Environmental Pollution 183 (2013) 30–39

Contents lists available at SciVerse ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

A cohort study of intra-urban variations in volatile organic compounds and mortality, Toronto, Canada

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ARTICLE INFO

Article history:
Received 15 August 2012
Received in revised form
19 December 2012
Accepted 21 December 2012

Keywords:
Volatile organic compounds
Air pollution
Nitrogen dioxide
Cohort study
Mortality
GIS
Cancer
Cardiovascular disease
Respiratory disease

ABSTRACT

This study investigated associations between long-term exposure to ambient volatile organic compounds (VOCs) and mortality. 58,760 Toronto residents (≥35 years of age) were selected from tax filings and followed from 1982 to 2004. Death information was extracted using record linkage to national mortality data. Land-use regression surfaces for benzene, n-hexane, and total hydrocarbons were generated from sampling campaigns in 2002 and 2004 and assigned to residential addresses in 1982. Cox regression was used to estimate relationships between each VOC and non-accidental, cardiovascular, and cancer mortality. Positive associations were observed for each VOC. In multi-pollutant models the benzene and total hydrocarbon signals were strongest for cancer. The hazard ratio for cancer that corresponded to an increase in the interquartile range of benzene (0.13 μg/m^3) was 1.06 (95% CI = 1.02–1.11). Our findings suggest ambient concentrations of VOCs were associated with cancer mortality, and that these exposures did not confound our previously reported associations between NO_2 and cardiovascular mortality.

1. Introduction

Ambient air pollution is associated with numerous acute and chronic health effects. While day-to-day increases in levels of pollution are associated with an increased number of deaths (Brook et al., 2007), physician visits (Burra et al., 2009), and hospital visits (Villeneuve et al., 2006; Wellenius et al., 2005), particularly for cardio-respiratory disorders, the health effects from long-term exposure to air pollution are thought to be far greater (Pope, 2000; Pope et al., 2010). In most cohort studies criteria air pollutants such as nitrogen dioxide (NO_2), ozone (O_3) and fine particulate matter (particles with a median aerodynamic diameter of 2.5 microns or less ($PM_{2.5}$)) have often been investigated. This emphasis has been motivated by both the availability of historical monitoring data for these pollutants, typically from fixed-site monitors, and with the knowledge that these pollutants, particularly O_3 and $PM_{2.5}$, can elicit oxidative stress in the lung, which may lead to systemic cardiopulmonary inflammation (Brook et al., 2007). Fine particulates may also carry toxic materials into the lungs where they can be absorbed into the bloodstream and carried to other parts of the body. Fine particulate matter has been shown to constrict airways, increase heart rate, affect heart rate variability, and promote atherosclerosis (Nogueira, 2009). Nitrogen dioxide is also an oxidative stressor in the lung; however, at the lower levels observed in ambient conditions in most urban areas, it appears unlikely that NO_2 could be solely responsible for the observed health effects. Instead, it has been suggested that this gaseous pollutant acts as an indicator of some other exposure such as a specific type of combustion particle, or volatile organic compound (Brook et al., 2007).

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0269-7491/$ – see front matter
http://dx.doi.org/10.1016/j.envpol.2012.12.022

In a review of epidemiological studies of air pollution and mortality (Chen et al., 2008), a 10 μg/m^3 increase in long-term exposure to $PM_{2.5}$ was associated with a 6% increased risk of non-accidental mortality, independent of age, gender, and geographic region. The corresponding risks for mortality from lung cancer and cardiovascular disease were 15%–21%, and 12%–14%, respectively. Recently, within the same cohort that forms the basis of this paper, a 5 ppb increase in concentrations of intra-urban NO_2 was associated with a 12% (95% confidence interval (CI): 7%–17%) increase in mortality from cardiovascular disease and a 15% increase (95%CI: 8%–21%) in mortality from ischemic heart disease (Chen et al., 2013).

Advances in our ability to characterize intra-urban variations in air quality through methods such as land-use regression have been an important development in environmental epidemiology (Hoek et al., 2008; Jerrett et al., 2005a). The relatively recent finding that within-city variations in pollution may be more important predictors than between-city contrasts (Jerrett et al., 2005b) has promoted more rigorous approaches to exposure assessment, and a heightened focus on evaluating air pollution effects at a more localized scale. For example, postmenopausal breast cancer was recently found to be positively associated with traffic-related NO_2 (Crouse et al., 2010).

Like NO_2, volatile organic compounds (VOCs) exhibit high spatial variability although there have been far fewer attempts to model how their concentrations vary within urban areas. Of the 25 published studies that used land-use regression modeling (Hoek et al., 2008) only four modeled VOCs. This is a critical research gap given the possible effects that VOCs may have on human health. These compounds have been shown to induce inflammatory reactions in airways (Wieslander et al., 1997), been associated with respiratory symptoms (Delfino et al., 2003), and reduce pulmonary function in adults (Elliott et al., 2006). Moreover, several VOCs, such as benzene, are classified as either suspected or recognized carcinogens (IARC, 1982, 2008).

In several occupational studies of highly exposed workers associations have been reported between long-term exposure to several VOCs, including benzene and styrene, and cancer and mortality (Lundberg and Milatou-Smith, 1998; Schnatter, 2000). In these studies, excesses of some cancers, particularly hematopoietic cancers and non-Hodgkin's lymphoma have been found, but the estimates of associations were likely attenuated because of the use of the general population as a referent ("healthy worker effect"). Although concentrations of VOCs are generally higher in the indoor environment than they are outdoors, some VOCs, such as benzene, have important outdoor sources such as incomplete combustion of fossil fuels and biomass burning. In a study that collected outdoor, indoor and personal exposure measures of VOC in Windsor, Canada, indoor concentrations of benzene were approximately twice as high as outdoor concentrations (Stocco et al., 2008). This study also showed that personal exposure to traffic-related VOCs (1,3-butadiene, acetaldehyde, benzene, *m*,p-xylene and toluene) could be predicted by using outdoor concentrations (Stocco et al., 2008).

There have been few epidemiological studies that have evaluated associations between either short or long-term exposures to background levels of VOCs and adverse health outcomes. Apart from a cohort study of 70,000 US male veterans (Lipfert et al., 2009), we know of no other epidemiological study in which associations were evaluated between mortality and long-term exposure in non-occupational settings to concentrations of VOCs. Lipfert et al. (2009) relied on between-county exposure gradients for selected pollutants to represent source profiles. Stronger associations were found for specific traffic related pollutants such as benzene; however, the county scale of analyses may have been subject to substantial exposure measurement error as VOCs such as benzene have important within-city variations (Su et al., 2010).

The objective of the present paper was to determine, within the context of a cohort study in Ontario, whether there was an association between long-term exposure to three different VOCs (benzene, total hydrocarbons, n-hexane) and cancer, cardiovascular, respiratory, and non-accidental mortality. Secondarily, we evaluated the extent to which previously reported associations between concentrations of NO_2 and mortality (Chen et al., 2013) may have changed after adjusting for these VOCs.

2. Methods

2.1. Study population

This study population consisted of residents of Toronto, Canada, who were part of the larger Ontario Tax Cohort study. Detailed descriptions of this cohort have been provided elsewhere (Chen et al., 2013; Villeneuve et al., 2012). Briefly, the larger cohort was assembled by randomly selecting from income tax filings Canadians who resided in one of 10 urban areas in the province of Ontario. These individuals were drawn from Statistics Canada's T1 Family File database that includes all Canadians who completed an annual income tax return. When compared to census data, the T1 Family File database captures more than 95% of the Canadian adult population. To be eligible for inclusion, individuals had to be 35 years of age and older at study entry, and were resident in one of the pre-determined 10 urban areas in Ontario in the early 1980s. Our analyses are restricted to 58,760 individuals who lived in the city of Toronto in 1982 whose residential addresses could be linked to existing VOC exposure surfaces (Su et al., 2010).

