Prenatal Risk Factors for Childhood CKD

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ABSTRACT

Development of CKD may be programmed prenatally. We sought to determine the association of childhood CKD with prenatal risk factors, including birth weight, maternal diabetes mellitus (DM), and maternal overweight/obesity. We conducted a population-based, case-control study with 1994 patients with childhood CKD (<21 years of age at diagnosis) and 20,032 controls in Washington state. We linked maternal and infant characteristics in birth records from 1987 to 2008 to hospital discharge data and used logistic regression analysis to assess the association of prenatal risk factors with childhood CKD. The prevalence of CKD was 126.7 cases per 100,000 births. High birth weight and maternal pregestational DM associated nominally with CKD, with respective crude odds ratios (ORs) of 1.17 (95% confidence interval [95% CI], 1.03 to 1.34) and 1.97 (95% CI, 1.15 to 3.37); however, adjustment for maternal confounders attenuated these associations to 0.97 (95% CI, 0.79 to 1.21) and 1.19 (95% CI, 0.51 to 2.81), respectively. The adjusted ORs for CKD associated with other prenatal factors were 2.88 (95% CI, 2.28 to 3.63) for low birth weight, 1.54 (95% CI, 1.13 to 2.09) for maternal gestational DM, 1.24 (95% CI, 1.05 to 1.48) for maternal overweight, and 1.26 (95% CI, 1.05 to 1.52) for maternal obesity. In subgroup analysis by CKD subtype, low birth weight and maternal pregestational DM associated significantly with increased risk of renal dysplasia/aplasia. Low birth weight, maternal gestational DM, and maternal overweight/obesity associated significantly with obstructive uropathy. These data suggest that prenatal factors may impact the risk of CKD. Future studies should aim to determine if modification of these factors could reduce the risk of childhood CKD.

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CKD is a growing epidemic public health problem now affecting 16.8% of those individuals aged≥20 years in the United States.[1] In parallel, diabetes mellitus (DM) and obesity rates are increasing at pandemic proportions. Obesity now affects 9.8% of men and 13.8% of women worldwide, with mean worldwide body mass index (BMI) rising globally since 1980.[2] Likewise, the incidence of DM has increased significantly since 1980, and it now affects >9% of men and women.[3] Today's obesity and DM pandemics may impact the health of future generations, because existing data suggest that maternal health and the *in utero* environment may predict future health of offspring, with kidney-specific sequelae.[4,5]

Data on the epidemiology of CKD are more limited in children compared with adults. Congenital renal anomalies cause almost 60% of pediatric CKD cases.[6] Moreover, low birth weight is associated with development of CKD in both childhood[7] and adulthood.[8] This suggests that the risk of

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Table 1. Maternal characteristics of children with and without CKD in WA, 1987–2008

Maternal Characteristics	Cases (*n*=1994; %)	Controls (*n*=20,032; %)	*P* Value
Age (yr)			0.001
<18	66 (3.3)	723 (3.6)	
18–24	588 (29.5)	6272 (31.3)	
25–29	549 (27.5)	5786 (28.9)	
30–34	488 (24.5)	4661 (23.3)	
35+	303 (15.2)	2581 (12.9)	
Missing	0	9 (0.04)	
Race			0.1
White	1524 (76.4)	14,798 (73.9)	
Black	76 (3.8)	842 (4.2)	
Asian/Pacific Islander	116 (5.8)	1392 (7.0)	
Native American	47 (2.4)	451 (2.3)	
Missing	231 (11.6)	2549 (12.7)	
Education			0.9
Below high school	279 (14.0)	2675 (13.4)	
High school graduate	430 (21.6)	4251 (21.2)	
Some college	782 (39.2)	7485 (37.4)	
Missing	503 (25.2)	5621 (28.1)	
Residence			0.5
Urban	1407 (70.6)	13,912 (69.5)	
Rural	427 (21.4)	4394 (21.9)	
Missing	160 (8.0)	1726 (8.6)	
Smoking status			0.1
Yes	256 (12.8)	2877 (14.4)	
No	1637 (82.1)	16,274 (81.2)	
Missing	101 (5.1)	881 (4.4)	
Previous pregnancies			1.0
0	608 (30.5)	6196 (30.9)	
1	524 (26.3)	5462 (27.3)	
2	408 (20.5)	3560 (17.8)	
3+	392 (19.7)	4248 (21.2)	
Missing	62 (3.1)	566 (2.8)	
Prenatal care			<0.001
Inadequate	145 (7.3)	1598 (8.0)	
Intermediate	222 (11.1)	2744 (13.7)	
Adequate	527 (26.4)	5725 (28.6)	
Intensive	339 (17.0)	2494 (12.5)	
Missing	761 (38.2)	7741 (37.3)	
Chronic HTN			0.52
No	1833 (91.9)	18,437 (92.0)	
Yes	27 (1.4)	238 (1.2)	
Missing	134 (6.7)	1357 (6.8)	
Gestational HTN			0.002
No	1733 (86.9)	17,719 (88.5)	
Yes	127 (6.4)	956 (4.8)	
Missing	134 (6.7)	1357 (6.8)	
Maternal DM			<0.001
No	1761 (88.3)	17,981 (89.8)	
PDM	16 (0.8)	83 (0.4)	
GDM	84 (4.2)	613 (3.1)	
Missing	133 (6.7)	1355 (6.8)	
Maternal BMI (kg/m^2)			<0.001
<18.5	33 (1.7)	451 (2.3)	
18.5–24.9	556 (27.9)	5680 (28.4)	
25–29.9	278 (13.9)	2390 (11.9)	

