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Short-Term Effects of Ambient Air Pollution on Asthma Hospitalization in Children: Case-crossover and Time Series Analyses

by

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment of the requirements for the MSc degree in Epidemiology

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ABSTRACT

Case-crossover and time series analyses were used to assess associations between ambient air pollutants and asthma hospitalization among children 6-12 years of age living in Toronto between 1981 and 1993. Exposures averaged over periods varying from one to seven days were used. The results from bi-directional case-crossover and time series analyses were similar. Coarse particulate matter ($PM_{10-2.5}$) was significantly associated with asthma hospitalization in both males and females. The data showed no significant effects of fine ($PM_{2.5}$) and thoracic (PM_{10}) particulate matter on asthma hospitalizations. Gaseous pollutants, including carbon dioxide (CO), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) were significantly related to asthma hospitalization in males or females or both sexes, but ozone (O_3) was not. These studies provide strong evidence for asthma hospitalization in children in relation to relatively low levels of ambient air pollution, and suggest that reducing current ambient levels of air pollution will have important population health benefits.

CHAPTER 1 INTRODUCTION

1.1 General

Asthma is one of the most prevalent chronic conditions of childhood in Canada and other developed countries (Clark et al., 1999; Millar and Hill, 1998), affecting approximately 10% to 15% children and teens in Canada (Millar and Hill, 1998; NIH, 1998; Bai et al., 2001). In Canada, asthma is the leading cause of school absenteeism (Millar and Hill, 1998). The total cost of the disease was estimated to be over Can $500 million annually (Health Canada, 1997).

Exposure to outdoor air pollution is a potential risk factor for the development and exacerbation of asthma. WHO (2001) estimated that air pollution from cars causes 395,000 extra asthma attacks in adults and 162,000 attacks in children each year in three European countries (Austria, France and Switzerland). Although ongoing efforts are being made to improve air quality (WHO, 2001), the burning of fossil fuels for heating and the persistent growth in motor vehicles continue to degrade the ambient air quality in industrialized countries (Tattersfield, 1996). Carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and ozone (O_3) represent major constituents of gaseous outdoor pollutants arising from motor vehicles exhaust in large urban areas such as Toronto (Tattersfield, 1996; Macfarlane et al., 2000), although nearly 60% of particles and 30% of sulfur dioxide are due to the use of fossil fuels for heating in that city (Macfarlane et al., 2000).

Although there have been a number of studies relating air pollution to asthma hospitalization or emergency room visits (Burnett et al., 1999; Norris et al., 1999; Sheppard et al., 1999; Morgan and Wlodarczyk, 1998; Lipsett et al., 1997; Wordley et al., 1997; Stieb et al., 1996; Schouten et al., 1996; Koren, 1995; Burnett and Krewski, 1994; Schwartz et al., 1993), the results are not entirely consistent. Some investigators have recently challenged the notion that fine particulate matter ($PM_{2.5}$, less than 2.5 microns in average aerodynamic diameter) is more relevant to adverse health effects than coarse particulate matter ($PM_{10\text{-}2.5}$, between 2.5 and 10 microns in average aerodynamic diameter) (Loomis, 2000; Burnett et al, 1999). Loomis (2000) suggested that exclusion of coarse particulate matter from consideration could ignore a potentially important contributor to adverse health effects. The U.S. Environmental Protection Agency (1995) has noted that coarse particulate matter deposited in the upper airways may be more relevant for asthmatic responses and irritation. However, most studies have failed to consider the potential effects of coarse particulate matter on asthma related outcomes. In addition, it is not clear whether there are associations between ambient levels of gaseous pollutants, such as CO, SO_2, NO_2 and O_3, and asthma hospitalization, especially in children.

Almost all of the previous epidemiological studies on the short-term effects of air pollution on asthma and other respiratory conditions have been based on time series analysis. However, some investigators have argued that time series analysis is somewhat model dependent, and therefore, hinders comparisons of results across different studies (Moolgavkar et al., 1995; Bateson and Schwartz, 1999).

Consequently, alternative analytic approaches may help to clarify the relationship between ambient air pollution and respiratory health.

Case-crossover analysis, an innovative epidemiologic technique developed by Maclure (1991), is used to study the transient effects on the risk of acute events. This analysis is an adaptation of the case-control study, in which cases serve as their own controls in order to eliminate potential confounding due to fixed characteristics of individuals. In particular, the case-crossover analysis 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 conventional case-crossover analysis uses uni-directional control sampling, might introduce a bias when time trends exist in data. The present study also used bi-directional case-crossover design to control the effects of time trends and seasonal patterns (Navidi, 1998; Cakmak et al, 1997). Although several studies have been used the case-crossover approach to assess the mortality effect of air pollution in recent years (Lee and Schwartz,1999; Neas and Schwartz, 1999), few studies have used case-crossover analysis to evaluate the relationship between air pollution and asthma hospitalization, and made direct comparisons with the results of time series analysis.

In this study, uni- and bi-directional case-crossover analyses and time series analyses were used to evaluate the associations between asthma hospitalizations and size fractionated particulate matter and gaseous pollutants among children 6-12 years of age in Toronto. One to seven day exposure averages were used to assess effects of prolonged exposure to air pollution on asthma hospitalization. Children are thought to

be more susceptible to air pollution due to the rapid growth and development of the lungs and greater amount of time spent outdoors as compared to adults (Macfarlane et al., 2000; Dugandzic et al., 2001).

1.2 Research Objectives

The objectives of the thesis are as follows.

Primary objective: To examine the associations between short-term exposure to ambient air pollution and hospital admissions for asthma among children 6-12 years of age in Toronto, using case-crossover analyses and to compare the resultant risk estimates with those derived from time series analyses.

Secondary objectives:

i) To evaluate the impact of using different control periods (within the case-crossover design) on estimates of risk;

ii) To assess the effects of prolonged exposure to air pollution on asthma hospitalization using one to seven day exposure averages;

iii) To examine possible gender differences in the relationships between air pollutants and asthma hospitalization in children; and

iv) To assess the role of fine versus coarse particulate matter in asthma hospitalization risk.

1.3 Hypotheses

It is hypothesized that a short-term exposure to ambient air pollution at a relatively low level is related to an increased risk of asthma hospitalization. Both

case-crossover and time series approaches have their advantages and limitations, and are used to test the hypothesis. It is also hypothesized that the effects of particulate matter on asthma hospitalization in children depend on particulate size.

CHAPTER 2 LITERATURE REVIEW

2.1 Childhood asthma

Asthma is a common disease among children (0-14 years of age) in Canada and other developed countries (NHLBI, 1998; Millar and Hill, 1998; NIH, 1998). Unlike many chronic diseases, asthma often appears very early in childhood. The lifelong consequences of social and economic burdens of asthma can be substantial. Asthma results in significant health care expenditures, reduces productivity, and seriously affects the quality of life for individuals with asthma and their families (Juniper, 1997; NIH, 1998). According to the report from World Health Organization, asthma affects over 100 million people worldwide (NIH, 1998). In Canada, 10 to 15% of children are reported to have asthma, though some experts believe the figure may be as high as 20% (Millar and Hill, 1998). The prevalence of asthma can be as high as 20-30% among certain populations, in Australia and New Zealand (NIH, 1998; NHLBI & WHO, 1995). According to the 1998/99 National Population Health Survey (NPHS), approximately 579,000 children under age 15 years had asthma in Canada (Bai et al, 2001). About 5.0 million children suffered from asthma in the United States between 1990 and 1994 (NHLBI, 1998). In Canada, asthma resulted in more than 60,000 hospital admissions (approximately 29,000 for children) and more than 450 deaths annually from 1990 to 1994 (Millar and Hill, 1998). Asthma is a leading cause of school absenteeism. The total cost for asthma has been estimated to be over $500 million per year (Health Canada, 1997).

2.1.1 Asthma definition, diagnosis and risk factors

Definition. Asthma is a chronic respiratory disorder characterized by paroxysmal or persistent symptoms of dyspnea, chest tightness, wheeze and cough. Airway inflammation plays a central role in asthma, causing recurrent episodes of asthma symptoms, and is usually associated with airflow obstruction, and airway hyperresponsiveness (NHLBI, 1997).

Diagnosis. Accurate diagnosis of asthma is difficult. It is generally believed that the disease is under-diagnosed (Sear, 1991). Because there are no well-validated noninvasive measurements of airway inflammation in relation to asthma, clinicians and epidemiologists commonly rely on the following surrogate indices: a history of recurrent symptoms, reversible airflow obstruction using spirometry, lung function tests, and exclusion of alternative diagnosis (NHLBI, 1997; NHLBI & WHO, 1995). Since international guidelines differ in their emphasis on confirmatory diagnostic testing, comparisons of epidemiological data from different countries is difficult (NHLBI & WHO, 1995).

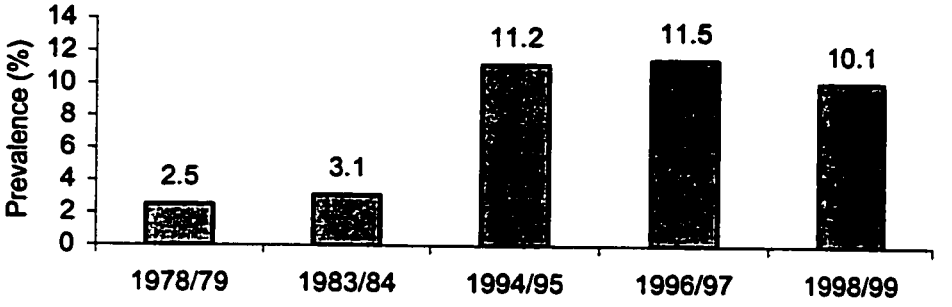
Risk factors. Asthma can be triggered by various factors, although the exact cause of asthma has not been well understood. Risk factors for asthma can be either inherent (part of one's own nature) or external (environmental characteristics). Family history of asthma is a strong risk factor. The risk of asthma in children is about 1 in 5 if one parent has asthma, and even as high as 2 in 3 if both parents have asthma (Vermeulen, 2002). During childhood, boys are more likely to have asthma than girls. After 12-14 years of age, females predominate through the rest of the age

range (Bjornson and Mitchell, 2000). Exposure to environmental tobacco smoke has been reported to be a risk factor for development of asthma (Bjorksten, 1994), although not all studies have identified such a link (Aberg et al., 1996). Smoking was found to exacerbate asthma. Smoking during pregnancy has been related with diminished lung functions, airway hyper-reactivity and allergy in the newborn (Dezateux et al., 2001). There is evidence that inhaled allergens including moulds, pollen, spores, pets, and cockroaches may lead to asthma (Bai et al., 2001; Lundback, 1998). Other factors such as air pollution, dampness, climatic conditions (Lundback, 1998), respiratory infections (Bai et al., 2001; Aberg et al., 1994) and stress/excitement (Vermeulen, 2002) can cause an asthmatic attack. Recently, obesity was found to be associated with asthma in women, but not in men (Chen et al., 2002).

2.1.2 Recent trends in asthma prevalence, hospitalization, and mortality

Prevalence. Internationally, it is estimated that the prevalence of asthma has increased approximately 50% over the last 10 to 15 years, with the highest prevalence found in the United Kingdom, New Zealand, Australia, and Ireland (NHLBI, 1998).

Figure 2.1 Trends in asthma prevalence among children under age of 15 years, Canada



Source:
Millar WJ, Hill GB. Childhood asthma. Health Rep 1998;10:9-21.
Bai T, Kenney A, Gorder BV. Chapter 4 Asthma. In: Respiratory disease in Canada. Canadian Institute for Health Information, Canadian Lung Association, Health Canada, and Statistics Canada, September 2001.

Data source:
National Population Health Survey 1994/95, 1996/97 and 1998/99, Statistics Canada. 1994/95 NPHS only included children aged 12-14 years.
1978/79 Canada Health Survey.
1983/84 Canadian Health and Disability Survey.

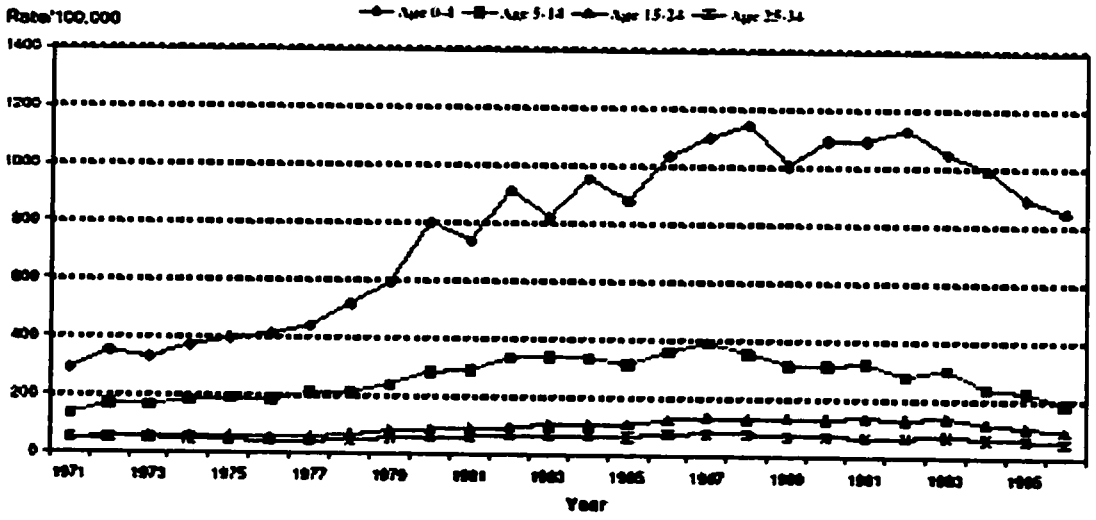
In Canada, the prevalence of self-reported asthma among children under 15 years of age increased from 2.5% in 1978/79 to 11.2% in 1994/95 (Figure 2.1) (Millar and Hill, 1998; Bai et al., 2001). This increase seems to have leveled off since 1994/95. The prevalence of asthma is higher among children than adults, and among boys as compared to girls (NACTF, 2000). Approximately 13% of boys and 9% of girls had asthma in Canada in1994/95 (Millar et al., 1998). In the United States, the prevalence among children 5 to 14 years of age increased from 4.3% in 1980 to 7.4% in 1993/94 (NHLBI, 1999). Similar trends have also been found in Sweden, Australia, and other developed countries (Aberg, 1989; Robertson et al, 1991). The possibility

of self-reporting bias is not considered to be a likely explanation for these increases (Weiss et al., 1993).

Hospitalization. In Canada, asthma remains the leading cause of hospitalization for children 1 to 4 years of age (Bai et al.,2001). Among older children, it ranks as the second or third cause of hospitalization (NACTF, 2000). Boys are more likely than girls to be hospitalized for asthma. Asthma hospitalization rates among children under 15 years of age increased until the late 1980s and then decreased (Figure 2.2) (NACTF, 2000). Similar trends in asthma hospitalization rates were also found among children 5-17 years of age and among adults in the U.S. (Weiss, et al, 1993). The recent decline in asthma hospitalization rates may reflect improved disease management and/or decreased exposure to possible risk factors for asthma. Downsizing in the hospital sector with reduced availability of beds may also have influenced asthma hospitalization (Bai et al.,2001). Since the 1970s, asthma hospitalization rates among children have increased in England, New Zealand, and Australia (Mitchell, 1985).

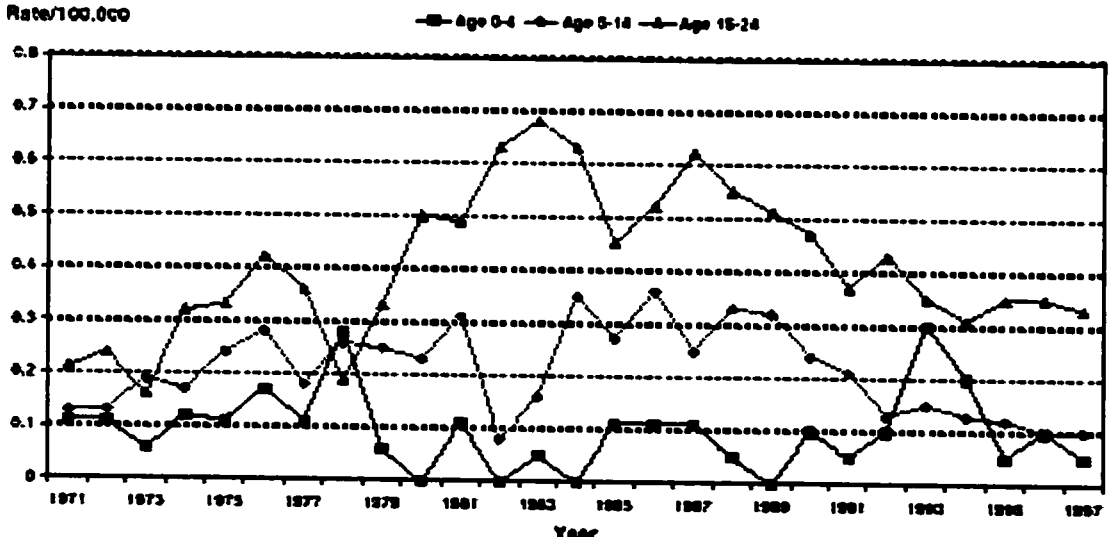
Mortality. Asthma mortality in children is uncommon. The age-adjusted mortality rates for asthma ranged from 0.1 to 0.4/100,000 among children 5-14 years of age in Canada, 1971-1996 (Figure 2.3) (NACTF, 2000). Asthma mortality rates increased in the 1980s, but have subsequently decreased (Figure 2.3) (NACTF, 2000). This pattern was most apparent in the 5-14 and 15-24 year old age groups.

Figure 2.2 Age-adjusted asthma hospitalization rates /100,000 in the younger age groups, Canada excluding territories, 1971-1996 (1991 standard population)



Source: The National Asthma Control Task Force (NACTF). The prevention and management of asthma in Canada: A major challenge now and in the future. 2000. Data source: LCDC 1999 - Using CIHI Data

Figure 2.3 Age-adjusted asthma mortality /100,000 in the younger age groups, Canada excluding territories, 1971-1996 (1991 standard population)



Source: The National Asthma Control Task Force (NACTF). The prevention and management of asthma in Canada: A major challenge now and in the future. 2000. Data source: LCDC 1999 - Using Statistics Canada Data

2.2 Outdoor ambient air pollution

2.2.1 Sources of outdoor air pollution

Outdoor air pollution arises from both natural and anthropogenic sources. Natural sources include eroded areas, forest fires, volcanoes, pollen, bacteria, spores, and viruses. Human activities create pollution, with the major sources of pollution in urban areas being the burning of fossil fuels for heating and in combustion-engine vehicles (Macfarlane et al., 2000). Industrial processes, manufacturing of chemicals, and power generation are also important sources of air pollution (Macfarlane et al., 2000). The concentration and constituents of outdoor air pollution are influenced by factors such as population density, the degree of industrialization, season, and weather conditions (WHO, 2001).

2.2.2 Trends

Since the 1970s, outdoor air quality has improved substantially in Canada's urban areas (Dugandzic et al.,2001). However, air pollution remains a problem in some areas of Canada.

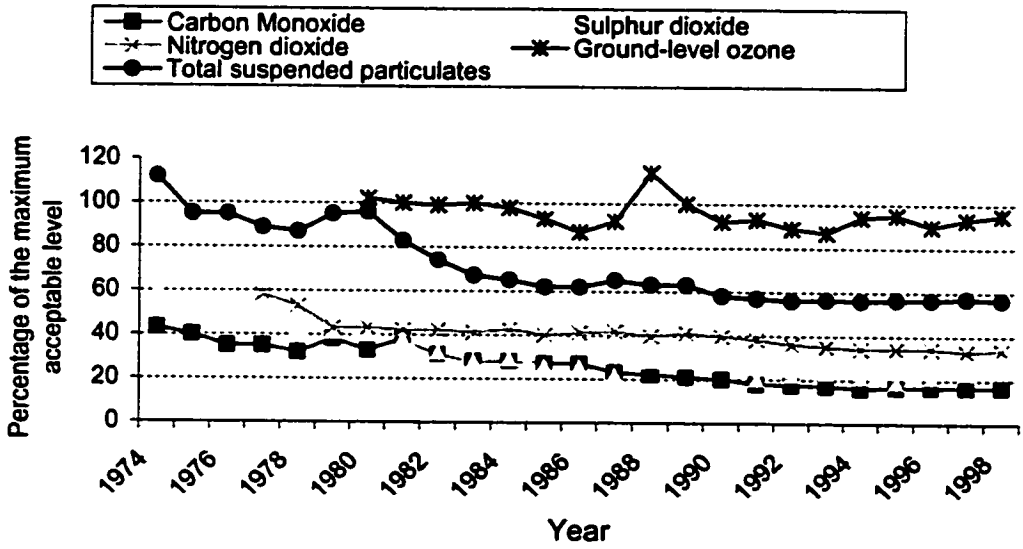
Airborne Particulate matter (PM). The commonly monitored and reported indicators of airborne particulate matter include total suspended particulate (TSP), thoracic particulate matter (PM_{10}, less than or equal to 10 micrometers in diameter), fine particulate matter ($PM_{2.5}$, less than or equal to 2.5 micrometers in diameter), and coarse particulate matter ($PM_{10\text{-}2.5}$, between 2.5 and 10 micrometers in diameter). The National Air Pollution Surveillance (NAPS) network began monitoring PM_{10} and

$PM_{2.5}$ in 1984 using specialized samplers (Burnett et al., 1999). Smaller particles, less than 10 micrometers in diameter, appear to pose a greater health risk because they are more likely to penetrate deep in the lungs (U.S. EPA, 1995). Fine particles result from fuel combustion in motor vehicles, power generation, and industrial facilities, as well as from residential fireplaces and wood stoves. Such particles are often formed by chemical reactions, and contain carbonaceous particles, sulphate and nitrate particles. Most coarse particles are formed directly from mechanical disruption, and contain mineral particles and windblown dust, as well as biological material such as bacteria, pollen, spores, and mites.

Average levels of airborne particulates in Canadian cities fell by 53% between 1975 and 1997 (Figure 2.4), primarily due to controls of vehicles and industrial emissions, an increase in road paving, and restrictions on the burning of garden wastes (Environment Canada, 1996). However, the current National Ambient Air Quality Objective for TSP is 120 $\mu g/m^3$ averaged over 24 hours, and is still exceeded at least 10% of the time in some Canadian cities (Stieb et al, 1995).

Carbon Monoxide (CO). Carbon monoxide is a colorless, odorless gas formed from the combustion of material containing carbon. It is produced by motor vehicle exhaust, industrial processes, and natural sources such as wildfires. Peak CO concentrations typically occur during the colder months of the year. In Canada, an average CO level in urban air declined by 70% between 1974 and 1997 (Figure 2.4), owing primarily to a reduction in automobile emissions (Environment Canada, 1996).

Figure 2.4. Common outdoor air quality trends in Canada, 1974-1998



Note. Maximum acceptable level: the concentration that provides adequate protection against adverse effects on human, animals, vegetation, soil, water, materials and visibility.

Source: Dugandzic R, Stieb D, Jessiman B, Rurmanczyk T. Chapter 3 Air quality and respiratory health. In: Respiratory disease in Canada. Canadian Institute for Health Information, Canadian Lung Association, Health Canada, and Statistics Canada, September 2001.

Data source: National Air Pollution Surveillance Network (NAPS), Pollution Data Branch, Environment Canada, 2000

Sulphur Dioxide (SO_2). Sulphur dioxide is a corrosive colourless gas with a strong odour that is chemically converted into acidic pollutants such as sulphate particles. Sulfur dioxide is a product of oil and gas processing, ore smelting, and burning of coal and heavy oil. It also is a major precursor to $PM_{2.5}$. Average sulphur dioxide levels in Canada decreased by 60% between 1974 and 1997 (Figure 2.4), primarily as a result of reductions in smelter and power plant emissions and a switch from oil to natural gas for home heating (Environment Canada, 1996).

Nitrogen dioxide (NO_2). Nitrogen dioxide is a reddish brown, highly reactive gas that is formed in ambient air through the oxidation of nitric oxide (NO). Nitrogen dioxide plays a major role in the formation of ground-level ozone. The major sources of man-made NO_2 emissions are high-temperature combustion processes, such as those occurring in automobiles and power plants. From 1974 to 1997, the Canadian annual mean nitrogen dioxide level decreased by 22% (Figure 2.4) (Dugandzic et al., 2001).

Ground-level ozone (O_3). Ground-level ozone is produced when nitrogen oxides and volatile organic compounds (VOCs) react in the presence of sunlight. Ozone levels tend to peak in the summer months. VOCs are emitted from a variety of sources, including motor vehicles, chemical plants, refineries, factories, consumer and commercial products, and other industrial sources. Ground-level ozone appeared to decrease between 1981 and 1998 (Figure 2.4) (Dugandzic et al., 2001). However, the maximum acceptable level for ozone of 82 ppb (daily1 hour maximum concentration) established by the federal government is frequently exceeded in southern Ontario, southern Quebec, southern New Brunswick, and the Fraser Valley (Stieb et al, 1995).

