Coarse Particulate Matter and Hospitalization for Respiratory Infections in Children Younger Than 15 Years in Toronto: A Case-Crossover Analysis

Mei Lin, MD, MPH, MSc*; David M. Stieb, MD, MSc†; and Yue Chen, MD, PhD*

ABSTRACT. Objectives. The purpose of this study was to examine the association between ambient air pollution and hospitalization for respiratory infections among children who were younger than 15 years in Toronto during a 4-year period (1998–2001).

Methods. Exposures averaged during periods that varied from 1 to 7 days were used to assess the effects of air pollutants, including thoracic particulate matter (PM10), fine (PM2.5) and coarse (PM10–2.5) particulate matter, carbon monoxide (CO), sulfur dioxide (SO2), nitrogen dioxide (NO2), and ozone (O3), on hospitalization for respiratory infections. A case-crossover design was used to calculate odds ratios for the hospitalization adjusted for daily weather conditions with an incremented exposure corresponding to the interquartile range in air pollution exposures.

Results. When particulate matter and gaseous pollutants were mutually taken into account, the effect remained pronounced for PM10–2.5 in both boys and girls. The adjusted odds ratio for 6-day average exposure to PM10–2.5 with an increment of 6.5 μg/m3 was 1.15 (95% confidence interval: 1.02–1.30) for boys and 1.18 (95% confidence interval: 1.01–1.36) for girls. The effect also remained for PM10 in boys and for NO2 in girls. PM2.5, CO, SO2, and O3 showed no significant effects on hospitalization for respiratory infection in both genders when other pollutants were taken into consideration.


ABBREVIATIONS. CO, carbon monoxide; SO2, sulfur dioxide; NO2, nitrogen dioxide; O3, ozone; PM10, thoracic particulate matter <10 μm in aerodynamic diameter; PM2.5, fine particulate matter <2.5 μm in aerodynamic diameter; TÉOM, tapered element oscillating microbalance; PM10–2.5, coarse particulate matter between 2.5 and 10 μm in aerodynamic diameter; OR, odds ratio; CI, confidence interval; TSP, total suspended particles.

L ower respiratory infection is a main cause of mortality and morbidity in children in developing countries. Morbidity from childhood respiratory infections is also high in developed countries. Although respiratory infections in children are usually nonfatal in developed countries, they heavily burden the health care systems. Additional progress in preventing the diseases will have a significant impact on children’s health.

Although there is abundant evidence linking outdoor air pollution with respiratory symptoms, reduced lung function, bronchial reactivity, and asthma, the relationship of hospital morbidity for respiratory infections to a relatively low level of exposure to air pollution in children has not been well studied and is considered a knowledge gap in developed countries. Most previous studies of hospital outcomes associated with air pollution exposures usually either aggregated respiratory infections with other respiratory conditions such as asthma and chronic obstructive pulmonary disease into a single study group or focused on the air pollution effect on respiratory infection in all ages, elderly, or very young children (aged 0–2 years). Children generally breathe more rapidly than adults, they may have more exposure to air pollutants per kilogram of body weight, and respiratory infections are generally more common in boys than in girls. So far it has not been clear whether there are gender differences in effects of ambient air pollutant exposures on respiratory infections in children. This study used a case-crossover design to examine the association between ambient air pollution and respiratory infections in boys, girls, and children as a whole who were younger than 15 years in Toronto, Ontario, Canada.

METHODS

The present analysis was based on daily air pollution and hospitalization data collected in metropolitan Toronto between 1998 and 2001. Hospitalization data were obtained from the Discharge Abstract Database. We selected hospitalizations for respiratory infections in the sub-age group (0–14 years) as our study population. Hospitalization for respiratory infections was defined as an admission for which respiratory infections were the primary diagnosis that caused the greatest number of hospital days of stay. Respiratory infections in this analysis included the following conditions: laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia, and influenza (International Classification of Diseases, Ninth Revision codes 464, 466, and 480–487). Admissions were restricted to children who both resided in Toronto and were admitted there. This study included only admissions to hospitals for acute care and active treatment that were considered as emergency or urgent. Both planned admissions and transfers from other institutions.
were excluded from this analysis. The data were grouped into
daily hospital admission counts for both boys and girls.

