Air Pollution and Hospitalization for Bronchiolitis among Young Children

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Abstract

Rational: Several studies have found higher risks for childhood respiratory illness, associated with exposure to particulate matter (PM) less than 10 μm in diameter (PM_{10}) and $PM_{2.5}$ and gaseous pollution.

Objectives: We analyzed the association between air pollution and hospitalizations due to bronchiolitis, an obstructive pulmonary disorder, commonly caused by respiratory syncytial virus infant infection.

Methods: Data were obtained from a local tertiary medical center providing services for a population of 700,000 comprising two ethnic groups: predominantly urban Jews and rural Bedouin Arabs. The latter group includes 30% residing in unrecognized villages in a temporary dwelling. We included all infants (0–2 yr) hospitalized with bronchiolitis between 2003 and 2013. Daily PM estimates were obtained from a satellite-based model incorporating daily remote sensing data and assigned to the family residence locality. Other air pollutants and meteorological parameters were obtained from a local monitoring site. We used case–crossover models with adjustment for temperature.

Results: We identified 4,069 bronchiolitis hospitalizations (3,889 children), with 55.3% being Bedouin Arabs, of whom 16.8% resided in temporary dwellings. An increase in interquartile range of average weekly air pollutants was associated with an increased odds of bronchiolitis (odds ratio [95% confidence interval]): PM_{10} (1.06 [1.02–1.09]), $PM_{2.5}$ (1.04 [1.02–1.06]) and nitrogen dioxide (1.36 [1.12–1.65]). Higher effect-estimates for PM were observed among Bedouin Arabs residing in temporary dwellings (1.14 [1.01–1.30] and 1.07 [1.01–1.15]) compared with Jewish individuals (1.05 [0.99–1.11] and 1.03 [1.01–1.07]) and other Bedouin Arabs (1.05 [1.01–1.10] and 1.03 [1.01–1.07]), and among males (1.11 [1.06–1.16] and 1.06 [1.03–1.09]) compared with females (0.99 [0.94–1.05] and 1.01 [0.97–1.04]).

Conclusions: High PM levels were positively associated with bronchiolitis. The stronger associations among Bedouin Arabs may be related to higher pollution infiltration and exposure in residents of temporary dwellings.

Keywords: air pollution; particulate matter; bronchiolitis; nitrogen dioxide; sulfur dioxide

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Bronchiolitis is the most common lower-respiratory infection of infancy, and is characterized by acute inflammation, edema, and necrosis of epithelial cells that line the small airways, increased mucus production, and bronchospasm (1, 2). The most frequent pathogen associated with bronchiolitis is the respiratory syncytial virus (RSV), which accounts for 50–80% of all bronchiolitis hospitalizations during seasonal epidemics in North America (3–7).

Several studies have shown an association between particulate matter (PM) less than 10 μm in diameter (PM_{10}) or $PM_{2.5}$ with a higher incidence of respiratory disease associated with PM exposure in the adult and infant population, mediated through an induced inflammatory response and oxidative stress (8). Among the various causes for the higher susceptibility of infants are an immature immune system, smaller airways, higher respiratory rate, and frequent physical activity (9). Most studies examined the effect of anthropogenic air pollution and dust storms on asthma incidence, and found that a high concentration of pollutants was associated with higher incidence of asthma exacerbations and hospital admission (10–13).

A small number of studies found an association between bronchiolitis or RSV infection and prolonged exposure to ambient air pollution (13–15). In a case–control study assessing the association between RSV-related bronchiolitis and lifetime $PM_{2.5}$ exposure, Karr and colleagues (13) found a modestly increased risk of bronchiolitis related to chronic PM exposure, particularly in infants born just before or during peak RSV season. Pino and colleagues (14) found increased risk for bronchiolitis associated with 1–9 lag days of exposure to $PM_{2.5}$. Ségala and colleagues (15) found PM_{10} and nitrogen dioxide (NO_2) to be positively associated with consultations and hospitalizations for bronchiolitis during the winter. Finally, Rahman and colleagues (16) found higher odds of acute bronchiolitis associated with exposure to PM_{10}, among children who reside in urban areas.

