Published in final edited form as:

Matern Child Health J. 2016 July ; 20(7): 1415–1423. doi:10.1007/s10995-016-1939-7.

Birth weight and Birth weight for Gestational Age in Relation to Risk of Hospitalization with Primary Hypertension in Children and Young Adults

Gaia Pocobelli^a, Sascha Dublin^{a,b}, Daniel A. Enquobahrie^{a,c}, and Beth A. Mueller^{a,d}

^aDepartment of Epidemiology, University of Washington, Seattle, Washington, 1959 NE Pacific Street, Health Sciences Building F-262, Seattle, WA, 98195-7236

^bGroup Health Research Institute, Seattle, Washington, 1730 Minor Avenue, Suite 1600, Seattle, WA, 98101

^cCardiovascular Health Research Unit, University of Washington, Seattle, Washington, 1730 Minor Ave, Suite 1360, Seattle, WA, 98101

^dPublic Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, Box 358080, 1100 Fairview Ave N., Arnold Building, P.O. Box 1192024, Mailstop: M4-C308, Seattle, WA, 98109-1024

Abstract

Introduction—Low birth weight has been associated with an increased risk of hypertension in children. Less clear is whether high birth weight is also associated with risk. We evaluated overall and age-specific risks of primary hypertension in children and young adults associated with birth weight and birth weight for gestational age.

Methods—We conducted a population-based case-control study using linked Washington State birth certificate and hospital discharge data from 1987–2003. Cases were persons hospitalized with primary hypertension at 8–24 years of age ($n = 533$). Controls were randomly selected among those born in the same years who were not hospitalized with hypertension ($n = 25,966$).

Results—Birth weight was not related to risk of primary hypertension overall, except for a suggestion of an increased risk associated with birth weight 4,500 grams relative to 3,500–3,999 grams (odds ratio (OR) 1.55; 95 % confidence interval (CI) 0.96–2.49). Compared to children born appropriate weight for gestational age, those born small (SGA) (OR 1.32; 95 % CI 1.02–1.71) and large for gestational age (LGA) (OR 1.30; 95 % CI 1.00–1.71) had increased risks of primary hypertension. These overall associations were due to increased risks of hypertension at 15–24 years of age; no associations were observed with risk at 8–14 years of age.

Discussion—In this study, both SGA and LGA were associated with increased risks of primary hypertension. Our findings suggest a possible nonlinear (U-shaped) association between birth weight for gestational age and primary hypertension risk in children and young adults.

Keywords

hypertension; children; young adults; birth weight

Introduction

The prevalence of high blood pressure among children in the U.S. has been increasing (Rosner, Cook, Daniels, & Falkner, 2013). National Health and Nutrition Examination Survey data from 1988–1994 and 1999–2008 indicate that, among children 8–17 years of age, high blood pressure increased from 16% to 19% in boys and 8% to 13% in girls (Rosner et al., 2013). High blood pressure in childhood has been associated with cardiovascular disease risk factors in adulthood including high blood pressure, carotid intima media thickness, and microalbuminuria (Thompson, Dana, Bougatsos, Blazina, & Norris, February 2013). Epidemiologic studies have reported an increased risk of childhood-onset primary (essential) hypertension in low birth weight infants (Edvardsson, Steinhorsdottir, Eliasdottir, Indridason, & Palsson, 2012; R. R. Huxley, Shiell, & Law, 2000; Mu et al., 2012; Zhou et al., 2015), possibly due to alterations in their renal or vascular systems related to reduced growth *in utero* (Barker, Bagby, & Hanson, 2006; Edvardsson et al., 2012; Hughson, Farris, Douglas-Denton, Hoy, & Bertram, 2003; Kaplan, 2014; Norman, 2008). Less clear however, is whether high birth weight, which may have long-term adverse metabolic effects, such as insulin resistance (Darendeliler et al., 2009; Mandy, 2014), is also a risk factor for the development of primary hypertension in childhood (Edvardsson et al., 2012).

Low birth weight has been linked to the development of hypertension in adults, and a number of other chronic conditions including coronary heart disease, type 2 diabetes mellitus, and breast cancer (Sallout & Walker, 2003). Results have been more mixed for an association between high birth weight and the development of chronic conditions in adults, such as hypertension and coronary heart disease (Palatianou, Simos, Andronikou, & Kiortsis, 2014).

We used linked Washington State birth certificate and hospital discharge data from 1987–2003 to evaluate overall and age-specific primary hypertension risks in children and young adults associated with birth weight and birth weight for gestational age.

Methods

Human Subjects Protection Committee approval was obtained prior to the conduct of this study.

