A Prospective Study of the Impact of Air Pollution on Respiratory Symptoms and Infections in Infants

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Rationale: **There is increasing evidence that short-term exposure to air pollution has a detrimental effect on respiratory health, but data from healthy populations, particularly infants, are scarce.**
Objectives: **To assess the association of air pollution with frequency and severity of respiratory symptoms and infections measured weekly in healthy infants.**
Methods: **In a prospective birth cohort of 366 infants of unselected mothers, respiratory health was assessed weekly by telephone interviews during the first year of life (19,106 total observations). Daily mean levels of particulate matter (PM_{10}), nitrogen dioxide (NO_2), and ozone (O_3) were obtained from local monitoring stations. We determined the association of the preceding week's pollutant levels with symptom scores and respiratory tract infections using a generalized additive mixed model with an autoregressive component. In addition, we assessed whether neonatal lung function influences this association and whether duration of infectious episodes differed between weeks with normal PM_{10} and weeks with elevated levels.**
Measurements and Main Results: **We found a significant association between air pollution and respiratory symptoms, particularly in the week after respiratory tract infections (risk ratio, 1.13 [1.02–1.24] per 10 $\mu g/m^3$ PM_{10} levels) and in infants with premorbid lung function. During times of elevated PM_{10} (>33.3 $\mu g/m^3$), duration of respiratory tract infections increased by 20% (95% confidence interval, 2–42%).**
Conclusions: **Exposure to even moderate levels of air pollution was associated with increased respiratory symptoms in healthy infants. Particularly in infants with premorbid lung function and inflammation, air pollution contributed to longer duration of infectious episodes with a potentially large socioeconomic impact.**

Keywords: birth cohort; respiratory tract infections; air pollution; healthy infants; lung function

Exposure to air pollution, such as traffic-related pollutants and tobacco smoke, is known to have detrimental effects on respiratory morbidity, lung function, and lung growth. This is best known for at-risk individuals with asthma and chronic lung disease, where short-term exposure to nitrogen dioxide (NO_2) and particulate matter (PM_{10}) has been shown to result in increased symptoms, exacerbations, and hospitalizations (1). Long-term exposure to air pollution and tobacco smoke has been shown to result in decreased lung function in adulthood (2, 3). More recent research shows that detrimental effects of air pollution begin in childhood, which is not surprising because children are more sensitive to their surrounding environment (4, 5). Exposure to air pollution has been shown to result in increased respiratory symptoms (6–9) and upper respiratory tract infections (RTIs) also in children (10–12). Larger effects on respiratory symptoms were found when air pollutants were time-lagged by 1–5 days (6, 13, 14). Again, best evidence for adverse effects of air pollution exists in children with allergies and asthma (13, 15, 16) or children of parents with asthma (14), with relatively scarce data on short-term impact of air pollution on respiratory morbidity in healthy infants. However, the research on effects of environmental exposures on respiratory health in infancy is particularly important, because it has been shown that early life exposures may have long-term consequences on lung growth and respiratory morbidity (14, 17–21).

Effects of these early life environmental exposures may be more pronounced in particularly vulnerable groups: children with premorbid lung mechanics (22, 23), restricted lung growth (24), or preexisting airway inflammation or oxidative stress (25).

In this prospective birth cohort of healthy infants, we investigated whether exposure to air pollution was associated with the frequency, severity, and duration of respiratory symptoms and RTIs during the first year of life and whether this association was modified by lung function levels. We compared this with effects of other known risk factors for respiratory morbidity and infections. Some of the results of this study have been previously reported in the form of an abstract (26).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

There is increasing evidence that short-term exposure to air pollution has a detrimental effect on respiratory morbidity, with substantial data from asthmatic and adult subjects. Studies in healthy populations, particularly infants, are scarce.

What This Study Adds to the Field

Our study found a small but significant impact of moderate levels of air pollution on respiratory health in healthy infants. Although exposure to air pollution was not associated with severity of respiratory tract infections in our population, it was related to a longer duration of infectious episodes. This was more pronounced in infants with premorbid lung function.

METHODS

Subjects

Healthy infants of unselected mothers from the prospective Bern-Basel Infant Lung Development cohort (www.birthcohorts.net) study (27)

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were included from April 1999 to February 2011. The Ethics Committee of the region of Bern approved this study.

Outcome Assessment

During the first year of life, the research nurse called the parents weekly to assess the child's health status and respiratory symptoms using a standardized symptom score (28, 29). RTIs were defined as more than 2 consecutive days with cough, wheeze, or breathing difficulties and upper respiratory tract symptoms or elevated temperature during the week preceding the interview. The parent detailed the duration of the RTI after recovery as number of days that the infant suffered from the RTI.

