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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 (NO2) and ozone (O3), 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 NO2 (all year) and O3 (warm season) at participants' residences. We performed time-stratified case-crossover and nested case-control analyses that provide two different epidemiological parameters of effect: the case-crossover design contrasts the same person at different times, and the nested case-control design 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 NO2 (8.8 ppb) of 3.0% (95% CI: -0.9, 6.9%) and for O3 (16.5 ppb) 3.5% (95% CI: -4.5, 12.1). For O3 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 NO2 in daily mortality was 2.9 % (95% CI: -0.9, 6.9%) and for O3 7.3% (95% CI: 3.0, 11.9%). We found evidence of effect modification between daily mortality and cumulative NO2 and O3 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 NO2 and O3 predicted from a back-extrapolation method using a land use regression model from dense sampling surveys. The methods used to assess exposure can have considerable influence on the estimated acute health effects of the two air pollutants.

Keywords	ambient air pollution; cohort study; congestive heart failure; mortality; nested case-control; case-crossover.
Taxonomy	Outdoor Air Pollution, Environmental Epidemiology

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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 time-stratified case-crossover and nested case-control analyses that provide two different epidemiological parameters of effect: the case-crossover design contrasts the same person at different times, and the nested case-control design 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 methods used to assess exposure can have considerable influence on the estimated acute health effects of the two air pollutants.

Keywords: ambient air pollution; cohort study; congestive heart failure; mortality; nested case-control; case-crossover; nitrogen dioxide; ozone.

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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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1. INTRODUCTION

The associations between ambient air pollution and acute health events (e.g., mortality, hospitalizations) 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 hospitalizations 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., 2001a; Goldberg et al., 2013; Goldberg et al., 2003b), 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 Ca 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., 2015b).

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 Figure B1 shows the boundaries of these districts from the 2001 Census Boundary Files (Statistics Canada, 2001).

Appendix B provides a detailed description of the methods used to construct the cohort and shows a schematic of the study design (Figure 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 0-123 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 spatially heterogeneous. We thus developed a series of alternative models of O_3 and NO_2 to estimate daily concentrations according to three-character postal code districts (Buteau et al., 2017), and we compared these to models that have been used commonly. Daily estimates of O_3 were restricted to the "warm season" (May-September) whereas estimates of NO_2 were for the whole year. Briefly, we computed, for each day of the study period, 24-hour mean concentrations of NO_2 and daily 8-hour mean concentrations of O_3 and assigned these to our postal code districts (Buteau et al., 2017):

1) Inverse-distance weighting interpolation from daily mean values of all fixed-site monitors using a first-order decay;
2) A back-extrapolation method (Chen et al., 2010) that used as baseline land-use regression surfaces (LUR) developed from two dense monitoring campaigns (129 monitoring sites for NO_2, Crouse et al., 2009; 76 sites for O_3, Deville Cavellin et al., 2016). These LUR surfaces were multiplied by an inverse-distance weighting surface interpolated for each day of study period from the ratios of concentrations observed at the same fixed-site monitors that were operational at baseline (i.e., year the land use regression surface was developed) and on the day of interest; and
3) A Bayesian maximum entropy model (BME) to estimate daily concentrations of O_3 that incorporated daily measurements from fixed-site monitors and spatial predictions from a LUR developed from fixed-site monitors (Adam-Poupart et al., 2014).

In addition, we developed two other exposure metrics that have been used often in the literature, namely:

4) The daily mean of concentrations measured at the nearest monitor; and
5) The average of concentrations across all monitoring stations. This daily estimate had no spatial variability and was only used in the case-crossover analysis in which comparisons were made across time.

We showed previously that depending on the methods used to predict concentrations there could be substantial differences in the daily mean exposure assigned to a postal code area on a given day (Buteau et al., 2017). In view of these differences, and because we lacked a gold standard to ascertain which model provided the "best" estimates, we thus decided to use, in both designs, the above set of spatially-resolved, daily residential exposures to NO_2 and O_3.

