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Race-specific relationship of birth weight and renal function among healthy young children

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Abstract

Background—Low birth weight is associated with diminished renal function. However, despite African Americans being at increased risk of low birth weight and chronic kidney disease, little is known about the association between birth weight and renal function in diverse groups. We examined racial differences in the relationship of birth weight and renal function among healthy, young children.

Methods—Birth weight and serum creatinine were available on 152 children (61.8% African American; 47.4% female) from a birth cohort. Estimated glomerular filtration rate (eGFR) was calculated using the bedside Schwartz equation and gender- and gestational-age adjusted birth weight Z-scores using the US population as a reference. Race-specific linear regression models were fit to estimate the association between birth weight Z-score and eGFR.

Results—Mean age was 1.5±1.3 years at first eGFR measurement. African Americans had lower eGFR than non-African Americans (median eGFR= 82 vs. 95 mL/min per 1.73m^2; P=0.06). Birth weight was significantly and positively associated with eGFR among African-American (P=0.012) but not non-African-American children (P=0.33).

Conclusions—We provide, for the first time, evidence suggesting birth weight is associated with renal function in African-American children. Future work is needed to determine if prenatal programming helps explain racial disparities in adult health.

Keywords

prenatal programming; race; disparity; birth weight; renal function

Introduction

Increasing evidence suggests that the predisposition to adult chronic disease may originate in the prenatal and gestational periods [1, 2]. Low birth weight is associated with smaller

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kidneys and fewer nephrons [3-7], and this pathophysiological change may predispose smaller infants to future kidney and cardiovascular diseases. In a recent systematic review, low birth weight individuals were estimated to have a 70% higher risk of developing chronic kidney disease (CKD) in later life [8]. Both conditions are more prevalent in African Americans relative to other race/ethnic groups in the United States. Chronic diseases of the kidney disproportionately affect African-American adults; for example, among Medicare patients, 11.4% of African Americans have prevalent CKD, compared to only 7.3% of Caucasians [9, 10]. There is a similar racial disparity in birth outcomes; African-American women are 50% more likely to have preterm deliveries and their infants are over twice as likely to be small-for-gestational age (SGA) as compared to non-Hispanic whites [11]. Birth weight depends on a complex interaction of many factors, including exposures occurring both before conception and during pregnancy [12]. Despite notable differences in the pregnancy experiences of African American compared to other American women, little is known about racial variation in the relationship between fetal and early life exposures with renal function in early childhood.

Fetal growth is associated with renal function in adults in some [13-15] but not all studies [16] and there are limited studies examining fetal growth with renal function in children. In a study comparing 40 children who were premature and weighed <1000 g at birth (mean age 8.6±1.8 years) to 43 control children (mean age 8.5±1.8 years), creatinine clearance was significantly lower in children born premature (117±17 m/min) than controls (131±17 m/min) [17]. In a study of 178 children born premature or SGA and 717 children with normal birth weight (all of Danish origin), ultrasonography was performed at 0, 3 and 18 months to determine kidney size [18]. At all ages, weight-for-gestational age was positively associated with kidney volume and with relative kidney growth from ages 0 to 18 months [18]. In a sample of 73 healthy Caucasian children (mean age 9.5±0.4 years), lower birth weight was associated with increased serum creatinine (SCr) and decreased estimated glomerular filtration rate (eGFR) [19]. A similar birth weight and eGFR relationship was found in study of 166 children (3-18 years) in Greece [20] and in a study of 50 white children in Switzerland [21].

Despite a similar burden of kidney disease and poor pregnancy outcomes among African Americans, there have been limited studies examining the race-specific relationship of birth weight and renal function. The data that do exist are conflicting and are largely limited to autopsy studies in adults. In one autopsy study of 62 African-American and 60 European American adults, overall, birth weight was positively correlated with total glomerular number; by race, however, birth weight was significantly correlated with total glomerular number in European Americans but not African Americans [6]. In contrast, in another autopsy study of slightly younger adults, birth weight was associated with glomerular number in both African Americans and European Americans [7].

To our knowledge, no studies have examined the race-specific relationship between birth weight and renal function in a pediatric population, thus, we examined this relationship in healthy, young children who were participants in the Wayne County Health, Environment, Allergy, and Asthma Longitudinal Study (WHEALS) birth cohort.

