Fetal and Infant Growth Patterns and Kidney Function at School Age

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ABSTRACT
Low birth weight is associated with ESRD. To identify specific growth patterns in early life that may be related to kidney function in later life, we examined the associations of longitudinally measured fetal and infant growth with kidney function in school-aged children. This study was embedded in a population-based prospective cohort study among 6482 children followed from fetal life onward. Fetal and childhood growth was measured during second and third trimesters of pregnancy, at birth, and at 6, 12, 24, 36, and 48 months postnatally. At the age of 6 years, we measured kidney volume by ultrasound. GFR was estimated using blood creatinine levels. Higher gestational age-adjusted birth weight was associated with higher combined kidney volume and higher eGFR (per 1 SD score increase in birth weight; 1.27 cm³ [95% confidence interval, 0.61 to 1.93] and 0.78 ml/min per 1.73 m² [95% CI, 0.16 to 1.39], respectively). Fetal weight, birth weight, and weight at 6 months were positively associated with childhood kidney volume, whereas higher second trimester fetal weight was positively associated with higher GFR (all P values, 0.05). Fetal and childhood lengths were not consistently associated with kidney function. In this cohort, lower fetal and early infant weight growth is associated with smaller kidney volume in childhood, whereas only lower fetal weight growth is associated with lower kidney function in childhood, independent of childhood growth. Whether these associations lead to an increased risk of kidney disease needs to be studied further.


Low birth weight is associated with higher risks of ESRD and hypertension in later life.1–3 Clearly, low birth weight is not the causal factor per se leading to kidney diseases in later life. Birth weight is the result of various exposures and growth patterns in fetal life and the starting point of childhood growth. It has been hypothesized that especially third trimester fetal growth restriction leads to persistently smaller kidneys with a reduced number of nephrons, which may predispose the individual to kidney disease in adulthood.4–6 This hypothesis is supported by both animal and human studies, showing that kidney volume and nephron number are reduced in fetal growth-restricted subjects and hypertensive subjects.7–9 Although nephrogenesis is known to continue until 36 weeks of gestation and cease thereafter, not much is known about the specific critical periods and early growth patterns related to kidney function in later life.10 Also, whether and to what extent the associations of low birth weight with CKD are explained by preterm birth are not known.1 Longitudinal studies suggested that the associations of low birth weight with hypertension were stronger in subjects with rapid weight gain in childhood, but results are inconclusive.11,12 A similar growth pattern has not been identified as a risk factor for kidney diseases yet.
Prospective studies linking fetal and early childhood growth patterns to kidney outcomes in later life might help to identify early critical periods for developing impaired kidney function in later life.

Therefore, we examined, in a population-based prospective cohort study among 6482 children followed from early fetal life onward (Figure 1), the associations of birth weight, gestational age, birth weight for gestational age, and longitudinally measured fetal and early childhood growth patterns with kidney size and function at school age. We used subclinical variations of kidney function in childhood as outcomes, because they relate to kidney disease in later life.\textsuperscript{13}

RESULTS

Subject Characteristics
Maternal and child characteristics are shown in Table 1. At the age of 6.0 years (90% range=5.7–7.4 years), mean (SD) total kidney volume was 120.3 (23.5) cm\(^3\), and eGFR was 118.8 (16.4) ml/min per 1.73 m\(^2\). Microalbuminuria was present in 7.6% of all children. In Table 2, all fetal, birth, and childhood growth characteristics are presented. Observed data before multiple imputations are presented in Supplemental Table 1. Differences in subject characteristics between children with and without blood samples are shown in Supplemental Table 2.

