Low birth weight is associated with chronic kidney disease only in men

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The association of low birth weight and chronic kidney disease was examined in a screened volunteer population by the National Kidney Foundation's Kidney Early Evaluation Program. This is a free, community-based health program enrolling individuals aged 18 years or older with diabetes, hypertension, or a family history of kidney disease, diabetes, or hypertension. Self-reported birth weight was categorized and chronic kidney disease defined as an estimated glomerular filtration rate less than 60 ml per min per 1.73 m^2 or a urine albumin/creatinine ratio $\geqslant$30 mg/g. Among 12 364 participants, 15% reported a birth weight less than 2500 g. In men, significant corresponding odds ratios were found after adjustment for demographic characteristics and health conditions to this low birth weight and chronic kidney disease, but there was no association among women. There was no significant interaction between birth weight and race for either gender. Efforts to clinically understand the etiology of this association and potential means of prevention are essential to improving public health.

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Low birth weight has been hypothesized to lead to systemic arterial hypertension and chronic kidney disease (CKD) in adult life.[1,2] Evidence has shown a direct relationship between birth weight and nephron number.[3–6] Some studies showed that birth weight was positively associated with glomerular filtration rate (GFR)[7,8] and negatively associated with serum creatinine level.[7] The association of low birth weight and increased risk of urinary albumin excretion measured by albumin/creatinine ratio (ACR; 30 mg/g or greater) was observed among Pima Indians with type II diabetes mellitus[9] and among Aborigines living in Australia.[10] Finally, the association between low birth weight and end-stage renal disease was confirmed in the southeastern United States[11] and among young adults with diabetes or hypertension in the Medicaid population.[12]

Study samples described in published studies of the association of low birth weight and CKD in adult life are rather small in size or limited to specific racial or ethnic groups. The Kidney Early Evaluation Program (KEEP), conducted by the National Kidney Foundation, is the first national study that targets adult populations at high risk for CKD. KEEP is a free, community-based screening program for CKD, enrolling individuals aged 18 years or older with a personal history of diabetes or hypertension or with a first-degree relative with kidney disease, diabetes, or hypertension. As part of the routine evaluation, participants are asked to recall their birth weights. Since its origin in 1997, KEEP has screened more than 70 000 participants in 48 states. Therefore, a large geographically, racially, and ethnically diverse population is now available to study the association between birth weight and prevalent CKD.

RESULTS

Among the 12 364 eligible KEEP participants included in this study, mean age was 49.1 years (s.d., 13.5); 28.7% were African American and 76.4% female. More than two-thirds of participants reported post-high-school education. Overall, 84.4% had health insurance coverage, 23.2% had been previously diagnosed with diabetes, 48.1% had been told that they had high blood pressure, 16.2% had

cardiovascular disease, and 23.7% had a family member with kidney disease.

The mean reported birth weight was 3195 g (median, 3175; s.d., 781). The distribution of participants in birth-weight categories stratified on gender is presented in Figure 1. The distributions of birth-weight categories within each characteristic are shown in Table 1. The 1845 participants whose birth weight was less than 2500 g were more likely to be African American or female, to have lower educational levels, and to report pre-existing comorbid conditions (diabetes, hypertension, or cardiovascular disease). Participants with high birth weights were more likely to have diabetic mothers.

We tested the interactions between birth weight and gender or race in the associations with CKD. The interaction between birth weight and gender was significant before adjustment for covariates ($P = 0.03$). Therefore, we present the prevalence of each of three kidney disease outcomes by birth-weight categories after gender stratification in Table 2. The prevalence of kidney disease outcomes is also presented for white and African American participants within each gender. By gender, a U-shaped trend was evident for all kidney disease outcomes for men but not for women; men with low birth weight (<2500 g) or high birth weight ($\geqslant 4500$ g) had significantly higher prevalence of each of the three kidney disease outcomes than men with normal birth weight (2500–4499 g). The association of birth weight with kidney disease outcomes was evident for white but not for African American men. However, the three-way interaction among birth weight, gender, and race was not significant.