Methods

Study Population

WHEALS, described in detail elsewhere [22, 23], recruited pregnant women with due dates from September, 2003 through January, 2008, and who were seeing a Henry Ford Health System (HFHS) practitioner at 1 of 5 clinics to establish an unselected birth cohort. All women were in their second trimester or later, were aged 21-49 years, and were living in a

predefined geographic area in western Wayne County that included the western portion of the city of Detroit as well as the suburban areas immediately surrounding the city. WHEALS participants have been followed extensively for allergic disease and related phenotypes [22, 23] and the current investigation is a secondary data analysis of this cohort. All participants provided written, informed consent and the study protocols were approved by the Institutional Review Board at HFHS.

The WHEALS cohort included 1258 babies. We excluded 18 twins. As some births occurred at non-HFHS hospitals, birth weight data was only available on 1142 babies (92.1%). Renal function measures were only available on a subset of WHEALS children obtaining their medical care at HFHS. A total of 226 renal function measures on 165 unique children with birth weight measures were available. Height was not available in 13 children with renal function measurements, precluding estimation of GFR. The final analytic sample consisted of 152 children with a total of 212 renal function measurements.

Renal Function

Automated databases, which include all laboratory test results for any encounter within HFHS, were searched based on WHEALS children's medical record number for SCr test results. All SCr measures were obtained from the same hospital-based laboratory system, thus the method used to estimate SCr was consistent for all participants. All SCr measures obtained were part of the child's routine medical care. Typical reasons for ordering these metabolic/biochemical panels included: abdominal pain, acute gastroenteritis, or fever, in addition to being ordered as part of a well-child visit. The Bedside Schwartz equation was used to calculate eGFR as: eGFR (mL/min per 1.73 m^2) = 0.413 × (Height (cm)/ SCr (mg/dL)) [24, 25]. Child height was abstracted from the electronic medical record (EMR) on or near the date of SCr measure. When height at SCr measure was not available, a height before and after the SCr measure was obtained and linear interpolation was done to calculate estimated height at SCr measure.

Birth Weight and Gestational Age

Delivery records for WHEALS women were abstracted to obtain birth weight and gestational age at time of delivery. Gender- and gestational-age adjusted birth weight Z-scores were calculated using the US population as a reference [26]. Race was defined as maternal self-reported race.

Statistical Analysis

Chi-square tests were used to compare dichotomous variables between African-American and non-African-American children. For normally distributed continuous variables, such as age, Student's t-tests were performed but as eGFR had a skewed distribution a Wilcoxon Rank Sum test was used to compare between the two race groups. eGFR was log-transformed prior to inclusion in all models to reduce non-normality.

Linear regression employing generalized estimating equations (GEE) to account for within child correlation was then performed with log-transformed eGFR as the outcome and birth weight (Z-score) as the main predictor. Race-specific models were fit unadjusted and adjusted for child's age at SCr measure. GEE allowed us to adjust for child age at measure, as well as reduce potential bias in creating a summary statistic of all available eGFR measures [27].

Results

Table 1 presents characteristics of the study population, by race. Among non-African Americans, 39 (67.2%) were Caucasian. Overall, SCr values are within the ranges reported in other healthy pediatric populations [28, 29]. eGFR was lower among African-American compared to non-African-American children; however, it did not achieve statistical significance (P=0.06). There was no difference in race, birth weight, or gestational age between WHEALS children with and without SCr measures (data not shown).

The average number of SCr measures per child was 1.4±0.9. Most children (76.3%; n=116) had 1 SCr measure; 23 (15.1%), 6 (4.0%), 4 (2.6%), 2 (1.3%) and 1 (0.7%) had 2, 3, 4, 5 and 6 measures, respectively.

Overall, birth weight Z-score was statistically significantly and positively associated with eGFR (P=0.026). For every one-unit increase in birth weight Z-score, there is an expected 0.06±0.03 unit increase in mean log (eGFR).

The race-specific relationship of birth weight Z-score and eGFR is presented in Table 2. Birth weight Z-score was not associated with eGFR in non-African-American children. In unadjusted models, birth weight Z-score was positively associated with log (eGFR) in African Americans (P=0.005). After adjustment for child's age at measure, birth weight Z-score remained significantly and positively associated with log (eGFR) among African-American children (P=0.012). For every one-unit increase in birth weight Z-score, among African-American children, there is an expected 0.089 unit increase (or 9% increase) in mean log (eGFR). Inferences remained the same after adjusting for additional available covariates known to be associated with birth weight (maternal prenatal smoking, being first-born, and maternal age at birth; data not shown).

We conducted a sensitivity analysis among our non-African-American children, restricting just to Caucasian children. In this sub-group, birth weight Z-score was also not associated with eGFR. We also conducted a sensitivity analysis removing children with ≥4 SCr measures; inferences remained the same after removing these participants, suggesting that these children with the most measures were not unduly influencing model results. Finally, restricting to a subsample of children with birth weight in the normal range (>2500 g) [11] (N=128) inferences were the same; thus, even within the normal range of birth weight, African-American children with lower birth weight Z-scores had diminished renal function.

