Air Pollution and Emergency Department Visits for Disease of the Genitourinary System

Authors: Szyszkowicz, Mieczysław, Schoen, Stephanie, and De Angelis, Nicholas

Source: Environmental Health Insights, 15(1)

Published By: SAGE Publishing

URL: https://doi.org/10.1177/11786302211025360

Air Pollution and Emergency Department Visits for Disease of the Genitourinary System

Environmental Health Insights
Volume 15: 1–10

DOI: 10.1177/11786302211025360
SAGE

Mieczysław Szyszkowicz[1], Stephanie Schoen[1] and Nicholas de Angelis[2]

[1]Environmental Health Science and Research Bureau, Health Canada, Ottawa, ON, Canada.
[2]Biomedical Program, Department of Mechanical and Aerospace Engineering, Carleton University, Ottawa, ON, Canada.

ABSTRACT: The aim of this study is to determine associations between ambient air pollution and the number of emergency department (ED) visits for diseases of the genitourinary tract in Toronto, Canada. We used the National Ambulatory Care Reporting System (NACRS) database to obtain the related ED visits and developed statistical models using daily data on ED visits, temperature, relative humidity, and outdoor air pollution concentration levels. The NACRS database contains data on hospital-based and community-based ambulatory care. The environmental data were retrieved from the National Air Pollution Surveillance (NAPS) program. The NAPS is the main source of ambient air quality data in Canada. We considered 2 air quality health indexes and 6 air pollutants: daily means of fine particulate matter $PM_{2.5}$, O_3, CO, NO_2, SO_2, and also maximum 8-hour average ozone. For every air pollutant, we fit 270 models (15 lags × 18 strata). We found that same-day air pollution concentrations have the highest number of statistically significantly positive associations with ED visits for genitourinary health outcomes. A total of 133 positive associations were identified over the 14 days lag. In subgroup (strata) analysis, females older than 60 years of age were found to have the most positive associations. In particular, nitrogen dioxide was found to be highly associated with ED visits for females over 60; an increase in NO_2 was associated with an increased relative risk (RR) of ED visits when lagged over 0, 1, and 2 days (RR = 1.040 [95% confidence interval: 1.028, 1.052], 1.020 [1.009, 1.032], and 1.025 [1.013, 1.036], respectively). The values of risks are reported for a 1 interquartile range increase in concentration (8.8 ppb). Our results suggest that urban ambient air pollution affect the number of ED visits due to genitourinary system conditions.

KEYWORDS: Air pollution, case-crossover, concentration, counts, genitourinary system, Poisson, strata, time-series

RECEIVED: December 21, 2020. **ACCEPTED:** May 27, 2021.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Mieczysław Szyszkowicz, Health Canada, 101 Tunney's Pasture, Ottawa, ON K1A 0K9, Canada. Email: mietek.szyszkowicz@canada.ca

Introduction

Ambient air pollution has been consistently associated with an increased risk in morbidity and mortality,[1-3] however the mainstream area of research in environmental epidemiology has typically considered the associations of air pollution with cardiopulmonary health problems. Over the past few years, the body of work exploring associations with other health conditions has been growing. These studies indicate that metabolic disorders, neurological disorders and dementia, depression, and suicide, may also be associated with ambient air pollution levels.[4] More recently, the association between air pollution and diseases related to kidney function have been the focus of several research studies, based on the hypothesis that kidney function may also be impacted by increases in inflammation caused by air pollution.[5]

Acute changes and increases in ambient air pollution have been associated with increased hospital admissions for issues resulting from imbalances in fluid and electrolytes (blood calcium or salt levels), kidney failure, chronic kidney disease, and urinary tract infection.[6,7] The association between air pollution and ED visits for urinary metabolic profile were seen in both short term[7] and long term studies.[8] At least 1 double-blind epidemiological study also supports the idea that air pollution levels influence changes in systemic metabolism.[9]

There has also been evidence in toxicological studies that ambient air pollution, especially fine particulate matter ($PM_{2.5}$) is associated with several different markers of kidney function, including estimated glomerular filtration rate (eGFR).[10]

In this study, we took a wide scope approach to investigate the potential relationship between air pollution and ED visits for genitourinary problems. All health conditions associated with ICD-10 codes N00-N99 (diseases of the genitourinary system) were qualified as a singular health outcome of interest in this study. The relationship between these health outcomes, ambient air pollution levels, and emergency department (ED) visits was investigated. The analysis is based on short- term exposure, with a 1-day exposure unit period, and exposure is lagged up to 14 days.

The relationship between these 3 parameters was quantified by assessing the daily counts of ED visits in the city of Toronto, as a measure of burden of air pollution on the genitourinary system. Based on previous epidemiological and toxicological evidence showing that air pollution may affect kidney function, we hypothesized that the number of ED visits for genitourinary issues is positively associated with ambient air pollution levels for some combinations of lags, strata, and air pollutants or air quality indexes.

Materials and Methods

Emergency department visits (ICD-10 codes: N00-N99)

The health outcome of interest in this study was emergency department (ED) visits for genitourinary system in Toronto, Canada between April 2004 and December 2015 (spanning 4292 days). The health data were retrieved from the National Ambulatory Care Reporting System database,[11] a health information system for ED cases in Canada. Toronto was chosen for analysis in this study because it represents the largest urban center in Canada. In the year 2016, the enumerated population of Toronto was 2 731 571 people. This census based estimation shows 6.2% population percentage change between the years 2011 and 2016. The NACRS database contains information for more than 97% of the ED visits in the province of Ontario, including sex, age, and date of ED visit. The NACRS database is accessible through Health Canada. The database was queried by using the International Classification of Diseases, Tenth Edition (ICD-10) codes N00 to N99 (Chapter XIV called "Diseases of the genitourinary system") for ED visits. Only primary causes of the ED visits were considered and used to establish the related health problems. The cases meeting this criterion were then summarized and used in the study as daily counts. The data were analyzed by the predefined strata; by sex (all, female, male), by season (warm: April-September, cold: October-March), age group ([0-10], [11-60], [61-61+]). Together 18 strata were defined and used in the study.