The interaction between birth weight and gender was still significant after adjustment for age; race; self-reported diabetes, hypertension, or cardiovascular disease; family history of kidney disease; region; education; insurance status; and hypertension control ($P = 0.03$). Adjusted odds ratios of CKD by gender and birth weight are presented in Figure 2 for men and Figure 3 for women. The U-shaped association between birth weight and CKD was still evident for men after controlling for covariates. Compared with men whose birth weight was between 3000 and 3999 g, those whose birth weight was less than 2500 g had 1.65-fold odds (95% confidence interval 1.24–2.20) of CKD and those with birth weight 4500 g and more had 1.41-fold odds (95% confidence interval 1.06–1.88) of CKD. Older age and a history of disease were significantly positively associated with CKD prevalence. Race identified as African American, region other than south, and hypertension control were significantly negatively associated with CKD prevalence.

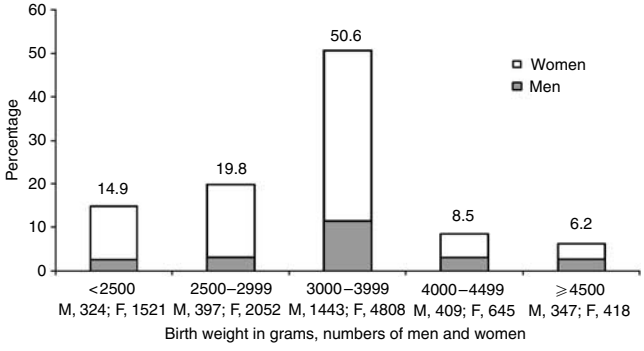

Figure 1 | Distribution of participants in birth-weight categories.

DISCUSSION

In this study, we demonstrate in a large population, aged 18–75 years, with a history of diabetes or hypertension or a family history of diabetes, hypertension, or kidney disease, a U-shaped association between birth-weight categories and several kidney disease outcomes among men but not women. These associations persisted despite multivariable adjustment for several other important kidney disease risk factors, and were similar in further stratifications on race within each gender. These findings are important in better identifying high-risk populations at an early stage in an effort to stem the epidemic of CKD.

In part, our findings showing the association of low and high birth weight with CKD are consistent with prior studies. Our finding of a strong association of low birth weight with kidney disease is consistent with several previous studies.[9–12] Our finding of an association between high birth weight and higher prevalence of CKD is partially consistent with two prior studies.[9,11] Nelson *et al.*[9] found a U-shaped association between birth weight and prevalence of elevated urinary albumin levels defined by ACR 30 mg/g or greater in 308 Pima Indians aged 20–61 years with type II diabetes. In that study, subjects with birth weight <2500 g had a significantly higher risk of ACR 30 mg/g or greater than those with normal birth weight. The association between birth weight $\geqslant 4500$ g and a higher risk of ACR 30 mg/g or greater became insignificant after adjusting for gender, duration of diabetes, HbA1c value, and blood pressure.[9] However, these authors did not find a gender interaction. In a case–control study of the association of birth weight and end-stage renal disease, Lackland *et al.*[11] also found a U-shaped relationship, with the highest odds ratio of renal failure in the lowest birth weight group. There was no association between birth weight $\geqslant 4000$ g and higher prevalence of renal failure in men (odds ratio 1.0). In women, birth weight $\geqslant 4000$ g was associated with a higher risk of renal failure but it was insignificant (odds ratio 1.4, 95% confidence interval 0.8–2.4). However, the association between birth weight $\geqslant 4000$ g and higher risk of renal failure was significant for persons with diabetes as the primary cause of end-stage renal disease (odds ratio 2.4, 95% confidence interval 1.3–4.2).[11]

Researchers have hypothesized potential mechanisms leading to kidney disease in persons with low birth weight.[1,2,13,14] For example, Brenner and Chertow[2] hypothesized that low birth weight due to intrauterine growth retardation or premature birth leads to impaired renal development, which reduces filtration surface area, and therefore leads to systemic glomerular hypertension, further