Air pollution data were obtained from the National Air Pollu-
tion Surveillance system, and weather data were obtained from
Environment Canada’s weather archive. Daily air pollution data
were available from a minimum of 4 to a maximum of 7 monitor-
ing stations, including carbon monoxide (CO) and sulfur dioxide
(SO2) from 5 monitoring stations, nitrogen dioxide (NO2) and
ozone (O3) from 7 stations, and particulate matter of median
aerometric diameter <10 and 2.5 μm (PM10 and PM2.5, respec-
tively) from 4 stations. The study region consisted of the cities of
Toronto, North York, East York, Etobicoke, Scarborough, and
York. These monitoring sites span the breadth of the region and
include major population areas. Figure 1 shows the locations of
monitoring stations for each air pollutant. CO, NO2, O3, and SO2
were measured using “reference methods” or “equivalent meth-
ods” as designated by the US Environmental Protection Agency.
CO was measured using nondispersive infrared spectrometry,
NO2 was measured using chemiluminescence, O3 was measured
using chemiluminescence/ultraviolet photometry, and SO2 was
measured using coulometry/ultraviolet fluorescence. PM2.5 and
PM10 were measured using tapered element oscillating microbal-
ce (TEOM) instruments. Although PM10 and PM2.5 TEOM sam-
pers were not necessarily co-located, we computed the average
crude fraction (PM10-2.5) as average PM10 minus average PM2.5
among sites in Toronto. Although in absolute terms this may
introduce error, it should accurately reflect relative day-to-day
changes in exposure to coarse particles (Tom Dann, Environment
Canada, personal communication, 2004). There is a reasonably
good correlation between PM10-2.5 from dichotomous monitor and
TEOM coarse fraction. The correlation was 0.85 between dichoto-
mous PM10-2.5 and the difference between TEOM PM10 and
TEOM PM2.5 at 1 site that had all 3 measures. The correlation was
0.74 when the values were averaged over all sites.

Daily averaging concentrations of each air pollutant were used
in this analysis, except daily maximum 1-hour level was used for
O3 because of its diurnal profile of exposures. Average values
were calculated when data were available from >1 monitoring
station.13 The concentrations of O3 are very low at night, peaking
in the late afternoon, and then falling off in the evening.14 Daily
information on weather conditions was obtained from Pearson
international airport and included daily mean temperatures and
dew point temperature.

A bidirectional case-crossover design was used in this study.
Bateson and Schwartz15 reported that the bidirectional case-cros-
sover design can control for different patterns of time trends in
exposures and outcomes. The level of air pollution at the time of
hospitalization for each case (the case period) was compared with
a level obtained in a specified period before and/or after the
health event (the control period). Cases in this analysis included
only children who were 0 to 14 years of age and were admitted to
a hospital in the study area, with respiratory infections as the
principal reason for the hospital stay during the period between

The acute effects of environmental exposure may be immediate
or may occur several days after exposure. In this study, we exam-
ined the acute effect of 1-day to multiple-day averages of air
pollution ending on the admission date. Previous studies have
documented that increased hospitalizations are most strongly as-
associated with air pollution on the day of admission or within up to
4 days.4,7,16 A recent study observed that the estimated effect of
multiple-day exposures to air pollution could be stabilized on 5 to
6 days.17 In this study, we calculated 1- to 7-day exposure aver-
ages ending on the admission date as the exposures in the case
period.

Control periods of 2 weeks before and after the admission date
were used in the bidirectional scheme to minimize autocorrelation
between case and control exposures and to control for seasonal
and long-term effects.17,18 To be matched with the case period,
exposures in the control period were expressed as 1- to 7-day
averages for each pollutant ending on the date 2 weeks before and
after the admission date.

This study applied conditional logistic regression models for
the case-crossover design by using the SAS 8.2 statistical package’s
PHREG procedure, a program for fitting the Cox proportional
hazards model.19 The conditional likelihood function for logistic
regression can be treated as a special case of Cox partial likelihood,
which is used to fit the proportional hazards model.20 We esti-
mated odds ratios (ORs) for hospitalization of respiratory infec-
tions in relation to various air pollutants during the case period as
compared with the control periods after adjustment for daily

Fig 1. Locations of air-pollution–monitoring stations in Toronto.
mean temperature and dew point temperature. On the basis of previous studies, we added squared terms of each of the weather conditions as additional covariates. The ORs were calculated on the basis of an increment in exposure corresponding to the interquartile range of each pollutant. The effects of particulate matter on hospitalization for respiratory infections were examined further, taking into consideration the effects of gaseous pollutants (CO, SO\textsubscript{2}, NO\textsubscript{2}, and O\textsubscript{3}). Particulate matter was also taken into account when the relationships between gaseous pollution and hospitalization for respiratory infections were examined. Because thoracic particulate matter (PM\textsubscript{10}) is a function of fine (PM\textsubscript{2.5}) and coarse (PM\textsubscript{10–2.5}) particulate matter, only fine and coarse particulate matter were considered in the analyses of gaseous pollutants in relation to hospitalization for respiratory infections.

