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Original Contribution

Evaluating the Relationship Between Birth Weight for Gestational Age and Adult Blood Pressure Using Participants From a Cohort of Same-Sex Siblings, Discordant on Birth Weight Percentile

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Many studies have described an inverse relationship between birth weight and blood pressure (BP). Debate continues, however, over the magnitude and validity of the association. This analysis draws on the Early Determinants of Adult Health study (2005–2008), a cohort of 393 US adults (mean age 43 years; 47% male), including 114 same-sex sibling pairs deliberately sampled to be discordant on sex-specific birth weight for gestational age (BW/GA) in order to minimize confounding in studies of fetal growth and midlife health outcomes. Every quintile increment in BW/GA percentile was associated with a 1.04–mm Hg decrement in adult systolic BP (95% confidence interval (CI): −2.14, 0.06) and a 0.63–mm Hg decrement in diastolic BP (95% CI: −1.35, 0.09), controlling for sex, age, site, smoking, and race/ethnicity. The relationship was strongest among those in the lowest decile of BW/GA. Adding adult body mass index to the models attenuated the estimates (e.g., to −0.90 mm Hg (95% CI: −1.94, 0.14) for systolic BP). In the sibling-pair subgroup, associations were slightly stronger but with wider confidence intervals (e.g., −1.22 mm Hg (95% CI: −5.20, 2.75) for systolic BP). In conclusion, we found a small inverse relationship between BW/GA and BP in cohort and sibling-pair analyses, but the clinical or public health significance is likely limited.

birth weight; blood pressure; cohort studies; gestational age; longitudinal studies; siblings

Abbreviations: BMI, body mass index; BP, blood pressure; BW, birth weight; BW/GA, sex-specific birth weight for gestational age; CI, confidence interval.

The relationship between lower birth weight (BW) and higher adult blood pressure (BP) is commonly cited as evidence for prenatal determinants of adult disease. Nearly 3 decades after an early description of this association (1), there is still debate as to its nature and its importance to clinical or public health. In the present study, same-sex siblings from 2 birth cohorts were deliberately sampled to be discordant on BW for gestational age (BW/GA) percentile. This unique design maximizes the potential for detecting the impact of BW/GA on adult BP and permits both cohort and sibling-pair analyses of the BW/GA–BP relationship, the latter of which may minimize confounding by genetics and shared early life environment.

There is compelling public health interest in understanding the etiology of high BP, because hypertension affects an estimated 1 billion people worldwide and kills approximately 9.4 million per year (2). In the United States, hypertension affects 29.6% of adults ≥18 years of age (3), incurring more than $93.5 billion annually in direct and indirect costs (4). Hypertension contributes to nearly half of all deaths from cardiovascular disease (5), the leading cause of disability-adjusted life years worldwide (6).

Associations between lower BW and higher BP in adulthood, as described by Barker et al. (1, 7, 8), have been replicated in cohorts worldwide (9–11). Huxley et al. (12) confirmed an inverse relationship between BW and systolic BP in a systematic review of 80 studies published between 1996 and 2000. In that meta-analysis, the association between BW and later systolic BP was small, with an increment of 0.4 mm Hg for each 1-kg decrement in BW (10). In their comparison of 5 European birth

cohorts, Hardy et al. (9) found likewise that BP increments associated with a 1-kg decrement in BW ranged between 1.1 mm Hg and 2.2 mm Hg. In a recent meta-analysis, Mu et al. (13) concluded that the relationship between low BW and hypertension was driven by an inverse association between BW and systolic BP.

Two limitations of most of the past analyses are 1) their focus on BW as an absolute measure, ignoring distinctions between babies "supposed" to be small and those born full-term but whose growth was restricted in utero, and 2) confounding by early life environment. The present study addresses these by exploring the relationship between BW/GA—an integrated measure of fetal growth—and adult BP in both cohort and sibling-pair analyses, as well as the possibility of mediation by adult body mass index (BMI).