Enormous progress has also been made in developing clean air implementation plans for urban areas in most other countries, especially in developed countries. Despite this, a substantial number of people living in urban areas - around 1.5 billion, or 25% of the global population - are still exposed to non-negligible concentrations of gaseous and particle pollution (WHO, 2001).

2.3 Epidemiological studies on short-term effects of low levels of air pollution on asthma hospitalization in children

It is likely that environmental factors, particularly outdoor air pollution, play an important role in development and/or exacerbation of asthma. However, the pathophysiological mechanism through which outdoor air pollutants, especially at low levels, contribute to the etiology of asthma is not well established (Stieb et al, 1995). Understanding the health effects of outdoor air pollution requires the interpretation and integration of data from controlled animal and human exposure studies and observational studies of human populations. This review focuses on epidemiological studies of short-term effects of major outdoor ambient air pollution on asthma hospitalization in children.

2.3.1 Methodological issues in epidemiological studies

Epidemiological studies are sometimes preferable to controlled exposure studies in that they provide information on responses in population and on the effects of actual exposures to air pollution. The information is directly applicable in regulatory evaluations, and the results may often be generalized to the broader population without extrapolation. In addition, cumulative, possibly irreversible effects can be measured.

On the other hand, epidemiological studies may not be able to explicitly identify the causal agent in the complex mixture of air pollutants to which we are exposed. Biases may be introduced by errors in measurement or classification of the exposures and health outcomes of interest. In most epidemiological studies, the air

pollution levels measured at centrally sited outdoor monitors are assumed to represent personal outdoor exposure.

The earliest studies focused on the relationships between severe air pollution episodes and mortality and morbidity. These studies simply compared the counts of events during, before, and after the episodes (Ciocco and Thompson, 1961; Logan and Glasg, 1953). In the 1980s, a few studies calculated Pearson correlations between ambient air pollution and daily health events (Bates et al., 1990; Pope, 1999). However, such simple correlation studies may not be sufficiently sensitive to detect the adverse effects of air pollution at current relatively low levels (Pope, 1999; WHO, 2001). Recent methodological advances in environmental epidemiology have strengthened our ability to study the short-term health effects of air pollution. Time series analysis has been the most common approach (Schwartz, 1993; Burnett, et al, 1994; Pope et al, 1996; Poper et al., 1999). Although earlier time series model used classic Poisson regression, this model was limited by inadequate control of time trends in both air pollution and health outcomes, and its inability to take into account overdispersion of daily counts of adverse health events (Pope III, 1999; Schwartz et al., 1996). Consequently, more sophisticated time series modeling techniques have been proposed. For example, the generalized additive model (Hastie and Tibshirani, 1990) applied nonparametric smoothing functions of relevant covariates to better control for seasonal and long-term time trends in the data, and has been used in more recent analyses of daily counts of mortality and hospitalization in relation to air

pollution (Burnett et al., 1999; Norris et al., 1999 Schwartz, 1993; Schwartz, 1994a; Schwartz, 1994b).

However, concerns have been expressed regarding model dependence of time series analyses (Moolgavkar,1995; Li and Roth, 1995). To address these concerns, Neas et al (1999) and Lee and Schwartz (1999) first applied the case-crossover analysis, an approach developed by Maclure (1991), to evaluate associations between ambient air pollution and mortality. This approach is an adaptation of the matched case-control study, in which cases serve as their own controls. As a consequence, the case-crossover approach can control for fixed individual charicteristics by design rather than by the application of modeling techniques (Maclure, 1991). Navidi (1998) proposed a bi-directional case-crossover design, in which air pollution exposures both before and after the health events of interest are considered in order to control for time trends in exposures and outcomes. Moreover, this approach focuses on individual events rather than daily counts, and facilitates evaluation of potential modifying effects. Case-crossover analysis represents a viable alternative to time series analysis, particularly when personal exposure measurements are avaible. However, few studies have applied case-crossover analyses to assess the relationship between air pollution and hospitalization, especially hospitalization. In the absence of greater experience with the case-crossover approach, it is not clear to what extent results from case-crossover and time series approaches differ.

2.3.2 Short-term effects of outdoor air pollution on asthma hospitalization in children

Airborne particulate matter (PM). Particle size is a critical factor in lung dosimetry. Coarse particles tend to deposit in the upper respiratory tract and fine particles may transport to the lower airways. Most recent studies have focused on the effects of fine particles on asthma hospitalization or emergency room visits. Fine particulate matter is believed to be more relevant to adverse health effects than coarse particles (Dreher et al, 1996; Schwartz and Neas, 2000). However, these are no consistent results for the impacts of low levels of fine particles on asthma hospitalization (Sheppard et al, 1999; Schwartz et al, 1993; Norris et al, 1999; Morgan et al, 1998; Wordley et al, 1997). The U.S. Environmental Protection Agency has noted that coarse particulate matter may be more relevant for asthmatic responses and irritation (1995). However, few studies have focused on the effect of coarse particulate matter on asthma hospitalization. At present, there is a lack of evidence for an association between coarse particulate matter and asthma hospitalization in children.

Ground-level ozone (O_3). The effects of ozone on human health include decreased lung function, inflammation of the lung, airway hyperactivity, and increased respiratory symptoms (Brunekreef et al., 1995). However, the reasons for the appreciable variability in individual responsiveness and discrepant results from different studies are not clear (WHO, 2001). Some studies have demonstrated a positive association between ozone concentrations higher than 110 ppb and asthma

hospitalization or emergency room visits (White et al, 1993; Thurston et al 1992). However, it is unclear whether low levels of ozone (with the 1-hr maximum O_3 concentration not exceeding 110 ppb most of the time) are associated with asthma hospitalization, especially in children. Some studies have found a positive association (Burnett et al, 1994; Burnett et al, 1999; Targonski et al, 1995; Weisel et al, 1995), while others observed no significant association between ozone and either asthma hospitalizations or emergency room visits (Norris et al, 1999; Schouten et al, 1996; Bate et al, 1990; Delfino et al, 1994).

Nitrogen dioxide (NO_2). Although NO_2 is most closely related to vehicle exhausts, there has been no convincing evidence that short-term exposures to current nitrogen dioxide (NO_2) concentrations lead to changes in airway responsiveness and lung function in individuals with pre-existing respiratory illnesses (Tattersfield, 1996). Only a few epidemiological studies have shown an association between NO_2 and asthma hospital admissions (Dab et al, 1996; Morgan et al, 1998); and most other studies have not reported such an association (Stieb et al, 1996; Norris et al, 1999; Schouten et al, 1996; Ponka et al, 1991).

Sulfur Dioxide (SO_2). SO_2 is a respiratory irritant that is more soluble than CO_2 in water. It is mostly absorbed in the upper airways, and may also deposit in deeper parts of lung after ventilation increases (Koren, 1995). Some controlled human studies have found that exposure to SO_2 even below 250 ppb altered lung function of asthmatics (Tattersfield, 1996), while other studies have demonstrated no effect for SO_2 at levels up to 1.0 ppm (WHO, 2001). There is limited epidemiological evidence

to support outdoor SO_2 concentration in relation to asthma hospitalization (Dab et al, 1996; Walter et al, 1994). An explanation for this is that the joint occurrence of particulate matter and sulfur dioxide may affect the evaluation of the individual effect of SO_2 (Koren, 1995; Brunekreef et al., 1995).

Carbon Monoxide (CO). Carbon monoxide enters the bloodstream through binding with hemoglobin in the capillaries of the lungs and reduces oxygen delivery to the body's organs and tissues. The health threat from lower levels of CO is most serious among those who suffer from cardiovascular disease. There has been no biologically plausible mechanism for the exacerbation of asthma to date (CEOHAATS, 1996). CO was found to be significantly associated with asthma hospitalization in children in Seattle, Washington. (Norris et al, 1999). However, a study conducted in Anchorage, Alaska (Gordian et al, 1996) did not find an association between CO and asthma emergency room visits.

2.3.3 Summary

Children are generally more susceptible than adults to outdoor air pollution since their respiratory systems are still developing, and they breathe more air relative to their body weight (Dugandzic et al.,2001). However, epidemiological studies have so far provided no consistent evidence that ambient air pollutants are associated with increased asthma hospitalization among children. The reasons for the discrepant results from previous epidemiological studies include: methodological differences, different study populations, complexity in concentrations and compositions of outdoor air pollution and other environmental related factors, and the different

outcomes studied. To clarify the relationship between ambient air pollution and asthma hospitalization in children, further research is needed, including: 1) alternative study designs and analyses to enhance the ability and accuracy of inference of the relationship; 2) studies identifying a duration of exposure to outdoor air pollution to induce asthma hospitalization in children; and 3) studies examining whether the short-term effect of outdoor air pollution on asthma hospitalization among children is modified by risk factors, such as environmental tobacco smoke, inhaled allergen status, and socio-economic status.

CHAPTER 3 MATERIALS AND METHODS

3.1 Materials

The present analysis was based on daily air pollution and asthma hospitalization data collected in metropolitan Toronto between 1980 and 1994. The study region consisted of the cities of Toronto, North York, East York, Etobicoke, Scarborough, and York (hereafter collectively referred to as Toronto). The study area had a total population of 2.13 million in 1980 and 2.42 million in 1994.

3.1.1 Hospitalization data

Hospitalization data were obtained from the Ontario Ministry of Health, as described previously by Burnett et al (1999). Subjects 6 to 12 years of age inclusive hospitalized for asthma were selected for this analysis for the following reasons. (1) Children are generally thought to be more susceptible to air pollution than adults under 65 years of age. (2) Asthma diagnosis remains problematic in infants and early childhood. In infants and children under five years of age, the only diagnostic steps used are the medical history and physical exam. It is not possible to do reliable spirometry (test for airflow obstruction) on a young child. Some children under 6 years of age experienced transient wheezing, which is resolved as they became older (Martinez et al., 1995). This may be partly due to the rapid growth and development of the lungs during infancy and childhood. (3) Regular smokers under age of 13 years are rare.

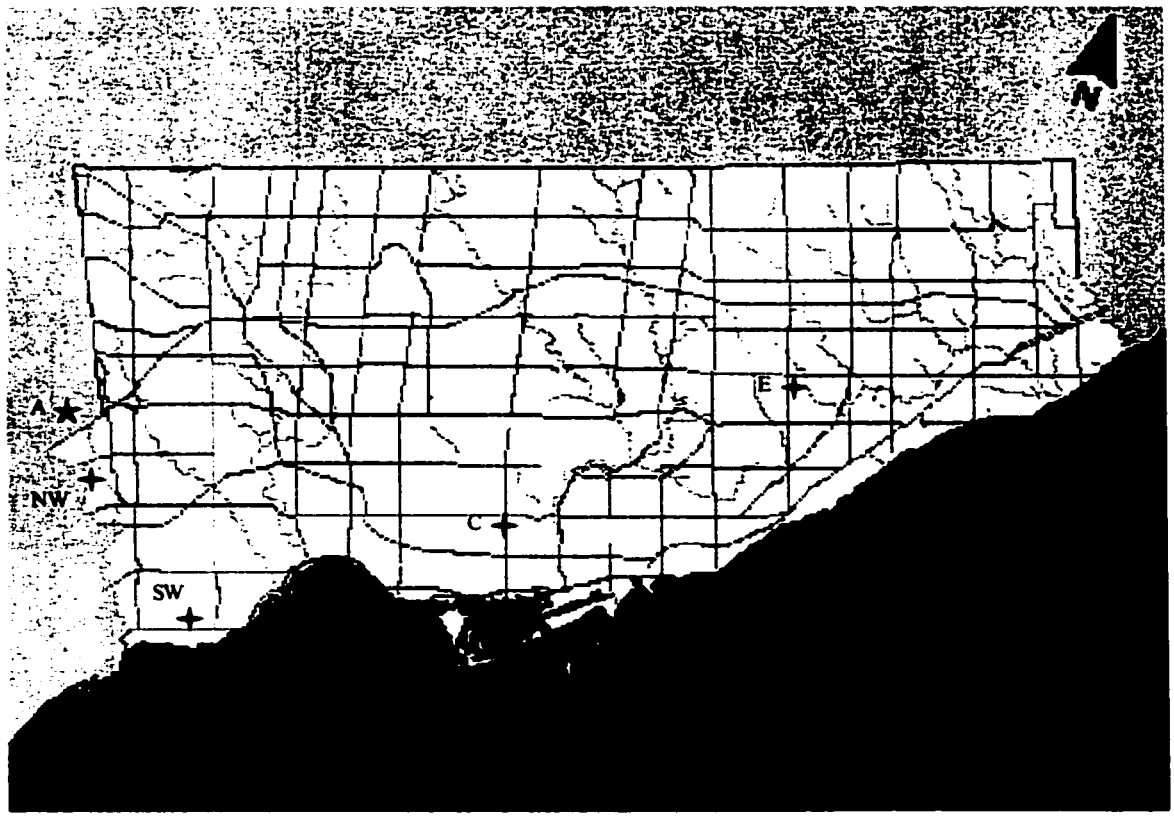
Asthma hospitalization was defined as an admission for which asthma was the primary diagnosis that caused the greatest number of hospital days of stay (International Classification of Diseases, 9th reversion, ICD 9, code 493). Admissions were restricted to children who both resided in Toronto and were admitted there. This study only included admissions to acute care active treatment hospitals that were considered as emergency or urgent. Both planned admissions and transfers from other institutions were excluded from this analysis. The data for each admission included the dates of admission and discharge, and the age and sex of the individuals admitted.

3.1.2 Environmental data

The environmental data included daily information on particulate matter, gas phase pollutants, and weather conditions from 1980 to 1994. These data were obtained from the Ontario Ministry of Environment and Energy (OMEE) and have been described elsewhere (Burnett et al, 1998). In brief, site selection for this study was based on the following criteria: sampling records were nearly continuous for the 1980-94 period, and the site was not significantly influenced by a local pollution source. Four stations met these criteria for the gaseous pollutants, while only one station located in the downtown of Toronto was acceptable for particulate pollutants (Burnett et al, 1998). The locations of the four stations are shown in Figure 3.1. The first station (Northwest, NW) is located in a park in residential areas of northern Etobicoke. The second site (Southwest, SW) is located in an open area surrounded by

commercial buildings within south Etobicoke. There is an access freeway approximately 75 meters north of the site. The third station is located in downtown Toronto (Central town, C), close to roads and commercial buildings. The fourth station is in an open area about 20 meters from a roadway in central Scarborough (East, E), surrounded by residential and commercial buildings. These sites span the breadth of the region and also represent several main ambient microenvironments relevant to personal exposure (Burnett et al., 1998).

Figure 3.1 Location of monitoring stations for air pollution (✛ : NW (Northwest), SW (Southwest), C (Central town) and E (East)) and weather conditions (★ : A (Airport)) in metropolitan Toronto



Gaseous pollutants were measured continuously using methods approved by the U.S. Environmental Protection Agency (EPA). Daily measurements of carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3) were averaged over the four monitoring stations within the study area. Daily gaseous data were available for over 99% of the total 5,479 days between 1980 and 1994. Missing data (representing less than 1% of the study period) were estimated using linear interpolation methods. For daily concentrations of each gaseous pollutant, the Pearson correlations among the four stations were calculated. The correlations for ozone were very high across the stations (0.83-0.91), probably due to the fact that ozone can be transported long distances and that the wind direction in this area in summertime is mostly from southwest (Burnett et al., 1998; Burnett et al., 1994). Moderate correlations were found for NO_2 (0.27-0.67) and SO_2 (0.35-0.68) (Burnett et al., 1998). The lowest correlations were observed for CO (0.26-0.44), likely due to the very specific source of CO in this area, with about 90% of CO coming from motor vehicles (Burnett et al., 1998; Macfarlane et al., 2000). The correlations tended to decrease with the increase of distance between stations.

Daily values of fine particulate matter ($PM_{2.5}$), coarse particulate matter ($PM_{10-2.5}$), and thoracic particulate matter (PM_{10}) were not available for the entire study period (1980-1994). Values of fine and coarse particulate matter were measured from a dichotomous sampler running every sixth day from 1984 to 1990, producing 272 measurements co-located with the central downtown monitoring station. By operating on one-day-in-six sampling schedule during the study period, each day of

the week is equally well sampled. Given a long enough sampling period, all conditions during the week are represented. Daily particulate values were predicted based on co-located monitors providing daily data on concentrations of sulfates, total suspended particulates (TSP), and the coefficient of haze (COH), which was obtained from a high volume sampler at the downtown site. The Northwest station, which is in a park, had the lowest levels of gaseous pollutants, while the Southwest station near the controlled access highway had the highest levels of gaseous pollutants. The concentrations of air pollution in downtown area were roughly around average levels of the four stations.

Two season-specific linear regression models were fit (one for April-September and another for October-March) for the 272 measurements, with the estimated regression parameters then used in conjunction with the daily values of TSP, sulfates and COH to construct a daily time series of the predicted particulate matter (Burnett et al., 1998). Sulfates explained 77% of the variation of fine particulate matter, 65% for thoracic particles, and only 20% for the coarse fraction. In contrast, TSP was a weak predictor of fine particles ($R^2 = 0.22$), a moderate predictor of thoracic particles ($R^2 = 0.50$), and a stronger predictor of the coarse fraction ($R^2 = 0.63$). COH was a weak predictor of all three particulate indices ($R^2 = 0.33$) (Burnett et al., 1998). Daily maximum and minimum temperatures, and daily average relative humidity were obtained from the Pearson international airport in Toronto (Burnett et al., 1998).

3.2 Methods

Case-crossover and time series analyses were used to examine the associations between air pollution and asthma hospitalization in children.

3.2.1 Case-crossover analysis

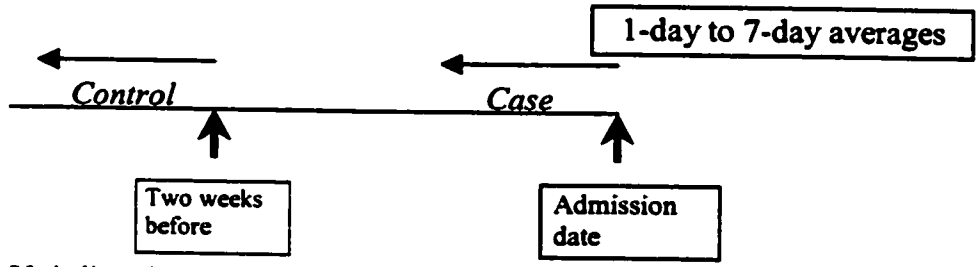
In this study, the level of air pollution at the time of asthma hospitalization for each case (the case period) was compared with a level obtained in a specified period before and/or after the health event (the control period). Cases in this analysis included only those children 6-12 years of age who were admitted to a hospital in the study area, with asthma as the principal reason for the hospital stay during the period from January 1, 1981 to December 31, 1993. Since the case-crossover design requires asthma hospitalization data to be matched to environmental data before and after the health event, only hospitalization data from 1981 to 1993 were used in this analysis.

The acute effects of environmental exposure may be immediate, or may occur several days subsequent to exposure. In this study, we examined the acute effect of one-day to multiple-day averages of air pollution ending on the admission date. This approach provided estimates for prolonged exposure effects, which reduce the effect of the short-term autocorrelation. Previous studies have documented that increased asthma hospitalizations are most strongly associated with air pollution on the day of admission or within up to 4 days (Burnett et al., 1999; Norris et al., 1999;

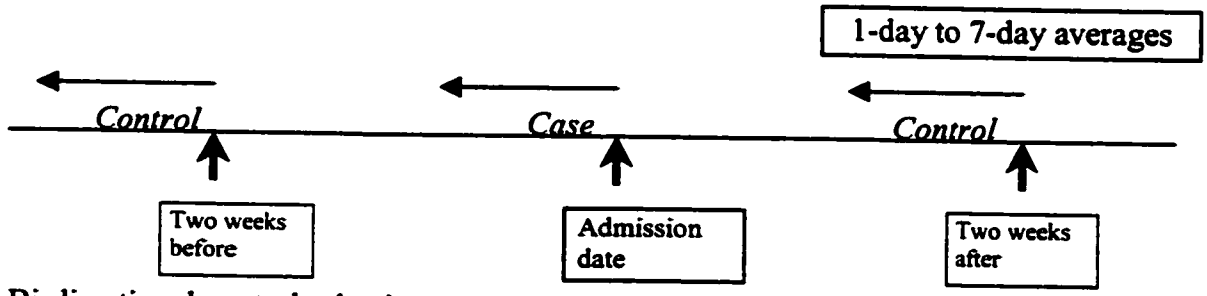
Schwartz et al., 1993). In this study, we calculated 1- to 7-day exposure averages ending on the admission date as the case period.

To examine whether time trends in data can change risk estimates, this study used both uni- and bi-directional control schemes in the case-crossover analysis. A period of two weeks prior to the admission date was selected as the control period for the uni-directional scheme, with periods of two weeks before and after the admission date used in the bi-directional scheme. To be matched with the case period, each control period was also expressed as 1-day or up to 7-day averages for each pollutant ending on the date two weeks before or after the admission date. Control periods were handled in the same manner as case periods (Figure 3.2).

Figure 3.2 Case-crossover study design



Uni-directional control selection



Bi-directional control selection

This study used conditional logistic regression models for the case-crossover design by using the SAS 6.12 statistical package (SAS Institute, Inc., 1996). We estimated relative risks (odds ratios) for asthma hospitalization in relation to various air pollutants during the case period as compared with the control periods. Separate models were fit for boys and girls.

In the uni-directional case-crossover analysis, let x_{1k} denote the covariate (exposure) for the case period and x_{0k} the covariate for the control period in the k^{th} stratum. The conditional likelihood for the k^{th} stratum is

$$L_k(\beta) = \frac{e^{\beta' x_{1k}}}{e^{\beta' x_{1k}} + e^{\beta' x_{0k}}}$$

$$= \frac{e^{\beta'(x_{1k} - x_{0k})}}{1 + e^{\beta'(x_{1k} - x_{0k})}}$$

This likelihood function is identical to an unconditional logistic regression model with a constant term of zero and covariate $x^* = x_{1k} - x_{0k}$. This allows us to use standard logistic regression software to compute the conditional maximum likelihood estimates and to obtain standard errors of the estimated coefficients.

For bi-directional case-crossover analysis, it is not possible to express the conditional likelihood in the form of the unconditional logistic model. However, conditional logistic regression for bi-directional case-crossover analysis can be performed using SAS's PHREG procedure, a program for fitting the Cox's proportional hazards (PH) model (SAS Institute, Inc, 1996). The conditional likelihood function for logistic regression can be treated as a special case of Cox's

partial likelihood, which is used to fit the PH model (Kleinbaum et al., 1998). Suppose that there are n_{1k} cases and n_{0k} controls in the k^{th} stratum. The conditional likelihood for the k^{th} stratum is then

$$L_k(\beta) = \frac{\prod_{j=1}^{n_{1k}} P(x_j) \prod_{j=n_{1k}+1}^{n_k} [1 - P(x_j)]}{\sum_i \left\{ \prod_{j=1}^{n_{1k}} P(x_{ij}) \prod_{j=n_{1k}+1}^{n_k} [1 - P(x_{ij})] \right\}},$$

where $P(x_j)$ is the probability of the observed outcome of the j^{th} case, and 1- $P(x_j)$ is the probability of obtaining the data for the j^{th} control. The denominator is the summation of probabilities for all possible $n_kCn_{1k} = (n_k)!/(n_{1k})!\ (n_k - n_{1k})!$ combinations of the case n_{1k} of the n_k observations in the stratum, where $n_k = n_{1k} + n_{0k}$. The full conditional likelihood is the product of the $L_k(\beta)$ over all the strata, is then given by

$$L(\beta) = \prod_{k=1}^{K} L_k(\beta).$$

Relative risks for each pollutant in relation to asthma hospitalization were calculated after adjustment for three weather conditions: daily maximum and minimum temperature, and average relative humidity. Cold and very hot temperatures and dampness are thought to be risk factors for asthma (CDPH, 2002; Lundback, 1998). Because dew point temperature is a function of temperature and humidity, we only considered temperature and humidity in the models. Based on results from previous studies (Schwartz et al., 1993; Schwartz et al., 1996) and locally weighted regression (LOESS) (Cleveland and Devlin, 1988) of smoothed asthma hospitalization and weather conditions, we added squared terms of each of the

weather conditions as additional covariates. The relative risk estimates (odds ratios) were calculated based on an increment in exposure corresponding to the interquartile range of each pollutant. The effects of particulate matter on asthma hospitalization were further examined taking the effects of gaseous pollutants (CO, SO_2, NO_2 and O_3) into consideration. Particulate matter was also taken into account when the relationships between gaseous pollution and asthma hospitalization were examined. Since thoracic particulate matter (PM_{10}) is a function of fine ($PM_{2.5}$) and coarse ($PM_{10-2.5}$) particulate matter, only fine and coarse particulate matter were considered in the analyses of gaseous pollutants in relation to asthma hospitalization.

