Progression from Asthma to Chronic Obstructive Pulmonary Disease
Is Air Pollution a Risk Factor?

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Abstract

Rationale: Individuals with asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS), have more rapid decline in lung function, more frequent exacerbations, and poorer quality of life than those with asthma or COPD alone. Air pollution exposure is a known risk factor for asthma and COPD; however, its role in ACOS is not as well understood.

Objectives: To determine if individuals with asthma exposed to higher levels of air pollution have an increased risk of ACOS.

Methods: Individuals who resided in Ontario, Canada, aged 18 years or older in 1996 with incident asthma between 1996 and 2009 who participated in the Canadian Community Health Survey were identified and followed until 2014 to determine the development of ACOS. Data on exposures to fine particulate matter ($PM_{2.5}$) and ozone (O_3) were obtained from fixed monitoring sites. Associations between air pollutants and ACOS were evaluated using Cox regression models.

Measurements and Main Results: Of the 6,040 adults with incident asthma who completed the Canadian Community Health Survey, 630 were identified as ACOS cases. Compared with those without ACOS, the ACOS population had later onset of asthma, higher proportion of mortality, and more frequent emergency department visits before COPD diagnosis. The adjusted hazard ratios of ACOS and cumulative exposures to $PM_{2.5}$ (per 10 $\mu g/m^3$) and O_3 (per 10 ppb) were 2.78 (95% confidence interval, 1.62–4.78) and 1.31 (95% confidence interval, 0.71–2.39), respectively.

Conclusions: Individuals exposed to higher levels of air pollution had nearly threefold greater odds of developing ACOS. Minimizing exposure to high levels of air pollution may decrease the risk of ACOS.

Keywords: air pollution; coexisting chronic disease morbidities; environmental exposures

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At a Glance Commentary

Scientific Knowledge on the Subject: Although there is a significant body of evidence linking air pollution to asthma or chronic obstructive pulmonary disease (COPD) exacerbations, the link between air pollution and the asthma–COPD overlap syndrome (ACOS) is not well understood.

What This Study Adds to the Field: ACOS is a newly recognized diagnosis gaining attention due to the significant morbidities associated with the disease. Understanding the effects of modifiable risk factors, such as air pollution, has the potential to decrease morbidity and mortality associated with ACOS.

Exposure to air pollution has been associated with compromised pulmonary immune defense mechanisms in both animals and humans (1, 2). Adverse health effects from acute (hours to days) and chronic (months to years) exposure to air pollution range from minor irritation of the upper respiratory system to impacting the morbidity of chronic respiratory diseases (asthma, chronic obstructive pulmonary disease [COPD]), heart disease, diabetes, hypertension, lung cancer, and death (3–8). More specifically, both acute and chronic exposure to fine particulate matter ($PM_{2.5}$) has been shown to induce a systemic inflammatory response, which can increase the risk of cardiorespiratory morbidity (9–11). $PM_{2.5}$ consists of particles with a median aerodynamic diameter of 2.5 μm or less, small enough to invade even the smallest airways, and is associated with adverse health impacts. It generally results from activities that burn fossil fuels, such as operating fuel-powered automotive engines, smelting, and metal processing. The World Health Organization has estimated that in 2010, $PM_{2.5}$ accounted for 3.1 million deaths and approximately 3.1% of the global disability-adjusted life years (DALYs) (12). In Canada, ambient particulate matter pollution was associated with 3.2% of total deaths and 1.58% of the total DALYs (13). Research has shown that short-term exposure (hours, days) and long-term exposure (months, years) to $PM_{2.5}$ was associated with aggravation of asthma, respiratory symptoms, and increased hospital admissions (12). Similarly, ground-level ozone (O_3) or ambient O_3 pollution is another major source of air pollution that is also associated with adverse health impacts. The World Health Organization has estimated that 0.1% of the global DALYs in 2010 were attributed to O_3 exposure (14). Research has shown that short-term exposure to O_3 was associated with decreased lung function (15) and increased hospitalizations for COPD (16–19), whereas long-term exposure to O_3 was associated with increased respiratory mortality (20) and increased mortality among persons with COPD (21).

According to the Government of Canada, Canadians rank air pollution among their main environmental concerns (22). More than half of Canadians live in areas where air pollution levels sporadically exceed healthy guidelines, where the Air Quality Health Index (AQHI; a composite measure of changes in NO_2, O_3, and $PM_{2.5}$) exceeds 3, signifying low to moderate health risk (23). In the last decade, associations between air pollution exposure and acute health outcomes have been demonstrated in a number of studies (3, 24–28). Researchers have found that, in addition to increasing mortality risks (1.2% increase in mortality per unit increase in AQHI) (24–26), air pollution also increases morbidity, especially in those with asthma and/or COPD (3, 27, 28). Using Ontario population data, our previous research estimated that each unit increase in AQHI was associated with a 6% increase in asthma outpatient visits, 2% increase in hospitalizations on Day 0 (with peak exposures to air pollution), and 1.3% increase in emergency department (ED) visits (on Day 2) (29).

It is well established that individuals with both asthma and COPD (or asthma–COPD overlap syndrome [ACOS]) have more frequent exacerbations, more rapid decline in lung function, and worse quality of life than those with asthma or COPD alone (30–33). Although it has been accepted that air pollution exposure is a risk factor for asthma and COPD exacerbations, its role in the natural history of those with ACOS is not well described. The objective of this study was to use population-based epidemiological data to measure the association between cumulative exposure to different markers of pollution and the development of related exacerbations of COPD in the asthma population.

Some of the results of this study have been previously reported in the form of an abstract and poster presentation at the American Thoracic Society Annual Conference in 2015 (34).

Methods

This study was set in Ontario, Canada, the province representing the largest population in the country, with more than 13 million residents. Ontario includes major urban areas, such as the Greater Toronto Area and National Capital Region of Ottawa, along with a diverse rural environment. A cohort approach was used to model the effect of markers of air pollution on the development of COPD in the Ontario asthma population aged 18 years or older in 1996. Individuals with ACOS may consist of various phenotypes (35–37): (*1*) asthma precedes COPD, (*2*) COPD precedes asthma, or (*3*) both are diagnosed at the same time. In this article, our focus was on those who have already had confirmed asthma and to determine the risk of subsequent development (or progression) of COPD and its association with cumulative exposures to two different markers of pollution: $PM_{2.5}$ and O_3. For simplicity, we hereafter refer to this subtype of asthma–COPD overlap syndrome as ACOS. To examine spatial variation in ACOS and markers of pollution, while protecting the anonymity of respondents, we examined data at the Census Division (CD) level throughout Ontario (Figure 1). Forty-nine CDs divide the province and vary in size (from approximately 663 km^2 to 439,000 km^2) and population density (from approximately 13,000 to 2.6 million people per CD or 0.1 to 4,150 people per square kilometer).