developing CKD in childhood and young adulthood may be largely determined *in utero* and depend on maternal factors. Some congenital kidney conditions, such as renal dysplasia, have been associated with maternal DM.[9] The risk of congenital kidney malformations in relation to maternal obesity and overweight is more equivocal, in that some studies show an increased risk[10] but others do not.[11] Many of these studies had few exposed cases and were likely underpowered to detect an association.[12]

We used Washington (WA) state birth records between 1987 and 2008 linked to hospital discharge data to conduct a case-control study of the relationship of prenatal and maternal factors to the risk of CKD in offspring. Specifically, we evaluated the effects of abnormal birth weight (low or high), maternal DM (pregestational [PDM] and gestational [GDM]), and maternal overweight/obesity on childhood CKD, hypothesizing that these maternal conditions would increase the risk of CKD in offspring.

RESULTS

Based on our CKD definition, which included renal dysplasia/aplasia and obstructive uropathy using International Classification of Diseases, version 9 (ICD-9) coding at hospital discharge, we found the overall prevalence of childhood CKD in WA between the years 1987–2008 to be 126.7 cases per 100,000 births, with 1994 cases. Maternal characteristics were similar by case or control status for race, education, urban/rural residence, smoking status, prior pregnancies, and chronic hypertension (HTN) (Table 1). Cases were more likely to have mothers with the following characteristics: aged≥30 years (P=0.001), received more intensive prenatal care (P<0.001), had gestational HTN (P=0.002), and had either maternal DM (P<0.001) or BMI≥25 kg/m^2 (P<0.001).

In terms of offspring characteristics (Table 2), most cases (82.2%) were below 12 months of age at the time of CKD diagnosis. There was a predominance of boys among cases versus controls (64.7% versus 51.4%; P<0.001). A greater proportion of cases than controls had a low birth weight between 400 and 2499 g (12.1% versus 5.5%;

Table 1. Continued

Maternal Characteristics	Cases (*n*=1994; %)	Controls (*n*=20,032; %)	*P* Value
≥30	242 (12.1)	1951 (9.7)	
Missing	85 (44.4)	9560 (47.7)	

CKD cases were defined using hospital discharge ICD-9 codes for renal dysplasia/aplasia (753.0 and 753.15) and obstructive uropathy (599.6 and 753.2).