Birth Outcomes and Childhood Kidney Outcomes
Figure 2 shows that a 1 SD longer duration of gestational age at birth was associated with a larger combined kidney volume in childhood ($P$ value for trend<0.05). Compared with term-born children (38.0–39.9 weeks), children born very preterm (<34 weeks) had a smaller kidney volume (difference=-10.48 cm\(^3\); 95% confidence interval [95% CI], −17.74 to −3.22). Post-term birth (>42 weeks) was associated with higher eGFR in childhood (difference=3.80 ml/min per 1.73 m\(^2\); 95% CI, 1.39 to 6.21). Gestational age at birth was not associated with the risk of childhood microalbuminuria. Birth weight not adjusted for gestational age was positively associated with combined kidney volume and eGFR ($P$ values for trend<0.01) in childhood. Gestational age-adjusted birth weight was positively associated with childhood combined kidney volume and eGFR ($P$ values for trend<0.05). Compared with children with size appropriate for gestational age, children born small for gestational age had smaller kidney volume (−3.74 cm\(^3\); 95% CI, −6.89 to −0.89). We performed a sensitivity analysis using the lower 10% and upper 10% as the definitions for small and large sizes for gestational age of children. These analyses showed the same results compared with a 5% cutoff (Supplemental Figure 1). Birth weight was not associated with risk of microalbuminuria. Results from models adjusted for sex and age only were similar, with some stronger effect estimates (Supplemental Table 3). Results from analyses on the data before imputation are shown in Supplemental Table 4. After additional adjustment for childhood kidney volume, the associations of birth outcomes with kidney function attenuated to nonsignificant (results are presented in Supplemental Table 5).

Fetal and Early Childhood Growth and Kidney Outcomes
We explored whether the associations of fetal and early childhood growth characteristics with childhood kidney function outcomes were independent from growth measures at other ages using conditional growth analyses. Figure 3 shows that higher second and third trimester fetal weights, birth weight, and weight at the age of 6 months were all independently associated
with a larger combined kidney volume in childhood (all \( P \) values < 0.05). Also, higher second trimester and third trimester fetal weights tended to be independent from weight at other ages (associated with higher eGFR; \( P \) value < 0.05 and \( P \) value = 0.05, respectively). When we additionally adjusted the models focused on eGFR for childhood kidney volume, we observed that these associations attenuated to nonsignificant (results are shown in Supplemental Figure 3). Conditional analyses for fetal and childhood length growth did not show consistent associations with childhood kidney volume and function outcomes (results are shown in Supplemental Figure 2).

Results from the normal multivariate regression models, which do not take into account growth measures at other ages, showed that longer length at different ages is associated with higher eGFR and an increased risk of microalbuminuria (all \( P \) values < 0.05). Higher weight at different ages is associated with larger kidney volume and higher eGFR (all \( P \) values < 0.05) but with the risk of microalbuminuria (basic and adjusted models are shown in Supplemental Tables 6 and 7).

### DISCUSSION

In this population-based prospective cohort study, we aimed to identify critical periods during fetal life and childhood for development of impaired kidney function. We observed that preterm birth was associated with smaller kidney volume and that smaller size for gestational age at birth was associated with a smaller kidney volume and lower eGFR. Higher fetal weight, birth weight, and weight at 6 months were independently positively associated with childhood kidney volume, whereas only higher fetal weight was independently positively associated with higher eGFR. Fetal life and early infancy may be critical periods for kidney function in later life.

### Strengths and Limitations

A major strength of our study is its prospective design from fetal life onward within a large population-based cohort. Our analyses were based on more than 6000 children with kidney volume and function measurements available. The study population comprised a multietnic group, with almost 40% being non-Western children. The largest non-Western groups were Moroccan, Surinamese, and Turkish, which are the largest ethnic minority groups in the Netherlands. Whether these results are generalizable to other populations should be further studied. Repeated fetal and childhood growth measures were available, which enabled us to identify critical growth periods that might influence kidney volume and function. We did take account the repeated growth measures by performing conditional growth analyses. Of all children, more than 80% did participate in the kidney follow-up studies. Because not all participants in the study gave consent for collecting blood samples, 67% of all children provided useful blood samples for measurements of creatinine levels. There were no differences in birth outcomes and fetal and early childhood growth measures between children with and without blood samples. However, children without blood samples had smaller kidney dimensions at the age of 6 years. These differences might have led to an underestimation of the observed associations. Furthermore, statistical power might have been reduced because of the missing data. We used kidney size as a measure of kidney development, because nephron number cannot be studied in vivo. Kidney size is correlated with the number of glomeruli and can be used in epidemiologic studies as a measure of kidney development. However, glomerular enlargement caused by hyperfiltration may attenuate the differences in childhood growth measures.
Table 2. Fetal and early childhood growth characteristics (n=6482)

