Growth before 2 years of age and serum lipids 60 years later: The Helsinki Birth Cohort Study

Eero Kajantie, 1* David J P Barker, 2,3 Clive Osmond, 4 Tom Forsén1,5 and Johan G Eriksson1,5

Accepted 16 November 2007

Background Small body size at birth and slow growth during the first 2 years after birth, leading to low body mass index (BMI) at 2 years, are associated with coronary heart disease and stroke in adult life. We tested the hypothesis that this path of growth is associated with an atherogenic lipid profile in later life.

Methods We measured serum lipid concentrations at age 57–70 years in 1999 members of the Helsinki Birth Cohort. They were randomly selected from an original cohort of 8760 people and had on average 11 measurements of height and weight between birth and 2 years of age.

Results The 18% of subjects who used lipid-lowering medication had a lower BMI at birth and at 2 years. These subjects were excluded from the analyses of lipid profiles. A 1 kg/m2 lower BMI at birth was associated with 0.051 mmol/l (95% CI –0.001 to 0.103; P = 0.05) higher non-HDL cholesterol and 0.018 g/l higher (0.005–0.031; P = 0.006) apolipoprotein B concentrations. A slower increase in BMI during the first 6 months after birth was associated with lower HDL and higher non-HDL cholesterol concentrations. A 1 kg/m2 lower BMI at 2 years was associated with 0.020 mmol/l lower (0.004–0.036; P = 0.02) HDL cholesterol and 0.059 mmol/l (0.020–0.099; P = 0.003) higher non-HDL cholesterol and 0.018 mmol/l higher (0.008–0.028; P < 0.001) apolipoprotein B concentrations. The age at weaning off breast milk was not associated with lipid profile in later life.

Conclusions Small body size at birth and slow weight gain during infancy are associated with an atherogenic lipid profile in adult life.

Keywords Infant growth, lipids, cholesterol, lipoproteins

1 The National Public Health Institute, Helsinki, Finland.
2 Department of Medicine, Heart Research Center, Oregon Health & Sciences University, Portland, OR, USA.
3 Developmental origins of Health and Disease Division, University of Southampton, Southampton General Hospital, Southampton, UK.
4 Medical Research Council Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton, UK.
5 Department of Public Health, University of Helsinki, Helsinki, Finland.
* Corresponding author. National Public Health Institute, Mannerheimintie 166, 00300 Helsinki, Finland.
E-mail: eero.kajantie@helsinki.fi
Introduction

Slow foetal growth is associated with increased rates of cardiovascular disease in adult life. Slow post-natal growth is also of importance: slow gain in weight during the first 2 years of life and low body mass index (BMI) at 2 years are associated with the later occurrence of coronary heart disease and stroke. Slow pre- and early post-natal growth have been shown to be associated with hypertension and impaired glucose regulation in later life. We have now examined their associations with adult serum lipid profiles.

Previous findings on relationships between body size at birth and serum lipids are inconsistent. However, there is evidence that points to the importance of the post-natal period in establishing life-long set points for lipid metabolism. There has been considerable speculation that the high cholesterol content of human milk may programme lipid metabolism throughout life.

The evidence from human and animal studies is conflicting, and the concentrations of cholesterol in infant’s food may have no more than transient effects on serum lipid concentrations. Follow-up studies of children have shown, however, that serum cholesterol concentrations tend to track so that children maintain their rank order of serum cholesterol concentrations from the age of 6 months.

Studies of men in Hertfordshire, UK, showed that low weight at 1 year of age was associated with raised serum total and LDL cholesterol and apolipoprotein B concentrations. One explanation for this association is that low growth rates during infancy are accompanied by resetting of liver metabolism, which regulates cholesterol synthesis and excretion. In the Hertfordshire study weight at 1 year was the only measurement of post-natal growth. We report findings in the Helsinki Birth Cohort where each individual has on average 11 measurements of height and weight between birth and 2 years. We hypothesized that slow growth between birth and 2 years and low BMI at 2 years are associated with an atherogenic lipid profile in later life.