Air pollution data

The air pollution concentrations were measured and collected by the National Air Pollution Surveillance (NAPS) program, maintained by Environment and Climate Change Canada (Environment and Climate Change Canada).[12] Hourly data from 7 air pollution monitor stations were averaged to get daily estimates of air pollution concentrations. The final data set used in the study contained both daily values of air pollutant levels and weather conditions (temperature, relative humidity); the same data set has been used in other studies assessing ambient air pollution exposure and short term mortality risks and excess mortality in Toronto.[13] SAS Enterprise Guide 7.1 software (SAS Institute, Cary, NC) was applied to merge 2 data sets: environmental, including meteorological and air pollution data, with daily ED visits.

Six ambient air pollutants were assessed in this study: carbon monoxide (CO), nitrogen dioxide (NO_2), 2 measurements of ground-level ozone (O_3, as a daily average, and O_3H8, as a maximum 8 hour average of ozone), fine particulate matter ($PM_{2.5}$), and sulfur dioxide (SO_2). The same exposure was assigned to all selected individuals. Postal codes (6 characters) were applied as the only geographic identifier. The study area is well defined by using the census division structure. The map which shows the population density and the location of the monitors is provided (see the file TorontoMapStation2015.jpg at https://github.com/szyszkowiczm/ResultsToronto).

In addition to these 6 individual air pollutants, the Air Quality Health Index (AQHI), an index based on 3 individual ambient air pollutants considered together (O_3, NO_2, and $PM_{2.5}$), was also examined. The AQHI was developed to estimate the increased risk associated with ambient air pollution and is based on mortality rates in large Canadian cities,[14] determined according to the formula

$$AQHI = \frac{1000}{10.4} \times \begin{pmatrix} e^{0.000537*O3} + e^{0.000871*NO2} \\ +e^{0.000487*PM2.5} - 3 \end{pmatrix}.$$

While these values are rounded and presented as integer numbers on a scale (1-10, 10+) to communicate the risk related to ambient air quality to the Canadian public, in this study, continuous values generated by the above formula were applied. In addition, another version of the index, called here the AQHIX, was estimated using O_3H8 concentration levels and the above formula. The AQHIX index has a higher weighting for ozone among its 3 air pollutant components as compared to the standard AQHI index. The calculated indexes were used to investigate multipollutant exposures and the models for the indexes were constructed separately.

Statistical analysis

We used case-crossover technique to investigate the association between air pollutant exposure and ED visits for genitourinary complaints. The design of the case-crossover (CC) technique applied in this study controls for all measured and unmeasured time-invariant confounders, such as socioeconomic status, smoking, and comorbidity.[15] In the constructed models, temperature and relative humidity were incorporated in the form of natural splines with 3 degrees of freedom. The time-stratified approach was used to group the data by the same day of week in 1 common month.[16] The coefficients (slope, Beta) and their standard errors related to air pollutants were determined and used to calculate the relative risk of ED visit. The statistical calculations were completed using conditional Poisson regression models.[17-20] The daily counts were grouped according to the CC methodology, but rather than conditional logistic regression using individual events, conditional Poisson regression using daily counts was applied. The calculations were completed in R using the procedure gnm (generalized nonlinear models)[21] with the option "quasipoisson" to adjust for overdispersion.[22] The realized models have the following form

$$\text{modelH} <- \text{gnm}\begin{pmatrix} \text{EDCount} \sim \text{AirPL} \\ + \text{ns}(\text{TempL},3) + \text{ns}(\text{RHumL},3), \\ \text{data} = \text{dataAMH}, \\ \text{family} = \text{quasipoisson}, \\ \text{eliminate} = \text{factor}(\text{Dcluster}) \end{pmatrix}.$$

Table 1. Statistics on ED visits for disease of the genitourinary system (ICD-10 codes: N00-N99). Toronto, Canada, April 2004 to December 2015.

STRATA	ED VISITS	MIN	Q1	MEDIAN	MEAN	Q3	MAX
All	882918	69	138	221	205.7	251	403
Female	531876	39	89	132	123.9	152	233
Male	351042	15	48	85	81.8	102	195
Warm all	460044	75	142	225	209.5	253	403
Warm female	277806	39	93	134	126.5	153	223
Warm male	182238	15	49	86	83.0	103	195
Cold all	422874	69	131	217	201.8	248	390
Cold female	254070	44	85	129	121.2	149	233
Cold male	168804	17	46	84	80.5	100	192
Age 0-10 all	28579	0	5	6	6.7	8	20
Age 0-10 female	12901	0	2	3	3.0	4	12
Age 0-10 male	15678	0	2	3	3.7	5	17
Age 11-60 all	547864	41	89	137	127.6	156	231
Age 11-60 female	384360	30	64	96	89.6	110	174
Age 11-60 male	163504	5	27	39	38.1	47	92
Age 60+ all	306475	10	40	74	71.4	89	173
Age 60+ female	134615	3	22	31	31.4	39	74
Age 60+ male	171860	2	19	41	40.0	52	112

Max, maximum; Min, minimum.
Column labeled as "ED visits" shows the number of ED visits, Warm: April to September, Cold: October to March, Q1-25th percentile, Q3-75th percentile.

Here, EDCount represents daily counts of ED visits, AirPL, TempL, and RHumL represent air pollutants, temperature, and relative humidity, respectively. These variables are lagged in reference to the date of ED visit. In the constructed models meteorological factors are represented by natural splines (ns). Temperature and humidity may affect health conditions and also are correlated with air pollutants. These weather factors are included in the models related various environmental epidemiology studies. The dataset dataAMH contains daily ED visit counts and daily values of air pollution concentration levels and meteorological factors. Hierarchical clusters were constructed and their structure is represented by the Dcluster factor variable and is defined in the R code as Dcluster = as.factor (Year: Month: Day-of-Week). This variable plays very important role as this factor controls time in the considered time-series type of the data. The coefficient related to air pollutant and its standard error are retrieved from the fitted models. They are used to calculate risks and their corresponding confidence intervals.