Case identification and control selection

We conducted a case-control study using linked Washington State birth certificate and hospital discharge records. We ascertained all infants born in Washington State during 1987–2011 who were subsequently hospitalized during this same period (1987–2011) in a non-government hospital in Washington State with an International Classification of Diseases, Ninth Revision [ICD-9] code Online Resource 1) indicating a diagnosis of any hypertension (ICD-9 401.x-405.x, 416.0, 459.3x and 642.x) (n = 3,203). When a person had >1

hospitalization with any of these codes, only the record from the first (index) hospitalization was used. The controls were drawn from all remaining infants born during 1987–2011, randomly sampled and frequency matched by birth year in a 10:1 control:case ratio ($n = 32,030$).

For the present analysis we sought to restrict our case group to persons with primary hypertension, and thus we excluded all those who did not have a diagnosis of primary hypertension at the index hospitalization ($n = 1,910$), leaving 1,293 cases. We additionally excluded those whose index hospitalization included a concurrent diagnosis of pregnancy-associated hypertension ($n = 15$) or secondary hypertension ($n = 4$) and those whose index hospitalization occurred before 8 years of age ($n = 666$). We set this age limit because hypertension in children <8 years of age is much more likely to be secondary than primary (Flynn, Zhang, Solar-Yohay, & Shi, 2012; Wyszynska, Cichocka, Wieteska-Klimczak, Jobs, & Januszewicz, 1992) and we wanted to reduce the likelihood that our cases included children with secondary hypertension who had been misclassified in the administrative data. After applying these exclusions, 612 cases born during 1987–2003 remained. All controls born after 2003 ($n = 3,390$) were excluded, leaving 28,640 controls.

We additionally excluded cases and controls diagnosed at birth with a condition that may be a cause of secondary hypertension in children (Yoon et al., 2012): congenital anomaly (ICD-9 and the birth certificate check box [62 cases/1,607 controls]), diseases of the genitourinary system (0 cases/9 controls); endocrine, nutritional or metabolic disease or immunity disorder (0 cases/3 controls), polycythemia (0 cases/27 controls); and chronic respiratory disease arising in the perinatal period (1 case/19 controls). No case or control had a diagnosis at birth for any of the following potential causes of secondary hypertension (Yoon et al., 2012): a circulatory system disease, musculoskeletal system or connective tissue disease, nervous system or sense organ disease, or neoplasm. Finally, we excluded cases and controls who were missing information on birth weight (1/612 cases, 88/28,640 controls), birth weight for gestational age (19/612 cases, 1,012/28,640 controls) or maternal age (0/612 cases, 82/28,640 controls), leaving 533 cases and 25,966 controls for analysis.

Exposure and covariate ascertainment

Birth weight (grams) and gestational age (weeks) were ascertained from the birth certificate. Birth weight was categorized as <2,500, 2,500–2,999, 3,000–3,499, 3,500–3,999, and 4,000 (or 4,000–4,499 and 4,500) grams. To compute birth weight for gestational age, the distribution of birth weight was determined for each week of gestational age among all Washington State births during 1989–2009 (Williams et al., 1982). Infants in the 10th percentile of birth weight given their gestational age were considered to be small for gestational age (SGA), those in the 90th percentile to be large for gestational age (LGA), and the remainder were considered to be appropriate for gestational age (AGA) (Williams et al., 1982).

The following maternal characteristics were ascertained from the birth certificate: age at delivery, race/ethnicity, marital status, years of education (for deliveries since 1992; 52% of the study population), health insurance status (Medicaid/private), parity, pregnancy weight gain (for deliveries since 1989; 80% of the study population), prepregnancy weight (for

deliveries since 1992), and smoking during pregnancy. Maternal and paternal occupation information was also available, and urban/rural residence was calculated based on the maternal residential location at delivery. Information on maternal diabetes (pregestational and gestational) and hypertension (chronic, preeclampsia or eclampsia, and gestational) during pregnancy was ascertained from both the birth certificate and the hospital discharge record for the delivery hospitalization. We considered each condition to be present during the pregnancy if it was indicated on the birth certificate or delivery hospitalization discharge records as the sensitivity of ascertainment of maternal conditions during pregnancy is improved when both sources are used (Lydon-Rochelle et al., 2005).

Neonatal characteristics, ascertained from the birth certificate, included year of birth, gestational age at delivery (based on clinical estimate when available [79% of subjects] or last menstrual period), sex, and race/ethnicity.

Analysis

Descriptive statistics were conducted to examine data quality and missing values. Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the associations of primary hypertension (yes/no) with categories of birth weight (reference category 3,500–3,999 grams), and of birth weight for gestational age (reference category AGA). Because hypertension is more likely to be secondary to an identified underlying disease (i.e. secondary hypertension) in prepubescent children (Flynn et al., 2012; Wyszynska et al., 1992), and because we relied on ICD-9 codes alone to distinguish primary from secondary hypertension, the specificity with which we ascertained case status may have been less in younger children. Therefore, we also evaluated age-specific risks (8–14 and 15–24 years of age at the index hospitalization) associated with weight at birth.