We used hourly weather data from a meteorological station that is operated by Environment Canada (Goldberg et al., 2013; Goldberg et al., 2006; Goldberg et al., 2009). The station is located at the Pierre-Elliott-Trudeau International Airport (Latitude: 45°28′05″N; Longitude: 73°44′29″W), approximately 30 km west of downtown Montreal. From the various metrics of weather available, we retained only daily mean maximum temperature and mean relative humidity for our analyses. With only one site for weather, we could not develop a spatiotemporal model for these variables.

2.4. Statistical analyses

We applied a case-crossover design that contrasts the same person at different times, and an incidence density case-control nested within the cohort that estimates rate ratios across subjects (Maclure, 2007; Maclure and Mittleman, 2000). Both models are suitable for investigating the acute effects of air pollution, as well as estimating possible effect modification. The rationale for using both analyses was that the regression coefficients (or smoothed functions) in each design are estimated consistently with alternative definitions of the risk sets, thus providing two parameters of effect with distinct inferential interpretation. In Appendix A, appealing to the partial likelihood function of the Cox model, we show explicitly how to interpret the estimates in each of these designs.

In both designs, we used the above set of spatially-resolved, daily residential exposures to NO_2 and O_3 and we used distributed lag nonlinear regression models (DLNMs) that account simultaneously for the delayed and possible non-linear effects of air pollution and weather on daily mortality (Armstrong, 2006; Gasparrini et al., 2010; Gasparrini, 2014).

2.4.1 Case-crossover analyses

The case-crossover design was developed originally to investigate acute responses to environmental triggers by using each subject as their own control in a matched analysis, similar to a matched case-control study (Maclure, 1991; Maclure and Mittleman, 2000; Maclure and Mittleman, 2008; Mittleman et al., 1995), and then using a conditional logistic model, or equivalently a stratified Cox model (Prentice and Breslow, 1978), to obtain a population "average". Therefore, by design, the case-crossover analysis estimates an average within-person

risk (Appendix A) and controls for individual time-independent factors throughout each subject's hazard period and allows for adjustments of causal factors between subjects. The design contrasts exposure of a plausible hazard period immediately preceding the event to that of referent periods assumed to be representative of the exposure distribution in the non-case time periods at risk.

We performed the case-crossover analysis using a time-stratified design (Levy et al., 2001; Lumley and Levy, 2000; Lumley and Sheppard, 2000), but we considered each subject separately rather than as a grouped analysis. Thus, for each subject we matched the day of death to all similar days of the week within the same month. The use of control periods after the event is suitable because the exposures cannot be influenced by the event. In grouped analyses, the time-stratified approach has been shown to minimize bias by controlling for unwanted secular trends in the air pollution and mortality time series (Janes et al., 2005; Mittleman, 2005).

We assigned time-varying exposures to case and control days using the daily mean concentrations across monitoring stations as well as the four spatially-resolved concentrations of O_3 and NO_2 estimated at participants' residences. We modelled each air pollutant and metric of exposure separately adjusting only for weather conditions, as time trends and time-independent factors were controlled implicitly by design. We modelled weather using maximum temperature and average relative humidity.

Rather than analyzing air pollutants, temperature and relative humidity at separate lags, we made use of the DLNMs (Gasparrini, 2014). We selected a lag period of four days for the effects of air pollution (i.e., lag 0 to lag 3, where lag 0 days corresponds to the case and referent days) as most studies, especially in Montreal (Goldberg et al., 2013), have not found effects for air pollution beyond this period. We used the same lag period for weather variables as for the air pollutants, as we suspected that using a longer lag structure could result in over-adjustment of the effects of air pollution (Goldberg et al., 2013) or possibly a loss of power (Gasparrini et al., 2016). Different smoothing functions were chosen for each predictor and lag spaces. Given our limited lag period, we used an unconstrained lag structure.

We performed the analysis using an extension of the Cox proportional hazards model for time-dependent variables (Fisher and Lin, 1999; Therneau and Grambsch, 2000). We accounted for the matched nature of the selection of cases and controls by defining time intervals that were specific

to each individual and not overlapping (this approach is equivalent to conditional logistic regression). Time-independent factors (e.g., gender, socio-economic status) are accounted for by design; thus, our final model was simple, comprising smoothing terms for the air pollutants, maximum temperature, and relative humidity, which were represented by their respective cross-basis functions.

