High Blood Pressure in 2.5-Year-Old Children Born Extremely Preterm

WHAT’S KNOWN ON THIS SUBJECT: Subjects born preterm have higher blood pressure (BP) in childhood and adolescence. Little is known about at what age the deviation from normal BP starts, and data are especially scarce for the new generation of survivors after extremely preterm birth.

WHAT THIS STUDY ADDS: In a population-based study, we found that BP was higher in 2.5-year-old children born extremely preterm compared with controls. This finding might have implications for follow-up programs after preterm birth, with the goal of improving later cardiovascular health.

OBJECTIVE: Adolescents and young adults born preterm have elevated blood pressure (BP). The objective of this study was to investigate if BP is elevated at 2.5 years of age after an extremely preterm birth (EXPT).

METHODS: In a regional subset of the national population-based cohort Extremely Preterm Infants in Sweden Study, BP at 2.5 years of age was studied in 68 survivors of EXPT (gestational age: 23.6–26.9 weeks; mean ± SD birth weight: 810 ± 164 g), and 65 matched controls born at term.

RESULTS: At follow-up at 2.5 years of corrected age, EXPT children had significantly higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) z scores than controls born at term, according to pediatric BP nomograms by age, gender, and height. The proportion of SBP ≥90th percentile was 44% (30 of 68) in EXPT children and 23% (15 of 65) in controls (P = .01). In logistic regression analyses stratified according to gender, EXPT was associated with an odds ratio for a SBP ≥90th percentile of 3.32 (95% confidence interval: 1.25–8.81) among boys. The corresponding odds ratio among EXPT girls was 2.18 (95% confidence interval: 0.62–7.61). In EXPT children, SBP and DBP z scores were inversely correlated to catch-up growth from 36 weeks’ postmenstrual age to follow-up at 2.5 years of age.

CONCLUSIONS: Children born extremely preterm have elevated office SBP and DBP at a corrected age of 2.5 years. This finding might have implications for their cardiovascular health later in life. Pediatrics 2012;129:e1199–e1204

AUTHORS: Anna-Karin Edstedt Bonamy, MD, PhD, Karin Källén, PhD, and Mikael Norman, MD, PhD

©Department of Women’s and Children’s Health, 2Unit for Clinical Epidemiology, Department of Medicine Solna, and ©Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden, and ©Center of Reproduction Epidemiology, Institute of Clinical Sciences, University of Lund, Lund, Sweden

KEY WORDS
blood pressure, extremely preterm birth, pediatrics, risk factors

ABBREVIATIONS
BP—blood pressure
BPD—bronchopulmonary dysplasia
CI—confidence interval
DBP—diastolic blood pressure
EXPRESS—Extremely Preterm Infants in Sweden Study
EXPT—extremely preterm birth
IVH—intraventricular hemorrhage
OR—odds ratio
PDA—patent ductus arteriosus
ROP—retinopathy of prematurity
SBP—systolic blood pressure

Dr Bonamy analyzed and interpreted the data and drafted the manuscript; Dr Källén designed, collected, and analyzed the data and drafted the manuscript; and Dr Norman was responsible for regional data acquisition in the Extremely Preterm Infants in Sweden Study, design and data collection in the present follow-up study, interpretation of the data, and drafting of the manuscript.

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This study was supported by grants from the Swedish Heart Lung Foundation, the Karolinska Institute, Stockholm County Council, The Swedish Order of Freemasons, and the Swedish Society for Medical Research.
Almost 13 million infants worldwide are born preterm every year. The vast majority of them do not suffer from perinatal injuries and will enter adulthood as apparently healthy individuals. However, follow-up studies showing increased blood pressure (BP) among adolescents and young adults born preterm raise concern that preterm birth may be associated with yet unknown developmental changes that eventually may affect later cardiovascular health.1–10

Existing data suggest that children born preterm have higher BP by school age and that those differences in BP between preterm and term subjects become more pronounced with age.1,11–15 However, little is known about what age BP starts to deviate from normal BP in children born preterm. Moreover, most previous studies have not investigated BP in the most immature subjects at birth (ie, those born >3 months before term).

