Maternal Smoking during Pregnancy, Household Smoking after the Child’s Birth, and Childhood Proteinuria at Age 3 Years

Maki Shinzawa,* Shiro Tanaka,* Hironobu Tokumasu,* Daisuke Takada,† Tatsuo Tsukamoto,† Motoko Yanagita,† and Koji Kawakami*

Abstract
Background and objectives Smoking is a well known risk factor of proteinuria in adults; however, clinical studies in children are limited. The purpose of this study is to clarify the associations of maternal smoking during pregnancy and household smoking after the child’s birth with the risk of proteinuria at age 3 years old.

Design, setting, participants, & measurements We performed a population–based retrospective cohort study on 44,595 children using data on prenatal health checkups, home visit neonatal health checkups, and health checkups at 4, 9, and 18 months and 3 years of age in Kobe City, Japan. Maternal smoking status (nonsmoker, past smoker, or current smoker) was collected with standardized questionnaires. The outcome of interest was the presence of proteinuria at 3 years of age defined as urinary protein ≥1+. To evaluate the association between child proteinuria and smoking status, we performed multivariate logistic regression model analyses adjusted for confounding factors.

Results The prevalence rates of children in the maternal smoking groups (none, past, and current) were 78.9%, 4.4%, and 16.7%, respectively. The frequencies of child proteinuria defined as ≥1+ urinary protein were 1.7% in the current smoking group, 1.6% in the past smoking group, and 1.3% in the nonsmoking group. Maternal smoking during pregnancy was associated with child proteinuria (odds ratio, 1.24; 95% confidence interval, 1.00 to 1.52; P=0.05) in the multiple logistic regression model, although nonmaternal family smoking during pregnancy was not significantly associated with child proteinuria (odds ratio, 0.97; 95% confidence interval, 0.79 to 1.19; P=0.77). We also found a similar association with household smoking after the child’s birth (odds ratio, 1.23; 95% confidence interval, 0.99 to 1.54; P=0.06), although this observation was not significant.

Conclusions Maternal smoking during pregnancy was one of the risk factors of childhood proteinuria. We also found a similar association with household smoking after the child’s birth, although this observation was not significant.


Introduction
Household smoking remains a continuing public health issue, and 40% of children in the world are estimated to be exposed to household smoking. Among neonates and children, exposure to household smoking is associated with childhood asthma, chronic lung disease, cancer, and dental caries (1–3). As to the fetus, maternal smoking during pregnancy or maternal exposure to household smoking is associated with neonatal asphyxia (4), preterm birth, and low birth weight (5,6). These exposures also probably affect the child’s health in later life as childhood behavioral difficulties (7) and cardiovascular disease and diabetes mellitus in adult life (8–10). The prevalence of women smokers is higher among those of childbearing age than those at other life stages (11). The prevalence of maternal smoking during the third trimester of pregnancy in the United States was approximately 10% in 2010 (12).

Smoking is also associated with proteinuria and CKD in healthy adults and patients with IgA nephropathy or lupus nephritis (13–17). In addition to effects on renal function, smoking indirectly affects endothelial function and BP, and such indirect effects could cause proteinuria and CKD among children. However, clinical studies in children are limited to a recent report on an association of secondhand smoke exposure with nephrotic-range proteinuria among children with CKD (18). The effects of household smoking on the developing kidney have not been studied. In the process of nephrogenesis, kidneys mainly develop from 9 to 36 weeks of gestation, and no new nephrons are formed after birth (19,20). Because the number of nephrons has been determined by birth, maternal smoking during pregnancy, one of the most influential factors among intrauterine conditions, may be a risk factor for proteinuria in children, although little has been reported on the effects of maternal smoking on nephrogenesis.

Therefore, the purpose of this study is to clarify the associations of maternal smoking during pregnancy

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and household smoking after the child’s birth with the risk of proteinuria at age 3 years old in a population–based retrospective cohort study in Japan, where urinary tests at age 3 years old are mandatory according to the Maternal and Child Health Act.