We assessed potential nonlinearity in the response functions for the three covariates (i.e., air pollutants, maximum temperature, relative humidity) by fitting univariate models using natural cubic splines, using two and three degrees of freedom (knots placed at equally spaced percentiles of the variable's distribution). The "best" fit was assessed through visual inspection of the response function and comparisons of the Akaike information criterion (a measure of goodness-of-fit; AIC; (Akaike, 1974)), with a lower AIC suggesting a better fit to the data, although we excluded smoothers that produced implausible "wiggles" in the response curves. Response functions that were consistent with linearity were replaced by linear functions.

2.4.2. Nested case-control analyses

We conducted nested case-control analyses using incidence density sampling with calendar time as the time axis. We generated a risk set at each failure time that was matched on gender, with up to 100 non-censored, matched subjects selected randomly at the failure time to serve as controls. One hundred controls provided a substantial computational benefit, yielding estimates similar to those obtained from an entire cohort analysis (Breslow et al., 1983; Essebag et al., 2003; Kass and Gold, 2005), and without affecting statistical precision (Breslow and Day, 1987; Breslow et al., 1983; Essebag et al., 2005). After the risk sets were created, we incorporated the spatial-temporally resolved daily concentrations of O_3 and NO_2 using each participant's three-character residential postal code at each failure time. In contrast to the case-crossover the daily mean across monitoring stations could not be used because this analysis requires variation in the daily exposure across individuals. This analysis provides an estimate of the between-person hazard ratio for immediate and slightly delayed effects of exposure.

We used the same modelling strategy as in the case-crossover analysis. Use of time intervals in the time-dependent Cox regression model to define each risk set, rather than strata, led to computational times that were 300 times faster (see Appendix F for an example of the R code).

Using the DLNM framework, we selected a lag period of 4 days, and we used the same strategy to assess the functional form of the air pollution-daily mortality association. In contrast to the case-crossover analysis, weather was controlled by design as cases and controls were matched by calendar time. We adjusted our models for current age (sex was a matching factor in defining the risk sets) and for the following area-based contextual variables: median household income; unemployment rate; percentage of adults who had not completed high school. These were all continuous variables that were extracted from the 1996 census (Statistics Canada) available for areas defined by the three-first characters of the postal code (thus matching the spatial level of information we had about residential location). Potential nonlinearity in the response functions for each air pollutant, age, and contextual variables was assessed using natural cubic splines using a range of degrees of freedom. We inspected the resulting fitted curves and compared the AICs.

2.4.3. Presentation of results

We present results of both analyses by pollutant, recognizing the different parameters being estimated. In both sets of analyses, the effects of NO_2 and O_3 were found to be linear (see results). To compare pollutant-specific estimates within each type of analysis, we report results as the mean percentage change from the estimated regression coefficient for an increase of the interquartile (IQR) in the daily mean concentration of each air pollutant metric, computed as: [exp(ln(OR) x IQR) -1] x 100%, where OR is the estimated odds ratio for a unit increase in the pollutant.

2.4.4. Potential effect modification by indicators of "health"

Individuals having congestive heart failure have different natural histories. We presumed that exogenous insults interfere in potential causal pathways linking air pollution and mortality by either "triggering" declines in health or causing exacerbations of concurrent conditions. These changes in health potentially modify a person's risk of experiencing adverse health effects related to daily fluctuation in air pollution. As there is no gold standard by which to define indicators of "health", we have developed from the administrative health data the following four indices that may reflect the underlying construct of "declining health": 1) the number of hospitalisations and

emergency room visits in the past three months and 2) in the past six months; 3) the cumulative number of hospitalisations during the whole follow-up; 4) the prescribed dose of furosemide (also referred as *Lasix*, a brand name under which the drug is marketed), which is a loop diuretic commonly used in the treatment of heart failure to prevent the body from absorbing too much salt and thus relieving symptoms of congestion. The first three indicators were treated as ordinal, with all cumulative counts greater than the 99th percentile of the marginal distribution rounded to this value. The fourth indicator based on furosemide was a four-level categorical variable (not taking furosemide, "mild" dose (0-40mg), "moderate" dose (41-80mg), "high" dose (>80mg, or intravenous or oral solution)). More details about the rationale and assumptions underlying each of these indicators are presented in Appendix D.