This study addresses 2 important clinical questions: Is BP already elevated in preschool-aged children born extremely preterm, and are there associations between neonatal morbidity and later BP? To investigate these issues, we performed a prospective population-based cohort study of BP in 2.5-year-old children born before 27 weeks of gestation in Stockholm, Sweden.

METHODS

Study Population

All children born extremely preterm (<27 weeks of gestation) in Sweden from April 1, 2004, to March 31, 2007, were included in a prospective national cohort study (EXPRESS [Extremely Preterm Infants in Sweden Study]). Detailed characteristics of the cohort, as well as data on neonatal morbidity and mortality, have been described previously.16,17 At 2.5 years of age (corrected for prematurity), parents of the participants in the EXPRESS cohort in Stockholm County (N = 105) were asked to let their child participate in a follow-up study. Ten term controls per cohort member were matched according to birth date, hospital, residency, and mothers’ country of birth from the Swedish Medical Birth Register. Invitations were sent until 1 control child for each cohort member accepted to participate in the study or until all controls had declined and the list of eligible control children was exhausted.

Eighteen children of extremely preterm births (EXPT) declined participation or had emigrated. Nineteen EXPT children and 18 controls were not able to cooperate satisfactorily to obtain BP and heart rate measurements. Finally, 68 of 105 EXPT children and 65 controls completed the study. Among EXPT children, nonparticipants did not differ significantly regarding gender (41% female), mean ± SD birth weight (799 ± 178 g), or gestational age (25.1 ± 1.3 weeks) from participants in the study.

BP and Heart Rate Measurements

After at least 15 minutes of calm acclimatization to the investigation room, the child was seated upright in the parent’s lap. A validated automated oscillometric device, Omron HEM 907 IntelliSense (Omron Healthcare, Kyoto, Japan), and an appropriately sized arm cuff were used to measure systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate 1 to 3 times in the right arm in each child, with at least 2 minutes between consecutive measurements. Specially trained pediatric nurses (n = 3) performed the measurements according to a predefined standard operating procedure. The number of successful BP measurements did not differ between EXPT and control children, and there was no difference in mean SBP or DBP among children in whom BP was measured 1, 2, or 3 times.

SBP and DBP z scores were computed according to age-, gender-, and height-adjusted BP nomograms for children.18

Anthropometric Data

Height and weight were measured according to standard clinical procedure. In EXPT children, z scores for birth weight and weight at a postmenstrual age of 36 weeks were calculated by using Swedish growth standards based on ultrasonically estimated fetal weights.19 The World Health Organization growth package for Stata (Stata Corp, College Station, TX) was used to calculate age- and gender-adjusted z scores for weight, height, and BMI (http://www.who.int/childgrowth/software/en/) at 2.5 years of age. For EXPT, neonatal growth was defined as change in z score from birth to 36 weeks’ postmenstrual age. Childhood growth was defined as change in z score from 36 weeks of postmenstrual age to 2.5 years of age.

Maternal and Perinatal Data

Maternal and perinatal data were obtained from the EXPRESS study cohort register.16,17 The regional ethics committee approved the study protocol, and the parents gave written informed consent for participation in the study.

Statistical Methods

Results are presented as mean ± SD, median (interquartile range), or proportions. The Shapiro-Wilk test was used to estimate departures from normality. Because the distributions of SBP and DBP z scores were significantly different from the normal distribution, all group differences in BPs were tested by using the Wilcoxon rank-sum test. Student’s t test was used to test for group differences in normally distributed data. Pearson’s χ² test was used to test for group differences in proportions. Spearman’s rank correlation coefficients were calculated.
to test associations between BP and selected covariates. Logistic regression analysis was used to calculate odds ratios (ORs) for hypertensive BP levels in EXPT children compared with controls.

At a significance level of 0.05, the sample size permitted 80% power to detect an OR of 2.0 for high SBP in EXPT children. In stratified analyses, the corresponding detectable ORs for high SBP were 2.5 and 3.0 for boys and girls, respectively.