3.2.2 Time-series analysis

For the time-series analysis, the generalized additive model (GAM) (Hastie and Tibshirani, 1990) was used to estimate the relationship between air pollution and asthma hospitalization in a nonparametric manner. The additive model is a generalization of the usual linear regression model, allowing some or all linear functions of the predictors to be replaced by nonparametric smooth functions of the predictors (Hastie and Tibshirani, 1990). The generalized additive model can be expressed:

$$Log\,(E(Y)) = \sum f_i(X_i),$$

where Y is the count of asthma hospitalizations on a given day, $E(Y)$ is the expected value of Y on that day, and X_i represents model covariates such as air pollution, weather, day of study or day of the week. The term f_i is a parametric or

nonparametric smooth functions of these covariates. To take into account possible overdispersion of daily hospital admission counts, quasi-likelihood estimation was used. Both asthma hospitalization and air pollution display strong temporal trends. The potential confounding effects of these cycles on the association between air pollution and asthma hospitalization were controlled by using a locally weighted smoothing function (LOESS) of days of the study with span of 93 days (Cleveland and Devlin, 1988). The result of the smoothing is a function that is less variable than the original data. It is nonparametric function rather than a rigid mathematical function. LOESS is a generalization of a weighted moving average. The smoother is characterized by defining a window of observations with fixed length about a specified day. The smoother places a greater weight on days close to the center of the window, with weights declining to zero at the boundaries of the window (Cakmak et al., 1999). The span is defined as the percentage of data points used as nearest neighbors (as a percent of total number of data points). The appropriate span was characterized by minimal autocorrelation in the residuals of asthma hospitalization and was determined using Bartlett's test to exclude significant serial correlation (Priestly, 1981). Figures 3.3 and 3.4 show that the span of 93 days displayed minimal autocorrelation, as compared with other spans. To achieve comparability with the results from the case-crossover analysis, similar strategies were used for the time-series analysis. In addition to the LOESS function of days of the study, day of week indicator variables and squares of weather conditions were also considered as covariates. Models with 1-day to 7-day averages of each pollutant were considered.

The time series analysis was run with S-PLUS 2000 Professional Edition for Windows (Data Analysis Products Division, MathSoft, Inc., 1999) using the generalized additive model function.

Figure 3.3 Plots of autocorrelation function (ACF) in the residuals of asthma hospitalization in ***males*** by lag days, with different spans, Toronto, 1981-93

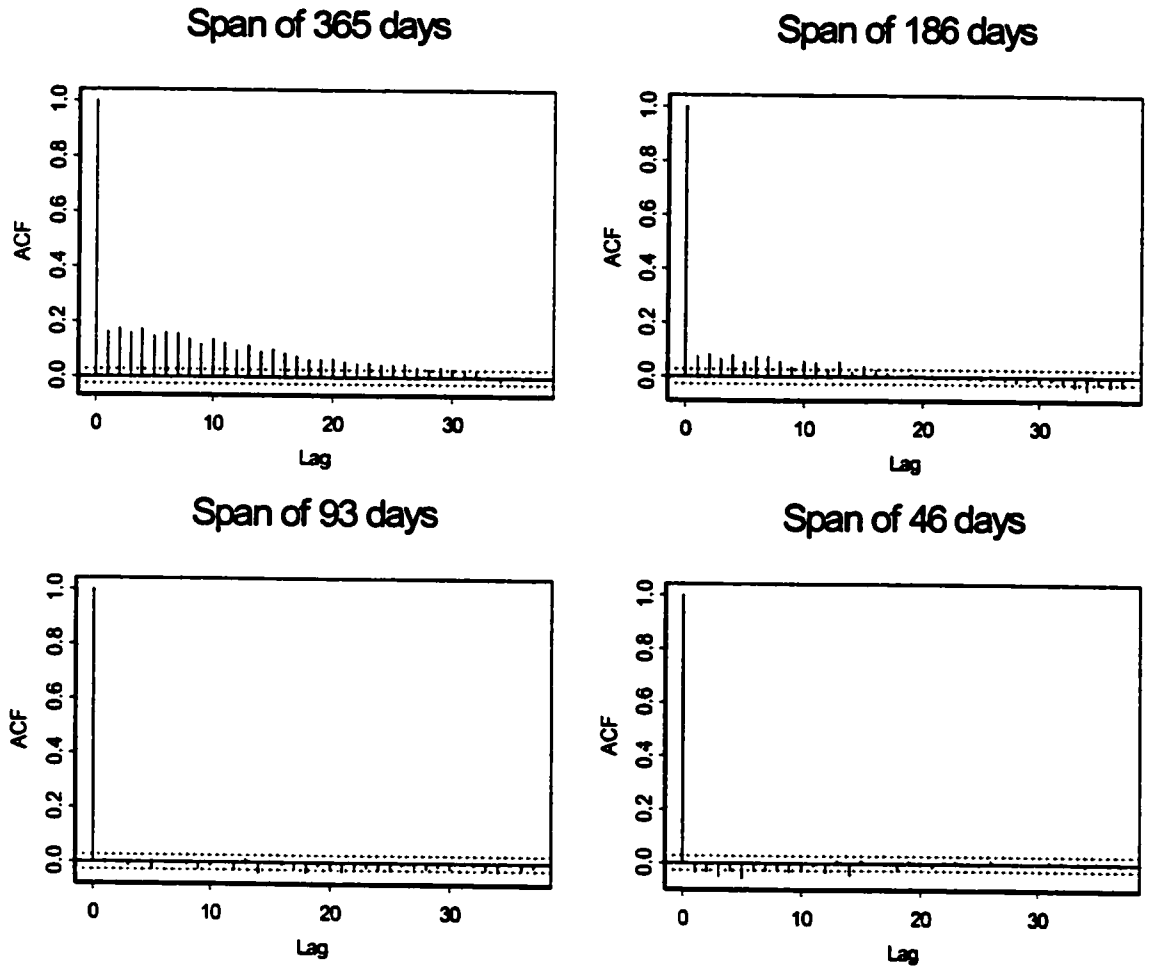
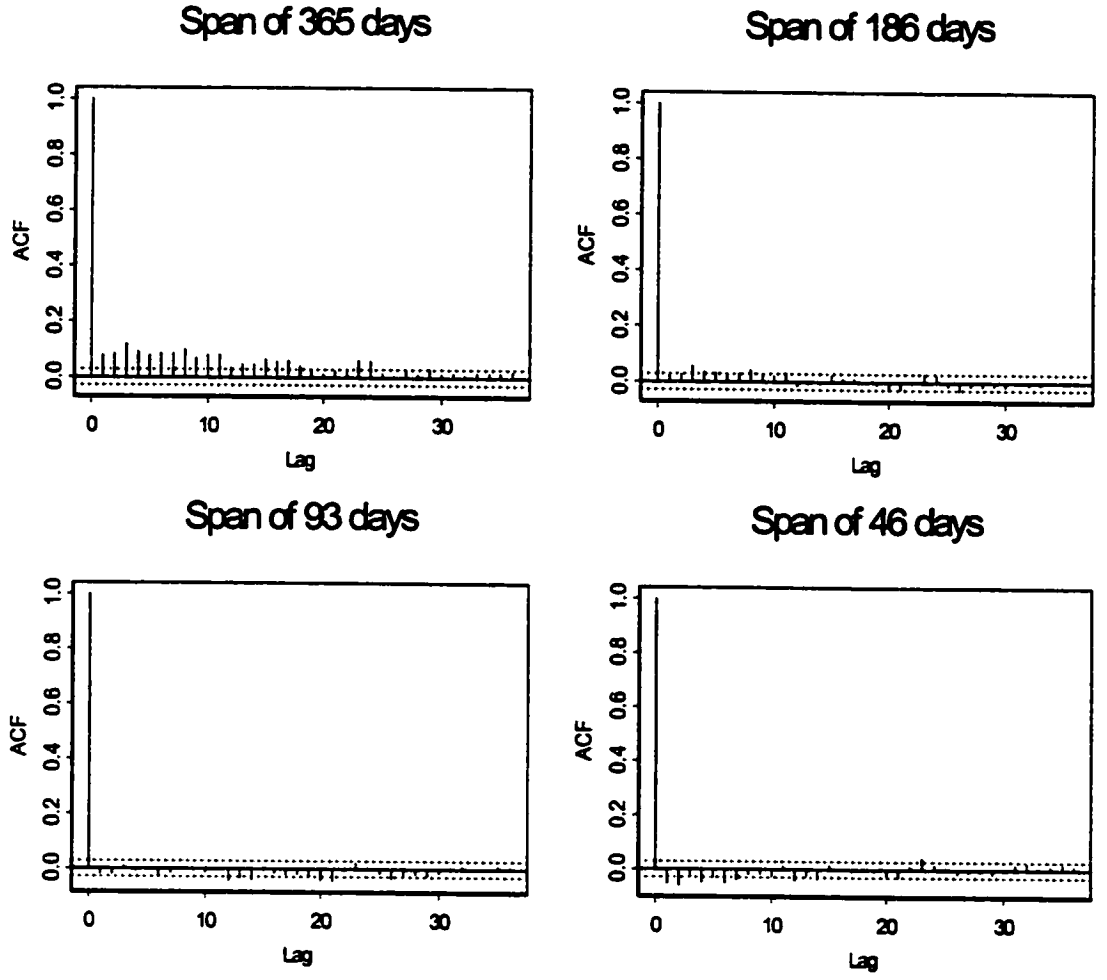


Figure 3.4 Plots of autocorrelation function (ACF) in the residuals of asthma hospitalization in ***females*** by lag days, with different spans, Toronto, 1981-93



CHAPTER 4 RESULTS

4.1 Summary statistics of air pollution, weather conditions and asthma hospitalization

Table 4.1 provides summary statistics for air pollution, weather conditions and asthma hospitalization. There were a total of 7,319 asthma hospitalizations for children 6-12 years of age (4,629 for males and 2,690 for females) with a daily average of 1.54 (0.97 for boys and 0.57 for girls) in Toronto during the period from 1981 to 1993. Air pollution levels were relatively low during the study period. There were no Canadian National Ambient Air Quality Objectives (CNAAQOs) available for PM_{10} and $PM_{2.5}$ of that time. The level of PM_{10} never exceeded the standard set by the U.S. Environmental Protection Agency (EPA) (2001), with an average level of PM_{10} being about 20% of the standard of 150 $\mu g/m^3$. For $PM_{2.5}$, the concentration exceeded the U.S. 24-hr standard of 65$\mu g/m^3$ on only 9 of the total of 5,479 days in the period 1980 to 1994. The Canadian Council of Ministers of the Environment (CCME) is developing the Canada Wide Standard (CWS) for $PM_{2.5}$, and has a target of 24-hr average of 30$\mu g/m^3$ to be achieved by 2010 (CCME, 2000). Approximately 8% of the days between 1980 and 1994 had the 24-hr average levels of $PM_{2.5}$ exceeding 30ug/m^3. The daily average levels of CO, SO_2, and NO_2 never exceeded the CNAAQOs (Health Canada, 2001), with the maximum values being only 47% of the guideline for CO (13.1 ppm), 49% for SO_2 (115 ppb), and 77% for NO_2 (106

ppb). The daily 1-hr maximum level of ozone exceeded the objective of 82 ppb on only 1.7% of the total of 5,479 days.

Correlations between air pollutants are shown in Table 4.2. $PM_{10-2.5}$ and $PM_{2.5}$ were both highly correlated with PM_{10} ($r = 0.87$ for $PM_{2.5}$, $r = 0.83$ for $PM_{10-2.5}$). The moderate correlation was found between $PM_{10-2.5}$ and $PM_{2.5}$ ($r = 0.44$). Gaseous pollutants were all positively correlated with each other, with the exception of ozone, which was weakly correlated with the other gaseous pollutants, and negatively correlated with CO ($r = -0.16$). The gaseous pollutants were all positively correlated with ambient particulate matter. Correlations between air pollution and weather conditions are shown in Table 4.4. Maximum and minimum temperatures were both positively correlated with particulate matter, although to a lesser degree for $PM_{2.5}$ than for $PM_{10-2.5}$ or PM_{10}. Relative humidity was negatively correlated with $PM_{10-2.5}$ ($r = -0.35$). Compared with other gaseous pollutants, ozone was more correlated with weather conditions. Ozone demonstrated a positive correlation with temperature and a negative correlation with relative humidity.

Table 4.1 Distribution of daily levels of air pollution, daily weather conditions and daily hospital admissions for asthma of children 6-12 years of age in Toronto

Variable	Mean	SD	Percentiles				
			Minimum	25th	50th	75th	Maximum
Air pollution (1980-94)							
Average $PM_{2.5}$ ($\mu g/m^3$)	17.99	8.49	1.22	12.43	16.21	21.71	89.59
Average $PM_{10-2.5}$ ($\mu g/m^3$)	12.17	7.55	0	6.97	10.40	15.42	68.00
Average PM_{10} ($\mu g/m^3$)	30.16	13.61	3.03	21.11	27.17	35.88	116.20
Average CO (ppm)	1.18	0.50	0	0.90	1.10	1.40	6.10
Average SO_2 (ppb)	5.36	5.90	0	1.00	4.00	8.00	57.00
Average NO_2 (ppb)	25.24	9.04	3.00	19.00	24.00	30.00	82.00
Maximum 1-hr O_3 (ppb)	30.39	17.87	0	18.00	26.00	38.00	141.00
Weather (1980-94)							
Maximum temperature (°C)	12.60	11.36	-21.00	3.10	13.00	22.50	37.60
Minimum temperature (°C)	2.54	10.03	-31.30	-3.80	2.60	10.80	24.30
Average relative humidity (%)	73.47	11.16	35.00	66.00	74.00	81.00	99.00
Hospital admissions for asthma (1981-93)							
Children 6-12 years of age (n=7319)	1.54	1.51	0	0	1	2	11
Males (n=4629)	0.97	1.14	0	0	1	1	11
Females (n=2690)	0.57	0.80	0	0	0	1	5

Abbreviations: SD, standard deviation; $PM_{10-2.5}$, coarse particulate matter between 2.5 and 10 microns in aerodynamic diameter; $PM_{2.5}$, particulate matter less than 2.5 microns in aerodynamic diameter; PM_{10}, particulate matter less than 10 microns in aerodynamic diameter; CO, carbon monoxide; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; O_3, ozone.

Table 4.2 Pearson correlation coefficients between daily concentrations of air pollutants[a] in Toronto from 1980 to 1994

Air pollutant	$PM_{2.5}$	$PM_{10-2.5}$	PM_{10}	CO	SO_2	NO_2	O_3
$PM_{2.5}$	1.00	0.44	0.87	0.45	0.46	0.50	0.21
$PM_{10-2.5}$		1.00	0.83	0.17	0.28	0.38	0.56
PM_{10}			1.00	0.38	0.44	0.52	0.44
CO				1.00	0.37	0.55	-0.16
SO_2					1.00	0.54	-0.01
NO_2						1.00	0.03
O_3							1.00

Abbreviations: CO, carbon monoxide; SO_2, sulfur dioxide; NO_2, nitrogen dioxide O_3, ozone; $PM_{2.5}$, particulate matter less than 2.5 microns in aerodynamic diameter; $PM_{10-2.5}$, coarse particulate matter between 2.5 and 10 microns in aerodynamic diameter; PM_{10}, particulate matter less than 10 microns in aerodynamic diameter.

Note.

[a] $PM_{10-2.5}$, $PM_{2.5}$, PM_{10}, CO, SO_2, and NO_2 : daily average level; O_3: daily maximum 1-hr level.

Table 4.3 Pearson correlation coefficients between daily weather conditions in Toronto from 1980 to 1994

Weather condition	Maximum temperature	Minimum temperature	Average relative humidity
Maximum temperature	1.00	0.94	-0.31
Minimum temperature		1.00	-0.14
Average relative humidity			1.00

Table 4.4 Pearson correlation coefficients between daily concentrations of air pollutants[a] and weather conditions in Toronto from 1980 to 1994

Air Pollutant/ Weather condition	$PM_{2.5}$	$PM_{10-2.5}$	PM_{10}	CO	SO_2	NO_2	O_3
Maximum temperature	0.15	0.47	0.36	-0.10	-0.07	-0.01	0.67
Minimum temperature	0.14	0.38	0.30	-0.09	-0.14	-0.05	0.57
Average relative humidity	0.22	-0.35	-0.06	0.27	0.04	0.09	-0.42

Abbreviations: CO, carbon monoxide; SO_2, sulfur dioxide; NO_2, nitrogen dioxide O_3, ozone; $PM_{2.5}$, particulate matter less than 2.5 microns in aerodynamic diameter; $PM_{10-2.5}$, coarse particulate matter between 2.5 and 10 microns in aerodynamic diameter; PM_{10}, particulate matter less than 10 microns in aerodynamic diameter.

Note.

[a] $PM_{10-2.5}$, $PM_{2.5}$, PM_{10}, CO, SO_2, and NO_2 : daily average level; O_3: daily maximum 1-hr level.

4.2 Temporal trends in air pollution and asthma hospitalization

The temporal trends in particulate matter and gaseous pollutants are given in Figures 4.1 and 4.2, respectively. On average, the concentrations of PM_{10} and $PM_{2.5}$ decreased over the study period. The levels of $PM_{10-2.5}$ also showed a modest decline. Concentrations of gaseous pollutants clearly declined over the study period, except for ozone levels, which appeared relatively stable over time. A modest decline was shown for daily asthma hospitalization for children (Figure 4.3).

The air pollution levels and asthma hospital admissions also varied by season and day of week. Table 4.5 shows the seasonal variation in air pollution concentrations and asthma hospitalizations among children 6-12 years of age during the study period. Figures 4.4 and 4.5 indicate the mean levels of daily air pollution and asthma admission counts by season. Levels of particulate matter and ozone were higher in summer than in winter, with the opposite pattern observed for CO, SO_2, and NO_2. The highest mean daily asthma hospital admissions occurred in the autumn months.

Distributions of daily air pollution levels and asthma hospitalizations by day of week are given in Table 4.6, Figures 4.6 and 4.7. The daily concentrations of air pollutants were higher on the weekdays than on the weekend, except for the levels of ozone, which were higher on the weekend. Daily asthma hospital admissions also varied by day of week and were higher on Monday and lower on the weekend.

Figure 4.1 Local weighted regression model, LOESS nonparametric smoothed function of particulate matter with a span of 93 days, Toronto, 1981-93.

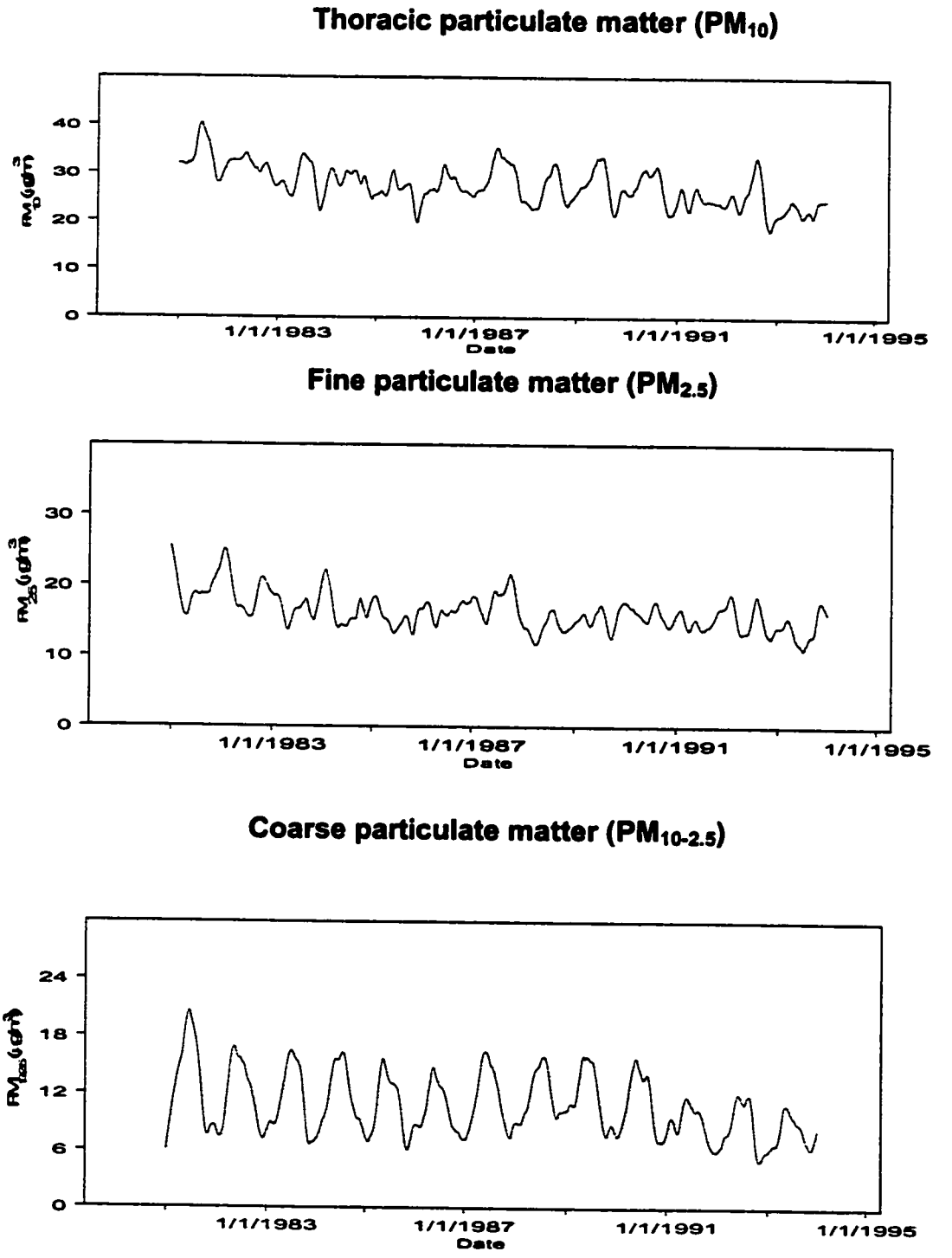
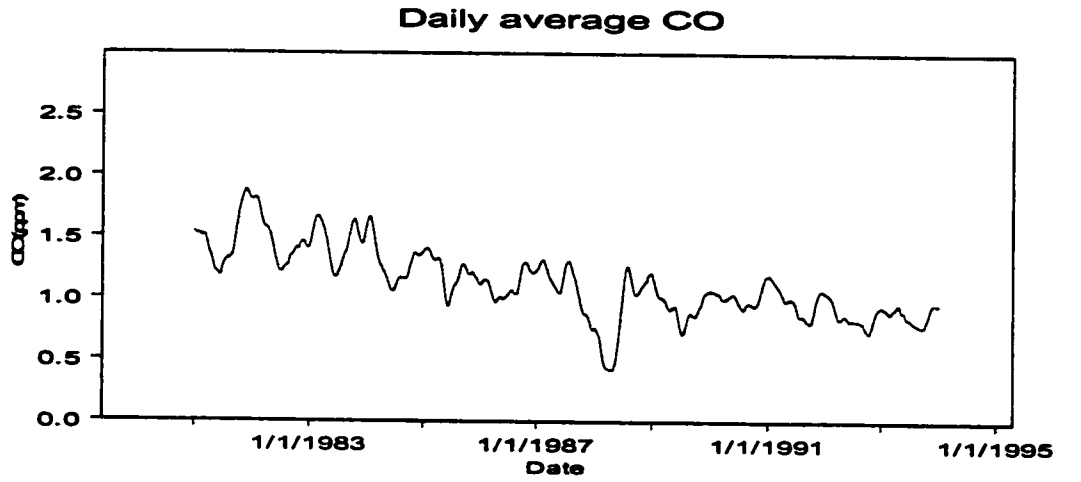
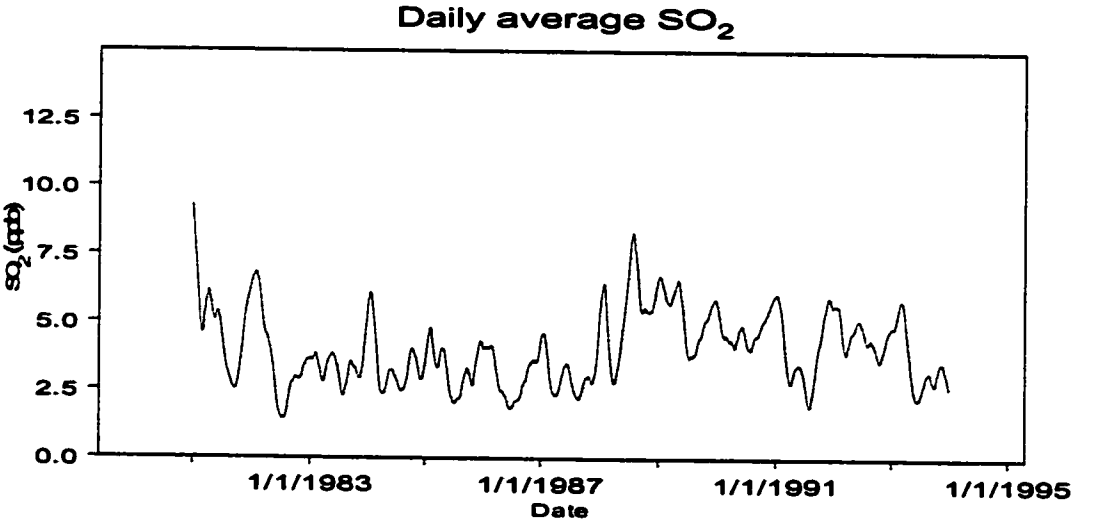


Figure 4.2 Local weighted regression model, LOESS nonparametric smoothed function of gaseous pollutants with a span of 93 days, Toronto, 1981-93.