Study Populations

The Ontario Asthma Surveillance Information System (OASIS), funded by the Government of Ontario, is a registry of all Ontario residents with asthma (2.1 million). The registry is generated using a previously validated case definition of one hospitalization or two or more ambulatory care claims for asthma in 2 years, yielding 89% sensitivity and 72% specificity in children (aged 0–17 yr), and 84% sensitivity

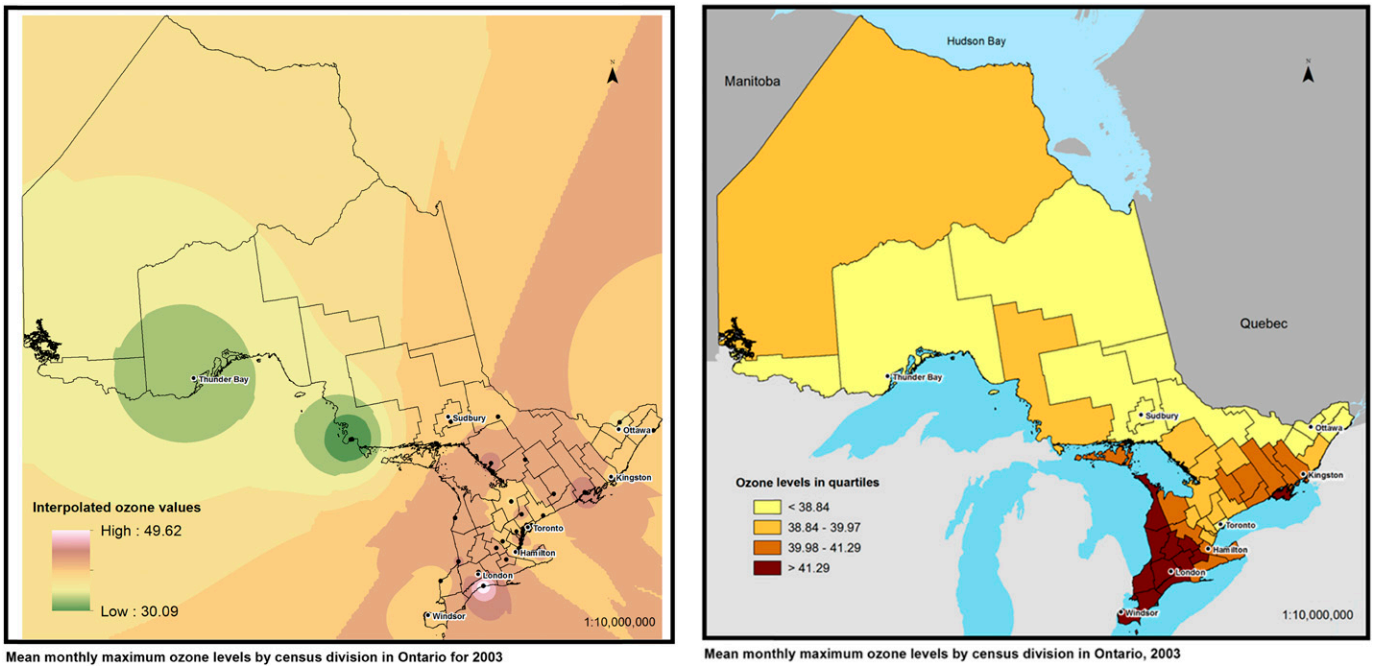

Figure 1. Example of air pollution interpolation in Ontario by Census Division.

and 76% specificity in adults (aged ⩾ 18 yr) (38–41). Individuals aged 18 years or older in 1996 with incident asthma between April 1, 1996, and March 31, 2009, were identified from OASIS.

Canadian Community Health Survey

Individuals with incident asthma identified in the OASIS registry were linked to the Canadian Community Health Survey (CCHS) to obtain data on potential risk factors (i.e., smoking history and obesity measured by body mass index [BMI]), which were not available in the health administrative databases. The CCHS is a cross-sectional survey of Canadians aged 12 years and older that was completed every 2 years from 2000 to 2007 and annually thereafter (42). This voluntary, self-report survey collects information over the phone and in person about health status, health determinants, and behaviors. The same questions were used across surveys, providing consistency. The response rates varied slightly depending on the year of the survey. In 2010, the overall response rates of the surveys were 72.3 and 70.0% in Canada and Ontario, respectively (43). The surveys have previously been used in health research to estimate the burden of diabetes and cardiovascular diseases in Canada (44, 45). Multiple cycles of CCHS (2000–2010) were used in this study. For individuals who participated in multiple cycles of CCHS, the most recent years of data were used.

Outcome

This study uses the physician diagnosis of COPD in the population of adults with asthma as the outcome. The case definition used in this study, of one hospitalization or three or more ambulatory care claims for COPD in 2 years, has been validated, yielding a sensitivity of 85.0% and a specificity of 78.4% in adults aged 35 years and older (46). To distinguish incident cases from prevalent cases, a minimum 5-year asthma- or COPD-free observation period before the incidence date was required. Individuals aged 18 years or older in 1996 with incident asthma between April 1, 1996 and March 31, 2009 who were identified from OASIS and completed the CCHS were followed until March 31, 2014 to determine who developed COPD (and thus, ACOS). The follow-up period for ascertainment of COPD was between April 1, 1996 and March 31, 2014, giving a minimum follow up of 5 years to a maximum of 18 years (for individuals with asthma incidence in 1996).

Ontario has a universal health care system that covers all physician and hospital services. Health service claims captured by the province provided individual-level outcome measures used in this study. Our primary outcome measures included: incidence of COPD and cumulative exacerbations (measured by ED visits and hospital admission with the main diagnosis being COPD). Data were available from four health administrative databases: (*1*) The Ontario Health Insurance Plan Database, containing information on all fee-for-service billings for physician services as well as ED visits in Ontario, including diagnosis; (*2*) the Canadian Institute for Health Information's Discharge Abstract Database, recording the primary diagnosis and up to 15 secondary diagnoses for all patients discharged from acute-care hospitals before 2002 and up to 24 secondary diagnoses after 2002; (*3*) the National Ambulatory Care Reporting System, containing visits to all hospital-based EDs; and (*4*) the Ontario Registered Persons Database, capturing information on sex, date of birth, residence postal code, and date of death. When an individual moved, the change of address or postal code was captured in the Registered Persons Database, allowing us to reassign exposures accordingly. Those who moved out of the province and/or died were censored using their last date of contact as the end date of follow up. These databases were then linked on an individual level using an encrypted unique health

card number given to all Ontario residents. Such linkage allows for protection of the identities of individuals while examining their health services use across health administrative databases.