METHODS

Study sample

This analysis uses data from the Early Determinants of Adult Health study, a cohort of same-sex siblings drawn from two birth cohorts: the New England Family Study (comprising the Boston, Massachusetts, and Providence, Rhode Island, sites of the Collaborative Perinatal Project), and the Child Health and Development Studies (drawn from members of Kaiser Permanente Health Plan in Oakland, California). Both recruited pregnant women from 1959–1966; at the time of the Early Determinants of Adult Health follow-up, the average offspring age was 43 years. The rationale and logistics of the Early Determinants of Adult Health study have been described previously (14). Briefly, a subject pool was identified of same-sex siblings born between 38 and 43 completed weeks of gestation who were discordant on BW/GA percentile. In the New England Family Study cohort, the lower BW/GA sibling was below the 20th percentile and the higher BW/GA sibling or siblings were at or above the 20th percentile, with at least 10 percentile points between them. Half of the Child Health and Development Studies subject pool was selected according to the same criteria; the other half included siblings whose BW/GA percentile differed by at least 10 points but where the lower BW/GA sibling was above the 20th percentile. Participants recruited from the subject pool had to live within commuting distance of the follow-up study sites in Boston, Massachusetts, or Oakland, California. Of the 393 recruits funding permitted to be assessed, 379 individuals who had BP measures were included in our full-cohort analysis, including 114 dyads in which both siblings had BP measures and were included in the sibling-pair analysis (Table 1).

Variables

BW and gestational age (determined by maternal self-report of last menstrual period) were abstracted from medical records. BW percentiles adjusted for sex and gestational age were calculated based on standards derived from US births in 2000 rather than standards contemporaneous with participants' birth years, because the recent tables allow for more continuous scaling of fetal growth (15, 16). Although the distribution may have shifted in the intervening years, the rank ordering of the percentiles would remain the same.

Height, weight, and BP were measured during clinic visits in adulthood. To minimize within-subject variation (17), BP was taken 5 times by trained nurses using a Dinamap monitor (Critikon, Inc., Johnson & Johnson, Tampa, Florida) with random zero and digital readout under standardized resting conditions using appropriate cuff sizes. The most extreme measurement was discarded and the remaining 4 were averaged. Demographic, lifestyle, and health information was collected from male participants via in-person interview; comparable information from female participants was collected via computer-assisted telephone interview as part of a related study (14).

Statistical analysis

We performed univariable analysis to assess the distributions of variables of interest and confirm that our outcome variables, systolic and diastolic BP, were normally distributed. We performed bivariable analyses to assess the relationships between potential covariates, selected based on theory and past literature, and BW/GA percentile as well as systolic and diastolic BP. Spearman correlation coefficients were used to compare continuous variables; one-way analysis of variance was used to compare continuous variables with categorical variables. Covariates associated with systolic or diastolic BP ($P < 0.05$) were selected for inclusion in subsequent analyses in order to account for some of the variance in the outcome measures and make it easier to detect small effects.

Reflecting the method of sampling our subjects (14) and following the model of our prior study on birth size and adult size conducted in this cohort (15), we divided the distribution of BW/GA percentiles into quintiles. We used generalized least squares random-effects models to perform linear regression while accounting for clustering by family, using BW/GA quintile as a linear predictor. We performed our non–sibling-pair analysis in 3 stages: first, regressing the outcomes on the exposure; second, adding covariates; and third, adding covariates and adult BMI. We repeated our analyses with stratification by sex and with a categorical predictor.

To explore the shape of associations between BW/GA percentile and BP, we created covariate-adjusted scatterplots of continuous BW/GA percentile versus the outcomes and regressed our outcome measures against a dichotomous BW/GA variable (<10th percentile vs. ≥10th percentile) to determine whether the associations were driven by those categorized as small for gestational age.

To control for confounding by early environment and to partially control for genetics (siblings who are not monozygotic twins share, on average, half of their genes), we explored whether BW/GA quintile predicted BP within families. Again following the model of our prior study (15), we used the 114 sibling pairs to create a series of exposure, outcome, and covariate difference measures (higher BW/GA sibling–lower BW/GA sibling) and repeated the sequence of regression models outlined above. All statistical procedures were performed using STATA, version 11.1 (StataCorp LP, College Station, Texas), and all statistical tests were 2-sided.