Methods

The original birth cohort consisted of 8760 men and women, who were born as singletons at Helsinki University Central Hospital during 1934–44, who attended child welfare clinics in the city of Helsinki and who were still resident in Finland in 1971. Their birth records include birth weight and length at birth. The child welfare clinic records include serial measurements of height and weight and father’s occupation. On average each person had been measured 11 times between birth and 2 years of age. We determined socio-economic status by father’s occupation, categorized in three groups (labourer, lower middle, upper middle) according to the classification used by Statistics Finland.

We traced people belonging to the cohort by social security number, which is a unique identifier for every resident of Finland. All 7047 people belonging to the original cohort who were still alive and resident in Finland were sent a questionnaire in the year 2000, and 4515 individuals provided adequate data. To achieve a sample size of over 2000 people for the clinical study, we used random number tables to select 2902 subjects. Of these subjects, 2003 agreed to participate in a clinical study, and 1999 of them (926 men and 1073 women) had complete measurements of their height and weight and plasma lipid concentrations. As compared with the remaining original cohort, these subjects had 30 g higher birth weight (95% CI 6–54 g; $P = 0.02$), 0.08 kg/m$^2$ higher BMI at birth (0.02–0.14; $P = 0.02$) and similar length and gestational age at birth. At 2 years, they were 0.2 cm taller (0.0–0.4; $P = 0.01$) and had 61 g (2–119; $P = 0.05$) higher weight and similar BMI. Although they had a more rapid growth in length between birth and 6 months (0.06 SD; 0.01–0.11; $P = 0.01$), no there were no other differences in growth of height, weight or BMI. The subjects were interviewed about their medical history including current use of medication. Serum total and HDL cholesterol and triglyceride concentrations were measured using standard enzymatic methods and apolipoprotein B using an immunoturbidimetric assay.

The study was approved by the Ethics Committee of the National Public Health Institute, and each participant signed an informed written consent.

Data were analysed by tabulation of means and multiple linear and logistic regression. We converted each measurement for each individual to a z-score (SD score). The z-score is the number of standard deviations by which an observation differs from the mean for the whole study group. Because the children were not measured exactly on their birthdays we obtained a z-score at monthly birthdays by interpolation if measurements. Each subject had been measured on average 11 times between birth and 2 years; the number of measurements was 1 or 2 for 10.1%; 3–6 for 21.9%; 7–11 for 26.3%; 12–20 for 28.0% and greater than 20 for 13.7% of the subjects. To measure how much size at any age differed from that predicted by the body size attained at an earlier age, we use the residuals of a regression analysis, which we refer to as conditional measurements. By this construction, these residuals are uncorrelated with the earlier size measurements. We chose these ages because 6 months corresponds to the median age of weaning off breast milk in this cohort (157 days), and 2 years has been used in previous analyses of the Helsinki Birth Cohort. We categorized duration of breastfeeding into four groups: not breastfed, breastfed for 0–3 months, for 3–6 months or for longer than 6 months. We similarly categorized the age at...
introduction of cow’s milk into at birth, 0–3 months, 3–6 months or more than 6 months. We analysed linear trends across these categories plus used them as dummy variables with the non-breastfed as a reference category. Otherwise, levels of significance refer to analyses of continuous variables. Subjects who used lipid-lowering medication were excluded from the analysis of plasma lipid concentrations. Plasma triglyceride concentrations were log-transformed for analysis. Interactions were assessed by including product terms of the main effects in the regression analysis. There was no interaction between the effects of sex and any early growth variable on lipid concentrations, and thus we present pooled analyses adjusted for sex, age and current BMI. Analyses with birth measurements are in addition adjusted for the length of gestation.

Results

The mean age of the study subjects was 62 (range 57–70) years. Table 1 shows the body size of the men and women during childhood and their body size and serum lipid concentrations during adulthood. For comparison, mean values of measurements are shown in standard deviation units according to Finnish and US Centers for Disease Control and Prevention (CDC) growth reference and WHO growth standards. Table 2 shows other clinical characteristics in childhood and at adult examination. A total of 18% of people were taking lipid-lowering medication (statin or fibrate) and we excluded them from analyses of serum lipid concentrations. We adjusted serum lipid concentrations for age, sex and current BMI.