All ORs were adjusted for birth year and maternal age. We additionally adjusted for those variables that changed the ORs by 10% or greater in any analysis (overall and age-specific) among the following (in order and categorized as shown in Table 1 unless otherwise indicated): maternal marital status at delivery, race/ethnicity, urban/rural residence, Medicaid/non-private health insurance, parity, smoking during pregnancy, diabetes, hypertensive disorder, pregnancy weight gain; and infant sex, and maternal-infant race/ethnicity discordance (whether the infant's race/ethnicity [Hispanic, white, black, Asian/Pacific islander, and all others] was discordant from that reported for the mother). Gestational age was also considered in analyses of birth weight. Only gestational age, maternal hypertensive disorder, and infant sex met our criterion for confounding and only in the analysis of birth weight. To have comparability in adjustment factors across both exposures, we also adjusted for maternal hypertensive disorder and infant sex in the analysis of birth weight for gestational age.

We evaluated whether infant sex was a potential effect modifier of the associations between primary hypertension risk and birth weight and birth weight for gestational age. We computed sex-specific adjusted risk estimates and tested whether an interaction term was significant ($p < 0.05$) using the likelihood ratio test, where the interaction term was the

product of birth weight or birth weight for gestational age, coded as an ordinal variable, and infant sex coded as a dummy variable.

Several sensitivity analyses were conducted to assess the robustness of our findings. We evaluated whether maternal education level and prepregnancy weight – available only for those born since 1992 – were confounders in the subset of the study population for whom information was available. In addition, because information on whether a study subject was hospitalized outside of Washington State after birth was not available, we conducted a subanalysis in which we excluded subjects whose mother or father had a military occupation at the time of their birth or whose mother was <18 years old at delivery. We additionally evaluated age-specific risk of hypertension in children 15–18 years of age.

Finally, because we did not have complete information on severity of maternal diabetes or hypertension, we conducted an analysis restricted to subjects born at term (37–<42 weeks of gestation) to a mother without diabetes or hypertension during her pregnancy.

All statistical tests were 2-sided and a P -value < 0.05 was considered statistically significant. Analyses were conducted using Stata/MP 12.1 (StataCorp LP, College Station, Texas).

Results

The largest proportion of cases (46 %) were first hospitalized with an ICD-9 code for primary hypertension at 8–14 years of age; 39 % were first hospitalized at 15–19 years and 15 % at 20–24 years old (data not shown). Cases were more likely than controls to be male (66 % versus 51 %) (Table 1). The distributions of gestational age at delivery and maternal-infant race/ethnicity discordance were similar between cases and controls. The distributions of maternal age, residence (rural versus urban), parity, pregnancy weight gain, and smoking status during pregnancy were also similar between cases and controls. However, cases were more likely to have a non-white mother or a mother with less education or Medicaid/non-private health insurance, or a greater prepregnancy weight. Mothers of cases were also more likely to have diabetes or a hypertensive disorder during pregnancy.

There was no association between birth weight category and risk of primary hypertension overall, except for a suggestion of an increased risk with birth weight 4,500 grams relative to 3,500–3,999 grams (OR 1.55; 95 % CI 0.96–2.49) (Table 2). Both SGA and LGA were associated with modest increases in overall risk compared to AGA (OR for SGA 1.32; 95 % CI 1.02–1.71 and OR for LGA 1.30; 95 % CI 1.00–1.71). In age-specific analyses, neither birth weight nor birth weight for gestational age were associated with risk of primary hypertension at 8–14 years of age (Table 3). However, birth weight 4,000 grams was associated with an increased risk of primary hypertension at 15–24 years of age (OR 1.63; 95 % CI 1.15–2.29) (Table 4). Both SGA (OR 1.56; 95 % CI 1.12–2.17) and LGA (OR 1.79; 95 % CI 1.29–2.50) were associated with increased risks of hypertension at 15–24 years of age (Table 4).

The ORs did not vary markedly when stratified by infant sex (data not shown) and none of the P -values for an interaction with infant sex approached statistical significance.

When we repeated our analysis of risk associated with primary hypertension at 15–24 years of age in the subset of the population with information on maternal education (110 cases/12,157 controls), we found no evidence of confounding (data not shown). When we repeated the analysis among those with information on maternal prepregnancy weight (95 cases/10,628 controls) we observed modest evidence of confounding (range of % change in OR: 4–15 %; data not shown). For example, the OR associated with SGA increased from 1.40 to 1.51 and the corresponding OR for LGA decreased from 2.23 to 1.98.

In subanalyses to assess the potential impact of underascertainment of primary hypertension due to children moving out of Washington State prior to developing the condition, we did not find evidence of an appreciable impact of this potential bias. The ORs for primary hypertension at 15–24 years of age were not meaningfully different when we excluded subjects whose parent(s) had a military occupation or whose mother was <18 years of age (247 cases/18,139 controls; data not shown); the ORs for hypertension at 15–24 years were 1.52 (95 % CI 1.05–2.18) for infants born SGA and 1.79 (95 % CI 1.26–2.55) for those born LGA. Results were not meaningfully different when we evaluated risk of primary hypertension at 15–<18 years of age (156 cases/20,772 controls; data not shown). For example, the ORs for hypertension at 15–<18 years of age were 1.55 (95 % CI 0.98–2.44) for SGA, and 1.70 (95 % CI 1.08–2.68) for LGA.