Probabilistic record linkage to the Canadian Mortality Database was used to identify deaths up to the end of 2004 (Howe and Lindsay, 1981). Registration of deaths is the responsibility of the provinces and territories, and this national database contains information on all deaths among Canadian residents that occur in Canada as well as many states in the US (Statistics Canada, 2011). Underlying causes of death between 1982 and 1999 were coded to the 9th revision of the ICD, while those from 2000 onwards were coded to the 10th revision. Previous studies have shown that less than 5% of deaths may be missed through record linkage to the Canadian Mortality Database, and that the information extracted from the Canadian Mortality Database allows for the underlying cause of death to be identified with high sensitivity and specificity (Goldberg et al., 1993; Schnatter et al., 1990).

We obtained ethical approval from the Research Ethics Boards of both Health Canada and the University of Toronto. To comply with the requirements regarding the release of Statistic's Canada data, all presented counts have been rounded off to the nearest ten.

2.2. Land-use regression models for nitrogen dioxide and volatile organic compounds

A description of the methods used to create the surfaces of VOCs in Toronto has been published (Su et al., 2010). Briefly, VOCs were measured between July 25 and August 9, 2006 at 50 locations that were chosen from among the 100 locations previously used for NO_2 using a location-allocation approach (Kanaroglou et al., 2005). Of the 50 VOC sites, 8 were within 200 m of expressway, 30 within 200 m of major road and 35 within 100 m of a residential area. TraceAir organic vapor monitors were used to monitor ambient VOCs (K&M Environmental, Virginia Beach, VA, USA). Two-sided samplers were deployed in pairs (yielding four observations per site) at a height of 2.5 m. The deployment of samplers took less than 72 h, and the samplers were removed 14 days after they were installed.

The land-use regression model was developed using the VOC measurements against chosen spatial covariates. As the distribution of concentrations of VOCs was skewed, logarithmic transformations were used to stabilize the variance of the sample (Bland, 2000). However, the spatial surface used in this study was based on the antilogarithm of these estimates. The same spatial covariates used to derive the NO_2 surface (described above) were used to create the spatial surfaces for the VOCs. The land-use regression models were found to explain approximately 66–68% of the variance in the spatial distribution of the VOCs.

For NO_2, the land-use regression model was derived from two dense measurement campaigns that were completed in 2002 (Jerrett et al., 2007) and 2004 (Jerrett et al., 2009). The samplers were set up at 100 locations and measures were obtained over two campaigns (September 9–24, 2002 and May 11–26, 2004). Fifty monitors were deployed at one set of locations for both sampling periods, while the locations of the other 50 samplers were changed in the second round of monitoring. Ogawa samplers were used to measure NO_2, and these data were analyzed according to manufacturer's specifications. Analysis at co-located government monitoring sites revealed that the two 2-week averages in the fall 2002 and spring 2004 from the

saturation monitoring campaign provided an accurate reflection of both annual and 5-year mean concentrations. (Jerrett et al., 2007, 2009) Further analyses of the 50 sites that were co-located between the two rounds of monitoring indicated that the spatial pattern appeared consistent over the two-year period, with correlations in the 0.8 range for measured concentrations around the sites. Manual forward-selection regression procedures were used to select the best predictors of intra-urban concentrations of NO_2. Six types of spatial predictors were used including highway and major road lengths and slope gradients, traffic density, land use (e.g., commercial, industrial, residential, and open), physical characteristics (e.g., elevation, latitude, longitude and distance to coast), population density and remote sensing derived indices of greenness and surface brightness. The R^2 of the land-use regression model for NO_2 in Toronto was about 70%. We averaged the two exposure surfaces derived from the different sampling campaigns because the observed concentrations of NO_2 were highly correlated (Pearson correlation coefficient (r) = 0.8).

Herein, we estimate associations between cause-specific mortality and benzene, n-hexane and total hydrocarbons. Total hydrocarbons include both reactive and non-reactive hydrocarbons. The major non-reactive hydrocarbon in the atmosphere is methane. The reactive hydrocarbons consist of many VOCs, some of which react with oxides of nitrogen in the atmosphere to form ozone. They generally occur at much lower concentrations than methane. In developing land-use regression models of VOCs, Su et al. (2010) reported on additional analyses that showed that n-hexane and total hydrocarbons were largely predicted by other land-use characteristics (e.g., industrial land use). In contrast, the land-use regression surfaces for both benzene and NO_2 were influenced to a much greater degree by expressway and major roads at smaller buffer radii (≤350 m). Concentrations of these two pollutants from expressway and major roadways were very high, but decreased with increasing distance from the roads.

2.3. Statistical analysis

2.3.1. Assignment of exposure

Individual-level estimates of concentrations were obtained by linking the centroids of the areas defined by each cohort member's residential six-character postal codes at baseline (in 1982) to the land-use regression surfaces. These postal codes were extracted from the subject' income tax filings. In Canadian urban areas, the six-character postal codes represent the face of a city block or a large apartment complex.

We used the Cox proportional hazards model to estimate adjusted rate ratios (RR) and their 95% confidence intervals (CI) for each of the pollutants. We modeled NO_2, and the three VOCs as continuous measures. We assessed non-linearity using natural cubic spline functions with 2 df. To allow us to better contrast the associations observed with each pollutant, we expressed the rate ratio for each exposure in relation to an increase in the interquartile range. The baseline hazard was stratified by single-year of age, and survival time was defined from the date of entry until the earliest of (i) date of death or (ii) December 31, 2004. Those for whom a match on the mortality linkage was not found were assumed to be alive at the end of follow-up.

We adjusted the rate ratios for individual-level measures of household income and marital status that were extracted from their 1982 income tax return. In addition, contextual measures of unemployment, average household income, and immigration were obtained from the 1981 Canadian Census. These contextual variables were based on census-enumeration areas that are small, relatively homogeneous geographic units that are composed of one or more blocks (400–700 persons).

As long-term exposure to NO_2 has frequently been reported to be associated with several health outcomes, we also fitted a series of two-pollutant models to evaluate the extent to which concentrations of VOCs altered or were effect modifiers of the NO_2 associations. We also explored how associations between the VOCs and mortality changed when all VOCs and NO_2 were simultaneously included in models. Lastly, we repeated analysis to derive risk estimates for the first 5 and 10 years of follow-up so as to evaluate the possible impact that residential mobility had on the strength of the associations.

Our cohort lacked individual-level information about smoking behaviors, and obesity. To evaluate the potential for uncontrolled confounding from these two risk factors to bias our air pollution risk estimate, we developed an indirect method of adjustment. This method was applied to take into account the spatial association between smoking, body mass index and $PM_{2.5}$. A description of this method is provided in (Villeneuve et al., 2011) and an extension of this method that we used here is described in Appendix I, which is based on the theory of partitioned regression (Ruud, 2000). Ancillary individual-level data on smoking and obesity and their relationship to concentrations of VOCs and NO_2 were obtained from Toronto participants, 35 years of age and older, of the 2001 Canadian Community Health Survey (Statistics Canada, 2005). This information along with estimates of the hazard rations between smoking status (Malarcher et al., 2000; Pope et al., 2004) and obesity (Whitlock et al., 2009) for each cause of death, were used to estimate the impact of uncontrolled confounding from these two risk factors on our measures of associations between each of the VOCs and NO_2 and mortality outcomes.

3. Results

The study population, by design, included approximately the same number of men and women (Table 1). Two-thirds were married at the time of enrolment, and the mean age at entry was 51.7 years (range 35–85). Our record linkage identified approximately 18,020 deaths during the follow-up interval and as expected, nearly a third of these were from cardiovascular disease (n = 6060) and from cancer (5970) (Table 2). The partial correlation coefficients of the terms included in the LURs models for NO_2 benzene, total hydrocarbons, and n-hexane are provided in Table 3. The largest coefficient denotes the most dominant term in the model. For NO_2 it was expressways; for benzene it was industrial area; for n-hexane it was the number of chimneys; and

Table 1
Characteristics of Toronto residents in the Ontario Tax Cohort, 1982–2004.