In both types of analyses, we considered these four indicators of health separately to determine whether they modified the associations between air pollution and mortality. In the case-crossover analyses, these indicators were time-invariant (we assigned the value at time of death), whereas in the nested case-control study they were time-dependent. We investigated effect modification using an interaction term between the indicator of health and the cross-basis function for the air pollutant (Gasparrini et al., 2015; Gasparrini et al., 2016). We report estimates of association and their 95% confidence intervals for an interquartile increment in the air pollutant. (Appendix E presents the procedure and an example of the R code used to investigate effect modification for both ordinal and categorical indicators of health.)

2.4.3. Other sensitivity analyses

For NO_2, we also conducted the analyses restricted to the warm season (May-September). For both pollutants and designs, we also investigated deviations from a multiplicative model by assessing effect modification by gender. For each metric of exposure, we included in our regression models an interaction term between gender and the distributed lag function for air pollutant, and we reported estimates of association and 95% confidence interval for each gender.

In a previous paper (Buteau et al., 2017), in which we developed spatially-resolved concentrations of O_3 and NO_2 of participants' residences in Montreal, we found that the spatial pattern of agreement differed between pollutants; for O_3, but not NO_2, postal code districts that

showed greater disagreement were mostly located near the city centre and along highways. We thus performed case-crossover analyses stratified by postal code area according to the level of absolute agreement in the daily exposure assigned to postal codes across the different metric of exposure. For each pollutant, we created two strata (one for postal code districts showing greater agreement across the different metrics and another for those of higher disagreement) using the median value of the mean absolute agreement intraclass correlation (ICC) across all pairs of metrics as the threshold for determining in which category each postal code was assigned (mean ICC=0.75 for NO_2; mean ICC = 0.65 for O_3).

3. RESULTS

3.1. Description of the cohort and outcomes

Tables 1 and 2 show a description of the cohort. (Table E1 shows additional details about characteristics of the cases and controls in the nested case-control analysis defined across all failures.) The cohort comprised 63,534 individuals who were residents of Montreal between 1991-2003, 65 years of age and older, and identified as having congestive heart failure. Mean age at entry in the cohort was approximately 77 years and with an average follow-up time of approximately four years. At time of entry in the cohort, many subjects had other important comorbid conditions in addition to congestive heart failure. The most frequent concurrent conditions were myocardial infarction, chronic pulmonary disease, and diabetes (about 20% of prevalence) (Table 2).

Of the 63,534 cohort members, 31,707 (14,062 men and 17,645 women) died during the follow-up period while being resident of Montreal (Figure 1 shows the spatial distribution of these deaths). Of these deaths, 11,824 (6,515 women and 5,309 men) occurred during the months of May to September, inclusive. However, 12 individuals (including one during May-September) were excluded from the analysis because of an erroneous postal code at time of death, which prevented us from assigning exposure. Therefore, a total of 31,695 and 11,823 persons who died during the follow-up period were included in our analyses for NO_2 (all year) and O_3 (May-September), respectively.

3.2. Air pollution and weather variables

Appendix Tables E2-E3 show the daily mean concentrations of NO_2 and O_3 that were assigned to individuals included in the case-crossover and in the nested case-control analysis, respectively. For each metric of exposure, the distribution of daily concentrations assigned was similar between the two designs. For NO_2, the back-extrapolation method had the lowest mean daily concentrations (16.6 ppb) whereas the other methods had similar mean estimates ranging from 20.1 to 21.6 ppb. The nearest station approach had the wider distribution of NO_2 (range: 0 to 169.5 ppb; interquartile range (IQR) = 13.6 ppb) as compared to the other metrics (maximum values ranging from 90.6-121.8 ppb; IQR ranging from 8.8 and 10.0 ppb).

For O_3, the daily 8-hour mean concentrations were similar between the nearest station, inverse-distance weighting, and BME methods (ranging from 28.7 to 30.8 ppb), whereas the back-extrapolation (21.1 ppb) and the mean of all stations (used in the case-crossover only; 21.6 ppb) method had a lower mean concentration. However, the back-extrapolation had the widest range of exposures (maximum values of 148.5-174.3 ppb), whereas the mean of all stations yielded to the most constrained one (maximum value of 66.6 ppb).

