Cardiovascular Risk Factors in Adolescents Born Preterm

WHAT’S KNOWN ON THIS SUBJECT: Adolescents and adults born early preterm have higher blood pressure and altered glucose metabolism compared with their term born peers. Evidence of an atherogenic lipid profile is inconsistent. Whether these risks apply to those born less preterm is not known.

WHAT THIS STUDY ADDS: In adolescence, girls have higher blood pressure and boys a more atherogenic lipid profile than their term born peers. Overall, our results are consistent with a dose-response relationship between shorter length of gestation and increasing levels of cardiovascular risk factors.

abstract

BACKGROUND: Adolescents and adults born as small preterm infants show more pronounced risk factors of cardiovascular disease. Whether similar risks apply across all degrees of preterm birth is poorly known.

METHODS: We studied the association between preterm birth and cardiovascular risk factors in 6642 16-year-old adolescents of the population-based Northern Finland Birth Cohort 1986. Of these, 79 (1.2%) were born at <34 gestational weeks (early preterm), 238 (3.6%) at 34 to 36 weeks (late preterm), and 6325 at term (controls).

RESULTS: Girls born early preterm had 6.7 mm Hg (95% confidence interval: 3.1–10.2) higher systolic blood pressure (BP) and 3.5 mm Hg (1.1–5.8) higher diastolic BP, but no difference in serum lipid levels compared with control girls. Boys showed no differences in BP, but boys born early preterm had 6.7% (0.2%–13.7%) higher total cholesterol, 11.7% (2.1%–22.3%) higher low-density lipoprotein cholesterol, and 12.3% (3.1%–22.4%) higher apolipoprotein B concentrations. The differences were similar (BP) or stronger (lipids) when adjusted for maternal smoking, birth weight SD score, parental education, pubertal stage, BMI, and lifestyle. There were similar associations with length of gestation as a continuous variable. Accordingly, mean differences between late preterm and controls were in the same direction but weaker, although most were not statistically significant.

CONCLUSIONS: Preterm birth was associated with elevated BP in adolescent girls and an atherogenic lipid profile in boys. Because these associations were strongest among those born early preterm, our findings are consistent with a dose-response relationship between shorter length of gestation and cardiovascular risk factors. Pediatrics 2014;134: e1072–e1081

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KEY WORDS: premature birth, blood pressure, hypertension, dyslipidemias, glucose metabolism.

ABBREVIATIONS: ApoA1—apolipoprotein A1; ApoB—apolipoprotein B; BP—blood pressure; CI—confidence interval; HDL—high-density lipoprotein cholesterol; HOMA-IR—homeostasis model assessment values for insulin resistance; LDL—low-density lipoprotein cholesterol; MET—metabolic equivalent hour; SGA—small for gestational age; TC—total cholesterol; TG—triglyceride; VLBW—very low birth weight.

(Continued on last page)
Approximately 11% of all live-born infants worldwide are born preterm—before 37 weeks of gestation. At least those born smallest and most immature show as children and adults more pronounced cardiovascular risk factors, for example increased blood pressure (BP), reduced glucose tolerance, and increased insulin resistance, compared with those born at term. As to plasma lipids, the results are mixed. Some associations between preterm birth and cardiovascular risk factors have been suggested to differ in men and women. For example, the difference in BP between those born with very low birth weight (VLBW; <1500 g) and those born at term may be greater in women than in men.

Few studies have been carried out to assess the long-term health of late/moderately preterm infants, although they constitute the great majority of preterm infants. For example, in the United States, up to 74% of preterm infants are born late preterm (34–36 weeks of gestation) and in Europe over 80% are moderately preterm (32–36 weeks). Results of the few existing studies suggest a dose-response relationship between the degree of prematurity and higher BP in young adults. Alarmingly, studies in older adults born preterm suggest higher rates of disease, including type 2 diabetes and stroke. These risks are likely to be largely attributable to late/moderately preterm births. The underlying mechanisms and preceding risk factors are, however, poorly known.

We hypothesized that adolescents born preterm (within the whole range of prematurity) have higher BP, impaired glucose regulation, and a more atherogenic lipid profile than full-term controls. We also hypothesized that the association between preterm birth and these outcomes may be different in boys and girls. In contrast to most previous studies concerning the later outcomes of preterm birth, we tested these hypotheses in a birth cohort study based on an unselected population born within a defined geographical area.