<table>
<thead>
<tr>
<th>Growth Characteristics</th>
<th>Boys (n=3257)</th>
<th>Girls (n=3225)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal growth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>20.6 (18.9–22.9)</td>
<td>20.5 (18.9–22.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Femur length (mm)</td>
<td>33.5 (3.6)</td>
<td>33.5 (3.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>Estimated fetal weight (g)</td>
<td>387 (98)</td>
<td>378 (91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Third trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>30.4 (29.0–32.4)</td>
<td>30.3 (28.8–32.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Femur length (mm)</td>
<td>57.4 (3.1)</td>
<td>57.6 (3.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Estimated fetal weight (g)</td>
<td>1633 (260)</td>
<td>1618 (268)</td>
<td>0.03</td>
</tr>
<tr>
<td>Birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>40.1 (37.0–42.1)</td>
<td>40.1 (36.9–42.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>50.6 (2.4)</td>
<td>49.9 (2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>3488 (569)</td>
<td>3362 (534)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Early childhood growth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age (mo)</td>
<td>6.2 (5.4–7.5)</td>
<td>6.2 (5.5–7.5)</td>
<td>0.65</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>68.5 (2.5)</td>
<td>66.7 (2.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>8176 (903)</td>
<td>7590 (832)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mo)</td>
<td>11.1 (10.2–12.3)</td>
<td>11.1 (10.2–12.3)</td>
<td>0.62</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>75.1 (2.5)</td>
<td>73.5 (2.5)</td>
<td>&lt;0.001</td>
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<tr>
<td>Weight (g)</td>
<td>9970 (1061)</td>
<td>9326 (991)</td>
<td>&lt;0.001</td>
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<tr>
<td>24 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mo)</td>
<td>24.8 (23.5–27.6)</td>
<td>24.8 (23.6–27.4)</td>
<td>0.35</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>88.9 (3.3)</td>
<td>87.7 (3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>13.2 (1.5)</td>
<td>12.7 (1.5)</td>
<td>&lt;0.001</td>
</tr>
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<td>36 mo</td>
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<tr>
<td>Age (mo)</td>
<td>36.7 (35.6–39.8)</td>
<td>36.7 (35.5–39.6)</td>
<td>0.17</td>
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<tr>
<td>Length (cm)</td>
<td>97.9 (3.8)</td>
<td>96.8 (3.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>15.4 (1.8)</td>
<td>15.0 (1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>48 mo</td>
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<td></td>
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<tr>
<td>Age (mo)</td>
<td>45.8 (44.8–48.0)</td>
<td>45.8 (44.7–47.9)</td>
<td>0.33</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>103.7 (4.1)</td>
<td>102.8 (4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>17.1 (2.2)</td>
<td>16.7 (2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>72 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mo)</td>
<td>72.6 (44.7–48.0)</td>
<td>72.6 (69.0–87.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>119.9 (6.1)</td>
<td>119.0 (6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>23.4 (4.1)</td>
<td>23.1 (4.5)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are means (SDs), medians (90% ranges), or percentages (numbers); t tests were used for comparison between boys and girls.

kidney volume and lead to an underestimation of the associations of interest. In the present study, eGFR was based on one random creatinine value, which is a limitation of the study. However, measurement error because of only one creatinine value is likely to be random and might have underestimated the observed differences. Mean values for eGFR and overall prevalence of microalbuminuria are in line with results of previous population-based studies in children of the same age range. We used the urine albumin to creatinine ratio to evaluate albuminuria in a random urine sample. Because the within-subject variation in urinary albumin excretion is large, the variability would probably be lower if we collected first morning void samples instead of random samples during the day. Finally, although we had information about a large number of confounders, residual confounding might still be an issue because of the observational design of the study.