Materials and Methods

Design and Settings

The Kobe Offspring Study was designed as a population–based retrospective cohort study using records from municipal health checkups in Kobe City, Japan (3). In Japan, prenatal and neonatal health checkups, prenatal care for women with the potential for childbearing, home visit neonatal health checkups for 1- to 3-month-old infants by a nurse or midwife, and home visit health checkups for 18-month-old and 3-year-old children are mandatory according to the Maternal and Child Health Act (21,22). The authors had access to deidentified data on health checkups from March 31, 2004 to April 1, 2014 after approval by the Planning and Coordination Bureau of Kobe. The authors managed the data on the basis of the Act of Personal Information Protection in Kobe City and take responsibility for their integrity. Because the data had been completely deidentified before being provided to us, this study was exempt from obtaining individual informed consent on the basis of the Ethical Guidelines for Epidemiologic Research by the Ministry of Health, Labor and Welfare. This study protocol was approved by the ethics committees of Kyoto University Graduate School and Faculty of Medicine (E2068).

Kobe City is the sixth largest city in Japan, with a population of about 1.5 million, and it is the capital city of Hyogo Prefecture on the southern side of the main island of Japan. According to the 2013 Vital Statistics, there were 90,216 births in Kobe between 2004 and 2010. All women of childbearing age and children ages 0–3 years old residing in Kobe City participated in the health checkup program. The selection criteria for this study were children who were born between April of 2004 and March of 2011 for whom information on maternal and household smoking status and dipstick test results for urinary protein were available.

Measurements

Baseline characteristics at birth included information gathered during the home visit neonatal health checkup, including sex, gestational week, birth weight and height, and the presence of an abnormality during pregnancy or at delivery. Maternal information was taken from the pregnancy notification form used to obtain prenatal care and included maternal age, maternal alcohol intake, trouble during pregnancy, and maternal and nonmaternal family smoking status during pregnancy.

Maternal smoking status and nonmaternal family smoking status (i.e., maternal exposure to household smoking during pregnancy) were identified with the standardized questionnaire in the pregnancy notification form. Smoking status of mothers, fathers, and other family members after the child’s birth was also assessed by standardized questionnaires provided at every health checkup for children 4, 9, and 18 months and 3 years of age. In this study, maternal smoking status during pregnancy was classified into three categories: none, past, and current maternal smoking during pregnancy, and nonmaternal family smoking status during pregnancy and household smoking status after the child’s birth were divided into two categories: yes or no. To assess the effect of exposure to household smoking after birth on childhood proteinuria, we defined household smoking after birth of the child as at least one yes response to smoking by parents and family members at a health checkup during the period when the infant was 4–18 months of age. Missing data on smoking status after the child’s birth were imputed by carrying the last observation forward, and 14 (0.03%) children had completely missing data from the age of 4–18 months old. Missing data other than smoking status (i.e., history of preeclampsia, maternal alcohol intake, and history of neonatal asphyxia) were assumed to be the absence of the disease or exposure. We used Birth Size Standards by Gestational Age for Japanese in 2010 as the standards of body size (23,24). Extreme outliers for birth weight and height were those participants with extremely small (less than one half of the third percentile) or large (more than 1.5 times the 97th percentile) birth weight and height for gestational age (3).

The 3-year health checkup included tests for urinary protein (−, ±, 1+, 2+, or 3+), and urinary blood (−, ±, 1+, 2+, or 3+). The outcome in this study was the presence of proteinuria at 3 years old defined as urinary protein of 1+, 2+, or 3+.

Statistical Analyses

Continuous variables were described as mean±SD or median (interquartile range), and categorical variables were described as frequency and proportion. Differences between children who were followed for 3 years and had result of urinary protein (n=44,595) and children who were not followed for 3 years or were followed for 3 years without result of urinary protein (n=19,770) were evaluated by the Wilcoxon rank sum test for continuous variables and the chi-squared test for categorical variables. After excluding the children (n=19,811) who were not followed for 3 years (n=17,167) or were followed for 3 years without result of urinary protein (n=2644), we compared baseline characteristics using the Wilcoxon rank sum test for trends for continuous variables and the Cochran–Armitage trend test for categorical variables.

To evaluate the associations of maternal and nonmaternal family smoking during pregnancy and household smoking after the child’s birth with the risk of childhood proteinuria, we performed univariate and multivariate logistic regression models and reported odds ratios (ORs), 95% confidence interval (95% CIs), and P values by Wald tests. Multivariate logistic models were adjusted for sex, gestational week, birth weight, neonatal asphyxia, maternal age, history of preeclampsia, and maternal alcohol intake as confounders. To avoid a potential multicollinearity problem, we initially examined the main effects of maternal and nonmaternal family smoking during pregnancy and household smoking after the child’s birth separately (multivariate models 1 and 2 in Table 5) and then, explored interactions between them in a logistic regression model (multivariate model 3 in Table 5).