Risk Factor Assessment

Potential risk factors, such as sociodemographic factors, prenatal and post-natal smoke exposure, and parental atopic disease, were assessed using standardized questionnaires (27). As surrogates for reduced lung function we used lung function measurements done at 5 weeks of age during quiet unsedated sleep as reported previously: functional residual capacity (FRC) reflecting lung growth, tidal breathing, and lung clearance index (LCI) reflecting lung mechanics. We used exhaled nitric oxide as surrogate of premorbid airway inflammation and oxidative stress (30) before the first infection.

Exposure Assessment: Air Pollution

Daily mean levels of PM_{10}, NO_2, and daily maximum ozone (O_3) were obtained from a local urban and rural monitoring station as part of the Swiss National Air Pollution Monitoring Network. Addresses were geo-coded and infants were classified as living either in an urban or rural environment.

Weekly postnatal exposure to air pollutants was estimated by weekly averages of air pollutants in the week preceding the day of each telephone interview. Lag structures of up to 10 days before the interview were constructed by shifting the window of weekly mean air pollutants by 1–10 days. As a proxy for traffic-related air pollution exposure, the distances from the mothers' home to the closest major road of at least 4- or 6-m width were computed using the geographic information system (ArcGIS, version 9; Environmental Systems Research Institute, Redlands, CA).

Statistical Analysis

We investigated the association between weekly levels of air pollution and weekly symptom occurrence, symptom scores, and RTIs. Because most symptoms occur during an RTI, analysis was then stratified by the presence of RTI. We also stratified the analysis by levels of neonatal lung function into children with higher (above-mean) and lower (below-mean) lung function.

The association between air pollution levels (exposures) and respiratory symptoms (outcomes) was investigated using generalized additive mixed-effects models (31) in R (version 2.12.1 [32]) with a quasi-Poisson distribution and an autocorrelated component to account for longitudinal symptoms in each infant. Simple models were adjusted for the week of the study (includes seasonal trends) and week of age. After excluding collinear variables, the remaining risk factors were investigated together in an adjusted model. NO_2 and PM_{10} were investigated separately because of strong colinearity. We determined the presence of an effect modification between air pollution and RTI and neonatal lung function by including an interaction term.

Additional details are provided in the online supplement.

RESULTS

Of the 378 infants enrolled in the study to date, 12 infants were lost to follow-up. We could thus include weekly symptoms in the first year of life of 366 infants with a total of 19,106 observations (Table 1). An example of fluctuations in air pollution and simultaneous changes in respiratory symptoms over 2 years for the whole cohort can be seen in Figure 1.

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION AND EXPOSURE TO AIR POLLUTION

	Summary Statistic
Anthropometrics	
Boys, n (%)	197 (54)
Length at birth, cm (SD)	49.5 (2.0)
Gestational age at birth, wk (SD)	39.9 (3.3)
Birth weight, kg (SD)	3.37 (0.44)
Symptoms	
Weeks with day symptoms (SD)	4.8 (4.6)
Weeks with night symptoms (SD)	3.95 (3.8)
Mean daytime symptom score (SD)	0.13 (0.44)
Infections	
Weeks with respiratory tract infections (SD)	2.07 (2.4)
Weeks with respiratory tract infections associated with cough or wheeze (SD)	1.69 (2.2)
Duration of respiratory tract infections, d (SD)	4.78 (9.6)
Mean daytime symptom score during respiratory tract infections (SD)	1.5 (0.99)
Risk factors	
Maternal smoking during pregnancy, n (%)	39 (11)
Passive smoking exposure during pregnancy, n (%)	48 (13)
Parental smoking at 1 yr, n (%)	12 (3)
Maternal atopy, n (%)	128 (34)
Maternal asthma, n (%)	41 (11)
Maternal eczema, n (%)	41 (11)
Maternal rhinitis, n (%)	89 (24)
Siblings, n (%)	
No siblings	188 (51)
1 sibling	118 (32)
2 or more	60 (16)
Nursery care, n (%)	76 (21)
Parents with higher education,* n (%)	201 (55)
Lung function	
MV, $ml \cdot min^{-1}$ (SD)	1,428 (280)
tPTEF/tE, % (SD)	35 (11)
LCI (SD)	6.9 (0.7)
FRC, $ml \cdot kg^{-1}$ (SD)	25 (4)
Exhaled nitric oxide, ppb (SD)	14 (6)
Environmental exposure	
Outdoor exposure	
Urban category,† n (%)	220 (60)
Distance to major road‡, m (SD)	126 (138)
Weekly average PM_{10}: rural, $\mu g/m^3$ (SD)	19.9 (10)
Weekly average NO_2: rural, $\mu g/m^3$ (SD)	15.2 (7)
Weekly average O_3: rural, $\mu g/m^3$ (SD)	85.5 (31)
Weekly average PM_{10}: urban, $\mu g/m^3$ (SD)	32.6 (13)
Weekly average NO_2: urban, $\mu g/m^3$ (SD)	48.2 (9)
Weekly average O_3: urban, $\mu g/m^3$ (SD)	62.5 (29)
Weekly mean temperature, °C (SD)	10.3
Urban PM exposure during pregnancy,§ $\mu g/m^3$ (SD)	34.2 (4.2)
Rural PM exposure during pregnancy,§ $\mu g/m^3$ (SD)	20.8 (2.5)
Indoor exposure	
Gas stove in the home, n (%) (n = 357)	108 (30)
Fireplace in the home, n (%) (n = 354)	28 (8)

