



Original Contribution

Risk of Hypertension Among Young Adults Who Were Born Preterm: A Swedish National Study of 636,000 Births

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Previous studies have reported an association between preterm birth and elevated blood pressure in adolescence and young adulthood. These studies were based on single-day blood pressure measurements and had limited ability to estimate risk of hypertension measured over a longer period and across the full range of gestational ages. The authors conducted a national cohort study of all infants born in Sweden from 1973 through 1979 ($n = 636,552$), including 28,220 born preterm (<37 weeks), followed to ages 25.5–37.0 years to determine whether individuals born preterm were more likely to be prescribed antihypertensive medications in 2005–2009 than those born full term. Antihypertensive medication data were obtained from all outpatient and inpatient pharmacies throughout Sweden. Young adults who were born preterm had an increased relative rate of antihypertensive medication prescription that increased monotonically by earlier gestational age and that was independent of fetal growth. The adjusted odds ratio for ≥ 1 antihypertensive medications/year ranged from 1.25 (95% confidence interval: 1.12, 1.39) for those born near term (35–36 weeks) to 2.51 (95% confidence interval: 1.11, 5.68) for those born extremely preterm (23–27 weeks) relative to those born full term. These findings suggest that preterm birth is strongly associated with hypertension in young adulthood, including an increased risk among those born near term.

antihypertensive agents; hypertension; premature birth

Abbreviations: ATC, Anatomical Therapeutic Chemical; CI, confidence interval; SD, standard deviation.

Hypertension is the most common outpatient diagnosis in the United States and the most common reason for use of prescription medications (1). It is estimated to affect 28% of the adult population in North America and 44% of Europeans (2), and it is a major independent risk factor for coronary artery disease, stroke, congestive heart failure, and kidney disease (3). A growing body of evidence has suggested that preterm birth is a risk factor for elevated blood pressure in adolescence and early adulthood (4). Given the increasing number of preterm births in recent years (5) and the extensive morbidity and mortality associated with hypertension, the public health implications of a link between preterm birth and hypertension are large and expected to increase. Clarification of this link and further estimation of the risk of hypertension following preterm birth are high priorities.

Several previous studies have reported an association between preterm birth and elevated blood pressure in adolescence (6, 7) and young adulthood (8–12). Because these studies were based on blood pressure measurements from a single day, they had limited ability to assess the risk of hypertension measured over a longer period. They also were unable to estimate this risk across the full range of gestational ages at birth, including extremely preterm.

To help address these gaps in the current knowledge, we conducted a national cohort study that is the largest to date of the association between preterm birth and subsequent risk of hypertension. Using 4.5 years of nationwide outpatient and inpatient medication data from all health-care settings throughout Sweden, we examined whether individuals who were born preterm were more likely to be prescribed antihypertensive medications in young

adulthood (ages 25.5–37.0 years) than those who were born full term.

MATERIALS AND METHODS

Data sources

This study was based on register data in a national research database, WomMed, located at the Center for Primary Health Care Research, Lund University, Malmö, Sweden. This database contains annual data from prenatal and birth records, hospital admissions, and death records for each mother and child in Sweden. Information on date of delivery, birth weight and length, and maternal and fetal complications is transferred from hospital records, together with prenatal care data, to the Swedish Medical Birth Register, which is the main register in the WomMed Database.

The WomMed Database also contains individual-level sociodemographic information for the parents, including age, marital status, and socioeconomic indicators, collected annually starting in 1990. For the current study, sociodemographic characteristics were identified by using the Swedish Population and Housing Census of 1990, the most recent census when the young adults in this study (who were then 11–17 years of age) were still likely to be residing in the same household as their mothers. This census information was used to identify maternal characteristics that would reflect the social conditions of these young adults during their upbringing that may be associated with subsequent risk of hypertension. An anonymous, serial-number version of the personal identification number (similar to the US Social Security number but nearly 100% complete) was used to link the mothers to their children.

Information on antihypertensive medication prescriptions was obtained by using a national pharmacy register maintained by the National Board of Health and Welfare. The national pharmacy register contains a record of each medication that is prescribed by a health-care provider and dispensed to a patient by any outpatient or inpatient pharmacy in Sweden. For inpatients, the register includes all medications prescribed to a patient upon discharge from the hospital. All outpatient and inpatient pharmacy data were linked to the national Medical Birth Register by using an anonymous identification number.