All P values are two tailed, and statistical significance was set at P<0.05. All statistical analyses were conducted using STATA, version 12.1 (STATA Corp., College Station, TX; http://www.stata.com) and JMP 10.0.0 (SAS Institute, Cary, NC; http://www.jmp.com).

Results

The database of the health checkup program in Kobe City consisted of records on 145,318 participants in that
program between 2004 and 2014. We initially identified 72,265 children who were born in Kobe City between April of 2004 and March of 2011 for whom their mother's pregnancy notification forms were available. Records of the home visit neonatal health checkup that included information on maternal and nonmaternal family smoking status were available for 68,385 (94.6%) of the children. Subsequently, 47,239 (65.4%) children further underwent the 3-year-old health checkup. After excluding children without results of the urinary protein dipstick test (2644; 3.7%), 44,595 (61.7%) children were included in this study (Figure 1).

Figure 1. | Flow chart for selection of study participants in the Kobe Offspring Study.
The baseline characteristics of children who were followed for 3 years with result of urinary protein (n=44,595) and children who were not followed for 3 years or were followed for 3 years without result of urinary protein (n=19,811) are listed in Table 1. Statistically significant differences were observed in maternal smoking status during pregnancy, nonmaternal family smoking status during pregnancy, and household smoking status after the child’s birth. Children who were followed for 3 years with result of urinary protein had higher prevalence of nonmaternal family smoking during pregnancy (46.5% versus 41.3%; P<0.001) and higher prevalence of household smoking status after the child’s birth (61.2% versus 55.4%; P<0.001). However, the difference in maternal smoking status during pregnancy did not reach a clinically meaningful level.

After excluding the children (n=19,811) who were not followed for 3 years (n=17,167) or were followed for 3 years without result of urinary protein (n=2644), there were 35,178 (78.9%), 1957 (4.4%), and 7460 (16.7%) children in the nonsmoking, past smoking, and current smoking groups, respectively. Baseline characteristics of all participants are provided in Table 2. Mothers in the current smoking group were 2 years younger (P<0.001) and had higher prevalence of nonmaternal family smoking during pregnancy (P<0.001). Moreover, mothers in current smoking group were more likely to have a history of preeclampsia (P<0.001) and maternal alcohol intake (P<0.001), and children in the current smoking group had higher prevalence of neonatal asphyxia (P<0.001). Because of the large sample size, gestational week was statistically significant, but the size of the difference was not clinically relevant.

The prevalence of household smoking in the presence of infants 4, 9, and 18 months old was significantly higher in the current smoking group (P<0.001) (Table 3). Similar trends were found in the questionnaires obtained for 3-year-old children: 4697 (62.9%) in the current smoking group, 1672 (85.5%) in the past smoking group, and 10,802 (30.7%) in the nonsmoking group.

The frequencies of childhood proteinuria defined as ≥1+ urinary protein by a dipstick test were 1.7% (n=125) in the current smoking group, 1.6% (n=31) in the past smoking group, and 1.3% (n=452) in the nonsmoking group (Table 4). Most of the childhood proteinuria was 1+ by the dipstick test; these values were found in 1.3% (n=96) of the current smoking group, 1.1% (n=21) of the past smoking group, and 0.9% (n=331) of the nonsmoking group. There was a significant trend of childhood proteinuria with maternal smoking during pregnancy (P<0.001).

In univariate logistic regression models, current maternal smoking during pregnancy (versus nonsmoking; OR, 1.31; 95% CI, 1.07 to 1.60; P<0.01) and birth weight (per 500 g; OR, 0.88; 95% CI, 0.80 to 0.97; P<0.01) were significantly associated with childhood proteinuria at 3 years (Table 5). Even after adjusting for maternal age, history of preeclampsia, maternal alcohol intake, gestational week, birth weight, and neonatal asphyxia, current maternal smoking during pregnancy was still one of the significant predictors of childhood proteinuria (versus nonsmoking; OR, 1.26; 95% CI, 1.03 to 1.56; P=0.03) as well as birth weight (per 500 g; OR, 0.88; 95% CI, 0.78 to 0.99; P=0.04) (Table 5, multivariate model 1). Past smoking during pregnancy (versus nonsmoking; OR, 1.15; 95% CI, 0.79 to 1.67; P=0.47) and nonmaternal family smoking during pregnancy (OR, 1.09;
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95% CI, 0.92 to 1.30; \( P = 0.30 \) were not significantly associated with childhood proteinuria. There were no significant interactions between maternal smoking status during pregnancy and covariates.