Finally, when we repeated our analyses of risk of primary hypertension at 15–24 years of age in the subset of subjects born at term (37–<42 weeks) to a mother without diabetes or hypertension during her pregnancy (194 cases/15,884 controls), our results were generally unchanged (data not shown). For example, the ORs associated with hypertension risk at 15–24 years of age were 1.52 (95% CI 1.01–2.29) for infants born SGA, and 1.73 (95 % CI 1.14–2.63) for infants born LGA. The exception was a slightly increased OR associated with birth weight <2,500 grams (OR 2.22; 95 % CI 0.87–5.70). The OR associated with birth weight 4,000 grams was 1.53 (95 % CI 1.01–2.31).

Discussion

In this large population-based case control study, we observed an increased risk of hospitalization with primary hypertension in children and young adults born SGA or LGA. These associations were due to an increased risk at 15–24 years of age; no associations were observed with risk at 8–14 years of age.

There are several limitations to this study. Blood pressure measures were not available. Instead, in this population-based vital records study, we had to rely on ascertainment of primary hypertension using hospital discharge data. Children with undiagnosed hypertension or who were treated only as outpatients would have been missed. Consequently, our results may be applicable to risk of more severe primary hypertension only. We also lacked information on hospitalizations that may have occurred outside of Washington State. If the misclassification of cases was unrelated to birth weight we would expect our risk estimates to be attenuated, otherwise our ORs may be over- or underestimates of the true association. In sensitivity analyses we found little evidence for this potential source of bias. The ORs for risk of hypertension at 15–18 years were similar to those for risk at 15–24 years of age, and

the estimates were generally similar when we restricted to subjects with non-military parents and whose mother was at least 18 years old.

Another limitation is potential misclassification of secondary hypertension as primary hypertension in the hospital discharge data, which could occur even though distinct ICD-9 codes exist for each condition. Such misclassification would likely be non-differential and bias our risk estimates toward the null. Any such misclassification may have had a greater impact on our estimates of risk associated with primary hypertension at 8–14 years of age as secondary hypertension is more common in this age group (Flynn et al., 2012; Wyszynska et al., 1992).

We were also limited in our ability to assess and adjust for some potential confounders as a result of missing data. Data on maternal education, a proxy for socioeconomic status, and prepregnancy weight, a proxy for body mass index (BMI), were available for children born since 1992 only. In subanalyses, we did not find evidence for confounding by maternal education, but we observed evidence of modest confounding by prepregnancy weight. Maternal BMI could be a stronger confounder than maternal prepregnancy weight. However, maternal BMI information was not available until 2003, the final birth year of this study population. We were also limited in our ability to ascertain severity of maternal hypertension and diabetes. However, residual confounding, if present, may have been modest, as our findings were generally unchanged in a subanalysis restricted to subjects born at term to mothers without hypertension or diabetes.

Numerous studies evaluating the association between birth weight and systolic blood pressure in children have reported inverse associations, typically, a 2–3 mmHg lower systolic blood pressure per 1 kilogram increase in birth weight (R. R. Huxley et al., 2000). Unlike the present analyses, most of these studies adjusted for the child's current weight (Edvardsson et al., 2012; R. R. Huxley et al., 2000), a variable that may be in a potential causal pathway between birth weight and hypertension (R. Huxley, Neil, & Collins, 2002; Tu, West, Ellison, & Gilthorpe, 2005). Our goal was to examine the association between birth weight and hypertension risk in children and young adults through whichever means birth weight may be acting to lead to hypertension, including possibly predisposing to a higher BMI in childhood.

An additional reason why it is difficult to directly compare our results to earlier studies is that in most prior studies, the outcome was systolic blood pressure modeled as a continuous variable (Edvardsson et al., 2012; R. R. Huxley et al., 2000), whereas we report risk of hospitalization with primary hypertension (yes/no). The U.S. Collaborative Perinatal Project cohort study, with 7 years of offspring follow-up for approximately 30,000 pregnant women who received care at 12 U.S. medical centers, reported unadjusted ORs of hypertension (yes/no) at 7 years of age associated with birth weight (Hemachandra, Howards, Furth, & Klebanoff, 2007). The OR for hypertension was 1.06 (95% CI: 0.98–1.14) per kilogram increase in birth weight when hypertension was defined as systolic blood pressure >90th percentile in the study population, and the corresponding OR was 1.11 (95% CI 1.03–1.21) when hypertension was defined as diastolic blood pressure > 90th percentile of the study population (Hemachandra et al., 2007). A strength of our analyses is that birth weight and

birth weight for gestational age were not modeled under the constraint of a linear relation with risk, which permitted detection of a possible U-shaped association.