All medication data are categorized according to the Anatomical Therapeutic Chemical (ATC) Classification developed by the World Health Organization Collaborating Center for Drug Statistics Methodology. We obtained information on medications prescribed for cardiovascular conditions (code C), subclassified as “antihypertensives” (C02, which includes centrally acting antiadrenergic agents and others), diuretics (C03), beta blockers (C07), calcium channel blockers (C08), and agents acting on the renin-angiotensin system (C09).

Study population

A total of 648,849 individuals, born from 1973 through 1979, were identified in the Swedish Medical Birth Register and who were still living in Sweden in 2005 (when the na-

tional pharmacy register was started). Of this total, we excluded 7,995 (1.2%) individuals who had significant congenital anomalies (i.e., other than undescended testicle, preauricular appendage, congenital nevus, or hip dislocation), 573 (<0.1%) who had missing information on gestational age at birth, and 1,888 (0.3%) who had missing information on birth weight. In order to remove possible coding errors, we also excluded 6 (<0.01%) individuals who had a reported gestational age of <23 weeks and 1,835 (0.3%) individuals who had a reported birth weight of >4 standard deviations above or below the mean birth weight for gestational age and sex from a Swedish reference growth curve (13). A total of 636,552 individuals (98.1% of the original cohort) remained for inclusion in the analysis.

Study period

All study participants, born from 1973 through 1979, were followed for prescription of antihypertensive medications from July 1, 2005, through December 31, 2009, the first 4.5 years that the national pharmacy register was kept. These individuals were between 25.5 and 37.0 years of age during the period of follow-up.

Independent variables

Infant's gestational age at birth. This was based on maternal report of the last menstrual period and categorized as 23–27 weeks, 28–32 weeks, 33–34 weeks, 35–36 weeks, 37–42 weeks (full term), and ≥ 43 weeks.

Infant's date of birth. This was modeled as a continuous variable. We included this in order to adjust for age and for changes in perinatal care that may have occurred during the period that these study participants were born (1973–1979).

Infant's gender. This variable was either female or male.

Maternal marital status in 1990. This variable was married/cohabiting, never married, divorced, or widowed.

Maternal education in 1990. This consisted of compulsory high school or less (≤ 9 years), practical high school or some theoretical high school (10–11 years), or theoretical high school and/or college (≥ 12 years).

Family income in 1990. This variable was calculated as the annual family income divided by the number of people in the family, or family income per capita, by using a weighted system whereby small children were given lower weights than adolescents and adults. The final variable was categorized in quartiles.

Maternal prescription of antihypertensive medications. Prescription of antihypertensive medications (ATC Classification codes C02, C03, C07, C08, and/or C09) to the mothers of the study participants during the follow-up period was dichotomized as < 1 or ≥ 1 prescription per year on average.

Fetal growth. Birth weight for gestational age and sex was used as a measure of fetal growth, categorized into 6 groups according to the number of standard deviations from the mean birth weight for gestational age and sex from a Swedish reference curve (13) (< -2 standard deviations (SDs); -2 SDs to < -1 SD; -1 SD to < 0 SDs; 0 SDs to < 1 SD; 1 SD to < 2 SDs; ≥ 2 SDs).

Outcome variables

The outcome was defined alternatively as ≥ 1 , ≥ 2 , ≥ 3 , or ≥ 4 prescriptions per year on average of any antihypertensive medication (ATC Classification codes C02, C03, C07, C08, and/or C09) during the follow-up period (July 1, 2005, through December 31, 2009). Defining the outcome by the criterion of larger numbers of prescriptions may increase the positive predictive value for hypertension or persistent hypertension.

Statistical analysis

Multivariate logistic regression was used to estimate odds ratios and 95% confidence intervals for the association between gestational age at birth (categorized as 23–27 weeks, 28–32 weeks, 33–34 weeks, 35–36 weeks, 37–42 weeks, ≥ 43 weeks) and prescription of antihypertensive medications (as defined above) in young adulthood (ages 25.5–37.0 years), by using full-term birth (37–42 weeks) as the reference category. Analyses were conducted unadjusted and then were adjusted in 2 different models. Adjusted model 1 included the following infant and maternal characteristics as potential confounders: infant's date of birth, infant's gender, maternal marital status, maternal education, family income, and maternal prescription of antihypertensive medications during the follow-up period; adjusted model 2 included the same set of variables and also fetal growth. We explored for first-order interactions between gestational age at birth and each of these infant and maternal characteristics with respect to antihypertensive medication prescription in young adulthood, using a likelihood ratio test to evaluate for statistical significance. All analyses were conducted by using STATA, version 11.0, statistical software (14).

