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Associations between ambient air pollution and daily mortality in a cohort of congestive heart failure: Case-crossover and nested case-control analyses using a distributed lag nonlinear model

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ABSTRACT

Background: Persons with congestive heart failure may be at higher risk of the acute effects related to daily fluctuations in ambient air pollution. To meet some of the limitations of previous studies using grouped-analysis, we developed a cohort study of persons with congestive heart failure to estimate whether daily non-accidental mortality were associated with spatially-resolved, daily exposures to ambient nitrogen dioxide (NO_2) and ozone (O_3), and whether these associations were modified according to a series of indicators potentially reflecting complications or worsening of health.

Methods: We constructed the cohort from the linkage of administrative health databases. Daily exposure was assigned from different methods we developed previously to predict spatially-resolved, time-dependent concentrations of ambient NO_2 (all year) and O_3 (warm season) at participants' residences. We performed two distinct types of analyses: a case-crossover that contrasts the same person at different times, and a nested case-control that contrasts different persons at similar times. We modelled the effects of air pollution and weather (case-crossover only) on mortality using distributed lag nonlinear models over lags 0 to 3 days. We developed from administrative health data a series of indicators that may reflect the underlying construct of "declining health", and used interactions between these indicators and the cross-basis function for air pollutant to assess potential effect modification.

Results: The magnitude of the cumulative as well as the lag-specific estimates of association differed in many instances according to the metric of exposure. Using the back-extrapolation method, which is our preferred exposure model, we found for the case-crossover design a cumulative mean percentage changes (MPC) in daily mortality per interquartile increment in NO_2 (8.8 ppb) of 3.0% (95% CI: −0.9, 6.9%) and for O_3 (16.5 ppb) 3.5% (95% CI: −4.5, 12.1). For O_3 there was strong confounding by weather (unadjusted MPC = 7.1%; 95% CI: 1.7, 12.7%). For the nested case-control approach the cumulative MPC for NO_2 in daily mortality was 2.9% (95% CI: −0.9, 6.9%) and for O_3 7.3% (95% CI: 3.0, 11.9%). We found evidence of effect modification between daily mortality and cumulative NO_2 and O_3 according to the prescribed dose of furosemide in the nested case-control analysis, but not in the case-crossover analysis.

Conclusions: Mortality in congestive heart failure was associated with exposure to daily ambient NO_2 and O_3 predicted from a back-extrapolation method using a land use regression model from dense sampling surveys. The

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methods used to assess exposure can have considerable influence on the estimated acute health effects of the two air pollutants.

1. Introduction

The associations between ambient air pollution and acute health events (e.g., mortality, hospitalisations) have been most often investigated using grouped analyses of parallel time series or grouped case-crossover designs (Goldberg et al., 2003), which estimate marginal changes in risk when the exposure is assumed to be the same across individuals living in a geographically circumscribed area (Lu et al., 2008; Lu and Zeger, 2007; Thomas, 2009). In these types of studies, the objective is to determine whether there are increases in the numbers of hospitalisations or deaths on the day, or the next few days, following an increase in the level of air pollution.

A limitation of these types of studies is that they rely on aggregated data, thus providing limited or no information on individual risk factors and not accounting for individual characteristics or clinical conditions that may vary on short time scales and which may confound the associations or modify the effects of air pollution (Goldberg and Burnett, 2005). An additional issue is that exposure is estimated from routine monitoring systems that are not dense enough to capture small-scale variability, particularly for air pollutants that exhibit greater spatial variability, such as some traffic-related air pollutants (Crouse et al., 2009; Deville Cavellin et al., 2016; Jerrett et al., 2007).

One group of persons that may be at higher risk of adverse health events after exposure to exogenous insults are those with congestive heart failure. In Canada, approximately 600,000 persons are affected by congestive heart failure, with 50,000 new cases diagnosed every year (Heart and stroke foundation of Canada, 2016). Epidemiological time-series and case-crossover studies, including time series of mortality conducted in Montreal (Quebec, Canada) (Goldberg et al., 2001; Goldberg et al., 2013; Goldberg et al., 2003), have reported some of the strongest positive associations between increases in ambient air pollution and daily mortality, hospitalisations and emergency department visits in people having congestive heart failure (Colais et al., 2012; Forastiere et al., 2007; Goldberg et al., 2003; Goldberg et al., 2013; Haley et al., 2009; Hsieh et al., 2013; Koken et al., 2003; Lee et al., 2007a; Lee et al., 2007b; Peel et al., 2007; Pope et al., 2008; Rappold et al., 2011; Stieb et al., 2009; Symons et al., 2006; Ueda et al., 2009; Wellenius et al., 2005; Wellenius et al., 2006; Yang, 2008; Zanobetti et al., 2009). Findings from panel studies also support that air pollution may affect health in persons with heart failure, as indicated by intermediate physiological parameters such as oxygen saturation, pulse rate and diastolic blood pressure (Goldberg et al., 2008; Goldberg et al., 2009; Goldberg et al., 2015a).