In total, we tested 2160 statistical models (15 lags × 18 strata × 8 air pollutants}. A P-value <.05 was considered statistically significant.

Ethics

The Health Canada Research Ethic Board determined that the study is institutional review board exempt, given that patient data were pre-existing and de-identified.

Results

Over the studied period, 882 918 ED visits were identified with ICD-10 codes N00 to N99 (Chapter XIV called "Diseases of the genitourinary system") as a primary cause of visit in Toronto-area hospitals. 531 876 (60.2%) of the visits were by females and 351 042 (39.8%) by males. The time unit in this work is 1 day. All the statistics are reported for the period of 4292 days. Table 1 summarizes the statistics on the daily counts of ED visits by the 18 strata used. In the warm period (April-September), there were 460 044 (52.1%) visits, compared to 422 874 (47.9%) ED visits in the cold period (October-March). There were 28 579 (3.2%) visits by children under 11 years of age, 547 864 (62.1%) visits by persons between 11 and 60 years of age, and 306 475 (34.7%) visits among older individuals. Table 2 summarizes the statistics on ambient air pollutants, temperature, and relative humidity for the considered period of

Table 2. Statistics on environmental factors. Toronto, Canada, 2004 to 2015.

VARIABLE	UNITS	MIN	Q1	MEDIAN	MEAN	Q3	MAX
$PM_{2.5}$	μg/m³	0.1	4.7	7.1	8.9	11.2	65.5
NO_2	ppb	3.2	11.1	15.0	16.1	19.9	59.8
O_3	ppb	1.7	16.8	23.0	23.5	29.6	62.1
O_3H_8	ppb	9.0	33.0	41.0	43.7	52.0	107.0
SO_2	ppb	−0.5	0.5	1.0	1.4	1.7	12.0
CO	ppm	0.0	0.2	0.2	0.3	0.3	1.1
AQHI	number	1.0	2.4	2.9	3.0	3.4	7.6
AQHIX	number	1.6	3.6	4.2	4.4	5.1	10.3
Temperature	°C	−22.2	1.7	10.0	9.5	18.4	31.2
Relative humidity	%	31.7	63.9	70.9	70.7	78.2	98.8

Max, maximum; Min, minimum.
Q1-25th percentile, Q3-75th percentile.

Lag	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
All	4	2	0	0	0	0	0	0	1	0	0	0	0	0	0	7
Female	4	0	0	0	0	1	0	0	1	0	0	0	0	0	0	6
Male	3	3	1	0	0	0	0	0	0	0	0	0	0	1	0	8
Warm All	5	1	2	0	1	1	0	1	1	0	0	0	0	1	0	13
Warm Female	5	0	2	0	0	2	0	0	1	1	1	0	0	0	0	12
Warm Male	3	0	1	0	1	0	0	1	1	0	0	0	0	0	0	7
Cold All	3	0	0	0	0	0	0	0	0	0	0	0	0	0	1	4
Cold Female	3	0	0	0	0	0	0	0	0	0	0	0	0	0	1	4
Cold Male	3	2	0	0	0	0	0	0	0	0	0	0	0	2	0	7
Age 0-10 All	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Age 0-10 Female	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Age 0-10 Male	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	2
Age 11-60 All	3	0	0	0	0	0	0	0	0	0	0	0	1	0	0	4
Age 11-60 Female	2	0	0	0	0	0	0	0	1	0	0	0	0	0	0	3
Age 11-60 Male	2	1	0	0	0	0	0	1	0	0	0	0	0	0	0	4
Age 60+All	5	4	3	0	0	1	0	0	2	0	0	0	0	0	1	16
Age 60+ Female	6	4	7	0	0	4	0	0	3	0	0	0	0	0	0	24
Age 60+ Male	4	3	2	0	0	0	0	0	1	0	0	0	0	0	1	11
Total	56	20	19	0	2	9	0	3	12	1	1	0	2	4	4	133

Figure 1. All pollutants combined. Total frequencies of positive associations: strata (rows), lags (columns). Toronto, Canada. 2004 to 2015.

the study. Mean daily values for $PM_{2.5}$, NO_2, SO_2, and O_3 were all below the WHO guidelines for ambient air pollution.[23]

Figures 1 to 3 show the frequencies of positive statistical significance associations (the Beta coefficient is positive) obtained for combinations of strata, air pollutant, and lag, given in the rows and columns. The cells show the total number of such associations. For example, the value for a cell with row identified as "All" and a column identified as "lag 0" gives the number of positive associations among all models (4). The colors in Figures 1 to 3 are applied to distinguish and emphasis the patterns of the association. The colors group the same number of the associations. The figures from 1 to 3 show the summary results for all pollutants, strata, and lags, respectively. The figures present values on the 2D planes as a sort of projections where all results are in 3D space.

Figure 1 is organized with the 18 population strata in rows and 15 lags in columns and visualizes the counts of positive statistically significant associations for the strata and lags for all pollutants combined. The concentrations lagged by 0 to 2 days had the most associations with hospitalization, representing a

Lag	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
AQHI	12	4	2	0	0	1	0	0	1	0	0	0	0	0	0	20
AQHIX	15	6	5	0	0	1	0	0	0	0	0	0	0	0	0	27
CO	7	0	3	0	0	0	0	0	9	0	0	0	0	0	0	19
NO_2	16	8	5	0	0	1	0	0	0	0	0	0	0	0	0	30
O_3	0	0	0	0	0	1	0	3	0	0	0	0	1	2	4	11
O_3H8	0	0	2	0	0	5	0	0	0	0	0	0	1	1	0	9
$PM_{2.5}$	1	2	1	0	2	0	0	0	2	1	1	0	0	1	0	11
SO_2	5	0	1	0	0	0	0	0	0	0	0	0	0	0	0	6
Total	56	20	19	0	2	9	0	3	12	1	1	0	2	4	4	133

Figure 2. All strata combined. Total frequencies of positive associations: air pollutants (rows), lags (columns). Toronto, Canada. 2004 to 2015.