Fetal and Early Childhood Growth and Childhood Kidney
To the best of our knowledge, the current study is the largest population-based prospective cohort study from fetal life onward focused on the associations of early growth with kidney function at school age. Several studies showed associations of low birth weight with renal disease and hypertension in later life. Results from a systematic review based on 31 studies among 49,387 subjects showed that low birth weight is associated with a 1.73 higher risk of kidney disease. Studies focused on the associations of birth weight with predictors of renal disease at younger ages are scarce. A Norwegian study among 7457 subjects showed that young adults born with a small size for gestational age had an increased risk of low-normal creatinine clearance compared with children with appropriate birth weight for gestational age. In contrast, a Dutch study among 82 severely growth-restricted children did not show associations of birth weight with renal function in young adulthood. A study among 86 children ages 9–12 years found no differences in kidney volume or function between preterm-born children, children born small for gestational age, and children born appropriate for gestational age. A study among 73 children aged 9.5 years showed a positive association of birth weight with eGFR. An observational cohort study among 426 children with congenital kidney disease showed that low birth weight and being small for gestational age are risk factors for poor growth outcomes in children with mild and moderate CKD. We observed that younger gestational age and lower gestational age-adjusted birth weight are associated with both a lower kidney volume and a lower eGFR in school-aged children. These findings are in line with previous studies showing that low birth weight for gestational age is associated with kidney function in childhood. We are not aware of other large population-based studies focused on the associations of birth weight taking into account gestational age with kidney function at young age.

Because birth weight is the result of various exposures and growth patterns in fetal life and the starting point of childhood growth, longitudinal fetal and early childhood growth patterns might be strongly associated with increased risk of renal disease.
in later life. Longitudinal studies linking fetal and early childhood growth patterns to kidney outcomes in later life might help to identify critical periods in later life. A study among 50 children 7.6 years old showed that children with low birth weight and slow growth rates had slightly lower GFR compared with children with appropriate growth. It has been postulated that rapid weight gain and obesity in childhood are associated with an increased risk of hypertension and type 2 diabetes in adulthood, which are risk factors for kidney disease.

In a retrospective cohort study among 80 children with proteinuric kidney disease, obese children who were born preterm had an increased risk of progression of kidney disease compared with obese children who were born at term, suggesting an additive risk of obesity and prematurity in the risks for progression of kidney disease. Experimental studies have shown that adequate feeding of low birth weight rats could restore nephron numbers to normal and that overfeeding of these rats led to low nephron numbers, hypertension, and renal injury. Overfeeding of normal birth weight rats also had adverse effects. In line with these findings, we observed that lower fetal weight gain and lower early infancy weight gain led to impaired kidney growth, whereas only lower fetal weight gain led to impaired kidney function. The results from our present study suggest that both fetal life and early infancy may be critical periods for the development of kidney diseases in later life. To our knowledge, this study is the first population-based study that shows that fetal growth and early growth are associated with kidney function in childhood. The present study was focused on the associations of fetal and childhood growth in relation to kidney outcomes. Previous studies, including those studies from the same cohort as the present study, suggested that children with fetal growth restriction followed by infant growth acceleration have higher BP. Both fetal growth in later pregnancy and growth in early infancy seem to be critical periods for childhood BP.