Definition of abbreviations: FRC = functional residual capacity; LCI = lung clearance index; MV = minute ventilation; NO_2 = nitrogen dioxide; O_3 = ozone; PM = particulate matter; tPTEF/tE = ratio of time to peak tidal expiratory flow and expiratory time.

N = 366 infants with 19,106 symptom observations.

* Couples with a higher than average education (4-yr apprenticeship).

† Urban living is defined as living within 500 m of a city of greater than 10,000 inhabitants.

‡ Shortest distance to a road of at least 4- or 6-m width.

§ Calculated as average PM_{10} exposure from estimated date of conception to infant date of birth.

Respiratory Symptoms

Exposures to NO_2 and PM_{10} were associated with increased respiratory symptom scores (Table 2). Associations became stronger when time-lagged windows of pollutant exposures were taken into consideration. The strongest time-lagged association between respiratory symptoms and air pollution exposure was

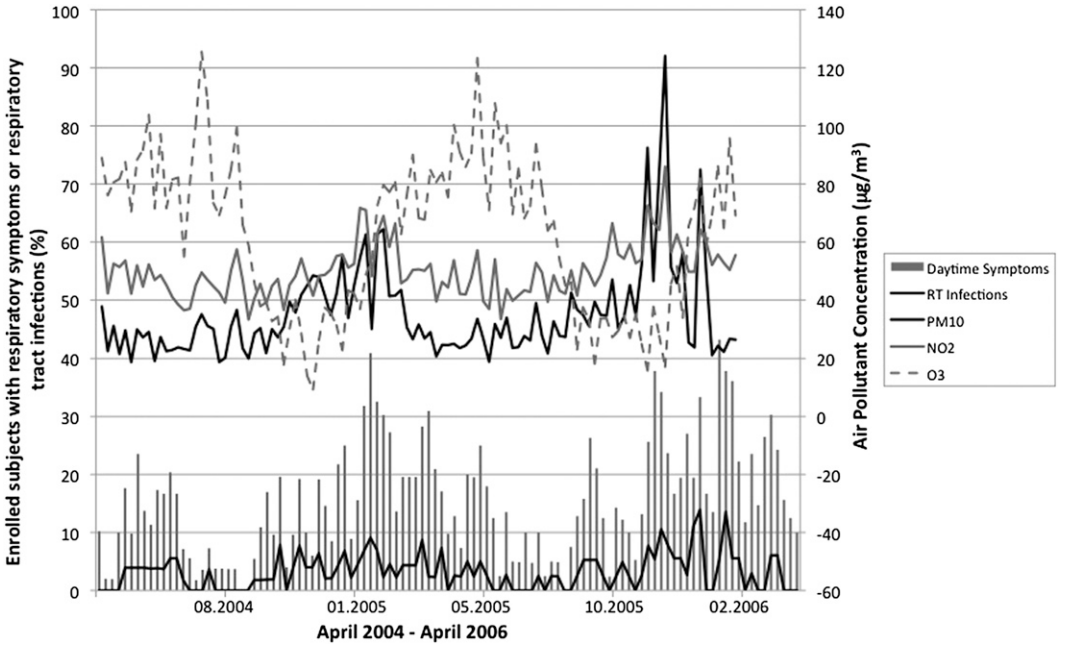

Figure 1. Air pollution concentrations, mean respiratory symptom scores, and mean respiratory tract infections from April 2004 to April 2006.

found for a time lag of 7 days for PM_{10} and for lags of 1–7 days for NO_2 exposure (Figure 2). For an increase in 10 $\mu g/m^3$ of PM_{10} exposure, the risk ratio for having respiratory symptoms was 1.04 (95% confidence interval [CI], 1.00–1.08; $P = 0.033$) and for NO_2 was 1.05 (95% CI, 1.01–1.09; $P = 0.020$) in the adjusted model. Exposure to O_3, distance to major first- or second-class road, maternal smoking during pregnancy, passive smoking, and presence of gas stove or fireplace in the home were not associated with an increased risk for respiratory symptoms (Table 2). Despite being statistically significant, the risk ratio for an increase in an air pollutant by 10 $\mu g/m^3$ was rather small compared with that of other known risk factors (Table 2).