	Number[a]	Percentage
Men	29,600	50.4
Women	29,150	49.6
Age-group		
35–<45	18,730	31.9
45–<60	24,500	41.7
60–<75	12,920	22.0
75–<85	2620	4.4
Marital status		
Married	39,190	66.7%
Widowed	4650	7.9%
Divorced	3050	5.2%
Separated	2780	4.7%
Single	6060	10.3%
Unknown	3020	5.1%
Family income		
<10,000	6220	10.6
10,000–<30,000	20,400	34.7
30,000–<50,000	17,860	30.7
50,000–<70,000	7700	13.1
70,000–90,000	2900	4.8
≥90,000	3700	6.4
Neighborhood-level risk factors from 1981 Canadian Census[b]		
Percentage of immigrants (S.D.)[c]	39.8 (13.3)	
Percentage with education less than high school (S.D.)	44.4% (15.8%)	
Mean Unemployment (S.D.)	4.0% (3.0)	
Mean Average household income in CAN $ (S.D.)	14,464 (5303)	

S.D. = Standard deviation.
[a] Rounded to the nearest 10 individuals for confidentiality reasons.
[b] The cohort was restricted to those 35 years of age and older who completed an income tax return in 1982, in contrast, the census included all households including a portion of individuals with low income who did not file taxes; these reasons contribute to the observed differences in household income.
[c] Immigrant population (or foreign born population) is defined as those who are, or who have been landed immigrants in Canada.

Table 2
Number of deaths among Toronto residents of the Ontario Tax Cohort, 1982–2004.

Underlying cause of death	ICD-9[a]	ICD-10[b]	Number of deaths
Non-accidental	<800	<V01	18,020
Cardiovascular	400–440	I10-I70	6060
Cancer	140–239	C01-C097	5970
Lung cancer	162	C33-C34	1470
Respiratory disease	460–519	J00-J99	1410

[a] ICD-9: International Classification of Diseases 9th Revision was used to determine underlying cause of death between 1982 and 1999.
[b] ICD-10: International Classification of Diseases 10th Revision was used to determine underlying cause of death between 2000 and 2004.

Table 3
Partial correlation coefficients for the predictors included in the NO_2, benzene, total hydrocarbon and n-hexane land use regression surfaces, Toronto.

Model predictor		NO_2	Benzene	n-Hexane	Total hydrocarbons
Road network	Expressway (m)	0.674 (350) [a]	0.292 (100)		
	Major road (m)	0.364 (50)	0.479 (50)		
	Local road (m)			−0.412 (50)	
	Rail (m)	0.318 (1100)			
Land use	Commercial (ha)	0.579 (3000)	0.356 (2900)		
	Industrial (ha)		0.515 (1200)	0.402 (100)	0.603 (100)
	Number of chimneys			0.648 (2050)	0.601 (1850)
	Open (ha)			−0.493 (50)	−0.338 (50)
					−0.327 (1200)
Population density (number per ha)				0.341 (1150)	
Soil brightness index		0.497 (3000)		0.563 (1650)	0.328 (1650)
X coordinate		−0.591			

[a] ( )'s represent buffer distances in meters that were used to create the LURs.

for THC it was industrial and chimney counts. Table 4 shows the distributions of concentrations of the three VOCs and NO_2. The greatest range in concentrations was observed for total hydrocarbons. As anticipated, NO_2 and n-hexane and benzene had correlation coefficients above 0.5 and the correlation between NO_2 and hydrocarbons was about 0.3 (Table 5), and the spatial variability of the benzene, n-hexane, and total hydrocarbons in Toronto is presented in Fig. 1. The corresponding surfaces for NO_2 are provided in Fig. 2.

Positive associations between all three VOCs were found for each cause of death examined (Table 6). The rate ratios for non-accidental mortality in relation to an interquartile range increase in benzene, n-hexane and total hydrocarbons were 1.05 (95% CI = 1.03, 1.08), 1.04 (95% CI = 1.02, 1.06), and 1.03 (95% CI = 1.01, 1.05). The addition of ambient concentrations of land use regression estimates of NO_2 decreased these rate ratios to 1.04, 1.03, and 1.02, respectively. We provided exposure–response plots for benzene in Fig. 3. For cancer and non-accidental mortality these plots were consistent with a linear relationship with benzene. Indirect adjustment for the joint effects of smoking and body mass index attenuated these associations slightly to 1.03, 1.02, and 1.01, respectively.

Table 7 shows the rate ratios in relation to the period of follow-up (5 years, 10 years, entire period). On average, stronger associations were observed when the follow-up interval was limited to the first 5 years of follow-up. In this follow-up interval, the strongest association was observed between benzene and lung cancer as the rate ratio in relation to an interquartile range increase in benzene was 1.26 (95% CI = 0.98, 1.61) for the first 5 years, which dropped to 1.09 (95% CI = 0.94, 1.28) when follow-up was extended to 10 years. Despite the large differences in these rate ratios, the confidence intervals were quite broad and overlapping, and this was due mostly to the small number of deaths in the first five years of follow-up.

Fig. 4 shows the impact that each of the VOCs had on the associations between NO_2 and each cause of death. Ambient concentrations of NO_2 were associated with non-accidental mortality, respiratory mortality, and cardiovascular mortality but not with all cancers combined or with lung cancer. The addition of any of the three VOCs, on their own, to the models that already included NO_2 did not fundamentally alter the elevated rate ratios for NO_2 that were observed for non-accidental and cardiovascular mortality. In contrast, in multi-pollutant models that contained all four pollutants the effects of NO_2 were diminished (Table S1), which is a reflection of the high degree of correlation amongst the four pollutants.

To assess the possibility that uncontrolled confounding from cigarette smoking or obesity may have confounded our associations, we compared mean concentrations of the VOCs across these risk factors among 937 participants of the 2001 Canadian Community Health Survey who lived in Toronto and who were over 35 years of age. We found little difference in the mean concentrations of the VOCs across smoking status categories. Specifically, the mean benzene levels among current, former, and never smokers were 0.66, 0.65, and 0.64 ppb, respectively. Similar mean concentrations were also noted across the categories of smoking status for n-hexane, and total hydrocarbons, and the means were similar across body mass index categories [data not shown].

4. Discussion

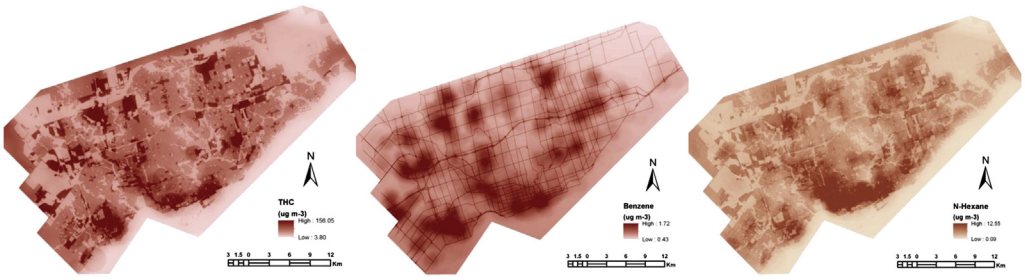
In this cohort of adults living in Toronto, an increase in the interquartile range of ambient concentrations of VOCs was associated with approximately 3%–8% increased mortality rate. There was no evidence of effect modification between NO_2 and any VOC for any cause of death, and our previously reported association between NO_2 and cardiovascular disease (Chen et al., 2013) was not confounded by any of the VOCs. While benzene and total

Table 4
Descriptive statistics for air pollutants based on land-use regression surfaces among Toronto residents of the Ontario Tax Cohort.

Pollutants	Units	Mean (Standard deviation)	IQR	Median	Range
NO_2	ppb	28.93 (6.34)	5.92	26.54	13.59–60.60
Benzene	$\mu g/m^3$	0.64 (0.10)	0.13	0.62	0.47–1.17
n-Hexane	$\mu g/m^3$	2.30 (1.27)	1.20	1.91	0.24–11.22
Total hydrocarbons	$\mu g/m^3$	28.83 (8.18)	9.02	26.54	5.83–98.90

Table 5
Pearson correlation coefficients between concentrations of select volatile organic compounds and nitrogen dioxide, among Toronto residents in the Ontario Tax Cohort.