Table 2. Characteristics of children with and without CKD in WA, 1987–2008

Characteristics	Cases (*n*=1994; %)	Controls (*n*=20,032; %)	*P* Value
Age at diagnosis of study definition of CKD[a] (yr)			N/A
<1	1639 (82.2)	N/A[b]	
1–5	202 (10.1)	N/A[b]	
6–10	81 (4.1)	N/A[b]	
11–20	72 (3.6)	N/A[b]	
Sex			<0.001
Boy	1291 (64.7)	10,287 (51.4)	
Girl	703 (35.3)	9745 (48.7)	
Birth weight (g)			<0.001
400–2499	241 (12.1)	1105 (5.5)	
2500–3999	1466 (73.5)	16,217 (81.0)	
≥4000	277 (13.9)	2608 (13.0)	
Missing	10 (0.5)	102 (0.5)	
Gestational length (wk)			<0.001
<37	294 (14.7)	1586 (7.9)	
37–42	1236 (62.0)	13,602 (67.9)	
>42	139 (7.0)	1913 (9.6)	
Missing	325 (16.3)	2931 (14.6)	
Multiple births			0.12
Singleton	1930 (96.8)	19,495 (97.3)	
Multiple	64 (3.2)	524 (2.6)	
Missing	0 (0)	13 (0.1)	

N/A, not applicable.
[a]CKD cases were defined using hospital discharge ICD-9 codes for renal dysplasia/aplasia (753.0 and 753.15) and obstructive uropathy (599.6 and 753.2).
[b]Controls were matched to cases by year of birth.

P<0.001) and gestational age<37 weeks (14.7% versus 7.9%; *P*<0.001). The distribution of singleton versus multiple births was similar in cases versus controls (3.2% versus 2.6%; *P*=0.12).

Primary Analyses

We estimated the association of birth weight with CKD (Table 3). Low birth weight (400–2499 g) was associated with increased CKD risk compared with normal birth weight (2500–3999 g). The increase in risk was more than 2-fold, with a crude odds ratio (OR) of 2.41 (95% confidence interval [95% CI], 2.08 to 2.80); this increased risk persisted after adjustment for maternal factors of DM, BMI, and smoking, with an adjusted OR (aOR) of 2.88 (95% CI, 2.28 to 3.63). For high birth weight (≥4000 g), the risk was also increased, with an OR of 1.17 (95% CI, 1.03 to 1.34); however, this finding was attenuated after adjustment for maternal BMI and smoking, with an aOR of 0.97 (95% CI, 0.79 to 1.21).

We estimated the association of childhood CKD with maternal DM (Table 4). Children with CKD were more likely to be born to mothers with PDM, with an OR of 1.97 (95% CI, 1.15 to 3.37); however, this risk was attenuated after adjustment for maternal BMI and smoking, with an aOR of 1.12 (95% CI, 0.44 to 2.84). Also, children with CKD were more likely to be born to mothers with GDM, with an OR of 1.40 (95% CI, 1.11 to 1.77). The risk was strengthened after adjustment for maternal BMI, gestational HTN, and smoking, with an aOR of 1.54 (95% CI, 1.13 to 2.09).

With respect to the association of childhood CKD with maternal overweight or obesity (Table 5), we found that children with CKD were more likely to be born to overweight mothers, with an aOR of 1.24 (95% CI, 1.05 to 1.48) after adjustment for maternal DM and gestational HTN; the aOR of 1.19 was similar to the crude OR (95% CI, 1.02 to 1.38). Likewise, children with CKD were more likely to be born to obese mothers, with an aOR of 1.26 (95% CI, 1.05 to 1.52) after adjustment for maternal smoking and education; again, this finding was similar to the crude OR (OR, 1.27; 95% CI, 1.08 to 1.49). Because the risk for childhood CKD was similar for both maternal overweight (BMI=25–29.9) and obesity (BMI≥30), we also evaluated the risk of childhood CKD with any maternal BMI≥25; the OR was 1.25 (95% CI, 1.10 to 1.41), and the aOR was 1.25 (95% CI, 1.08 to 1.44) after adjustment for maternal DM, gestational HTN, and smoking.

Subgroup Analyses

More CKD cases were diagnosed as obstructive uropathy than renal dysplasia/aplasia, with *n*=1663 (83.4%) versus *n*=372 (18.7%). A few cases had both obstructive uropathy and renal dysplasia/aplasia (*n*=41; 2.1%). In analyses by case subgroup (Tables 6 and 7), children with dysplastic/aplastic CKD were more likely to be born with low birth weight, with an OR of 4.51 (95% CI, 3.47 to 5.85), or to mothers with PDM, with an OR of 7.52 (95% CI, 3.97 to 14.24). No covariates for maternal confounders in examining the risk for dysplastic/aplastic CKD with prenatal risk factors remained in the models after stepwise logistic regression. No other maternal factors were significantly associated with renal dysplasia/aplasia.

