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Original Investigation

Fetal Smoke Exposure and Kidney Outcomes in School-Aged Children

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Background: Fetal smoke exposure may result in developmental adaptations that permanently affect the developing kidney. In this study, the associations of maternal and paternal smoking during pregnancy with childhood kidney size and function were assessed.

Study Design: Prospective cohort study from fetal life onward.

Setting & Participants: This study was conducted in a group of 5,622 children in Rotterdam, the Netherlands.

Predictors: Maternal and paternal smoking were assessed during pregnancy by questionnaires.

Outcomes & Measurements: At a median age of 6.0 (5th-95th percentile, 5.6-7.9) years, we measured childhood kidney volumes, estimated glomerular filtration rate (eGFR), and albumin-creatinine ratio.

Results: The confounder model, which included size at birth, shows that compared with children from mothers who did not smoke during pregnancy, those from mothers who continued smoking during pregnancy had smaller combined kidney volumes at the age of 6 years. The strongest effect estimate was observed for mothers who smoked 5 or more cigarettes per day during pregnancy (difference for combined kidney volume, −2.80 [95% CI, −5.15 to −0.45] cm^3). Similarly, continued maternal smoking during pregnancy also was associated with a lower eGFR in childhood (difference, −2.25 [95% CI, −3.70 to −0.79] mL/min/1.73 m^2). First-trimester-only smoking was associated with a higher risk of increased albumin-creatinine ratio (OR, 1.45; 95% CI, 1.05-2.01). Among mothers who did not smoke during pregnancy, paternal smoking was associated with smaller childhood combined kidney volume (difference, −1.78 [95% CI, −3.48 to −0.07] cm^3), but not with childhood kidney function measures.

Limitations: Smoking behavior was measured with questionnaires. Follow-up measurements were available for only 70% of the children.

Conclusions: Continued maternal smoking during pregnancy is associated with smaller combined kidney volume and lower eGFR in school-aged children. Stronger effect estimates for maternal versus paternal smoking suggest that intrauterine adaptive responses may play a role as underlying mechanisms.
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INDEX WORDS: Maternal smoking; pregnancy; paternal smoking; tobacco use; cigarette exposure; fetal influences; intrauterine development; kidney size; kidney ultrasound; glomerular filtration rate (GFR); renal function; albumin-creatinine ratio (ACR); kidney development; nephrogenesis; nephron number; epidemiology; Generation R Study.

Fetal kidney development can be adversely affected by adverse exposures. Because nephrogenesis continues until 36 weeks of gestation and largely ceases thereafter, adverse exposures during this critical period may lead to impaired kidney development.[1,2] Impaired fetal kidney growth with a reduced number of nephrons might lead to glomerular hyperfiltration and sclerosis, subsequently predisposing the individual to decreased kidney function and chronic kidney disease (CKD) in adulthood.[3,4] This hypothesis is supported by various studies showing associations of low birth weight, as a result of an adverse fetal environment, with CKD in later life.[5]

To date, not much is known about the specific adverse fetal exposures leading to decreased kidney function in later life. Maternal smoking during pregnancy is an important modifiable adverse fetal exposure and is related strongly to increased risks of low birth weight and preterm birth.[6-8] Maternal smoking during pregnancy also may have direct adverse effects on fetal kidney and vascular development.[9,10] Previously, we have shown that maternal smoking during pregnancy is associated with third-trimester fetal kidney development.[11] Also, several animal studies showed structural changes in kidney morphology after prenatal cigarette exposure.[12,13] Whether these changes in early life persist and affect kidney function

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in later life is not known. Although any observational association between maternal smoking and kidney development may be the result of direct intrauterine effects of fetal smoke exposure on kidney development, it also may reflect family-based, socioeconomic-based, or lifestyle-related characteristics. Comparing the strength of effects of maternal and paternal smoking could help in disentangling the underlying mechanisms. Stronger effects for maternal compared to paternal smoking during pregnancy would suggest direct intrauterine effects, whereas similar effects for paternal and maternal smoking imply a role for shared family lifestyle–related characteristics or genetic factors.[14,15]

In a large population-based prospective cohort study of 5,622 children, we evaluated the associations of maternal and paternal smoking during pregnancy with kidney size and function, measured with blood and urine samples, in school-aged children. We used subclinical changes in kidney function as outcomes because they precede clinical disease in later life.[3]

METHODS

Study Design and Population for Analysis

The study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life onward in Rotterdam, the Netherlands.[16] Enrollment in the study was aimed at early pregnancy but was allowed until the birth of the child. The study has been approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all parents of participants. In total, 8,879 mothers were enrolled in the study during pregnancy, of whom 8,244 (84.3%) provided information about their smoking habits. For the present study, only singleton live births were included (n = 8,024), of which 5,658 (70.5%) children attended the follow-up visit from March 2008 through January 2012. Children with evidence of congenital kidney abnormalities on ultrasound examination were excluded from the study (n = 10). Kidney ultrasound, blood samples, or urine samples were obtained successfully in 5,622 (99.3%) children (Fig 1).