Episodes of RTIs

We then assessed the effect of exposure to air pollution on episodes of RTI in detail. There was no association between exposure to PM_{10} or NO_2 and occurrence of RTI (PM_{10} risk ratio, 1.0; 95% CI, 0.94–1.07; $P = 0.97$) (NO_2 risk ratio, 1.05; 95% CI, 0.95–1.16; $P = 0.34$). Exposure to air pollution was not associated with increased occurrence or increased severity of symptoms during RTI (Table 3). However, in the week after the RTI subsided, there was an association between exposure to PM_{10} lagged by 3–6 days (Figure 3) and occurrence and severity of symptoms outside of an RTI (Table 3). Using a different approach, we then compared duration of RTI during weeks with pollutant levels above the 75th percentile (NO_2 >49 $\mu g/m^3$; PM_{10} >33.3 $\mu g/m^3$) with all other weeks. Mean NO_2 levels above 49 $\mu g/m^3$ were associated with an 18% increase in number of days with RTI (95% CI, 0.1–39% and $P = 0.048$, corresponding to an increase in duration of RTI from 3.9 days [95% CI, 0–9] to 4.7 days [95% CI, 1–10]) and PM_{10} levels above 33.3 $\mu g/m^3$ were associated with a 20% increase in number of days with RTI (95% CI, 2–42% and $P = 0.031$, corresponding to an increase in duration of RTI from 3.9 days [95% CI, 0–8] to 4.7 days [95% CI, 0–11]). Increases in O_3 above the 75th percentile and distance to major roads were not associated with duration of RTI. The association between air pollution and an increased duration of symptoms after an RTI was confirmed by a significant interaction term in the adjusted multilevel model between RTIs and NO_2 ($P = 0.019$) and PM_{10} ($P = 0.021$). The onset of RTI did not occur at a significantly younger age in infants exposed to high pollution levels.

Influence of Neonatal Lung Function

We investigated whether the association between air pollution and respiratory symptoms and infections was modified by preexisting lung function deficits, by stratifying infants into two groups: those with neonatal lung function levels above and those with lung function below the mean. As shown in Table 4, we found a stronger association between air pollution and respiratory symptoms in infants with lower baseline lung function. For an increase in 10 $\mu g/m^3$ of NO_2, the risk ratio for having RTI was 1.10 (1.00–1.20; $P = 0.039$) in infants with low LCI compared with 1.05 (0.98–1.13; $P = 0.159$) in infants with high LCI. Comparably, the effect of air pollution was consistently larger in infants with altered lung mechanics or airway inflammation (Table 4), but formal interaction tests provide little to no support for effect modification (e.g., interaction P value of 0.218 in the above example).

In a sensitivity analysis, we investigated these associations with alternative pollution lags and found that the results remained significant, with comparable risks for lags of 0–10 days for NO_2 and 5 and 7 days for PM_{10}.

DISCUSSION

We studied the association of weekly exposure to air pollution and subsequent changes in respiratory health in the first year of life in 366 healthy infants participating in the Bern-Basel Infant Lung Development birth cohort. The high resolution of symptom scores with 19,106 observations enabled us to investigate immediate and short-term associations of air pollution with respiratory symptoms in detail. Using time series analysis, we could show that time-lagged short-term exposure to moderate levels of air pollution has a significant effect on respiratory symptoms. In comparison with known risk factors, their quantified relative impact was small but constant throughout the first year of life. Furthermore, we found that levels of PM_{10} and NO_2 were not associated with more severe symptoms during episodes of viral infection. However, exposure to pollution was associated with increased respiratory symptom scores the week after an