We *a priori* calculated eGFR with the 2009 bedside Schwartz equation which has not been validated outside the range of 15 to 75 ml/min per 1.73m^2 [24, 25]. However, inferences were the same using previous versions of the eGFR equation [30, 31]. Additionally, age 3 years appears to be a critical age for the bedside Schwartz equation to switch from over to underestimating eGFR [32]; repeating the analysis in 129 children with 178 measures taken at ages <3 years, all model inferences were the same.

Discussion

The current study describes, for the first time, an association between birth weight and renal function, measured as eGFR, in African-American but not in non-African-American children. Strengths of the current study include use of a well-defined birth cohort unselected on the basis of any risk factors with considerable racial and sociodemographic diversity and the use of medical chart review to obtain birth weight and gestational age, rather than relying on self-reported measures.

During gestation, nephrogenesis continues until week 36, making the kidney particularly susceptible to prenatal insults [33]. It is estimated that for every 1-kg increase in birth weight, glomeruli number increases by approximately 260,000 [7, 34]. Reduced nephron number is associated with compensatory mechanisms including glomerular hyperfiltration, which can ultimately lead to CKD; this process is exacerbated by hypertension [35, 36]. Potential mechanisms for the reduction in nephron number during gestation include alterations in DNA methylation, increased apoptosis in the developing kidney, renin-angiotensin system alterations, vitamin A and other nutritional deficiencies, and increased fetal glucocorticoid exposure [37, 38].

African-American infants are more likely to be pre-term or SGA [11]. Our results provide preliminary evidence that some of the racial disparities in adult chronic disease, such as kidney disease, may have its origins in the prenatal period and may be evident in early childhood. Previous studies in adults have provided contradictory evidence for a racial difference in the relationship between birth weight and glomerular number [6, 7], however, these results may be subject to the inherent bias in autopsy studies [39]. Glomerular function and/or size, rather than total number, may be a better indicator of renal health; for instance, hypertensive African-American adults have a greater total glomerular volume, which may reflect glomerular filtration rate, compared to their Caucasian counterparts [6]. Better identification of pre-conceptual or prenatal risk factors for lower birth weight and prematurity may lead to interventions to reduce disparities in both birth outcomes and adult disease. Examples include maternal smoking, which is associated with kidney volume in the offspring [40] and preeclampsia, which is known to impact birth outcomes [41] and the maternal kidney [42], and could potentially damage the developing fetal kidney.

Evidence from studies of a related phenotype (blood pressure) suggests a similar race-specific birth weight-health outcome relationship in children. In the US National Collaborative Perinatal Project, birth weight was positively associated with systolic blood pressure (SBP) measured at age 7 years in African Americans but not whites [43]. In the Successive Small for Gestational Age Study, birth weight was inversely associated with SBP in white children, but was positively associated with SBP in African-American children at age 5 years [44]. Finally, among older children (ages 15 to 17 years) participating in the Bogalusa Heart Study, birth weight accounted for racial differences in blood pressure, suggesting that improving birth outcomes among black women could reduce hypertension at a later age [45]. The race-specific association detected in the current study may be due to an underlying pathophysiological difference in the kidneys, a lower power to detect an association in our non-African-American sample or simple chance.

Nephron adaptation, in which structural and functional changes in the available nephrons occur to compensate for reduce nephron number, generally preserves GFR.[46] Given this adaptive mechanism, it may be surprising to detect an association between birth weight and eGFR among young children, however, others have demonstrated similar associations in slightly older children [19-21]. In animal models, protein intake modifies nephron adaptation [46]. Formula-fed infants have marked differences in kidney size relative to breast-fed infants, most likely attributable to increased protein levels in formula [47]. African-American women are less-likely to initiate and sustain breast-feeding [48] and African-American children consume more protein than Caucasian children [49]. These early-life feeding practice differences may also partially explain why we are detecting an association in our African-American but not non-African-American children (i.e. in the kidney susceptible to further injury due to low birth weight, early life feeding practice differences may provide the second “injury” needed to cause demonstrable function differences at an early age).

Extracellular volume depletion (EVD) may cause a temporary increase in SCr and a corresponding decrease in eGFR. Examining the EMR of a subset of children with the highest SCr values, there was little evidence these values were elevated due to EVD or prerenal azotemia. We are relying on measures of SCr that were obtained during routine clinical care and which were run as part of a metabolic or biochemical laboratory profile. Although there was no difference in race, birth weight, or gestational age between WHEALS children with and without SCr measures, it is possible that this is a highly selected group of children, which may reduce our generalizability. Age at SCr measurement varied across the study population; although we adjusted for age at measurement, we are unlikely fully accounting for normal variability in renal function as part of growth and development. Still needed is replication of these results in a larger and broader cohort of similarly aged children.