	NO_2	Benzene	Hydrocarbons
Benzene	0.57		
Hydrocarbons	0.29	0.58	
n-Hexane	0.50	0.58	0.55



Total Hydrocarbons **Benzene** **n-Hexane**

Fig. 1. Land-use regression surfaces for total hydrocarbon, benzene, and n-hexane concentrations, Toronto, Canada.

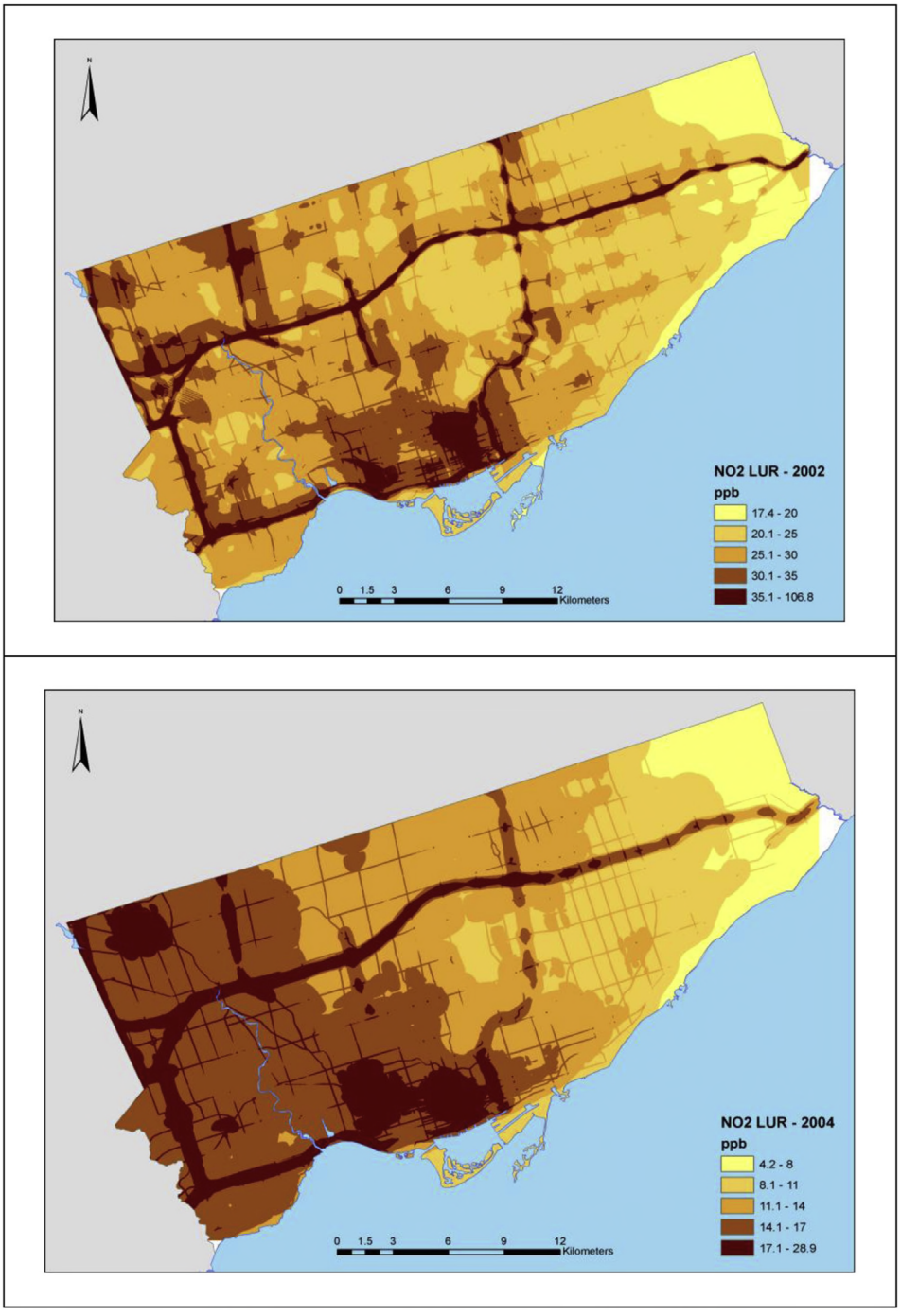


Fig. 2. Land-use regression surfaces for NO_2, Toronto, 2002 and 2004

Table 6
Adjusted rate ratios (RR) and associated 95% confidence intervals (CI) of cause-specific mortality in relation to an increase in the interquartile range of selected volatile organic compounds, with and without adjustment for NO_2, Toronto residents of the Ontario Tax Cohort, 1982–2004.

Cause of death	IQR (μg/m^3)	Adjusted RR		Adjusted RR + NO_2		Adjusted RR + NO_2 + indirect adjustment	
		RR (1)	95% C.I.	RR (2)	95% C.I.	RR (3)	95% C.I.
Benzene							
Non-accidental causes	0.13	1.05	1.03–1.08	1.04	1.01–1.07	1.03	1.01–1.06
Cardiovascular disease		1.03	0.99–1.07	1.02	0.97–1.06	1.03	0.98–1.07
Non-malignant respiratory disease		1.07	0.98–1.16	1.03	0.94–1.13	1.04	1.00–1.09
Cancer		1.05	1.01–1.10	1.06	1.02–1.11	1.04	0.99–1.09
Lung cancer		1.06	0.97–1.14	1.07	0.98–1.18	1.05	0.96–1.14
n-Hexane							
Non-accidental causes	1.20	1.04	1.02–1.06	1.03	1.01–1.05	1.02	1.00–1.04
Cardiovascular disease		1.03	1.00–1.06	1.02	0.98–1.05	1.00	0.97–1.03
Non-malignant respiratory disease		1.07	1.01–1.14	1.05	0.98–1.12	1.05	0.99–1.11
Cancer		1.03	1.00–1.05	1.03	1.00–1.07	1.01	0.97–1.05
Lung cancer		1.03	0.97–1.08	1.05	0.98–1.11	1.03	0.97–1.10
Total hydrocarbons							
Non-accidental causes	9.02	1.03	1.01–1.05	1.02	1.00–1.04	1.01	0.99–1.03
Cardiovascular disease		1.00	0.97–1.04	1.00	0.97–1.03	0.98	0.94–1.01
Non-malignant respiratory disease		1.04	0.97–1.10	1.02	0.96–1.09	1.01	0.95–1.07
Cancer		1.05	1.02–1.09	1.06	1.02–1.09	1.03	1.00–1.06
Lung cancer		1.05	0.99–1.11	1.05	0.99–1.12	1.04	0.98–1.10

IQR, Interquartile range; RR, rate ratio.
RR(1): adjusted for single-year age, sex, family income, marital status, and census area measures of income, immigration, and unemployment; RR(2): adjusted for all the terms in (1) and land-use regression estimates of NO_2; RR(3) adjusted for all the terms in (1), land-use regression estimates of NO_2, and indirect adjustment for smoking and body mass index.

hydrocarbons were associated with an increased risk of cancer, NO_2 was not. Given that the highest partial correlation coefficients for the NO_2 surface were observed with roadways measures while for benzene and total hydrocarbons they were from industrial and chimney sources, this suggests that non-traffic sources of VOCs contribute to the positive associations that were observed with cancer. By the same reasoning, this also suggests that increases in traffic-related pollution contributed to increased cardiovascular mortality. Benzene is a recognized carcinogen that has been consistently associated with an increased incidence of leukemia in many occupational studies (Galbraith et al., 2010), and recently, reports have suggested links between ambient benzene concentrations and childhood leukemia (Steffen et al., 2004; Vinceti et al., 2012). Unfortunately, we did not have a sufficient number of cases