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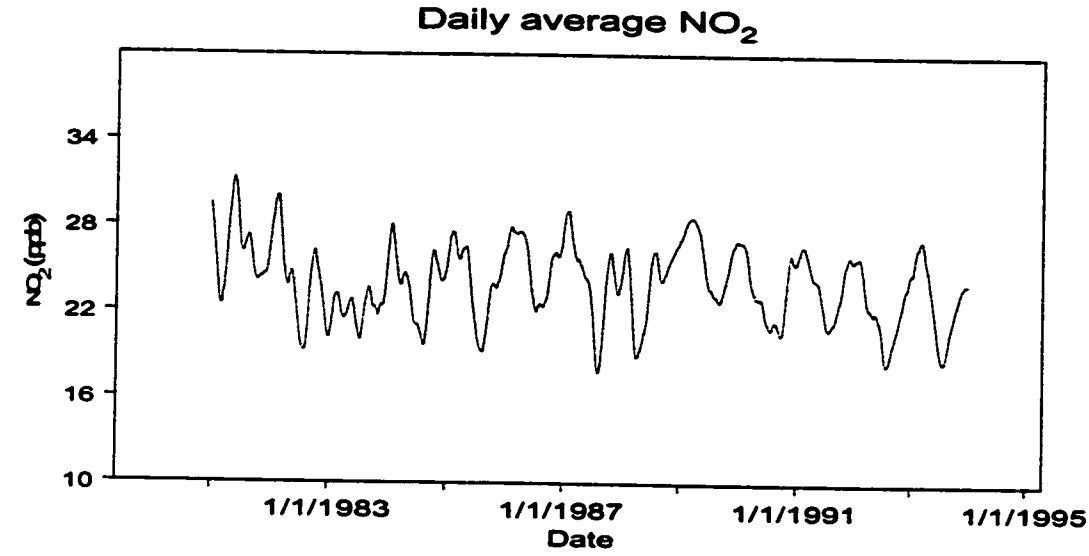


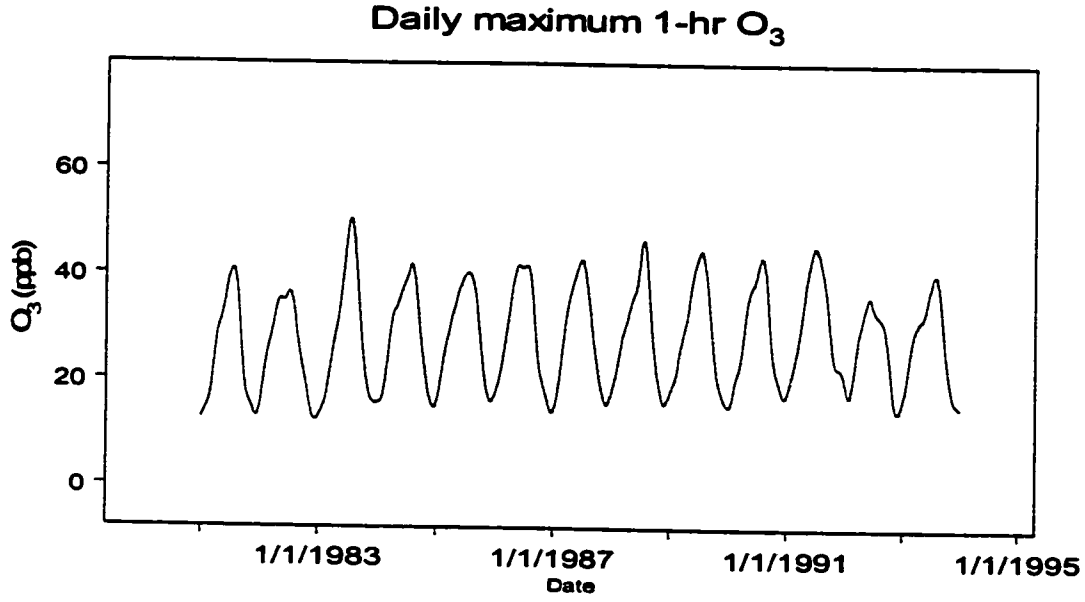


Figure 4.3 Local weighted regression model, LOESS nonparametric smoothed function of daily asthma hospitalizations for boys and girls with span of 93 days, Toronto, 1981 to 1993.

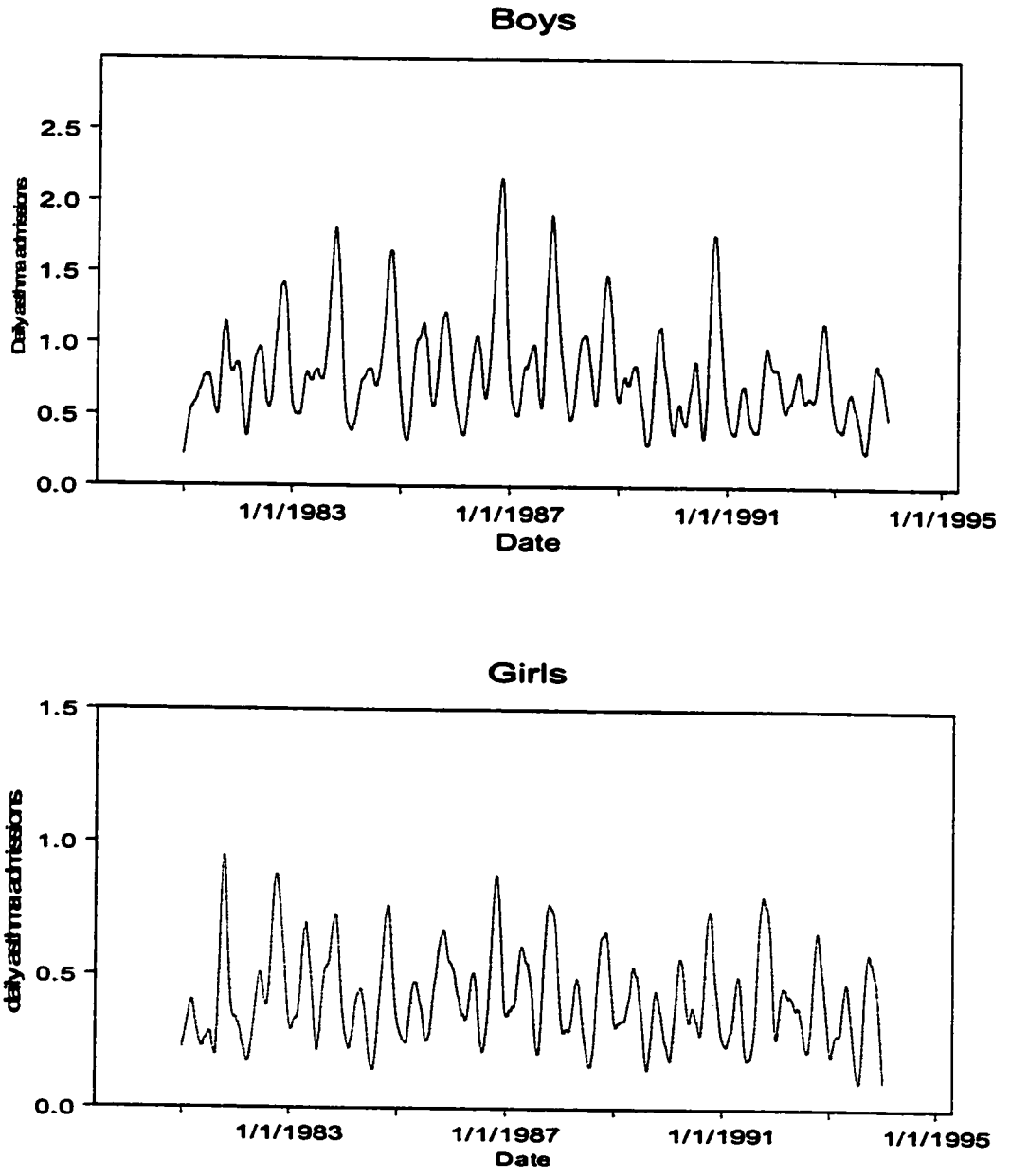
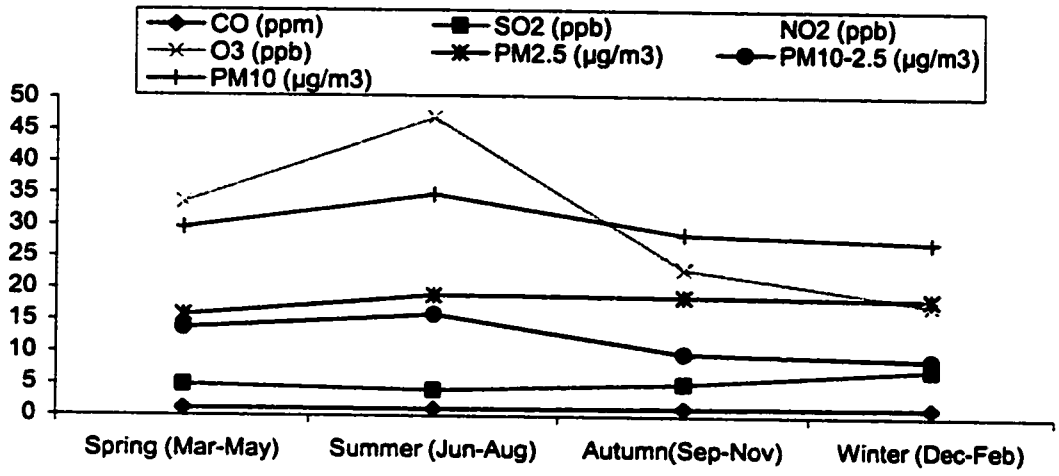


Table 4.5 Mean (Standard Deviation) of daily air pollution levels, daily weather conditions and daily hospital admissions for asthma in children 6-12 years of age by season in Toronto.

Variable	Spring (Mar-May)	Summer (Jun-Aug)	Autumn (Sep-Nov)	Winter (Dec-Feb)
Air pollution (1980-94)				
Average $PM_{2.5}(\mu g/m^3)$	15.83 (6.03)	**18.94 (10.19)**	18.76 (10.16)	18.45 (6.19)
Average $PM_{10-2.5}(\mu g/m^3)$	13.80 (7.62)	**15.95 (8.35)**	9.84 (6.30)	8.99 (5.27)
Average $PM_{10}(\mu g/m^3)$	29.63 (11.32)	**34.90 (17.04)**	28.61 (14.66)	27.44 (8.58)
Average CO(ppm)	1.13 (0.45)	1.07 (0.39)	1.22 (0.54)	**1.31 (0.55)**
Average SO_2 (ppb)	4.83 (4.79)	4.05 (4.48)	5.13 (5.70)	**7.45 (7.60)**
Average NO_2 (ppb)	26.26 (9.84)	23.04 (8.98)	25.13 (9.29)	**26.57 (7.43)**
Maximum 1-hr O_3 (ppb)	33.62 (12.88)	**47.00 (19.95)**	23.08 (12.69)	17.54 (6.73)
Weather (1980-94)				
Average relative humidity (%)	69.52 (12.84)	68.82 (10.65)	76.81 (8.92)	**78.87 (7.84)**
Maximum temperature (°C)	11.61 (8.50)	**25.36 (4.18)**	13.84 (7.31)	-0.63 (5.74)
Minimum temperature (°C)	1.05 (7.03)	**13.58 (3.90)**	4.13 (6.10)	-8.78 (6.84)
Hospital admission for asthma (1981-93)				
Children 6-12 years of age	1.34 (1.24)	1.08 (1.13)	**2.50 (1.89)**	1.07 (1.10)
Males	0.82(0.94)	0.70(0.87)	**1.62(1.47)**	0.64(0.83)
Females	0.52(0.73)	0.38(0.65)	**0.88(0.99)**	0.43(0.66)

Abbreviations: CO, carbon monoxide; SO_2, sulfur dioxide; NO_2, nitrogen dioxide O_3, ozone; $PM_{2.5}$, particulate matter less than 2.5 microns in aerodynamic diameter; $PM_{10-2.5}$, coarse particulate matter between 2.5 and 10 microns in aerodynamic diameter; PM_{10}, particulate matter less than 10 microns in aerodynamic diameter.

Figure 4.4 Mean of daily concentrations of air pollutants by season in Toronto, 1980-94



Note. PM2.5, PM10-2.5, PM10, CO, SO2, NO2: daily average level; O3: daily maximum 1-hr level.

Figure 4.5 . Mean of daily asthma hospitalizations of children 6-12 years of age by season in Toronto, 1981-93

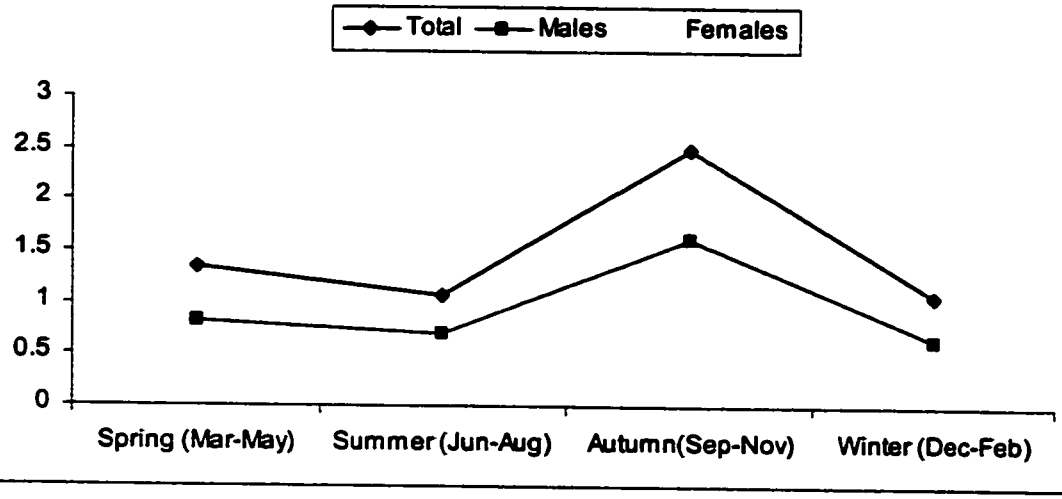
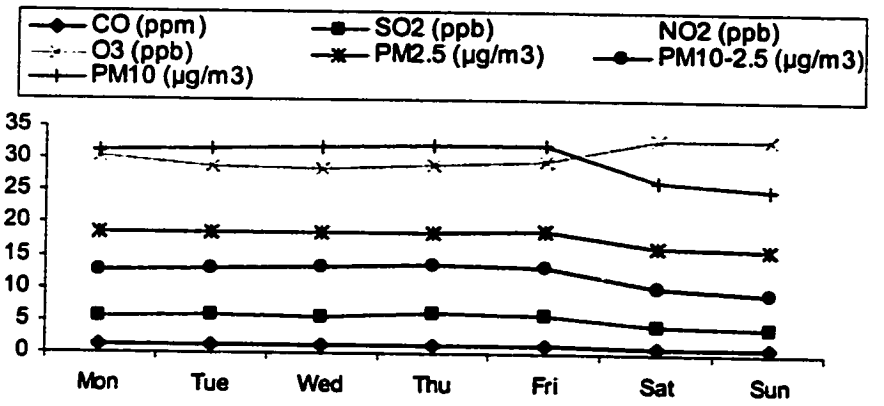


Table 4.6 Mean (Standard Deviation) of daily air pollution levels, and daily hospital admissions for asthma in children 6-12 years of age in different week days in Toronto.

Variable	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Air pollution (1980-94)							
Average $PM_{2.5}$ ($\mu g/m^3$)	18.60 (8.98)	18.63 (8.52)	18.58 (8.69)	18.67 (8.36)	**18.84 (8.80)**	16.43 (7.57)	16.20 (7.99)
Average $PM_{10-2.5}$ ($\mu g/m^3$)	12.56 (7.44)	12.88 (7.61)	13.31 (7.84)	**13.54 (7.38)**	13.31 (8.54)	10.29 (6.55)	9.28 (6.14)
Average PM_{10} ($\mu g/m^3$)	31.16 (13.92)	31.50 (13.47)	31.89 (14.12)	**32.21 (13.17)**	32.15 (14.70)	26.72 (11.72)	25.48 (12.20)
Average CO (ppm)	1.24 (0.54)	1.26 (0.49)	1.24 (0.49)	1.26 (0.51)	**1.27 (0.49)**	1.06 (0.42)	0.93 (0.41)
Average SO_2 (ppb)	5.72 (6.53)	5.89 (5.95)	5.67 (5.62)	**6.08 (6.05)**	5.79 (5.80)	4.19 (5.19)	4.15 (5.73)
Average NO_2 (ppb)	26.25 (8.76)	27.13 (8.59)	27.19 (8.93)	**27.68 (8.86)**	27.49 (9.41)	22.01 (7.33)	18.93 (7.20)
Maximum 1-hr O_3 (ppb)	30.32 (17.26)	28.82 (16.89)	28.48 (16.86)	29.15 (17.66)	29.73 (18.31)	33.07 (19.53)	**33.17 (17.88)**
Hospital admission for asthma (1981-93)							
Children 6-12 years of age	**1.86 (1.69)**	1.60 (1.55)	1.48 (1.47)	1.36 (1.33)	1.35 (1.43)	1.26 (1.32)	1.57 (1.56)
Males	**1.13 (1.24)**	1.05 (1.22)	0.92 (1.12)	0.85 (1.00)	0.85 (1.11)	0.83 (1.02)	0.98 (1.15)
Females	**0.73 (0.91)**	0.56 (0.80)	0.55 (0.78)	0.51 (0.75)	0.49 (0.73)	0.44 (0.69)	0.58 (0.84)

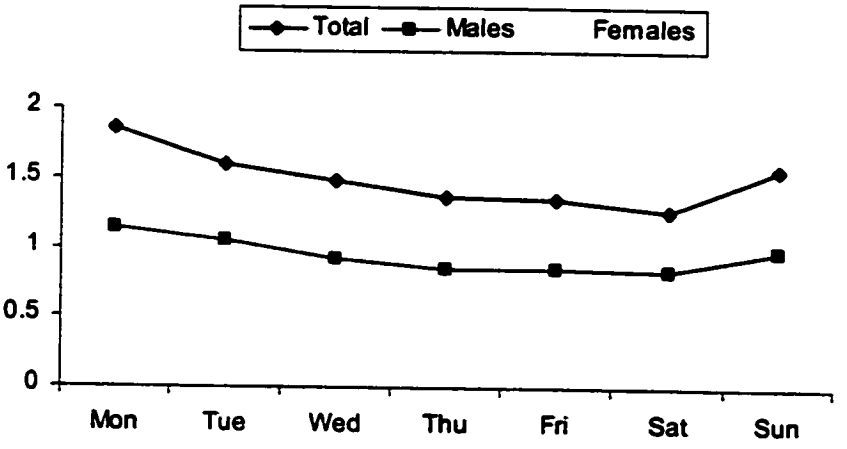
Abbreviations: CO, carbon monoxide; SO_2, sulfur dioxide; NO_2, nitrogen dioxide O_3, ozone; $PM_{2.5}$, particulate matter less than 2.5 microns in aerodynamic diameter; $PM_{10-2.5}$, coarse particulate matter between 2.5 and 10 microns in aerodynamic diameter; PM_{10}, particulate matter less than 10 microns in aerodynamic diameter.

Figure 4.6 Mean of daily levels of air pollutants by day of the week in Toronto, 1980-94



Note. PM2.5, PM10-2.5, PM10, CO, SO2, NO2: daily average level; O3: daily maximum 1-hr level.

Figure 4.7 Mean of daily asthma hospitalizations of children 6-12 years of age by day of the week in Toronto, 1981-93



4.3 Relative risk estimates for each air pollutant in relation to asthma hospitalization

In general, the relative risk for each air pollutant in relation to asthma hospitalization from uni-directional case-crossover analysis was more sensitive to the adjustment for weather conditions, as compared to those from bi-directional case-crossover and time series analyses. Coarse particulate matter and ozone appeared to be slightly more sensitive to control for weather conditions than other pollutants. The uni-directional case-crossover design tended to produce greater effects of air pollution on asthma hospitalization when considering weather conditions, as compared with bi-directional case-crossover design and time series analysis. Such differences were more pronounced for multi-day exposure averages. The relative risks estimated from bi-directional case-crossover analysis were comparable to those from time series analysis, although small differences were observed between these two approaches. The results from the bi-directional case-crossover analysis showed wider confidence intervals as compared to those from time series analysis. On the other hand, the relative risk estimates for some air pollutants (i.e., the effects of carbon monoxide and nitrogen dioxide in males and the effects of sulfur dioxide and nitrogen dioxide in females) in relation to asthma hospitalization from the bi-directional case-crossover analysis were slightly higher than those based on time series analysis, especially for multi-day exposure averages.

4.3.1 Relative risk estimates for particulate matter

Estimated relative risks for coarse particulate matter ($PM_{10-2.5}$). Tables 4.7a and 4.7b show crude and adjusted relative risks and 95% confidence intervals (CIs) for coarse particulate matter in males and females separately. Bi-directional case-crossover and time series analyses produced similar results, including significant effects of multi-day exposure (5 to 6 days) to coarse particulate matter on asthma hospitalization in males and females. In the bi-directional case-crossover analyses, the estimated relative risks for 6-day average coarse particulate matter were 1.14 (95% CI: 1.02,1.28) for males and 1.18 (95% CI: 1.02, 1.36) for females, based on an exposure increment of 8.4 $\mu g/m^3$. The corresponding relative risks for the time series analysis were 1.10 (95% CI: 1.03,1.18) and 1.18 (95% CI: 1.08,1.30), respectively.

The positive effects of coarse particulate matter on asthma hospitalization remained after further consideration of gaseous pollutants. Figure 4.8 shows the relative risks for 1- to 7-day exposures to coarse particulate matter using the three approaches in males and females, separately. The effects appeared to increase with increasing number of days of exposure, and to stabilize around 6 days.

Table 4.7a Crude and adjusted [a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily average coarse particulate matter in relation to asthma hospitalization in males 6-12 years of age, Toronto, 1981-93.

$PM_{10-2.5}$(8.4μg/m^3)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	0.96	0.91,1.01	0.93	0.87,0.99	0.91	0.85,0.98	0.90	0.83,0.97	0.87	0.80,0.95	0.86	0.78,0.94	0.83	0.76,0.92
Adjusted A	1.08	1.01,1.16	1.08	0.99,1.17	1.09	0.99,1.20	1.11	1.00,1.22	1.13*	1.01,1.26	1.16*	1.03,1.31	1.18*	1.04,1.34
Bi-directional case-crossover analysis														
Crude	1.03	0.98,1.08	1.02	0.97,1.09	1.04	0.98,1.11	1.04	0.97,1.12	1.04	0.96,1.12	1.04	0.95,1.12	1.03	0.94,1.13
Adjusted A	1.06	1.00,1.14	1.06	0.98,1.14	1.08	0.99,1.18	1.09	0.99,1.20	1.12*	1.01,1.24	1.14*	1.02,1.28	1.16*	1.04,1.31
Adjusted B	1.07	0.99,1.15	1.06	0.97,1.15	1.09	0.99,1.20	1.10	0.98,1.23	1.14*	1.01,1.28	1.17*	1.03,1.33	1.20*	1.05,1.37
Time series analysis														
Crude	1.03	0.99,1.06	1.02	0.99,1.06	1.03	0.99,1.08	1.02	0.98,1.07	1.02	0.98,1.07	1.02	0.97,1.07	1.02	0.97,1.07
Adjusted A	1.08*	1.03,1.12	1.07*	1.01,1.13	1.07*	1.01,1.13	1.08*	1.01,1.15	1.09*	1.02,1.16	1.10*	1.03,1.18	1.12*	1.04,1.20
Adjusted B	1.09*	1.03,1.04	1.09*	1.02,1.16	1.11*	1.03,1.19	1.11*	1.03,1.20	1.14*	1.05,1.23	1.15*	1.06,1.25	1.19*	1.09,1.30

Abbreviations: $PM_{10-2.5}$, coarse particulate matter between 2.5 and 10 microns in aerodynamic diameter

Note:

[a] Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);

Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and gaseous pollutants (CO, SO_2, NO_2, and O_3).