Those without a valid health card number for data linkage, missing residence postal code, age of COPD diagnosis less than 35 years, with a COPD diagnosis before asthma, or with an asthma and COPD diagnosis at the same time were excluded from this study. Those with incident COPD less than or equal to 2 years from the incidence of asthma were also excluded, to minimize false-positive ACOS that might have occurred because an initial asthma diagnosis was later changed to COPD.

Exposure Data

Air quality data provided hourly and daily measurements of markers of pollution ($PM_{2.5}$ and O_3) from January 1, 1996, to December 31, 2013, from 49 continuous fixed-site monitors in Ontario. Continuous hourly data for $PM_{2.5}$ were only available from 2003 to 2013. All air pollution data were aggregated to mean monthly maximum for each monitoring station. Although land-use regression models have been used to characterize air pollution exposure and health effects for individuals residing within urban areas, we did not have accurate province-wide traffic data and land use data to expand the land-use regression approach to the provincial level. Thus, we applied inverse distance-weighted (47–49) interpolation to the air pollution data from the continuous fixed-site monitors to create a monthly air pollution surface for Ontario. Mean monthly values were assigned for each CD in Ontario, on the basis of the mean values. Using O_3 as an example, Figure 1 illustrates the assignment of the O_3 levels to the 49 CDs on the basis of the O_3 surface generated using inverse distance weighting. Long-term exposures were calculated based on mean daily maximum of markers of pollution measured from time of asthma incidence to COPD incidence or end of study for the group without ACOS.

Statistical Analysis

The hazard ratios (HRs) of COPD in the asthma population in association with cumulative exposure to markers of pollution were estimated using the Cox proportional hazards regression. Single-pollutant regression models ($PM_{2.5}$ and O_3 individually) and two-pollutant regression models were assessed separately. We adjusted for potential confounding variables in our multivariable regression analysis. These variables included: age at asthma incidence (10-year age groupings), sex, rural residence, neighborhood-level socioeconomic status (SES), coexisting morbidities, smoking status, and BMI. To assess neighborhood-level SES, we used material deprivation quintiles by incorporating multiple census-based measures (proportions of high school graduation, lone-parent families, government transfers, unemployment, low income, homes needing major repairs) (50, 51). Rural living was determined using postal code and was defined as living in a town or municipality with fewer than 10,000 people. Nine chronic diseases and conditions were included as comorbidities (acute myocardial infarction, angina, congestive heart failure, diabetes, hypertension, ischemic heart disease, stroke, cancers). Details on the International Classification of Diseases codes used to define these conditions are included in Table E1 in the online supplement. Smoking history was classified using CCHS data as: daily, occasional, past, or never smoker. BMI was calculated based on self-reported body weight and height using the formula: $BMI = weight/height^2$. The calculated BMI is divided into four categories: underweight (<18.4), healthy body weight (≥ 18.4 and <25.0), overweight (≥ 25.0 and <30.0), and obese (≥ 30.0).

Results of the Cox proportional hazards regression analysis were presented as HRs with 95% confidence intervals (CIs) per unit (10 $\mu g/m^3$) increase in $PM_{2.5}$ and

Table 1. Demographic Characteristics of Study Population with and without Asthma–Chronic Obstructive Pulmonary Disease Overlap Syndrome

Characteristic	ACOS (*n* = 630)		Non-ACOS (*n* = 5,410)		*P* Value
	No.	%	No.	%	
Age at asthma incidence, yr					<0.001
18–29	8	1.3	799	14.8	
30–49	40	6.3	1,299	24.0	
40–49	94	14.9	1,129	20.9	
50–59	150	23.8	989	18.3	
60–69	180	28.6	690	12.8	
70–79	125	19.8	397	7.3	
80–99	33	5.2	107	2.0	
Mean age ± SD	59.91 ± 12.96		48.45 ± 15.61		<0.001
Sex					0.014
Female	394	62.5	3,647	67.4	
Male	236	37.5	1,763	32.6	
Deprivation quintile (proxy measure of SES)					0.016
Q1 (least marginalized)	90	14.4	1,032	19.3	
Q2	122	19.6	1,118	20.9	
Q3	142	22.8	1,236	23.1	
Q4	141	22.6	1,034	19.3	
Q5 (most marginalized)	128	20.5	925	17.3	
Rural residence	153	24.3	987	18.2	<0.001
Coexisting chronic disease morbidity					
Acute myocardial infarction	39	6.2	168	3.1	<0.001
Angina	206	32.7	902	16.7	<0.001
Congestive heart failure	97	15.4	306	5.7	<0.001
Diabetes mellitus	161	25.6	1,106	20.4	0.003
Hypertension	401	63.7	2,484	45.9	<0.001
Ischemic heart disease	268	42.5	1,390	25.7	<0.001
Stroke	105	16.7	498	9.2	<0.001
Lung cancer	11	1.7	38	0.7	0.006
Nonlung cancers	74	11.7	502	9.3	0.046
Deaths	174	27.6	362	6.7	<0.001

Definition of abbreviations: ACOS = asthma–chronic obstructive pulmonary disease overlap syndrome; SES = socioeconomic status.
All percentages are adjusted for missing data.

(10 ppb) in O_3. Proportionality assumptions were checked and met in all models presented in this study. Additional analyses to evaluate the potential overadjustment by including comorbidity as a covariate were completed by repeating the analysis without adjusting for comorbidities. Results were summarized and presented in Table E1. All analyses were performed using SAS Enterprise guide 6.1 (SAS Institute Inc., Cary, NC).