Table 4 also shows that the frequency of childhood proteinuria at 3 years was significantly higher in children with household smoking after the child’s birth: 1.5% (\( n = 406 \)) with household smoking after the child’s birth and 1.2% (\( n = 202 \)) without household smoking after the child’s birth (\( P < 0.01 \)). There was a significant trend across maternal smoking status among children without household smoking after the child’s birth (\( P = 0.02 \)); 1.9% in the current smoking group, 1.7% in the past smoking group, and 1.1% in the nonsmoking group (Table 4). In contrast, the association with maternal smoking during pregnancy was not monotonic among children exposed to household smoking after the child’s birth: 1.6% in the current smoking group, 1.6% in the past smoking group, and 1.4% in the nonsmoking group. Household smoking after the child’s birth was significantly associated with childhood proteinuria at 3 years in the univariate model (OR, 1.28; 95% CI, 1.08 to 1.51; \( P < 0.01 \)) and multivariate model 2 (OR, 1.26; 95% CI, 1.06 to 1.50; \( P = 0.001 \)).

To evaluate the associations with maternal and nonmaternal family smoking during pregnancy and household smoking after the child’s birth, we performed a multivariate logistic regression model. After adjustment for all founders, maternal smoking during pregnancy (OR, 1.24; 95% CI, 1.00 to 1.54; \( P = 0.05 \)) and birth weight (per 500 g; OR, 0.88; 95% CI, 0.78 to 0.99; \( P = 0.04 \)) were associated with childhood proteinuria, although statistical significance for household smoking after the child’s birth was not observed (Table 5, multivariate model 3).

Discussion

This is the first study to investigate the association between proteinuria at the age of 3 years old and maternal smoking during pregnancy. In this cohort of 44,595 children, the prevalence rates of maternal smoking during pregnancy and household smoking after the child’s birth were >20% and 60%, respectively. Nonmaternal family smoking during pregnancy was not statistically significantly associated with childhood proteinuria (OR, 0.97; 95% CI, 0.79 to 1.19; \( P = 0.77 \)), but maternal smoking during pregnancy was associated with childhood proteinuria (OR, 1.24; 95% CI, 1.00 to 1.54; \( P = 0.05 \)). We also found a similar association with household smoking after the child’s birth (OR, 1.23; 95% CI, 0.99 to 1.54; \( P = 0.06 \)), although this observation was not significant.

Table 2. Data related to 44,595 children according to maternal smoking during pregnancy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Current, ( n = 7460 )</th>
<th>Past, ( n = 1957 )</th>
<th>None, ( n = 35,178 )</th>
<th>( P_{\text{trend}} ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal information during pregnancy</td>
<td></td>
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</tr>
<tr>
<td>Age, yr</td>
<td>30.0 [26.4–33.4]</td>
<td>30.1 [25.9–34.0]</td>
<td>32.0 [29.2–34.9]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of preeclampsia</td>
<td>195 (2.6)</td>
<td>64 (3.3)</td>
<td>825 (2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>1500 (20.1)</td>
<td>462 (23.6)</td>
<td>6212 (17.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonmaternal family smoking</td>
<td>5250 (70.4)</td>
<td>1635 (83.5)</td>
<td>13,841 (39.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Information on child at birth</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Girl</td>
<td>3642 (48.8)</td>
<td>912 (46.6)</td>
<td>17,102 (48.6)</td>
<td>0.57</td>
</tr>
<tr>
<td>Gestational week</td>
<td>39 [38–40]</td>
<td>39 [38–40]</td>
<td>39 [38–40]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3031 [2786–3285]</td>
<td>2930 [2670–3166]</td>
<td>3016 [2770–3268]</td>
<td>0.40</td>
</tr>
<tr>
<td>Neonatal asphyxia</td>
<td>83 (1.1)</td>
<td>22 (1.1)</td>
<td>277 (0.8)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data is presented as \( n \) (%) or median [interquartile range].

