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Ambient nitrogen oxides exposure and early childhood respiratory illnesses

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ABSTRACT

Acute respiratory infections are common in children below 5 years and recent studies suggest a possible link with air pollution. In this study, we investigated the association between ambient nitrogen oxides (NO_x) and bronchitis or upper airway inflammation.

This longitudinal study was conducted in Teplice and Prachatice districts, Czech Republic. Children were followed from birth to 4.5 years of age. Data were compiled from medical records at delivery and at follow up, and from self-administered questionnaires from the same two time points. Air pollution monitoring data were used to estimate exposure over five different averaging periods ranging from three to 45 days prior to an episode. To quantify the association between exposure and outcome, while accounting for repeated measure correlation we conducted logistic regression analysis using generalized estimating equations.

During the first 2 years of life, the adjusted rate ratio for bronchitis associated with interquartile increase in the 30-day average NO_x was 1.31 [95% confidence interval (CI): 1.07, 1.61] and for two to 4.5 year olds, it was 1.23 (95% CI: 1.01, 1.49). The 14-day exposure also had stable association across both age groups: below 2 years it was 1.25 (95% CI: 1.06, 1.47) and for two to 4.5 years it was 1.21 (95% CI: 1.06, 1.39). The association between bronchitis and NO_x increased with child's age in the under 2 years group, which is a relatively novel finding.

The results demonstrate an association between NO_x and respiratory infections that are sufficiently severe to come to medical attention. The evidence, if causal, can be of public health concern because acute respiratory illnesses are common in preschool children.

1. Introduction

About 20% (1.9 million) of annual deaths in children under 5 years of age are due to acute lower respiratory illness (Williams et al., 2002). Recent studies have linked air pollution with respiratory illnesses (Chauhan and Johnston, 2003; Kim et al., 2004). Young children are particularly vulnerable while respiratory bronchioles, the epithelium and the immune cells are developing. For example, infants are born with only 1/10th the number of alveoli of adults, which increase about 10 fold in the first 4 years (Bateson and Schwartz, 2008). Similarly, lymphocytes undergo differentiation and maturation. In this critical period, toxic exposure may have lasting effects (Bateson and Schwartz, 2008).

Air pollutants may alter host immunity and cause cellular dysfunctions, increasing susceptibility to respiratory infections (Akaike and Maeda, 2000; Ciencewicki and Jaspers, 2007). Short term exposure has been suggested to result in airway responsiveness, while long term exposure may cause impaired immunity and respiratory infections (Han and Naeher, 2006). We previously demonstrated that short term exposures to polycyclic aromatic hydrocarbons (PAH) and particulate matter <2.5 μm ($PM_{2.5}$) were associated with bronchitis in early life (Hertz-Picciotto et al., 2007). This report extends those findings by investigating a different class of pollutant, nitrogen oxides (NO_x), predominantly produced from anthropogenic sources (Delmas et al., 1997). NO_x primarily comprise nitrogen dioxide (NO_2) and nitric oxide. NO_2 is a free radical producing oxidant with low water solubility, and a deep lung irritant (Solomon et al., 2000). Nitric oxide has more diverse roles from innate resistance to suppression of Th1 functions to induction of oxidative injury (Akaike and Maeda, 2000). In addition to direct toxicity, NO_2 is also considered a marker of combustion related pollutants from traffic and indoor sources. Respiratory illnesses are major causes of morbidity, affecting the entire family (Esposito et al., 2008), and can threaten survival in less developed countries. We therefore investigated exposure to ambient NO_x in

Abbreviations: CHAPS, Childhood Health and Air Pollution Study; POS, Pregnancy Outcome Study; IBS, Immune Biomarker Study; ICD, International Classification of Diseases; RR, rate ratios; DAG, directed acyclic graph.

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association with bronchitis and upper airway inflammation episodes, in a longitudinal study.

2. Materials and methods

2.1. Enrollment

The Childhood Health and Air Pollution Study (CHAPS) was conducted in Teplice and Prachatice districts, Czech Republic. Ninety percent of women who delivered in the two districts between May 1994 and March 1999 participated in the Pregnancy Outcome Study (POS) ($n=7502$), (Dejmek et al., 2000) from which a systematic stratified random sample of 1492 mother–infant pairs (~20%) was recruited into the Immune Biomarker Study (IBS), with an effort to oversample preterm or low birth weight infants, described previously (Hertz-Picciotto et al., 2005). When the IBS child was three or 4.5 years old, their families were contacted: 148 (10%) were ineligible (moved or not found, child or mother died, or the child was adopted) and 79 (5%) born after 1998 were not contacted for administrative reasons, leaving a total of 1265 eligible for follow up. Of these, 1133 (90%) were followed up and constitute the CHAPS sample.

2.2. Data collection

At delivery, data were obtained from medical records and maternal questionnaires collecting reproductive histories, medical conditions, medications, smoking status, drinking and other lifestyle habits, and occupational information (Hertz-Picciotto et al., 2005). At follow up three or 4.5 years later, pediatricians identified the IBS children in their practice, administered informed consent, distributed maternal questionnaires and oversaw medical record data abstraction. In the Czech Republic, pediatricians used a standard form for office visits or hospitalizations and coded all diagnoses using ICD 10 (Hertz-Picciotto et al., 2007). The follow up questionnaire was designed to capture detailed *time-varying information* about the child's early life environment, breastfeeding, day care attendance, exposure to second-hand tobacco smoke, and other factors described below.