Results

Descriptive Statistics

The OASIS registry contained 414,568 individuals from Ontario aged 18 years or older in 1996 with incident asthma between 1996 and 2009. Approximately 1.5% (n = 6,040) of the study population participated in the CCHS and provided data on risk factors of interest. Of these CCHS participants, 630 (10.4%) developed COPD and were ACOS cases. Table 1 shows the demographic characteristics of the study population stratified by those who developed COPD (the ACOS group) and those who did not (the non-ACOS group). The ACOS group, when compared with the non-ACOS group, was significantly older at the time of asthma incidence (59.9 ± 13.0 vs. 48.5 ± 15.6 yr, $P < 0.001$). Both groups had a higher proportion of women than men (62.5 vs. 67.4%, $P = 0.014$). The ACOS group also had more coexisting major comorbid chronic diseases, including angina, congestive heart failure, diabetes, hypertension, ischemic heart disease, stroke, acute myocardial infarction, and lung and nonlung cancers.

Exposure to $PM_{2.5}$ and O_3

Table 2 summarizes the mean daily maximum levels of exposure to $PM_{2.5}$ ($\mu g/m^3$; from 2003 to 2013) and O_3 (ppb; from 1996 to 2013) in ACOS and non-ACOS groups. There were no statistically significant differences in the average of maximum exposure levels between the two groups. Information on lifestyle factors (smoking status and BMI) was available from the CCHS data. The level of exposure to markers of pollution did not differ between smokers and nonsmokers or between those who were classified as obese (BMI ⩾ 30) and underweight or healthy body weight (BMI < 30).

Figure 2 shows the distributions of O_3 from 1996 to 2013 and $PM_{2.5}$ from 2003 to 2013. Although the level of $PM_{2.5}$ showed a steady decline over time, the level of O_3 remained relatively stable.

Association between Exposure and ACOS

Table 3 shows the level of health services use in the ACOS and non-ACOS groups. In general, the ACOS group had a higher mean health service use per 100 persons per year before COPD diagnosis, specifically for ED visits (42 compared with 23 in non-ACOS) and physician office visits (239, compared with 155 in non-ACOS) for asthma or asthma-related causes.

Table 4 shows results from the Cox proportional hazards regression analysis.

Table 2. Mean Daily Maximum Exposure Levels to $PM_{2.5}$ (2003–2013) and O_3 (1996–2013) in Patients with and without Asthma–Chronic Obstructive Pulmonary Disease Overlap Syndrome by Smoking Status and Body Mass Index

Groups	No.	$PM_{2.5}$ ($\mu g/m^3$)				O_3 (*ppb*)			
		Median	Mean	SD	IQR	Median	Mean	SD	IQR
Overall	6,040	15.1	15.0	1.6	13.6–16.0	39.2	39.3	1.4	38.4–40.4
Smoking status									
Smokers	3,135	14.8	14.9	1.6	13.6–16.0	39.3	39.3	1.4	38.5–40.3
Nonsmokers	2,905	15.4	15.0	1.5	13.8–16.0	39.2	39.3	1.5	38.3–40.4
Weight categories									
Underweight and normal (BMI < 30)	4,101	15.2	15.0	1.6	13.7–16.0	39.2	39.3	1.5	38.3–40.3
Obese (BMI ⩾ 30)	1,504	14.8	14.9	1.6	13.6–16.0	39.3	39.4	1.4	38.6–40.3
Missing BMI	435	15.4	15.2	1.7	13.8–16.1	39.3	39.3	1.5	38.3–40.4
ACOS									
Overall	630	15.4	15.2	1.7	13.8–16.2	39.3	39.5	1.4	38.6–40.5
Smoking status									
Smokers	474	15.2	15.1	1.7	13.8–16.2	39.3	39.4	1.4	38.6–40.4
Nonsmokers	156	15.6	15.4	1.7	14.2–16.4	39.3	39.5	1.5	38.5–40.5
Weight categories									
Underweight and normal (BMI < 30)	379	15.6	15.3	1.7	13.8–16.2	39.3	39.5	1.4	38.6–40.5
Obese (BMI ⩾ 30)	170	15.1	15.0	1.7	13.6–16.1	39.3	39.5	1.4	38.7–40.4
Missing BMI	81	15.2	15.3	1.8	13.9–16.3	39.3	39.4	1.4	38.3–40.2
Non-ACOS									
Overall	5,410	15.1	14.9	1.6	13.6–16.0	39.2	39.3	1.5	38.3–40.3
Smoking status									
Smokers	2,661	14.8	14.9	1.6	13.5–16.0	39.2	39.3	1.4	38.4–40.3
Nonsmokers	2,749	15.3	15.0	1.5	13.8–15.9	39.2	39.2	1.5	38.3–40.4
Weight categories									
Underweight and normal (BMI < 30)	3,722	15.2	14.9	1.5	13.6–15.9	39.2	39.2	1.5	38.3–40.3
Obese (BMI ⩾ 30)	1,334	14.8	14.9	1.6	13.5–16.0	39.2	39.3	1.4	38.6–40.3
Missing BMI	354	15.4	15.2	1.7	13.8–16.0	39.2	39.3	1.6	38.3–40.4

Definition of abbreviations: ACOS = asthma–chronic obstructive pulmonary disease overlap syndrome; BMI = body mass index; IQR = interquartile range; O_3 = ozone; $PM_{2.5}$ = particulate matter ⩽ 2.5 μm.
Smokers included those self-identified as an ever smoker, and obese individuals were those with calculated BMI ⩾ 30.