[b] RR estimates were calculated for an interquartile range increment of coarse particulate matter, which was calculated based on daily average levels.

* p-value<=0.05

Table 4.7b Crude and adjusted[a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily average coarse particulate matter in relation to asthma hospitalization in females 6-12 years of age, Toronto, 1981-93.

$PM_{10-2.5}$(8.4μg/m^3)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	0.96	0.89,1.03	0.96	0.88,1.04	0.96	0.87,1.05	0.96	0.87,1.07	0.98	0.88,1.10	0.97	0.86,1.10	0.94	0.83,1.07
Adjusted A	1.07	0.97,1.18	1.16*	1.03,1.31	1.27*	1.11,1.44	1.33*	1.16,1.54	1.41*	1.21,1.65	1.46*	1.24,1.73	1.44*	1.21,1.72
Bi-directional case-crossover analysis														
Crude	0.96	0.90,1.03	0.98	0.91,1.06	0.99	0.91,1.08	1.00	0.91,1.10	1.03	0.93,1.14	1.02	0.91,1.13	1.00	0.89,1.12
Adjusted A	0.98	0.90,1.07	1.05	0.94,1.16	1.10	0.98,1.24	1.13	1.00,1.28	1.17*	1.03,1.34	1.18*	1.02,1.36	1.14	0.98,1.33
Adjusted B	0.99	0.90,1.09	1.06	0.94,1.19	1.10	0.97,1.26	1.11	0.97,1.29	1.15	0.98,1.35	1.16	0.98,1.38	1.12	0.94,1.34
Time series analysis														
Crude	0.98	0.94,1.03	1.00	0.95,1.05	1.01	0.96,1.07	1.03	0.97,1.09	1.05	0.99,1.11	1.05	0.98,1.11	1.03	0.97,1.10
Adjusted A	1.00	0.94,1.06	1.05	0.98,1.13	1.08*	1.00,1.16	1.12*	1.03,1.22	1.17*	1.08,1.28	1.18*	1.08,1.30	1.20*	1.09,1.31
Adjusted B	1.01	0.94,1.08	1.07	0.99,1.17	1.11*	1.02,1.22	1.13*	1.03,1.25	1.14*	1.02,1.26	1.15*	1.04,1.29	1.14*	1.02,1.28

Abbreviations: $PM_{10-2.5}$, coarse particulate matter between 2.5 and 10 microns in aerodynamic diameter

Note:

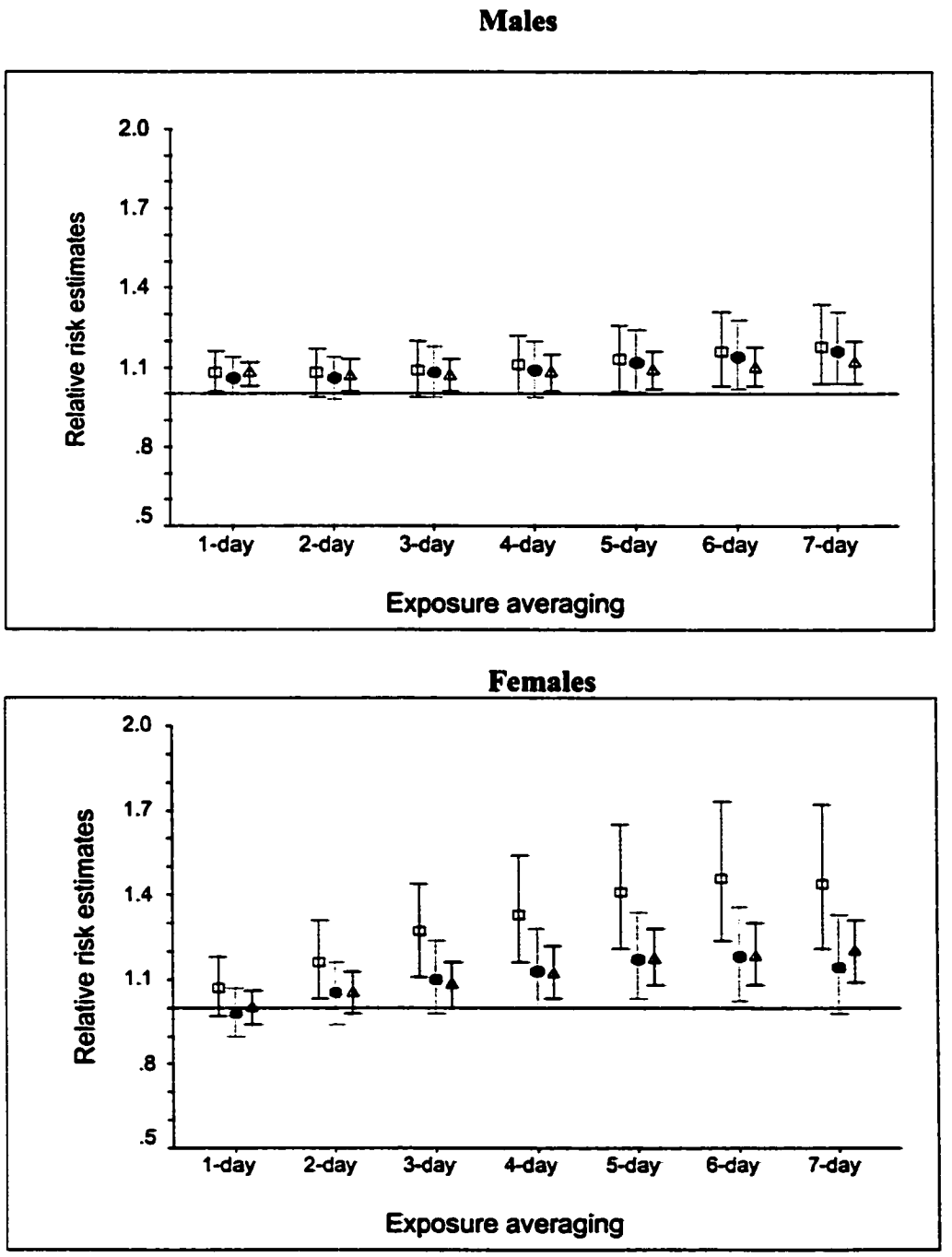
[a]Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);

Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and gaseous pollutants (CO, SO_2, NO_2, and O_3).

[b]RR estimates were calculated for an interquartile range increment of coarse particulate matter, which was calculated based on daily average levels.

* p-value<=0.05

Figure 4.8 Relative risk estimates and 95% confidence intervals for ***daily average coarse particulate matter ($PM_{10-2.5}$)*** in children 6-12 years of age, Toronto, 1981-1993, adjusted for weather conditions. (□: Uni-directional case-crossover analysis; ●: Bi-directional case-crossover analysis; Δ: Time series analysis.)



Estimated relative risks for fine particulate matter (PM2.5). Tables 4.8a and 4.8b show the estimated association between fine particulate matter and asthma hospitalization in males and females separately. No significant association was found in either sex using bi-directional case-crossover and time series analyses, with and without adjustment for weather conditions and gaseous pollutants. Only uni-directional case-crossover analysis showed a significant effect of fine particulate matter on asthma hospitalization. Figure 4.9 illustrates the relationship between fine particulate matter and asthma hospitalization after adjustment for weather conditions.

Estimated relative risks for thoracic particulate matter (PM_{10}). As with fine particulate matter, thoracic particulate matter was not significantly related to asthma hospitalization in both sexes in bi-directional case-crossover and time series analyses. The results are shown in Tables 4.9a and 4.9b and Figure 4.10.

Table 4.8a Crude and adjusted [a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily average fine particulate matter in relation to asthma hospitalization in males 6-12 years of age, Toronto, 1981-93.

$PM_{2.5}$ (9.3μg/m³)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	1.01	0.96,1.05	0.98	0.93,1.03	0.97	0.92,1.03	0.95	0.90,1.02	0.94	0.88,1.01	0.94	0.87,1.01	0.93	0.86,1.01
Adjusted A	1.09*	1.04,1.15	1.09*	1.02,1.16	1.11*	1.03,1.19	1.09*	1.01,1.18	1.10*	1.01,1.19	1.10*	1.00,1.20	1.10	1.00,1.21
Bi-directional case-crossover analysis														
Crude	1.01	0.97,1.05	1.00	0.95,1.04	0.99	0.94,1.05	0.98	0.92,1.04	0.98	0.92,1.04	0.97	0.90,1.04	0.98	0.91,1.05
Adjusted A	1.01	0.97,1.06	0.99	0.93,1.05	1.00	0.93,1.06	0.97	0.90,1.04	0.97	0.90,1.05	0.96	0.88,1.04	0.97	0.88,1.05
Adjusted B	1.00	0.95,1.06	0.96	0.90,1.03	0.97	0.89,1.05	0.93	0.85,1.02	0.94	0.85,1.03	0.92	0.83,1.02	0.93	0.83,1.04
Time series analysis														
Crude	1.00	0.97,1.03	0.99	0.95,1.02	0.99	0.95,1.03	0.98	0.94,1.02	0.98	0.93,1.02	0.98	0.93,1.02	0.98	0.93,1.03
Adjusted A	1.00	0.97,1.04	0.98	0.94,1.02	0.98	0.94,1.03	0.97	0.92,1.02	0.97	0.92,1.02	0.96	0.90,1.01	0.96	0.91,1.02
Adjusted B	0.99	0.95,1.04	0.96	0.91,1.01	0.97	0.92,1.03	0.95	0.89,1.01	0.96	0.90,1.02	0.94	0.88,1.01	0.96	0.89,1.03

Abbreviations: $PM_{2.5}$, particulate matter less than 2.5 microns in aerodynamic diameter.

Note:

[a] Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);

Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and gaseous pollutants (CO, SO_2, NO_2, and O_3).

[b] RR estimates were calculated for an interquartile range increment of fine particulate matter, which was calculated based on daily average levels.

* p-value<=0.05

Table 4.8b Crude and adjusted [a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily average fine particulate matter in relation to asthma hospitalization in females 6-12 years of age, Toronto, 1981-93.

$PM_{2.5}$ (9.3μg/m^3)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	1.00	0.95,1.07	1.02	0.96,1.10	1.02	0.94,1.10	1.04	0.95,1.13	1.06	0.97,1.16	1.06	0.96,1.17	1.04	0.94,1.15
Adjusted A	1.06	0.99,1.14	1.11*	1.02,1.21	1.16*	1.05,1.28	1.20*	1.08,1.33	1.24*	1.11,1.39	1.26*	1.11,1.42	1.22*	1.07,1.38
Bi-directional case-crossover analysis														
Crude	1.00	0.95,1.06	1.03	0.97,1.10	1.03	0.96,1.10	1.04	0.97,1.12	1.06	0.98,1.15	1.05	0.96,1.14	1.04	0.95,1.13
Adjusted A	0.99	0.93,1.06	1.02	0.94,1.09	1.02	0.94,1.11	1.03	0.94,1.13	1.04	0.95,1.15	1.04	0.94,1.15	1.00	0.90,1.11
Adjusted B	1.00	0.93,1.08	1.01	0.92,1.11	1.00	0.90,1.11	0.99	0.88,1.11	0.96	0.85,1.09	0.93	0.82,1.06	0.86	0.75,0.99
Time series analysis														
Crude	1.00	0.96,1.04	1.01	0.97,1.06	1.02	0.97,1.07	1.04	0.99,1.10	1.06	1.01,1.13	1.07	1.00,1.13	1.06	1.00,1.13
Adjusted A	0.99	0.95,1.04	1.00	0.95,1.06	1.01	0.95,1.06	1.02	0.95,1.08	1.06	0.99,1.13	1.05	0.97,1.12	1.06	0.98,1.13
Adjusted B	0.99	0.94,1.05	1.01	0.95,1.08	1.01	0.93,1.08	1.01	0.93,1.09	1.01	0.93,1.10	0.98	0.90,1.08	0.96	0.87,1.05

Abbreviations: $PM_{2.5}$, particulate matter less than 2.5 microns in aerodynamic diameter.

Note:

[a] Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);

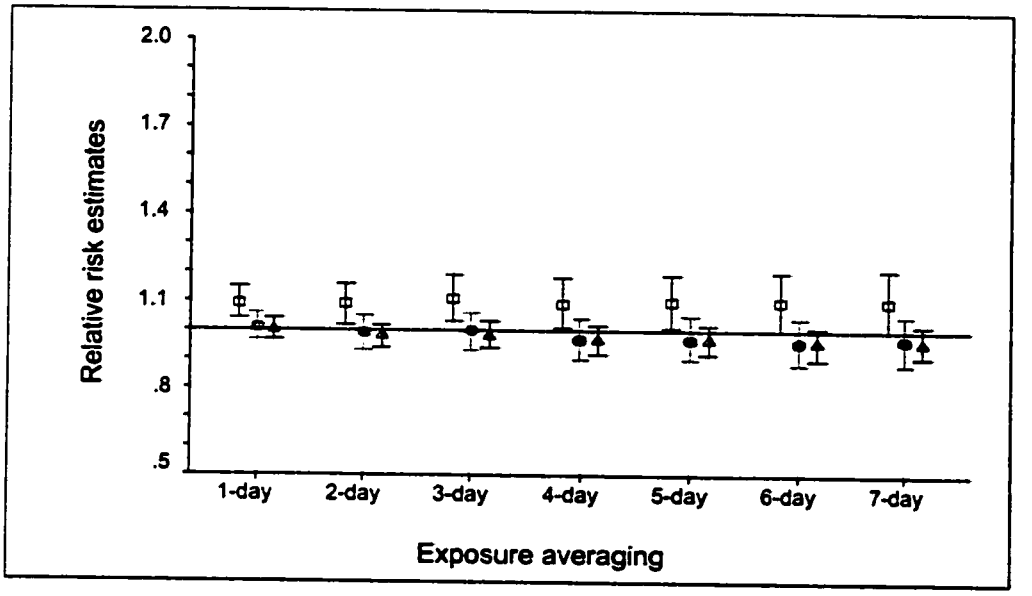
Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and gaseous pollutants (CO, SO_2, NO_2, and O_3).

[b] RR estimates were calculated for an interquartile range increment of fine particulate matter, which was calculated based on daily average levels.

* p-value<=0.05

Figure 4.9 Relative risk estimates and 95% confidence intervals for ***daily average fine particulate matter ($PM_{2.5}$)*** in children 6-12 years of age, Toronto, 1981-1993, adjusted for weather conditions. (□: Uni-directional case-crossover analysis; ●: Bi-directional case-crossover analysis; Δ: Time series analysis.)

Males



Females

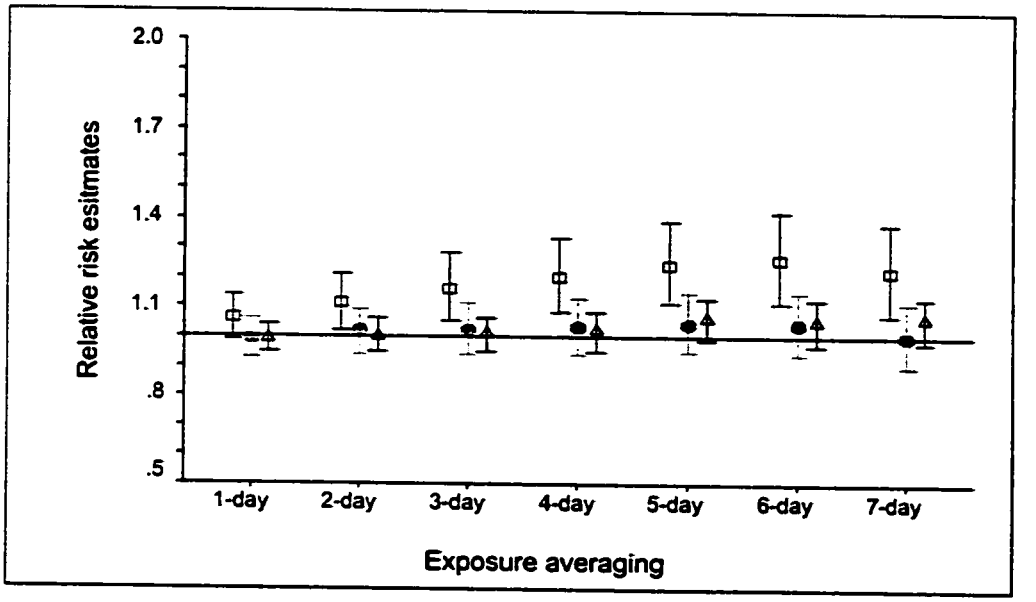


Table 4.9a Crude and adjusted [a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily average thoracic particulate matter in relation to asthma hospitalization in males 6-12 years of age, Toronto, 1981-93.

PM_{10} ($14.8\mu g/m^3$)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	0.99	0.94,1.03	0.96	0.91,1.01	0.95	0.89,1.00	0.93	0.87,0.99	0.91	0.85,0.98	0.90	0.83,0.97	0.89	0.82,0.96
Adjusted A	1.10*	1.04,1.17	1.10*	1.02,1.17	1.11*	1.03,1.20	1.11*	1.02,1.20	1.12*	1.02,1.22	1.13*	1.03,1.24	1.14*	1.03,1.26
Bi-directional case-crossover analysis														
Crude	1.02	0.97,1.06	1.01	0.96,1.06	1.01	0.96,1.07	1.00	0.94,1.07	1.00	0.94,1.07	1.00	0.93,1.07	1.00	0.92,1.08
Adjusted A	1.04	0.98,1.09	1.01	0.95,1.08	1.03	0.96,1.10	1.01	0.93,1.09	1.02	0.94,1.11	1.02	0.93,1.11	1.03	0.94,1.13
Adjusted B	1.03	0.97,1.10	0.99	0.92,1.08	1.01	0.93,1.11	0.99	0.90,1.09	1.01	0.90,1.12	1.01	0.90,1.13	1.03	0.91,1.17
Time series analysis														
Crude	1.01	0.98,1.04	1.00	0.97,1.04	1.01	0.97,1.05	1.00	0.95,1.04	0.99	0.95,1.04	0.99	0.94,1.04	0.99	0.94,1.04
Adjusted A	1.03	0.99,1.07	1.01	0.96,1.05	1.01	0.97,1.06	1.00	0.95,1.06	1.00	0.95,1.06	1.00	0.94,1.07	1.01	0.95,1.08
Adjusted B	1.04	0.99,1.09	1.01	0.95,1.07	1.02	0.96,1.09	1.01	0.94,1.09	1.03	0.95,1.11	1.02	0.94,1.11	1.05	0.96,1.14

Abbreviations: PM_{10}, particulate matter less than 10 microns in aerodynamic diameter.

Note:

[a] Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);

Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and gaseous pollutants (CO, SO_2, NO_2, and O_3).

[b] RR estimates were calculated for an interquartile range increment of thoracic particulate matter, which was calculated based on daily average levels.

*p-value<=0.05

Table 4.9b Crude and adjusted [a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily average thoracic particulate matter in relation to asthma hospitalization in females 6-12 years of age, Toronto, 1981-93.

PM_{10} (14.8μg/m³)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	0.99	0.93,1.05	1.00	0.93,1.07	1.00	0.92,1.08	1.01	0.93,1.10	1.03	0.94,1.14	1.03	0.93,1.14	1.00	0.90,1.12
Adjusted A	1.07	0.99,1.16	1.15*	1.04,1.26	1.22*	1.10,1.35	1.27*	1.13,1.43	1.33*	1.17,1.50	1.36*	1.19,1.55	1.32*	1.14,1.51
Bi-directional case-crossover analysis														
Crude	0.99	0.93,1.05	1.01	0.95,1.08	1.01	0.94,1.09	1.03	0.95,1.11	1.05	0.97,1.14	1.04	0.95,1.14	1.02	0.93,1.13
Adjusted A	0.99	0.92,1.06	1.03	0.95,1.12	1.05	0.96,1.15	1.07	0.97,1.18	1.09	0.98,1.21	1.09	0.97,1.22	1.05	0.93,1.18
Adjusted B	0.99	0.91,1.08	1.03	0.93,1.15	1.04	0.93,1.18	1.04	0.91,1.18	1.02	0.89,1.17	0.99	0.85,1.15	0.92	0.78,1.07
Time series analysis														
Crude	0.99	0.95,1.03	1.01	0.96,1.06	1.02	0.97,1.07	1.04	0.98,1.10	1.05	0.99,1.12	1.06	0.99,1.12	1.06	0.99,1.13
Adjusted A	0.99	0.94,1.04	1.02	0.96,1.08	1.03	0.97,1.09	1.04	0.97,1.12	1.08	0.99,1.16	1.07	0.98,1.16	1.07	0.98,1.16
Adjusted B	1.00	0.94,1.07	1.04	0.97,1.13	1.05	0.97,1.14	1.06	0.97,1.17	1.05	0.95,1.17	1.03	0.93,1.15	1.01	0.90,1.14

Abbreviations: PM_{10}, particulate matter less than 10 microns in aerodynamic diameter.

Note:

[a] Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);

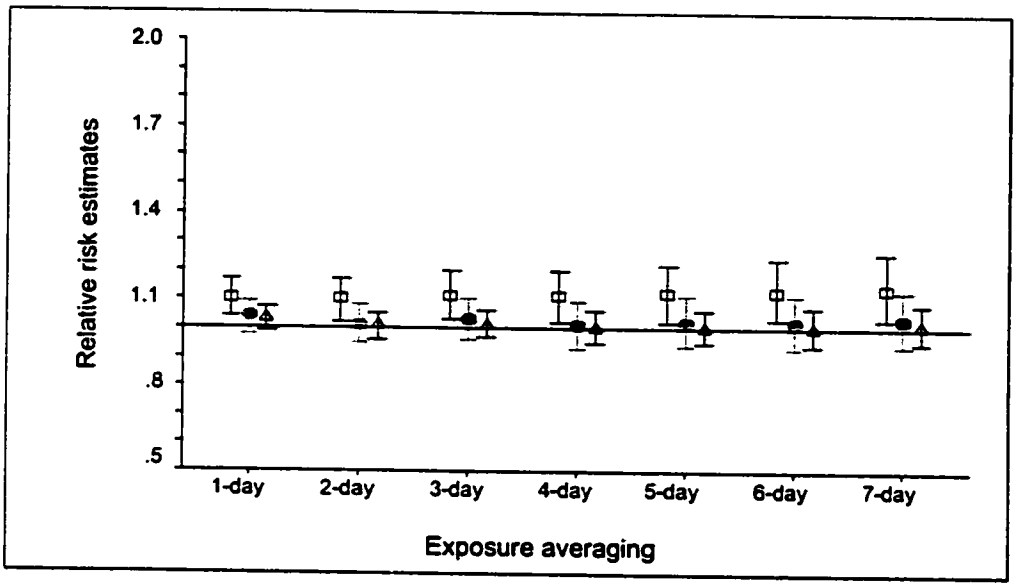
Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and gaseous pollutants (CO, SO_2, NO_2, and O_3).

[b] RR estimates were calculated for an interquartile range increment of thoracic particulate matter, which was calculated based on daily average levels.

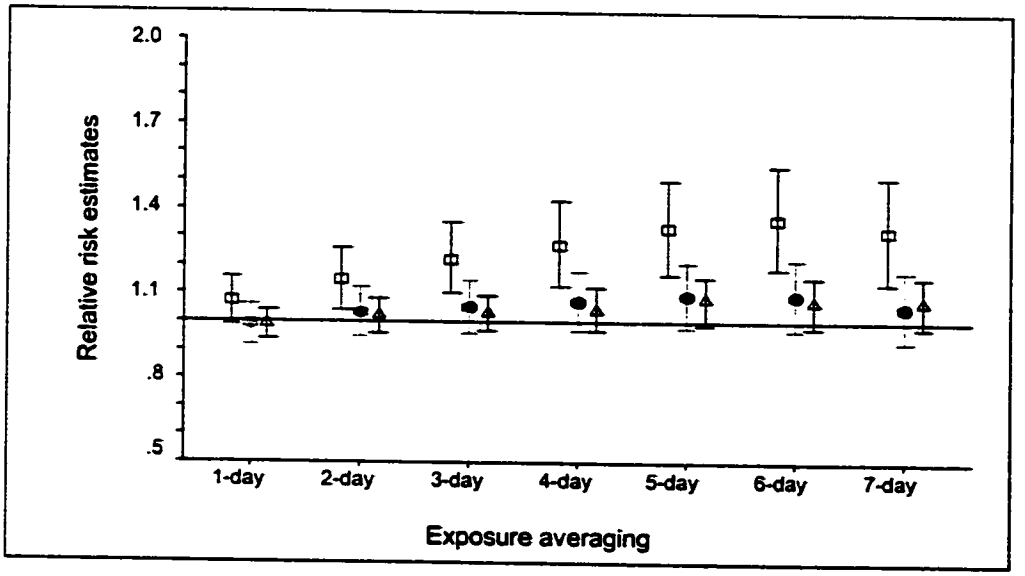
* p-value<=0.05

Figure 4.10 Relative risk estimates and 95% confidence intervals for ***daily average thoracic particulate matter (PM_{10})*** in children 6-12 years of age, Toronto, 1981-1993, adjusted for weather conditions. (□: Uni-directional case-crossover analysis; ●: Bi-directional case-crossover analysis; Δ: Time series analysis.)