The study was approved by the Ethical Committee of the Regional Institute of Hygiene of Central Bohemia, Prague, and by the Human Subjects Committee of the School of Medicine at the University of California, Davis.

2.3. Exposure assessment

In 1992, an air monitoring program initiated by the Czech Ministry of Environment and the U.S. Environmental Protection Agency (USEPA) installed one monitor in each of the two districts. NO_x was measured daily year round using chemiluminescence, whereas PAH, PM_{10} and $PM_{2.5}$, were monitored intermittently in some months (Hertz-Picciotto et al., 2007). Daily average NO_x obtained from central site monitors was used to derive exposures for each child. For each day of follow up, NO_x concentrations were averaged for the previous 3, 7, 14, 30 and 45 days, applying no lag. Daily temperature was also available for which similar averages were calculated. The seven day temperature correlations with different NO_x averaging periods had the narrowest range compared to other combinations (Table 1) and were used for temperature adjustment. Adjustment using other periods yielded similar results.

2.4. Outcome assessment

We focused on acute bronchitis (J20) because of higher likelihood to result in physician visits, as compared with upper respiratory infections but also investigated upper airway inflammation. Bronchitis was defined as acute inflammation of the bronchi. We conducted a validation study to assess consistency across practices, which indicated that the pediatricians did not use the distinction, typically made in the US, between bronchiolitis (J21) and bronchitis (Hertz-Picciotto et al., 2007); hence these were combined, hereafter designated bronchitis. With regard to upper airway inflammation, laryngitis/tracheitis (J04) was preferentially coded over croup/epiglotitis (J05) at a 500:1 ratio. In the survey of pediatricians in the two districts, the vast majority of respondents reported coding "a viral disease of young children with subglottic narrowing presenting as inspiratory stridor and a seal-like barking cough" as J04. For this reason, we have combined J04 and J05 and refer to those episodes as upper airway inflammation.

The diagnosis date served as a surrogate for the time of illness. To include only incident events, identical diagnoses within 1 month for the same child were considered the same illness; in other words, 29 days following the first diagnosis were censored out of the follow up time. Two diagnoses separated by ≥30 days were considered distinct events.

Table 1
Pearson's coefficients of correlation between nitrogen oxides (μg/m^3) and temperatures (°C) for different averaging periods from May 1994 to December 2000 (birth–<2 years) and from May 1996 to June 2003 (2–4.5 years) in Teplice and Prachatice, Czech Republic.

		Nitrogen oxides				
		3-day	7-day	14-day	30-day	45-day
Temperature	Birth–2 years					
	3-day	−0.29	−0.32	−0.36	−0.38	−0.39
	7-day[a]	**−0.32**	**−0.34**	**−0.37**	**−0.40**	**−0.40**
	14-day	−0.32	−0.36	−0.39	−0.41	−0.42
	30-day	−0.31	−0.35	−0.39	−0.42	−0.43
	45-day	−0.27	−0.31	−0.36	−0.40	−0.42
Temperature	2−4.5 years					
	3-day	−0.33	−0.37	−0.41	−0.45	−0.46
	7-day[a]	**−0.36**	**−0.39**	**−0.43**	**−0.46**	**−0.47**
	14-day	−0.37	−0.41	−0.44	−0.47	−0.48
	30-day	−0.34	−0.39	−0.43	−0.47	−0.49
	45-day	−0.31	−0.36	−0.40	−0.45	−0.48

[a] 7 day correlations (in bold) across different nitrogen oxides averaging periods had the narrowest range compared to other combinations. This was the preferred averaging period for temperature adjustment in the logistic regression GEE models.

2.5. Variable construction

NO_x was the exposure. Time-independent covariates were: residential district, birth year (sampling design variables); child's sex, mother's age at delivery (<20, ≥20–<30, and ≥30 years), mother's education (primary schooling, some secondary schooling and completed secondary or higher schooling) and ethnicity (central or eastern European/Roma). The time-dependent covariates were season (winter—December to February; spring—March to May; summer—June to August; and autumn—September to November), one or more other children at home aged ≤14 years, second-hand tobacco smoke (y/n), child's attendance at daycare (y/n), breastfeeding status (currently breastfed, stopped breastfeeding within the last 3 months, stopped 3 months ago or never breastfed for follow up to 2 years; and ever breastfed — y/n for the two to 4.5 year follow up period), child's age (birth–≤3, >3–≤6, >6–≤12 and >12 months for the younger group; and 24–≤36 and >36 to end of follow up for the older group), indoor fuel use for cooking or heating (electricity, gas and coal) and daily mean temperature. Based on similarity of sampling fractions, we combined birth years 1994–1996, and similarly 1997–1998.

Longitudinally, each observation was a child-day at risk for an illness from birth to 4.5 years, in which either an event occurred or did not. Because baseline incidence and the relationship to breastfeeding differed comparing younger (<2 years) with older children (two to 4.5 years), we constructed separate models for these two age periods.