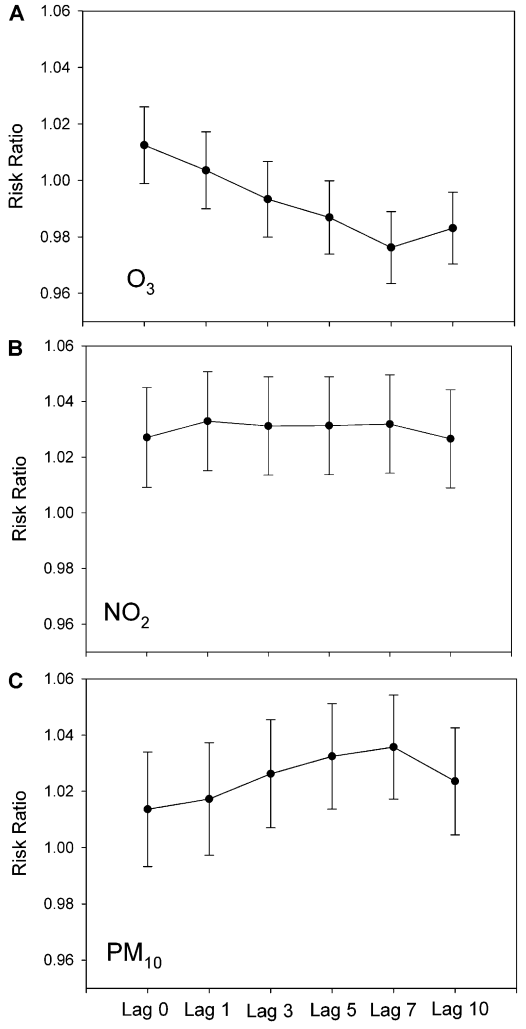

Figure 2. Association between respiratory symptoms and increases in ozone (O_3) (*A*), nitrogen dioxide (NO_2) (*B*), and particulate matter (PM_{10}) (*C*) by 10 $\mu g/m^3$ in 1-week windows of lags of 0, 1, 3, 5, 7, and 10 days. Data derived from generalized additive mixed-effects models estimating a quasi-Poisson distribution and adjusted for week of study (seasonal component) and week of age.

RTI and infectious episodes lasted longer during times of higher air pollution. Infants with surrogate markers of altered lung function and premorbid airway inflammation and oxidative stress were particularly susceptible.

Comparison with Literature

Epidemiologic studies on the impact of outdoor air pollution have found an association between long-term exposure to ambient levels of air pollution with increased respiratory symptoms (6, 7, 10–13, 33–35), bronchitis (33, 36), and lung function decreases (4, 13, 37, 38) in children. This has been shown not only in areas where pollution levels are well above suggested standards of the World Health Organization, but also in northern European communities, where mean air pollution rarely exceeds the recommended maximum levels (6, 11, 18, 33).

Short-term exposure to daily levels of NO_2 and total suspended particles in children has been shown by Schwartz and coworkers (12) to be associated with increased hospital admissions for viral croup in five German cities. Another study found that frequency and duration of respiratory symptoms was associated with NO_2 levels in preschool children from Switzerland (6). Investigation of time-lagged air pollution exposures by 1–5 days has shown an even greater association with respiratory symptoms (6, 13, 14). There are few studies providing evidence of an effect of mean long-term air pollution exposure on respiratory health in very early life (7, 14, 17, 18), but evidence of short-term effects of air pollution on respiratory health in infants is lacking.

This study is particularly powerful, because unlike many studies that focus on the effect of air pollution on respiratory health outcomes, we look at the relative effect of weekly levels of air pollution with other known risk factors on weekly respiratory health assessed prospectively in the first year of life. We found that short-term increases in NO_2 lagged by 5 days and in PM_{10} lagged by 7 days, resulted in a 5% and 4% increase in respiratory symptom scores in infants in the first year of life. Although the effect of air pollutants on respiratory symptoms was relatively small compared with the effect of other risk factors related to RTIs, exposure to air pollution was found to result in a consistent increase in respiratory symptom scores throughout the first year of life. Indoor exposures, such as gas stove for cooking and fireplace used mainly for recreational purposes in Swiss homes, did not affect respiratory symptoms in infancy.

Recent evidence has shown that exposure to air pollution may increase susceptibility to and severity of respiratory virus infections. This has been well-established in developing countries where high indoor exposures to biomass used for heating and cooking is common (39). The relationship between outdoor air pollution and respiratory infections is not as clear. The study by Schwartz and coworkers (12) assessing the effect of air pollution in five German cities on respiratory morbidity linked increases in total suspended particles and NO_2 levels from 10–70 $\mu g/m^3$ with a 27% and 28% increase in cases of croup, respectively. A study in Finland found that living in cities with higher levels of air pollution resulted in an increased odds ratio of two for upper RTIs (11). Other studies have suggested that air pollution may modify symptoms in individuals who are

TABLE 2. SIMPLE* AND ADJUSTED† MODELS, SHOWING THE ASSOCIATION OF RISK FACTORS WITH DAYTIME RESPIRATORY SYMPTOM SCORES

	Simple Model			Adjusted Model		
Variable	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Male sex	1.49	1.30–1.70	<0.001	1.41	1.23–1.61	<0.001
Siblings	1.47	1.28–1.68	<0.001	1.28	1.17–1.39	<0.001
Nursery care	1.38	1.20–1.59	<0.001	1.38	1.19–1.60	<0.001
Maternal smoking in pregnancy‡	1.14	0.94–1.39	0.176	1.16	0.92–1.45	0.210
Distance to major road	0.95	0.89–1.00	0.052	0.95	0.90–1.01	0.097
Gas stove	0.95	0.86–1.05	0.324			
Fireplace	0.90	0.78–1.05	0.173			
NO_2, lag 5§	1.03	1.00–1.07	0.080	1.05	1.01–1.09	0.020
O_3, lag 0§	1.01	0.99–1.04	0.360	1.03	1.00–1.06	0.081
PM_{10}, lag 7§	1.04	1.00–1.07	0.057	1.04	1.00–1.08	0.033

Definition of abbreviations: CI = confidence interval; NO_2 = nitrogen dioxide; O_3 = ozone; PM = particulate matter; RR = relative risk.