Air Pollutant:	AQHI	AQHIX	CO	NO2	O3	O3H8	PM2.5	SO2	Total
All	1	2	2	2	0	0	0	0	7
Female	1	1	2	1	0	1	0	0	6
Male	2	2	0	3	1	0	0	0	8
Warm All	1	2	3	2	1	1	2	1	13
Warm Female	1	2	2	1	1	2	2	1	12
Warm Male	0	1	3	1	1	0	1	0	7
Cold All	1	1	0	1	1	0	0	0	4
Cold Female	1	1	0	1	1	0	0	0	4
Cold Male	1	2	0	2	1	1	0	0	7
Age 0-10 All	0	0	0	1	0	0	0	0	1
Age 0-10 Female	0	0	0	0	0	0	0	0	0
Age 0-10 Male	0	0	0	1	1	0	0	0	2
Age 11-60 All	1	1	0	1	0	1	0	0	4
Age 11-60 Female	0	1	1	1	0	0	0	0	3
Age 11-60 Male	0	1	0	2	1	0	0	0	4
Age 60+All	3	3	2	3	1	1	2	1	16
Age 60+ Female	5	4	3	4	0	2	4	2	24
Age 60+ Male	2	3	1	3	1	0	0	1	11
Total	20	27	19	30	11	9	11	6	133

Figure 3. All lags combined. Total frequencies of positive associations: strata (rows), air pollutants (columns). Toronto, Canada. 2004 to 2015.

respective 56, 20, and 19 positive associations among all 133 associations identified.

Figure 2 is organized with 8 air pollutants in rows and 15 lags in columns for all strata combined. Figure 2 indicates that nitrogen dioxide (NO_2) has the highest number of positive statistically significant associations. In total, there are 30 positive associations for NO_2, as well as 27 and 20 associations with the indexes: AQHIX and AQHI, respectively. $PM_{2.5}$, often identified in other studies as a pollutant associated with kidney-related injury, only demonstrated 11 associations.

Figure 3 shows 18 population strata in rows and the 8 air pollutants in columns for all lag days combined. The greatest number of associations (24) was observed in female patients older than 60 years of age.

Figure 4 is a map to the table with numerical values (slope and its standard error). For each air pollutant, Figure 4 shows the associations as values: 0 if there is no association, 1 if there is a positive statistically significant association (associated with higher risk of hospitalization), and −1 if there is a negative statistically significant association (associated with lower risk of hospitalization). Colors are used to emphasize these relations (white, red, and green, respectively). The columns are lags from 0 to 14. The corresponding numerical values (Beta and its standard error) are available in Supplemental Materials (see the file URINARYToronto.csv at https://github.com/szyszkowiczm/ResultsToronto). In this study, the values of relative risks are not presented directly as so many models were tested. The provided values (in total 2160) of the coefficients and their standard errors allow us to determine the corresponding *P*-values. These values can be applied to categorize the associations as being statistically significant or not at an assumed level. For example, using a P-value $<.05$ 133 RR values were statistically positively significant, while 37 RR values remain statistically positively significant when P-value was set at $<.001$.

As nitrogen dioxide shows the highest number of positive associations among considered air pollutants, the relative risks were calculated for its concentration increase. Table 3 summarizes the RR values and 95% CIs estimated for a 1 IQR (8.8 ppb) increase in exposure lagged by 0 to 2 days. Statistically significant increases in risk of ED visit for genitourinary complaints were seen for all lags in individuals over 60 years of age (All, males only, and females only), and for males (all ages).

Figure 5 (a forest plot) shows the estimated RR values and their corresponding 95% CIs for a 1 IQR (=1) increase of the AQHI level. The AQHI is a health protection tool and its values are communicated to public. It is a scale developed to help the individuals make decisions to reduce their outdoor activities to limit short-term exposure to air pollution. In our study we use it also as a mimic of multi-pollutant exposure. The

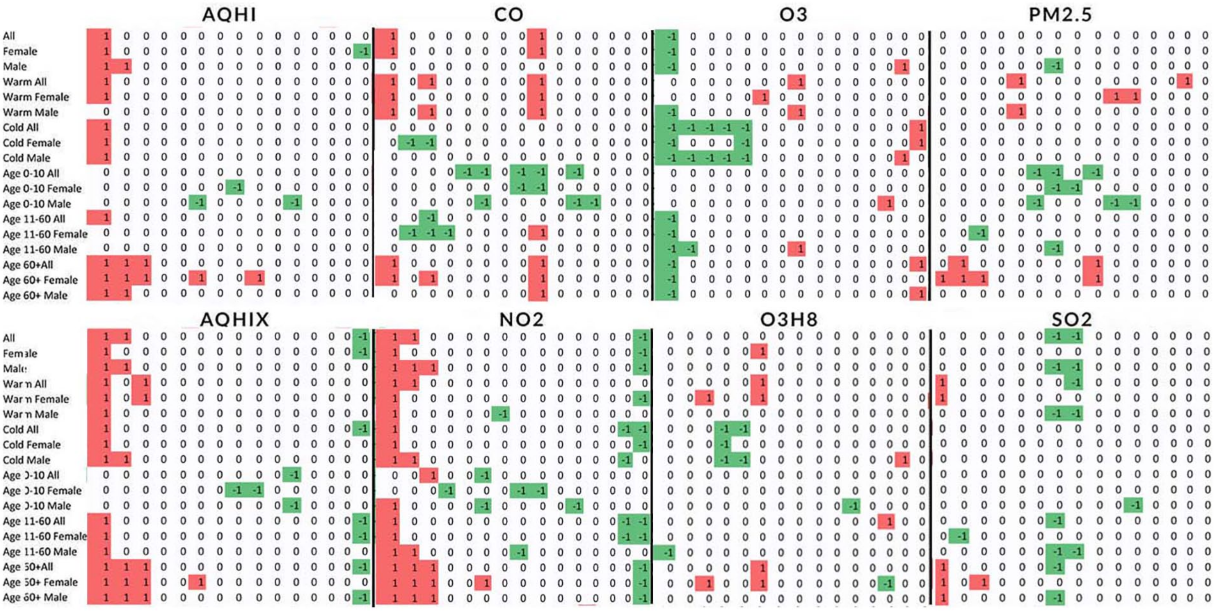

Figure 4. A map to numerical results; strata (rows), lags (columns). 0/white – no associations, and statistically significant: –1/green – negative, 1/red – positive. The results are grouped by air pollutants. Toronto, Canada. 2004 to 2015.