Body size at birth

Subjects with low birth weight were more likely to be taking lipid-lowering medication (OR per 1 kg birth weight 0.69; 95% CI 0.52–0.91; \( P = 0.01 \) adjusted for length of gestation). Low birth weight was also associated with higher serum triglycerides (\( r = -0.08; P < 0.001 \)) but not with any other lipid concentrations. Table 3 shows that low BMI at birth was associated with higher non-HDL cholesterol, apolipoprotein B and triglyceride concentrations. The associations were slightly weaker when adult BMI was not included in the model. The correlation coefficient between BMI at birth and adult BMI was 0.10. Length at birth was not associated with any of the lipid variables.

BMI at age 2 years

Figure 1 shows the correlation of HDL and non-HDL cholesterol and apolipoprotein B with body size at 3-month intervals between birth and 2 years. By the age of 2 years BMI had become positively correlated with HDL cholesterol and inversely related to non-HDL cholesterol and apolipoprotein B. These associations are shown in Table 4, which also shows that low BMI at 2 years was associated with higher triglyceride concentrations. The associations were slightly weaker when adult BMI was not
Table 3 Cohort characteristics in childhood and at adult examination

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Men (n = 926)</th>
<th>Women (n = 1073)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N missing</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Child</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of gestation (days)</td>
<td>123</td>
<td>279.7</td>
</tr>
<tr>
<td>Breastfed (%)</td>
<td>81.8</td>
<td></td>
</tr>
<tr>
<td>Age at weaning from breast milk (days)²</td>
<td>330</td>
<td>152 (84–244)</td>
</tr>
<tr>
<td>Age at initiation of cow’s milk (days)³</td>
<td>576</td>
<td>71 (30–152)</td>
</tr>
<tr>
<td>Socio-economic status in infancy (%)</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>Labourer</td>
<td>66.1</td>
<td></td>
</tr>
<tr>
<td>Lower middle</td>
<td>19.8</td>
<td></td>
</tr>
<tr>
<td>Upper middle</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td><strong>Adult</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0</td>
<td>61.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0</td>
<td>176.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0</td>
<td>86.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0</td>
<td>27.5</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>5</td>
<td>100.8</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>0</td>
<td>5.76</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>0</td>
<td>1.46</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mmol/l)</td>
<td>0</td>
<td>4.29</td>
</tr>
<tr>
<td>Apolipoprotein B (g/l)</td>
<td>1</td>
<td>1.08</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)²</td>
<td>0</td>
<td>1.40</td>
</tr>
<tr>
<td>Statin or fibrate (%)</td>
<td>0</td>
<td>20.7</td>
</tr>
</tbody>
</table>

To convert to mg/dL, multiply total, HDL and non-HDL cholesterol by 38.6, and triglycerides by 88.5.

²Median (25th and 75th percentiles) among people who were breastfed.

³Geometric means and SDs.