Some studies of the relation between birth weight and hypertension or cardiovascular disease in adults have observed a U-shaped association (Baker, Olsen, & Sorensen, 2008; Palatianou et al., 2014); however most have found an increased risk associated with low birth weight only (Mu et al., 2012). Biologic mechanisms proposed to explain a possible association between low birth weight and hypertension include decreased fetal growth leading to alterations in the vascular system (e.g. increased aortic stiffness) (Edvardsson et al., 2012; Norman, 2008), and kidneys (Hughson et al., 2003). An association between low birth weight and reduced nephron number has been observed based on autopsy findings of adults and children without known kidney disease (Hughson et al., 2003). Pathways to alterations in the vascular system or reduced nephron numbers may include impaired endothelium-dependent vasodilation, excess fetal exposure to maternal glucocorticoids, and epigenetic changes during fetal life (Nuyt, 2008). Another consideration is that women who deliver low birth weight or SGA infants have been shown to be at increased risk of developing hypertension (Xu, Barinas-Mitchell, Kuller, Youk, & Catov, 2014) and cardiovascular disease (Bonamy, Parikh, Cnattingius, Ludvigsson, & Ingelsson, 2011; Pell, Smith, & Walsh, 2004) later in life, which suggests that delivering a low birth weight or SGA infant may be a sign of a woman's genetic predisposition to hypertension, which is then inherited by her offspring. High birth weight may increase risk of obesity (Eriksson, Tynelius, & Rasmussen, 2008; Monteiro, Victora, Barros, & Monteiro, 2003) and insulin resistance (Darendeliler et al., 2009; Mandy, 2014) in childhood – conditions which may predispose to hypertension (Bucher et al., 2013; Falkner et al., 2006; Mattoo, 2013). In the present analysis we did not observe an association with hospitalization risk at 14 years of age. One possible explanation is that any relevant biological processes which start *in utero* may take many years to ultimately result in hypertension.

In conclusion, we observed an increased risk of hospitalization with primary hypertension in children and young adults associated with both SGA and LGA. These associations were due to an increased risk of primary hypertension at 15–24 years of age; no association was observed with risk at 8–14 years of age. This study suggests that any relation between birth weight for gestational age and hypertension risk in adolescents and young adults may be nonlinear whereby infants on both ends of the spectrum may be at increased risk.

References

- Baker JL, Olsen LW, Sorensen TI. Weight at birth and all-cause mortality in adulthood. *Epidemiology*. 2008; 19(2):197–203. DOI: 10.1097/EDE.0b013e31816339c6 [PubMed: 18300695]
- Barker DJ, Bagby SP, Hanson MA. Mechanisms of disease: in utero programming in the pathogenesis of hypertension. *Nat Clin Pract Nephrol*. 2006; 2(12):700–707. DOI: 10.1038/ncpneph0344 [PubMed: 17124527]
- Bonamy AK, Parikh NI, Cnattingius S, Ludvigsson JF, Ingelsson E. Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth. *Circulation*. 2011; 124(25):2839–2846. DOI: 10.1161/CIRCULATIONAHA.111.034884 [PubMed: 22124377]