Table 3. Estimated RRs and their 95% confidence intervals (95% CI) CIs for an increase of concentration of nitrogen dioxide (NO_2) by 1 interquartile range (IQR = 8.8 ppb). Toronto, Canada, April 2004 to December 2015.

EXPOSURE BY LAGS:	LAG 0		LAG 1		LAG 2	
STRATA	RR	95% CI	RR	95% CI	RR	95% CI
All	1.029	(1.021, 1.037)	1.011	(1.003, 1.019)	1.006	(0.999, 1.014)
Female	1.026	(1.018, 1.034)	1.006	(0.998, 1.014)	1.003	(0.995, 1.011)
Male	1.033	(1.023, 1.043)	1.017	(1.007, 1.028)	1.011	(1.001, 1.021)
Warm all	1.031	(1.020, 1.043)	1.012	(1.001, 1.023)	1.011	(0.999, 1.023)
Warm female	1.030	(1.018, 1.042)	1.011	(0.999, 1.023)	1.010	(0.999, 1.022)
Warm male	1.033	(1.018, 1.049)	1.014	(0.999, 1.029)	1.012	(0.996, 1.027)
Cold all	1.027	(1.017, 1.038)	1.011	(1.000, 1.021)	1.005	(0.994, 1.016)
Cold female	1.024	(1.013, 1.035)	1.004	(0.993, 1.015)	1.000	(0.989, 1.011)
Cold male	1.033	(1.019, 1.046)	1.02	(1.006, 1.034)	1.012	(0.999, 1.026)
Age 0-10 all	1.014	(0.991, 1.037)	0.993	(0.971, 1.016)	1.026	(1.003, 1.049)
Age 0-10 female	0.981	(0.948, 1.014)	0.980	(0.947, 1.013)	1.020	(0.987, 1.055)
Age 0-10 male	1.039	(1.008, 1.072)	1.003	(0.973, 1.035)	1.030	(0.999, 1.062)
Age 11-60 all	1.024	(1.016, 1.031)	1.006	(0.998, 1.014)	0.998	(0.990, 1.006)
Age 11-60 female	1.022	(1.014, 1.031)	1.002	(0.994, 1.011)	0.995	(0.986, 1.003)
Age 11-60 male	1.026	(1.016, 1.037)	1.014	(1.004, 1.025)	1.006	(0.995, 1.017)
Age 60+ all	1.039	(1.028, 1.050)	1.021	(1.010, 1.032)	1.019	(1.008, 1.030)
Age 60+ female	1.040	(1.028, 1.052)	1.020	(1.009, 1.032)	1.025	(1.013, 1.036)
Age 60+ male	1.038	(1.025, 1.051)	1.022	(1.008, 1.035)	1.015	(1.002, 1.028)

95% CI, 95% Confidence Interval; RR, Relative Risk.
Warm: April to September, Cold: October to March.

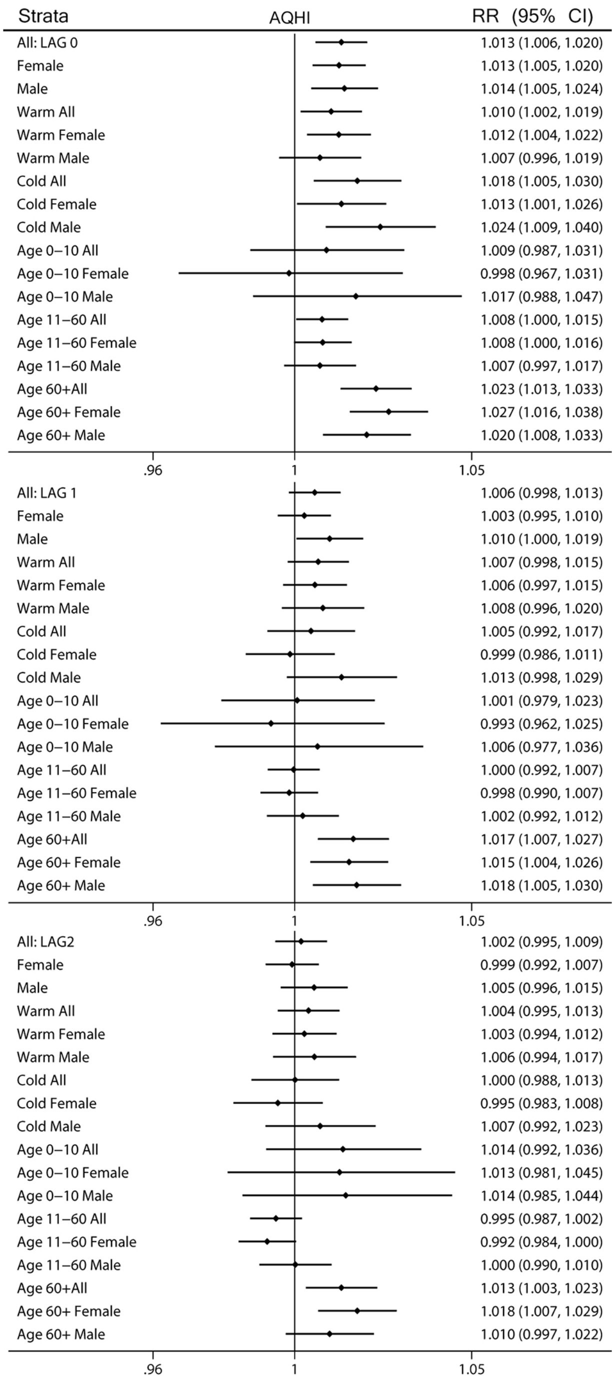

Figure 5. Relative risks (RR) and their 95% confidence intervals (95% CI) for a 1 IQR increase for the AQHI level.

results are presented for lags 0 to 2 for all defined strata. The results indicate the age group (60, 60+) as the most effected by the acute changes in the AQHI levels.