The underlying mechanisms for the associations between early growth and kidney function are not known. Adverse fetal growth may lead to a persistently reduced congenital nephron number and smaller kidney volume with glomerular hyperfiltration and subsequent glomerulosclerosis. These adaptations may predispose individuals to impaired renal function and hypertension. Specifically, third trimester growth is important in kidney development, because approximately 60% of the total nephron number develops during the third trimester of gestation. In line with this hypothesis, we observed that fetal growth was positively associated with kidney growth and eGFR. We also observed that, after additional adjustment for kidney volume, most associations of birth outcomes focused on kidney function outcomes attenuated. Other mechanisms may also be involved. Experimental studies showed alterations in the renin angiotensin system in experimentally induced intrauterine growth-restricted individuals at adult age, and these differences were not present at younger age. Several markers of the renin angiotensin system were increased in intrauterine growth-restricted subjects with hypertension. Future studies are needed to identify possible

Figure 2. Associations of birth outcomes with kidney outcomes (n=6482). Bars represent regression coefficients (95% CI) based on multiple regression models and reflect the difference for each outcome for the birth weight or gestational age group compared with the reference group. Models are adjusted for maternal age, body mass index, parity, ethnicity, educational level, folic acid supplementation, and smoking during pregnancy as well as child sex, breastfeeding, current age, and body surface area. β-Value for trend (95% CI) is shown. Results from models adjusted for sex and age only are given in Supplemental Table 3. Results for models additionally adjusted for kidney volume are given in Supplemental Table 5.
underlying mechanisms. The observed effect estimates in the present study are small and without clinical significance at young age. However, they are important from an etiological developmental perspective. The presented results suggest that birth characteristics, fetal growth, and early childhood growth influence kidney function throughout the life course. Whether and to what extent the observed variations in kidney function relate with kidney disease in later life are not known yet. Tracking of BP from childhood to adulthood has been described previously but is less clear for kidney function. Studies showing that lower eGFR relates with renal disease development many decades later suggest that subclinical variation in kidney function precedes the developmental of renal disease.

In conclusion, lower fetal weight gain and lower early infant weight gain led to smaller kidneys, whereas only lower fetal weight gain led to a lower eGFR. Although the observed effect estimates are small and without direct individual clinical consequence, they suggest that suboptimal early growth affects kidney function in later life. Future studies are needed to evaluate the long-term consequences of the observed associations.

**CONCISE METHODS**

**Design and Study Population**

This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life onward in Rotterdam, The Netherlands. All children were born between April of 2002 and January of 2006. Written informed consent was obtained from all parents. The study has been approved by the Medical Ethics Committee of the Erasmus Medical Center. In total, 8305 children participated in the follow-up measurements at the age of 6 years; of these children, 6494 (78%) children visited the research center with successful measurements of kidney size. We excluded children with kidney abnormalities (n=12). Blood samples for kidney function measurements were successfully obtained in 4336 (67%) children (Figure 1). Missing blood samples were mainly because of nonconsent.

**Fetal and Childhood Growth Measurements**

Gestational age was established by first trimester ultrasound measurements. Second and third trimester fetal growth examinations were performed at median (90% range) gestational ages of 20.6 (18.9–22.9) and 30.4 (29.0–33.1) weeks, respectively. Fetal head circumference (HC), abdominal circumference (AC), and femur length (FL) were measured, and estimated fetal weight was calculated using the formula by Hadlock et al.:

\[
\log_{10} \text{estimated fetal weight} = 1.5662 - 0.0108(\text{HC}) + 0.0468(\text{AC}) + 0.171(\text{FL}) + 0.00034(\text{HC})^2 - 0.003685(\text{AC})^2 + 0.003685(\text{FL})^2.
\]

At birth, gestational age, length, and weight were obtained from community midwife and hospital registries. Small and large sizes for gestational age were defined as the lower 5% and the upper 5% of birth weight SD score, respectively.
We measured childhood length and weight using standardized methods at the median (90% range) ages of 6.2 (5.4–7.5), 11.1 (10.2–12.3), 24.8 (23.5–27.6), 36.7 (35.6–39.7), 45.8 (44.8–48.0), and 72.6 (68–95.5) months. All growth characteristics were converted into SD score using fetal,\(^3\) birth weight,\(^36\) and childhood\(^37\) reference growth charts (Growth Analyzer 3.5; Dutch Growth Research Foundation, Rotterdam, The Netherlands).