Males



Females



4.3.2 Relative risk estimates for gaseous pollutants

Estimated relative risks for carbon monoxide (CO). Both bi-directional case-crossover and time series analyses showed a significant positive association between CO and asthma hospitalization after adjustment for weather conditions and particulate matter in males (Table 4.10a), but not in females (Table 4.10b). Figure 4.11 shows the relative risks for 1- to 7-day exposure with adjustment for weather conditions from the three approaches in males and females, separately. The lag time for manifestation of a significant effect of CO in males was about 1 to 2 days. Such effects persisted up to about 3 days using both bi-directional case-crossover and time series analyses. The relative risk estimates in males were slightly larger using bi-directional case-crossover analysis as compared with time series analysis.

Estimated relative risks for sulfur dioxide (SO_2). In contrast to CO, SO_2 showed a significant effect on asthma hospitalization in females (Table 4.11b), with both bi-directional and time series analyses, although the effect was not apparent in males (Table 4.11a). Figure 4.12 shows that the estimated effect of SO_2 in females increased with the increasing days of exposure, and was significant for 6 to 7 day exposure averages.

Estimated relative risks for nitrogen dioxide (NO_2). When bi-directional case-crossover analysis was used, NO_2 was significantly associated with asthma hospitalization in both males and females, as shown in Tables 4.12a and 4.12b. The relative risk estimates for NO_2 from bi-directional case-crossover analyses appeared

to be larger than those from time series analyses, especially for those with multi-day average exposures. In males, the NO_2 effect was not significant when time series analysis was used. In bi-directional case-crossover analyses, the lag time for the NO_2 effect appeared to be different in males and females. In males, NO_2 showed no significant effect until 3 days of average exposure, and appeared to increase slightly with increasing number of days of exposure averaging up until 6 days. In females, only 6- and 7-day exposure averages of NO_2 consistently showed a significant effect on asthma hospitalization, after adjustment for exposure to particulate matter.

Estimated relative risks for ozone (O_3). No significant and positive association between O_3 and asthma hospitalization was found before and after controlling for weather conditions and particulate matter. The results are showed in Tables 4.13a and 4.13b and Figure 4.14.

In general, the adjusted relative risk estimates for gaseous pollutants from time series analyses were closer to those from bi-directional case-crossover analyses as compared with those from uni-directional case-crossover analyses. Some gaseous pollutants displayed more pronounced positive effects on asthma hospitalization when bi-directional case-crossover analysis was used as compared to time series analysis, especially for multi-day exposure averages. Greater adjusted relative risk estimates for multi-day average measures of CO and NO_2 in males and for SO_2 and NO_2 in females were obtained with bi-directional case-crossover analysis as compared with time series analysis.

Table 4.10a Crude and adjusted [a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily average carbon monoxide in relation to asthma hospitalization in males 6-12 years of age, Toronto, 1981-93.

CO (0.5 ppm)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	1.04	0.99,1.10	1.08*	1.02,1.15	1.08*	1.01,1.15	1.09*	1.01,1.17	1.09*	1.00,1.18	1.11*	1.01,1.21	1.12*	1.03,1.23
Adjusted A	1.10*	1.04,1.16	1.17*	1.10,1.25	1.19*	1.10,1.29	1.21*	1.11,1.31	1.21*	1.10,1.32	1.22*	1.11,1.35	1.23*	1.11,1.36
Bi-directional case-crossover analysis														
Crude	1.04	0.99,1.09	1.06*	1.01,1.13	1.07*	1.00,1.13	1.07*	1.00,1.15	1.07	0.99,1.15	1.07	0.99,1.16	1.09	1.00,1.18
Adjusted A	1.05	1.00,1.11	1.07*	1.01,1.14	1.08*	1.01,1.16	1.08*	1.00,1.17	1.07	0.99,1.16	1.07	0.98,1.17	1.07	0.98,1.17
Adjusted B	1.05	0.99,1.11	1.08*	1.01,1.16	1.09*	1.01,1.18	1.10*	1.02,1.20	1.09	1.00,1.18	1.09	0.99,1.19	1.09	0.99,1.20
Time series analysis														
Crude	1.03	1.00,1.07	1.04	1.00,1.08	1.03	0.99,1.08	1.03	0.99,1.08	1.03	0.98,1.07	1.04	0.99,1.09	1.04	0.99,1.10
Adjusted A	1.04*	1.00,1.07	1.04*	1.00,1.08	1.03	0.99,1.08	1.03	0.98,1.08	1.01	0.96,1.06	1.02	0.97,1.08	1.02	0.97,1.08
Adjusted B	1.04*	1.00,1.08	1.05*	1.01,1.10	1.04	1.00,1.10	1.04	0.99,1.10	1.03	0.98,1.09	1.04	0.98,1.10	1.04	0.98,1.10

Abbreviations: CO, carbon monoxide.

Note:

[a] Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);
Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and particulate matter (coarse and fine particulate matter).

[b] RR estimates were calculated for an interquartile range increment of carbon monoxide, which was calculated based on daily average levels.

* p-value<=0.05

Table 4.10b Crude and adjusted [a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily average carbon monoxide in relation to asthma hospitalization in females 6-12 years of age, Toronto, 1981-93.

CO (0.5 ppm)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	1.01	0.94,1.08	1.04	0.96,1.13	1.03	0.94,1.13	1.02	0.92,1.14	1.06	0.95,1.18	1.08	0.96,1.21	1.09	0.96,1.23
Adjusted A	1.03	0.95,1.11	1.07	0.97,1.17	1.08	0.97,1.20	1.07	0.96,1.20	1.12	0.99,1.26	1.15*	1.01,1.31	1.16*	1.01,1.33
Bi-directional case-crossover analysis														
Crude	1.01	0.95,1.08	1.05	0.97,1.12	1.03	0.95,1.12	1.03	0.94,1.13	1.06	0.96,1.16	1.07	0.97,1.19	1.10	0.99,1.22
Adjusted A	1.00	0.93,1.06	1.01	0.94,1.10	1.00	0.91,1.09	0.98	0.89,1.09	1.01	0.91,1.13	1.03	0.92,1.16	1.04	0.93,1.17
Adjusted B	1.00	0.93,1.07	1.01	0.92,1.10	0.99	0.90,1.09	0.97	0.87,1.08	0.99	0.89,1.11	1.02	0.90,1.15	1.05	0.93,1.20
Time series analysis														
Crude	1.00	0.96,1.04	1.02	0.97,1.07	1.01	0.96,1.07	1.01	0.95,1.07	1.03	0.97,1.10	1.05	0.99,1.12	1.07	1.00,1.14
Adjusted A	0.99	0.94,1.03	1.00	0.94,1.05	0.98	0.93,1.04	0.96	0.90,1.02	1.00	0.93,1.06	1.00	0.94,1.08	1.04	0.97,1.11
Adjusted B	0.99	0.94,1.04	0.99	0.94,1.05	0.98	0.92,1.04	0.94	0.88,1.01	0.96	0.90,1.03	0.98	0.91,1.06	1.01	0.94,1.09

Abbreviations: CO, carbon monoxide.

Note:

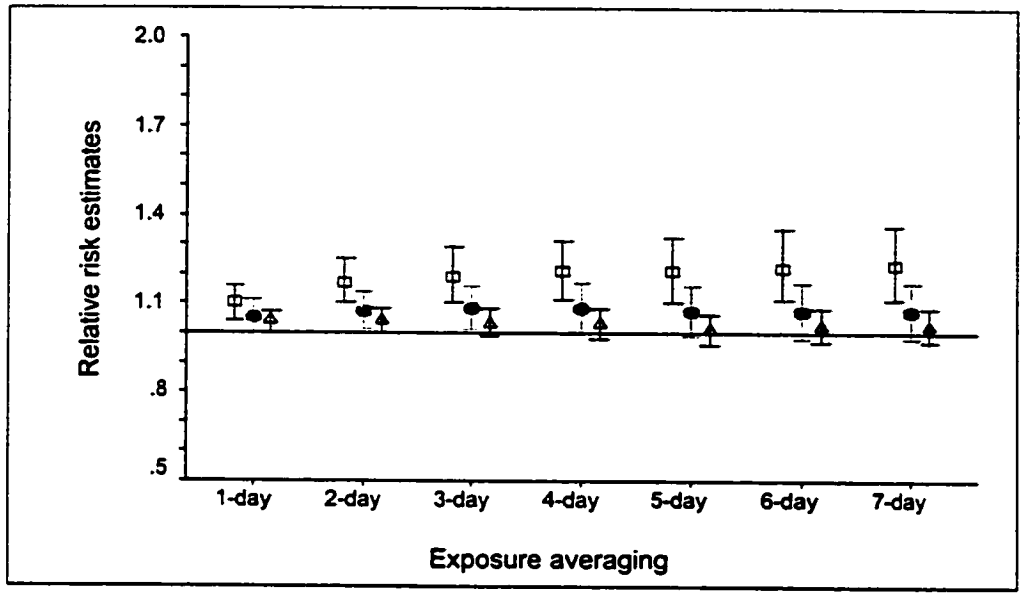
[a] Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);
Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and particulate matter (coarse and fine particulate matter).

[b] RR estimates were calculated for an interquartile range increment of carbon monoxide, which was calculated based on daily average levels.

* p-value<=0.05

Figure 4.11 Relative risk estimates and 95% confidence intervals for ***daily average carbon monoxide (CO)*** in children 6-12 years of age, Toronto, 1981-1993, adjusted for weather conditions. (□: Uni-directional case-crossover analysis; ●: Bi-directional case-crossover analysis; Δ: Time series analysis.)

Males



Females

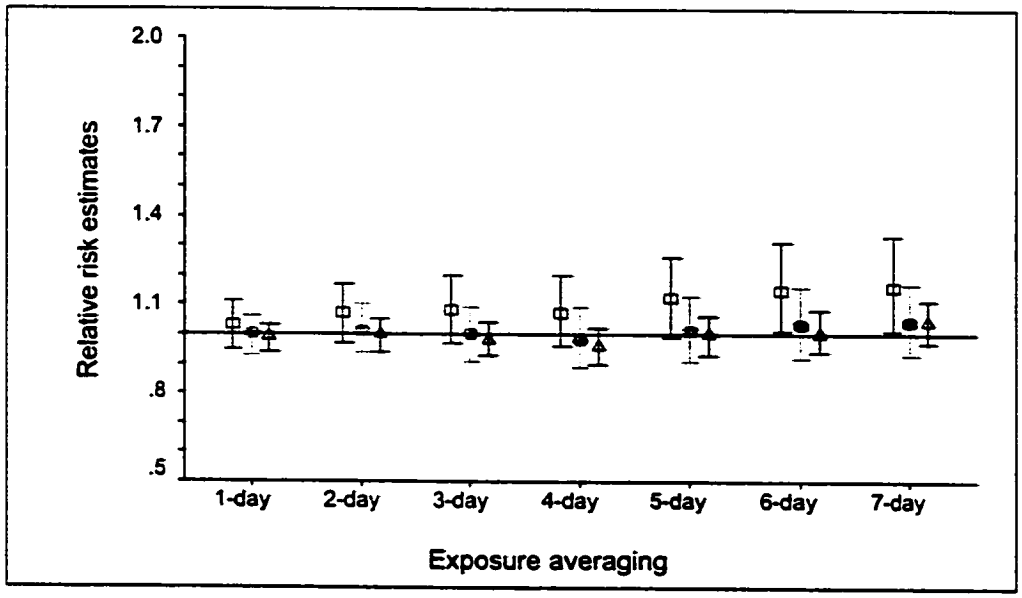


Table 4.11a Crude and adjusted[a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily average sulfur dioxide in relation to asthma hospitalization in males 6-12 years of age, Toronto, 1981-93.

SO_2 (7 ppb)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	1.02	0.97,1.08	1.02	0.96,1.09	1.00	0.92,1.08	0.98	0.90,1.07	0.98	0.89,1.08	0.98	0.88,1.09	1.00	0.89,1.12
Adjusted A	1.08*	1.02,1.15	1.11*	1.03,1.19	1.10*	1.01,1.20	1.09	0.99,1.21	1.12*	1.01,1.26	1.12*	1.00,1.27	1.17*	1.02,1.33
Bi-directional case-crossover analysis														
Crude	0.99	0.95,1.04	0.99	0.93,1.05	0.97	0.90,1.05	0.96	0.88,1.04	0.95	0.86,1.04	0.93	0.84,1.02	0.93	0.83,1.03
Adjusted A	1.00	0.95,1.05	0.99	0.93,1.06	0.98	0.90,1.06	0.96	0.87,1.05	0.95	0.86,1.05	0.93	0.83,1.03	0.93	0.83,1.04
Adjusted B	0.98	0.93,1.04	0.99	0.91,1.06	0.96	0.88,1.05	0.95	0.85,1.05	0.94	0.84,1.06	0.91	0.80,1.04	0.91	0.80,1.04
Time series analysis														
Crude	0.98	0.95,1.02	0.98	0.94,1.03	0.96	0.92,1.02	0.95	0.90,1.01	0.94	0.89,1.01	0.93*	0.87,0.99	0.92*	0.86,0.99
Adjusted A	0.99	0.95,1.03	0.98	0.93,1.03	0.97	0.92,1.02	0.94	0.88,1.00	0.94	0.88,1.00	0.92*	0.85,0.99	0.92*	0.86,1.00
Adjusted B	0.97	0.93,1.02	0.98	0.92,1.03	0.95	0.89,1.02	0.93	0.86,1.00	0.93	0.86,1.01	0.91*	0.83,0.99	0.90*	0.83,0.99

Abbreviations: SO_2, sulfur dioxide.

Note:

[a] Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);
Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and particulate matter (coarse and fine particulate matter).

[b] RR estimates were calculated for an interquartile range increment of sulfer dioxide, which was calculated based on daily average levels.

* p-value<=0.05

Table 4.11b Crude and adjusted [a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily average sulfur dioxide in relation to asthma hospitalization in females 6-12 years of age, Toronto, 1981-93.

SO_2 (7 ppb)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	1.06	0.99,1.13	1.06	0.98,1.16	1.07	0.96,1.18	1.10	0.98,1.23	1.17*	1.03,1.32	1.23*	1.07,1.41	1.30*	1.12,1.51
Adjusted A	1.10*	1.02,1.18	1.15*	1.04,1.26	1.21*	1.07,1.35	1.26*	1.11,1.43	1.35*	1.17,1.55	1.45*	1.24,1.70	1.56*	1.32,1.85
Bi-directional case-crossover analysis														
Crude	1.04	0.98,1.11	1.04	0.96,1.12	1.03	0.94,1.13	1.07	0.96,1.18	1.11	0.99,1.24	1.14*	1.01,1.29	1.19*	1.04,1.36
Adjusted A	1.04	0.97,1.11	1.04	0.95,1.13	1.05	0.95,1.16	1.09	0.98,1.22	1.13	1.00,1.28	1.17*	1.02,1.34	1.20*	1.04,1.39
Adjusted B	1.06	0.98,1.14	1.03	0.93,1.14	1.04	0.92,1.17	1.08	0.95,1.23	1.12	0.97,1.29	1.18*	1.00,1.38	1.28*	1.08,1.51
Time series analysis														
Crude	1.01	0.96,1.06	0.99	0.94,1.05	1.00	0.94,1.07	1.04	0.97,1.12	1.08*	1.00,1.16	1.10*	1.01,1.19	1.13*	1.04,1.23
Adjusted A	1.01	0.96,1.06	0.99	0.93,1.05	1.01	0.94,1.08	1.03	0.96,1.12	1.09*	1.01,1.18	1.09*	1.00,1.19	1.16*	1.06,1.26
Adjusted B	1.01	0.96,1.07	0.98	0.91,1.05	1.00	0.92,1.08	1.01	0.93,1.11	1.05	0.96,1.16	1.06	0.96,1.18	1.15*	1.03,1.28

Abbreviations: SO_2, sulfur dioxide.

Note:

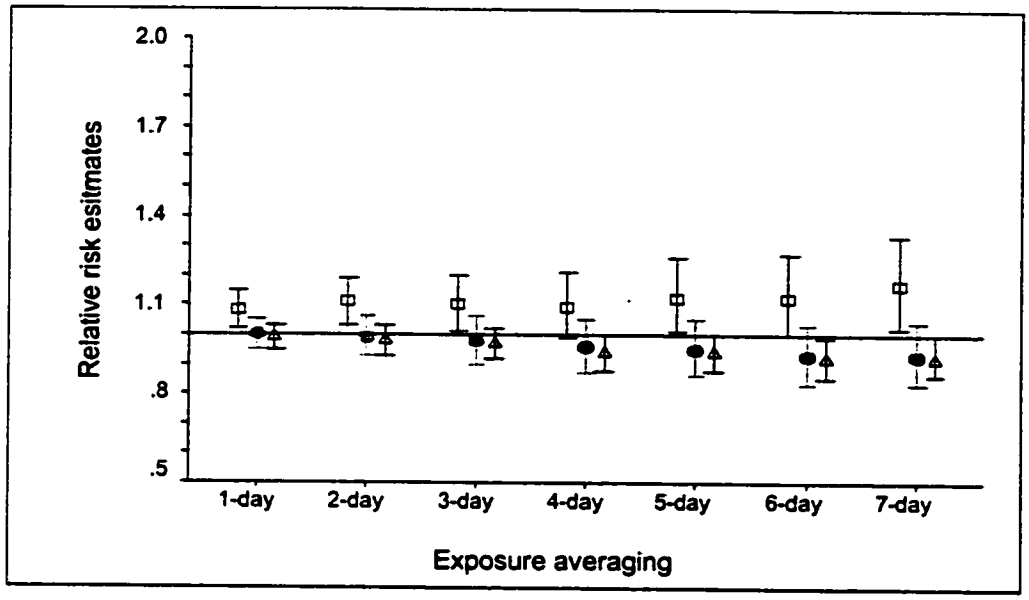
[a] Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);
Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and particulate matter (coarse and fine particulate matter).

[b] RR estimates were calculated for an interquartile range increment of sulfer dioxide, which was calculated based on daily average levels.

* p-value<=0.05

Figure 4.12 Relative risk estimates and 95% confidence intervals for ***daily average sulfur dioxide (SO_2)*** in children 6-12 years of age, Toronto, 1981-1993, adjusted for weather conditions. (□: Uni-directional case-crossover analysis; ●: Bi-directional case-crossover analysis; Δ: Time series analysis.)

Males



Females

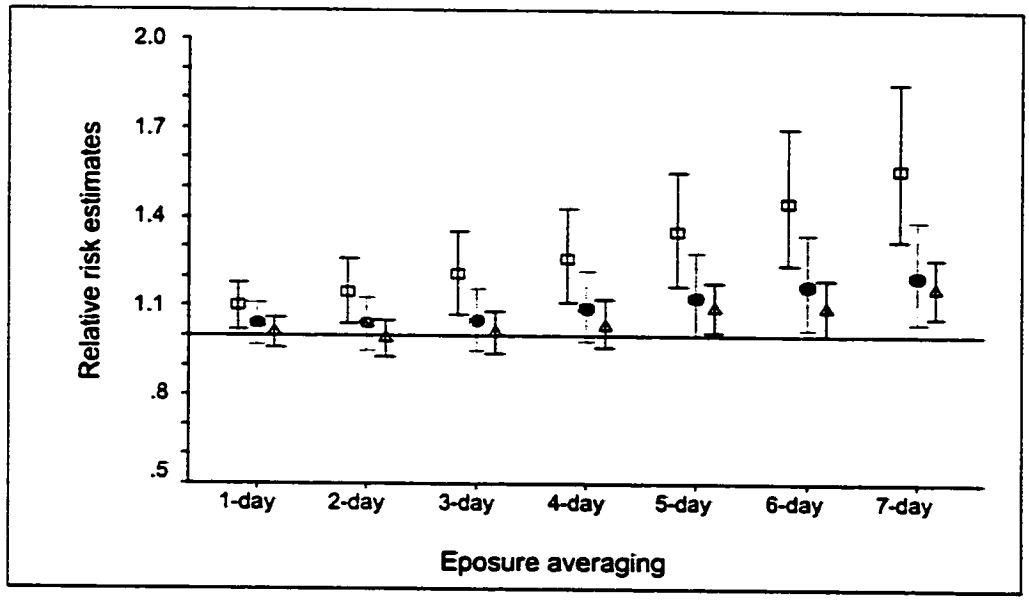


Table 4.12a Crude and adjusted [a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily average nitrogen dioxide in relation to asthma hospitalization in males 6-12 years of age, Toronto, 1981-93.

NO_2 (11ppb)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	1.04	0.98,1.09	1.06	1.00,1.14	1.06	0.98,1.14	1.08	0.99,1.17	1.08	0.99,1.18	1.10*	1.00,1.21	1.12*	1.01,1.23
Adjusted A	1.11*	1.04,1.18	1.18*	1.10,1.27	1.21*	1.11,1.31	1.23*	1.12,1.36	1.25*	1.13,1.38	1.29*	1.15,1.43	1.30*	1.16,1.46
Bi-directional case-crossover analysis														
Crude	1.03	0.98,1.09	1.06*	1.00,1.13	1.07*	1.00,1.15	1.10*	1.01,1.18	1.09*	1.00,1.18	1.11*	1.01,1.21	1.11*	1.01,1.22
Adjusted A	1.04	0.99,1.10	1.07	1.00,1.14	1.09*	1.01,1.17	1.10*	1.01,1.20	1.10*	1.00,1.20	1.12*	1.01,1.23	1.11*	1.00,1.24
Adjusted B	1.03	0.97,1.10	1.09*	1.01,1.18	1.10*	1.01,1.21	1.15*	1.04,1.27	1.13*	1.01,1.26	1.16*	1.03,1.31	1.15*	1.01,1.30
Time series analysis														
Crude	1.02	0.98,1.06	1.03	0.99,1.08	1.03	0.98,1.09	1.04	0.99,1.10	1.03	0.98,1.10	1.05	0.99,1.12	1.05	0.99,1.12
Adjusted A	1.03	0.99,1.07	1.03	0.99,1.08	1.03	0.98,1.08	1.04	0.98,1.10	1.02	0.97,1.09	1.04	0.98,1.11	1.03	0.97,1.10
Adjusted B	1.02	0.97,1.06	1.05	0.99,1.11	1.04	0.98,1.11	1.06	0.99,1.14	1.05	0.97,1.13	1.07	0.99,1.16	1.06	0.98,1.15

Abbreviations: NO_2, nitrogen dioxide.

Note:

[a] Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);
Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and particulate matter (course and fine particulate matter).

[b] RR estimates were calculated for an interquartile range increment of nitrogen dioxide, which was calculated based on daily average levels.

* p-value<=0.05

Table 4.12b Crude and adjusted [a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily average nitrogen dioxide in relation to asthma hospitalization in females 6-12 years of age, Toronto, 1981-93.

NO_2 (11ppb)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	1.02	0.95,1.10	1.06	0.97,1.16	1.09	0.98,1.21	1.11	0.99,1.24	1.19*	1.05,1.35	1.23*	1.08,1.40	1.25*	1.09,1.44
Adjusted A	1.05	0.97,1.14	1.12*	1.02,1.24	1.21*	1.08,1.36	1.24*	1.09,1.41	1.33*	1.16,1.52	1.40*	1.20,1.62	1.42*	1.21,1.66
Bi-directional case-crossover analysis														
Crude	1.00	0.94,1.07	1.04	0.96,1.13	1.06	0.97,1.16	1.09	0.98,1.20	1.15*	1.04,1.28	1.16*	1.04,1.30	1.19*	1.05,1.34
Adjusted A	0.99	0.92,1.06	1.03	0.94,1.12	1.07	0.96,1.18	1.09	0.97,1.21	1.14*	1.02,1.28	1.16*	1.02,1.31	1.16*	1.02,1.32
Adjusted B	0.99	0.92,1.08	1.02	0.92,1.12	1.05	0.93,1.18	1.07	0.93,1.22	1.12	0.98,1.29	1.16*	1.00,1.35	1.21*	1.03,1.42
Time series analysis														
Crude	1.00	0.96,1.05	1.02	0.97,1.08	1.04	0.97,1.11	1.06	0.99,1.14	1.11*	1.03,1.20	1.14*	1.06,1.23	1.15*	1.06,1.25
Adjusted A	1.00	0.95,1.05	1.01	0.95,1.08	1.03	0.97,1.10	1.04	0.97,1.12	1.11*	1.03,1.19	1.11*	1.03,1.21	1.14*	1.06,1.24
Adjusted B	1.00	0.94,1.07	1.00	0.93,1.08	1.03	0.94,1.12	1.02	0.93,1.11	1.07	0.97,1.18	1.09	0.98,1.20	1.13*	1.02,1.26

Abbreviations: NO_2, nitrogen dioxide.