Table 4 summarizes 14 most frequent diagnosed ED visits. This table provides information on the structure of the considered ED daily counts in the Chapter XIV.

Discussion

The results observed in this study suggest that increases in air pollution concentration may be associated with higher ED visit rates for genitourinary concerns in Toronto, Canada, particularly for older populations. There appears to be an association between the risk of ED visits and an increase in ambient NO_2 concentration for exposure lagged by 0 to 2 days. Unlike many previously published studies, this study found that NO_2 is most frequently associated with adverse health outcomes. $PM_{2.5}$ has been more commonly associated with negative effects on health related to the genitourinary system, particularly in the case of chronic kidney disease and progression.[6,8] In our study, $PM_{2.5}$ was one of the least commonly associated air pollutants.

Our findings are similar to those in a Taiwanese study of urban-dwelling seniors (age 65+), which found that increased NO_2 exposure over 1 year was associated with a decrease in eGFR rates, as well as an increased risk of chronic kidney disease (CKD) progression.[8] Two cross sectional studies of adults in South Korea also found associations between annual average NO_2 and decreased eGFR.[24,25] While these studies focused on kidney-specific problems, our study considers the entire 14th ICD-10 chapter (ICD-10 codes N00-N99), which includes female breast complaints, male and female genital and pelvic organ conditions. Therefore, we are studying not only kidney problems, but also genital and pelvic problems or others under common classification. This might be one of the reasons that our results are different from those reported in literature.

$PM_{2.5}$ has more readily been associated with general reasons for ED admissions. In a large study of Medicaid claims in the United States over the span of 12 years (2000-2012), $PM_{2.5}$ was associated with an increase in hospital admissions for urinary tract infections (UTI; ICD 10 code N39), acute and unspecified renal failure (ICD 10 code N17), and fluid and electrolyte disorders.[7] The population in the Wei et al[7] study was older (all over age 65) than the population observed in our study, and assessed the impact of only $PM_{2.5}$ on all hospital admissions, whereas we investigated 6 individual air pollutants and 2 indexes. Similarly, Lin et al[26] found that increased ambient $PM_{2.5}$ concentrations were associated with an increase in hospitalization for nephrotic syndrome. They also found that individuals with the highest quartile of exposure to SO_2 had twice the risk of hospitalization for nephrotic syndrome compared to the lowest quartile of exposure. A study of hospital admissions in Italy[27] found that an increase in $PM_{2.5}$ was associated with higher hospitalizations for bladder cancer (ICD-9 code 188) and kidney cancer (ICD-9 code 189).

Increased $PM_{2.5}$ has also been associated with a decrease in eGFR in several studies[8,25,28,29] and an increased risk of having CKD, CKD progression, and excess death related to CKD.[6,8,29,30] Conversely, there have also been several studies that found null associations between $PM_{2.5}$ and kidney function; Yang et al[31] found no association between $PM_{2.5}$ and eGFR or CKD incidence in a population of adults in Taipei city. Given that our patient population contains individuals with a wide spectrum of genitourinary diseases (not limited to kidney disease), some associations assessed can be different than those reported in studies restricted to kidney health problems.

Table 4. The most frequent ED visits diagnosed with the ICD-10 codes in the range N00 to N99. Toronto, Canada, 2004 to 2015.

DESCRIPTION	ICD10	COUNTS	%
Other disorders of urinary system	N39	210 581	23.9
Chronic kidney disease	N18	65 811	7.5
Unspecified renal colic	N23	58 673	6.7
Hyperplasia of prostate	N40	54 709	6.2
Calculus of kidney and ureter	N20	44 183	5.0
Other abnormal uterine and vaginal bleeding	N93	36 961	4.2
Dysplasia of cervix uteri	N87	30 658	3.5
Cystitis	N30	24 023	2.7
Noninflammatory disorders of ovary	N83	23 238	2.6
Urethral stricture	N35	22 396	2.5
Polyp of female genital tract	N84	21 619	2.5
Excessive, frequent and irregular menstruation	N92	21 030	2.4
Tubulo-interstitial nephritis, not specified as acute or chronic	N12	20 442	2.3
Other disorders of bladder	N32	20 426	2.3

Our finding of an increased risk of ED visits most common at lag 0 to 2 days agrees with findings from the United States that examined $PM_{2.5}$ at lags 0 to 1.[7] Most other studies that have investigated endpoints relating to the genitourinary system have used average air pollution values over months or years.[6,8,24,27,30,32,33]

When examining the highest frequency cause of visits within the ICD-10 chapter (Table 4), it is found that the most common causes for ED visits are N39 (Other diseases of the urinary system) and N18 (Chronic kidney disease). N39 consists of many different conditions such as various types of incontinence or UTI, and therefore it is difficult to relate air pollution to a particular sub-group of this code. However, chronic kidney disease may be impacted by air pollution, given that CKD is sensitive to changes in blood pressure. High blood pressure is among the 2 most common causes of CKD (the other being high blood glucose), and many studies have shown that air pollution can have an impact on elevated blood pressure.[34,35] Given that CKD interferes with the release of hormones controlling blood pressure, episodes of hypertension may be the reason behind an ED visit, whose underlying cause is kidney damage.

This study fills a knowledge gap in terms of the number of ED visits using high-level data on genitourinary complaints, which would include concerns such as kidney disease. While this study focuses on high-level groupings of diagnoses, there have been numerous recent studies[7] that have found a relationship between ambient air pollution and a variety of kidney function and disease measurements, which would be captured in visits to the ED for diseases of the genitourinary system.