Children with obstructive CKD were more likely to have low birth weight (aOR, 2.53; 95% CI, 1.95 to 3.29; after adjustment for maternal DM, BMI, and smoking) or be born to mothers with GDM (aOR, 1.50; 95% CI, 1.07 to 2.09; after adjustment

Table 3. Association of birth weight with development of CKD

CKD	Low Birth Weight (400–2499 g)		High Birth Weight (>4000 g)	
	Yes	No	Yes	No
Yes	241	1466	277	1466
No	1105	16,217	2608	16,217
Crude OR (95% CI)	2.41 (2.08 to 2.80)		1.17 (1.03 to 1.34)	
Adjusted OR (95% CI)	2.88 (2.28 to 3.63)[a]		0.97 (0.79 to 1.21)[b]	

Exposure reference group is offspring with normal birth weight (2500–3999 g).
[a]Adjusted for maternal DM, BMI, and smoking.
[b]Adjusted for maternal BMI and smoking.

Table 4. Association of maternal DM with the development of CKD in offspring

CKD	PDM		GDM	
	Yes	No	Yes	No
Yes	16	1761	84	1761
No	83	17,981	613	17,981
Crude OR (95% CI)	1.97 (1.15 to 3.37)		1.40 (1.11 to 1.77)	
Adjusted OR (95% CI)	1.12 (0.4 to 2.84)[a]		1.54 (1.13 to 2.09)[b]	

Exposure reference group is mothers without DM; mothers with unknown DM status were excluded from analysis.
[a]Adjusted for maternal BMI and smoking.
[b]Adjusted for maternal BMI, gestational HTN, and smoking.

Table 5. Association of maternal overweight/obesity with development of CKD in offspring

CKD	Overweight		Obesity	
	Yes	No	Yes	No
Yes	278	556	242	556
No	2390	5680	1951	5680
Crude OR (95% CI)	1.19 (1.02 to 1.38)		1.27 (1.08 to 1.49)	
Adjusted OR (95% CI)	1.24 (1.05 to 1.48)[a]		1.26 (1.05 to 1.52)[b]	

Exposure reference group is mothers with normal BMI; mothers with low BMI were excluded from analysis.
[a]Adjusted for maternal DM and gestational HTN.
[b]Adjusted for maternal smoking and education.

Table 6. Association of birth weight and maternal risk factors (maternal DM [PDM and GDM] and overweight/obesity) with development of renal dysplasia and aplasia

Risk Factor	*N*	Crude OR	95% CI
Low birth weight[a] (400–2499 g)	78	4.51	3.47 to 5.85
High birth weight[a] (>4000 g)	38	0.93	0.66 to 1.32
Maternal PDM[b]	11	7.52	3.97 to 14.24
Maternal GDM[b]	16	1.48	0.89 to 2.46
Maternal overweight[c]	44	1.02	0.71 to 1.45
Maternal obesity[c]	46	1.30	0.91 to 1.85

No maternal confounders remained in the analysis after stepwise regression.
[a]Exposure reference group is offspring with normal birth weight (2500–3999 g).
[b]Exposure reference group is mothers without DM.
[c]Exposure reference group is mothers with normal BMI.

for maternal BMI and smoking), overweight (aOR, 1.27; 95% CI, 1.05 to 1.52; after adjustment for maternal DM and gestational HTN), or obesity (aOR, 1.27; 95% CI, 1.05 to 1.55; after adjustment for maternal smoking). The OR for the association between obstructive uropathy and maternal PDM was decreased but not statistically significant because of small numbers (n=5; aOR, 0.52; 95% CI, 0.13 to 2.16).

Sensitivity Analyses

When we broadened our definition of CKD to also include the ICD-9 codes for CKD by eGFR (585.x), there were only 98 additional cases, for a total of 2080 cases; 12 of the original 1994 cases in our study also had CKD by the ICD-9 585.x code definition: 7 cases had renal dysplasia/aplasia and 5 cases had obstructive uropathy. The aORs were not significantly different from the primary analysis with our original CKD definition, with the following aORs: 2.95 (95% CI, 2.34 to 3.71) for low birth weight, 0.98 (95% CI, 0.79 to 1.21) for high birth weight, 1.08 (95% CI, 0.43 to 2.75) for PDM, 1.49 (95% CI, 1.10 to 2.03) for GDM, 1.24 (95% CI, 1.05 to 1.47) for maternal overweight, and 1.27 (95% CI, 1.06 to 1.52) for maternal obesity.