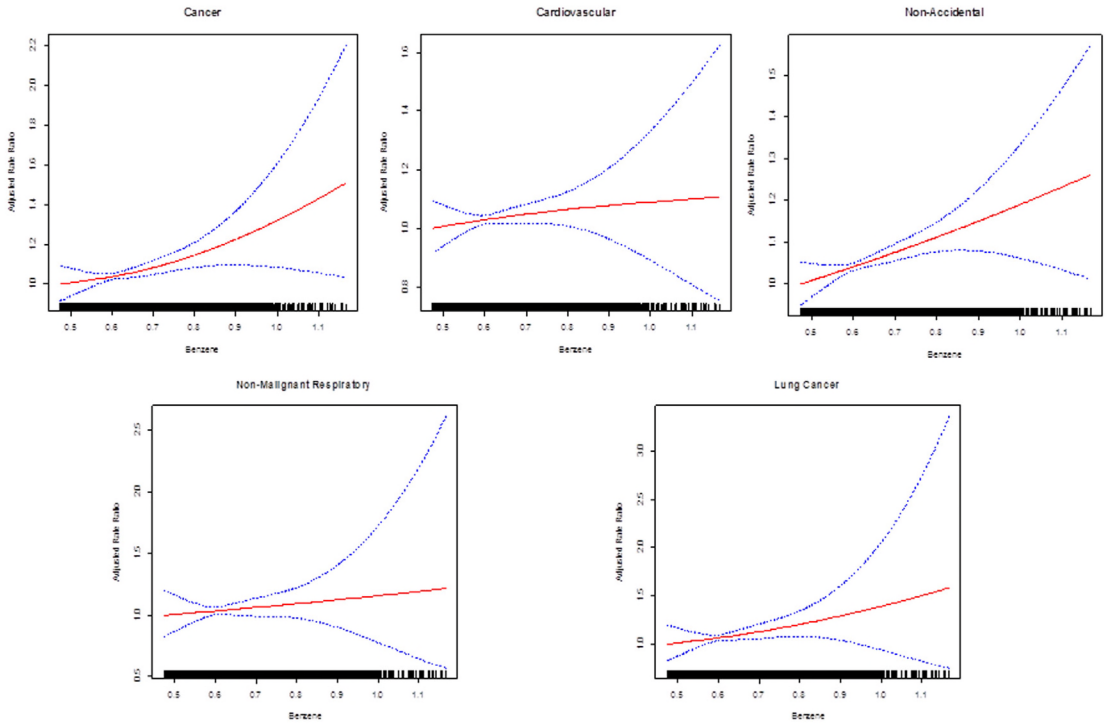


Fig. 3. Exposure response functions between benzene and different causes of deaths.

Table 7
Adjusted rate ratios[a] (RR) and associated 95% confidence intervals (CI) of cause-specific mortality in relation to an increase in the interquartile range of selected volatile organic compounds by follow-up period, Toronto residents of the Ontario Tax Cohort, 1982–2004.

Cause of death	IQR (μg/m^3)	First 5 years of follow-up			First 10 years of follow-up			Follow from 1982 to 2004		
		Deaths	RR	95% C.I.	Deaths	RR	95% C.I.	Deaths	RR	95% C.I.
Benzene										
Non-accidental causes	0.13	2099	1.09	1.01–1.18	5534	1.05	1.00–1.10	18,020	1.04	1.01–1.07
Cardiovascular disease		814	1.11	0.99–1.26	2045	1.04	0.97–1.13	6020	1.02	0.97–1.06
Non-malignant respiratory disease		768	1.10	0.82–1.48	2007	1.08	0.90–1.31	1410	1.03	0.94–1.13
Cancer		176	1.07	0.95–1.22	493	1.06	0.98–1.15	5970	1.06	1.02–1.11
Lung cancer		142	1.26	0.98–1.61	363	1.09	0.94–1.28	1410	1.07	0.98–1.18
n-Hexane										
Non-accidental causes	1.20	2099	1.06	1.00–1.12	2099	1.04	1.01–1.07	18,020	1.03	1.01–1.05
Cardiovascular disease		814	0.97	0.88–1.07	814	1.00	0.95–1.06	6020	1.02	0.98–1.05
Non-malignant respiratory disease		768	1.06	0.86–1.31	768	1.07	0.94–1.22	1410	1.05	0.98–1.12
Cancer		176	1.08	0.98–1.16	176	1.05	0.99–1.06	5970	1.03	1.00–1.07
Lung cancer		142	1.09	0.92–1.26	142	1.06	0.95–1.18	1410	1.05	0.98–1.11
Total hydrocarbons										
Non-accidental causes	9.02	2099	1.06	1.00–1.12	2099	1.02	0.99–1.06	18,020	1.02	1.00–1.04
Cardiovascular disease		814	1.02	0.94–1.12	814	1.00	0.95–1.06	6020	1.00	0.97–1.03
Non-malignant respiratory disease		768	0.96	0.77–1.20	768	1.06	0.93–1.21	1410	1.02	0.96–1.09
Cancer		176	1.06	0.98–1.16	176	1.04	0.99–1.10	5970	1.06	1.02–1.09
Lung cancer		142	1.01	0.84–1.21	142	1.01	0.91–1.13	1410	1.05	0.99–1.05

[a] All presented rate ratios were adjusted for single-year age, sex, family income, marital status, and census area measures of income, immigration, unemployment, and land-use regression estimate of NO_2.

to analyze leukemia. Evidence has been accumulating that benzene may also increase the risk of lung cancer. For example, an exposure-response pattern between benzene soluble materials and the risk of lung cancer that was independent of smoking was observed in a cohort of aluminum reduction plant workers (Spinelli et al., 2006). Elsewhere, two papers from a cohort of Chinese workers exposed to benzene found a 2.3 fold increased risk of lung cancer among non-smokers relative to an unexposed control cohort (Yin et al., 1989), while the second study reported a 40% increased risk of developing lung cancer relative to unexposed workers (Yin et al., 1996). In a cohort study of 70,000 US male veterans, ambient pollution was found to increase the risk of overall mortality by up to 10%, with some of the strongest associations observed with benzene.

We assigned concentrations of ambient pollution to residential addresses based on measures obtained from sampling campaigns that were done after the follow-up of the cohort had ended. Therefore, our associations are based on the assumption that the spatial variability in exposures in the mid 2000s was representative of intra-urban differences in VOC concentrations during follow-up. To evaluate changes in the spatial variability of NO_2 in Toronto over time, we back-extrapolated the land use regression models to each year between 1982 and 2002 using previously developed methods (Chen et al., 2010). We then estimated the

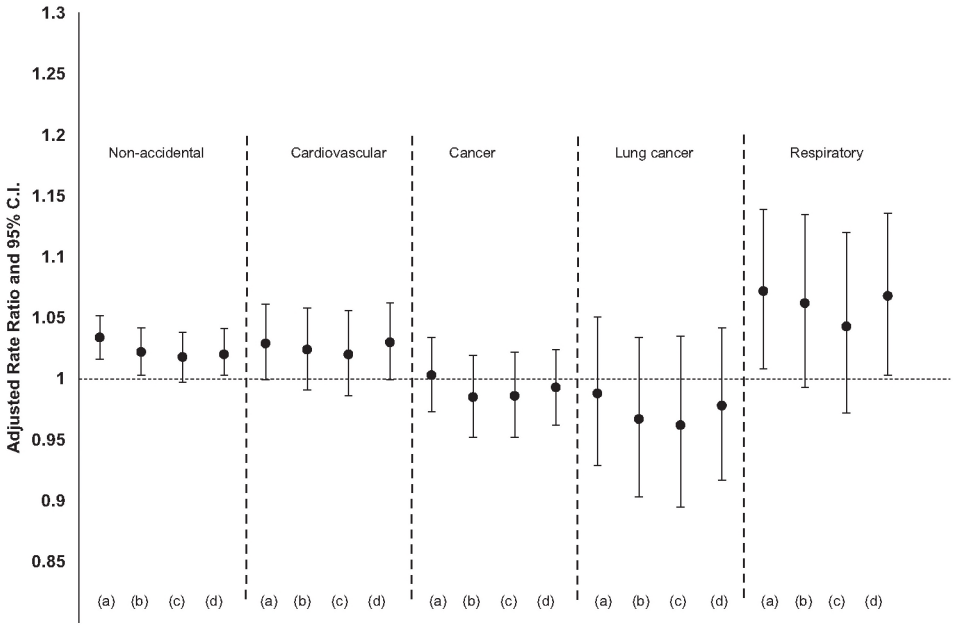


Fig. 4. Adjusted rate ratios of cause-specific mortality in relation to an increase in the interquartile range of NO_2 (5.9 ppb) with adjustment for each of the other volatile organic compounds, Toronto residents of the Ontario Tax Cohort, 1982–2004.

pairwise correlations between the historically extrapolated estimates of NO_2 and those from the original land use regression models that were developed for 2002 and 2004 at 5000 random sites in Toronto. The Pearson correlation coefficients were fairly stable over time (varied from 0.85 to 0.95, depending on the year), suggesting that variability in the concentrations of NO_2 in Toronto was primarily spatial, and not temporal, in nature (Chen et al., 2013). Unfortunately, historical fixed-site monitoring data for ambient VOCs in Toronto were lacking and we could not directly evaluate spatial changes in their concentrations over time using this approach. However, published VOC data for a nearby city (Windsor, Ontario), suggests that the rank ordering of high to low concentrations remained consistent over a three-year interval (Miller et al., 2012).

