Risk of High Blood Pressure Among Young Men Increases With the Degree of Immaturity at Birth

Stefan Johansson, MD; Anastasia Iliadou, MSc, PhD; Niklas Bergvall, MSc; Torsten Tuvelmo, MD, PhD; Mikael Norman, MD, PhD; Sven Cnattingius, MD, PhD

Background—Survivors of preterm birth constitute a new generation of young adults, but little is known about their long-term health. We investigated the association between gestational age (GA) and risk of high blood pressure (HBP) in young Swedish men and whether GA modified the risk of HBP; ie, whether HBP was related to being born small for gestational age (SGA).

Methods and Results—This population-based cohort study included 329 495 Swedish men born in 1973 to 1981 who were conscripted for military service in 1993 to 2001. Multivariate linear- and logistic-regression analyses were performed. Main outcome measures were systolic and diastolic BPs at conscription. Linear-regression analyses showed that systolic BP increased with decreasing GA (regression coefficient $-0.31$ mm Hg/wk, $P<0.001$). Systolic and diastolic BPs both increased with decreasing birth weight for GA, but the association with systolic BP was most evident (regression coefficient $-0.67$ mm Hg per SD score in birth weight for GA, $P<0.001$). Compared with men born at term (GA, 37 to 41 weeks), the adjusted odd ratios (95% confidence intervals [CIs]) for high systolic BP ($\geq 140$ mm Hg) were as follows: moderately preterm (33 to 36 weeks), 1.25 (1.19 to 1.30); very preterm (29 to 32 weeks), 1.48 (1.30 to 1.68); and extremely preterm (24 to 28 weeks), 1.93 (1.34 to 2.76). Being SGA was associated only with an increased risk of high systolic BP among men born at 33 weeks or later. The risk estimates for high diastolic BP ($\geq 90$ mm Hg) increased with decreasing GA, but the risk reached significance only among men born moderately preterm.

Conclusions—Preterm birth, a common pregnancy complication, is a risk factor for HBP in young men. The risk of high systolic BP associated with birth weight for GA is modified by GA, suggesting that perinatal contributions to BP elevation later in life may be induced by different biological pathways. (Circulation. 2005;112:3430-3436.)

Key Words: infant ■ premature birth ■ blood pressure ■ epidemiology ■ adult

The development of neonatal intensive care during recent decades has led to improved survival rates among preterm infants. However, the life-long health effects after very or extremely preterm birth are virtually unknown, and late morbidity could be an increasing problem. Low birth weight is related to the unfavorable constellation of high blood pressure (HBP), glucose intolerance, and hyperlipidemia later in life, predisposing low-birth-weight infants to increased mortality in coronary heart disease and stroke. It has been suggested that the association between low birth weight and the risk of cardiovascular disease is mediated by fetal growth restriction in term birth rather than preterm birth. However, that study was based on a birth cohort from the early 20th century, when mortality rates among preterm infants were very high. Today, the most common cause of low birth weight in most countries is preterm birth.

Although a developmental origin for cardiovascular disease is a well-supported hypothesis, methodological weaknesses, including publication bias and inappropriate adjustment for current weight, may have led to overestimation of the association between birth weight and BP later in life. Moreover, the independent effects of low birth weight due to preterm birth or fetal growth restriction and the possible influence of childhood growth have not been fully elucidated. Preterm birth may attenuate the association between being born small for gestational age (SGA) and the risk of HBP, and GA may modify the association between body mass index (BMI) in adulthood and BP. In addition, accelerated weight gain in childhood may itself be a risk factor for BP elevation later in life.

In small clinical studies, adolescents and young adults born very preterm have structural changes in the vascular tree and higher systolic BPs (SBPs) than individuals born at term. Results from Swedish population-based cohort studies suggest that GA may be inversely associated with BP. However, the strength of the association has not been studied.
among survivors of very short gestations, and one of the previous studies did not include individuals with GAs <35 weeks. Moreover, those studies did not account for genetic and socioeconomic factors, which may influence both GA and the risks for cardiovascular diseases. Finally, intrauterine growth restriction is overrepresented among preterm births, emphasizing the importance of using reference curves based on fetal growth rather than recorded birth weights when assessing the relation between birth weight for GA and later BP.