Table 3 Serum lipid concentrations according to BMI at birth

<table>
<thead>
<tr>
<th>BMI at birth (fifths)</th>
<th>Using lipid lowering drugs (%)</th>
<th>N included</th>
<th>Total cholesterol (mmol/l)</th>
<th>HDL cholesterol (mmol/l)</th>
<th>Non-HDL cholesterol (mmol/l)</th>
<th>Apolipoprotein B (g/l)</th>
<th>Triglycerides² (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>20.1</td>
<td>321</td>
<td>6.04</td>
<td>1.61</td>
<td>4.43</td>
<td>1.10</td>
<td>1.36</td>
</tr>
<tr>
<td>2</td>
<td>18.9</td>
<td>329</td>
<td>6.16</td>
<td>1.64</td>
<td>4.52</td>
<td>1.12</td>
<td>1.35</td>
</tr>
<tr>
<td>3</td>
<td>20.2</td>
<td>325</td>
<td>6.14</td>
<td>1.63</td>
<td>4.51</td>
<td>1.11</td>
<td>1.38</td>
</tr>
<tr>
<td>4</td>
<td>15.1</td>
<td>326</td>
<td>6.07</td>
<td>1.63</td>
<td>4.45</td>
<td>1.09</td>
<td>1.33</td>
</tr>
<tr>
<td>Highest</td>
<td>14.5</td>
<td>324</td>
<td>5.99</td>
<td>1.64</td>
<td>4.35</td>
<td>1.07</td>
<td>1.22</td>
</tr>
<tr>
<td>Change (95% CI) per SD increase in BMI³</td>
<td>0.86</td>
<td></td>
<td>(-0.036)</td>
<td>(0.015)</td>
<td>(-0.051)</td>
<td>(-0.018)</td>
<td>(-4.5%)</td>
</tr>
<tr>
<td></td>
<td>(0.78–0.96)</td>
<td></td>
<td>(-0.091–0.019)</td>
<td>(-0.006–0.037)</td>
<td>(-0.103–0.001)</td>
<td>(-0.031 to -0.005)</td>
<td>(-6.7 to -2.3%)</td>
</tr>
<tr>
<td>P for trend³</td>
<td>0.005</td>
<td></td>
<td>0.2</td>
<td>0.2</td>
<td>0.05</td>
<td>0.006</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change (95% CI) per SD increase in BMI³</td>
<td>0.88</td>
<td></td>
<td>(-0.031)</td>
<td>(0.003)</td>
<td>(-0.034)</td>
<td>(-0.013)</td>
<td>(-2.9%)</td>
</tr>
<tr>
<td></td>
<td>(0.79–0.98)</td>
<td></td>
<td>(-0.085–0.034)</td>
<td>(-0.009–0.025)</td>
<td>(-0.087–0.018)</td>
<td>(-0.026 to -0.000)</td>
<td>(-5.2% to -0.5%)</td>
</tr>
<tr>
<td>P for trend³</td>
<td>0.01</td>
<td></td>
<td>0.3</td>
<td>0.8</td>
<td>0.2</td>
<td>0.05</td>
<td>0.02</td>
</tr>
</tbody>
</table>

The concentrations are adjusted for age, sex and BMI. To convert to mg/dL, multiply total, HDL and non-HDL cholesterol by 38.6, and triglycerides by 88.5.

²These subjects are excluded from the analysis of lipid concentrations.

³Geometric means.

⁴Adjusted for sex, current age and length of gestation.

⁵Adjusted for sex, current age and length of gestation.
Figure 1 Cross-sectional correlation coefficients of serum HDL cholesterol (a), non-HDL cholesterol (b) and apolipoprotein B (c) concentrations with height, weight and BMI between birth and 2 years, calculated at 3-month intervals by interpolation of successive measurements. The correlation coefficients are adjusted for sex, current age and BMI. Dashed lines represent 95% CI.
included in the model. The correlation coefficient between BMI at 2 years and adult BMI was 0.12.

**Change in body size from birth to 6 months**

We examined the associations between serum lipid concentrations and changes in body size from birth to 6 months of age. BMI at 6 months was correlated with BMI at birth ($r = 0.33$). We calculated BMI at birth 6 months conditional on BMI at birth, i.e. the difference between the BMI measured at 6 months of age and that predicted by BMI at birth. Table 5 shows that a lower conditional BMI at 6 months was associated with lower values of HDL cholesterol and apolipoprotein B but not with total cholesterol or triglyceride concentrations. Changes in height between birth and 6 months were not related to serum lipid concentrations.

**Change in body size from 6 to 24 months**

We examined the associations between serum lipid concentrations and changes in body size from 6 to 24 months of age. The correlation coefficient between BMI at 6 and 24 months was 0.65. BMI at 24 months conditional on BMI at birth and 6 months was not associated with total, HDL or non-HDL cholesterol concentrations or with apolipoprotein B. However, a 1 SD higher conditional BMI at 24 months was associated with 3.9% lower (95% CI 1.9–5.9; $P < 0.001$) serum triglyceride concentration.

The correlation coefficient between length at 6 and 24 months was 0.76. We calculated length at 24 months conditional on length at birth and 6 months. A 1 SD higher conditional length at 24 months was associated with 0.061 mmol/l (95% CI 0.010–0.111; $P = 0.02$) lower total cholesterol, 0.064 mmol/l (0.016–0.112; $P = 0.009$) lower non-HDL cholesterol, 0.019 (0.007–0.031; $P = 0.002$) g/l lower apolipoprotein B and 2.2% (0.1–4.2%; $P = 0.04$) lower triglyceride concentration.