Lumley and Levy\textsuperscript{22} first pointed out that a standard conditional logistic regression analysis for bidirectional case-crossover designs is only approximately correct and in some cases estimates would be biased. Some design strategies have been suggested by several studies\textsuperscript{18,22,23} to eliminate or reduce these biases. Lumley and Levy\textsuperscript{23} have a concern that short-term autocorrelations in the exposures may introduce bias analogous to overmatching in a case-control study. However, such bias will be largely reduced when the interval between case and control periods is weekly based. A 1-week interval allows exclusion of a short-term autocorrelation and ensures independence among observations. A simulation study\textsuperscript{23} suggested that selection bias in a case-crossover study design could be reduced by choosing a shorter interval period. A 2-week interval between case and control periods was selected in the present study with considerations of control of short-term autocorrelation and time-varying trends and assessment of potential multiple-day exposure effects. Another simulation study conducted by Levy et al\textsuperscript{18} showed that there is little bias (0.4%) when an interval of 2 weeks is used.

### RESULTS

Table 1 provides summary statistics for air pollution, weather conditions, and hospitalizations for respiratory infections. There were a total of 6782 hospitalizations for respiratory infections in children who were 0 to 14 years of age (3998 for boys and 2784 for girls) with a daily average of 4.64 (2.74 for boys and 1.91 for girls) in Toronto during the period from 1998 to 2001. Daily information for gaseous pollutants (Table 1) was available for the whole study period. Estimated effects of air pollution on hospitalization for respiratory infections in boys were significant only before and after adjustment for gaseous pollutants (Table 3). The adjusted OR for a 6-day average exposure to PM\textsubscript{10–2.5} with an increment of 6.5 \mu g/m\textsuperscript{3} was 1.15 (95% CI: 1.02–1.30) for boys and 1.18 (95% CI: 1.01–1.36) for girls. The corresponding OR for PM\textsubscript{10} with an increment of 12.5 \mu g/m\textsuperscript{3} was 1.25 (95% CI: 1.01–1.54) in boys. There was no significant association between fine particulate matter (PM\textsubscript{2.5}) and hospitalization for respiratory infections in boys, girls, or children as a whole when gaseous pollutants were taken into account.

For gaseous pollutants associated with hospitalization for respiratory infections, only the effect of 5- to 7-day average exposures to NO\textsubscript{2} in girls but not in boys was significant, and the adjusted OR for a 6-day exposure to NO\textsubscript{2} was 1.31 (95% CI: 1.05–1.63; Table 3). The associations between gaseous pollutants, including CO, SO\textsubscript{2}, and NO\textsubscript{2}, and hospitalizations of respiratory infections in boys were significant only before adjustment for particulate matter. O\textsubscript{3} showed no significant effect on hospitalizations for respiratory infections in either boys or girls before and after adjustment for particulate matter.

### TABLE 1.

Distribution of Daily Concentrations of Air Pollutants, Weather Conditions, and Hospitalization for Respiratory Infections Among Children 0 to 14 Years of Age: Toronto, 1998–2001