Furthermore, we performed an additional subgroup analysis using only the 585.x ICD-9 codes to define CKD cases; there were 98 such cases, as noted above. In this analysis, there was a significantly increased risk for CKD associated with low birth weight, with an OR of 6.36 (95% CI, 4.00 to 10.12). No covariates for maternal confounders remained in the model after stepwise regression, and the risks were variable with high birth weight, maternal overweight, and maternal obesity, with ORs of 1.24 (95% CI, 0.67 to 2.31), 0.88 (95% CI, 0.37 to 2.09), and 1.23 (95% CI, 0.54 to 2.80), respectively. There were inadequate numbers to generate risk estimates for the exposures of maternal PDM and GDM.

DISCUSSION

In this population-based, case-control study, we have shown significant associations between childhood CKD and primary prenatal exposures of low birth weight and maternal factors, including GDM, PDM, overweight, and obesity. We identified cases of CKD with structural kidney malformations, one of the criteria for CKD according to both Kidney Disease Outcomes Quality Initiative and Kidney Disease Improving Global Outcomes.[13,14] The WA birth record linkage enabled the largest study to date of these hypotheses. Low birth weight, a surrogate for both poor fetal growth and low nephron number,[4,15] is a risk factor for postnatal CKD in both childhood[7] and adulthood.[8] Although there is some data that high birth

Table 7. Association of birth weight and maternal risk factors (maternal DM [PDM and GDM] and overweight/obesity) with development of obstructive uropathy

Risk Factor	*N*	Crude OR	95% CI	aOR	95% CI
Low birth weight (400–2499 g)	170	2.01	1.69 to 2.39	2.53[a]	1.95 to 3.29
High birth weight (>4000 g)	244	1.22	1.06 to 1.41	1.05[b]	0.84 to 1.32
Maternal PDM[c]	5	0.73	0.30 to 1.80	0.52[d]	0.13 to 2.16
Maternal GDM[c]	68	1.34	1.04 to 1.74	1.50[b]	1.07 to 2.09
Maternal overweight[e]	240	1.22	1.03 to 1.42	1.27[f]	1.05 to 1.52
Maternal obesity[e]	199	1.23	1.03 to 1.46	1.27[g]	1.05 to 1.55

[a]Adjusted for maternal DM, BMI, and smoking.
[b]Adjusted for maternal BMI and smoking.
[c]Exposure reference group is mothers without DM.
[d]Adjusted for maternal BMI and smoking.
[e]Exposure reference group is mothers with normal BMI.
[f]Adjusted for maternal DM and gestational HTN.
[g]Adjusted for maternal smoking.

weight, in the setting of exposure to maternal DM, is associated with albuminuria[16] and may contribute to postnatal CKD, we do not show an increased risk of postnatal CKD with high birth weight. Thus, our data show that only low birth weight seems to be associated with postnatal CKD.

Existing literature also suggests that maternal DM may adversely compromise fetal programming, resulting in abnormal renal development. This result is suggested by a murine model of maternal DM, which shows altered transcription of inflammatory cytokines and subsequent aberrant nephrogenesis in offspring of diabetic compared with nondiabetic mothers.[17] In humans, the timing of treatment in mothers with DM is also known to reduce the risk of congenital malformations.[18] When intensive education and insulin therapy were provided to women with DM both pre- and postconception, the rate of congenital anomalies in the offspring of women treated preconception was significantly lower than the rate in offspring of women treated postconception (1.2% versus 10.9%). In the human fetus, kidney development occurs between 5 and 34 weeks of gestation.[19] This information, along with evidence that preconception intensive glycemic control in diabetic women is associated with a reduced risk of congenital malformations in offspring, supports the biologic plausibility of maternal DM as a risk factor for congenital malformations in offspring.