**RESULTS**

In the EXPT group, 6% of the mothers were smoking at registration for antenatal care, 7% had preeclampsia or hypertension during pregnancy, and 76% were treated with antenatal steroids before delivery to enhance fetal lung maturation. In the neonatal period, 66% of EXPT children were treated for a hemodynamically significant patent ductus arteriosus (PDA); 44% suffered from bronchopulmonary dysplasia (BPD), defined as a requirement of supplemental oxygen therapy at 36 weeks of postmenstrual age; 43% experienced retinopathy of prematurity (ROP) stage $\geq$3; and 16% had intraventricular hemorrhage (IVH) grade $\geq$3 and/or cystic periventricular leukomalacia. Maternal and infant data and neonatal morbidity are presented in Table 1.

At follow-up at 2.6 years of age (corrected age), EXPT children were significantly shorter and lighter and had a lower BMI than controls (Table 2).

**Risk for Hypertensive BP After EXPT**

EXPT children had significantly higher age-, gender-, and height-adjusted $z$ scores for both SBP and DBP than children born at term (Table 3). In logistic regression analyses, the OR for an age-, gender-, and height-adjusted SBP $\geq$90th percentile was 2.63 (95% confidence interval [CI]: 1.24–5.57; $P = .011$) in EXPT children compared with controls. Heart rate did not differ between the 2 groups and was not related to BP. In unadjusted analyses, median SBP did not differ significantly between the 2 groups, but median DBP was significantly higher in EXPT children than in controls.

**TABLE 1** Maternal and Infant Characteristics in 2.5-Year-Old Children Born Extremely Preterm

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Extremely Preterm Infants ($n = 68$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal data, n (%)</td>
<td></td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Preeclampsia/eclamps</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Antenatal steroid treatment</td>
<td>52 (76)</td>
</tr>
<tr>
<td>Infant data</td>
<td></td>
</tr>
<tr>
<td>Gestational length, wk</td>
<td>25.4 ± 1.0</td>
</tr>
<tr>
<td>Range</td>
<td>23.6–26.9</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>810 ± 164</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>494–1167</td>
</tr>
<tr>
<td>Birth weight $z$ score, mean ± SD</td>
<td>−0.6 ± 1.1</td>
</tr>
<tr>
<td>Weight at 36 wk, $z$ score, mean ± SD</td>
<td>−2.2 ± 1.1</td>
</tr>
<tr>
<td>Neonatal morbidity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>58 (85)</td>
</tr>
<tr>
<td>BPD</td>
<td>30 (44)</td>
</tr>
<tr>
<td>PDA treatment</td>
<td>45 (68)</td>
</tr>
<tr>
<td>NEC</td>
<td>8 (12)</td>
</tr>
<tr>
<td>ROP stage $\geq$3</td>
<td>29 (43)</td>
</tr>
<tr>
<td>IVH grade $\geq$3 or cystic PVL</td>
<td>11 (16)</td>
</tr>
</tbody>
</table>

NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia.

**TABLE 2** Anthropometric Data on EXPT Children and Term Controls at Follow-up at 2.5 Years of Corrected Age

<table>
<thead>
<tr>
<th>Variable</th>
<th>EXPT Infants ($n = 68$)</th>
<th>Controls Born at Term ($n = 65$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, female, n (%)</td>
<td>28 (41)</td>
<td>28 (44)</td>
<td>NA</td>
</tr>
<tr>
<td>Follow-up data, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>2.6 ± 0.1</td>
<td>2.6 (0.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>12.6 ± 1.8</td>
<td>14.6 ± 1.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>88.7 ± 4.5</td>
<td>93.4 ± 3.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>15.6 ± 1.8</td>
<td>16.7 ± 1.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Weight $z$ score</td>
<td>−0.6 ± 1.2</td>
<td>0.6 ± 0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Height $z$ score</td>
<td>−0.9 ± 1.3</td>
<td>0.2 ± 1.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI $z$ score</td>
<td>−0.2 ± 1.3</td>
<td>0.7 ± 0.9</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

$P$ values according to Student’s t test shown where appropriate.