RESULTS

Of the 636,552 individuals who were identified, 28,220 (4.4%) were born prematurely (<37 weeks), including 174 (0.03%) born at 23–27 weeks, 3,167 (0.5%) born at 28–32 weeks, 5,685 (0.9%) born at 33–34 weeks, and 19,194 (3.0%) born at 35–36 weeks (Table 1). Compared with individuals who were born full term, those who were born prematurely were more likely to be male, and their mothers were more likely to be divorced or never married, to have the lowest educational attainment and lowest family incomes, and to be prescribed antihypertensive medications during the follow-up period.

Among individuals who were born preterm (<37 weeks), a monotonic trend of increasing prescription rates was noted by earlier gestational age at birth (Table 2). A total of 9,438 (1.5%) young adults from the entire cohort were prescribed ≥ 1 antihypertensive medications/year, including 3.5% of those who were born extremely preterm (23–27 weeks). Young adults who were born near term (35–36 weeks) were also more likely to be prescribed antihypertensive medications than those born full term.

Table 3 presents odds ratios and 95% confidence intervals for the association between gestational age at birth and

antihypertensive medications in young adulthood. Young adults who were born preterm had an increased relative rate of antihypertensive prescriptions that increased monotonically by earlier gestational age at birth. Adjustment for infant and maternal characteristics, with or without fetal growth, had little effect on any of the odds ratios. In the fully adjusted model (adjusted model 2), the odds ratio for ≥ 1 antihypertensive medications/year ranged from 1.25 (95% confidence interval (CI): 1.12, 1.39) among those born near term (35–36 weeks) to 2.51 (95% CI: 1.11, 5.68) among those born extremely preterm (23–27 weeks) relative to those born full term. When larger numbers of prescriptions were examined, a gradient effect appeared among those who were born extremely preterm: The adjusted odds ratios increased to 3.75 (95% CI: 1.66, 8.49), 3.83 (95% CI: 1.42, 10.4), and 4.68 (95% CI: 1.49, 14.7) for ≥ 2 , ≥ 3 , and ≥ 4 prescriptions/year, respectively, relative to full-term births.

Table 4 presents adjusted odds ratios for the joint effect of gestational age at birth and fetal growth with respect to antihypertensive prescriptions in young adulthood, including individuals who were born full term (37–42 weeks) with birth weight of ≥ 0 SDs and <1 SD above the mean reference birth weight as the reference category. No significant interaction was found between gestational age at birth and fetal growth with respect to antihypertensive prescription in young adulthood ($P = 0.82$).

We explored for other possible first-order interactions between preterm birth and each of the variables listed in Table 1 with respect to antihypertensive medications in young adulthood. No interactions were found that were statistically significant at the $P < 0.01$ level.

DISCUSSION

This national cohort study is the largest to date of preterm birth and the subsequent risk of hypertension, which was assessed on the basis of antihypertensive medication data from 4.5 years of follow-up. The results suggest that preterm birth is associated with hypertension in young adulthood (ages 25.5–37.0 years) independently of fetal growth, with relative risks that increase monotonically by earlier gestational age at birth. Extreme prematurity (23–27 weeks) was associated with a 2.5-fold increased relative rate of antihypertensive medication prescription (≥ 1 /year) in young adulthood compared with full-term birth. Defining the outcome alternatively as ≥ 2 , ≥ 3 , or ≥ 4 antihypertensive medication prescriptions/year produced even larger odds ratios for the earliest gestational age groups, providing further consistent evidence for an association between prematurity and hypertension in young adulthood.

Another important finding was an increased risk of hypertension among young adults who were born near term, at gestational ages 35–36 weeks. These individuals constitute two-thirds of the total preterm births in this cohort, a proportion consistent with data from other populations (5). Given the large and increasing number of near-term births, even a modestly elevated relative risk of hypertension among these individuals may have a major public health impact (3).