<table>
<thead>
<tr>
<th>Variables</th>
<th>Days</th>
<th>Mean</th>
<th>SD</th>
<th>Percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Minimum</td>
</tr>
<tr>
<td>Air pollution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM\textsubscript{10–2.5} \mu g/m\textsuperscript{3}</td>
<td>1442</td>
<td>10.86</td>
<td>5.37</td>
<td>0</td>
</tr>
<tr>
<td>PM\textsubscript{2.5} \mu g/m\textsuperscript{3}</td>
<td>1461</td>
<td>9.59</td>
<td>7.06</td>
<td>0.25</td>
</tr>
<tr>
<td>PM\textsubscript{10} \mu g/m\textsuperscript{3}</td>
<td>1461</td>
<td>20.41</td>
<td>10.14</td>
<td>4.00</td>
</tr>
<tr>
<td>CO ppm</td>
<td>1461</td>
<td>1.16</td>
<td>0.38</td>
<td>0.38</td>
</tr>
<tr>
<td>SO\textsubscript{2} ppb</td>
<td>1461</td>
<td>4.73</td>
<td>2.58</td>
<td>1.00</td>
</tr>
<tr>
<td>NO\textsubscript{2} ppb</td>
<td>1461</td>
<td>24.54</td>
<td>7.56</td>
<td>9.20</td>
</tr>
<tr>
<td>O\textsubscript{3} ppb</td>
<td>1461</td>
<td>38.06</td>
<td>17.48</td>
<td>3.30</td>
</tr>
<tr>
<td>Weather conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average temperature, °C</td>
<td>1461</td>
<td>9.44</td>
<td>10.25</td>
<td>−18.40</td>
</tr>
<tr>
<td>Average dew point temperature, °C</td>
<td>1461</td>
<td>3.45</td>
<td>9.45</td>
<td>−26.90</td>
</tr>
</tbody>
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Hospitalizations for respiratory infections, n

<p>| | | | | | | | | |</p>
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</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 6782)</td>
<td>1461</td>
<td>4.64</td>
<td>3.57</td>
<td>0</td>
<td>2.00</td>
<td>4.00</td>
<td>6.00</td>
<td>22.00</td>
</tr>
<tr>
<td>Boys (n = 3998)</td>
<td>1461</td>
<td>2.74</td>
<td>2.36</td>
<td>0</td>
<td>1.00</td>
<td>2.00</td>
<td>4.00</td>
<td>14.00</td>
</tr>
<tr>
<td>Girls (n = 2784)</td>
<td>1461</td>
<td>1.91</td>
<td>1.81</td>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
<td>3.00</td>
<td>11.00</td>
</tr>
</tbody>
</table>
daily average concentration decreased from 17.99 g/m³ to 9.59 g/m³ for PM2.5 and from 30.16 g/m³ to 20.41 g/m³ for PM10. For O₃, however, there was an increase in the mean level of daily maximum 1-hour concentration, and such an increase could be related to warmer summers. The level of PM₁₀ and PM₂.₅ never exceeded the US National Ambient Air Quality Standards, with an average level being ~13% of the standard of 150 μg/m³ for PM₁₀ and 15% of the standard of 65 μg/m³ for PM₂.₅. For gaseous pollutants, similarly, the means of daily average levels of CO, SO₂, NO₂, and O₃ were below the National Ambient Air Quality Standards, whereas NO₂ exceeded the standard of 53 ppb on 2 days and O₃ exceeded the standard of 120 ppb on 1 day.

Although air pollution levels are relatively low in Toronto, coarse and thoracic particulate matter in this study showed significant effects on hospitalization for respiratory infection. When gaseous pollutants were included in regression models, the effects of coarse PM remained significant for both genders, and that of thoracic PM was significant for boys.

### DISCUSSION

Air pollution levels are relatively low in Toronto as compared with many other cities of a similar size in the world. Air pollution levels during the study period from 1998 to 2001 generally were lower as compared with those in previous years, between 1980 and 1994.7 The maximum daily concentration of each pollutant was largely reduced, with a reduction ranging from 12% for O₃ to 65% for SO₂. The mean daily average concentration decreased from 17.99 μg/m³ to 9.59 μg/m³ for PM₂.₅ and from 30.16 μg/m³ to 20.41 μg/m³ for PM₁₀. For O₃, however, there was an increase in the mean level of daily maximum 1-hour concentration, and such an increase could be related to warmer summers. The level of PM₁₀ and PM₂.₅ never exceeded the US National Ambient Air Quality Standards, with an average level being ~13% of the standard of 150 μg/m³ for PM₁₀ and 15% of the standard of 65 μg/m³ for PM₂.₅. For gaseous pollutants, similarly, the means of daily average levels of CO, SO₂, NO₂, and O₃ were below the National Ambient Air Quality Standards, whereas NO₂ exceeded the standard of 53 ppb on 2 days and O₃ exceeded the standard of 120 ppb on 1 day.
particulate matter was not associated with hospitalization for respiratory infections in either gender.