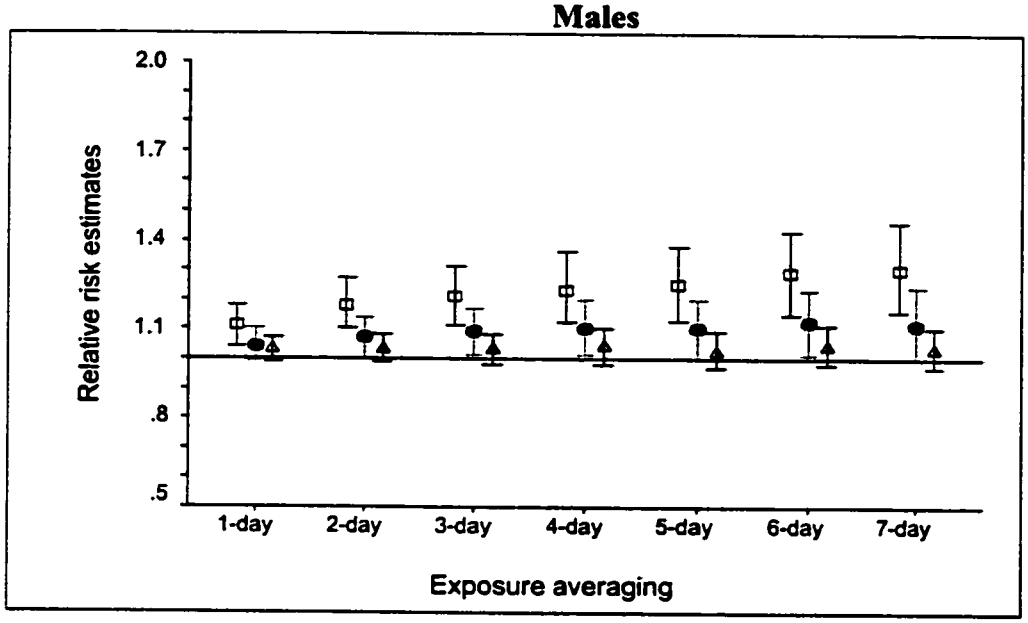
Note:

[a] Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);
Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and particulate matter (coarse and fine particulate matter).

[b] RR estimates were calculated for an interquartile range increment of nitrogen dioxide, which was calculated based on daily average levels.

* p-value<=0.05

Figure 4.13 Relative risk estimates and 95% confidence intervals for ***daily average nitrogen dioxide (NO_2)*** in children 6-12 years of age, Toronto, 1981-1993, adjusted for weather conditions. (□: Uni-directional case-crossover analysis; ●: Bi-directional case-crossover analysis; Δ: Time series analysis.)



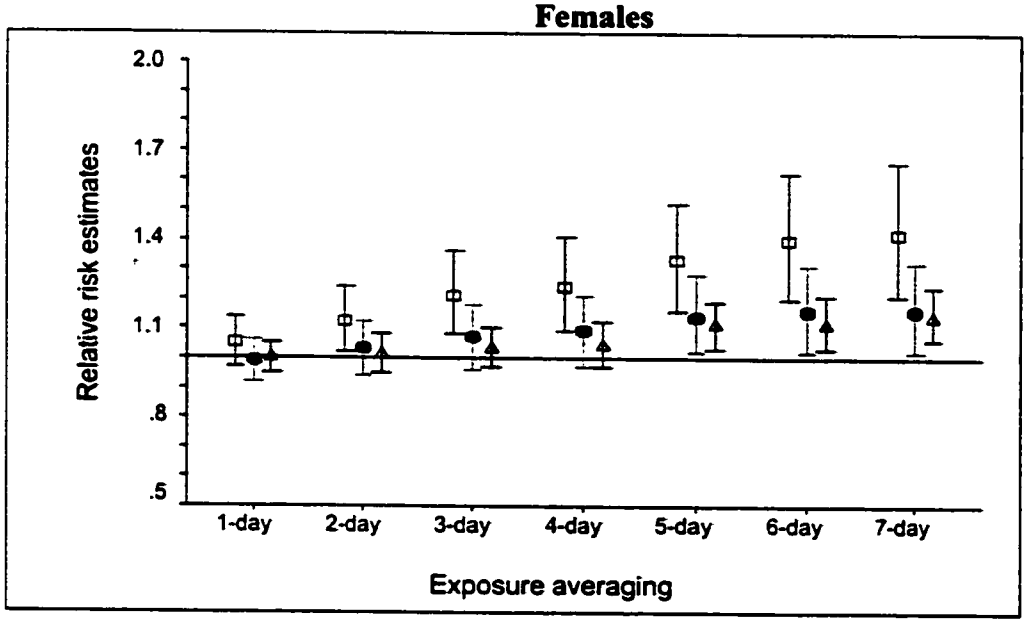


Table 4.13a Crude and adjusted [a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily maximum 1-hr ozone in relation to asthma hospitalization in males 6-12 years of age, Toronto, 1981-93.

O_3 (20 ppb)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	0.86*	0.81,0.93	0.80*	0.74,0.87	0.75*	0.68,0.83	0.68*	0.61,0.76	0.63*	0.56,0.71	0.58*	0.51,0.65	0.52*	0.46,0.60
Adjusted A	0.92	0.85,1.01	0.86*	0.78,0.96	0.82*	0.72,0.93	0.76*	0.66,0.88	0.74*	0.63,0.86	0.69*	0.58,0.82	0.66*	0.55,0.79
Bi-directional case-crossover analysis														
Crude	0.95	0.90,1.02	0.95	0.88,1.03	0.95	0.87,1.04	0.92	0.84,1.02	0.91	0.82,1.01	0.89*	0.79,0.99	0.85*	0.76,0.96
Adjusted A	0.96	0.88,1.04	0.94	0.85,1.04	0.93	0.82,1.04	0.89	0.79,1.02	0.91	0.79,1.05	0.90	0.77,1.05	0.88	0.75,1.04
Adjusted B	0.95	0.87,1.03	0.93	0.84,1.03	0.91	0.81,1.02	0.88	0.77,1.00	0.89	0.77,1.03	0.87	0.74,1.02	0.85	0.71,1.00
Time series analysis														
Crude	0.97	0.93,1.00	0.96*	0.92,0.99	0.96*	0.93,1.00	0.95*	0.91,0.99	0.93*	0.89,0.97	0.91*	0.87,0.95	0.88*	0.85,0.92
Adjusted A	1.00	0.95,1.06	0.98	0.91,1.05	0.98	0.91,1.05	0.98	0.90,1.06	0.98	0.89,1.07	0.96	0.88,1.06	0.96	0.87,1.05
Adjusted B	0.99	0.93,1.05	0.97	0.90,1.04	0.95	0.89,1.03	0.96	0.88,1.05	0.96	0.87,1.05	0.94	0.85,1.04	0.92	0.83,1.02

Abbreviations: O_3, ozone.

Note:

[a] Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);
Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and particulate matter (coarse and fine particulate matter).

[b] RR estimates were calculated for an interquartile range increment of ozone, which was calculated based on daily maximum 1-hr levels.

* p-value<=0.05

Table 4.13b Crude and adjusted [a] relative risk estimates (RRs)[b] and 95% confidence intervals (CIs) for daily maximum 1-hr ozone in relation to asthma hospitalization in females 6-12 years of age, Toronto, 1981-93.

O_3 (20 ppb)	Exposure averaging													
	1 day		2 days		3 days		4 days		5 days		6 days		7 days	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Uni-directional case-crossover analysis														
Crude	0.84*	0.77,0.92	0.81*	0.73,0.90	0.78*	0.69,0.88	0.78*	0.68,0.89	0.79*	0.68,0.91	0.75*	0.64,0.88	0.69*	0.59,0.82
Adjusted A	0.86*	0.77,0.97	0.90	0.77,1.04	0.93	0.78,1.10	0.98	0.81,1.19	1.07	0.87,1.32	1.09	0.87,1.37	1.02	0.80,1.31
Bi-directional case-crossover analysis														
Crude	0.89*	0.82,0.96	0.89*	0.80,0.97	0.87*	0.78,0.97	0.89	0.79,1.00	0.92	0.81,1.04	0.89	0.78,1.02	0.85*	0.74,0.98
Adjusted A	0.86	0.78,1.04	0.90	0.78,1.02	0.92	0.79,1.07	0.95	0.80,1.13	1.02	0.84,1.23	1.00	0.82,1.23	0.93	0.75,1.16
Adjusted B	0.86	0.78,0.96	0.88	0.77,1.01	0.89	0.76,1.04	0.92	0.77,1.10	0.97	0.80,1.18	0.95	0.78,1.17	0.89	0.72,1.12
Time series analysis														
Crude	0.93*	0.89,0.98	0.92*	0.88,0.97	0.91*	0.87,0.96	0.92*	0.87,0.97	0.92*	0.87,0.98	0.90*	0.84,0.95	0.86*	0.81,0.91
Adjusted A	0.94	0.87,1.01	0.96	0.88,1.04	0.96	0.88,1.05	0.98	0.88,1.09	1.03	0.92,1.15	1.02	0.90,1.14	0.97	0.85,1.10
Adjusted B	0.94	0.87,1.01	0.94	0.86,1.03	0.92	0.84,1.02	0.95	0.85,1.06	0.97	0.86,1.10	0.96	0.85,1.09	0.90	0.79,1.03

Abbreviations: O_3, ozone.

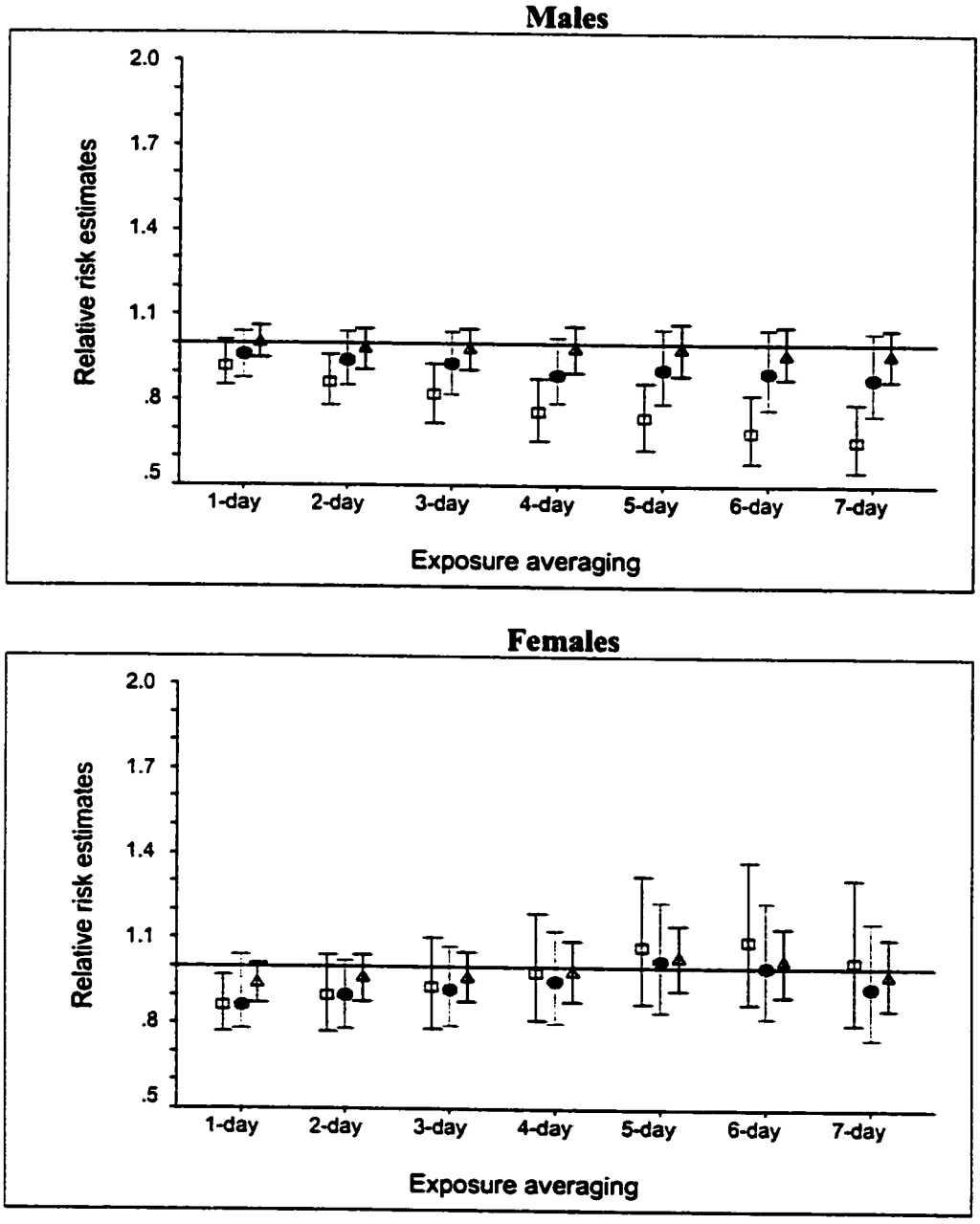
Note:

[a] Adjusted A, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity);
Adjusted B, adjusted for daily weather conditions (maximum temperature, minimum temperature and average relative humidity) and particulate matter (coarse and fine particulate matter).

[b] RR estimates were calculated for an interquartile range increment of ozone, which was calculated based on daily maximum 1-hr levels.

* p-value<=0.05

Figure 4.14 Relative risk estimates and 95% confidence intervals for ***daily maximum 1-hr ozone (O_3)*** in children 6-12 years of age, Toronto, 1981-1993, adjusted for weather conditions. (□: Uni-directional case-crossover analysis; ●: Bi-directional case-crossover analysis; Δ: Time series analysis.)



CHAPTER 5 DISCUSSION

5.1 General

In this investigation, uni-directional case-crossover analysis tended to produce more pronounced associations between air pollution and asthma hospitalization, as compared with bi-directional case-crossover and time series analyses. The estimated associations after adjustment for weather conditions from bi-directional case-crossover analysis and time-series analysis were more similar.

In the bi-directional case-crossover analysis, coarse particulate matter ($PM_{10-2.5}$) and nitrogen dioxide (NO_2) were positively associated with asthma hospitalization in both sexes. A significant short-term effect of carbon monoxide (CO) was found in males, and sulfur dioxide (SO_2) showed a significant effect of prolonged exposure in females. Fine ($PM_{2.5}$) and thoracic (PM_{10}) particulate matter and ozone (O_3) showed no significantly positive effects on asthma hospitalization in both males and females. The corresponding results from time series analyses were generally similar. Some air pollutants (CO and NO_2 for males, SO_2 and NO_2 for females) showed slightly lower relative risk estimates with time series analyses, as compared with bi-directional case-crossover analyses.

5.2 Uni-directional, and bi-directional case-crossover and time series analytic approaches

The case-crossover analysis developed by Maclure (1991) is used to assess transient effects on the risk of acute events. The conventional case-crossover design uses uni-directional retrospective control sampling. However, recent simulation studies have demonstrated that results using uni-directional control sampling can be biased when time trends in exposures and outcomes are present, since it may lead to systematically higher or lower exposure levels for control periods than for case periods (Bateson and Schwartz, 1999; Navidi, 1998). Navidi (1998) proposed a bi-directional case-crossover design, in which control information is assessed both before and after the event in order to control for the time trends. Bateson and Schwartz (1999) have reported that the bi-directional case-crossover design can control for different patterns of time trends in exposures and outcomes. Another potential benefit of bi-directional control sampling relative to uni-directional control selection is to double the size of the sampling frame and consequently achieve a small but valuable improvement in precision (Mittleman et al., 1995)

Time-series analysis has been the most popular technique for studying associations between environmental exposure and daily counts of morbidity and mortality over time (Schwartz et al., 1993; Burnett and Krewski, 1994; Burnett et al., 1997; Burnett et al., 1998; Morgan and Wlodarczyk,1998; Burnett et al., 1999; Norris et al., 1999). Sophisticated modeling techniques have been introduced to better

control for the temporal trends including generalized additive models, in which a nonparametric smooth function of time is used to control for temporal trends in the data. However, some investigators have argued that time series analysis is somewhat model dependent, requiring decisions on the selection of the length of the smoothing window, and lacks a standard approach permitting comparisons of results from different studies (Moolgavkar et al., 1995; Bateson and Schwartz, 1999). Although some recent studies advocated minimizing autocorrelation in the residuals as a principle for the selection of the length of the window (Burnett and Krewski, 1994; Schwartz et al., 1996; Burnett et al., 1998), this technique also involves an element of subjectivity. Associations between air pollution and health outcomes using time-series analysis can be sensitive to the length of the window (Cakmak et al., 1997). Consequently there is a fundamental trade-off between bias and variance in the time series analysis. This trade-off is governed by the indefinite degree of smoothing.

Compared to time-series analysis, the case-crossover analysis has the advantage of controlling for confounding factors by design rather than by complex modeling. Bi-directional control sampling design can control for time trends through the selection of control periods in both directions from the case period (Navidi, 1998; Bateson and Schwartz, 1999).

The interval between the case and control periods in the case-crossover design needs to be selected carefully. The seasonal and long-term trends may not be controlled when the interval is too wide; short-term autocorrelation (probably within one week) would be a concern when the interval is too narrow. In a simulation study,

Bateson and Schwartz (1999; 2001) suggested that a separation time of seven days between case and control periods could better control for time trends in data, and that choosing a shorter separation time could reduce bias due to time-varying factors. In the present study, however, an interval of one week between case and control periods could be too close when multi-day exposure effects are examined. A simulation study conducted by Levy et al.(2001) showed there is little bias (0.4%) when an interval of 2 weeks was used. In this study, considering the potential effect of multi-day exposure averages up to 7 days, an interval of 14 days between case and control periods was selected to minimize autocorrelation between case and control exposures and to control for seasonal and long-term effects.

The time series analysis is a type of ecologic design, in which a time series of daily counts of health events in one area is linked to a time series of environmental exposure, as measured at fixed monitoring stations. Ecological studies are limited by the unavailability of individual information on exposure and other risk factors. In contrast, individual measurements of exposure can be incorporated into case-crossover analyses, although this advantage cannot be demonstrated in this study. The analytical methods used in the case-crossover design (primarily logistic regression) are similar to those used in a matched case-control study, and are simpler to apply than time series methods. The design in this study has another desirable characteristic of controlling for the day of week, which is related to both exposures and outcomes.

The findings of stronger associations between air pollution and asthma hospitalizations with control of weather conditions from most uni-directional case-

crossover analyses as compared with bi-directional case-crossover and time-series analyses are consistent to some extent with those from a simulation study conducted by Bateson and Schwartz (1999). They found that the effect estimates from bi-directional case-crossover and time-series analyses with control for time trends were close to the true values, while effect estimates from uni-directional case-crossover analysis were overestimated in the presence of time trends in the data. The time trends in the present data (Figures 4.1 to 4.3) may provide an explanation for this bias in the uni-directional case-crossover analysis.

The direction of the bias caused by time trends in exposure and outcome data is however not clear. In a simulation study, Navidi (1998) found underestimation of risk in the uni-directional case-crossover design, even in the absence of a clear overall temporal trend in the exposure data. There is a possibility that the direction of such a bias in the uni-directional case-crossover analysis is related to multiple factors, such as the degree and direction of temporal trends, as well as the interrelationships between time trends in exposures and health outcomes. These issues need to be further explored in simulation studies. In addition, the much wider confidence intervals on the relative risk estimate from the uni-directional case-crossover analysis as compared with that from the bi-directional case-crossover analysis found in this study indicates that the bi-directional case-crossover analysis also provides a better precision relative to the uni-directional case-crossover analysis, as discussed previously.

In this study, the results from the bi-directional case-crossover analysis were closer to those from the time series analysis as compared with those from the uni-directional case-crossover analysis. This is likely due to the ability of the bi-directional case-crossover design to control for time trends. The confidence intervals for the relative risk estimates from the bi-directional case-crossover analysis were wider than those from time series analysis, implying lower efficiency of the bi-directional case-crossover design, which is consistent with the findings from previous studies (Mittleman et al., 1995; Neas et al., 1999; Pope, 1999). The loss in efficiency will increase whenever there are some days on which no events are observed. On the other hand, the point estimates of relative risk for some air pollutants (CO and NO_2 in males, SO_2 and NO_2 in females) in relation to asthma hospitalization were found to be slightly higher in the bi-directional case-crossover analysis as compared with the time series analysis, especially for multi-day exposure averages. As discussed previously, the trade-off between bias and variance in the time series analysis is governed by the indefinite degree of smoothing. Because of the uncertainty in span selection for the smoothed function, there is a possibility that the time series analysis may filter out some patterns of effects over several days, which may result in potential bias if these effects exist (Schwartz et al., 1996).

However, it cannot be determined whether the case-crossover analysis is necessarily superior or inferior to the time-series approaches. A simulation study has shown similar effects of 1-day exposure to air pollution from bi-directional case-crossover and time series analyses (Bateson and Schwartz, 1999). However, that

study did not consider multi-day exposure, which may produce a more pronounced effect in the present study and in a previous study (Lipsett et al., 1997). Recently, some researchers found that potential biases might be introduced in the case-crossover analysis (Lee et al., 2000; Lumley and Levy, 2000). Lee et al. (2000) reported that bi-directional case-crossover analysis could be biased when using exposures with incomplete waves, which is occurring in a situation that some air pollutants may be monitored only part of the year. However, this bias is unlikely to exist in this study since data with complete calendar years between 1981 and 1993 were used. Lumley and Levy (2000) have a concern that short-term autocorrelations in the exposures may introduce bias analogous to over-matching in a case-control study. However, such bias will be largely reduced and the conditional logistic regression analysis will be approximately valid when the interval between case and control periods is weekly based.

A serious concern has recently been raised about some non-parametric smoothing functions used in generalized additive models. In a simulation study, Dominici et al (2002) found that when a relative risk estimated is small and at least two nonparametric smooth functions are included in the model (Loess smoothers), the default convergence parameters in 'gam' function in the S-Plus software package may be too lax to assure convergence of the backfitting algorithm and may produce a upward biased estimate with a smaller standard error. They suggested that using a function of Natural Cubic Splines would produce less significant estimates than Loess function and give better estimates and standard errors of the air pollution effect. We

re-ran the time series analysis using Natural Cubic Splines for 3-day average exposures for our data. The result, however, were similar in general as compared to those from the analysis using Loess approach (Table 5.1). For some pollutants (coarse particulate matter ($PM_{10-2.5}$) and NO_2), the point estimates from Natural Cubic Splines were even higher and were more likely to be significant (Table 5.1).

Table 5.1 Estimated relative risks (RR)[a] and 95% confidence intervals (CIs) for daily levels of air pollutants[b] in relation to asthma hospitalization in males, using time series analysis with functions of Loess or Natural Cubic Splines

Air pollutant	Loess		Natural Cubic Splines	
	RR	95% CI	RR	95% CI
$PM_{10-2.5}$	1.07	1.01, 1.13	1.14	1.07, 1.22
$PM_{2.5}$	0.98	0.94, 1.03	0.98	0.93, 1.03
PM_{10}	1.01	0.97, 1.06	1.03	0.98, 1.09
CO	1.03	0.99, 1.10	1.04	0.98, 1.10
SO_2	0.97	0.92, 1.02	0.99	0.93, 1.05
NO_2	1.03	0.98, 1.08	1.07	1.01, 1.13
O_3	0.98	0.91, 1.05	0.96	0.89, 1.04

Note:
[a]RR estimates were calculated for an interquartile range increment of air pollutants, which was calculated based on daily average levels, with adjustment of weather conditions.
[b]Three-day average exposures to air pollutants.