Obesity has also been shown to be associated with malformations of the urogenital system,[10] although the data are conflicting.[20] The mechanism by which obesity is associated with CKD may be independent of its association with maternal DM. Obese women may be at increased risk of metabolic alterations, such as hyperglycemia or hyperinsulinemia, independent of the presence of DM or elevated estrogen levels. These factors may increase the risk of having an offspring with a birth defect if they were present during the period of organogenesis.[20] Our study supports previous findings that maternal obesity increases the risk of congenital urogenital malformations in offspring, namely obstructive kidney disease.[10] This finding is independent of the presence of DM, because obese mothers were more likely to have children with obstructive CKD than nonobese mothers after adjusting for maternal DM.

Current knowledge about CKD epidemiology is based mainly on data on the most advanced stage of CKD or ESRD, when dialysis or transplantation is necessary to sustain life.[21] Little is known about the prevalence of earlier stages of CKD. There is evidence that ESRD represents the tip of the iceberg of CKD and that earlier CKD stages may exceed in prevalence those cases reaching ESRD by as much as 50 times.[22] The ItaliKid study showed that, in children with mild CKD (estimated creatinine clearance [CCr]=51–75 ml/min) at registration, the risk of developing ESRD by age 20 years was not trivial (37%), although it was smaller than the risks with moderate CKD (CCr=25–50 ml/min) and severe CKD (CCr<25 ml/min; estimated at 70% and 97%, respectively). Thus, evaluating the epidemiology of milder stages of CKD as we do here is warranted, because children with milder stages of CKD may also be at increased risk for progression to ESRD.

Our study includes 1994 CKD cases diagnosed from 1987 to 2008 compared with 1197 cases in the ItaliKid study, an Italian study that was the first prospective population-based study on the epidemiology of CKD in children.[23] We report a childhood CKD prevalence of 126.7 per 100,000, whereas the ItaliKid study reported a point prevalence of 74.7 per 1,000,000. Based on our definition of CKD, the prevalence was almost 17 times higher than the prevalence reported by the ItaliKid project. Some of this difference in prevalence may be explained by our more inclusive definition of CKD; ItaliKid included only CKD cases with estimated CCr less than 75 ml/min, whereas our study includes children with structural kidney disease, some of whom might have had normal estimated kidney function had they undergone CCr testing. It is also possible that we have a higher false positive rate for CKD cases than the ItaliKid study; whereas we used hospitalization diagnosis codes to identify cases, ItaliKid used more detailed inpatient and outpatient medical records to identify cases.

Our study has a number of limitations, which include missing maternal BMI data at the time of birth certificate completion in 44.4% of cases and 47.7% of controls, the use of self-reported data for maternal weight in the prepregnancy BMI calculation when it was not available from the mother's medical chart or physician, and variation in ICD-9 coding for CKD between physicians. Nevertheless, birth certificate data seem to be both reliable and valid when used for research purposes, with recall or reporting bias having minimal effect.[24] The BMI data are thought to be missing at random, because entry into the dataset depended on documentation by WA data entry staff using medical chart data, physician report, or maternal recall, and they should not be a source of bias.

Moreover, our case definition may underestimate the prevalence of CKD in WA. Although use of ICD-9 codes to identify CKD cases has variable sensitivity, it is a reliable way to identify CKD cases with high specificity.[25,26]

In conclusion, using a broad definition of CKD, we identified a large number of pediatric CKD cases and found that children with CKD were highly likely to have abnormal prenatal history, including low birth weight, maternal overweight/obesity, and maternal DM. Combined with data suggesting that milder CKD can progress to ESRD,[23] we propose that there is some use in applying broader definitions of CKD in future epidemiologic studies.

As mentioned above, previous data show that, if we educate and provide intensive DM care early to diabetic mothers, the rate of congenital malformations in births to diabetic mothers decreases to levels comparable with the rate in nondiabetic mothers.[18] Additionally, children with CKD were significantly more likely to have obese mothers; thus, our data underscore the potential impact of maternal obesity on future generations. Maternal overweight is also not without risk, because it was found to be associated with childhood obstructive CKD. Ultimately, we hope that our results will serve as an impetus to larger prospective studies evaluating the risk factors for and clinical outcomes of children with all stages of CKD, with the goals of elucidating the pathophysiology of and improving outcomes for CKD and whether modification of these factors can reduce the incidence of childhood CKD.