Table 1. Infant and Maternal Characteristics by Gestational Age at Birth, Sweden, 1973–1979

	Gestational Age, %					
	23–27 Weeks (n = 174)	28–32 Weeks (n = 3,167)	33–34 Weeks (n = 5,685)	35–36 Weeks (n = 19,194)	37–42 Weeks (n = 589,573)	≥43 Weeks (n = 18,759)
Infant's gender						
Female	44.8	43.7	44.4	44.8	48.8	49.9
Male	55.2	56.3	55.6	55.2	51.2	50.1
Maternal marital status in 1990						
Married/cohabiting	74.3	70.4	70.3	72.0	76.4	72.9
Never married	13.5	13.0	12.9	11.7	9.4	11.5
Divorced	12.3	15.8	15.7	14.8	13.0	14.6
Widowed	0.0	0.8	1.1	1.5	1.2	1.0
Maternal education in 1990						
Compulsory high school or less (≤9 years)	29.2	31.2	32.0	30.8	26.9	29.4
Practical high school or some theoretical high school (10–11 years)	47.4	46.7	47.1	46.5	47.2	47.4
Theoretical high school and/or college (≥12 years)	23.4	22.1	20.9	22.7	25.9	23.1
Family income in 1990						
Lowest quartile	29.9	28.4	27.6	26.1	23.0	24.1
Second quartile	21.8	25.3	24.8	25.8	25.7	25.3
Third quartile	25.3	24.7	24.7	25.0	25.7	25.8
Highest quartile	23.0	21.6	22.9	23.1	25.6	24.8
Maternal prescription of antihypertensive medications ^a from July 1, 2005, through December 31, 2009	29.3	30.8	32.4	31.2	29.1	28.9

^a Defined as 1 or more prescriptions per year of any antihypertensive medication (Anatomical Therapeutic Chemical (Classification) code(s) C02, C03, C07, C08, and/or C09).

Previous studies measuring blood pressure in children who were born prematurely have generally reported either no association or very slight increases in blood pressure among those who were born preterm (15–19). Studies that have included adolescents are generally slightly more positive but mixed, with some (6, 7) but not all (18, 20) reporting a modest association between preterm birth and elevated blood pressure.

There are relatively few previous studies of association between preterm birth and hypertension in young adults, and most of these have focused on ages in the range of 18–26 years. A study of 329,495 Swedish male military conscripts aged 18 years (including 14,192 who were born preterm and

162 born at 24–28 weeks) reported an increased risk of elevated blood pressure (based on 1 or the lower of 2 measurements) by earlier gestational age at birth (8). Several other much smaller studies of young adults with average ages of 19–26 years also reported an association between preterm birth and elevated blood pressure, all based on single-day blood pressure measurements (9–12).

Data from middle-aged and older adults are very limited. One study of 6,269 older Swedish adults born in 1925–1949 (including 2,502 who were born preterm) reported an association between small for gestational age, but not preterm birth, and hypertension that was identified on the basis of hospital discharge diagnoses from 1987 to 2006 (21). These

Table 2. Prescription of Antihypertensive Medications in Young Adulthood (Ages 25.5–37.0 Years) by Gestational Age at Birth (1973–1979), Sweden

Antihypertensive Medication (ATC Code ^a) Prescriptions/Year	Gestational Age											
	23–27 Weeks (n = 174)		28–32 Weeks (n = 3,167)		33–34 Weeks (n = 5,685)		35–36 Weeks (n = 19,194)		37–42 Weeks (n = 589,573)		≥43 Weeks (n = 18,759)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
≥1	6	3.5	73	2.3	110	1.9	356	1.9	8,588	1.5	305	1.6
≥2	6	3.5	52	1.6	83	1.5	246	1.3	5,794	1.0	219	1.2
≥3	4	2.3	35	1.1	64	1.1	159	0.8	3,736	0.6	142	0.8
≥4	3	1.7	24	0.8	40	0.7	95	0.5	2,281	0.4	87	0.5

Abbreviation: ATC, Anatomical Therapeutic Chemical (Classification).

^a Code(s) C02, C03, C07, C08, and/or C09.

Table 3. Odds Ratios for Association Between Gestational Age at Birth (1973–1979) and Prescription of Antihypertensive Medications in Young Adulthood (Ages 25.5–37.0 Years), Sweden