Here, we explore the association between air pollution exposure and bronchiolitis in an area of unique climate. Southern Israel (Negev region) is a semiarid region located in the global dust belt, which extends from West Africa to the Arabian Desert, and is frequently subjected to dust storms. These storms can increase daily PM_{10} above the 50 $\mu g \cdot m^{-3}$ threshold defined by the World Health Organization (17) to levels above 4,200 $\mu g \cdot m^{-3}$ (18). In a recent study, we have found a strong positive association between exposure to dust storms and asthma hospitalizations and asthma medication purchase in children (19). In this population-based analysis with 11 years of follow-up, we explored the association between PM_{10}, $PM_{2.5}$, sulfur dioxide (SO_2), and NO_2 and bronchiolitis hospitalizations, using data from a tertiary medical center and satellite-based data of PM estimates.

Methods

Study Population

We included all infants aged 0–2 years admitted to Soroka University Medical Center (Beer Sheva, Israel) with bronchiolitis (*International Classification of Diseases*, *Ninth Revision*, 466) between the years 2003 and 2013. Soroka University Medical Center is the only medical center in the area, serving a total population of 700,000, with those younger than 4 years of age comprising 12%. The population in southern Israel comprises two main ethnic groups: Jewish children (40%) are mostly urban and reside in permanent houses, whereas the Bedouin Arab children are predominantly rural, and about 30% of them reside in unrecognized villages in temporary dwellings. The population in these villages resides in temporary shacks and tents, and has limited access to municipal infrastructure (20). Computerized individual demographic, clinical, laboratory, and medication prescription data were fully available. We obtained the following patient data: age; sex; ethnicity; comorbidities; and medications. Hospitalizations within 30 days after the index hospitalization were excluded from the analysis based on the assumption that these hospitalizations were most likely associated with complications from the previous hospitalization or a result of an early discharge from the previous hospitalization.

The study was approved by the institutional review board of Soroka University Medical Center.

Air Pollution and Meteorological Data

Daily average PM concentrations were assessed using a hybrid satellite-based model incorporating daily satellite remote sensing data at 1×1-km spatial resolution (21). Briefly, we used an algorithm, Multi-Angle Implementation to Atmospheric Correction, developed by the National Aeronautics and Space Administration (Washington, DC) (22), which provides aerosol optical depth data at high resolution. Using mixed models, we regressed daily PM_{10} and $PM_{2.5}$ mass concentration from the Ministry of Environmental Protection monitoring sites against aerosol optical depth traditional land use regression temporal and spatial predictors. Good model performance was achieved, with out-of-sample cross-validation R^2 of 0.79 and 0.72 for PM_{10} and $PM_{2.5}$, respectively. More in-depth details can be found in the work by Kloog and colleagues (21).

Exact home addresses were not available for the majority of the patients. The 1×1-km estimates of daily average concentrations of the pollutants were therefore averaged in each locality, and were assigned for each patient based on his/her place of residence.

Average daily data on gaseous air pollutants (SO_2 and NO_2), temperature, and relative humidity for the study period were obtained from a central monitoring site located in the center of the largest city in the region.

Statistical Analysis

Results are presented by mean ($\pm$SD) and median with interquartile range (IQR) for continuous variables and as percentages for categorical data.

We examined the association between bronchiolitis and PM_{10} or $PM_{2.5}$ using a case–crossover design (23). We used a time-stratified approach for control selection to account for the possibility of confounding by seasonal patterns, and matched control days on day of the week from the same month of the same year (24). Case period was defined as the hospitalization day, or moving average exposure of lagged exposures 0–1, 0–4, and 0–7 days. Associations with each air pollutant were tested separately and were adjusted for daily average temperature. Because each subject serves as his/her own control, all measured and unmeasured confounders that do not vary over time are matched by design.

Stratified Analyses

To assess the modification of the association by personal characteristics, we added interaction terms with sex, comorbidities, medications use, and ethnicity. The results are presented in stratification by the tested modifiers.

The data were analyzed using conditional logistic regressions (coxph, R statistical software, version 3.1.1; Vienna, Austria). Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs) for an IQR increase of the pollutants' daily average concentration.