Data derived from generalized additive mixed-effects models estimating a quasi-Poisson distribution.

* Adjusted for week of study (seasonal component) and week of age.

† Adjusted for all variables in the table and birth weight, postnatal smoking of the mother, atopy of the mother, education of the parents, and distance to major 4- or 6-m road. NO_2 and PM_{10} were not taken simultaneously into the model because of colinearity.

‡ Maternal active smoking during pregnancy.

§ Risk ratio for an increase in pollution levels of 10 $\mu g/m^3$, additionally adjusted for temperature.

TABLE 3. ADJUSTED MODEL* OF ASSOCIATION OF AIR POLLUTION WITH RESPIRATORY SYMPTOM SCORES STRATIFIED BY PRESENCE OF RESPIRATORY TRACT INFECTION

				Symptoms outside of RTI					
	Symptoms during RTI ($n = 620$)			Infection Week Before ($n = 470$)			No Infection Week Before ($n = 18,016$)		
Variable	RR	95% CI	*P* Value	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Male sex	1.04	0.95–1.13	0.389	0.93	0.69–1.25	0.641	1.34	1.15–1.57	<0.001
Siblings	0.96	0.91–1.02	0.208	1.02	0.83–1.25	0.859	1.24	1.12–1.38	<0.001
Nursery care	0.98	0.89–.08	0.707	0.98	0.70–1.38	0.913	1.36	1.14–1.62	0.001
Maternal smoking in pregnancy†	1.06	0.93–1.21	0.384	0.79	0.44–1.42	0.429	1.02	0.76–1.37	0.916
NO_2, lag 5‡	0.99	0.97–1.02	0.579	1.05	0.96–1.15	0.298	1.04	0.99–1.09	0.104
O_3, lag 0‡	1.02	1.00–1.04	0.067	1.04	0.97–1.12	0.268	1.02	0.98–1.05	0.406
PM_{10}, lag 7‡	0.99	0.96–1.02	0.431	1.13	1.02–1.24	0.016	1.04	1.00–1.09	0.078

Definition of abbreviations: CI = confidence interval; NO_2 = nitrogen dioxide; O_3 = ozone; PM = particulate matter; RR = relative risk; RTI = respiratory tract infection. Data derived from generalized additive mixed-effects models estimating a quasi-Poisson distribution.

*Adjusted for all variables in the table and the week of study (seasonal component); week of age; temperature; birth weight; postnatal smoking of the mother; atopy of the mother; education of the parents; and distance to major 4- or 6-m road. NO_2 and PM_{10} were not taken simultaneously into the model because of colinearity.

† Active maternal smoking during pregnancy.

‡ Risk ratio for an increase in pollution levels of 10 $\mu g/m^3$.

already infected. A study of short-term effects of SO_2 and PM in children with asthma found increased respiratory symptoms during infections (15). Another study in adults found increased effects of O_3 on persons who were experiencing an RTI (40). It is therefore important to understand the interplay between exposure to air pollution and viral infections on respiratory morbidity. Although this link has been established in children with asthma (41), there is a lack of data in healthy infants and children.

By investigating symptoms during times of reported RTIs associated with cough and wheeze in our sample of healthy infants, we found that fluctuations in air pollutants did not result in an increase of symptom severity during RTIs (Table 3), but rather were associated with an increase in symptom severity outside of an RTI, especially in the week after an RTI. Weeks with elevated NO_2 and PM_{10} levels above the 75th percentile compared with all other weeks of mean levels in Switzerland were associated with an increased number of days with RTIs by around 18 and 20%, respectfully. The combination of these two analyses supports the idea that although exposure to moderate levels of air pollution does not seem to increase the prevalence of RTIs, it seems to increase the duration of those episodes.

Our results are in line with previous studies linking premorbid lung function to respiratory disease in the first years of life (22–25). In our study we found a trend toward an increased impact of air pollution on respiratory morbidity in infants with premorbid lung mechanics, reduced lung growth, and increased airway inflammation without statistically significant interaction tests. The independent involvement of several lung function parameters reflecting different aspects of lung development highlights the complex interaction between lung development, airway growth, and immune maturation on one side, and environmental triggers, respiratory viruses, and resulting symptoms on the other side (42).