Table 3. Maternal smoking during pregnancy and household smoking after birth in 44,595 children

<table>
<thead>
<tr>
<th>Household Smoking after the Child’s Birth</th>
<th>Maternal Smoking during Pregnancy</th>
<th>( P_{\text{trend}} ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At any month, ( n ) (%)</td>
<td>Current, ( n = 7460 )</td>
<td>Past, ( n = 1957 )</td>
</tr>
<tr>
<td>At 4 mo(^a)</td>
<td>6340 (85.0)</td>
<td>1897 (96.9)</td>
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<tr>
<td>At 9 mo(^a)</td>
<td>5703 (76.8)</td>
<td>1818 (93.4)</td>
</tr>
<tr>
<td>At 18 mo(^a)</td>
<td>5069 (71.7)</td>
<td>1610 (91.6)</td>
</tr>
</tbody>
</table>

\(^a\)In total, <0.1%–10.2% of children had missing data on each item.
Along with the prevalence of maternal smoking during pregnancy, this study clarified that maternal cigarette smoking during pregnancy was a significant risk factor for childhood proteinuria at the age of 3 years old. Few studies of childhood proteinuria have found an association with secondhand smoking. The association between childhood proteinuria and secondhand smoking was identified in a cross-sectional study using part of the CKD in Children (CKiD) Study (18). In that study, 366 children ages 1–16 years old were assessed for the association between childhood renal outcomes and urine cotinine level. Results showed that secondhand smoke was independently associated with nephrotic-range proteinuria in children with CKD. Our study using data from a population-based retrospective cohort study with 44,595 children did not evaluate the urine cotinine level; nevertheless, our findings of an association between childhood proteinuria and household smoking after the child’s birth were compatible with those of the CKiD Study. In addition, our study is the first large-sample size study to evaluate the association between childhood proteinuria in young children and maternal smoking during pregnancy resulting in passive smoking for the fetus. Considering nephrogenesis and the mechanism of kidney damage, cigarette smoking may affect the fetus and the child differently; however, the effects of smoking on the kidney and the interaction between secondhand smoking during pregnancy and after the child’s birth are still unknown.

In adults, two mechanisms mainly underlie the association between smoking and CKD onset and progression: endothelial damage and oxidative stress (14) causing mesangial proliferation, glomerulosclerosis, and tubulointerstitial fibrosis (25–27). These mechanisms may be extrapolated to infants and young children (18). Moreover, maternal smoking during pregnancy affected nephrogenesis. Cigarette smoking releases nicotine and other harmful or potentially harmful substances, such as nitrogen oxide, polycarbonate, and carbon monoxide (28), some of which cross the placenta. Indeed, the level of neonatal urine cotinine, a nicotine metabolite, was higher in newborns with mothers who smoked during the pregnancy than newborns with nonsmoking mothers (29). These transplacental substances may affect nephrogenesis, and they be associated with epigenetic modification, which may account for the association between maternal smoking during pregnancy and postnatal outcomes in children (30–35).

The number of nephrons was lower in the neonatal mice exposed to maternal smoking than in the neonatal mice that were born to nonsmoking mothers (36). Low nephron number was a risk factor for proteinuria and onset and progression of CKD. On the basis of our previous hypothesis, maternal smoking might be associated with urinary protein in young children.

This study has several limitations. First, the follow-up rate was 61.7%, and our results may be subject to selection bias. The relatively low participation rate in the 3-year health checkup might be due to families moving during the interval between the child’s birth and third year. Infant and young child mortality would not be considered a major reason, because mortality among infants and children in Japan is low (37). Second, the outcome measurement was conducted only once, because the purpose of urinalysis at the 3-year health checkup is screening (38). Third, information on smoking status was obtained by standardized questionnaires completed by mothers, and biomarkers, such as serum cotinine levels, were not available in this study. In particular, the prevalence of maternal smoking during pregnancy may be under-reported. Furthermore, the timing of smoking during pregnancy is unknown, although it is important in nephrogenesis. Fourth, in the process of nephrogenesis, gestational week and birth weight were important factors; however, proteinuria was not associated with gestational week, but it was associated with birth weight in the univariate model and multivariate models. To clarify the association between proteinuria, gestational week, and birth weight, additional study is needed.