The specific mechanism by which air pollution is related to genitourinary concerns is believed to be related to inflammation. There are many published papers on air pollution causing inflammation and oxidative stress in experimental and epidemiological panel studies.[36,37] One small randomized control trial in China looked at changes in the urinary metabolome associated with reducing $PM_{2.5}$ using air filters, and found that in the experimental condition with higher particulate matter, subjects had biomarkers that suggested higher inflammation.[9] Toxicological evidence in mice also suggests that an increase in $PM_{2.5}$ exposure may be associated with signs of fibrosis in kidney tissues (a response to chronic inflammation), as well as capillary congestion and a reduction in glomerular urinary space.[10] Other common arguments suggest that air pollutants may increase the occurrence of bacteria, viruses, or other pathogens in ambient air,[38] and that ambient air pollution may act as an immunosuppressive factor that can undermine the normal human body defenses.[39,40]

There are some limitations in our study. Our study relied on ICD-10 codes for diagnostic information. This code group includes diagnosis such as Disorders of the Breast (ICD codes N60-N65) that are unlikely to be related to air pollution. In addition, using ICD-10 codes may have led to missing cases in our study, although this would be unlikely to differ by air pollution levels. One review of ICD-9 codes related to kidney diseases also determined that renal disease codes have good specificity (⩾90%) but poor sensitivity (not coded kidney disease if kidney disease is present).[41] While ICD-10 coding improves on ICD-9 codes, it is likely that there may still be concerns related to sensitivity. Our study had many subgroup analyses, but we did not stratify for education, income, race, and may have missed associations related to a high-risk group as a result. Studies in US populations have found that minority communities, particularly non-Hispanic Black and African American individuals, are significantly more likely to experience a higher burden of death related to air pollution.[6] The exposure assessment in this study is based on 7 (9) fixed monitors in Toronto, which will not fully reflect the full variation in concentration levels among individuals living in the large city. The land area considered in this study is 630.2 km^2. The enumerated population of Toronto is assessed as 2.7 million people. We estimated, that the majority of patients were all living within 5 to 8 km radius from an air pollution monitor. Another potential risk of inaccurate results comes from the administratively ascertained ED data through NARCS, which may decrease the sensitivity of the study should the primary diagnosis be falsely attributed to genitourinary causes. However, the CIHI (which manages the NARCS) uses a high-level data management process (General Statistical Business Process Model) to ensure a high accuracy and quality standard of any data published by the institute. However, given that the quality of the data is ultimately in the hands of hospitals and health care providers, the CIHI publishes many standards and tools to ensure accurate data collection at the source. Finally, we performed a high number of hypothesis tests in this study (2160), increasing the risk of false positive associations; however, groupings of significant associations for some exposures (strata and lags) and health outcomes were the focus of the results.[42]

The biological mechanisms linking air pollution and the disease of the genitourinary system is not fully understanding. In the recent publication related to the disease of kidney, Bowe et al[32] their authors wrote: "The biological mechanism or mechanisms underpinning the reported associations is not entirely clear. Several hypotheses have been proposed to explain the extra pulmonary effects of air pollution. One hypothesis suggests that inhaled pollutants might lead to pulmonary inflammation, which could then trigger systemic inflammation. The second hypothesis posits that pollutants might provoke the lung autonomic nervous system. The third (and most widely accepted) hypothesis postulates that air pollutants might traverse the alveolar space and enter the bloodstream where they can produce an untoward effect on remote organs."

The main purpose of the presented work was to investigate the associations between the number of ED visits for disease of the genitourinary system and urban ambient air pollution. Among 2160 constructed models, 133 of them show positive statistically significant associations. This represents only 6% of the all tested correlations; 71% of all observed positive relationships hold for lag between 0 and 2 days. In such a large number of tests, the main approach is to identify patterns of the relationships. It is expected, if the associations do really exist, to see some confirmations for the used strata, lags, or air pollutants. Here, air pollution concentrations lagged by 0 to 2 days have the highest number of significant associations.

This study provides support that higher concentrations of ambient air pollution are associated with increased risk of the disease of the genitourinary system. The study uses the adequate statistical models, a good quality and well defined health (daily ED visits) and environmental data. Numerical values (slopes and their standard errors) are given for all constructed models. We proposed an approach of the "massive" calculations by air pollutants, their lags and strata. The created maps of allow to identify the patterns of the relations. The presented method can be applied in other locations to confirm the consistency of the obtained findings.

Conclusion

Ambient air pollution exposure from the same day as ED visits, showed the largest number of positive associations. The presence of nitrogen dioxide in the ambient air in particular had largest number of the positive associations among air pollutants and indexes, where AQHIX shows the second largest number of such associations. In conclusion, urban ambient air pollution may be related to an increased number of ED visits for genitourinary issues. The effects are mostly visible for older persons.

Acknowledgements

The author acknowledges Environment and Climate Change Canada for providing the air pollution data from the National Air Pollution Surveillance (NAPS) network. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed herein are not necessarily those of CIHI.

ORCID iD

Mieczysław Szyszkowicz https://orcid.org/0000-0001-7022-3267

REFERENCES

1. Burbank AJ, Peden DB. Assessing the impact of air pollution on childhood asthma morbidity: how, when, and what to do. *Curr Opin Allergy Clin Immunol*. 2018;18:124–131.
2. Burnett R, Chen H, Szyszkowicz M, et al. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci*. 2018;115:9592-9597.
3. Szyszkowicz M, Thomson EM, Colman I, Rowe BH. Ambient air pollution exposure and emergency department visits for substance abuse. *PLoS One*. 2018;13:e0199826.
4. Szyszkowicz M, Zemek R, Colman I, et al. Air pollution and emergency department visits for mental disorders among youth. *Int J Environ Res Public Health*. 2020;17:4190.
5. Afsar B, Elsurer Afsar R, Kanbay A, et al. Air pollution and kidney disease: review of current evidence. *Clin Kidney J*. 2019;12:19-32.
6. Bowe B, Xie Y, Yan Y, Al-Aly Z. Burden of cause-specific mortality associated with PM2.5 air pollution in the United States. *JAMA Netw Open*. 2019;2:e1915834.
7. Wei Y, Wang Y, Di Q, et al. Short term exposure to fine particulate matter and hospital admission risks and costs in the Medicare population: time stratified, case crossover study. *BMJ*. 2019;367:l6258.
8. Chen SY, Chu DC, Lee JH, Yang YR, Chan CC. Traffic-related air pollution associated with chronic kidney disease among elderly residents in Taipei City. *Environ Pollut*. 2018;234:838-845.
9. Chen C, Li H, Niu Y, et al. Impact of short-term exposure to fine particulate matter air pollution on urinary metabolome: a randomized, double-blind, crossover trial. *Environ Int*. 2019;130:104878.