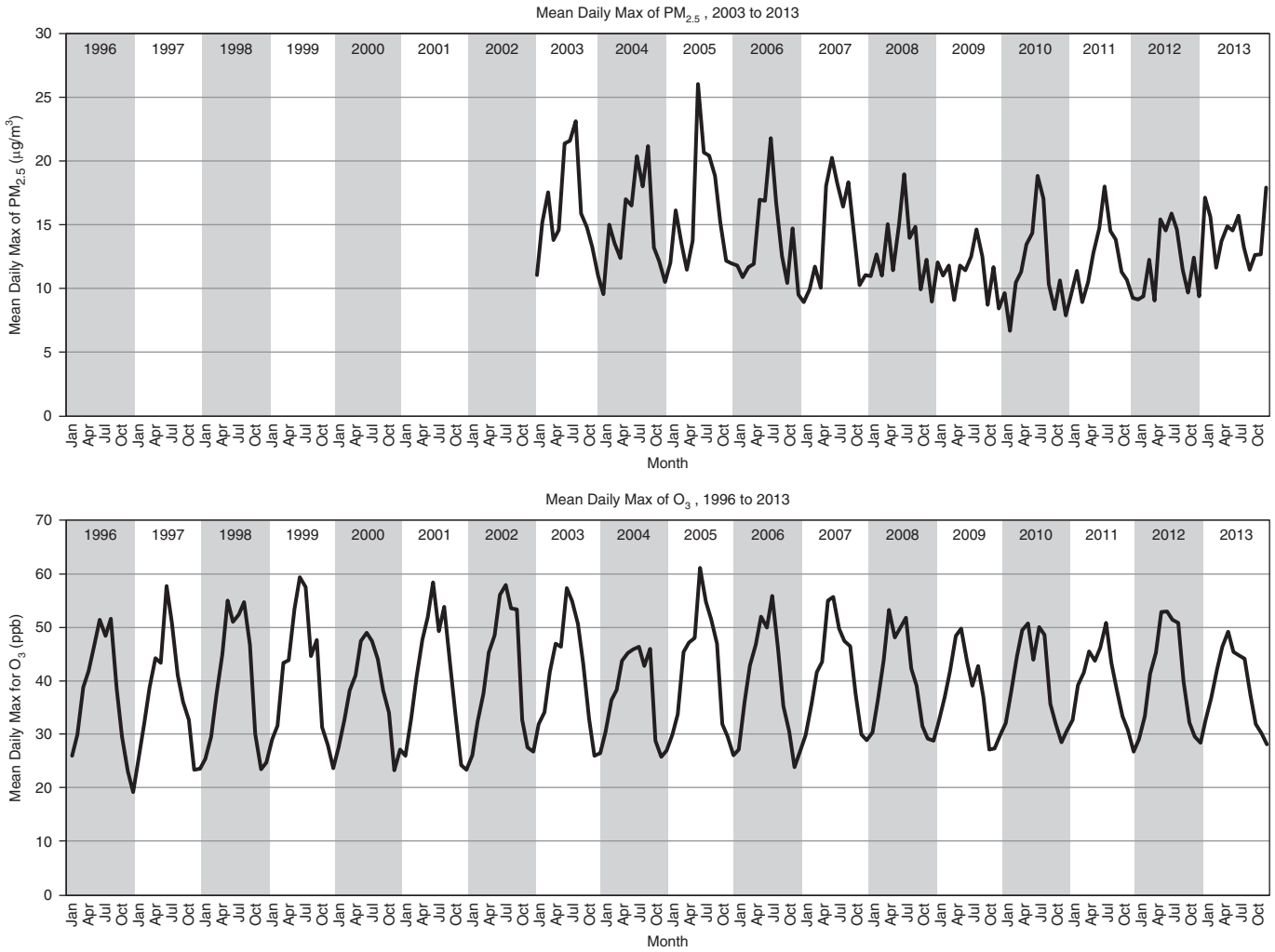

Figure 2. Distribution of mean levels of markers of pollution in Ontario, 1996 to 2013. O_3 = ozone; $PM_{2.5}$ = particulate matter ≤ 2.5 μm.

All regression models were adjusted for age at asthma incidence, sex, rural residence, SES, and coexisting morbidities. Overall, the HRs of $PM_{2.5}$ and O_3 were higher in the single-pollutant regression models. Although O_3 was statistically significant in the single-pollutant model, when adjusted by the levels of $PM_{2.5}$ in the two-pollutant model, its coefficient was reduced and was no longer statistically significant. The coefficient of $PM_{2.5}$ was also reduced in the two-pollutant model but remained statistically significant. Based on the two-pollutant model, the estimated adjusted HR of ACOS and cumulative exposures to $PM_{2.5}$ (per 10 $\mu g/m^3$) and O_3 (per 10 ppb) were 2.78 (95% CI, 1.62–4.78) and 1.31 (95% CI, 0.71–2.39), respectively. Detailed HRs of all covariates can be found in Table E2A.

Additional sensitivity analyses were conducted to assess the potential overadjustment by including comorbidity as a covariate. The regression model without adjusting for comorbidities yielded HRs slightly higher than the adjusted model for $PM_{2.5}$ but showed relatively no change for O_3. For $PM_{2.5}$ and O_3, the HRs of the unadjusted and adjusted models changed from 2.86 to 2.78 (2.8% change) and 1.30 to 1.31 (0.8% change), respectively. The lower HRs after adjustment indicated that a small fraction of the risk of COPD could be attributed to existing comorbidities. Coexistence of congestive heart failure and angina showed the highest HRs, albeit statistically nonsignificant (*see* details in Table E2B).

Discussion

This study found the risk of developing COPD in those with asthma was nearly tripled when exposed to higher levels of $PM_{2.5}$ after adjusting for potential confounders. Despite a decrease in levels of air pollution, this population-based study found an increase in the subsequent development of COPD in the population with asthma (ACOS) over time. The ACOS group also had higher health service use than the non-ACOS group, which included more frequent asthma- and COPD-related hospitalizations and ED and physician office visits.

Although others suggested common risk factors for asthma and COPD (such as age, smoking, bronchial hyperresponsiveness, etc.), the Dutch hypothesis (35, 52) further postulated that asthma and bronchial hyperresponsiveness predispose individuals to the development of COPD later in life and that asthma,

Table 3. Health Services Use per 100 Person-Years in Patients with and without Asthma–Chronic Obstructive Pulmonary Disease Overlap Syndrome

HSU (*per Person per Year*)	ACOS (*n = 630*)				Non-ACOS (*n = 5,410*)			
	No. People with HSU	Median	Mean	SD	No. People with HSU	Median	Mean	SD
Asthma specific								
Hospitalization	62	14.0	21.5	19.6	275	8.0	12.0	11.7
ED visits	108	19.2	33.2	68.5	667	10.5	15.7	20.9
Physician office visits	573	45.0	82.4	115.3	5,065	22.7	40.3	61.6
Asthma related								
Hospitalization	67	14.7	18.5	12.6	371	8.4	12.9	12.2
ED visits	274	22.7	34.2	44.5	1,955	12.7	20.5	22.8
Physician office visits	595	120.7	171.6	170.1	5,211	84.5	120.5	121.1
Asthma specific or asthma related								
Hospitalization	117	15.7	22.0	18.4	596	8.8	13.6	13.4
ED visits	312	25.6	41.5	66.1	2,202	13.9	23.0	28.5
Physician office visits	626	178.5	238.6	226.5	5,384	115.1	154.6	144.1

Definition of abbreviations: ACOS = asthma–chronic obstructive pulmonary disease overlap syndrome; ED = emergency department; HSU = health service use.
For ACOS, HSU was counted between asthma incidence and COPD diagnosis date. For non-ACOS, HSU was counted between asthma incidence and the end of the study (March 31, 2014). Only people with HSU were included in the analysis. Asthma-related causes include: acute respiratory infections, pneumonia and influenza, atopic dermatitis, gastroesophageal reflux disorder, heartburn, and allergic contact dermatitis.