CONCISE METHODS

We conducted a population-based, case-control study using birth certificate data from WA for 1987–2008. Additional information was obtained by linkage of birth records to discharge data for the birth and subsequent hospitalizations in all hospitals licensed by the WA Department of Health using the Comprehensive Hospital Abstract Reporting System (CHARS).[27] The CHARS hospital discharge data contained hospital inpatient coded discharge information (derived from billing systems) available for 1987–2008 in WA and included additional information consisting of age at hospitalization, ICD-9 diagnoses and procedure codes, payer information, and length of stay. The study was approved by the University of Washington Human Subjects Division and deemed as exempt from review by the Institutional Review Board, because we only had access to anonymous data that did not allow identification of individual patients or their medical charts.

Primary Analyses

Our case definition included the two most common congenital etiologies of childhood CKD in children<21 years old as outlined in the 2008 North American Pediatric Renal Trials and Collaborative Studies Annual Report.[6] These diagnoses and their respective ICD-9 codes are renal dysplasia/aplasia (753.0 and 753.15) and obstructive uropathy (599.6 and 753.2). We identified 1994 cases ages<21 years with CKD-related hospitalizations during 1987–2008. We did not have access to individual medical charts for confirmation of the diagnosis of CKD beyond the discharge ICD-9 codes. The two CKD case groups (dysplasia/aplasia and obstructive uropathy) were not mutually exclusive, in that a case could have more than one subtype of CKD; 41 of 1994 cases had both renal dysplasia/aplasia and urinary obstruction. Controls were randomly selected from births with no recorded history of CKD in CHARS and frequency-matched by year of birth to cases in a 10:1 ratio.

The primary exposures of interest were offspring birth weight, maternal DM, and maternal overweight/obesity. Birth weight was categorized as low, normal, or high using weight categories 400–2499, 2500–3999, and ≥4000 g, respectively. Information on maternal DM was noted as present or absent on the WA birth certificate and additionally classified as PDM (diagnosed before pregnancy) or GDM (diagnosed during pregnancy). Maternal obesity or overweight was determined using the prepregnancy BMI reported on the birth certificate and defined as normal (BMI=18.5–24.9 kg/m^2), overweight (BMI=25–29.9 kg/m^2), and obese (≥30 kg/m^2).[28] Mothers who were underweight (BMI<18.5 kg/m^2) were excluded from the analysis.

We performed the analyses using Stata 11.2 software. For the exposures of birth weight and maternal factors, we used forward stepwise logistic regression to evaluate candidate covariates as confounders and only included covariates in the model that might improve prediction, with coefficient $P<0.05$. The exposure of interest was forced into the model; then, each candidate confounder was entered into the multiple logistic regression-model separately, and the variable that explained the largest percentage of variability in the outcome of childhood CKD was included. Next, the remaining variables were added individually, and they were added to the final adjusted model if they were significantly associated with childhood CKD and decreased the Akaike information criterion. We evaluated the following covariates as potential confounders: maternal race (white, black, Asian/Pacific Islander, or other/missing), residence of census tract (urban, rural, or missing), parity (0, 1, 2, or 3+ prior pregnancies or missing), maternal chronic HTN (yes, no, or missing), gestational HTN (yes, no, or missing), maternal education (less than high school graduate, high school graduate, some college, or missing), and smoking (yes, no, or missing). We also evaluated maternal BMI (18.5–24.9, 25–29.9, and ≥30 kg/m^2) as a potential confounder for the association of maternal DM with childhood CKD and *vice versa*. We evaluated both maternal BMI and maternal DM as potential confounders for the association of low or high birth weight with childhood CKD. The covariates that remained in the model are reported in Results with the aORs. If no covariates remained in the model after stepwise regression, only the crude ORs were reported.

Subgroup and Sensitivity Analyses

We repeated the above analysis for each subgroup of CKD separately (dysplasia/aplasia versus obstructive uropathy). Next, we performed a sensitivity analysis adding ICD-9 codes for CKD (585.x) to our case definition to determine how much the association between CKD and prenatal risk factors would change. Additionally, we also did an additional subgroup analysis, with only CKD using 585.x in the definition. For the sensitivity analyses, we used the same methods as outlined above for the primary analysis, and the results are outlined above.

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DISCLOSURES

None.

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