- Bucher BS, Ferrarini A, Weber N, Bullo M, Bianchetti MG, Simonetti GD. Primary hypertension in childhood. *Curr Hypertens Rep.* 2013; 15(5):444–452. DOI: 10.1007/s11906-013-0378-8 [PubMed: 23897423]
- Darendeliler F, Poyrazoglu S, Sancakli O, Bas F, Gokcay G, Aki S, Eskiuyurt N. Adiponectin is an indicator of insulin resistance in non-obese prepubertal children born large for gestational age (LGA) and is affected by birth weight. *Clin Endocrinol (Oxf).* 2009; 70(5):710–716. DOI: 10.1111/j.1365-2265.2008.03394.x [PubMed: 18759869]
- Edvardsson VO, Steinthorsdottir SD, Eliasdottir SB, Indridason OS, Palsson R. Birth weight and childhood blood pressure. *Curr Hypertens Rep.* 2012; 14(6):596–602. DOI: 10.1007/s11906-012-0311-6 [PubMed: 23054892]
- Eriksson M, Tynelius P, Rasmussen F. Associations of birthweight and infant growth with body composition at age 15--the COMPASS study. *Paediatr Perinat Epidemiol.* 2008; 22(4):379–388. DOI: 10.1111/j.1365-3016.2008.00944.x [PubMed: 18578752]
- Falkner B, Gidding SS, Ramirez-Garnica G, Wiltrout SA, West D, Rappaport EB. The relationship of body mass index and blood pressure in primary care pediatric patients. *J Pediatr.* 2006; 148(2):195–200. DOI: 10.1016/j.jpeds.2005.10.030 [PubMed: 16492428]
- Flynn J, Zhang Y, Solar-Yohay S, Shi V. Clinical and demographic characteristics of children with hypertension. *Hypertension.* 2012; 60(4):1047–1054. DOI: 10.1161/HYPERTENSIONAHA.112.197525 [PubMed: 22892814]
- Hemachandra AH, Howards PP, Furth SL, Klebanoff MA. Birth weight, postnatal growth, and risk for high blood pressure at 7 years of age: results from the Collaborative Perinatal Project. *Pediatrics.* 2007; 119(6):e1264–1270. DOI: 10.1542/peds.2005-2486 [PubMed: 17545358]
- Hughson M, Farris AB 3rd, Douglas-Denton R, Hoy WE, Bertram JF. Glomerular number and size in autopsy kidneys: the relationship to birth weight. *Kidney Int.* 2003; 63(6):2113–2122. DOI: 10.1046/j.1523-1755.2003.00018.x [PubMed: 12753298]
- Huxley R, Neil A, Collins R. Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? *Lancet.* 2002; 360(9334):659–665. DOI: 10.1016/S0140-6736(02)09834-3 [PubMed: 12241871]
- Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens.* 2000; 18(7):815–831. [PubMed: 10930178]
- Kaplan, N. Possible role of low birth weight in the pathogenesis of primary (essential) hypertension. In: Bakris, G., editor. *UpToDate*. Waltham, MA: UpToDate; 2014.
- Lydon-Rochelle MT, Holt VL, Cardenas V, Nelson JC, Easterling TR, Gardella C, Callaghan WM. The reporting of pre-existing maternal medical conditions and complications of pregnancy on birth certificates and in hospital discharge data. *Am J Obstet Gynecol.* 2005; 193(1):125–134. DOI: 10.1016/j.ajog.2005.02.096 [PubMed: 16021070]
- Mandy, G. Large for gestational age newborn. In: Weisman, L., editor. *UpToDate*. Waltham, MA: UpToDate; 2014.
- Mattoo, T. Epidemiology, risk factors, and etiology of hypertension in children and adolescents. In: Stapleton, F., editor. *UpToDate*. Waltham, MA: UpToDate; 2013.
- Monteiro PO, Victora CG, Barros FC, Monteiro LM. Birth size, early childhood growth, and adolescent obesity in a Brazilian birth cohort. *Int J Obes Relat Metab Disord.* 2003; 27(10):1274–1282. DOI: 10.1038/sj.ijo.0802409 [PubMed: 14513077]
- Mu M, Wang SF, Sheng J, Zhao Y, Li HZ, Hu CL, Tao FB. Birth weight and subsequent blood pressure: a meta-analysis. *Arch Cardiovasc Dis.* 2012; 105(2):99–113. DOI: 10.1016/j.acvd.2011.10.006 [PubMed: 22424328]
- Norman M. Low birth weight and the developing vascular tree: a systematic review. *Acta Paediatr.* 2008; 97(9):1165–1172. DOI: 10.1111/j.1651-2227.2008.00904.x [PubMed: 18554273]
- Nuyt AM. Mechanisms underlying developmental programming of elevated blood pressure and vascular dysfunction: evidence from human studies and experimental animal models. *Clin Sci (Lond).* 2008; 114(1):1–17. DOI: 10.1042/CS20070113 [PubMed: 18047465]