Results

Population

We identified 4,297 hospitalizations with a primary diagnosis of bronchiolitis between the years 2003 and 2013. After excluding hospitalizations that occurred within 30 days of the index hospitalization, we observed 4,069 hospitalizations of 3,889

Table 1. Population characteristics

Population Characteristics	Hospitalizations (*n* = *4,069*) % (*n*)
Personal characteristics	
Male sex	56.8 (2,314)
Ethnicity	
Jewish	44.7 (1,806)
Bedouin, permanent dwelling	38.5 (1,556)
Bedouin, temporary dwelling	16.8 (680)
Age	
0–12 mo	93.8 (3,814)
12–24 mo	6.2 (255)
Comorbidities	
Prematurity	2.0 (82)
Cyanotic heart disease	4.2 (172)
History of respiratory illness	4.7 (192)
Neuromuscular disease	0.3 (14)
Immune deficiency	0.0 (1)
Steroid treatment	
1–10 d before hospitalization	22.7 (926)

subjects, with the majority of the cases observed in the winter (83.5%). The majority of the hospitalizations were for children younger than 12 months, half were males, and 55.3% were of Bedouin descent (of whom 13% were residents of temporary dwelling). Approximately 5% of the hospitalizations were of children with a known history of respiratory illness. In 22.7% of the cases, the child received systemic steroidal treatment within 10 days before the hospitalization (Table 1).

Air Pollution and Meteorology

The IQR of the pollutants during the study period was: 25 μg/m^3 for PM_{10} (maximal value of 420 μg/m^3); 5 μg/m^3 for $PM_{2.5}$ (maximal value of 161μg/m^3); 13 μg/m^3 for NO_2 (maximal value of 47.9 μg/m^3); and 3.14 μg/m^3 for SO_2 (maximal value of 20.2 μg/m^3). The percentage of days with pollutant concentrations higher than the World Health Organization threshold were: 40% for PM_{10} (50 μg/m^3 threshold); 22% for $PM_{2.5}$ (25 μg/m^3 threshold); and 0.5% for NO_2 (20 μg/m^3 threshold). Daily $PM_{2.5}$ and PM_{10} concentrations were higher in the winter, and NO_2 concentrations were higher in the winter and fall seasons. The average daily temperature in the study period was 14.3°C, reaching a maximal temperature of 33.3°C in the summer (Table 2).

Table 2. Summary statistics of air pollution and meteorology

Parameter	Winter	Spring	Summer	Fall
Cases, % (n)	83.5 (3,401)	6.4 (264)	2.7 (113)	7.1 (291)
PM_{10}, μg/m^3				
IQR	35.7–62.9	37.6–65.0	35.0–44.9	38.1–57.8
Mean ± SD	59.8 ± 47.4	57.3 ± 35.4	40.8 ± 11.1	49.7 ± 18.3
$PM_{2.5}$, μg/m^3				
IQR	16.8–24.5	16.6–25.7	18.0–21.9	17.1–23.6
Mean ± SD	24.1 ± 15.6	22.3 ± 8.9	20.0 ± 3.8	21.0 ± 5.9
NO_2, μg/m^3				
IQR	3.3–28.0	3.7–19.9	1.1–17.1	4.3–29.5
Mean ± SD	22.2 ± 9.4	16.4 ± 6.5	14.02 ± 5.0	23.5 ± 8.4
SO_2, μg/m^3				
IQR	0.0–6.2	0.2–6.0	0.5–5.2	0.5–7.0
Mean ± SD	4.8 ± 0.2	5.0 ± 2.1	4.1 ± 1.7	5.2 ± 2.6
Temperature				
IQR	11.3–14.6	16.7–22.0	24.4–26.5	16.2–21.5
Mean ± SD	13.1 ± 3.1	19.7 ± 3.8	25.5 ± 1.7	18.8 ± 3.4
Relative humidity				
IQR	59.0–80.0	51.0–72.0	63.9–74.0	47.6–75.0
Mean ± SD	68.6 ± 16.4	60.3 ± 16.3	67.7 ± 10.8	60.4 ± 19.6

Definition of abbreviations: IQR = interquartile range; NO_2 = nitrogen dioxide; $PM_{2.5}$ = particulate matter less than 2.5 μm; PM_{10} = particulate matter less than 10 μm; SO_2 = sulfur dioxide.

Air Pollution and Bronchiolitis

The odds of bronchiolitis-related hospital admissions was associated with increases of IQR average daily concentrations of PM_{10} (OR [95% CI]: 1.06 [1.02–1.09]), $PM_{2.5}$ (1.04 [1.02–1.06]), and NO_2 (1.36 [1.12–1.65]) 1 week before hospitalization, but not with pollutants 0–4 days before hospitalization. We observed no association with SO_2 (Figure 1).