5.3 The associations between air pollution and asthma hospitalization in children

5.3.1 Associations between particulate matter and asthma hospitalization

In Toronto, daily average concentrations of particulate matter between 1980 and 1994 were generally well below the standard set by the U.S. Environmental Protection Agency (2001) and declined moderately over time. Heating, motor vehicles and road dust are the main sources of ambient particles (CEPA/FPAC Working Group on Air Quality Objectives and Guidelines, 1998). Particles in the air are made of different materials, which can contain various components including acid aerosols, metals, or poly aromatic hydro-carbons. Some are directly emitted into the air, while others are the result of atmospheric interactions. SO_2, NO_2, volatile organic compounds (VOCs), and ammonia are involved in the formation of secondary particles such as sulphates and nitrates, which are mostly very fine particles (CEPA/FPAC Working Group on Air Quality Objectives and Guidelines, 1998). Toronto Public Health (Macfarlane et al., 2000) published a report, which documented that particles were responsible for 26% of air pollution related respiratory hospitalizations in Toronto in 1995.

In the present study, the results from both bi-directional case-crossover and time series analyses have shown that only coarse particulate matter ($PM_{10-2.5}$) with 5- to 6-day average exposures were significantly associated with asthma hospitalization for both sexes. These results are consistent with previous findings using time series analysis (Burnett et al, 1999; Sheppard et al., 1999). One study in Toronto (Burnett et

al., 1999) found the coarse fraction ($PM_{10-2.5}$) to be a better predictor of asthma admissions than the fine ($PM_{2.5}$) and thoracic (PM_{10}) fractions in subjects of all ages. The estimated relative risks for $PM_{10-2.5}$, $PM_{2.5}$, and PM_{10} corresponding to an increase of $10\mu g/m^3$ with a 3-day averaging were 1.04,1.01, and 1.01, respectively. The effect of coarse particulate matter ($PM_{10-2.5}$) on asthma hospitalization found in the present study was larger than that reported in the above study (Burnett et al., 1999). Possible reasons for this include the following. (1) This analysis included children only, who are more susceptible to environmental exposures. (2) There was a stronger effect of the prolonged period of exposure. (3) Time series analysis might underestimate the relative risks slightly for multi-day average exposures.

Another time-series study relating air pollution and non-elderly asthma hospital admissions in Seattle from 1987 to 1994 (Sheppard et al., 1999) also found a significant association for coarse particulate matter lagged one day, with an estimated relative risk of 1.04 for an increase of 9.3 $\mu g/m^3$. The present study showed a stronger relationship between asthma hospitalization and coarse particulate matter, particularly with longer averaging exposures of around 5 to 6 days. The association for 1- to 2-day average coarse particulate matter was not clear. Although the results using different lag structures may not be strictly comparable, the longer lag time identified in the present study may be explained in part by the relatively low concentration of coarse particulate matter in Toronto compared with that in Seattle (Sheppard et al., 1999).

Although the relationship between coarse particulate matter ($PM_{10-2.5}$) and asthma hospitalization has not been well documented, there is evidence that coarse particulate matter has stronger positive effects on other health outcomes such as mortality from all causes, respiratory diseases, and cardiovascular disease, as well as on hospitalizations for cardiovascular diseases (Loomis et al., 2000; Ostro et al., 1999). Most coarse particles are of geologic origin such as oxides of iron, calcium, silicon and aluminum, and may include biological material such as bacteria, pollen and fungal spores (WHO, 2001). Silica was found to produce an inflammatory response in experimental animals at high exposure levels (Warheit et al., 1991). Toxicological studies have found both sulfate and coarse particles (dominated by road dust) caused suppression of alveolar macrophage function in rats (Kleinman et al., 1995). Coarse particles may also contain endotoxin, a potent inflammatory agent derived from bacteria (Ostro et al., 1999; Monn and Becker, 1999). Whether respiratory effects of fine particulate matter are stronger than coarse particulate matter has been questioned recently. Loomis (2000) suggested that such a conclusion only applies to lower respiratory symptoms. Burnett et al. (1999) found that coarse particles are a better predictor of asthma hospitalizations and fine particles are stronger predictor for respiratory infections.

Since PM_{10} from most urban areas consists primarily of fine particulate matter ($PM_{2.5}$) (Ostro et al., 1999), the magnitude of association for PM_{10} and $PM_{2.5}$ in such areas is expected to be similar (Schwartz et al., 1993; Burnett et al., 1999; Norris et al., 1999). This was the case with our data. Similar patterns were also observed for

PM_{10} and $PM_{2.5}$ (Figure 4.1). There were no significant effects of PM_{10} and $PM_{2.5}$ on asthma hospitalization in either bi-directional case-crossover or time series analyses.

Previous studies have shown no consistent results regarding the effects of PM_{10} and $PM_{2.5}$ on asthma hospitalization. A study conducted in Sydney, Australia from 1990 to 1994 (Morgan and Wlodarczyk, 1998) indicated no significant effects of fine particulate (approximately $PM_{2.0}$) on asthma hospitalization for both children and adults. Another study from Birmingham, England (Wordley et al.,1997), where the maximum level of PM_{10} (130.9 $\mu g/m^3$) exceeded the levels found in Toronto (Table 4.1) and Seattle (Schwartz et al., 1993) by over 30%, also showed no significant effect of PM_{10} on asthma hospitalization. However, the results from a number of other studies are in conflict with this finding. Significant effects of PM_{10} and $PM_{2.5}$ were found in Seattle, with estimated relative risks of 1.05 (19$\mu g/m^3$) and 1.04 (11.8 $\mu g/m^3$), respectively (Sheppard et al., 1999). Three time-series analyses conducted in the same area found significant effects of fine ($PM_{2.0}$) and thoracic particulate matter (PM_{10}) on asthma emergency department visits for those aged less than 18 years of age (Norris et al., 1999) and less than 65 years of age (Schwartz et al., 1993), and on decreased lung function in elementary school children (Koenig et al., 1993). Stronger effects of PM_{10} related to asthma hospitalizations or emergency room visits were found in Utah Valley (Pope, 1991), and Santa Clara County, California (Lipsett et al., 1997).

Although there are no obvious explanations for the discrepancies regarding the influences of thoracic and fine particulate matter on asthma hospitalization, possible reasons may include variability in population characteristics, natural systems, and the complex mixture of fine particles with a varying concentrations and compositions over time and space. It is likely that the stronger effects found in Santa Clara county (Lipsett et al., 1997) and Utah valley (Pope, 1991) are related to higher mean and maximum concentrations of PM_{10} as compared to those shown in the present study and those in studies from Seattle (Schwartz et al., 1993; Norris et al., 1999; Sheppard et al., 1999). Also, the degree of correlation between fine and thoracic particles and gas pollutants varies from one area to another. One study from Seattle (Norris et al., 1999) showed relatively high correlations between fine and thoracic particles and CO ($r = 0.74$) and NO_2 ($r = 0.66$ for thoracic particles, and $r = 0.59$ for fine particles), while the correlations in the present study were moderate for CO ($r = 0.45$ for $PM_{2.5}$ and $r = 0.38$ for PM_{10}) and even lower for NO_2.

5.3.2 Associations between gaseous pollutants and asthma hospitalization

The daily average concentrations of CO, SO_2 and NO_2 remained below the Canadian National Ambient Air Quality Objectives (NAAQOs) (Health Canada, 2001) during the study period from 1980 through 1994. In particular, the daily 1-hr maximum level of ozone exceeded the objective of 82 ppb on only 1.7% of the total of 5,479 days. Concentrations of gaseous pollutants except ozone, clearly declined over the study period (Figure 4.3). In Toronto, more than half of the gaseous pollution

came from transportation sources such as cars, buses, trains and aeroplanes in 1995 (Macfarlane et al., 2000). Using the bi-directional case-crossover design approach, the present study found CO, SO_2 and NO_2 to be positively associated with asthma hospitalization, although the strength of the relationship varied between males and females.

The present study found a significant association between CO and asthma hospitalization in males in both bi-directional and time series analyses when 2-day averaging exposure was used. CO was also found to be associated with asthma hospitalization in two previous studies conducted in Seattle (Sheppard et al.,1999) and Toronto (Burnett et al., 1999). CO was commonly thought to be an air pollutant closely associated with adverse effects on the heart. CO binds with haemoglobin in the blood, reducing the ability of the blood to carry oxygen. There has been no plausible mechanism by which CO exacerbates asthma (CEOHSAATS, 1996). Norris et al. (1999) postulated that a CO effect could be explained by acting as a surrogate for the effect of particulate matter. However, the CO effect remained significant in males even after adjustment for particulate matter in the present study. Further studies are needed to clarify the mechanism by which CO may exacerbate asthma in different populations.

Six- and seven-day average exposures to SO_2 showed a significant effect on asthma hospitalization in females but not in males in this study when bi-directional case-crossover and time series analyses were used. Some studies have found that

asthmatic children are more sensitive to SO_2 than healthy subjects, with SO_2 concentrations below 250 ppb resulting in temporary breathing impairment and reduced lung function (Tattersfield, 1996). Most previous epidemiological studies have not demonstrated a significant effect of SO_2 on asthma hospitalization or emergency room visits (Burnett et al., 1999; Norris et al., 1999; Stieb et al., 1996; Schouten et al., 1996; Schwartz et al., 1993). However, SO_2 exposures of 80ppb or less were related to asthma hospitalization in all age groups in Paris, France (Dab et al., 1996) and Birmingham, England during wintertime (Walter et al., 1994).

There are several possible explanations for these inconsistent results. First, since SO_2 can only reach the gas-exchange region of the lungs after sorption onto fine particles (WHO, 2001), SO_2 effects may not be observed at high concentrations. Second, most previous studies did not examine the effects of prolonged exposure to SO_2. And third, the effects of SO_2 appear to be age- and gender-related, which have not been well studied in previous investigations.

This study found a significant association between NO_2 and asthma hospitalization after controlling for weather conditions in both males and females. As discussed previously, the estimated NO_2 effect, especially for the multi-day exposure average resulted from time series analysis was relatively weak, as compared with that from bi-directional case-crossover analysis. In males, the NO_2 effect was not significant when time series analysis was used. In addition to the possibility that time series analysis may underestimate the exposure effect over several days, there are also

mechanistic arguments supporting an association between NO_2 and asthma. NO_2 has a greater airway deposition than O_3 due to its relatively higher water solubility (Evans et al., 1973). A bronchoconstrictive response in asthmatics is much more susceptible to NO_2 than SO_2 (WHO, 2001). The body readily absorbs NO_2 through the lung, throat and nose. People with asthma or other lung diseases, children, and the elderly are at increased risk (Macfarlane et al., 2000). Studies have shown that low levels of NO_2 (as low as 200 ppb) can exacerbate breathing difficulties through the narrowing of the airways (WHO, 2001). Recent research suggests that NO_2 could cause adverse effects at much lower levels (Dab et al., 1996; Burnett et al., 1999). NO_2 was more responsible for air pollution related early-deaths and hospital admission due to lung and heart problems than any other air pollutant (including particulate matter, CO, SO_2, and O_3) in Toronto during 1995 (Macfarlane et al., 2000). Significant associations between ambient NO_2 and asthma hospitalization were observed in all ages in a study from Paris (Dab et al., 1996), and in children in a study conducted in Sydney, Australia (Morgan and Wlodarczyk, 1998). However most studies failed to link NO_2 exposure to asthma hospitalization (Ponka, 1991; Stieb et al., 1996; Schouten et al., 1996; Norris et al, 1999). Increased susceptibility to NO_2 in children, different concentrations of NO_2, and the potential cumulative nature of the effects may partly explain the discrepancies between studies.

This study did not detect any association between ozone and asthma hospitalization in bi-directional and time series analyses in either sex. Ground-level ozone is formed when NO_2 and volatile organic compounds (VOCs) react together in

the presence of sunlight. Although ozone may produce toxic effects in the small airways, including irritative cough and decreased inspiratory capacity (CEOHSAATS, 1996), there has been considerable variation in the ozone effect on asthma hospitalization or emergency room visits, especially at low levels of exposure. Positive associations have been found in Toronto (Burnett et al., 1999), Chicago (Targonski et al., 1995) and New Jersey (Weisel et al., 1995), but no analyses of children were conducted in these studies. In Saint John, Canada, a significant relationship between ozone and asthma emergency room visits was found in adults (>15 years of age), but not in children (<=15 years of age) (Stieb et al., 1996). Similar results were also found in London, England (Ponce de Leon et al., 1996). White et al. (1994) observed an effect of ozone on pediatric asthma visits in Atlanta, Georgia when ozone concentrations exceeded 110 ppb, but no effect was found at levels less than 110 ppb. Other studies found no relationship between ozone and asthma hospitalization, including those conducted in Seattle (Norris et al., 1999), Amsterdam (Schouten et al., 1996), Barcelona (Castellsague et al., 1995), Vancouver (Bate et al., 1990) and Montreal (Delfino et al., 1994), where ozone concentrations were below 110 ppb most of the time. In this investigation, 99.8% of the total of 5479 days had the ozone concentrations below 110 ppb. Delfino et al. (1994) reported that the ozone effect on respiratory hospitalization disappeared after adjustment for temperature. Moderate correlations between weather conditions and ozone were found in this study. However, the present study found no significant ozone effect either with or without controlling for weather conditions. Some studies have suggested that the

association between ozone and asthma hospitalization or emergency room visits differs among age groups (Bate et al., 1990; Stieb et al., 1996; Ponce de Leon et al., 1996). The reasons for the lack of a significant effect of ozone on asthma hospitalization in children 6 to 12 years of age in the present study are unknown.

5.4 Possible confounding effects of weather conditions in the relationship between air pollution and asthma hospitalization

Weather conditions such as temperature and humidity may confound the relationship between air pollution and health outcomes. The dependence of mortality or morbidity on weather conditions is usually non-linear, with elevated rates on both very hot and very cold days (Schwartz et al., 1996). In this study, the U-shaped dependence of asthma hospitalization on weather conditions based on smoothed function implied that linear and quadratic terms of each weather condition are adequate to describe the meteorological data. Applying bi-directional case-crossover and time series analyses, weather conditions modified the effects of coarse particulate matter and ozone to a greater extent than other air pollutants. Relatively high correlations between coarse particulate matter, ozone, and weather conditions may be part of the explanation for these effects (Table 4.4).

5.5 Effect of each air pollutant on asthma hospitalization after adjustment for other pollutants

Some investigators have raised concerns about a possible surrogate role of air pollutants due to joint exposure to gases and particulate matter (Lipsett et al., 1997; Burnett et al., 1997). In this study, gaseous pollutants were all moderately correlated with particulate matter (Table 4.2). To assess possible joint effects of measured air pollutants, the study further examined possible two-way interaction terms for the measured pollutants and they were all not statistically significant at alpha level of 0.10. The study assessed the effects of particulate matter on asthma hospitalization after taking the effects of gaseous pollutants (CO, SO_2, NO_2 and O_3) into consideration. Particulate matter was also taken into consideration when the relationships between gaseous pollution and asthma hospitalization were examined. The effect of each pollutant remained after adjustment for concomitant exposure to particulate matter or gaseous pollutants.

5.6 Changing effects of multi-day air pollution exposures

Asthma hospitalization may be precipitated by exposure to air pollutants at either the same-day or the previous several days. Two lag structures have been commonly used in previous studies, with consideration of up to 4 days of exposure (Stieb et al., 1996; Sheppard et al., 1999; Morgan et al., 1998; Lipsett et al., 1997; Schwartz et al., 1993). One approach is to examine the effect of exposures on a single day, either is the day of admission or some specified day prior to admission. The lags

varied from 0 to 3 days in different studies (Stieb et al., 1996; Sheppard et al., 1999; Morgan et al., 1998). However, there have been no consistent results with respect to which lag is associated with the greatest effects. Some researchers have argued that such a lag structure may lead to unstable estimates due to the existence of short-term autocorrelation (within 5-7 days) in environmental variables and increase the possibility of a spurious association (Lipfert and Hammerstrom, 1992; Schwartz et al., 1996).

This study applied a cumulative lag structure, which assessed the effects of 1-day to multi-day average exposures ending on the day of the event. This structure has the advantage of reducing short-term autocorrelation in the exposure series and is helpful in identifying potential multi-day effects (Pope et al., 1991; Schwartz et al., 1996). In this study, the magnitude of the effects of some air pollutants appeared to increase with increasing days of exposure averaging and stabilize around 6 days for most models, including the effects of coarse particulate matter and NO_2 in both sexes, and the effect of SO_2 in females. A similar trend was found in a previous study conducted by Lipsett et al. (1997). One explanation for this observation may be the features of diurnal variations of air pollution levels. Particulate matter and gaseous pollutants such as CO, SO_2 and NO_2 generally exhibit 2-fold increases during the day, with peaks occurring in the late afternoon and at night. The manifestation of asthma symptoms may not be observed on the same day of exposure, and may be more related to exposures occurring on previous days. Another explanation is that multi-day exposure effects may reflect the distribution of determination of admission for

asthma. Although the lag time of air pollution effect on asthma hospitalization in children may partly contribute to the induction time between exposure and the occurrence of a health effect, the multi-day exposure effects might also related to other factors affecting the decision of asthma hospitalization, such as severity of a specific asthma attack, and ability of parental management of symptoms, and willingness to use of hospital services. The optimal exposure averaging period for each air pollutant remains to be established.

5.7 Possible sex differences in effects of gaseous pollutants

In this study, sex differences with respect to responses to different gaseous pollutants are of interest. Asthma hospitalization appeared to be more strongly related to CO in males than in females, while the SO_2 effect was more pronounced in females. Although there was a significant association between NO_2 and asthma hospitalization in both sexes, different response patterns were also observed. The lag time for manifestation of an NO_2 effect was shorter for boys (approximately 2 to 3 days) than for girls (approximately 6-7 days). These data suggest that boys exhibit prompt response to gaseous pollutants, including CO and NO_2, in terms of asthma hospitalization. Boys have smaller airways relative to their lung volume than girls, and may consequently be more prone to wheezing in response to specific stimuli (Bjornson and Mitchell, 2000). Asthma is also more common in boys than in girls (Millar and Hill, 1998; NHLBI, 1999). In addition to relative airway size, the different responses to gaseous pollutants between boys and girls may also be

influenced by differences in smooth muscle and vascular functions, and hormonal status (Redline and Gold, 1994). Chen et al. (unpublished data) have demonstrated age- and sex-related differences in the risk of hospital admission due to asthma, with the risk being higher in boys than in girls; the difference between sexes disappeared during puberty, and reversed after puberty. Host factors such as age and sex also affect asthma prevalence and incidence. The susceptibility to various gaseous pollutants is expected to vary differentially with age and gender, although there is no clear explanation for the greater difference in response to CO, NO_2 and SO_2 in this analysis.

5.8 Public health importance and implication

Although there has been a common understanding that severe air pollution episodes could result in adverse health impacts, the adverse effects of low levels of air pollutants, such as those currently experienced across Canada, are still open to debate. The present data suggest that particulate matter and gaseous pollutants are linked to increased asthma hospitalization in children 6 to 12 years of age at relatively low levels. Similar results from bi-directional case-crossover and time series analyses in this study indicate that the associations between air pollution and asthma hospitalization are relatively robust. Further reductions in ambient levels of air pollutants are expected to have population health benefits, such as improvements in vehicle technology, traffic management schemes, better public transportation, and vehicle inspection programs. Cleaner fuels represent one of the simplest, quickest,

and most cost-effective ways to improve air quality, as evidenced by the experience of clean-air programs in North America and Europe (WHO, 2001).

This study observed a positive effect of coarse particulate matter ($PM_{10-2.5}$) on asthma hospitalization in both sexes. These size fractionated particles have been thought to be generally of natural origin, and have been ignored by many previous studies. Epidemiological studies have focused on fine particulate matter ($PM_{2.5}$), since two large U.S. studies found a significant mortality effect of long-term exposure to fine particulate matter (Dockery et al., 1993; Pope et al., 1995). Fine particles are believed having greater acute respiratory effects as compared with coarse particles (Dreher et al., 1996; Bonner et al., 1998; Schwartz and Neas, 2000). The U.S. Environmental Protection Agency (EPA) (2001) established a new National Ambient Air Quality Standard (NAAQS) for $PM_{2.5}$ that is designed to protect the public from exposure to harmful particulate matter in 1997. Currently, the Canadian Council of Ministers of the Environment (CCME) is in the process of promulgating a Canada Wide Standard for $PM_{2.5}$ (CCME, 2000). The results in this study suggest that only focusing on fine particles risks neglects the potential adverse effects of the coarse fraction. Although the nature of health effects of particles we breathe is still unclear, the public has the burden of proving that coarse particulate matter is toxic. Further evaluation of the adverse health effects of different size fractionated particles in different areas and different age groups is needed, taking coarse particulate matter into account when setting air quality guidelines. This approach is consistent with the precautionary principle, which has been defined as "when an activity raises threats of

harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically" (Ashford et al., 1998). The precautionary principle has become an important aspect of environmental risk management throughout the world, and offers the public and decision-makers a forceful and common-sense approach to environmental and population health problems (Tickner et al., 2002).

5.9 Limitation and future work

It is possible that some admission counts are autocorrelated. A cohort study on childhood asthma admissions in Ontario from 1989-1992 found that about 29% of the children with asthma were readmitted to hospital during a 4-year study period (To et al., 1996). A number of individuals who are admitted to asthma are likely to be at increased risk of re-admission. It is not known about the extent to which this autocorrelation exists in our data since individuals could not be identified. Autocorrelation may exist in our data. However, the probability of a recurrent event over a few weeks is believed to be small for children 6-12 years of age. In addition, we used a nonparametric smoothing function in the time series analysis, and applied a bi-directional control scheme in the case-crossover analysis, to control time trend, which may diminish the impact of potential autocorrelation. A simulation study has showed that the bi-directional case-crossover analysis has the potential to control for different patterns of time trends in both exposures and outcomes (Bateson and

Schwartz, 1999). However, it would be of interest to evaluate whether air pollution has a different effect on the first and subsequent asthma hospitalizations.

The present results along with those from most other epidemiologic studies are based on the assumptions that centrally sited out-door monitors adequately represent personal exposure and that children's exposures to indoor air pollution is independent of and uncorrelated with, outdoor ambient air pollution. However, more studies are needed to examine the associations between personal exposures and ambient monitoring. Studies using personal monitors have demonstrated that people are exposed to higher levels of carbon monoxide than the levels measured at fixed monitoring stations because pollution concentrations vary greatly according to the microenvironment (Macfarlane et al., 2000). There may also be some random misclassification of exposure resulting in underestimation of the associations.

Lag structures and multi-day exposure effects have shown no consistent patterns, thereby limiting comparisons of results from different studies. Although bi-directional case-crossover and time series analyses produced generally similar results, small difference still exist, including higher relative risk estimates from bi-directional case-crossover analyses as compared with time series analyses, especially for multi-day average exposures found in some models. A recent simulation study by Fung et al. (submitted) showed that the estimated relative risks for asthma hospitalization in relation to multi-day exposure to $PM_{2.5}$ from time series analyses were closer to true values than those from bi-directional case-crossover analyses, based on data

generated using time series model. In addition, due to lack of information on other risk factors such as socioeconomic status, allergy and parental smoking, the potential modifying and confounding effects of these variables could not be assessed in this study.

CHAPTER 6 CONCLUSION

Both case-crossover and time series analyses were used to examine the effects of short-term exposure to outdoor air pollution on asthma hospitalization with consideration of weather conditions and co-pollutans in children 6-12 years of age in Toronto between 1981 and 1993. Most uni-directional case-crossover analytic models produced stronger associations between air pollution and asthma hospitalization, as compared to bi-directional case-crossover and time series analyses. The estimated associations after adjustment for weather conditions from bi-directional case-crossover analyses and time-series analyses were comparable, although small differences were observed. Slightly wider confidence intervals were resulted from bi-directional case-crossover analysis, and there is a possibility of underestimating the effects of multi-day average exposures using time series analysis.

This study found positive relationships between particulate matter as well as gaseous pollutants and asthma hospitalization in children, using both bi-directional case-crossover and time series analyses. Such significant effects were observed at relatively low air pollution levels. Although the effects were small, the overall influence on population health could be substantial. Further efforts to reduce current levels of air pollution are necessary to better protect population health.

More specifically, this study found a stronger positive effect of coarse particulate matter ($PM_{10-2.5}$) on asthma hospitalizations as compared to fine ($PM_{2.5}$) and thoracic particulate matter (PM_{10}) in both sexes, especially for multi-day

exposure averages of 5 to 6 days. Positive relationships between gaseous pollutants including CO, SO_2 and NO_2 and asthma hospitalization in children were also found. Asthma admissions were related to CO in males and to SO_2 in females. NO_2 was related to asthma admission in both sexes. O_3 was not associated with asthma hospitalization either with or without control of weather conditions and particulate matter. The lag time for induction of significant effects of certain specific gaseous pollutants appeared to be shorter in boys than in girls. Furthermore, the effects of particulate matter (gaseous pollutants) persisted after adjustment for the effects of gaseous pollutants (particulate matter).

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