**Breastfeeding**

All except 274 people were breastfed. The lipid concentrations of children who were not breastfed were similar to those who were ($P$'s $\leq 0.2$). Neither the age of weaning off breast milk nor the age at introduction of cow’s milk were related to any of the serum lipid concentrations ($P$'s $\geq 0.2$), and adjustment for breastfeeding, its duration or the age of introduction of cow’s milk had little effect on the associations between lipids and body size.

**Socio-economic status in infancy**

The family’s socio-economic status, as indicated by the father’s occupation, was not associated with the infant’s gain in BMI. Infants in middle class families, however, gained more height between birth and 2 years than infants in labourers’ families (36.2 compared with 35.7 cm; $P = 0.001$). The family’s socio-economic status did not affect lipid concentrations, and the associations between linear growth and lipid concentrations were little changed by allowing for it.
We have shown that the serum lipid concentrations of men and women aged 62 years are related to their growth up to the age of 2 years. Our study sample was randomly selected from the Helsinki Birth Cohort. In previous analyses of this cohort we have shown that slow growth in infancy and low BMI at 2 years are associated with increased rates of coronary heart disease \(^8\) and stroke. \(^9\) Our current findings suggest that the development of an atherogenic lipid profile may be one process underlying this association.

We found that serum cholesterol concentrations were associated with changes in BMI between birth and 6 months of age, but thereafter they were associated with linear growth. Undernutrition initially reduces BMI but subsequently slows linear growth. \(^34\) We conclude that lipid metabolism is adversely affected by undernutrition during infancy, which may be a consequence of either inadequate food intake or diversion of nutrients to combat recurrent infections. A larger increase in BMI between birth and 6 months, which was the average period of breastfeeding, was associated with a more favourable lipid profile, reflected in high HDL and low non-HDL cholesterol and apolipoprotein B concentrations. After 6 months of age slow linear growth was associated with high non-HDL cholesterol concentrations, but not with HDL cholesterol concentrations. This suggests that the time between birth and 6 months of age may be a sensitive period for the establishment of HDL cholesterol metabolism.

While the associations we found between body size and growth during infancy and serum lipid levels are relatively weak in comparison with the associations with coronary heart disease \(^8\) and stroke \(^9\), they seem to at least as strong as those previously reported for birth weight. For example, two recent meta-analyses have reported an overall association of \(0.02 \text{ mmol/l lower total cholesterol per 1 SD higher birth weight,}^{15,16}\) which compares to our finding of \(0.033 \text{ mmol/l lower total cholesterol per 1 SD (0.83 kg/m}^2\) higher BMI at 2 years.

We have previously discussed the limitations of the Helsinki Birth Cohort. \(^8,35\) Our study was restricted to people who had attended child welfare clinics, but the majority of children attended these clinics, which were free. The social class distribution of the children in our study, as defined by father’s occupation, was similar to that in Helsinki as the whole. The participation rate was 69% of those invited. However, our results were based on internal comparisons with the sample. Selection bias would be expected to affect the results only if the relationship between early growth and adult lipid concentrations were different in participants as compared with non-participants. This is unlikely but cannot be excluded. Eighteen per cent of our study sample were taking lipid-lowering medication and it was necessary to exclude them from the analyses of lipid profiles.

### Table 5 Serum lipid concentrations according to BMI at age 6 months conditional on BMI at birth

<table>
<thead>
<tr>
<th>BMI at age 6 months conditional on BMI at birth (fifths)</th>
<th>Using lipid lowering drugs (%)</th>
<th>N included</th>
<th>Total cholesterol (mmol/l)</th>
<th>HDL cholesterol (mmol/l)</th>
<th>Non-HDL cholesterol (mmol/l)</th>
<th>Apolipoprotein B (g/l)</th>
<th>Triglycerides (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>21.0</td>
<td>312</td>
<td>6.09</td>
<td>1.61</td>
<td>4.49</td>
<td>1.11</td>
<td>1.35</td>
</tr>
<tr>
<td>2</td>
<td>18.2</td>
<td>324</td>
<td>6.08</td>
<td>1.60</td>
<td>4.48</td>
<td>1.11</td>
<td>1.31</td>
</tr>
<tr>
<td>3</td>
<td>14.9</td>
<td>337</td>
<td>6.12</td>
<td>1.64</td>
<td>4.48</td>
<td>1.09</td>
<td>1.37</td>
</tr>
<tr>
<td>4</td>
<td>16.9</td>
<td>329</td>
<td>6.15</td>
<td>1.64</td>
<td>4.52</td>
<td>1.11</td>
<td>1.32</td>
</tr>
<tr>
<td>Highest</td>
<td>18.2</td>
<td>323</td>
<td>5.96</td>
<td>1.66</td>
<td>4.30</td>
<td>1.06</td>
<td>1.29</td>
</tr>
</tbody>
</table>