We hypothesized that the risk of HBP in young men increases with the degree of immaturity at birth, independent of socioeconomic and familial factors. In addition, we wanted to explore interactions between GA, birth weight for GA, and BMI in young adulthood with regard to the risk for HBP.

Methods

Study Design and Population
This cohort study was based on 4 population-based Swedish registers: the Medical Birth Register, the Conscript Register, the Multigeneration Register, and the Population and Housing Census 1990. The national registration number, assigned to each Swedish resident at birth, was used for individual record linkage.

The Medical Birth Register contains data on >99% of all births in Sweden since 1973. Starting at the first prenatal visit, information is prospectively collected on standardized records and forwarded to the registry. Mortality data are added through linkage to the Cause of Death Register. The Medical Birth Register has recently been validated, and the quality of the variables included in the present investigation is considered high.

The Conscript Register contains information about young men assessed for military service. Conscription is mandatory and is enforced by law, but men with severe handicaps or congenital malformations generally receive an exemption. Conscription starts with an interview, including questions about health, followed by an IQ test. Men with acceptable cognitive function and a good physical history undergo a physical examination, including BP measurements.

The Multigeneration Register includes information about first-degree relatives for Swedish residents and was used to identify full brothers within the study population.

In the Population and Housing Census 1990, data on individuals and families were collected by postal enquiries, including information on socioeconomic characteristics such as education, profession, and housing. Participation was mandatory for all residents in Sweden with an age of 16 years and older. The response rate was 97.5%.

From 1973 to 1981, there were 458 371 male live births recorded in the Medical Birth Register. To increase the homogeneity of the study population, we excluded multiple births, congenital malformations, infants to non-Nordic mothers, and those who died before 18 months of age (n = 54 649). Thus, the study population included 404 306 men, of whom 379 963 (94%) were conscripted between 1991 and 2001. GA was classified as extremely preterm (24 to 28 completed gestational weeks), very preterm (29 to 32 weeks), moderately preterm (33 to 36 weeks), term (37 to 41 weeks), and postterm (42 to 43 weeks). The classification of extremely preterm birth was introduced to include a sufficient number of individuals for statistical analyses. Birth weight for GA was classified as small, appropriate, and large for gestational age (SGA, AGA, and LGA, respectively), according to the Swedish reference curve for normal fetal growth. The reference curve defines SGA and LGA as a birth weight >2 SDs below and above the mean reference weight for GA, respectively. Birth weights for GA >5 SDs above or below the mean were judged implausible and hence, considered missing (n = 46).

At the time of military conscription, weight was measured in kilograms and height in centimeters. BP was measured under standardized circumstances according to written instructions (Dr Wågermark, National Service Administration, Stockholm, Sweden; personal communication, 2005). After the subjects rested for 5 to 10 minutes in the supine position, nurses assigned for fitness testing measured the BP in the right arm. BP was determined from the appearance (Korotkoff sound phase 1) and disappearance (Korotkoff sound phase 5) of pulsations auscultated over the brachial artery. Before 1998, different cuffs were used for different diameters of the upper arm, but from 1998, the so-called Tri-cuff device was introduced. The Tri-cuff has 3 air chambers, and the width of the air chamber depends on the diameter of the arm. When BP was considered elevated (SBP ≥135 mm Hg or DBP ≥85 mm Hg), a second measurement was performed, and the lower measurement was recorded. High SBP was defined as ≥140 mm Hg, and high DBP was defined as ≥90 mm Hg. BMI at conscription was calculated as weight divided by the square of height (kg/m²). Low weight was defined as a BMI ≤18.4 kg/m², normal weight as a BMI 18.5 to 24.9 kg/m², overweight as a BMI 25.0 to 29.9 kg/m², and obesity as a BMI ≥30 kg/m², as suggested by the World Health Organization.

Information about parental socioeconomic and educational status and family structure was obtained from the Population and Housing Census 1990. We defined each household’s socioeconomic status as the highest socioeconomic status in the family, and the household’s educational status was defined analogously. Family structure was defined as living with both parents, living with a single parent, or with living foster parents. The study was approved by the research ethics committee at Karolinska Institute.