- Palatianou ME, Simos YV, Andronikou SK, Kiortsis DN. Long-term metabolic effects of high birth weight: a critical review of the literature. *Horm Metab Res*. 2014; 46(13):911–920. DOI: 10.1055/s-0034-1395561 [PubMed: 25473824]
- Pell JP, Smith GC, Walsh D. Pregnancy complications and subsequent maternal cerebrovascular events: a retrospective cohort study of 119,668 births. *Am J Epidemiol*. 2004; 159(4):336–342. [PubMed: 14769636]
- Rosner B, Cook NR, Daniels S, Falkner B. Childhood blood pressure trends and risk factors for high blood pressure: the NHANES experience 1988–2008. *Hypertension*. 2013; 62(2):247–254. DOI: 10.1161/HYPERTENSIONAHA.111.00831 [PubMed: 23856492]
- Sallout B, Walker M. The fetal origin of adult diseases. *J Obstet Gynaecol*. 2003; 23(5):555–560. DOI: 10.1080/0144361031000156483 [PubMed: 12963520]
- Savitz DA, Danilack VA, Engel SM, Elston B, Lipkind HS. Descriptive epidemiology of chronic hypertension, gestational hypertension, and preeclampsia in New York State, 1995–2004. *Matern Child Health J*. 2014; 18(4):829–838. DOI: 10.1007/s10995-013-1307-9 [PubMed: 23793484]
- Thompson, M., Dana, T., Bougatsos, C., Blazina, I., Norris, S. Screening for Hypertension in Children and Adolescents to Prevent Cardiovascular Disease: Systematic Review for the U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare and Research Quality; Feb. 2013 Evidence Synthesis No. 99. AHRQ Publication No. 13-05181-EF-1
- Tu YK, West R, Ellison GT, Gilthorpe MS. Why evidence for the fetal origins of adult disease might be a statistical artifact: the “reversal paradox” for the relation between birth weight and blood pressure in later life. *Am J Epidemiol*. 2005; 161(1):27–32. DOI: 10.1093/aje/kwi002 [PubMed: 15615910]
- Williams RL, Creasy RK, Cunningham GC, Hawes WE, Norris FD, Tashiro M. Fetal growth and perinatal viability in California. *Obstet Gynecol*. 1982; 59(5):624–632. [PubMed: 7070736]
- Wyszynska T, Cichocka E, Wieteska-Klimczak A, Jobs K, Januszewicz P. A single pediatric center experience with 1025 children with hypertension. *Acta Paediatr*. 1992; 81(3):244–246. [PubMed: 1511199]
- Xu J, Barinas-Mitchell E, Kuller LH, Youk AO, Catov JM. Maternal hypertension after a low-birth-weight delivery differs by race/ethnicity: evidence from the National Health and Nutrition Examination Survey (NHANES) 1999–2006. *PLoS One*. 2014; 9(8):e104149.doi: 10.1371/journal.pone.0104149 [PubMed: 25093324]
- Yoon EY, Cohn L, Rocchini A, Kershaw D, Freed G, Ascione F, Clark S. Antihypertensive prescribing patterns for adolescents with primary hypertension. *Pediatrics*. 2012; 129(1):e1–8. DOI: 10.1542/peds.2011-0877 [PubMed: 22144698]
- Zhou Y, Qian Z, Vaughn MG, Boutwell BB, Yang M, Zeng XW, ... Dong GH. Epidemiology of elevated blood pressure and associated risk factors in Chinese children: the SNEC study. *J Hum Hypertens*. 2015; doi: 10.1038/jhh.2015.104

Significance

What is already known on this subject?

Epidemiologic studies have reported an increased risk of childhood-onset primary (essential) hypertension in low birth weight infants. Less clear however, is whether high birth weight is also a risk factor for the development of primary hypertension in children.

What does this study add?

Both small and large birth weight for gestational age were associated with increased risks of hospitalization with primary hypertension. Our findings suggest a possible nonlinear (U-shaped) association between birth weight for gestational age and risk of hospitalization with primary hypertension in children and young adults.

Table 1

Infant and maternal characteristics of children born during 1987–2003 in Washington State who were hospitalized with primary hypertension at 8–24 years of age, and their controls

	Cases (N = 533)		Controls (N = 25,966)	
	n	%	n	%
Infant characteristics				
Sex				
Male	353	66.2	13,178	50.8
Female	180	33.8	12,788	49.3
Missing	0		0	
Gestational age at delivery (weeks)				
21–<32	4	0.8	234	0.9
32–<37	34	6.4	1,386	5.3
37–<39	111	20.8	4,651	17.9
39–<42	355	66.6	18,198	70.1
42–<45	29	5.4	1,497	5.8
Missing	0		0	
Race/ethnicity discordant from mother's				
No	488	94.9	23,596	95.1
Yes	26	5.1	1,207	4.9
Missing	19		1,163	
Maternal characteristics				
Age at delivery				
<25	198	37.2	9,332	35.9
25–29	163	30.6	7,717	29.7
30–34	110	20.6	6,048	23.3
35–49	62	11.6	2,869	11.1
Missing	0		0	
Race/ethnicity				
White	385	73.9	20,310	79.9
Black	25	4.8	931	3.7
Hispanic	49	9.4	2,044	8.0
Asian/Pacific Islander	37	7.1	1,505	5.9
Other	25	4.8	620	2.4
Missing	12		556	
Residence				
Rural	105	21.7	5,066	22.5
Urban	380	78.4	17,468	77.5
Missing	48		3,432	
Marital status				
Married	389	73.1	19,496	75.2
Single	143	26.9	6,434	24.8

	Cases (N = 533)		Controls (N = 25,966)	
	n	%	n	%
Missing	1		36	
Education (years) (deliveries in 1992 or later)				
<12	62	20.2	2,212	18.2
12	116	37.8	3,997	32.9
13–16	108	35.2	4,819	39.7
17	21	6.8	1,117	9.2
Missing	34		1,346	
Medicaid/non-private health insurance				
No	303	68.7	16,149	72.1
Yes	138	31.3	6,240	27.9
Missing	92		3,577	
Parity				
0	209	40.0	10,640	41.3
1	178	34.0	8,486	33.0
2	136	26.0	6,603	25.7
Missing	10		274	
Prepregnancy weight (lbs, quartiles) (deliveries in 1992 and later)				
<124	52	19.6	2,777	26.2
124–<140	64	24.2	2,663	25.1
140–<164	72	27.2	2,707	25.5
164	77	29.1	2,471	23.3
Missing	76		2,873	
Pregnancy weight gain (lbs, quartiles) (deliveries in 1989 and later)				
<23	90	24.9	3,837	23.0
23–<30	62	17.2	3,185	19.1
30–<40	116	32.1	5,363	32.2
40	93	25.8	4,289	25.7
Missing	90		4,182	
Smoked during pregnancy				
No	353	77.1	16,167	77.7
Yes	105	22.9	4,648	22.3
Missing	75		5,151	
Diabetes				
No	507	95.1	25,086	96.6
Pregestational	4	0.8	126	0.5
Gestational only	22	4.1	754	2.9
Missing	0		0	
Hypertensive disorder ^a				
None	465	87.2	24,020	92.5
Chronic hypertension	19	3.6	340	1.3