Table 1. Characteristics of the Study Sample From the Early Determinants of Adult Health Cohort, United States, 2005–2008

Characteristic	All Participants ($n = 379$)			Sibling Pairs ($n = 114$ pairs)		
	No. of Individuals	%	Mean (SD)	No. of Individuals	%	Mean (SD)
Birth weight centile adjusted for sex and gestational age						
Quintile 1: <20th	133	35.09		78	34.21	
Quintile 2: 20th–39th	87	22.96		57	25.00	
Quintile 3: 40th–59th	74	19.53		39	17.11	
Quintile 4: 60th–79th	53	13.98		35	15.35	
Quintile 5: 80th–100th	32	8.44		19	8.33	
Race/ethnicity						
White	262	69.13		153	67.11	
Black	69	18.21		49	21.49	
Other	48	12.66		26	11.40	
Sex						
Male	178	46.97		86	37.72	
Female	201	53.03		142	62.28	
Study site						
CHDS	231	60.95		142	62.28	
NEFS	148	39.05		86	37.72	
Current smoking status						
Smoker	66	17.41		31	13.60	
Nonsmoker	313	82.59		197	86.40	
Gestational age, weeks			39.8 (1.3)			39.9 (1.3)
Birth weight, g			3,289 (416)			3,282 (420)
Age, years			43.26 (2.06)			43.35 (2.00)
Body mass index[a]			29.4 (7.1)			29.7 (7.5)
Systolic BP, mm Hg			117 (16)			116 (14)
Diastolic BP, mm Hg			71 (10)			70 (9)

Abbreviations: BP, blood pressure; CHDS, Child Health and Development Studies; NEFS, New England Family Study; SD, standard deviation.

[a] Body mass index was calculated as weight (kg)/height $(m)^2$.

RESULTS

The median BW/GA percentile for our study population was the 34th percentile (percentile range, 0–98), reflecting the deliberate sampling technique described above, as well as an increase in BW/GA over time. The mean systolic BP was 117 mm Hg (standard deviation, 16; range, 81–185) and the mean diastolic BP was 71 mm Hg (standard deviation, 10; range, 43–104), both in line with national averages (18). The sample was 47% male, with a median age of 43 years (range, 39–48 years) and a mean adult BMI of 29.4 (standard deviation, 7.1; range, 16.8–70.5).

Among the 379 individuals with BP measures, BW/GA quintile was inversely but not statistically significantly associated with both systolic and diastolic BP when covariate-adjusted for sex, age, study site (New England Family Study vs. Child Health and Development Studies), current smoking (yes/no), and race/ethnicity (black, white, other). For every quintile increase in BW/GA, we observed a 1.04–mm Hg decrease in systolic BP (95% confidence interval (CI): −2.14, 0.06) and 0.63–mm Hg decrease in diastolic BP (95% CI: −1.35, 0.09). When we added a continuous measure of adult BMI—which was positively and statistically significantly associated with systolic and diastolic BP in bivariable analysis (Spearman correlation coefficients 0.38 and 0.22, respectively)—to the covariate-adjusted models, BP decrements per increment of BW/GA quintile were reduced to 0.90 and 0.59, respectively (Table 2). The results were comparable when we stratified by sex and when we modeled the BP quintiles as a categorical variable.

Nonparametric locally weighted, scatterplot-smoothed regression curves superimposed on covariate-adjusted scatterplots indicated that the inverse association between BW/GA

Table 2. Estimated Mean Change in Adult Blood Pressure Per Quintile Increment in Sex-Specific Birth Weight for Gestational Age, Early Determinants of Adult Health Cohort, United States, 2005–2008

Blood Pressure Component	Among Individual Participants						Between Siblings					
	Unadjusted ($n = 379$)		Adjusted[a] ($n = 379$)		Adjusted[a] Plus BMI ($n = 376$)		Unadjusted ($n = 114$)		Adjusted[b] ($n = 114$)		Adjusted[b] Plus BMI ($n = 111$)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Systolic BP, mm Hg	−1.40	−2.59, −0.20	−1.04	−2.14, 0.06	−0.90	−1.94, 0.14	−1.52	−5.47, 2.42	−1.22	−5.20, 2.75	−2.00	−5.89, 1.89
Diastolic BP, mm Hg	−1.01	−1.79, −0.23	−0.63	−1.35, 0.09	−0.59	−1.31, 0.13	−1.34	−3.90, 1.22	−1.23	−3.82, 1.35	−1.32	−3.99, 1.35

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval.