Antihypertensive Medication (ATC Code ^a) Prescriptions/Year ^b by Gestational Age ^c	Unadjusted		Adjusted Model 1 ^d		Adjusted Model 2 ^e	
	OR	95% CI	OR	95% CI	OR	95% CI
≥1 prescriptions/year						
23–27 weeks	2.42	1.07, 5.46	2.49	1.10, 5.63	2.51	1.11, 5.68
28–32 weeks	1.60	1.26, 2.02	1.57	1.24, 1.98	1.51	1.20, 1.91
33–34 weeks	1.33	1.10, 1.61	1.28	1.06, 1.55	1.24	1.03, 1.51
35–36 weeks	1.28	1.15, 1.42	1.26	1.13, 1.40	1.25	1.12, 1.39
37–42 weeks	1.00		1.00		1.00	
≥43 weeks	1.12	1.00, 1.25	1.05	0.94, 1.18	0.97	0.86, 1.09
≥2 prescriptions/year						
23–27 weeks	3.60	1.59, 8.13	3.71	1.64, 8.40	3.75	1.66, 8.49
28–32 weeks	1.68	1.28, 2.21	1.65	1.25, 2.17	1.58	1.20, 2.09
33–34 weeks	1.49	1.20, 1.86	1.43	1.15, 1.77	1.38	1.11, 1.72
35–36 weeks	1.31	1.15, 1.49	1.28	1.13, 1.46	1.27	1.12, 1.45
37–42 weeks	1.00		1.00		1.00	
≥43 weeks	1.19	1.04, 1.36	1.11	0.97, 1.28	1.02	0.89, 1.17
≥3 prescriptions/year						
23–27 weeks	3.69	1.37, 9.95	3.78	1.40, 10.2	3.83	1.42, 10.4
28–32 weeks	1.75	1.25, 2.45	1.71	1.22, 2.39	1.65	1.18, 2.30
33–34 weeks	1.79	1.39, 2.29	1.70	1.32, 2.18	1.65	1.29, 2.12
35–36 weeks	1.31	1.12, 1.54	1.28	1.09, 1.50	1.27	1.08, 1.49
37–42 weeks	1.00		1.00		1.00	
≥43 weeks	1.20	1.01, 1.42	1.11	0.94, 1.32	1.02	0.86, 1.21
≥4 prescriptions/year						
23–27 weeks	4.52	1.44, 14.2	4.62	1.47, 14.5	4.68	1.49, 14.7
28–32 weeks	1.97	1.31, 2.94	1.90	1.27, 2.85	1.80	1.20, 2.70
33–34 weeks	1.82	1.33, 2.50	1.72	1.26, 2.35	1.65	1.20, 2.26
35–36 weeks	1.28	1.04, 1.57	1.25	1.01, 1.53	1.23	1.00, 1.51
37–42 weeks	1.00		1.00		1.00	
≥43 weeks	1.20	0.97, 1.49	1.11	0.90, 1.38	0.99	0.80, 1.23

Abbreviations: ATC, Anatomical Therapeutic Chemical (Classification); CI, confidence interval; OR, odds ratio.

^a Code(s) C02, C03, C07, C08, and/or C09.

^b Outcome variable.

^c Predictor variable.

^d Adjusted for infant's date of birth, infant's gender, maternal marital status, maternal education, family income, and maternal prescription of antihypertensive medications (≥1 prescriptions/year) during the follow-up period (July 1, 2005, through December 31, 2009).

^e Adjusted for the same variables included in adjusted model 1, as well as fetal growth.

findings are more difficult to interpret given that hypertension is typically managed in the outpatient setting. Another study of 430 Swedish men aged 49 years (including 44 who were born preterm) reported a correlation between earlier gestational age at birth among low-birth-weight individuals (≤2,500 g) and high blood pressure based on a single reading (22).

The mechanisms by which preterm birth may affect the development of hypertension are complex and may involve nutrition, oxidative stress, epigenetic changes, and endocrine and renal changes (23). There is epidemiologic and experimental evidence that poor perinatal nutrition is associated with impaired endothelium-dependent vasodilatation

at birth and in childhood (24, 25). Human and animal data have also suggested that oxidative stress and inflammation associated with prematurity or low birth weight may initiate perinatal programming of vascular dysfunction and elevated blood pressure (23). Transgenerational mechanisms may also be important, either through maternal-child transmission of vascular dysfunction via a deprived intrauterine environment or by epigenetic modification of the germline by DNA methylation (26). Other mechanisms involving alterations of the autonomic nervous system (19, 27), hypothalamus-pituitary-adrenal axis (28), and activation of the renin-angiotension system are also possible and are still being clarified.