COPD, chronic bronchitis, and emphysema are different expressions of a single airway disease. It is recognized that these conditions or their expressions may be influenced by both the host and environmental factors (32), including exposures to air pollution. To date, limited epidemiological studies have actually identified and/or quantified the risk of ACOS. Our study adds evidence to research that chronic exposure to air pollution may contribute to significant morbidity and contribute to the development of COPD in individuals with preexisting asthma. Better knowledge of the risk of environmental exposures and ACOS may help understand and develop preventative strategies to modify the progressive deterioration of lung function that leads to COPD (32).

This study found that although ACOS and non-ACOS groups were exposed to similar mean maximum levels of air pollution over time, those who were exposed to higher absolute values of $PM_{2.5}$ and O_3 were at higher risk of developing ACOS. Although the ACOS and non-ACOS groups were exposed to similar levels of air pollution, they differed significantly in SES, age, and prevalence of coexisting morbidities. Previous research has suggested that healthy adults who were exposed to air pollutants in a controlled environment (i.e., in a clinical trial setting) expressed much variability in the observed or measured effects (53). This suggests that the same environmental exposures may influence variability in disease (or health effect) risks depending on host factors such as age, sex, early life exposures, family history, and disease comorbidities (54). The degree of sensitivity to environmental exposures may vary among different at-risk subpopulations too. It has been suggested that host factors such as atopy, nutritional status, SES, and chronic stress may influence the effects of air pollution on asthma (55–59). There is also research that suggested a link between chronic exposure to PM during childhood and vulnerability to COPD in adulthood (60). It is important for future research to examine the interplay between gene–environment interactions and the

Table 4. Unadjusted and Adjusted Hazard Ratios of Asthma–Chronic Obstructive Pulmonary Disease Overlap Syndrome and Exposures to Air Pollutants from Cox Regressions

Covariates	Single Pollutant: $PM_{2.5}$				Single Pollutant: O_3				Two Pollutants: $PM_{2.5}$ and O_3			
	Adjusted* HR	95% CI		*P* Value	Adjusted* HR	95% CI		*P* Value	Adjusted* HR	95% CI		*P* Value
		Lower	Upper			Lower	Upper			Lower	Upper	
$PM_{2.5}$, 10 $\mu g/m^3$	3.06	1.86	5.04	<0.0001					2.78	1.62	4.78	0.0002
O_3, 10 ppb					2.05	1.17	3.60	0.0122	1.31	0.71	2.39	0.3851
Ever smoker	3.18	2.64	3.83	<0.0001	3.13	2.60	3.78	<0.0001	3.17	2.63	3.82	<0.0001
BMI ⩾ 30	1.32	1.09	1.60	0.0043	1.30	1.08	1.58	0.0063	1.32	1.09	1.60	0.0042

Definition of abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; O_3 = ozone; $PM_{2.5}$ = particulate matter ⩽ 2.5 μm.
*Other covariates included: age at asthma incidence, sex, socioeconomic status proxy measured by deprivation quintile, rural residence, other coexisting chronic diseases morbidity.

host response to environmental air pollutants. Results may help to identify susceptible subpopulations that are vulnerable to air pollution and to target preventive strategies.

This study also showed that those who developed ACOS had higher levels of health service use, including asthma-specific and asthma-related hospitalizations and ED and physician office visits. This higher frequency of health service use is important to note, as it may serve as a risk marker of developing COPD due to poor asthma control, frequent asthma exacerbations, and remodelling of airways to a fixed airway disease.

In addition to increasing frequency of health service use, it can be hypothesized from previous research that these individuals have more symptoms that affect their daily living, are more likely to take more time off from work, and have lower health-related quality of life (30–33). The public health message is not to reduce outdoor activities but rather to revise the schedule of these outdoor activities to avoid maximum adverse health impact (e.g., avoid running during times when $PM_{2.5}$ is at its peak during traffic commute times). Recent research (61) has begun to explore the utility of mobile health applications and real-time web portals that advise individuals of current air pollutant levels. Interventions such as these have the potential to increase self-management and enhance patient empowerment as air quality fluctuates over time and across different geographical regions.

This study has several strengths, including the use of large-scale population-based data covering an 18-year period and well-defined geographic regions. Data were also linked to multiple years of provincial air pollution data and population survey data to allow for a broader evaluation of the impact of confounding and risk factors on the development of COPD in the asthma population. The study is also strengthened by the adjustment of important health risk factors, including smoking status and BMI, in the analysis of the relationship between air pollution and COPD.

Despite these strengths, a few limitations should be noted. First, the use of fixed exposure monitoring sites may lead to potential misclassification, particularly in the large northern CDs where there are a limited number of monitors. However, it has been shown that with exposure measured on a numerical scale, it leads to minimal bias in regression (62). In addition, although the individual health administrative data definitions of asthma and COPD have been previously validated through chart abstraction studies (38, 40, 46), the definition of ACOS has not yet been validated. Currently, a validated definition of ACOS that can be applied to health administrative data does not exist; therefore, there is still a potential for misclassifying asthma as COPD. Research has suggested that exposure to air pollution may increase airway remodelling in individuals with asthma who then develop chronic/fixed airflow limitation/obstruction or COPD. By restricting our study population to those with asthma, it allowed us to estimate the probability of disease "progression." However, individuals with asthma may be susceptible to develop "COPD" from air pollution and therefore they may have two diseases. Our study based on health administrative data lacks detailed clinical measures to either differentiate phenotypes of ACOS or fully study the natural history of ACOS. Nonetheless, the use of population-based data with large sample sizes allowed us to adjust our Cox regression models to be fully adjusted for multiple potential confounders (i.e., age of asthma incidence, sex, SES, coexisting morbidities, smoking history, and BMI) when estimating the hazard risk for COPD. As the overlap of asthma and COPD are being recognized more commonly, future research should consider validating a health administrative definition of ACOS that can be used globally to identify individuals with ACOS and link them to other health administrative data.