Previous studies showed inconsistent results regarding particulate matter and respiratory infections. \( \text{PM}_{10} \) was found to be associated with hospitalizations for pneumonia in all ages in Birmingham, UK, between 1992 and 1994\(^{26}\) and in elderly people in Minnesota in the period 1986–1989.\(^{27}\) One study in German cities found that total suspended particles (TSP) was significantly related to pediatrician-reported croup but not to bronchitis.\(^{28}\) Another study in Rome, Italy, found no relationship between TSP and emergency department admissions for acute respiratory infections in children.\(^{29}\)

\( \text{PM}_{10-2.5} \) tended to have a greater effect on hospitalization for respiratory infections than \( \text{PM}_{2.5} \), which is consistent with previous findings for asthma hospitalizations in children.\(^{7,17}\) There is also evidence for other health outcomes, including mortality from all causes, respiratory diseases, and cardiovascular disease and hospitalizations for cardiovascular diseases.\(^{30}\) Coarse particles deposit in the upper airways of the lungs and are associated with increased cytotoxicity and proinflammatory cytokines interleukin-6 and interleukin-8.\(^{32}\) An experimental study showed that exposure to coarse particles significantly exacerbated pulmonary infection in mice.\(^{33}\) Particulate matter is likely immunosuppressive and may undermine normal pulmonary antimicrobial defense mechanisms.\(^{34}\) Additional studies are needed to explore the potential mechanisms.

In our study, some gaseous pollutants showed significant effects on hospitalization for respiratory infections, but the influences were no longer significant when particulate matter was taken into consideration. The only exception is the effect of NO\(_2\) in girls, which remained significant even after controlling for particulate matter. Several previous studies have linked respiratory infection to exposure to NO\(_2\).\(^{28,29,35,36}\) Two of these studies also looked at the effect of TSP,\(^{26,29}\) and only 1 study\(^{28}\) found an association between TSP and croup cases. None of these studies considered the exposure to inhalable particulate matter with aerometric diameter \( \leq 10 \mu \text{m} \). Most of these studies did not perform gender-specific analyses. Only 1 case-control study in Stockholm found that wheezing bronchitis was related to outdoor NO\(_2\) exposure in girls but not in boys, which was consistent with our finding of NO\(_2\) effects on respiratory infections. NO\(_2\) exposure was found to be associated with a reduction in peak expiratory flow with virus infection by up to 75%.\(^{5}\)

Boys have smaller airways relative to their lung volume than girls.\(^{37}\) Other factors such as smooth muscle and vascular functions and hormonal status may also play a role in the gender-related susceptibility in air pollution effects on respiratory infections. In the present study, boys were more likely to be admitted to the hospital for respiratory infection than girls. A recent study\(^{38}\) suggested that in children who were younger than 15 years, the hospitalization for respiratory infection was more common in boys than in girls, but such a gender difference decreased with increasing age and reversed in children and young adults. There is a lack of consistent results for gender differences in health effects of various air pollutants.

It remains unclear how ambient outdoor air pollutants interact with respiratory infectious agents. Experimental evidence suggests that exposures to ambient air pollution may adversely affect lung defense functions such as aerodynamic filtration, mucociliary clearance, particle transport, and detoxification by alveolar macrophages. Macrophages can inhibit viral replication and also limit viral infections by removing the debris of destroyed cells and by presenting viral antigens to T lymphocytes.\(^{5}\)

The present study applied averaged air pollution exposures over centrally sited outdoor monitors to be a surrogate of personal exposures. Misclassification of individual exposures would be a concern when exposure measurement is at the population level. Such an exposure error generally does not lead to substantial bias in the risk estimates while the variance of the estimate is increased.\(^{38}\) Although the case-crossover study has the advantage of incorporating measurements of exposure or potential effect modifiers into the analysis when this information is available on an individual level, the hospitalization data for the present study were available only at the aggregated level. Future studies applying geospatial modeling would be powerful to estimate environmental exposure concentrations at the neighborhood or even the individual level and therefore take into account variations in environmental exposures across a study region.\(^{39}\)

CONCLUSIONS

Our study suggested a detrimental effect of relatively low levels of ambient particulate matter and gaseous pollutants on hospitalization for respiratory infections in children. After adjusting for other pollutants, hospitalization for respiratory infections was still significantly associated with coarse particulate matter in both genders, with thoracic particulate matter in boys, and with NO\(_2\) in girls. Effects of fine particulate matter CO, SO\(_2\), and O\(_3\) were not significant when other pollutants were included in the models.

ACKNOWLEDGMENTS

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