METHODS

The Original Birth Cohort

The Northern Finland Birth Cohort 1986 is a longitudinal cohort of all births in the 2 northernmost provinces of Finland with expected delivery date between July 1, 1985, and June 30, 1986. The data are prospectively collected from the first antenatal clinic visit onwards.

Birth weight SD score was calculated on the basis of Finnish standards; small for gestational age (SGA) was defined as more than 2 SD below the mean.

Study Participants

The latest clinical examination of the offspring was conducted in 2001–2002, in which 74% (n = 6798) of 16-year-old cohort members residing in Finland participated (Fig 1). In our analysis, we included those 6642 subjects with data on length of gestation and at least 1 of the following variables: BMI, waist circumference, BP, serum lipid levels, and plasma glucose and serum insulin concentrations. In total, 79 (1.2%) of the study subjects were born before 34 weeks of gestation (early preterm), 238 (3.6%) at 34 to 36 weeks inclusive (late preterm), and 6325 (95.2%; controls) were born at 37 weeks or later.

We compared those included in analyses with the members of the original cohort not included. In those not included, the mean length of gestation was 0.27 weeks shorter (P ≤ .001), the proportion of individuals born preterm larger (P < .001; Fig 1), birth weight 77 g lower (P < .001), birth weight SD score 0.1 SD lower (P < .001), and the proportion of those born SGA higher (P = .006).

Clinical Examination at 16 Years of Age

The clinical examination has been described. Briefly, systolic and diastolic BPs (mm Hg) were measured from the...
right arm after 15 minutes of rest with the subject sitting, using an automated oscillometric device (Omron 705CP, Omron Corporation, Shiojiki, Horikawa, Kyoto, Japan) or, if this failed, a mercury sphygmomanometer. The mean of 2 measurements taken 2 minutes apart was calculated. Prehypertension was classified as BP ≥ 120/80 mm Hg and hypertension as ≥ 140/90 mm Hg.33

Blood samples were collected between 8:00 AM and 11:00 AM after an overnight fast. Samples of serum for insulin measurement were stored at −20°C and analyzed by radioimmunoassay with commercial reagents (Pharmacia Diagnostics, Uppsala, Sweden) within 7 days. Plasma glucose (enzymatic reference method with hexokinase), and serum total cholesterol (TC), high-density and low-density lipoprotein cholesterol (HDL-C and LDL-C), triglycerides (TGs; enzymatic, colorimetric method), and apolipoprotein A1 and B (ApoA1 and ApoB; immunoturbidimetric method) concentrations were analyzed within 24 hours of sampling at Oulu University Hospital laboratory by using a Cobas Integra 700 automatic analyzer (Roche Diagnostics, Basel, Switzerland).29,34 Homeostasis model assessment values for insulin resistance (HOMA-IR) were calculated from paired assessment values for insulin resistance (SIPOLA-LEPPÄNEN et al e1074) were calculated from paired measurements of insulin resistance and transformed to total metabolic equivalent hours (METs) per week, assuming 3 METs per week for commuting, and 5 METs per week for moderate-to-vigorous physical activity. Pubertal stage was self-assessed with the help of drawings representing different stages of Tanner’s classification.37 All subjects and their guardians provided written informed consent, and the Ethics Committee of the University of Oulu approved the study.

Statistical Methods

Our main predictive variable was length of gestation, categorized into 3 groups: (1) 33 weeks 6 days or less corresponding to “early preterm,” (2) 34 weeks 0 days to 36 weeks 6 days, corresponding to “late preterm” as defined in an American Academy of Pediatrics Clinical Report,36 and (3) a control group, subjects born at 37 weeks 0 days or later. We refer to this group as “term,” even though the group includes 250 subjects technically born postterm (at 42 weeks 1 day or later). In addition, we report the analyses with length of gestation as a continuous variable.

All main outcome variables except BPs were logarithmically transformed to normalize their distributions. Descriptive data were compared by using Student’s t test or the χ² test. Group means of outcome variables were compared by linear regression. The full regression model included age, BMI, height, birth weight SD score, maternal smoking during pregnancy, educational attainment of the more educated parent (dummy coded, with a separate category of those with missing data), smoking of the subject, physical activity, and Tanner pubertal stage. We performed analyses separately in boys and girls, because of statistically significant interactions between early preterm birth and gender as regards LDL-C (P = .02), ApoB (P = .03), and systolic BP levels (P = .009), and between late preterm birth and gender as regards HOMA-IR (P = .036). All P values are 2-tailed.

