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# Prenatal and postnatal tobacco smoke exposure and risk of severe bronchiolitis during infancy

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ABSTRACT

*Background:* Maternal prenatal smoking has adverse effects on the growing fetus including those of respiratory nature. Although postnatal smoke exposure is a risk factor for respiratory infections, the effects of prenatal smoking independent of postnatal smoke exposure are less established. We hypothesized that both maternal prenatal smoking, and postnatal smoke exposure are risk factors for severe bronchiolitis during infancy.

*Methods:* We performed a case-control study of 1353 children born between 1996 and 2011 at a single teaching hospital. Cases were admitted to the same hospital for bronchiolitis during infancy. Maternal prenatal smoking was collected from birth records. Postnatal smoke exposure was collected from review of electronic health records. Multivariable logistic regression was used to evaluate the independent associations of the two smoking variables with severe bronchiolitis.

*Results:* 6% of cases were exposed to maternal prenatal smoking, compared with 4% of controls (P = 0.10). Postnatal smoke exposure was present in the households of 17% of cases compared with 3% of controls (P < 0.001). In a multivariable model with both smoking variables and adjustment for 10 covariates, maternal prenatal smoking was not a significant risk factor for severe bronchiolitis (adjusted OR = 1.02, 95%CI 0.56–1.84). By contrast, postnatal smoke exposure was associated with > 300% increased odds (adjusted OR 4.19, 95%CI 2.51–6.98).

*Conclusions:* Although maternal prenatal smoking has many known adverse effects, it was not associated with increased odds of severe bronchiolitis in either unadjusted or multivariable analyses. Postnatal smoke exposure was a consistently strong risk factor. Our findings support ongoing efforts to decrease infant exposure to ambient smoke.

## 1. Introduction

Maternal prenatal smoking is a known risk factor for many pediatric conditions including preterm delivery, low birth weight, and childhood asthma [1,2]. Both maternal prenatal smoking and passive smoke exposure during pregnancy can damage fetal lung development which could later increase the risk of bronchiolitis, pneumonia and asthma [2–6]. Postnatal tobacco smoke exposure places infants and children at increased risk for asthma, wheezing, otitis media, cough and acute lower respiratory tract infections, including bronchiolitis especially with exposure in the first two years of life [2,7,12]. One systemic review reported that environmental tobacco smoke exposure specifically increases the risk of hospitalization as well as the severity of RSV-related lower respiratory tract infections in infants and children [7].

Bronchiolitis is one of the major reasons for emergency department visits and hospitalizations in younger children in the U.S. with approximately 2%–3% of children younger than 1 year old hospitalized with bronchiolitis annually [8–10]. In 2009 bronchiolitis resulted in more than $ 1.7 billion in hospital charges [8]. Although the association between postnatal smoke exposure and childhood respiratory problems is an established risk factor for respiratory diseases [3,7,14], the effects of prenatal maternal smoking – independent from postnatal smoke

*Abbreviations:* TSE, tobacco smoke exposure; AD, atopic dermatitis; CHD, congenital heart disease; MDPH, Massachusetts Department of Public Health; MOMS, Massachusetts General Hospital Obstetric Maternal Study

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exposure – on the development of severe bronchiolitis among infants have not been studied as extensively. Some studies, which investigated maternal prenatal smoking and postnatal smoke exposure, found that prenatal maternal smoking increases the risk of severe bronchiolitis in children, whereas postnatal smoke exposure does not significantly increase the risk for bronchiolitis requiring hospitalization [15,20,21]. From a methodological standpoint, it is important to note that maternal smoking during pregnancy is likely a measure of both prenatal and postnatal tobacco smoke exposure (TSE), as it is challenging to separate in utero TSE from maternal smoking during postnatal period. Another study, a meta-analysis in 2012, looked at the effects of both maternal prenatal and postnatal TSE and reported that exposure to postnatal maternal smoking had the strongest association with the incidence of wheezing in children younger than 2 years [11]. The inconsistent results of past studies on the effects of pre-and postnatal smoke exposure warrant further research.

In the current study, we investigated the relations of both prenatal maternal smoking and postnatal smoke exposure to the risk of developing severe bronchiolitis during infancy. Given the prevalence of bronchiolitis during infancy and its burden on the healthcare system, it is imperative to establish the significance of potential risk factors including pre-and postnatal TSE. Also, since parents who smoke during pregnancy are likely to continue smoking or return to it after birth, it is important that smoking cessation interventions go on after pregnancy. We hypothesized that both maternal prenatal smoking and postnatal smoke exposure are risk factors for severe bronchiolitis during infancy.