It is likely there would be some exposure misclassification introduced by relying on exposure assignment to the place of residence at time of entry given the lengthy follow-up interval and that a portion of the cohort would have moved. Under a classical error model assumption, this would introduce non-differential exposure measurement error that would serve to understate any true association. Our sensitivity analysis by restricting follow-up to the first 5 and 10 years suggested this was indeed the case. While these estimates from this restricted time interval had slightly poorer precision, they were slightly higher especially for the benzene and lung cancer association than those derived from the entire follow-up period.

We did not adjust our tests of significance for multiple comparisons, as this approach has been criticized for creating more problems than intended to solve (Goldberg and Silbergeld, 2011). The two-pollutant models that were fit to explore whether NO_2 associations were altered with the addition of VOC exposure revealed that there was little attenuation of the NO_2 effects for cardiovascular and non-accidental mortality. Our results from modeling all pollutants simultaneously are more difficult to interpret due to a high degree of correlations amongst them. As noted by others (Goldberg, 2007; Mauderly et al., 2010), under such a scenario, it becomes difficult to interpret the independent effects of the pollutants given their interrelationships, the influence of meteorology, and the fact that many of the pollutants are derived from common sources. As there are few published studies of health outcomes that have NO_2 and VOC data, further research is needed to confirm our findings.

Although we had individual-level risk factor sociodemographic information (income and marital status) as well as neighborhood level measures from the Canadian census, an important limitation of our study was the lack of individual-level data for risk factors such as smoking and body mass index. Despite this, uncontrolled confounding appears unlikely to change our key findings. A necessary condition for confounding to occur is that the confounder is associated with both the health outcome and exposure of interest. Our analyses of individual-level data from those who participated in the Canadian Community Health Survey (a separate study population) revealed little difference in VOC concentrations across categories of smoking status or body mass index. In addition, we applied an indirect adjustment method to jointly account for body mass index, and smoking status and the risk estimates changed only slightly. Other studies in Toronto that used this same NO_2 surface in a separate cohort of susceptible subjects attending a respiratory clinic in Toronto also reported significant associations between pollution and mortality (Jerrett et al., 2009) and ischemic heart disease (Beckerman et al., 2012) even after controlling directly for smoking status.

This study adds to the growing literature that suggests: (i) long-term exposure to ambient air pollution contributes to increased mortality risks, (ii) intra-urban variation in exposures are important, and (iii) ambient VOC concentrations may be relevant for cancer outcomes. Our exploratory multi-pollutant modeling implicated benzene rather than nitrogen dioxide as the pollutant that may be responsible for the increase in cancer-related mortality, whereas the opposite held true for cardiovascular disease mortality. Like other observational epidemiological studies of long-term exposure to ambient pollution some exposure misclassification is inevitable and the possibility remains that there is some residual confounding from the effects of other risk factors. For these reasons, and because few studies have evaluated associations between VOCs and mortality, further work is needed so we can better understand the sources of harmful ambient pollution concentrations.

Acknowledgments

We thank Lana Marjama of Statistics Canada for overseeing the record linkage of the cohort to the Canadian Mortality Database, and Sonia Demers and Hung Pham for their assistance with the management of data from the T1 Family File database. We are also grateful to Dores Zuccarini for her contributions to the original study design. We thank Dr. Dave Verma for assistance with processing and interpreting the VOC samples. This study was funded by the Canadian Institutes of Health Research and by Health Canada. The authors have no conflicts of interest to declare.

Appendix I

Indirect adjustment method

The relationship between predictors of mortality available in the cohort (i.e., air pollution, marital status, income) and survival was examined using the Cox Proportional Hazards regression model which has the form:

$$h^{(s)}(t) = h_0^{(s)}(t)\exp\{\gamma' x\}$$

where $h^{(s)}(t)$ is the probability of the occurrence of death at time t for a subject in strata s, γ is an unknown parameter vector relating the vector of covariates x to the hazard function with $h_0^{(s)}(t)$ the baseline hazard function defined as the hazard when $x = 0$. Strata were defined by single-year age and sex groupings.

Let the vector of L estimates of the regression parameters be denoted by $\widehat{\gamma}$ from the Cox regression model. We wish to indirectly adjust these parameter estimates for a set of R missing risk factors, such as cigarette smoking status and obesity. Let $\tilde{U}$ be a $n \times R$ design matrix of the R risk factors for n subjects from the Canadian Community Health Survey (CCHS) representing indicator functions of cigarette smoking and categories of body mass index. Further let $\tilde{X}$ be a $n \times L$ design matrix of the L risk factors that are available in the Ontario Tax Cohort dataset with values obtained from the CCHS. We augment $\tilde{X}$ to include a vector of 1s to represent the baseline hazard function and additional indicator variables representing the age-sex strata.

The indirectly adjusted parameter vector $\widehat{\beta}$, is given by

$$\widehat{\beta} = \widehat{\gamma} - \left(\tilde{X}'\tilde{X}\right)^{-1}\tilde{X}'\tilde{U}\tilde{\lambda} \equiv \widehat{\gamma} - \widetilde{\Delta}\tilde{\lambda}, \tag{A1}$$

where $\tilde{\lambda}$ is a $R \times 1$ vector of the regression parameter estimates of the R risk factors on the response obtained from the literature. We note that the indirect adjustment for the lth regression parameter, corresponding to air pollution for example, $\widehat{\beta}_l$ is given by $\widehat{\beta}_l = \widehat{\gamma}_l - \widetilde{\Delta}_{(l)}\tilde{\lambda}$, where $\widetilde{\Delta}_{(l)}$ is the lth row of $\widetilde{\Delta}$. Then the variance of $\widehat{\beta}_l$ is given by

$$\mathrm{var}\left(\tilde{\beta}_l\right) = \mathrm{var}\left(\widehat{\gamma}_l\right) + \widetilde{\Delta}_{(l)}\mathrm{Cov}\left(\tilde{\lambda}\right)\widetilde{\Delta}'_{(l)} + \tilde{\lambda}'\mathrm{Cov}\left(\widetilde{\Delta}_{(l)}\right)\tilde{\lambda}$$

with $\mathrm{var}(\widehat{\gamma}_l)$ obtained directly from the primary dataset analysis model. Here $\mathrm{Cov}(\tilde{\lambda})$ is obtained from the literature and

$$\mathrm{Cov}\left(\widetilde{\Delta}_{(l)}\right) = \left(\tilde{X}'\tilde{X}\right)^{-1}_{(l,l)} * \tilde{\Sigma}$$

where

$$\tilde{\Sigma} = \tilde{U}'\left(I_n - \tilde{X}\left(\tilde{X}'\tilde{X}\right)^{-1}\tilde{X}'\right)\tilde{U}/n$$

with $(\tilde{X}'\tilde{X})^{-1}_{(l,l)}$ is the lth diagonal element of $(\tilde{X}'\tilde{X})^{-1}$ and I_n an identity matrix of order n.