Statistical Analysis
We estimated odds ratios (OR) and 95% confidence intervals (CIs) according to the GENMOD procedure in version 8 of the SAS software package (SAS Institute, Inc.). Interactions were tested with the same procedure, and a probability value for the overall effect is given. The outcome variables were SBP and DBP. Covariates in the analyses were categorized and included GA, birth weight for GA, maternal age, parity, BMI and height at conscription, conscription year, family structure of the conscript, and parents’ educational and socioeconomic status. Conscription year was added to the model to control for possible cohort effects. Using linear-regression analyses, we also calculated regression coefficients with SEs per 1-week change in GA, per 1-unit change in SD score in birth weight for GA, and per 1-unit change in BMI. We corrected for clustering effects between brothers in the cohort according to the generalized estimating equation method. Because BMI could be an intermediate variable in a possible causal chain between birth characteristics and risk of HBP, we analyzed our data with and without BMI as a covariate in the multivariate-regression models.

We assessed whether an association between GA and HBP was confounded by familial factors by performing analyses between and
within families. Familial effects on the risk of HBP include shared genetic and environmental factors. The analyses were restricted to males with at least 1 full brother in the cohort (n=106 576). In analyses of familial effects on an association between exposure and outcome, the exposure was decomposed into between- and within-family components. The between-family component was measured by the family mean of the exposure measurement (X̄, where i = family member number), and the within-family component was measured by the individual deviation from the family mean (Xi – X̄, where i = family number and j = individual in family i). If familial factors are important, they tend to make family members more alike. Hence, the within-family component would be nonsignificant, whereas the between-family component would be significant. If the within-family component remains significant, this indicates that the association between exposure and outcome depends on other than familial factors. Our between-family component estimated the change in risk of HBP per 1–gestational week decrease in the family mean. Our within-family component estimated the change in the risk of HBP per 1–gestational week difference from their family mean.

Results
The characteristics of the conscripted men are presented in Table 1. Multivariate linear-regression analyses showed that SBP increased with decreasing GA, decreasing birth weight for GA, and increasing BMI (Table 2). DBP also increased with decreasing birth weight for GA and increasing BMI, but there was no linear association with GA.

A large proportion (20%) of the conscripted men were assessed as having a high SBP (≥140 mm Hg). The proportion of men with a high SBP varied from 32% among men born extremely preterm (≤28 weeks) to 19% among men born postterm (≥42 weeks; Table 3). The risk of high SBP consistently increased with decreasing GA. Compared with men born at term (37 to 41 weeks), men born extremely preterm faced an almost 2-fold increased risk of high SBP (Table 3). Being born SGA was associated with a 10% increased risk of high SBP compared with being born AGA.

A small proportion (0.6%) of the conscripted men were assessed as having a high DBP (≥90 mm Hg). The proportion of men with a high DBP varied from 1.2% among men born extremely preterm (≤28 weeks) to 0.6% among men born postterm (≥42 weeks; Table 3). The risk of high DBP increased with decreasing GA, but only men born moderately preterm (33 to 36 weeks) had a significantly increased risk of high DBP (Table 3). Being born SGA was not associated with risk for high DBP in the logistic-regression analyses.

The risk estimates for high SBP related to GA and birth weight for GA did not essentially change when BMI was included as a covariate in the regression models (Table 3). Compared with men with a normal BMI at conscription,
obese men faced a 2-fold increase in risk of high SBP and a 3-fold increase in risk of high DBP.

To further explore the association between GA and the risk of HBP, analyses were repeated with regard to an SBP of 145 mm Hg (prevalence, 4.5%) and a DBP of 85 mm Hg (prevalence, 2.3%). Compared with men born at term, the adjusted ORs (95% CIs) were as follows: moderately preterm (33 to 36 weeks), 1.44 (1.27–1.62); very preterm (29 to 32 weeks), 1.21 (1.16–1.26); and extremely preterm (24 to 28 weeks), 1.24 (1.19–1.30). Compared with men born at term, the adjusted ORs (95% CIs) were as follows: moderately preterm (33 to 36 weeks), 1.25 (1.11–1.40); very preterm (29 to 32 weeks), 1.53 (1.12 to 2.09); and extremely preterm (24 to 28 weeks), 1.84 (0.80 to 4.20).