10. Tavera Busso I, Mateos AC, Juncos I, et al. Kidney damage induced by subchronic fine particulate matter exposure. *Environ Int*. 2018;121:635–642.
11. NACRS. The National Ambulatory Care reporting system. Published 2020. https://www.cihi.ca/en/national-ambulatory-care-reporting-system-metadata
12. NAPS. Environment and climate change Canada. National Air Pollution Surveillance Program. Published 2020. http://maps-cartes.ec.gc.ca/rnspa-naps/data.aspx
13. Vicedo-Cabrera AM, Sera F, Liu C, et al. Short term association between ozone and mortality: global two stage time series study in 406 locations in 20 countries. *BMJ*. 2020;368:m108.
14. Stieb DM, Burnett RT, Smith-Doiron M, et al. 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.
15. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133:144–153.
16. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiology*. 2005;16:717–726.
17. Szyszkowicz M. Use of generalized linear mixed models to examine the association between air pollution and health outcomes. *Int J Occup Med Environ Health*. 2006;19:224–227.
18. Armstrong BG, Gasparrini A, Tobias A. Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. *BMC Med Res Methodol*. 2014;14:122.
19. Szyszkowicz M. Case-crossover method with a short time-window. *Int J Environ Res Public Health*. 2019;17:202.
20. Szyszkowicz M. Use of two-point models in "Model choice in time-series studies of air pollution and mortality." *Air Qual Atmos Health*. 2020;13:225–232.
21. Turner H, Firth D. Generalized nonlinear models in R: an overview of the GNM package. For GNM version 1.1-1. Published February 2, 2020. https://cran.r-project.org/web/packages/gnm/vignettes/gnmOverview.pdf
22. R Core Team. R: a language and environment for statistical computing. Published 2018. http://www.r-project.org/
23. World Health Organization. WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide: global update 2005. Published 2005. https://doi.org/10.1016/0004-6981(88)90109-6
24. Kim H-J, Min J-Y, Seo Y-S, Min K-B. Association between exposure to ambient air pollution and renal function in Korean adults. *Ann Occup Environ Med*. 2018;30:14.
25. Jeong SM, Park JH, Kim HJ, Kwon H, Hwang SE. Effects of abdominal obesity on the association between air pollution and kidney function. *Int J Obes*. 2020;44:1568-1576.
26. Lin SY, Hsu WH, Lin CL, et al. Association of exposure to fine-particulate air pollution and acidic gases with incidence of nephrotic syndrome. *Int J Environ Res Public Health*. 2018;15:2860.
27. Gandini M, Scarinzi C, Bande S, et al. Long term effect of air pollution on incident hospital admissions: results from the Italian Longitudinal Study within LIFE MED HISS project. *Environ Int*. 2018;121:1087-1097.
28. Bowe B, Xie Y, Li T, et al. Particulate matter air pollution and the risk of incident CKD and progression to ESRD. *J Am Soc Nephrol*. 2018;29:218-230.
29. Blum MF, Surapaneni A, Stewart JD, et al. Particulate matter and albuminuria, glomerular filtration rate, and incident CKD. *Clin J Am Soc Nephrol*. 2020;15:311-319.
30. Bragg-Gresham J, Morgenstern H, McClellan W, et al. County-level air quality and the prevalence of diagnosed chronic kidney disease in the US Medicare population. *PLoS One*. 2018;13:e0200612.
31. Yang YR, Chen YM, Chen SY, Chan CC. Associations between long-term particulate matter exposure and adult renal function in the Taipei metropolis. *Environ Health Perspect*. 2017;125:602-607.
32. Bowe B, Xie Y, Li T, et al. Associations of ambient coarse particulate matter, nitrogen dioxide, and carbon monoxide with the risk of kidney disease: a cohort study. *Lancet Planet Health*. 2017;1:e267-e276.
33. Wang HH, Zhang SC, Wang J, et al. Combined toxicity of outdoor air pollution on kidney function among adult women in Mianyang City, southwest China. *Chemosphere*. 2020;238:124603.
34. Ibald-Mulli A, Stieber J, Wichmann HE, Koenig W, Peters A. Effects of air pollution on blood pressure: a population-based approach. *Am J Public Health*. 2001;91:571.
35. Chuang KJ, Yan YH, Cheng TJ. Effect of air pollution on blood pressure, blood lipids, and blood sugar: a population-based approach. *J Occup Environ Med*. 2010;52:258-262.
36. Liu L, Kauri LM, Mahmud M, et al. Exposure to air pollution near a steel plant and effects on cardiovascular physiology: a randomized crossover study. *Int J Hyg Environ Health*. 2014;217:279-286.
37. Liu L, Urch B, Szyszkowicz M, et al. Influence of exposure to coarse, fine and ultrafine urban particulate matter and their biological constituents on neural biomarkers in a randomized controlled crossover study. *Environ Int*. 2017;101:89-95.
38. Frontera A, Martin C, Vlachos K, Sgubin G. Regional air pollution persistence links to COVID-19 infection zoning. *J Infect*. 2020;81:318-356.
39. Ciencewicki J, Jaspers I. Air pollution and respiratory viral infection. *Inhal Toxicol*. 2007;19:1135-1146.
40. Glencross DA, Ho TR, Camiña N, Hawrylowicz CM, Pfeffer PE. Air pollution and its effects on the immune system. *Free Radic Biol Med*. 2020;151:56-68.
41. Grams ME, Plantinga LC, Hedgeman E, et al. Validation of CKD and related conditions in existing data sets: a systematic review. *Am J Kidney Dis*. 2011;57:44-54.
42. Szyszkowicz M, de Angelis N. Ambient air pollution and emergency department visits in Toronto, Canada. *Environ Sci Pollut Res Int*. 2021;28:28789-28796.