RESULTS

Clinical Characteristics

The pre- and neonatal characteristics of the groups are presented in Table 1 and characteristics at a mean age of 16.0 years (range, 14.6–17.0) are presented in Supplemental Table 4. Subjects born preterm were 0.1 years older than controls. Parents of early preterm subjects were less educated. Weight, height, BMI, waist circumference, and waist-to-hip ratio were similar in the individual genders in the preterm groups and their controls (Supplemental Table 4), even when adjusted for birth weight SD score, age, parental education, smoking, and physical activity. Girls born preterm were at an earlier pubertal stage than controls. Among boys, timing of puberty was similar between the groups.

Blood Pressure

Girls born early preterm had higher systolic and diastolic BPs than control girls (Table 2; Fig 2). The difference was similar after full adjustment. They were also more likely to have prehypertension or hypertension (Supplemental Table 5). There was no difference in mean BP (Table 3, Fig 2). We also used length of gestation as a continuous variable; among girls, 1 week of gestation longer corresponded to 0.5 mm Hg (95% CI: 0.3–0.8) lower systolic BP, and 0.2 mm Hg (95% CI: 0.0–0.3) lower diastolic BP (Supplemental Table 5). There was no quadratic relationship between length of gestation and BP in either gender (all P > .1).

Lipid Profile

Among girls, lipid profiles were similar in all study groups (Table 2; Fig 2). As for boys, those born early preterm had higher mean TC, LDL-C, and ApoB concentrations than their controls. Boys
born preterm also had higher TG levels, but the difference reached statistical significance only in late preterm boys. Concentrations of HDL-C and ApoA1 were similar between groups (Fig 2). The value of P for interaction between early preterm birth and gender as regards LDL-C was 0.02, and for ApoB it was 0.03. Among boys, 1 week of gestation longer corresponded to 0.5% (95% CI: 0.1%–0.9%) lower TC, 1.0% (0.4%–1.6%) lower LDL-C, and 1.0% (0.4%–1.5%) lower ApoB, adjusted by variables in the full model (Supplemental Table 5). There were no quadratic relationships between the length of gestation and lipid concentrations (all P > .1).

**Glucose Metabolism**

Boys born late preterm had higher insulin levels and HOMA-IR values than boys born at term. There were no other differences in glucose or insulin concentrations in either gender (Table 3, Fig 2).

**Perinatal Factors Accompanying Preterm Birth**

We reran comparisons of the preterm groups with controls after excluding subjects (1) born postterm and (2) with uncertain length of gestation (n = 221, as described in Methods). The results remained similar.

We further reran the comparisons after excluding those born SGA. The differences in the main outcomes strengthened; adjusted for variables in the full model, systolic BP was 8.2 mm Hg (95% CI: 4.3 to 12.3) and diastolic BP 4.1 mm Hg (1.5 to 6.7) higher in girls born early preterm than in their controls. Among boys born early preterm, levels of TC were 10.4% (95% CI: 2.7% to 18.6%) higher, those of LDL-C 19.3% (7.7% to 32.2%), and those of ApoB 18.0% (7.2% to 29.9%) higher than in their controls. There was no difference between subjects born preterm SGA and the remaining subjects born preterm (P > .09). In addition, we reran the analysis with adjustment only for birth weight SD score to assess the effect of birth weight separately from the effect of other covariates; in girls born early preterm, BPs were 7.1 mm Hg (3.6 to 10.7)/3.6 mm Hg (1.2 to 6.0) higher than in controls. In boys born early preterm, TC was 5.4% (>1.0% to 12.2%) higher, LDL-C was 10.3% (0.9% to 20.6%) higher, ApoB was 8.7% (−0.2% to 18.4%) higher, and TG 16.7% (0.1% to 35.9%) higher compared with controls. In boys born late preterm, TG was 12.8% (4.2% to 22.0%) higher, fasting insulin 13.2% (3.1% to 24.3%) higher, and HOMA-IR 12.6% (2.6% to 23.6%) higher than in controls.