Stratified Analysis

In a stratified analysis by ethnicity, although the interaction was not significant, we observed stronger associations with PM_{10} and $PM_{2.5}$ among Bedouins who reside in temporary dwellings (1.14 [1.01–1.30] and 1.07 [1.01–1.15], respectively). The association with NO_2 was more pronounced among Bedouin children who reside in permanent dwellings (1.56 [1.16–2.09]). The associations with the particulate pollutants were significantly stronger among males (1.11 [1.06–1.16] for PM_{10} and 1.06 [1.03–1.09] for $PM_{2.5}$) compared with females (0.99 [0.94–1.05] for PM_{10} and 1.01 [0.97–1.04] for $PM_{2.5}$). Similar effects were observed among children who were not treated with steroids (Table 3).

Discussion

In this study, we estimated the association between air pollution and bronchiolitis, as assessed by hospitalization with a diagnosis of acute bronchiolitis. Our analysis shows an increased risk of hospitalizations associated with exposure to PMs and NO_2, implying an increased risk of more severe cases of bronchiolitis. Although the interaction was not significant, Bedouin patients residing in temporary dwellings were found to be more susceptible to particulate air pollution–related bronchiolitis in comparison with other groups.

The role of air pollution in the pathogenesis of bronchiolitis is not completely known. The most accepted convention is that air pollution causes an injury to the host's immune system and