The indirect adjustment Equation (A1) can be written in terms of hazard ratios. Denote the hazard ratio for the lth indirectly adjusted variable by $\mathrm{HR}_l^{\mathrm{adj}} = \exp\{\widehat{\beta}_l\}$, the unadjusted hazard ratio by $\mathrm{HR}_l^{\mathrm{unadj}} = \exp\{\widehat{\gamma}_l\}$, and the hazard ratio of the rth missing covariate by $\mathrm{HR}_r = \exp\{\tilde{\lambda}_r\}$. Then we have

$$\mathrm{HR}_l^{\mathrm{adj}} = \frac{\mathrm{HR}_l^{\mathrm{unadj}}}{\prod_{r=1}^{R}\mathrm{HR}_r^{\widetilde{\Delta}_{(l,r)}}},$$

where $\widetilde{\Delta}_{(l,r)}$ is the (l,r) element of $\widetilde{\Delta}$ representing the linear association between the lth indirectly adjusted variable and the rth adjusting variable. The amount of adjustment is dependent on the magnitude of both the hazard ratios of the adjusting variables and the relationship between the adjusted and adjusting variables.

We simultaneously indirectly adjusted the regression coefficient for air pollution for two missing covariates by characterizing cigarette smoking habits using two binary variables: former versus never cigarette smoker and current versus never smoker. We modeled the effects of obesity on cause-specific mortality with body mass index (kg/m^2) by using four binary variables describing ranges: 25–30, 30–35, 35–40, and >40 compared to <25. We obtained hazard ratio estimates for current versus never smokers, and former versus never smokers based on the American Cancer Society Cancer Prevention II (ACS CPS II) cohort (Malarcher et al., 2000; Pope et al., 2004). We also obtained an estimate of the hazard ratio of mortality, for each cause of death, associated with body mass index (Whitlock et al., 2009). The hazard ratio per 5 kg/m^2 increase in body mass index above 25 kg/m^2 was 1.39 (95%CI: 1.34–1.44). We then calculated the hazard ratio based on the difference between the group mean body mass index and 25 kg/m^2.

The association between the variables in the survival model and the six indirect adjustment variables was also required. This relationship was estimated using CCHS (Statistics Canada, 2005), a biannual population based cross-sectional survey of Canadians that started in 2001. We assigned the concentrations of the three VOCs and NO_2 to the centroid of the home address of the six-character postal code of all subjects ≥35 years old who lived in Toronto and who completed the 2001 CCHS. The six-digit postal code represents a block face in cities but can represent a much large area in rural settings.

We included in the design matrix $\tilde{X}$, data from the CCHS for the same variables and category definitions as in the survival model applied to the cohort of Toronto residents. These variables consisted of: age, sex, marital status, household income.

Table S1
Adjusted rate ratios per interquartile increase in VOCs and NO_2 with all terms included simultaneously in the model, Toronto residents of the Ontario Tax Cohort

Underlying cause of death	Total hydrocarbons	n-Hexane	Benzene	NO_2
Non-accidental	1.01 (0.98–1.03)	1.02 (1.00–1.04)	1.03 (1.00–1.06)	1.01 (0.99–1.04)
Cardiovascular	0.99 (0.95–1.02)	1.02 (0.98–1.06)	1.02 (0.97–1.07)	1.02 (0.98–1.05)
Cancer	1.04 (1.01–1.08)	1.01 (0.97–1.05)	1.03 (0.98–1.08)	0.98 (0.95–1.02)
Lung cancer	1.03 (0.96–1.11)	1.02 (0.96–1.10)	1.04 (0.94–1.15)	0.96 (0.89–1.03)
Non-malignant respiratory	1.00 (0.93–1.08)	1.05 (0.98–1.13)	1.01 (0.91–1.12)	1.04 (0.97–1.12)

*All presented rate ratios were adjusted for single-year age, sex, family income, marital status, and census area measures of income, immigration, and unemployment.

References

Beckerman, B.S., Jerrett, M., Finkelstein, M., Kanaroglou, P., Brook, J.R., Arain, M.A., Sears, M.R., Stieb, D., Balmes, J., Chapman, K., 2012. The association between chronic exposure to traffic-related air pollution and ischemic heart disease. J. Toxicol. Environ. Health A 75, 402–411.

Bland, M., 2000. An Introduction to Medical Statistics, third ed. Oxford Medical Publications, New York.

Brook, J.R., Burnett, R.T., Dann, T.F., Cakmak, S., Goldberg, M.S., Fan, X., Wheeler, A.J., 2007. Further interpretation of the acute effect of nitrogen dioxide observed in Canadian time-series studies. J. Expo. Sci. Environ. Epidemiol. 17 (Suppl. 2), S36–S44.

Burra, T.A., Moineddin, R., Agha, M.M., Glazier, R.H., 2009. Social disadvantage, air pollution, and asthma physician visits in Toronto, Canada. Environ. Res. 109, 567–574.

Chen, H., Goldberg, M.S., Villeneuve, P.J., 2008. A systematic review of the relation between long-term exposure to ambient air pollution and chronic diseases. Rev. Environ. Health 23, 243–297.

Chen, H., Goldberg, M.S., Crouse, D.L., 2010. Back-extrapolation of estimates of exposure from current land-use regression models. Atmos. Environ. 44, 4346–4354.

Chen, H., Goldberg, M.S., Burnett, R.T., Jerrett, M., Wheeler, A.J., Villeneuve, P.J., 2013. Long-term exposure to traffic-related air pollution and cardiovascular mortality. Epidemiology 24, 35–43.

Crouse, D.L., Goldberg, M.S., Ross, N.A., Chen, H., Labreche, F., 2010. Postmenopausal breast cancer is associated with exposure to traffic-related air pollution in Montreal, Canada: a case-control study. Environ. Health Perspect. 118, 1578–1583.

Delfino, R.J., Gong Jr., H., Linn, W.S., Pellizzari, E.D., Hu, Y., 2003. Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. Environ. Health Perspect. 111, 647–656.

Elliott, L., Longnecker, M.P., Kissling, G.E., London, S.J., 2006. Volatile organic compounds and pulmonary function in the Third National Health and Nutrition Examination Survey, 1988–1994. Environ. Health Perspect. 114, 1210–1214.

Galbraith, D., Gross, S.A., Paustenbach, D., 2010. Benzene and human health: a historical review and appraisal of associations with various diseases. Crit. Rev. Toxicol. 40 (Suppl. 2), 1–46.

Goldberg, M., Silbergeld, E., 2011. On multiple comparisons and on the design and interpretation of epidemiological studies of many associations. Environ. Res. 111, 1007–1009.

Goldberg, M.S., Carpenter, M., Theriault, G., Fair, M., 1993. The accuracy of ascertaining vital status in a historical cohort study of synthetic textiles workers using computerized record linkage to the Canadian Mortality Data Base. Can. J. Public Health 84, 201–204.

Goldberg, M.S., 2007. On the interpretation of epidemiological studies of ambient air pollution. J. Expo. Sci. Environ. Epidemiol. 17 (Suppl. 2), S66–S70.

Hoek, G., Beelen, R., de Hoogh, H., Vienneau, D., Gulliver, J., Fischer, P., Briggs, D., 2008. A review of land-use regression models to assess spatial variation of outdoor air pollution. Atmos. Environ. 42, 7561–7578.

Howe, G.R., Lindsay, J., 1981. A generalized iterative record linkage computer system for use in medical follow-up studies. Comput. Biomed. Res. 14, 327–340.

IARC, 1982. Benzene, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. In: Some Industrial Chemicals and Dyestuffs, vol. 29. International Agency for Research on Cancer, Lyon, pp. 93–148.

IARC, 2008. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. In: 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide), vol. 97. International Agency for Research on Cancer, Lyon.

Jerrett, M., Arain, A., Kanaroglou, P., Beckerman, B., Potoglou, D., Sahsuvaroglu, T., Morrison, J., Giovis, C., 2005a. A review and evaluation of intraurban air pollution exposure models. J. Expo. Anal. Environ. Epidemiol. 15, 185–204.

Jerrett, M., Burnett, R.T., Ma, R., Pope 3rd, C.A., Krewski, D., Newbold, K.B., Thurston, G., Shi, Y., Finkelstein, N., Calle, E.E., Thun, M.J., 2005b. Spatial analysis of air pollution and mortality in Los Angeles. Epidemiology 16, 727–736.