The distribution of selected weather variables, for the study period 1991-2003, is presented in Appendix Table E4. The average maximum daily temperature was 11.3°C, varying from -24.0 to 35.4°C (interquartile range (IQR) of 20.6°C). For the months of May-September, the average maximum daily temperature was 22.7°C, varying from -1.2 to 35.4°C (IQR of 6.8°C). Maximum temperature was highly correlated with other metrics of temperature (i.e., minimum and mean) as well as with the humidex index (Spearman and Pearson correlation coefficients of about 99%; data not shown).

Appendix Table E5 shows Spearman correlation coefficients for the selected weather variables and same-day air pollutants concentrations for the different metrics. Maximum temperature was positively correlated with both air pollutants, with stronger correlations for O_3. Relative humidity was negatively correlated with both pollutants, but there was no correlation with NO_2.

3.2. Associations between daily non-accidental mortality and ambient NO_2 and O_3

The adjusted response-functions fitted as natural cubic splines with three degrees of freedom

between the odds (case-crossover) and hazards (nested case-control) of non-accidental mortality accumulated over the 4-day lag period (referred to as the "cumulative lag") and the different metrics of NO_2 and O_3 are shown in Appendix Figures E1-E4. Using two rather than three degrees of freedom removed many of the "wiggles" (data not shown), thus suggesting that these variations were attributable to under-smoothing (i.e., using too many degrees of freedom). In all instances, the 2-df fitted response curves appeared linear and we found a lower AIC, suggesting an improved fit, when using the linear structure in the fully adjusted models (see Appendix Table E6). Therefore, we concluded that for the two types of analyses all response functions for the air pollutants were consistent with linearity.

In the case-crossover analysis, we used a distributed lag non-linear model accumulated over lags 0 to 3 days for maximum temperature (non-linear structure fitted as natural cubic splines with three degrees of freedom (df)) and relative humidity (linear), and time-invariant characteristics were controlled by design. The unadjusted response-functions between these weather variables and the odds of non-accidental mortality are shown in Appendix Figure E5.

In the nested case-control analyses, our sampling scheme controlled for gender, weather and time-related factors, and we adjusted explicitly for age (natural cubic splines with 3 df), and time-varying area-based contextual variables (median household income and unemployment rate fitted as natural cubic spline functions with 3 df, and percentage of adults who had not completed high school fitted as linear). Appendix Figure E6 shows the response-functions of the univariate models between mortality and age and the contextual covariates.

3.2.1. Associations between daily non-accidental mortality and ambient NO_2

Figure 1 shows the fully-adjusted mean percentage change (and 95% confidence intervals (CI)) in daily non-accidental mortality for single-day lagged effects from lag 0 to lag 3-days, as well as for cumulative effects for an interquartile range increase in the daily 24-hour mean NO_2 exposure (all year), according to each type of analysis and metric of exposure. (Appendix Table E7 shows the numerical values of these figures.)

For the nested case-control analysis, we found negative associations for the nearest station and inverse-distance weighting, with overall cumulative effects of -5.5% (95% CI: -8.1, -2.9%) and -

9.0% (95% CI: -15.2, -2.4%), respectively. In contrast, using daily concentrations from the LUR model that was back-extrapolated, the cumulative risk of non-accidental daily mortality over the 4-day lag period was 2.9% (95% CI: -0.9, 6.9%).

For the case-crossover analyses, results were consistent across the different metrics of exposure. All cumulative response-functions were positive and the mean percentage change in the cumulative risk of daily non-accidental mortality ranged from 2.3% (mean of stations; 95% CI: -0.8, 5.6%) to 3.0% (back-extrapolation from LUR; 95% CI: -0.3, 6.1%). The effects at single day lags were similar across all methods; the estimates were essentially null at lag 0 days and increased in magnitude until lag 2 days, with a negative mean percentage change at lag 3-days. The cumulative effects from the case-crossover were confounded slightly by weather. The unadjusted mean percentage changes were between 0.6% and 0.8% higher than in the fully adjusted estimates (Appendix, Table E8).