To meet some of the limitations of the studies using grouped-analysis, we developed a cohort study of persons with heart failure, with the objectives to estimate whether non-accidental mortality rates among people diagnosed with congestive heart failure were associated with spatially-resolved, daily exposures to ambient nitrogen dioxide (NO_2) and ozone (O_3), and whether these associations were modified according to a series of indicators potentially reflecting a complication or worsening in a person's health. We report herein two distinct types of analyses suitable for estimating the acute effects of air pollution, as well as estimating possible effect modification: a case-crossover design that contrasts the same person at different times, and a nested case-control design that contrasts different persons at similar times (Appendix A).

2. Methods

2.1. The cohort of persons with congestive heart failure

We included persons 65 years of age and older, who were resident of Montreal and having congestive heart failure during the study period of January 01, 1991 to December 31, 2002. We linked administrative health databases as described previously (Goldberg et al., 2013; Goldberg and Burnett, 2005). The databases covered the period 1989–2002, inclusive, and included the registration file from the universal Quebec Medicare system (Régie de l'assurance maladie du Québec, RAMQ), the hospital discharge file, the drug prescription file that included all prescriptions reimbursed during this time period by the Quebec Medicare system for individuals 65 years of age and older, the fee-for medical service file, and the mortality file. These files also include sex and date of birth, as well changes in participants' addresses, according to geographical districts defined by the first three characters of the six-character postal code. These districts represent a block face or a large apartment complex and reflect “natural neighbourhoods” (Ross et al., 2004). There were 98 three-character postal code districts in Montreal in 2001, ranging from 0.3 to 28 km^2 (average of approximately 6 km^2) depending on the population density. Appendix Fig. B1 shows the boundaries of these districts from the 2001 Census Boundary Files (Statistics Canada, 2002).

Appendix B provides a detailed description of the methods used to construct the cohort and shows a schematic of the study design (Fig. B2). Briefly, the date of initiating the cohort was January 1, 1991 and the last date of entry was January 1, 2001, thus leaving a potential of at least two years of follow-up, as the follow-up ended for all non-censored subjects on December 31, 2002. Those entering the cohort were followed until death, migration out of the Montreal area, or termination of follow-up. The cohort was dynamic and because of the information about residential locations was time-varying, it allowed for a person who moved out of Montreal to re-enter the cohort later if they moved back into the study area.

2.2. Definition of congestive heart failure

We defined congestive heart failure using algorithms developed previously (Goldberg et al., 2013): 1) a diagnosis of congestive heart failure in the hospital discharge record or; 2) one or more procedures for congestive heart failure and at least one prescription for a diuretic and digoxin or; 3) one or more procedures for congestive heart failure and at least one prescription for a diuretic and an angiotensin converting enzyme inhibitor. Congestive heart failure diagnoses and procedures were identified using the *International Classification of Diseases* (ICD), *9th Revision* codes (see Appendix Table C1 for details).

2.3. Daily estimates for ambient air pollution and weather

NO_2 and O_3 were two pollutants measured in Montreal routinely by the Canadian National Air Pollution Surveillance network of fixed-site monitors (https://www.ec.gc.ca/rnspa-naps/), administered by the City of Montreal. According to previous land use regression surfaces developed from dense sampling surveys in Montreal, NO_2 (Crouse et al., 2009) and O_3 (Deville Cavellin et al., 2016) exhibit substantial intra-urban spatial variability (predicted annual average concentrations ranging from 4.2–35.9 ppb for NO_2 and from 0 to 123 ppb for O_3.)

Errors may result when fixed-site ambient monitoring station data are used to estimate small-scale fluctuations of air pollutants that are