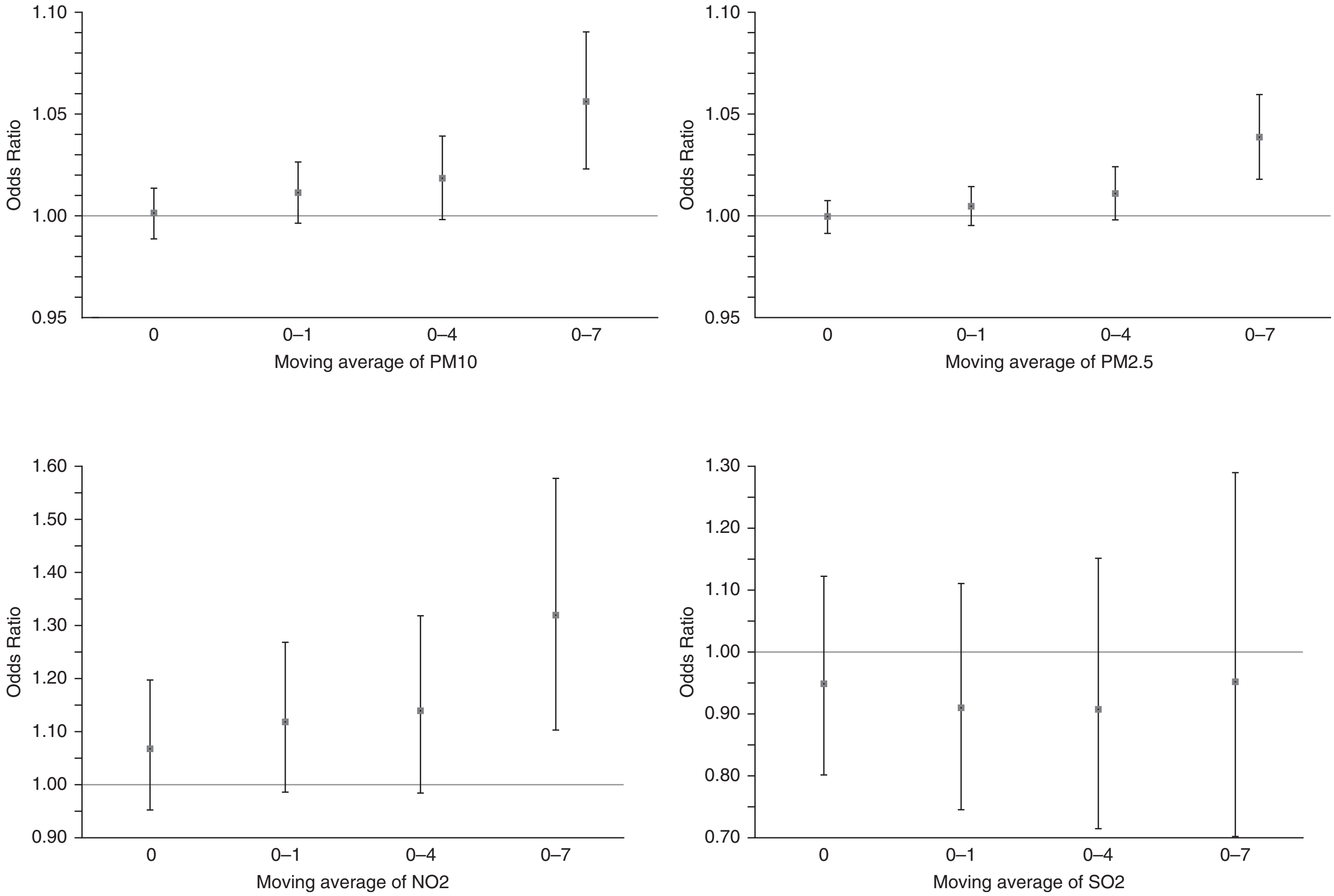

Figure 1. The association between air pollution and bronchiolitis: case–cross-over data showing the results of single-pollutant models of the association between bronchiolitis and moving average concentrations of the pollutants 0, 0–1, 0–4, and 0–7 days before the event. Each exposure was modeled separately and was adjusted for the average temperature that corresponds to the period of the exposure tested. Results are presented as odds ratios and 95% confidence intervals for interquartile range increase in particulate matter (PM) less than 10 μm (PM_{10}; 25 $\mu g/m^3$), PM less than 2.5 μm ($PM_{2.5}$; 5 $\mu g/m^3$), nitrogen dioxide (NO_2; 13 $\mu g/m^3$), or sulfur dioxide (SO_2; 3.14 $\mu g/m^3$).

interferes with the ability of the already immature immune system to clear bacteria and other pathogens from the lung (13, 25, 26). A number of *in vivo* studies showed the effect on mice. Harrod and colleagues (27) showed an increase in several inflammatory proteins and viral DNA. Lambert and colleagues (28) showed a synergistic effect between air pollution and exposure to RSV. Another study (29) did not find a direct association between exposure to NO_2 and an effect on the respiratory system, but did find an effect on the immune system. Specifically, RSV-induced IL-6 and IL-8 production was significantly reduced in cells exposed to NO_2. A less common hypothesis is that the presence of viral particles in dust may contribute to the pathogenesis of respiratory diseases via modulation of the immune system (28, 30–32). The investigators showed how carbon particle exposure after exposure to RSV enhanced bronchoalveolar lavage (BAL) total protein, and virus-associated chemokines, including monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, and regulated upon activation, normal T cell expressed and secreted. Macrophage inflammatory protein-1α mRNA expression was increased in the alveolar epithelium, where ultrafine particles deposit in the lung.

The repeated daily exposure to PM, at least in mice, causes an increase in cytokine levels in both BAL fluid and serum, indicating a systemic response. Lung mRNA levels of antioxidant/phase II detoxifying enzymes are reduced after exposure to PM. Furthermore, disruption of lung tissue oxidant–inflammatory/defense balance is evidenced by increased levels of lipid and protein oxidation; thus, such tissue insult may represent an important mechanism that predisposes the lung to acute bronchiolitis (33).

Other investigators assessed the role of PM exposure on the bacterial attack on the respiratory system. Zhao and colleagues (34) showed how exposure of rats to $PM_{2.5}$ significantly increased levels of IL-6 in BAL; prior $PM_{2.5}$ exposure markedly increased the susceptibility and mortality of rats to subsequent Staphylococcus aureus infection. Recently, investigators assessed gene expression profiles in subjects living in two regions of the Czech Republic differing in levels and sources of air pollution. They found that chronic exposure to air pollution resulted in reduced gene expression

Table 3. The association between bronchiolitis and moving average concentrations of particulate matter less than 10 μm and particulate matter less than 2.5 μm 1 week before hospitalization: results of case–cross-over models stratified by sex, ethnicity, and steroid treatment

	PM_{10} OR (95% CI)	*P* Value	Interaction *P* Value	$PM_{2.5}$ OR (95% CI)	*P* Value	Interaction *P* Value	NO_2 OR (95% CI)	*P* Value	Interaction *P* Value
All available cases	1.06 (1.02–1.09)	<0.01		1.04 (1.02–1.06)	<0.01		1.36 (1.12–1.65)	0.001	
Sex									
Male	1.11 (1.06–1.16)	<0.01	0.014	1.06 (1.03–1.09)	<0.01	0.057	1.34 (1.05–1.71)	0.018	0.615
Female	0.99 (0.94–1.05)	0.905	0.953	1.01 (0.97–1.04)	0.530	0.934	1.41 (1.02–1.94)	0.033	0.309
Ethnicity	1.05 (0.99–1.11)	0.058	0.406	1.03 (1.01–1.07)	0.024	0.471	1.25 (0.93–1.67)	0.124	0.734
Jewish									
Bedouin, permanent dwelling	1.05 (1.01–1.10)	0.023		1.03 (1.01–1.07)	0.017		1.56 (1.16–2.09)	0.003	
Bedouin, temporary dwelling	1.14 (1.01–1.30)	0.049		1.07 (1.01–1.15)	0.029		1.15 (0.65–2.04)	0.614	
Steroid treatment 10 d before hospitalization									
Yes	1.07 (1.01–1.13)	0.013		1.04 (1.01–1.08)	0.027		1.33 (0.98–1.81)	0.061	
No	1.05 (1.01–1.09)	0.019	0.582	1.04 (1.01–1.07)	0.002	0.952	1.38 (1.07–1.78)	0.011	0.849