Change (95% CI) per one SD increase in conditional BMI:

- Total cholesterol: \(-0.082\) to \(-0.020\)
- HDL cholesterol: \(-0.0102\) to \(-0.004\)
- Non-HDL cholesterol: \(-0.028\) to \(-0.004\)
- Apolipoprotein B: \(-0.0031\) to \(-0.0022\)
- Triglycerides: \(-0.031\) to \(-0.022\)

**P for trend**:

<table>
<thead>
<tr>
<th></th>
<th>(0.2)</th>
<th>(0.1)</th>
<th>(0.03)</th>
<th>(0.03)</th>
<th>(0.01)</th>
<th>(0.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change (95% CI)</td>
<td>(0.93)</td>
<td>(-0.029)</td>
<td>(0.016)</td>
<td>(-0.045)</td>
<td>(-0.014)</td>
<td>(-0.8)</td>
</tr>
<tr>
<td>per one SD increase in conditional BMI</td>
<td>(0.81) to (1.03)</td>
<td>(-0.080) to (-0.022)</td>
<td>(-0.005) to (-0.037)</td>
<td>(-0.094) to (-0.005)</td>
<td>(-0.026) to (-0.001)</td>
<td>(-3.1) to (-1.4)</td>
</tr>
</tbody>
</table>

**P for trend**:

<table>
<thead>
<tr>
<th></th>
<th>(0.1)</th>
<th>(0.3)</th>
<th>(0.1)</th>
<th>(0.07)</th>
<th>(0.03)</th>
<th>(0.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change (95% CI)</td>
<td>(0.91)</td>
<td>(-0.029)</td>
<td>(0.016)</td>
<td>(-0.045)</td>
<td>(-0.014)</td>
<td>(-0.8)</td>
</tr>
<tr>
<td>per one SD increase in conditional BMI</td>
<td>(0.81) to (1.03)</td>
<td>(-0.080) to (-0.022)</td>
<td>(-0.005) to (-0.037)</td>
<td>(-0.094) to (-0.005)</td>
<td>(-0.026) to (-0.001)</td>
<td>(-3.1) to (-1.4)</td>
</tr>
</tbody>
</table>

The concentrations are adjusted for age, sex and BMI. To convert to mg/dL, multiply total, HDL and non-HDL cholesterol by 38.6, and triglycerides by 88.5.

**a**These subjects are excluded from the analysis of lipid concentrations.

**b**Geometric means.

**c**Adjusted for sex, current age and BMI.

**d**Adjusted for sex, and current age.
The use of lipid-lowering medication was, however, associated with low BMI at birth and at 2 years, which strengthens our conclusion that slow foetal and infant growth are associated with unfavourable lipid profiles. We used non-HDL cholesterol concentration as a proxy of LDL cholesterol concentration, since we did not have direct measurements of LDL cholesterol; but we used direct measurements of apolipoprotein B, which is a precursor of LDL cholesterol and a well-established risk factor for cardiovascular disease.36–38 There has been considerable debate on whether the findings relating slow growth during infancy with adult diseases such as coronary heart disease8 and stroke9 can be generalized to younger populations.39 This debate has arisen from randomized trials in infants born prematurely, showing that nutrient-enriched formula or rapid weight gain during the first 2 weeks of life are associated with cardiovascular risk factors such as increased fasting proinsulin concentration,40 lower endothelium-dependent flow mediated artery dilatation41 and higher LDL to HDL cholesterol ratio.42 However, the generalizability of our findings is supported by findings in a range of population-based studies showing associations of small body size or slow growth during the first years of life with an unfavourable lipid profile later in life. These include studies in Swedish adolescents born in the 1980s,43 Japanese 20-year-olds born in 1965–74,44 Croatian 20-year-olds born in late 1960s45 and 53-year-old members of the Great Britain 1946 birth cohort.46 Our results obviously do not exclude the possibility that accelerated growth during infancy may imply long-term risk of cardiovascular disease for subgroups of newborn infants, including those born prematurely or small for gestational age or both.