In conclusion, our population-based retrospective cohort study on the basis of child health checkups showed that the odds of childhood proteinuria at 3 years of age was increased by 1.2-fold among those exposed to maternal smoking during pregnancy and household smoking after the child’s birth, although the association with household smoking after the child’s birth was not statistically significant. Additional research is necessary to determine the long-term effects of secondhand smoke on CKD in adulthood.

**Acknowledgments**

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<table>
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<th>Covariates</th>
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<tr>
<td></td>
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<td>OR [95% CI]</td>
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<td><strong>Maternal information during pregnancy</strong></td>
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<tr>
<td>Maternal age, per 5 yr</td>
<td>0.95 [0.87 to 1.03]</td>
<td>0.23</td>
<td></td>
<td>0.97 [0.89 to 1.07]</td>
<td>0.56</td>
<td>0.97 [0.88 to 1.06]</td>
<td>0.47</td>
<td>0.98 [0.89 to 1.07]</td>
<td>0.66</td>
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<td>Preeclampsia</td>
<td>1.16 [0.71 to 1.88]</td>
<td>0.56</td>
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<td>1.07 [0.65 to 1.75]</td>
<td>0.78</td>
<td>1.07 [0.65 to 1.75]</td>
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<td>1.06 [0.65 to 1.74]</td>
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<td>None</td>
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<td>1.24 [0.86 to 1.78]</td>
<td>0.26</td>
<td>1.15 [0.79 to 1.67]</td>
<td>0.47</td>
<td>1.12 [0.77 to 1.63]</td>
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<td>Past</td>
<td>1.31 [1.07 to 1.60]</td>
<td>&lt;0.01</td>
<td></td>
<td>1.26 [1.03 to 1.56]</td>
<td>0.03</td>
<td>1.24 [1.00 to 1.52]</td>
<td>0.05</td>
<td>0.97 [0.79 to 1.19]</td>
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<tr>
<td>Current</td>
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<td>1.16 [0.99 to 1.36]</td>
<td>0.07</td>
<td>1.09 [0.92 to 1.30]</td>
<td>0.30</td>
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<td>Nonmaternal family smoking during pregnancy</td>
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<tr>
<td>Household smoking after the child’s birth</td>
<td>1.28 [1.08 to 1.51]</td>
<td>&lt;0.01</td>
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<td>1.26 [1.06 to 1.50]</td>
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<td>1.23 [0.99 to 1.54]</td>
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<tr>
<td>Girl</td>
<td>1.05 [0.89 to 1.23]</td>
<td>0.58</td>
<td></td>
<td>1.03 [0.87 to 1.21]</td>
<td>0.76</td>
<td>1.02 [0.87 to 1.21]</td>
<td>0.77</td>
<td>1.02 [0.87 to 1.21]</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational week, per 5 wk</td>
<td>0.85 [0.67 to 1.07]</td>
<td>0.17</td>
<td></td>
<td>1.02 [0.76 to 1.37]</td>
<td>0.89</td>
<td>1.03 [0.76 to 1.38]</td>
<td>0.87</td>
<td>1.02 [0.76 to 1.37]</td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight, per 500 g</td>
<td>0.88 [0.80 to 0.97]</td>
<td>&lt;0.01</td>
<td></td>
<td>0.88 [0.78 to 0.99]</td>
<td>0.04</td>
<td>0.88 [0.78 to 0.99]</td>
<td>0.04</td>
<td>0.88 [0.78 to 0.99]</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal asphyxia</td>
<td>1.16 [0.51 to 2.60]</td>
<td>0.73</td>
<td></td>
<td>1.06 [0.47 to 2.39]</td>
<td>0.89</td>
<td>1.08 [0.48 to 2.44]</td>
<td>0.85</td>
<td>1.07 [0.47 to 2.41]</td>
<td>0.87</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multivariate model 1 was adjusted for sex, gestational week, birth weight, neonatal asphyxia, maternal age, history of preeclampsia, maternal alcohol intake, maternal smoking during pregnancy, and nonmaternal family smoking during pregnancy. Multivariate model 2 was adjusted for sex, gestational week, birth weight, neonatal asphyxia, maternal age, history of preeclampsia, maternal alcohol intake, and household smoking after the child’s birth. Multivariate model 3 was adjusted for sex, gestational week, birth weight, neonatal asphyxia, maternal age, history of preeclampsia, maternal alcohol intake, maternal smoking during pregnancy, nonmaternal family smoking during pregnancy, and household smoking after the child’s birth. 95% CI, 95% confidence interval.


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