Definition of abbreviations: CI = confidence interval; NO_2 = nitrogen dioxide; OR = odds ratio; $PM_{2.5}$ = particulate matter less than 2.5 μm; PM_{10} = particulate matter less than 10 μm.
Presented are the results of single-pollutant models of the association between bronchiolitis and moving average concentrations of the pollutants 1 week before the event. Each exposure was modeled separately and was adjusted for a moving average of temperature 1 week before the event. Results are presented as OR and 95% CI for interquartile range increase in PM_{10} (25 μg/m^3), $PM_{2.5}$ (5 μg/m^3), and NO_2 (13 μg/m^3).

response. This finding may also be part of the explanation as to why children exposed to PM cannot respond properly to acute infection with RSV (35).

The observed association between hospitalization and air pollution is consistent with other studies (13, 14) that demonstrated an increased risk for RSV bronchiolitis hospitalization associated with air pollution. Pino and colleagues (14) found that the largest increase in "wheezing bronchitis" was observed 9 days after exposure to high levels of $PM_{2.5}$. Ségala and colleagues (15) found a significant increase in bronchiolitis consultations and hospitalizations associated with increases of PM_{10}, SO_2, and NO_2.

Adding to the aforementioned studies, in which the major source of air pollution was from traffic emissions, the particulate pollution measured in the south of Israel is dust of natural origin as well. Regarding the timing of the clinical signs, similar to the delayed effect reported by Pino and colleagues (14), we found 7 days of exposure to pollutants to be associated with higher risk of bronchiolitis. These findings are in accordance with the usual 7-day gap from the exposure until the infant develops the symptoms (36).

Our results suggest stronger associations with PM_{10} and $PM_{2.5}$ among Bedouins who reside in temporary dwellings. As reported in previous studies conducted in the Negev region, bronchiolitis is more common among Bedouins, especially those living in temporary dwellings (37). The higher prevalence may be attributed to a lower socioeconomic level, greater number of family members, poor sanitation, malnutrition, and lower quality of local medical treatment in Bedouin localities (38). As previously shown, the stronger association with PM among Bedouins who live in temporary dwellings may be attributed to higher indoor pollution infiltration, in addition to the aforementioned factors (19). In addition to the natural pollution infiltration, indoor smoke exposure due to cooking on an open fire is very common in this population (39). Therefore, the effect in this population may be even stronger than the effect found in our study, which may have been attenuated due to larger exposure measurement error.

Our study had several notable strengths. The semiarid climate of the Negev region allowed us to examine the associations with air pollution under extreme environmental conditions. In addition, the unique living conditions of the Bedouin population allowed the investigation of the effect of air pollution among a highly exposed population, in which the outdoor pollution estimates are expected to approximate the indoor measurements due to greater pollution infiltration (40).

Our study had a number of limitations. First, the use of the average pollution exposure in the locality of residence may have caused an exposure measurement error. However, the use of novel, spatially, and temporally resolved satellite models to estimate exposure to PM is expected to reduce the error. Second, the study population was limited to the severely ill patients who required hospitalization, and did not include milder cases of bronchiolitis. Third, potential modifiers, such as smoking, household crowding, and access to health care, were not available for this analysis. Finally, given the multiple pollutants and exposure windows tested, it is possible that part of the associations in the stratified analyses were significant by chance. However, the associations found in the main analysis were highly significant, even after considering multiple comparisons correction.

In conclusion, we observed an association between exposure to high PM and NO_2 concentrations and hospitalizations due to acute bronchiolitis. Bedouin children appear to be at particular risk, possibly due to residing in temporary dwellings. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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