The liver regulates lipid metabolism. Altered liver growth during gestation may permanently alter LDL cholesterol metabolism. Animal experiments have demonstrated that undernutrition during gestation permanently changes lipid metabolism47,48 and the microstructure of the liver.49 In rats a brief 4-day period of maternal undernutrition at the time of conception reduced liver size at birth.50 People who were conceived during the war-time famine in Holland had a more atherogenic lipid profile than people who were not exposed to the famine in utero.51 Moreover, a study of men and women born in Sheffield, UK, showed a relationship between high total cholesterol concentrations and a small abdominal circumference at birth, a marker of slow prenatal liver growth.52 Therefore, we suggest that set points for non-HDL cholesterol metabolism are established in response to foetal nutrition and liver growth in utero.

The liver’s development is not complete at birth.53 The association between slow infant growth and an unfavourable lipid profile is consistent with findings in the Hertfordshire cohort, in which low weight at 1 year was associated with increased mortality from coronary heart disease and raised serum apolipoprotein B.24 We suggest that the association reflects reduced liver growth during infancy and accompanying alterations in metabolic set points.

The high cholesterol content of human milk is thought to be important in establishing how the liver synthesizes and excretes cholesterol throughout life.17,20,54 A systematic review of 37 studies concluded that breastfeeding is associated with lower serum concentrations of total and LDL cholesterol in adult life.17 We found no association between serum lipid profiles and either breastfeeding, its duration or the age at introduction of cow’s milk, which contains considerably less cholesterol than human milk.55,56 Only a small number of people, however, were not breastfed.

We found that slow foetal and infant growth were associated with raised serum triglyceride concentrations. Raised serum triglyceride concentrations are closely linked to insulin resistance, and this finding is consistent with the associations between slow early growth and insulin resistance already reported in this cohort.5,12 Babies who have low birth weight and grow slowly during infancy lack muscle,57 a deficiency that will persist into childhood, since there is little cell replication in muscle after infancy.48 Insulin resistance is thought to reflect poor muscular development and the development of a body composition with high fat but low lean mass.58 Slow linear growth during infancy was associated with poor living conditions, as indicated by family’s low socio-economic status. Poor living conditions, however, did not affect the lipid profile. This contrasts with hypertension in the same cohort whose cumulative incidence was higher among people born into the families of labourers.59

In conclusion, our findings are further evidence that the period between conception and 2 years of age is critical for the establishment of lipid metabolism. Resetting of lipid metabolism may be a key mechanism linking early life events with adult cardiovascular disease.

**Acknowledgements**

This study was supported by Academy of Finland; British Heart Foundation; Finnish Foundation for Cardiovascular Research; Finnish Foundation for Pediatric Research; Finnish Diabetes Foundation; Finnish Medical Society Duodecim; Finska Läkaresällskapet; Juho Vainio Foundation; Novo Nordisk Foundation; Päivikki and Sakari Sohlberg Foundation; Signe and Ane Gyllenberg Foundation and Yrjö Jahnsson Foundation. We thank our research nurses Hanna Alastalo, Terhi Eerola, Paula Nyholm and Tuula Tenkula and our data manager Sigrid Rosten for their invaluable contribution.

**Conflict of interest:** None declared.
KEY MESSAGES

- People who are small and thin at age 2 years have higher non-HDL cholesterol and apolipoprotein B concentrations in adult life. Thinness at 2 years is also associated with lower adult HDL cholesterol concentrations.
- A more detailed analysis of early growth shows that an adverse lipid profile in late adulthood is predicted by a slow growth in BMI between birth and 6 months and slow linear growth between 6 and 24 months.
- While the mechanisms of these associations remain to be elucidated, they may in part underlie the previously reported relationship between slow early growth and coronary heart disease and stroke.

References

EARLY GROWTH AND ADULT SERUM LIPIDS