Table 4. Adjusted Odds Ratios^a for the Joint Effect of Fetal Growth and Gestational Age at Birth (1973–1979) With Respect to Antihypertensive Medications (≥ 1 Prescriptions/Year) in Young Adulthood (Ages 25.5–37.0 Years), Sweden^b

Fetal Growth, SD ^c	Gestational Age at Birth											
	23–27 Weeks (n = 174)		28–32 Weeks (n = 3,167)		33–34 Weeks (n = 5,685)		35–36 Weeks (n = 19,194)		37–42 Weeks (n = 589,573)		≥ 43 Weeks (n = 18,759)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
< -2 (n = 19,199)	NE		3.34	1.95, 5.74	1.93	1.11, 3.35	1.51	0.99, 2.28	1.47	1.31, 1.65	1.68	1.26, 2.24
-2 to < -1 (n = 88,370)	NE		1.92	1.12, 3.27	1.30	0.80, 2.10	1.72	1.33, 2.22	1.29	1.20, 1.37	1.25	1.02, 1.52
-1 to < 0 (n = 210,831)	5.50	1.70, 17.8	1.06	0.62, 1.80	1.20	0.82, 1.76	1.37	1.12, 1.68	1.08	1.03, 1.14	1.06	0.87, 1.30
0 to < 1 (n = 203,170)	2.76	0.67, 11.4	1.61	0.98, 2.65	1.47	1.01, 2.13	1.22	0.99, 1.51	1.00	Reference	0.78	0.57, 1.09
1 to < 2 (n = 88,377)	2.72	0.36, 20.2	1.15	0.51, 2.59	1.33	0.78, 2.27	1.23	0.93, 1.62	0.99	0.92, 1.06	0.87	0.45, 1.68
≥ 2 (n = 26,605)	NE		2.82	1.44, 5.52	1.49	0.79, 2.79	1.36	0.95, 1.93	1.01	0.90, 1.14	1.69	0.54, 5.35

Abbreviations: CI, confidence interval; NE, not estimable; OR, odds ratio; SD, standard deviation.

^a Adjusted for infant's date of birth, infant's gender, maternal marital status, maternal education, family income, and maternal prescription of antihypertensive medications (≥ 1 prescriptions/year) during the follow-up period (July 1, 2005, through December 31, 2009).

^b $P_{\text{interaction}} = 0.82$.

^c Number of standard deviations from the mean reference birth weight for gestational age and sex.

The current study has several limitations and strengths. One potential limitation is the use of antihypertensive medication prescriptions as a surrogate measure for hypertension. Antihypertensive medications are sometimes prescribed for conditions other than hypertension, such as heart failure or arrhythmias; however, these conditions are relatively uncommon in young adults. To enhance the positive predictive value for hypertension, we evaluated multiple prescriptions of antihypertensive medications defined alternatively as ≥ 1 , ≥ 2 , ≥ 3 , or ≥ 4 prescriptions/year. As noted, examining larger numbers of prescriptions resulted in larger odds ratios among the earliest gestational ages at birth, providing additional consistent evidence for a true association between preterm birth and hypertension.

The use of antihypertensive medications as a proxy for hypertension will fail to identify the substantial number of individuals who have hypertension but remain untreated (3). If this occurs nondifferentially with respect to preterm birth status, it biases the results toward the null hypothesis, in which case the reported odds ratios in the current analysis underestimate the true effect sizes. We are unable, however, to exclude the possibility of diagnostic or prescription bias among individuals in this cohort who were born preterm.

Other limitations include the possibility of residual confounding by factors such as maternal hypertension or maternal behavioral characteristics (e.g., smoking). The effect of preterm birth on hypertension in later life may also be modified by postnatal weight gain that was not available for this cohort. Finally, gestational age was based on maternal report of last menstrual period rather than by ultrasound, which was not yet widely used at the time these study participants were born (1973–1979). Any misclassification that resulted from this is expected to be nondifferential with respect to preterm birth status and therefore to bias the results toward the null hypothesis.

This study also has several important or unique strengths. As the largest study to date, it has greater power to evaluate the risk of hypertension across the full range of gestational ages, including extremely preterm births. It adds to previous

evidence from single-day blood pressure measurements by evaluating antihypertensive medications from 4.5 years of follow-up, which may better indicate sustained or persistent hypertension. These nationwide data from a national cohort are remarkably complete, because they are obtained from all outpatient and inpatient pharmacies from all health-care settings throughout Sweden. Multiple antihypertensive prescriptions were examined in order to enhance their positive predictive value for hypertension.

In summary, this national cohort study suggests a strong, consistent association between preterm birth and hypertension in young adults who were born during 1973–1979 in Sweden. Among young adults who were born preterm, the risk of hypertension increased monotonically by earlier gestational age at birth and was independent of fetal growth. Given the increasing number and proportion of births that occur prematurely and the extensive disease burden due to hypertension, the public health impact of the observed association is large and expected to increase. Future priorities include research to clarify the etiologic pathways, more effective prevention of preterm birth, and effective detection and treatment of hypertension in individuals who are born preterm.

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