* Age corrected for prematurity.

**TABLE 3** SBP, DBP, and Heart Rate at 2.5 Years of Corrected Age in EXPT Children Compared With Controls Born at Term

<table>
<thead>
<tr>
<th>Variable</th>
<th>EXPT Infants ($n = 68$)</th>
<th>Controls Born at Term ($n = 65$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP $z$ score$^a$</td>
<td>1.07 (0.37–1.61)</td>
<td>0.67 (0.24–1.13)</td>
<td>.03</td>
</tr>
<tr>
<td>DBP $z$ score$^a$</td>
<td>1.83 (1.26–2.56)</td>
<td>1.3 (0.8–1.71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>99 (93–105)</td>
<td>99 (93–103)</td>
<td>.63</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>64 (59–73)</td>
<td>60 (57–66)</td>
<td>.005</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>107 (99–113)</td>
<td>108 (102–116)</td>
<td>.21</td>
</tr>
</tbody>
</table>

$P$ values according to Wilcoxon rank-sum test. Data are presented as median (interquartile range).

* According to pediatric BP nomograms by age, gender, and height.$^{14}$
associated with an OR for an age-, height, and gender-adjusted SBP ≥ 90th percentile of 3.32 (95% CI: 1.25–8.81 [P = .016]) among preterm boys compared with control boys born at term. The corresponding OR for girls born preterm was 2.18 (95% CI: 0.62–7.61 [P = .22]) compared with girls born at term. The OR for DBP ≥ 90th percentile was 2.69 (95% CI: 0.82–8.83 [P = .10]) among EXPT boys and 3.33 (95% CI: 1.10–10.12 [P = .03]) among EXPT girls compared with control boys and girls, respectively.

**Perinatal Exposures and Later BP After EXPT**

In bivariate analyses, there were no associations between maternal hypertensive disease or antenatal steroid treatment and later offspring BP or BP scores. Moreover, BP and BP z scores did not correlate with any major neonatal morbidity (mechanical ventilation, PDA, BPD, IVH grade ≥ 3, ROP stage ≥ 3, or necrotizing enterocolitis).

**Growth and Later BP After EXPT**

At birth, 5 (7.4%) of 68 EXPT infants were small for gestational age (defined as a birth weight 2 SDs below the mean in a Swedish reference for normal fetal growth). At 36 weeks’ postmenstrual age, the corresponding proportion of EXPT infants with a weight 2 SDs below the mean was 33 of 64 (52%). At follow-up at 2.5 years of age, the proportion of EXPT children having a z score for weight < 2 SDs below the mean was 7 of 66 (11%). SBP and DBP z scores were inversely associated with change in weight z score from 36 weeks’ postmenstrual age to follow-up at 2.5 years of corrected age (Spearman’s ρ: −0.28; P = .03 [for both SBP and DBP z scores]); that is, lower BP percentiles were found among children with a larger post-neonatal weight gain. BP at follow-up did not correlate with fetal growth (ie, weight z score at birth), neonatal growth (ie, change in weight z score from birth to 36 weeks’ postmenstrual age), or with BMI at 2.5 years of age.

**DISCUSSION**

We report 3 major findings. First, EXPT was associated with higher BP at 2.5 years of age. Secondly, at this age, the effect on SBP was confined to boys, whereas higher DBP was seen in both boys and girls. Finally, higher BP after EXPT was related to slower growth between the neonatal period and follow-up at 2.5 years of corrected age.

There is no previous population-based, controlled study on BP in 2.5-year-old children born extremely preterm. The finding of an increased BP at this early age supports the concept that high BP in adolescents and adults born preterm has a perinatal origin, linked primarily to low gestational age. The underlying mechanisms have not yet been clarified. However, long-lasting adaptations known to accompany preterm birth include cardiovascular growth arrest and remodeling, altered autonomic control with sympathtoadrennal overactivity, and smaller kidneys/fewer nephrons. These developmental changes after preterm birth may all contribute to a higher BP.