Furthermore, we reran the analyses after (1) excluding subjects exposed to maternal gestational diabetes and (2) excluding those exposed to maternal hypertension or preeclampsia, and the results remained similar. Moreover, after further adjustment of the full regression model for maternal gestational diabetes, preeclampsia, and gestational or chronic hypertension, the results again remained similar.

**Current Disability and Chronic Disease**

Of the subjects, 32 (2 early preterm and 30 controls) had cerebral palsy or mental or physical disability, and 19 had type 1 diabetes (1 late preterm and 18 controls). We reran the analysis after exclusion of all these subjects. The differences in BP among girls were attenuated being 6.0 mm Hg (95% CI: 2.5 to 9.4)/2.7 mm Hg (95% CI: 0.4 to 5.0) higher in the early preterm group and 1.4 mm Hg (95% CI: −0.9 to 3.6)/0.5 mm Hg (95% CI: −1.0 to 2.0) higher in the late preterm group compared with controls. Otherwise the differences remained similar.

**DISCUSSION**

There are 2 main findings in this study. First, our results suggest that in adolescence the association between preterm birth and cardiovascular risk factors seems to be different in girls and boys. Among girls, preterm birth conferred a risk of higher BP. Among boys, it was associated with an atherogenic lipid profile and reduced insulin sensitivity. Second, our findings are consistent with a dose-response...
relationship between shorter length of gestation and cardiovascular risk factors; the highest mean levels of these factors were seen among those born early preterm, whereas those born late preterm had intermediate levels that were not always significantly different from those in the group born at term. Accordingly, the associations were also present when length of gestation was used as a continuous variable. These findings were not explained by background factors such as maternal pregnancy disorders, fetal growth, family socioeconomic status, or maternal smoking during pregnancy, or by current age, pubertal stage, body size, smoking, or physical activity.

**Blood Pressure**

Our results on BP are partly consistent with those in previous studies showing that adolescents and adults born preterm with VLBW have higher systolic and/or diastolic BP than those born at term.6,7,8,10,12,13,39,40 Some investigators have reported that this difference is greater among women than among men,6,10 which was confirmed in a recent meta-analysis.17 Although we found no difference among boys, it may become apparent later in life. The association between late preterm birth and

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**TABLE 2** Means (SD) in Controls and Mean Differences in BP and Biochemical Characteristics in Girls

<table>
<thead>
<tr>
<th></th>
<th>Controls, Mean (SD)</th>
<th>Modela</th>
<th>Early Preterm</th>
<th>Late Preterm</th>
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<td>Early Preterm</td>
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<td>Mean Differenceb</td>
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<td>Systolic BP, mm Hg</td>
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<td>6.7***</td>
<td>3.2 to 10.2</td>
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<td>2</td>
<td>6.8***</td>
<td>3.4 to 10.2</td>
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<td>6.4***</td>
<td>3.0 to 9.8</td>
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<td>4</td>
<td>6.4***</td>
<td>3.0 to 9.8</td>
<td>1.5</td>
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<tr>
<td>Diastolic BP, mm Hg</td>
<td>66.8 (7.2)</td>
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<td>3.5**</td>
<td>1.1 to 5.9</td>
<td>0.7</td>
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<td>3.5**</td>
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<td>3.1**</td>
<td>0.9 to 5.4</td>
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<td>TC, mmol/L</td>
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<td>3.0 to 8.0</td>
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<td>1.9</td>
<td>3.3 to 7.5</td>
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<td>1.8</td>
<td>3.6 to 7.6</td>
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<td>LDL-C, mmol/L</td>
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<td>−8.3 to 6.9</td>
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<td>−10.2</td>
<td>−20.4 to 1.4</td>
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<td></td>
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<td>−4.3</td>
<td>−15.6 to 8.5</td>
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<td>ApoB, mmol/L</td>
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<td>1.4</td>
<td>−5.5 to 8.8</td>
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<td>−5.3 to 9.5</td>
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<td>Insulin, µU/L</td>
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<td>0.2</td>
<td>−11.2 to 13.1</td>
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<td>−14.0 to 9.3</td>
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<td>HOMA-IR</td>
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<td>−13.5 to 15.2</td>
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<td></td>
<td></td>
<td>4</td>
<td>−3.8</td>
<td>−16.0 to 10.1</td>
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HOMA-IR, homeostasis model assessment for insulin resistance.

a Models: 0, Unadjusted; 1, Age; 2, Model 1 + BMI and height; 3, Model 2 + SD for birth weight, maternal smoking during pregnancy, and educational level of more educated parent; 4, Model 3 + smoking of the subject, physical activity, and Tanner Pubertal Stage.

b Mean difference as a percentage, except for systolic and diastolic BPs, where the difference is in mm Hg.