Possible Mechanisms

Our study suggests that there might be a relationship between exposure to air pollution and the ability of airways to clear infectious agents and reduce concomitant inflammatory processes underlying symptom development. This may be caused by an increased susceptibility of an epithelium toward viruses when exposed to high levels of pollutants. There are a limited number of controlled, experimental studies showing the effect of pollutant exposure on respiratory infections in humans. One small study that investigated alveolar macrophage function after *in vivo* exposure to high levels of NO_2 for 15 minutes and infection *in vitro* found a depressed inactivation of the virus in half of the cells compared with control values (43). Another study found that in subjects exposed to ambient levels of PM, alveolar macrophages in bronchoalveolar lavage had a 42% reduction in ability to phagocytose opsonized yeast (44). Studies in animals have investigated the link between pollutants on pulmonary antibacterial activity in controlled experiments. Results have shown that mice exposed to NO_2 either before or after a bacterial challenge had an increased mortality (45) and risk of reinfection 30 days later (46). Thus, our study provides further epidemiologic support to controlled biologic experiments suggesting that outdoor air pollution exposure may adversely affect defense mechanisms to airway infections. We speculate that the lack of correlation between air pollution

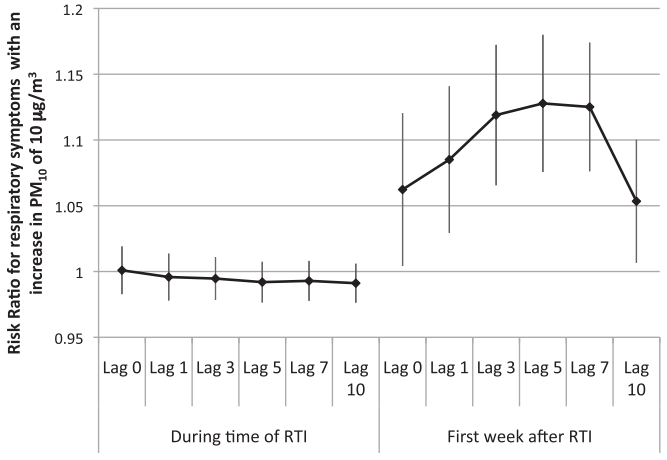

Figure 3. Risk ratios between particulate matter (PM_{10}) and respiratory symptoms, with lag windows of 0–10 days during a respiratory tract infection (RTI) and 1 week after an RTI. Data derived from generalized additive mixed-effects models estimating a quasi-Poisson distribution and adjusted for week of study, week of age, birth weight, postnatal smoking of the mother, atopy of the mother, education of the parents, and distance to major 4- or 6-m road. Nitrogen dioxide and PM_{10} were not taken simultaneously into the model because of colinearity.

TABLE 4. CHANGE IN RISK RATIO* OF AIR POLLUTANTS AND DAYTIME RESPIRATORY SYMPTOM SCORES OR RESPIRATORY INFECTIONS IN GROUPS OF LUNG FUNCTION MEASUREMENTS

	NO_2				PM_{10}			
	RR	95% CI	*P* Value	Int. *P* Value§	RR	95% CI	*P* Value	Int. *P* Value§
Respiratory symptoms								
Adjusted model†	1.05	1.01–1.09	0.020		1.04	1.00–1.08	0.033	
High LCI	1.02	0.97–1.07	0.492		1.02	0.97–1.08	0.348	
Low LCI	1.07	1.01–1.14	0.019	0.278	1.05	1.00–1.11	0.062	0.984
High FRC††	1.04	0.99–1.09	0.151		1.04	1.00–1.09	0.068	
Low FRC	1.08	1.02–1.15	0.009	0.922	1.05	0.99–1.11	0.123	0.409
High MinV	1.04	0.99–1.09	0.091		1.06	1.02–1.11	0.009	
Low MinV	1.04	0.98–1.11	0.209	0.774	1.01	0.95–1.07	0.828	0.103
High tPTEF/tE	1.03	0.97–1.08	0.369		1.00	0.95–1.06	0.979	
Low tPTEF/tE	1.05	1.00–1.11	0.061	0.773	1.06	1.01–1.12	0.011	0.103
High eNO	1.03	0.98–1.09	0.178		1.05	1.00–1.10	0.052	
Low eNO	1.05	0.99–1.11	0.098	0.268	1.03	0.97–1.09	0.338	0.591
Respiratory infections								
Adjusted model†	1.05	0.95–1.16	0.341		1.00	0.94–1.07	0.972	
High LCI	1.05	0.98–1.13	0.159		1.01	0.94–1.09	0.769	
Low LCI	1.10	1.00–1.20	0.039	0.218	1.07	0.98–1.17	0.134	0.861
High FRC††	1.05	0.98–1.12	0.204		1.03	0.95–1.11	0.519	
Low FRC	1.13	1.03–1.23	0.009	0.656	1.07	0.98–1.17	0.150	0.458
High MinV	1.03	0.96–1.10	0.449		1.04	0.97–1.11	0.290	
Low MinV	1.11	1.00–1.22	0.041	0.095	1.01	0.91–1.12	0.844	0.519
High tPTEF/tE	1.05	0.97–1.14	0.266		0.99	0.91–1.08	0.840	
Low tPTEF/tE	1.08	1.00–1.17	0.039	0.839	1.07	0.99–1.16	0.084	0.321
High eNO	1.09	1.02–1.17	0.017		1.03	0.96–1.12	0.394	
Low eNO	1.04	0.95–1.13	0.435	0.157	1.03	0.94–1.13	0.483	0.750

Definition of abbreviations: CI = confidence interval; eNO = exhaled nitric oxide; FRC = functional residual capacity; LCI = lung clearance index; MinV = minute ventilation; NO_2 = nitrogen dioxide; PM = particulate matter; RR = relative risk; tPTEF/tE = ratio of time to peak tidal expiratory flow and expiratory time.