Conclusions

In conclusion, this study found that those with asthma who were exposed to higher levels of $PM_{2.5}$ and O_3 had a greater risk of developing COPD (ACOS). The ACOS group also had higher health service use than the non-ACOS group. Future research should consider validating a health administrative definition of ACOS and further exploring the interaction between smoking, obesity, and other lifestyle risk factors and exposures to air pollution on the development of COPD in individuals with asthma. ■

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References

1. Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. *Environ Res* 2012;117:100–111.
2. Billionnet C, Sherrill D, Annesi-Maesano I; GERIE study. Estimating the health effects of exposure to multi-pollutant mixture. *Ann Epidemiol* 2012;22:126–141.
3. Burnett RT, Cakmak S, Brook JR. The effect of the urban ambient air pollution mix on daily mortality rates in 11 Canadian cities. *Can J Public Health* 1998;89:152–156.
4. Andersen ZJ, Raaschou-Nielsen O, Ketzel M, Jensen SS, Hvidberg M, Loft S, Tjønneland A, Overvad K, Sørensen M. Diabetes incidence and long-term exposure to air pollution: a cohort study. *Diabetes Care* 2012;35:92–98.
5. Hoffmann B, Luttmann-Gibson H, Cohen A, Zanobetti A, de Souza C, Foley C, Suh HH, Coull BA, Schwartz J, Mittleman M, *et al*. Opposing effects of particle pollution, ozone, and ambient temperature on arterial blood pressure. *Environ Health Perspect* 2012;120:241–246.
6. Ko FW, Hui DS. Air pollution and chronic obstructive pulmonary disease. *Respirology* 2012;17:395–401.
7. Lavigne E, Villeneuve PJ, Cakmak S. Air pollution and emergency department visits for asthma in Windsor, Canada. *Can J Public Health* 2012;103:4–8.
8. Wellenius GA, Burger MR, Coull BA, Schwartz J, Suh HH, Koutrakis P, Schlaug G, Gold DR, Mittleman MA. Ambient air pollution and the risk of acute ischemic stroke. *Arch Intern Med* 2012;172:229–234.
9. Fink R, Erzen I, Medved S. Environmentally induced health impacts among elderly with cardio-vascular disease. *Health Med* 2012;6: 3841–3849.
10. Nachman KE, Parker JD. Exposures to fine particulate air pollution and respiratory outcomes in adults using two national datasets: a cross-sectional study. *Environ Health* 2012;11:25.
11. Stieb DM, Judek S, Burnett RT. Meta-analysis of time-series studies of air pollution and mortality: effects of gases and particles and the influence of cause of death, age, and season. *J Air Waste Manag Assoc* 2002;52:470–484.
12. World Health Organization. Health effects of particulate matter. Geneva: World Health Organization; 2013.
13. Institute for Health Metrics and Evaluation (IHME). GBD compare. 2015 [accessed 2015 Dec 24]. Available from: http://vizhub.healthdata.org/gbd-compare