P values for differences in preterm groups compared with full-term controls: * P < .05; ** P < .01; *** P < .001.
later BP has been less well studied. In a cohort born in 1966 in the same geographical area as the present cohort, women born preterm had higher systolic BP than those born at term. This association was not seen among men. However, in a Swedish cohort study that included only young men, those born between 33 and 36 weeks of gestation had higher systolic BP than those born at term. Both studies revealed a dose-response relationship, with increasing BP with decreasing gestational age at birth.

Elevated BP is associated strongly with cardiovascular mortality and is currently the globally leading risk factor of death and disease. Based on population studies, the difference of 6.8 mm Hg in systolic BP we found between girls born early preterm and girls born at term translates to 16% higher mortality from coronary heart disease and 26% higher mortality from stroke.

**Lipid Profile**

We found that adolescent boys born early preterm have higher levels of serum TC, LDL-C, and ApoB than boys born at term. ApoB is the primary apolipoprotein component of LDL-C and an even more accurate indicator of cardiovascular risk. Previous findings concerning later life serum lipid levels of those born preterm are inconsistent. Several investigators have found no relationship between preterm birth/lower gestational age and standard serum lipid measurements in adults. However, in a recent meta-analysis, it was concluded that adults born preterm have on average 0.15 mmol/L higher LDL-C concentrations than controls, although this result was driven by previously unpublished data from one of the cohorts. This compares to differences we found that correspond to 0.22 mmol/L in the crude and 0.35 mmol/L...
in the adjusted model. Furthermore, studies involving measurement of lipids after a meal or detailed lipid profiling by metabolomics have indicated a more atherogenic lipid profile in adults born preterm.

We believe that these differences among boys are a consequence of preterm birth rather than slow fetal growth, because the difference was stronger when boys born SGA were excluded. A male-specific association between low birth weight and serum LDL-C levels in Filipino adolescents and TC in young Swedish adults suggests that slow fetal growth can have similar gender-specific associations as preterm birth as regards lipid profile later in life. The magnitude of these associations, 0.19 mmol/L for TC and 0.26 mmol/L for LDL-C, is similar to corresponding differences we found between boys born early preterm versus controls (0.23 mmol/L for TC and 0.22 mmol/L for LDL-C). In addition, among the general population, there is a weak but consistent association between low birth weight and serum TC among men (0.04 mmol/L per kg) that may not exist among women. The mechanisms behind these gender differences are not known. In this cohort, girls born at term had slightly higher TC, LDL-C, and ApoB concentrations than boys born at term; in other words, boys born early preterm approached the concentrations

| TABLE 3 Means (SD) in Controls and Mean Differences in BP and Biochemical Characteristics in Boys |
|------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Systolic BP, mm Hg | 121.0 (12.1) | 0 | -7.3 to 5.8 | 1.0 | -1.4 to 3.5 |
| Diastolic BP, mm Hg | 68.6 (7.9) | 0 | -3.1 to 3.8 | -0.2 | -1.7 to 1.4 |
| TC, mmol/L | 4.0 (1.2) | 0 | -0.7 to 12.4 | 2.0 | -1.2 to 5.5 |
| LDL-C, mmol/L | 2.1 (1.3) | 0 | -1.2 to 21.0 | 4.3 | -0.4 to 9.2 |
| ApoB, mmol/L | 0.63 (1.3) | 0 | -2.3 to 21.0 | 4.9* | 0.5 to 9.5 |
| TGs, mmol/L | 0.73 (1.5) | 0 | -1.3 to 37.5 | 13.8** | 5.2 to 23.0 |
| Insulin, mU/L | 9.6 (1.6) | 0 | -12.5 to 21.1 | 13.7** | 6.6 to 25.5 |
| HOMA-IR | 1.42 (0.93) | 0 | -11.5 to 34.5 | 13.0* | 3.0 to 24.0 |
| n | 3174 | 3116 | 3081 | 3094 | 2781 | 3100 | 3081 | 3081 | 2711 | 3159 | 3153 | 3081 | 3081 | 2767 | 3100 | 3095 | 3082 | 3082 | 3082 | 3081 | 3081 | 2711 | 3116 | 3111 | 3088 | 3088 | 2730 | 2918 | 2903 | 2903 | 2561 |