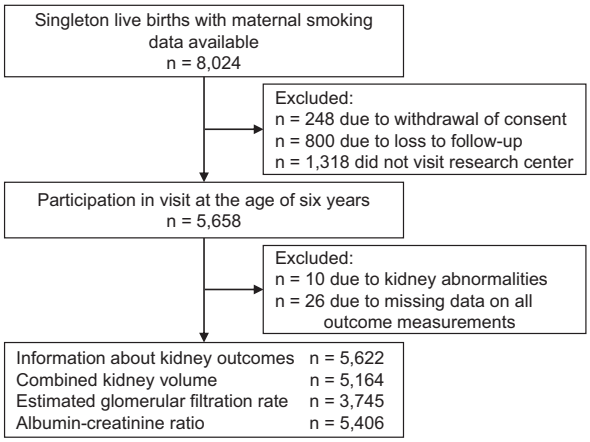

Figure 1. Flowchart.

Maternal and Paternal Smoking During Pregnancy

As we have described before,[17] we asked each mother at enrollment whether she smoked during pregnancy (no smoking, smoking until pregnancy was acknowledged [first-trimester-only smoking], or continued smoking during pregnancy). Mothers who were enrolled before a gestational age of 18 weeks and at 18 to 25 weeks of gestation also received a second- and third-trimester questionnaire, respectively. Mothers who reported in the first questionnaire that they smoked during the first trimester only (n = 921) but still reported to smoke in the second- or third-trimester questionnaire (n = 312) were reclassified into the continued-smoking-during-pregnancy category. The same strategy was used for women who reported no smoking in the first questionnaire, but reported smoking in the second or third questionnaire (n = 80). Paternal smoking was assessed in the first questionnaire by asking the mother whether the father smoked during pregnancy (yes, no, or do not know). Among mothers and fathers who smoked, the number of cigarettes smoked daily was categorized as fewer than 5 or 5 or more cigarettes per day. Information about the number of cigarettes was not available for 236 mothers and 29 fathers. Similar information completed by the father was available for 3,558 (64%) participants. Agreement between these assessments by the mother and father was good (sensitivity, 91%; specificity, 95%).[17] Tobacco smoke exposure at the child's home was assessed by questionnaire around the age of 6 years (no, seldom, or never; yes, but less than once a week; or yes, more than once a week).

Kidney Outcomes in Children

Childhood Kidney Dimensions

Left and right kidney biometrics were at the median age of 6.0 (5th-95th percentile, 5.6-7.9) years. As we described in previous publications,[18,19] we identified the left and right kidney in the sagittal plane along its 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 (cm^3) = 0.523 × length (mm) × width (mm) × depth (mm).[20] Combined kidney volume was calculated by summing right and left kidney volume. We previously showed that intra- and interobserver intraclass correlation coefficients ranged from 0.93 to 0.99 and 0.64 to 0.90, respectively.[21]

Childhood Kidney Function

Serum creatinine was measured with an enzymatic method on a Cobas c 502 analyzer (Roche Diagnostics) as previously described.[18,19] Quality control samples demonstrated intra- and interassay coefficients of variation ranging from 0.51% to 1.37%. Estimated glomerular filtration rate (eGFR) was calculated according to the revised Schwartz 2009 formula[22]; eGFR = 36.5 × height (in cm)/creatinine (in μmol/L).[22] Urine creatinine (in mmol/L) and urine albumin (in mg/L) levels were determined with a Beckman Coulter AU analyzer, and creatinine was measured according to the Jaffé method. We calculated albumin-creatinine ratio (ACR). Increased ACR was defined as 2.5 to 25 mg/mmol for boys and 3.5 to 25 mg/mmol for girls.[23]

Covariates

Information for maternal age, parity, educational level, prepregnancy body mass index, and maternal and paternal ethnicity was obtained from questionnaires.[24] Maternal and paternal blood pressures at intake were measured with the validated Omron 907 automated digital oscillometric sphygmomanometer (OMRON Healthcare B.V. Hoofddop).[25] Child sex, gestational age at birth,