14. World Health Organization. Global burden of diseases. Geneva: World Health Organization; 2011.
15. Rice MB, Ljungman PL, Wilker EH, Gold DR, Schwartz JD, Koutrakis P, Washko GR, O'Connor GT, Mittleman MA. Short-term exposure to air pollution and lung function in the Framingham Heart Study. *Am J Respir Crit Care Med* 2013;188:1351–1357.
16. Medina-Ramón M, Zanobetti A, Schwartz J. The effect of ozone and PM10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: a national multicity study. *Am J Epidemiol* 2006;163:579–588.
17. Ko FW, Tam W, Wong TW, Chan DP, Tung AH, Lai CK, Hui DS. Temporal relationship between air pollutants and hospital admissions for chronic obstructive pulmonary disease in Hong Kong. *Thorax* 2007;62:780–785.
18. Halonen JI, Lanki T, Tiittanen P, Niemi JV, Loh M, Pekkanen J. Ozone and cause-specific cardiorespiratory morbidity and mortality. *J Epidemiol Community Health* 2010;64:814–820.
19. Arbex MA, de Souza Conceição GM, Cendon SP, Arbex FF, Lopes AC, Moysés EP, Santiago SL, Saldiva PHN, Pereira LAA, Braga ALF. Urban air pollution and chronic obstructive pulmonary disease-related emergency department visits. *J Epidemiol Community Health* 2009;63:777–783
20. Jerrett M, Burnett RT, Pope CA III, Ito K, Thurston G, Krewski D, Shi Y, Calle E, Thun M. Long-term ozone exposure and mortality. *N Engl J Med* 2009;360:1085–1095.
21. Zanobetti A, Schwartz J. Ozone and survival in four cohorts with potentially predisposing diseases. *Am J Respir Crit Care Med* 2011; 184:836–841.
22. Democracy in the 21st century-Trudeau Foundation annual survey: people and their natural environment. The Environics Institute; 2015 Oct 31 [accessed 2016 Apr 28]. Available from: http://environicsinstitute.org/institute-projects/completed-projects/trudeau-foundation-collaboration
23. To T, Licskai C, Dell S. Using the air quality health index to measure the impact of poor air quality on chronic diseases in Ontario. Toronto: The Hospital for Sick Children; 2012.
24. Villeneuve PJ, Jerrett M, Su J, Burnett RT, Chen H, Brook J, Wheeler AJ, Cakmak S, Goldberg MS. A cohort study of intra-urban variations in volatile organic compounds and mortality, Toronto, Canada. *Environ Pollut* 2013;183:30–39.
25. Turner MC, Krewski D, Pope CA III, Chen Y, Gapstur SM, Thun MJ. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. *Am J Respir Crit Care Med* 2011;184:1374–1381.
26. Stieb DM, Burnett RT, Smith-Doiron M, Brion O, Shin HH, Economou V. A new multipollutant, no-threshold air quality health index based on short-term associations observed in daily time-series analyses. *J Air Waste Manag Assoc* 2008;58:435–450.
27. Lin M, Stieb DM, Chen Y. Coarse particulate matter and hospitalization for respiratory infections in children younger than 15 years in Toronto: a case-crossover analysis. *Pediatrics* 2005;116:e235–e240.
28. Stieb DM, Szyszkowicz M, Rowe BH, Leech JA. Air pollution and emergency department visits for cardiac and respiratory conditions: a multi-city time-series analysis. *Environ Health* 2009;8:25.
29. To T, Shen S, Atenafu EG, Guan J, McLimont S, Stocks B, Licskai C. The air quality health index and asthma morbidity: a population-based study. *Environ Health Perspect* 2013;121:46–52.
30. Kauppi P, Kupiainen H, Lindqvist A, Tammilehto L, Kilpeläinen M, Kinnula VL, Haahtela T, Laitinen T. Overlap syndrome of asthma and COPD predicts low quality of life. *J Asthma* 2011;48:279–285.
31. Menezes AM, Montes de Oca M, Pérez-Padilla R, Nadeau G, Wehrmeister FC, Lopez-Varela MV, Muiño A, Jardim JR, Valdivia G, Tálamo C; PLATINO Team. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. *Chest* 2014;145:297–304.
32. Papaiwannou A, Zarogoulidis P, Porpodis K, Spyratos D, Kioumis I, Pitsiou G, Pataka A, Tsakiridis K, Arikas S, Mpakas A, *et al*. Asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS): current literature review. *J Thorac Dis* 2014;6:S146–S151.
33. Miravitlles M, Soriano JB, Ancochea J, Muñoz L, Duran-Tauleria E, Sánchez G, Sobradillo V, García-Río F. Characterisation of the overlap COPD-asthma phenotype: focus on physical activity and health status. *Respir Med* 2013;107:1053–1060.
34. To T, Zhu J, Larsen K, Williams D, Simatovic J, Gershon A, Lougheed D, Licskai C, Chen H, Vileneuve P, *et al*., Canadian Respiratory Research Network. Progression from asthma to asthma and COPD overlap syndrome (ACOS): is air pollution a risk factor [abstract]? *Am J Respir Crit Care Med* 2015;191:A5239.
35. Orie NG. The Dutch hypothesis. *Chest* 2000;117:299S.
36. Gibson PG, McDonald VM. Asthma-COPD overlap 2015: now we are six. *Thorax* 2015;70:683–691.
37. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax* 2009;64: 728–735.
38. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. *Can Respir J* 2009;16: 183–188.
39. To T, Dell S, Dick P, Cicutto L, MacLusky I, Tassoudji M, Harris JK. Defining asthma in children for surveillance. *Am J Respir Crit Care Med* 2004;169:A383.
40. To T, Dell S, Dick PT, Cicutto L, Harris JK, MacLusky IB, Tassoudji M. Case verification of children with asthma in Ontario. *Pediatr Allergy Immunol* 2006;17:69–76.
41. To T, Wang C, Guan J, McLimont S, Gershon AS. What is the lifetime risk of physician-diagnosed asthma in Ontario, Canada? *Am J Respir Crit Care Med* 2010;181:337–343.
42. Statistics Canada. Canadian community health survey - annual component (CCHS). 2015 [accessed 2015 Aug 26]. Available from: http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=3226&lang=en&db=imdb&adm=8&dis=2
43. Statistics Canada. Canadian community health survey (CCHS) - annual component, user guide 2010 and 2009-2010 microdata files. 2010 [accessed 2016 January]. Available from: http://www23.statcan.gc.ca/imdb-bmdi/document/3226_D7_T9_V8-eng.htm
44. Chen H, Burnett R, Kwong J, Villeneuve P, Goldberg M, Brook R, van Donkelaar A, Jerrett M, Martin R, Brook J, *et al*. Risk of incident diabetes in relation to long-term exposure to fine particulate matter in Ontario, Canada. *Environ Health Perspect* 2013;121: 804–810.
45. Chen H, Burnett RT, Kwong JC, Villeneuve PJ, Goldberg MS, Brook RD, van Donkelaar A, Jerrett M, Martin RV, Kopp A, *et al*. Spatial association between ambient fine particulate matter and incident hypertension. *Circulation* 2014;129: 562–569.
46. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying individuals with physcian diagnosed COPD in health administrative databases. *COPD* 2009;6:388–394.
47. Philip GM, Watson DF. A precise method for determining contoured surfaces. *Australian Petroleum Exploration Association Journal* 1982; 22:205–212.
48. Watson DF, Philip GM. A refinement of inverse distance weighted interpolation. *Geoprocessing* 1985;2:315–327.
49. Lipsett MJ, Ostro BD, Reynolds P, Goldberg D, Hertz A, Jerrett M, Smith DF, Garcia C, Chang ET, Bernstein L. Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. *Am J Respir Crit Care Med* 2011;184: 828–835.
50. McMaster University. ON-Marg: Ontario marginalization index. 2006 [accessed 2015 Aug 26]. Available from: https://crunch.mcmaster.ca/ontario-marginalization-index
51. Matheson FI, Moineddin R, Dunn JR, Creatore MI, Gozdyra P, Glazier RH. Urban neighborhoods, chronic stress, gender and depression. *Soc Sci Med* 2006;63:2604–2616.
52. Postma DS, Weiss ST, van den Berge M, Kerstjens HA, Koppelman GH. Revisiting the Dutch hypothesis. *J Allergy Clin Immunol* 2015; 136:521–529.
53. Yang IA, Fong KM, Zimmerman PV, Holgate ST, Holloway JW. Genetic susceptibility to the respiratory effects of air pollution. *Thorax* 2008; 63:555–563.
54. Sacks JD, Stanek LW, Luben TJ, Johns DO, Buckley BJ, Brown JS, Ross M. Particulate matter-induced health effects: who is susceptible? *Environ Health Perspect* 2011;119:446–454.

55. McConnell R, Berhane K, Yao L, Jerrett M, Lurmann F, Gilliland F, Künzli N, Gauderman J, Avol E, Thomas D, *et al*. Traffic, susceptibility, and childhood asthma. *Environ Health Perspect* 2006;114:766–772.
56. Gordian ME, Haneuse S, Wakefield J. An investigation of the association between traffic exposure and the diagnosis of asthma in children. *J Expo Sci Environ Epidemiol* 2006;16:49–55.
57. Clougherty JE, Kubzansky LD. A framework for examining social stress and susceptibility to air pollution in respiratory health. *Environ Health Perspect* 2009;117:1351–1358.
58. Burte E, Nadif R, Jacquemin B. Susceptibility factors relevant for the association between long-term air pollution exposure and incident asthma. *Curr Environ Health Rep* 2016;3:23–39.
59. Kelly FJ, Fussell JC. Air pollution and airway disease. *Clin Exp Allergy* 2011;41:1059–1071.
60. Grigg J. Particulate matter exposure in children: relevance to chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2009;6: 564–569.
61. Licskai C, Sands TW, Ferrone M. Development and pilot testing of a mobile health solution for asthma self-management: asthma action plan smartphone application pilot study. *Can Respir J* 2013;20: 301–306.
62. Armstrong BG. Effect of measurement error on epidemiological studies of environmental and occupational exposures. *Occup Environ Med* 1998;55:651–656.