	Cases (N = 533)		Controls (N = 25,966)	
	n	%	n	%
Preeclampsia or eclampsia	41	7.7	1,262	4.9
Gestational hypertension	8	1.5	344	1.3
Missing	0		0	

^aCases and controls were first classified according to whether or not their mother had chronic hypertension during her pregnancy. All those whose mother did not have chronic hypertension during her pregnancy were then classified according to whether or not their mother had preeclampsia or eclampsia during her pregnancy. Finally, all those whose mother did not have preeclampsia or eclampsia during her pregnancy were classified according to whether or not their mother had a diagnosis of gestational hypertension (modified from Savitz et al.) (Savitz, Danilack, Engel, Elston, & Lipkind, 2014).

Table 2

Primary hypertension risk in children and young adults in relation to birth weight and birth weight for gestational age.

	Controls (N = 25,966)		Cases (N = 533)		OR	95% CI
	n	%	n	%		
Birth weight (grams) ^{a,b}						
<2,500	1,086	4.2	26	4.9	1.22	0.74–2.02
2,500–2,999	3,224	12.4	74	13.9	1.22	0.91–1.64
3,000–3,499	9,247	35.6	187	35.1	1.11	0.90–1.38
3,500–3,999	8,784	33.8	161	30.2	1.00	Reference
4,000–4,499	2,971	11.4	65	12.2	1.15	0.86–1.54
4,500	654	2.5	20	3.8	1.55	0.96–2.49
Birth weight for gestational age ^c						
Small	2,687	10.3	70	13.1	1.32	1.02–1.71
Appropriate	20,834	80.0	400	75.1	1.00	Reference
Large	2,516	9.7	63	11.8	1.30	1.00–1.71

^aORs adjusted for maternal age, birth year (1987–1990–1991–1994–1995–1998, and 1999–2003), gestational age, maternal hypertensive disorder, and infant sex.

^bOR for 4,000 grams versus 3,500–3,999 was 1.22 (95% CI: 0.94–1.60)

^cORs adjusted for maternal age, birth year (1987–1990–1991–1994–1995–1998, and 1999–2003), maternal hypertensive disorder, and infant sex.

Table 3

Primary hypertension risk in children 8–14 years of age in relation to birth weight and birth weight for gestational age

	Controls (N = 25,966)		Cases (N = 244)		OR	95% CI
	n	%	n	%		
Birth weight (grams) ^a						
<2,500	1,086	4.2	9	3.7	0.91	0.40–2.05
2,500–2,999	3,224	12.4	32	13.1	1.01	0.65–1.56
3,000–3,499	9,247	35.6	94	38.5	1.08	0.79–1.46
3,500–3,999	8,784	33.8	82	33.6	1.00	Reference
4,000	3,625	14.0	27	11.1	0.80	0.51–1.24
Birth weight for gestational age ^b						
Small	2,672	10.3	26	10.7	1.06	0.70–1.61
Appropriate	20,789	80.1	199	81.6	1.00	Reference
Large	2,505	9.7	19	7.8	0.80	0.49–1.28

^aORs adjusted for maternal age, birth year (1987–1990–1991–1994–1995–1998, and 1999–2003), gestational age, maternal hypertensive disorder, and infant sex.

Table 4

Primary hypertension risk in adolescents and young adults 15–24 years of age in relation to birth weight and birth weight for gestational age

	Controls (N = 20,772)		Cases (N = 289)		OR	95% CI
	n	%	n	%		
Birth weight (grams) ^a						
<2,500	857	4.1	17	5.9	1.54	0.81–2.94
2,500–2,999	2,555	12.3	42	14.5	1.46	0.98–2.17
3,000–3,499	7,422	35.7	93	32.2	1.14	0.84–1.55
3,500–3,999	6,983	33.6	79	27.3	1.00	Reference
4,000	2,955	14.2	58	20.1	1.63	1.15–2.29
Birth weight for gestational age ^b						
Small	2,198	10.6	44	15.2	1.56	1.12–2.17
Appropriate	16,570	79.8	201	69.6	1.00	Reference
Large	2,004	9.7	44	15.2	1.79	1.29–2.50

^aORs adjusted for maternal age, birth year (1987–1989–1990–1992, and 1993–1996), gestational age, maternal hypertensive disorder, and infant sex.