Groups were based on mean lung function values and categorized into low (below mean) and high (above mean) lung function parameters. Data derived from generalized additive mixed-effects models estimating a quasi-Poisson distribution.

* Risk ratio is given for an increase in pollution levels of 10 $\mu g/m^3$.

† Adjusted for sex, number of siblings, nursery care, prenatal and postnatal smoking of the mother, atopy of the mother, birth weight, education of the parents, and distance to major 4- or 6-m road.

‡ FRC was further normalized by weight at date of study.

§ *P* value of the interaction term of above and below mean lung function categories with air pollution exposure on respiratory symptoms and infections in the adjusted model.

and sole occurrence of viral-induced respiratory symptoms in the first year of life may be explained by the dominating effect of viral epidemiology on this particular outcome measure. It thus seems crucial to include direct measures (e.g., viral polymerase chain reaction) or indirect proxies for exposure to viruses (number of siblings or nursery care) into studies that examine associations between exposure to air pollution and respiratory symptoms during early childhood.

Reduced lung mechanics, diminished lung growth, and increased airway inflammation may all be indicative of underlying pathology increasing the susceptibility to prolonged respiratory morbidity in response to environmental exposures. Infants predisposed to poor antiviral response develop more severe infections, possibly resulting in abnormal repair and remodeling during the critical postnatal stages of lung growth and development leading to long-term changes in airway structure (47, 48). This is supported by *in vivo* and *in vitro* studies showing that respiratory syncytial virus and human rhinovirus increase the synthesis of factors that influence lung repair, growth, and development (49–51).

The extent of viral response has also been shown to be highly dependent on epithelial barrier function. Human rhinovirus replication has been shown to be greater in damaged epithelium (52), which can be caused by exposure to air pollution (41). Viral infections themselves also compromise the epithelium, possibly leading to increased absorption of irritants across the airway wall (25). Taken together, premorbid lung function may be indicative of an underlying predisposition to abnormal responses to environmental pollutants and more severe respiratory morbidity and a higher risk of developing recurrent lung disease later in life (53).

Methodologic Considerations

This dataset has a number of strengths. Most studies of air pollution effects on respiratory health in infancy have investigated long-term prenatal or post-natal exposure levels on retrospectively assessed respiratory health by questionnaires to the parents. The results of these studies are therefore subject to recall bias. Our study investigated the effect of outdoor air pollution exposure on respiratory health assessed prospectively by weekly telephone interviews using time-series analysis. Furthermore, we have detailed data on other risk factors for respiratory symptoms in the first year of life, allowing adjustment for confounders. Because of the design of the study, we have weekly data on respiratory symptoms, enabling us to only assess associations between pollution in the week before the interview and weekly symptoms. The daily resolution of pollution levels, however, enabled us to shift the lag window between exposure and outcome by days. This implies that our lag effects refer to the average difference between symptom occurrence and air pollution exposure window. In contrast, information on RTIs is more detailed, so that we were able to look at the exact duration of RTIs on a daily basis.

Pollution measured at a central monitoring station does not exactly reflect personal exposure, but rather fluctuations represent weekly relative differences in air pollution and are still valid to investigate effect of air pollution on respiratory health

outcomes. With improvement of the personal exposure model, misclassification bias should be reduced and a more accurate effect of air pollution on respiratory health in infants might be assessed.

Relevance

This is the first study that compares weekly assessed respiratory symptoms with air pollution levels in the first year of life in term-born, healthy infants using time-series analysis. We showed that, even when taking other risk factors for respiratory symptoms into account, moderate exposure to air pollution has a small but constant impact on respiratory symptoms in the first year of life. This impact seems to be especially important in susceptible airways (e.g., after respiratory tract RTI and in those infants with reduced premorbid lung function). Although other risk factors were associated with increased severity of respiratory symptoms, air pollution seemed to affect particularly the duration of RTIs in the first year of life. We have to keep in mind that even a small risk in a large air pollution–exposed population has significant impact on population health. Because in polluted areas infants suffer from symptoms up to 20% longer after an RTI, parental work capacity and day care use are affected. By reducing these preventable detrimental influences of air pollution for the individual infant, we may be able to reduce respiratory morbidity at this vulnerable age and furthermore may avoid adverse cumulative effects on lung development and respiratory outcome later in life.

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