Linear interpolation was done to estimate height at SCr measure for 71 observations. However, growth in stature, especially among pre-pubertal children, is not a steady process, but rather is typically comprised of periods of spurts and stasis [50]. Any misclassification of height would most likely be non-differential with respect to both birth weight and renal function, and thus would attenuate our results.

Staples et al. (2010) recently validated the 2009 bedside Schwartz equation in a predominantly non-CKD sample, suggesting that the equation is valid even in very young children [32]. Under age 3 years the equation tends to overestimate eGFR while it underestimates eGFR in older children [32]. In our sample we would expect the bias to be non-differential with respect to birth weight, and thus if bias was impacting the results demonstrated here, it would attenuate our results.

In children, renal function, measured as SCr, is associated with renal size [36]. However, serum cystatin C may be a better marker of renal function in children, as it is less influenced by the increases in muscle mass that are part of normal growth [29]. Given the known difference in SCr between African Americans and Caucasians, even at relatively young ages (12-19 years) [51], and the lack of a childhood equation for eGFR with different coefficients for race (in contrast to adult eGFR equations which do take into account race and gender) future studies examining fetal origins of racial disparities in renal function should consider an additional measure of renal function such as cystatin C.

Anthropometric and metabolic characteristics of the children were largely unavailable at the time of SCr measurement, although there is evidence that they are associated with eGFR in healthy children (e.g. increasing numbers of metabolic syndrome components are positively associated with eGFR) [20]. Future studies should examine body composition, as well as other markers of renal and cardiovascular health (e.g. blood pressure) within the context of the relationship between birth weight and renal function.

Summary

We provide preliminary evidence that lower birth weight is associated with diminished renal function in healthy, young African-American children. Future work is needed to determine if prenatal programming events help explain racial disparities in adult kidney health.

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Table 1

Descriptive statistics of study population, by race; data are N (%) or mean (standard deviation) unless otherwise noted

	African American (N=94)	Non-African American (N=58)	*P*
Maternal Factors at delivery			
Married	47 (50.0%)	50 (86.2%)	<0.01
≥High school education	76 (80.9%)	52 (89.7%)	0.15
Age (years)	29.1 (5.7)	30.1 (5.3)	0.32
Prenatal smoking	9 (9.6%)	5 (8.6%)	0.84
Total household income <$40,000[a]	32 (40.0%)	13 (23.2%)	0.04
Child factors			
Female	44 (46.8%)	28 (48.3%)	0.86
Firstborn	36 (38.3%)	31 (53.4%)	0.07
Birth weight (g)	3242 (612)	3301 (466)	0.53
	range 1032 - 5150	range 2360 – 4338	
Birth weight Z-score	−0.25 (1.00)	−0.11 (1.00)	0.40
Gestational age (weeks)	38.6 (1.5)	38.8 (1.6)	0.45
	range 32 - 42	range 33 - 41	
Child factors at 1st measurement			
Age (years)	1.5 (1.3)	1.6 (1.4)	0.52
Height (cm)	77 (18)	78 (17)	0.57
SCr (mg/dL)	0.38 (0.12)	0.36 (0.15)	0.29
eGFR (mL/min per 1.73 m^2)[b]	82 (71-99)	95 (69-130)	0.06

[a] 16 refused to answer

[b] Data are median (Interquartile range) SCr, serum creatinine; eGFR, estimated glomerular filtration rate

Table 2

Unadjusted and adjusted relationship of birth weight Z-score with log (estimated glomerular filtration rate), by race

	African American		Non-African American	
Birth weight Z- score	**Parameter estimate[a] ±se**	***P***	**Parameter estimate[a] ±se**	***P***
Unadjusted	0.101 ± 0.036	0.005	0.010 ± 0.029	0.73
Adjusted for child age	0.089 ± 0.036	0.012	−0.025 ± 0.025	0.33

se, standard error

[a]Due to log-transformation of dependent variable, parameter estimate (β) can be interpreted as ($e^{\beta} - 1$)% change with every 1 unit increase in birth weight Z-score. So for African-American children, unadjusted, ($e^{0.101} = 1.11$) is an 11% increase in eGFR, on average, when comparing children with a group of children with 1-unit higher Z-score on their birth weight. This contrasts with a 1% ($e^{0.010} = 1.01$; non-significant at P=0.73) change in the unadjusted non-African-American children.