3.2.2. Association between daily non-accidental mortality and ambient O_3

Figure 2 shows the results for the daily 8-hour mean exposure to O_3 (May-September) using the same lags as in the analyses of NO_2. (Numerical values of the estimates are shown in Appendix Table E7.) Note that the scale of the y-axis differs considerably between the two designs. In the case-crossover analysis we were concerned that adjusting for weather may lead to over-adjustments, as ozone formation during the warm season is generally strongly dependent on weather conditions, particularly temperature and relative humidity (Camalier et al., 2007; Jacob and Winner, 2009); therefore, we presented the estimates adjusted and unadjusted for weather.

In the nested case-control analysis, we found a positive cumulative effect for the nearest station (6.7%; 95%CI: 0.3, 13.5%), inverse-distance weighting (18.5%; 95%CI: -2.6, 44.1%) and back-extrapolation (7.3%; 95%CI: 3.0, 11.9%), whereas the cumulative effect for the BME was close to null (0.8%; 95%CI: -7.3%, 9.5%). There were substantial differences in the magnitude of estimated effects at single day lags across the different metrics of exposure, but stronger effects was found at lag 0 and 3 days for the nearest station, inverse-distance weighting and back-extrapolation methods.

For the case-crossover analysis, the adjusted cumulative estimate was negative for the BME (-3.0%; 95%CI: -10.0, 4.5%) and the nearest station (-2.2%; 95%CI: -19.2, 5.2%). In contrast, inverse-distance weighting (2.4%; 95%CI: -4.9, 10.3%) and back-extrapolation (3.5%; 95%CI: -4.5, 12.1%) yielded positive associations, whereas the cumulative association was essentially null for the mean of all stations (0.1%; 95%CI: -5.7, 6.3%). The 95% confidence intervals for all adjusted estimates substantially overlapped across metrics of exposure and included the null. Single lag day effects were stronger at lag 0 days for the nearest station and the back-extrapolation analyses, both showed a mean increase of 1.6% in the risk of non-accidental daily mortality per interquartile increase in daily mean 8-hour O_3 exposure. For the other metrics of exposure, the larger increase in the risk of mortality was observed at lag 1-day, with magnitude of the effect ranging between 2.2% (95%CI: -2.5, 7.1%) and 2.8% (95%CI: -2.6, 8.5%).

Adjusting for weather in the case-crossover analysis did not yield a meaningful improvement in the fit of the model (Appendix Table E8); however, there was strong confounding by weather on O_3 during the warm season, particularly for the BME (from 4.3% to -2.2%) and for the nearest station (from 4.0% to -3.0%). The unadjusted results were fairly consistent across the different metrics, with cumulative percentage changes ranging from 4.0% (95%CI: -0.1, 8.3%) to 7.0% (95%CI: 1.7, 12.7%). For all metrics, the effects at lag 0 days were positive and stronger effects were observed at lag-1 day, ranging from 2.1% (nearest station; 95%CI: -1.6, 6.0%) to 4.7% (BME; 95%CI: 0.6, 8.9%).

3.2.3. Potential heterogeneity in the associations between non-accidental mortality and air pollution

Appendix Figure E7 shows the response-functions of the univariate models between daily mortality and each of the four indicators of health. Appendix Table E9 shows the effects of adjustments for each indicator of health on the model fit and hazard of non-accidental mortality in the nested case-control analyses (in the case-crossover analysis, these were controlled by design). In general, the influence on the estimates was modest but adjustment for the indicator of hospitalisations and emergency department visits yielded lower AICs.

Figure 3 shows the cumulative risk of non-accidental mortality over the entire lag period per interquartile increase in each air pollutant, according to the prescribed dose of furosemide. In the nested case-control analyses, we found evidence of effect modification for both air pollutants. However, in the case-crossover analyses, the confidence intervals were wide, particularly for the high dose category arising from a limited number of subjects, and there was no evidence of heterogeneity.

The results of the assessment of effect modification according to the number of hospitalisations and emergency room in the past three months, six months and the number of hospitalisations since the beginning of follow-up, are presented in Appendix Figures E8-E10. There were some positive trends in the estimated mean effect according to values of these indicators, particularly for O_3 during the warm season. However, for all three indicators, the confidence intervals of the estimated effects were wide, particularly for the higher values of the indicators, and there was substantial overlap between the different values of the indicators.