**Childhood Kidney Outcomes**

Left and right kidney biometrics were measured at the median age of 6.0 (90% range=5.7–7.5) years. We identified the left and right kidneys in the sagittal plane along the longitudinal axis. We performed measurements of maximal bipolar kidney length, width, and depth. Kidney width and depth were measured at the level of the hilum. The cross-sectional area in which the kidney appeared symmetrically round at its maximum width was used. Kidney volume was calculated using the equation of an ellipsoid: volume (centimeters\(^3\)) =0.523×length (millimeters)×width (millimeters)×depth (millimeters),\(^38\) Combined kidney volume was calculated by summing right and left kidney volumes. We previously reported good intraobserver and interobserver correlation coefficients.\(^39\)

Blood creatinine levels were measured with an enzymatic method on a Cobas c 502 analyzer (Roche Diagnostics). Quality control samples showed intra- and interassay coefficients of variation ranging from 0.51% to 1.37%. eGFR was calculated according to the revised 2009 formula by Schwartz et al.\(^40\): eGFR=36.5×(height [centimeters]/creatinine [micromoles per liter]).\(^40\) Urine creatinine (micromoles per liter) and urine albumin (milligrams per liter) levels were determined on a Beckman Coulter AU analyzer, and creatinine levels were measured according to the Jaffe method. We calculated the albumin-to-creatinine ratio. For boys, microalbuminuria was defined as an albumin-to-creatinine ratio between 2.5 and 25 mg/mmol; for girls, we used a ratio between 3.5 and 25 mg/mmol.\(^41\)

**Covariates**

Information on maternal age, prepregnancy weight, parity, ethnicity, educational level, smoking during pregnancy, folic acid supplementation during pregnancy, and breastfeeding was obtained by questionnaires.\(^44\) Maternal height was measured without shoes, and prepregnancy body mass index was calculated (kilograms per meter\(^2\)). Infant sex was obtained from midwife and hospital registries. At the age of 6 years, child height and weight were measured without shoes and heavy clothing, and body surface area was calculated.

**Statistical Analyses**

First, we explored differences in characteristics between boys and girls by t tests for continuous variables and chi-squared tests for categorical variables. Second, we performed multiple linear or logistic regression models to explore the associations of birth outcomes (gestational age at birth, birth weight, and gestational age adjusted birth weight) with childhood combined kidney volume, eGFR, and microalbuminuria. These models were adjusted for sex and age only, and additionally, they were adjusted for potential confounders. Potential confounders were based on their associations with kidney outcomes or a change in effect estimate of more than 10%. The associations with kidney function outcomes were additionally adjusted for kidney volume to explore whether any association was explained by kidney growth. We performed a sensitivity analysis using the lower 10% and upper 10% as the definitions for small and large size, respectively, for gestational age of children. Third, we assessed the associations of fetal (second and third trimesters and birth) and childhood (6, 12, 24, 36, 48, and 72 months) weight and length measures with kidney outcomes at the age of 6 years using multiple linear regression models. Because fetal and childhood growth measurements at different ages are strongly correlated, we additionally performed conditional regression analyses to explore the independent associations of fetal and early childhood growth with kidney outcomes, taking account for their correlation.\(^42\) For these analyses, we constructed length and weight variables for each time point, which are statistically independent from each other, using standardized residuals obtained from regression of growth measures at a specific time point on prior growth measures.\(^42\) Because conditional growth measures are statistically independent of each other, this approach allows inclusion of growth measures simultaneously in one linear regression model. Thus, the associations of fetal and childhood growth measures at specific ages with kidney outcomes can be assessed, adjusted for, and compared with fetal and childhood growth measures at other ages.\(^43,44\) Results from these datasets were pooled and presented in the conditional growth results. All statistical analyses were performed using the Statistical Package for the Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, IL).

**ACKNOWLEDGMENTS**

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**DISCLOSURES**

None.
REFERENCES


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