Jerrett, M., Arain, M.A., Kanaroglou, P., Beckerman, B., Crouse, D., Gilbert, N.L., Brook, J.R., Finkelstein, N., Finkelstein, M.M., 2007. Modeling the intraurban variability of ambient traffic pollution in Toronto, Canada. J. Toxicol. Environ. Health A 70, 200–212.

Jerrett, M., Finkelstein, M.M., Brook, J.R., Arain, M.A., Kanaroglou, P., Stieb, D.M., Gilbert, N.L., Verma, D., Finkelstein, N., Chapman, K.R., Sears, M.R., 2009. A cohort study of traffic-related air pollution and mortality in Toronto, Ontario, Canada. Environ. Health Perspect. 117, 772–777.

Kanaroglou, P., Jerrett, M., Morrison, J., Beckerman, B., Arain, M.A., Gilbert, N.L., Brook, J.R., 2005. Establishing an air pollution monitoring network for intra-urban population exposure assessment: a location allocation approach. Atmos. Environ. 39, 2399–2409.

Lipfert, F.W., Wyzga, R.E., Baty, J.D., Miller, J.P., 2009. Air pollution and survival within the Washington University-EPRI veterans cohort: risks based on modeled estimates of ambient levels of hazardous and criteria air pollutants. J. Air Waste Manag. Assoc. 59, 473–489.

Lundberg, I., Milatou-Smith, R., 1998. Mortality and cancer incidence among Swedish paint industry workers with long-term exposure to organic solvents. Scand. J. Work Environ. Health 24, 270–275.

Malarcher, A.M., Schulman, J., Epstein, L.A., Thun, M.J., Mowery, P., Pierce, B., Escobedo, L., Giovino, G.A., 2000. Methodological issues in estimating smoking-attributable mortality in the United States. Am. J. Epidemiol. 152, 573–584.

Mauderly, J.L., Burnett, R.T., Castillejos, M., Ozkaynak, H., Samet, J.M., Stieb, D.M., Vedal, S., Wyzga, R.E., 2010. Is the air pollution health research community prepared to support a multipollutant air quality management framework? Inhal. Toxicol. 22 (Suppl. 1), 1–19.

Miller, L., Xu, X., Grgicak-Mannion, A., Brook, J., Wheeler, A., 2012. Multi-season, multi-year concentrations and correlations amongst the BTEX group of VOCs in an urbanized industrial city. Atmos. Environ. 61, 305–315.

Nogueira, J.B., 2009. Air pollution and cardiovascular disease. Rev. Port Cardiol. 28, 715–733.

Pope 3rd, C.A., Burnett, R.T., Thurston, G.D., Thun, M.J., Calle, E.E., Krewski, D., Godleski, J.J., 2004. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation 109, 71–77.

Pope, C.I., Brook, R.D., Burnett, R.T., Dockery, D.W., 2010. How is cardiovascular disease mortality risk affected by duration and intensity of fine particulate matter exposure? An integration of the epidemiologic evidence. Air Qual. Atmos. Health 4, 5–14.

Pope 3rd, C.A., 2000. Particulate matter-mortality exposure-response relations and threshold. Am. J. Epidemiol. 152, 407–412.

Ruud, P.A., 2000. An Introduction to Classical Econometric Theory. Oxford University Press, New York, USA.

Schnatter, A.R., Acquavella, J.F., Thompson, F.S., Donaleski, D., Theriault, G., 1990. An analysis of death ascertainment and follow-up through statistics Canada's Mortality Data Base system. Can. J. Public Health 81, 60–65.

Schnatter, R., 2000. Petroleum worker studies and benzene risk assessment. J. Toxicol. Environ. Health A 61, 433–437.

Spinelli, J.J., Demers, P.A., Le, N.D., Friesen, M.D., Lorenzi, M.F., Fang, R., Gallagher, R.P., 2006. Cancer risk in aluminum reduction plant workers (Canada). Cancer Causes Control 17, 939–948.

Statistics Canada, 2005. Canadian Community Health Survey 2003: User Guide for the Public Use Microdata File. Health Statistics Division, Statistics Canada, Ottawa, 59 pp.

Statistics Canada, 2011. Vital Statistics – Death Database. Statistics Canada, Ottawa, Canada.

Steffen, C., Auclerc, M.F., Auvrignon, A., Baruchel, A., Kebaili, K., Lambilliotte, A., Leverger, G., Sommelet, D., Vilmer, E., Hemon, D., Clavel, J., 2004. Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; a case-control study. Occup. Environ. Med. 61, 773–778.

Stocco, C., MacNeill, M., Wang, D., Xu, X., Guay, M., Brooks, J., Wheeler, D.A., 2008. Predicting personal exposure of Windso, Ontario residents to volatile organic compounds using indoor measurements and survey data. Atmos. Environ. 42, 5905–5912.

Su, J.G., Jerrett, M., Beckerman, B., Verma, D., Arain, M.A., Kanaroglou, P., Stieb, D., Finkelstein, M.M., Brook, J., 2010. A land use regression model for predicting ambient volatile organic compound concentrations in Toronto, Canada. Atmos. Environ. 44, 3529–3537.

Villeneuve, P.J., Chen, L., Stieb, D., Rowe, B.H., 2006. Associations between outdoor air pollution and emergency department visits for stroke in Edmonton, Canada. Eur. J. Epidemiol. 21, 689–700.

Villeneuve, P.J., Goldberg, M.S., Burnett, R.T., van Donkelaar, A., Chen, H., Martin, R.V., 2011. Associations between cigarette smoking, obesity, socio-demographic characteristics and remote-sensing-derived estimates of ambient $PM_{2.5}$: results from a Canadian population-based survey. Occup. Environ. Med. 68, 920–927.

Villeneuve, P.J., Jerrett, M., Su, J.G., Burnett, R.T., Chen, H., Wheeler, A.J., Goldberg, M.S., 2012. A cohort study relating urban green space with mortality in Ontario, Canada. Environ. Res. 115, 51–58.

Vinceti, M., Rothman, K.J., Crespi, C.M., Sterni, A., Cherubini, A., Guerra, L., Maffeis, G., Ferretti, E., Fabbi, S., Teggi, S., Consonni, D., De Girolamo, G., Meggiato, A., Palazzi, G., Paolucci, P., Malagoli, C., 2012. Leukemia risk in children exposed to benzene and PM(10) from vehicular traffic: a case-control study in an Italian population. Eur. J. Epidemiol. 27, 781–790.

Wellenius, G.A., Schwartz, J., Mittleman, M.A., 2005. Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. Stroke 36, 2549–2553.

Whitlock, G., Lewington, S., Sherliker, P., Clarke, R., Emberson, J., Halsey, J., Qizilbash, N., Collins, R., Peto, R., 2009. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 373, 1083–1096.

Wieslander, G., Norback, D., Edling, C., 1997. Airway symptoms among house painters in relation to exposure to volatile organic compounds (VOCS)–a longitudinal study. Ann. Occup. Hyg. 41, 155–166.

Yin, S.N., Li, G.L., Tain, F.D., Fu, Z.I., Jin, C., Chen, Y.J., Luo, S.J., Ye, P.Z., Zhang, J.Z., Wang, G.C., et al., 1989. A retrospective cohort study of leukemia and other cancers in benzene workers. Environ. Health Perspect. 82, 207–213.

Yin, S.N., Hayes, R.B., Linet, M.S., Li, G.L., Dosemeci, M., Travis, L.B., Li, C.Y., Zhang, Z.N., Li, D.G., Chow, W.H., Wacholder, S., Wang, Y.Z., Jiang, Z.L., Dai, T.R., Zhang, W.Y., Chao, X.J., Ye, P.Z., Kou, Q.R., Zhang, X.C., Lin, X.F., Meng, J.F., Ding, C.Y., Zho, J.S., Blot, W.J., 1996. A cohort study of cancer among benzene-exposed workers in China: overall results. Am. J. Ind. Med. 29, 227–235.