The risk of a high SBP (≥140 mm Hg) per 1-week decrease in GA increased both within and between families (adjusted ORs [95% CIs] were 1.03 [1.01 to 1.05] and 1.06 [1.04 to 1.08], respectively), indicating that an association between GA and SBP exists after controlling for common genetic and shared environmental factors after birth. Analyses for within and between families with regard to high DBP

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<th>TABLE 3. Adjusted ORs With 95% CIs for HBP at Conscription, Without or With Adjustment for BMI</th>
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*Model 1 included the following covariates: GA, birth weight for GA, age and parity of the mother, height at conscription, conscription year, family situation of the conscriptee, and parents' educational level and socioeconomic status.
†Model 2 included the covariates in model 1 and BMI.
‡Reference category.
monly suffer from metabolic problems such as transient increased vascular resistance.9,10 Autonomic BP regulation is development induced by preterm birth may contribute to through several mechanisms. Abnormal vascular growth and GA and DBP. This discrepancy may be due to a nonlinear relation between preterm (33 to 36 weeks) faced a significantly increased risk. with decreasing GA, although only men born moderately DBP. However, the risk of high DBP increased consistently with regard to high DBP (≥90 mm Hg) were not possible because of the small numbers of very preterm–born men with high DBP.

There was a significant interaction between GA and birth weight for GA (P = 0.03) with regard to high SBP (≥140 mm Hg). To enable stratified analyses by GA, we collapsed extremely and very preterm births into 1 category (≥32 weeks). SGA was not a risk factor for high SBP among men born at 24 to 32 gestational weeks but increased the risk of high SBP among men with longer gestations (Table 4). We found no significant interactions between GA and BMI at conscription (P = 0.16) or between birth weight for GA and BMI at conscription (P = 0.23). Interaction analyses with regard to high DBP (≥90 mm Hg) were not possible because of the small numbers of very preterm–born men with high DBP.

Table 4. Adjusted ORs With 95% CIs for High SBP at Conscription by Birth Weight for GA, Stratified by GA

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<td>SGA</td>
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<td>841</td>
<td>1.33 (1.12–1.57)</td>
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<tr>
<td>AGA†</td>
<td>1244</td>
<td>1.00</td>
<td>10957</td>
<td>1.00</td>
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<tr>
<td>LGA</td>
<td>108</td>
<td>0.82 (0.50–1.37)</td>
<td>862</td>
<td>0.98 (0.83–1.17)</td>
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*Model included GA, birth weight for GA, age and parity of the mother, BMI and height at conscription, conscription year, family situation of the conscriptee, and parents’ educational level and socioeconomic status. †Reference category.

Discussion

In today’s generation of young Swedish men, preterm birth was identified as a perinatal risk factor for high SBP, and the risk increased with decreasing GA. SGA was also associated with an increased risk for high SBP but only among men born at 33 weeks or later. SGA and preterm birth represent different clinical entities, and their relative contributions to high SBP are not easily compared. Analyses of DBP showed less consistency. Decreasing birth weight for GA was associated with increasing DBP in linear-regression analyses, whereas logistic-regression analyses showed no association between SGA and the risk of high DBP. The latter finding could be due to the low prevalence of high DBP in the study cohort. SGA may also be less expressive for the risk of high DBP compared with the risk of high SBP. No linear association was found between GA and DBP. However, the risk of high DBP increased consistently with decreasing GA, although only men born moderately preterm (33 to 36 weeks) faced a significantly increased risk. This discrepancy may be due to a nonlinear relation between GA and DBP.

Individuals born preterm may be prone to BP elevation through several mechanisms. Abnormal vascular growth and development induced by preterm birth may contribute to increased vascular resistance.9,10 Autonomic BP regulation is immature in very preterm infants, and the postnatal matura-

hyperglycemia despite relatively high levels of insulin.26 Increased postnatal levels of insulin may cause persisting changes in glucose and lipid metabolism, predisposing to increased BP later in life.27 Activation of the hypothalamic-pituitary-adrenal axis has been suggested to link low birth weight at term to high SBP in adulthood.28 The immature hypothalamic-pituitary-adrenal axis in preterm infants29 and the possibility of early programming of the numbers of glucocorticoid receptors30 may be important for the association between preterm birth and HBP later in life. Finally, a reduction in nephron number cannot be ruled out as another etiologic factor, but at least women born preterm exhibit HBP despite normal kidney function.11