[a] Adjusted for sex, study site (New England Family Study vs. Child Health and Development Studies), current smoking status, and race/ethnicity.

[b] Adjusted for differences in age and current smoking status.

percentile and both systolic and diastolic BP was strongest among individuals at the lowest end of the BW/GA spectrum. When we regressed the outcome variables on a covariate-adjusted dichotomous BW/GA predictor (<10th percentile vs. ≥10th percentile), those in the lowest 10th percentile for BW/GA had on average 3.28–mm Hg higher systolic BP (95% CI: −0.39, 6.94) and 0.89–mm Hg higher diastolic BP (95% CI: −1.66, 3.43) than the remaining cohort.

Analyzing the 114 sibling pairs, we performed multilevel linear regression of the difference between siblings' systolic and diastolic BP on the difference between their BW/GA quintile. Although the magnitudes of the adjusted coefficients were slightly larger than in the full cohort analysis (−1.22 vs. −1.04 for systolic, −1.23 vs. −0.63 for diastolic), the confidence intervals were wide and included the null in both covariate-unadjusted and covariate-adjusted relationships (Table 2).

DISCUSSION

Among 379 participants of the Early Determinants of Adult Health study, we found inverse but not statistically significant relationships between BW/GA quintile and both systolic and diastolic BP, when controlling for sex, age, cohort, smoking status, and race/ethnicity. Among the 114 sibling pairs, we found stronger magnitudes of association but wider confidence intervals.

The results using all 379 participants are consistent with previous studies that found a small inverse relationship between BW and BP. Whereas many prior studies found adjustment for adult BMI strengthened the relationship (9–11), we found the associations to be attenuated when adult BMI was added to the non–sibling-pair models. This attenuation suggests that BMI may be a relevant intermediary in the pathway between BW/GA and BP (19). The results of the sibling-pair analyses are consistent with a meta-analysis of prior research using monozygotic twins that found each 1-kg increment in BW to be associated with a 1.47–mm Hg decrement in systolic BP, although the results were not statistically significant (10). The larger effect estimates in our sibling-pair versus nonpair analyses suggest that common genetic and/or early environmental factors may have blunted the strength of the associations seen in the overall analyses and that the association may be driven by maternal, paternal, or environmental factors that differed between pregnancies or from nonshared genes (20, 21). These conclusions are speculative, however, because of the imprecision of our finding within sibling pairs, which results from the small sample size of sibling pairs (22).

The theory of fetal origins of adult disease is predicated on the assumption that changes in fetal physiology and metabolism may have lifelong effects on health. It has been hypothesized that restricted intrauterine growth may affect fetal vascularization and kidney development in such a way as to precipitate hypertension later in life (23). We were not able to assess these physiologic changes in this cohort. The main strengths of our study were 1) the use of BW/GA, which mitigates the influence of gestational age that may drive the results of studies that use BW alone, and 2) a sibling-pair design tailored to explore outcomes of discordant BW/GA, with participants drawn from well-defined birth cohorts. Limitations of our study include its small sample size, especially of sibling pairs; the use of reported last menstrual period to calculate gestational age, because ultrasound was not prevalent at the time; the inability to account for daily variance in BP; and the restricted generalizability of our results to full-term births.

Our findings, using fetal growth operationalized as the exposure variable BW/GA, accord with small inverse associations found by many of our predecessors who used BW and suggest that the clinical importance of prenatal origins of adult BP is limited. Future studies should focus on modifiable factors, either during gestation or more proximal to the outcome, that may have greater public health relevance as predictors of adult BP.

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