We did not control for socioeconomic status in the current study and had no information on parental cardiovascular risk factors, other than maternal hypertension and preeclampsia. We thus cannot exclude the possibility that the association between preterm birth and high BP reflects common genetic traits rather than a causal relationship. However, studies of siblings and twins have demonstrated that not only BP but also prevalence of hypertension are associated with preterm birth or low birth weight irrespective of commonly shared genetic and familial factors; this is also after controlling for other BP determinants such as socioeconomic factors, smoking, alcohol intake, and BMI.

In the current study, the risk of high SBP was confined to EXPT boys, although there was a similar nonsignificant trend among girls born extremely preterm. The lack of a significant association in EXPT girls could reflect limitations in power, and these limitations in power also introduce uncertainty regarding the presence of gender differences at this early age. Teen-aged girls and adult women born preterm have previously been found to have higher BP than their peers born at term. However, boys are known to be more vulnerable both as fetuses and as neonates. They suffer higher rates of neonatal morbidity, which may be another explanation for our finding of a gender difference. In support of male gender being a risk factor for later BP elevation in subjects born preterm, adolescent boys born very preterm
have been found to have significantly higher BPs than adolescent girls. Postnatal nutrition and early growth patterns have previously been reported to affect later BP in young people born very preterm. Providing breast milk to preterm infants reportedly results in lower BP at the age of 13 to 16 years compared with infant nutrition with preterm formula. We found an association between postneonatal normalization of weight and lower BP in 2.5-year-old children born extremely preterm. In contrast, Vohr et al reported that higher weight gain between birth and 36 months predicts higher BP in 16-year-old subjects born very preterm. Contradictory results regarding the influence of early postnatal growth (in the first 2 weeks of postnatal life) after preterm birth on later vascular endothelial function in young adulthood have also been reported.

Strengths of the current study include the prospective collection of neonatal data that have been controlled for accuracy, the high follow-up rate, and the matched controls from population-based registers. There are limitations as well. The sample size was small, and BP could not be measured in ~20% of the participating children in both groups. Accordingly, the differences in the proportion of high SBP and DBP may have been somewhat attenuated if BP had been measured in all infants. Finally, this is a cross-sectional study. BP tracking over time has not been studied in extremely preterm infants, and more research is needed to confirm that children facing BP elevation early in childhood are at risk later in life. However, a recent large study suggests that preterm birth is an important risk factor for antihypertensive medication use in young adult life. We propose that all very preterm children should have their BP measured regularly throughout childhood to detect and treat hypertension. Continued follow-up of the EXPRESS cohort, including echocardiographic assessment of the heart, is also warranted and underway.

CONCLUSIONS
Children born extremely preterm have elevated office SBP and DBP at a corrected age of 2.5 years. This finding might have implications for their cardiovascular health later in life.

ACKNOWLEDGMENTS
The authors acknowledge Jessica Schiött, Ellinor Ihre, and Lena Swartling for collecting the BP data. We also acknowledge the contributions of the members of the EXPRESS Group and especially Mats Blennow, Hugo Lagèrcrantz, Magnus Westgren, and Karel Marsál.

REFERENCES

18. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation,


High Blood Pressure in 2.5-Year-Old Children Born Extremely Preterm
Anna-Karin Edstedt Bonamy, Karin Källén and Mikael Norman
Pediatrics 2012;129:e1199; originally published online April 2, 2012;
DOI: 10.1542/peds.2011-3177

Updated Information & Services
including high resolution figures, can be found at: /content/129/5/e1199.full.html

References
This article cites 35 articles, 12 of which can be accessed free at:
/content/129/5/e1199.full.html#ref-list-1

Citations
This article has been cited by 3 HighWire-hosted articles:
/content/129/5/e1199.full.html#related-urls

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Fetus/Newborn Infant
/cgi/collection/fetus:newborn_infant_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml
High Blood Pressure in 2.5-Year-Old Children Born Extremely Preterm
Anna-Karin Edstedt Bonamy, Karin Källén and Mikael Norman
Pediatrics 2012;129;e1199; originally published online April 2, 2012;
DOI: 10.1542/peds.2011-3177

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/129/5/e1199.full.html