Cumulative estimates of associations by gender are presented in Appendix Figure E11. For NO_2, there was no evidence of heterogeneity by gender. For O_3, in the nested case-control study, men were found to be at greater risk when exposure was estimated from the nearest station (women: -1.4% (95%CI: -8.7, 6.6%); men: 46.2% (95%CI: 13.6, 88.3%) and inverse-distance weighting (women: -2.2% (95%CI: -23.5, 24.9%); men: 46.2% (95%CI: 13.6, 88.3%)), whereas there was no evidence of heterogeneity by gender for the other metric of exposure as well as in the case-crossover analysis.

For NO_2, restricting the analyses to the "warm" season generally lead to attenuated estimates, but confidence intervals were broad and substantially overlapped, thus we concluded that there was no evidence of effect modification (Appendix, Table E10). For both pollutants, we also found no evidence of heterogeneity for three-character postal code districts that showed higher agreement between the different metrics as compared to postal code districts that showed lower agreement (Appendix Table E11).

4. DISCUSSION

In these individual-level analyses of the associations between daily mortality and short-term exposures to NO_2 and O_3, we estimated the acute effect of air pollution on mortality using case-crossover and nested case-control designs, as both designs are suitable for investigating the acute effects of air pollution, as well as estimating effect modification. Although from a statistical point of view, the case-crossover and nested case-control designs can be viewed as two similar conditional models using different risk sets, we emphasize that the inferential questions addressed by each design are distinctly different. The case-crossover design, which contrasts the same persons at different times, addresses the question "Why this person dies now rather than one or a few weeks ago?", whereas the nested case-control, which contrasts different persons at the similar time, addresses the question "Why this persons dies now whereas others did not?" (Maclure, 2007; Maclure and Mittleman, 2000). Moreover, another conceptual difference between the nested case-control and the case-crossover designs resides in their study base, as persons who did not die were excluded from the case-crossover analysis. Both designs are valid and can be used to assess the hypothesis that increases in daily ambient air pollution increases the risk of daily mortality.

In the case-crossover analyses, we made use of five alternative exposure metrics and found similar positive associations between daily mortality and daily ambient NO_2. These metrics were the same as the ones we published previously (Buteau et al., 2017), and in that paper we concluded that, in view of the substantial differences in daily concentrations of NO_2 and O_3 predicted at participants' residences by these different metrics, health effects should be analysed using multiple exposure assessment methods.

For O_3, the direction of the associations varied, although statistical variability was substantial. However, we were concerned with potential over-adjustments by weather. In the eastern United-States, for example, daily maximum 8-hour concentrations of O_3 were found to be explained (R^2 as high as 80%) by weather, with temperature and relative humidity being the most important factors (Camalier et al., 2007). Because of this strong dependence, we suggest that weather acts to some extent as a surrogate for O_3, particularly during episodes of high O_3 concentrations, and thus it seems plausible to assume that the true effects of O_3 maybe in between the adjusted and unadjusted values. In the nested case-control analyses, results for NO_2 varied amongst the four alternative exposure metrics, but suggested a positive association for O_3.

We found that the estimates of risk depended on which exposure method was used. This influence was more pronounced in the nested case-control design for which the contrast in exposures was essentially driven by the spatial component, as the analysis contrasted same day exposures between persons living at different location in Montreal. In contrast, the case-crossover contrasted exposures from the same individual, thus living at the same spatial location, on different days; thus, the contrast in exposures was essentially temporal.

Although we cannot state which exposure method is the most valid, our preference in exposure models is the back-extrapolation from a land use regression model because it made use of measurements from dense sampling surveys that captured the influence of very local sources such as roadways, whereas the other methods relied solely on measurements from the sparse, fixed-site monitoring network. Using this exposure metric, in the case-crossover the cumulative mean percentage changes in daily mortality were 3.0% (95% CI: -0.9, 6.9%) and 3.5% (95% CI: -4.5, 12.1) per interquartile increment in NO_2 (8.8 ppb) and O_3 (16.5 ppb), respectively. For O_3, the increases in daily mortality unadjusted for weather was 7.1% (95%CI: 1.7, 12.7%). In the nested case-control approach, the cumulative increases in daily mortality was 2.9 % (95% CI: -0.9, 6.9%) for NO_2 and 7.3% (95% CI: 3.0, 11.9%) for O_3. These positive associations were consistent with the findings of the latest time-series study conducted in Montreal (Goldberg et al., 2013); for similar increments in ambient NO_2 and O_3, the cumulative increases in non-accidental mortality among the elderly with heart failure were approximately 3.3% (95%CI: 1.2, 5.4%) and 3.4% (95%CI: -2.1, 9.0%), respectively.