## 2. Methods

### 2.1. Study design

Using a case-control design, we analyzed electronic health record (EHR) data for children born at a single teaching hospital, and birth certificate data from the Massachusetts Department of Public Health (MDPH) for these same children. EHR data include demographics, patient diagnoses, billing codes, and patient notes from inpatient and outpatient locations. MDPH birth certificate data were collected from parents (i.e., birth certificate worksheet completed at the time of birth) and from the hospital of birth. Data include demographics, maternal exposures, maternal diseases, and details of delivery (e.g., type of delivery, complications to mother or infant, delivery interventions), and other information.

### 2.2. Case and control definitions

Children diagnosed with severe bronchiolitis during infancy (age < 1 year) were identified as study cases. More specifically, children hospitalized for bronchiolitis, with an International Classification of Diseases, Ninth Revision (ICD-9) billing code for: 466.xx, respiratory syncytial virus (RSV) (ICD-9079.6), viral pneumonia (ICD-9480.x), asthma (ICD-9493.xx), or wheezing (ICD-9786.07), at age < 1 year were considered to have severe bronchiolitis. Study controls were children who did not have a bronchiolitis hospitalization during the first year of life. Controls were matched 1:1 to cases by birth year.

### 2.3. Exposure definitions

The primary exposures of interest were maternal cigarette smoking during pregnancy and postnatal smoke exposure. Maternal prenatal smoking status was obtained from MDPH birth certificate data; mothers were asked average number of cigarettes they smoked per day during pregnancy on the birth certificate worksheet. Postnatal smoke exposure status was gathered through chart review by a single trained reviewer (LPT) who looked for documentation of smoking by any household member during infancy; the reviewer was blinded to case-control status.

### 2.4. Covariate definitions

From the MDPH birth certificate data, data were collected on: child sex, race, ethnicity, presence of older siblings, maternal smoking status prior to pregnancy, maternal age at delivery, mode of delivery, gestational age at birth, and breastfeeding status at discharge.

Relevant childhood conditions were identified using ICD-9 codes from the EHR. Participants who had ≥2 billing codes for atopic dermatitis (AD) or dermatitis due to food taken internally, with the first code billed during the first year of life, were considered to have a diagnosis of AD.

We also examined diagnoses of congenital heart disease (CHD; ICD-9745.xx, 746.xx, or 747.xx). A diagnosis of CHD was made if a child had ≥3 billing codes for CHD to exclude the possibility that the child received an initial (rule-out) evaluation. Maternal history of asthma was defined as the presence of ≥3 billing codes (ICD-9493.xx) for asthma in the mothers' lifetime EHR. In instances where information was available in both the EHR and the MDPH birth certificate dataset, information was reviewed for concordance, with clarification by chart review, as needed.

### 2.5. Statistical analyses

All statistical analyses were performed using Stata 14.1 (Stata Corp, College Station, TX). Data are presented as proportions with 95% confidence intervals (95%CIs) and medians with interquartile ranges (IQR). Unadjusted analyses of the potential risk factors for severe bronchiolitis were conducted using chi-square test, Fisher's exact test, or Mann-Whitney test, as appropriate. All *P*-values were two-tailed, with $P < 0.05$ considered statistically significant.

We performed multivariable logistic regression to investigate potential risk factors for severe bronchiolitis. Some covariates were identified *a priori* (such as race, maternal asthma status) and others were considered for inclusion in the model if they were found to be associated with the outcome in unadjusted analyses ($P < 0.20$) or were thought to be clinically important. Results of the logistic regression models are reported as odds ratios (ORs) with 95%CIs.

Additionally, to investigate possible underreporting of maternal prenatal smoking, we used unique medical record numbers to link a subset of our subjects to their data available from another local study, the Massachusetts General Hospital Obstetric Maternal Study (MOMS), a prospective cohort of pregnant women enrolled during 1998–2005 (n = 9930) [16]. The details of this cohort have been described previously. We checked for exposure concordance between prenatal smoking status data provided at birth from MDPH (current study) with the data collected at the mothers' first prenatal visit interview from the MOMS study.

## 3. Results

From EHRs, we identified 1353 children (671 bronchiolitis cases, 682 controls) born between 1996 and 2011 at a single teaching hospital. Maternal and infant characteristics are shown in Table 1 and stratified by case-control status. Among severe bronchiolitis cases, 42 (6%) had a history of maternal prenatal smoking compared to 29 (4%) infant controls ($P = 0.10$); postnatal household smoke exposure was present among 113 (17%) cases compared to 22 (3%) controls ($P < 0.001$). Several other characteristics were found to be associated with severe bronchiolitis in unadjusted analyses, including: Hispanic ethnicity, mother's education level less than 12 years, presence of one or more siblings in the home, younger maternal age at delivery, cesarean delivery, gestational age < 37 weeks, and AD during infancy. Breastfeeding status was not significantly related to severe bronchiolitis.

Fig. 1 highlights that postnatal smoke exposure was associated with significantly higher risk of severe bronchiolitis. There was no significant