediate, infant, and childhood weight velocity SDs were 1.67, 0.67, and 0.40, respectively.
† Model 1 was adjusted for weight velocity in other periods, allocation to the intervention or control arm in the original trial, adult age, sex, and gestational age.
‡ Model 2: model 1 plus maternal smoking during pregnancy, childhood social class, adult social class, smoking, and alcohol consumption.
§ CI, confidence interval; VWF, von Willebrand factor antigen.
associations changes from inverse to positive, although a conventional statistically significant association was found for only childhood height velocity and D-dimer.

Because of the paucity of evidence with regard to the nature and magnitude of associations of hemostatic factors with cardiovascular disease, it is difficult to quantify our results in terms of risk of cardiovascular disease. However, we believe that the value of these findings lies in suggesting potential biologic pathways by which growth patterns might affect cardiovascular disease risk later in the life course.

In a cohort of men and women born between 1934 and 1944 in Helsinki, Finland (7), participants who experienced a coronary event had a lower birth weight and body mass index at the age of 2 years compared with participants who did not experience an event. Furthermore, from about 2 years of age, participants who experienced a coronary event had greater height, weight, and body mass index increases compared with participants who remained free of coronary events in adulthood. Present findings are in line with those from the Helsinki study.

It has been suggested that in-uterine exposures such as undernutrition impair liver growth and function, including metabolism of fibrinogen, factor VII, VWF, and possibly factor VIII (15). The associations we found could be interpreted as supporting this hypothesis if we assume that liver damage is expressed as increased levels of hemostatic factors. However, 

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<td>Birth length</td>
<td>−0.07</td>
<td>−0.14, −0.00</td>
</tr>
<tr>
<td>Immediate (0–&lt;5 months)</td>
<td>−0.04</td>
<td>−0.11, 0.02</td>
</tr>
<tr>
<td>Infant (5 months–&lt;1 year 9 months)</td>
<td>0.01</td>
<td>−0.07, 0.09</td>
</tr>
<tr>
<td>Childhood (1 year 9 months–5 years)</td>
<td>0.03</td>
<td>−0.05, 0.11</td>
</tr>
<tr>
<td>Factor VIII (IU/dl), n = 517</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth length</td>
<td>−0.50</td>
<td>−3.14, 2.14</td>
</tr>
<tr>
<td>Immediate (0–&lt;5 months)</td>
<td>−2.38</td>
<td>−4.84, 0.09</td>
</tr>
<tr>
<td>Infant (5 months–&lt;1 year 9 months)</td>
<td>−0.36</td>
<td>−3.50, 2.78</td>
</tr>
<tr>
<td>Childhood (1 year 9 months–5 years)</td>
<td>1.92</td>
<td>−1.19, 5.02</td>
</tr>
<tr>
<td>VWF§ (IU/dl), n = 510</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth length</td>
<td>−0.82</td>
<td>−4.71, 3.08</td>
</tr>
<tr>
<td>Immediate (0–&lt;5 months)</td>
<td>−2.88</td>
<td>−6.53, 0.76</td>
</tr>
<tr>
<td>Infant (5 months–&lt;1 year 9 months)</td>
<td>−0.06</td>
<td>−4.70, 4.58</td>
</tr>
<tr>
<td>Childhood (1 year 9 months–5 years)</td>
<td>3.82</td>
<td>−0.77, 8.41</td>
</tr>
</tbody>
</table>

* The birth length SD was 1.92; the immediate, infant, and childhood height velocity SDs were 2.98, 1.18, and 0.59, respectively.
† Model 1 was adjusted for height velocity in other periods, allocation to the intervention or control arm in the original trial, adult age, sex, and gestational age.
‡ Model 2: model 1 plus maternal smoking during pregnancy, childhood social class, adult social class, smoking, and alcohol consumption.
§ CI, confidence interval; VWF, von Willebrand factor antigen.
this assumption may be oversimplistic because circulating levels of hemostatic factors are determined by rates of both synthesis and degradation as well as by extrahepatic sources. Furthermore, VWF is synthesized by endothelial cells and not by hepatocytes; therefore, liver damage cannot explain the association between growth and VWF.

An alternative mechanism that may explain the observed associations between growth and adult levels of hemostatic factors is infection. Both acute and chronic infections can impair linear growth—indirectly, by affecting nutritional status, and directly, by affecting cells directly involved in bone remodeling (30). Smaller children may also be more prone to infections. Inflammation may shift the hemostatic balance in favor of coagulation. Inflammatory mediators can elevate platelet count, platelet reactivity, endothelial products (including VWF and t-PA), and coagulation factors, including fibrinogen and factor VIII; down-regulate natural anticoagulant mechanisms and stimulate fibrin formation (of which D-dimer is one measure); and impair fibrinolytic potential (31). Therefore, inflammation may be the common origin of both decreased growth velocities and increased levels of hemostatic factors. Unfortunately, inflammatory markers such as C-reactive protein were not measured in study participants in childhood, so we could not explore this hypothesis further.

Our study has several advantages as well as limitations. Data on growth patterns in the first 5 years of life are unique. Hemostatic factors were measured at the age of 25 years, ruling out any marked effects of reverse causality due to preexisting atherosclerosis. Not all participants in the original trial were traced in the follow-up study. However, the proportion of loss to follow-up was similar in the intervention and control arms (32), and the childhood social and demographic characteristics of the subjects who were and were not followed up in adulthood were similar (33). In addition, not all participants in the follow-up study were included in the present analysis, but our results would be biased only if associations for participants who were included in the analyses were different than for those not included. It is possible that some of our associations are chance findings because of multiple comparisons. Finally, given our sample size, we lacked power to demonstrate modest associations at conventional levels of statistical significance.

In conclusion, our results support the view that the immediate postnatal period may be important in determining adult risk of cardiovascular disease (6, 7). Future, larger studies are needed to replicate these associations. Before any public health intervention can be advocated, further follow-up of this cohort, as well as other growth trials, is required to determine whether the size of the associations diminishes, remains constant, or amplifies with age and whether promotion of early growth has an overall beneficial or detrimental effect in terms of both cardiovascular disease and other causes of morbidity.

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Conflict of interest: none declared.

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