* Models: 0, Unadjusted; 1, Age; 2, Model 1 + BMI and height; 3, Model 2 + SD for birth weight, maternal smoking during pregnancy, and educational level of more educated parent; 4, Model 3 + smoking of the subject, physical activity, and Tanner Pubertal Stage.

b Mean difference as a percentage, except for systolic and diastolic BPs, where the difference is in mm Hg.

P values for differences in preterm groups compared with full-term controls: * P < .05; ** P < .01; *** P < .001.
of girls. These concentrations increase with puberty. Earlier puberty, which has been observed in adolescents born preterm at VLBW,\textsuperscript{48} could in part explain the gender differences we found. However, in the current study, the self-reported Tanner stages did not suggest an earlier puberty in either gender.

**Glucose Metabolism**

Boys born late preterm had higher fasting insulin levels and HOMA-IR values than controls; otherwise we did not find any difference between adolescents born preterm and controls in outcomes used to assess glucose metabolism. Fasting insulin and HOMA-IR may, however, not be sufficiently sensitive indicators of insulin resistance. Studies in prepubertal children\textsuperscript{18} and young adults\textsuperscript{7,8,50} born preterm have shown insulin resistance that was clearly indicated by intravenous\textsuperscript{18,50} and oral glucose tolerance tests, and also higher fasting insulin levels.\textsuperscript{7} Our findings, together with the results of these studies, are consistent with the hypothesis that preterm birth is associated with impaired glucose regulation later in life.

**Possible Mechanisms**

Although those born preterm had been more often exposed to maternal pregnancy disorders, maternal smoking, or were more often born SGA, these conditions did not in general explain their more pronounced cardiovascular risk factors compared with those born at term. The differences in plasma lipids in boys, however, attenuated slightly when adjusted for birth weight SD score. This suggests that the higher rates of slow fetal growth among those born preterm could in part underlie the higher plasma lipid concentrations in boys born preterm. The differences could also be explained by differences in adolescent lifestyle.\textsuperscript{51} However, physical activity, smoking, or socioeconomic status did not explain the difference in cardiovascular risk factors in our study.

**Study Limitations**

Adolescents born preterm were less likely to participate in the study, and it is possible that subjects with impairments associated with preterm birth are underrepresented. This would, however, only be expected to result in more conservative estimates. The number of subjects born early preterm was too small for detailed subgroup analysis of maternal pregnancy disorders. In addition, missing values exist for some covariates. This may have resulted in less precise estimates. Pubertal stage was self-reported, which may further introduce inaccuracy. However, most, although not all,\textsuperscript{52,53} previous studies support the validity and reliability of self-assessment throughout pubertal development.\textsuperscript{54–57}

**CONCLUSIONS**

We found that adolescents born early preterm have more pronounced risk factors of cardiovascular disease than adolescents born at term: girls have higher BP; boys have a more atherogenic lipid profile. Our findings are also consistent with a dose-response relationship between the degree of prematurity and these risk factors, although the specific magnitude of the risk factors in those born late preterm remains to be confirmed. The risk factors we found are modifiable. Therefore, our results prompt vigilance in the promotion of a healthy lifestyle and screening of hypertension and dyslipidemias in children and adults born preterm.

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).
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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.
FUNDING: Supported by the Academy of Finland (SAIVE program for 2009–2012 and grants 127437, 128506, 130326, 134791 and 263924 to EK); the European Commission (Framework 5 award QLG1-CT-2000-001643); the Doctoral Programs of Public Health, University of Tampere (to MSL); the Yrjö Jahnsson Foundation (6201 to MSL); and the Sigrid Jusélius Foundation (to EK and MSL), the Finnish Foundation for Pediatric Research (to EK), Emil Aaltonen Foundation (to EK), Signe and Ane Gyllenberg Foundation (to EK), and Novo Nordisk Foundation (to EK).
POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
Cardiovascular Risk Factors in Adolescents Born Preterm
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Pediatrics 2014;134;e1072
DOI: 10.1542/peds.2013-4186 originally published online September 1, 2014;

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