Whereas preterm birth per se may be conditional for the risk of HBP later in life, postnatal environmental exposures are likely to have an impact as well. In a randomized, controlled trial, preterm infants fed breast milk had lower BPs at follow-up in adolescence compared with those receiving formula.31 In addition, postnatal nutrient intake and growth patterns have been associated with insulin resistance32 and with vascular endothelial function in infancy33 and later in life.34 The full nature of these associations needs to be clarified, but they indicate that the risk for HBP in adults born preterm could be already modulated in the neonatal nursery. SGA was not a risk factor for BP elevation among men born very preterm, and similar conclusions have been drawn in smaller clinical studies.5,6 One may argue that the strong effect of very-preterm birth could mask a smaller effect of being SGA. However, there may also be principally different pathways of inducing later BP elevation in individuals born preterm and term. For example, dysfunction of the vascular endothelium, causing impaired vascular relaxation, has been found in infants and children born SGA at term, whereas very-preterm infants had normal endothelial function regardless of birth weight for GA.33,34

We did not find any interaction between GA and BMI in adulthood, which is in contrast to results from a recent study.7 Differences in study populations may contribute to this discrepancy, including different distributions of GA and differences in age when BP was measured. Because accelerated weight gain in childhood has been reported to influence the risk of HBP,8 we were somewhat surprised that there was no interaction between birth weight for GA and BMI at conscription. However, we had no longitudinal information on weight and height during childhood and adolescence, and

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negative findings for these 2 interaction analyses should be interpreted cautiously.

Our study was based on a national cohort of individuals born when neonatal intensive care was developing rapidly and survival rates for preterm infants were increasing. We used a reference curve for normal fetal growth instead of a reference curve based on birth weight and could therefore apply a more accurate definition of SGA in our cohort. Data for the main exposures (GA and birth weight) were registered prospectively. All analyses were adjusted for perinatal, maternal, and socioeconomic factors. In addition, the associations between GA and risks of high SBP were similar among men from different families and within families of full brothers. Thus, it is unlikely that the risk of high SBP related to short GA was confounded by common genetic and shared environmental factors in childhood.

Our cohort included only men, and conclusions should be restricted to men. GA was determined by the last menstrual period, which may slightly underestimate GA and hence, the effect of preterm birth on the risk of HBP. Conception rates varied across the GA range, with the lowest conception rate among men born extremely preterm. Because conceived men probably are healthier than those not conceived, this potential selection bias would, if anything, underestimate the effect of preterm birth. We had no information about maternal smoking and pre eclampsia, which are associated with risks of preterm birth and may also influence their offspring’s risk of HBP.

Despite standardized circumstances for the physical assessment of BP at conscription in Sweden, validation studies are lacking. In addition to the usual problems of BP measurement, it is reasonable to believe that young men experience some stress and hence, a moderate BP elevation, during military conscription similar to so-called ‘white coat hypertension.’ Because a differential misclassification of SBP elevation (≥140 mm Hg) between individuals with different GAs or birth weights is unlikely, such limitations would, if anything, attenuate our results. When we repeated our analyses with a narrower definition of high SBP (≥145 mm Hg), the association between preterm birth and risk of high SBP became even stronger. Similarly, the strong association between preterm birth and high DBP, when defined as ≥85 mm Hg, also lends support to the hypothesis that preterm birth predisposes to BP elevation later in life.

The strong effect of preterm birth on later BP may have important public health implications, because BP elevation could lead to hypertension with time. In Sweden, 6% of pregnancies end preterm, and the corresponding figure in the United States is reported to be as high as 12%. Hence, a similarly large proportion of offspring could be at risk for increased BP later in life. A proposed strategy to diagnose BP elevation in early life includes measurement of BP at any time a preterm-born child presents for health care. If our results can be confirmed, it would be appropriate to suggest routine follow-up of preterm-born infants with regard to BP. A more active approach to interventions in childhood may also be needed to avoid end-organ damage in adulthood.

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References
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