One main advantage of the case-crossover design is that the self-matching accounts for within-person, time-invariant confounding (Maclure and Mittleman, 2000; Mittleman and Mostofsky, 2014; Weinberg, 2017). Therefore, risk factors, such as smoking history, obesity, physical activity, are eliminated by design. These are risk factors for which information at the individual level is typically lacking in cohorts constructed from administrative health data, like ours. In the nested case-control analyses, we adjusted for these factors by using some area-based indicators of socioeconomic status, but it is possible that some residual confounding remained. We could not perform indirect adjustments (Shin et al., 2014; Steenland and Greenland, 2004; Villeneuve et al., 2011) for smoking behaviour and obesity due to unavailability of data at the geographical level that we used. In some previous cohort studies of air pollution conducted in Canada, indirect

adjustments for smoking and obesity have had limited impact, generally in the range of ±1–2% in the hazard ratios for non-accidental mortality (Chen et al., 2013; Crouse et al., 2015; Villeneuve et al., 2013).

Historical exposures as well as disease severity and comorbidity are among factors that were controlled by self-matching in the case-crossover design but may have varied considerably in the nested case-control analysis between persons in a given risk set. While we consider that these factors may play an important role in the development of congestive heart failure and contribute in putting individuals at different risks for exogenous exposures, these are not a common cause of both acute mortality and daily exposures. Therefore, under our hypothetical model, not controlling or matching for factors such as disease severity, comorbidities and historical air pollution exposures should not be expected to bias the results, as these may act not as confounders but rather as potential effect modifiers. This is the same implicit assumption made in grouped time series and case-crossover studies. Specifically, we could not assess potential effect modification by historical exposures to air pollution as we lacked information about residential locations of participants prior to our study period, we did not have exposure data prior to the study, and we had no reason to believe that their exposure at entry into the cohort or during the follow-up period was representative of their exposure decades ago. In addition, in the context of modeling association using the DLNMs, adjusting for historical exposures will lead to spurious effects as the "long-term" temporal component cannot be incorporated properly.

In the present study, we estimated whether a worsening in one's health, as reflected by our indicators of health, modified the risk of mortality associated with daily exposures to ambient air pollution. In the nested case-control analyses, we found evidence of effect modification according to the prescribed dose of furosemide, but not in the case-crossover analysis. The differences in the two designs of the results of effect modification may be explained by the study bases, which differed between the two designs, as the case-crossover is restricted to persons who died. In addition, in the case-crossover analyses, the indicators of health did not vary substantially over the one month time period that included the case and referent time periods The definition of "health" is complex and multidimensional (Goldberg et al., 2015a), and definitions of our indicators of health were limited by the information that was available in the administrative data.

To the best of our knowledge, similar indicators have not been used in previous studies of acute air pollution. The modeling framework used here can form the basis of future investigations to elucidate factors, such as physiological conditions, disease processes and concurrent comorbidity, that may modify the underlying risk profile of persons. Such investigations may contribute important insights both for clinical management and public health in the current context of ageing populations and increasing rates of age-related diseases, notably cardiovascular diseases.

A main strength of this study was its population-based design conducted over a 12 year follow-up period and to nearly capturing the entire population of persons 65 years and older residing in Montreal. To our knowledge, cohort studies have been used only twice (Beverland et al., 2012; Lepeule et al., 2006) to investigate the associations between acute exposures to ambient air pollution and daily mortality. In these two cohort studies (Beverland et al., 2012; Lepeule et al., 2006), age rather than calendar time was used to generate risk sets and thus daily means of fixed-monitors were used in principle to distinguish spatial exposures. Although this is a clever way to solve the problem of resolving exposures spatially, secular trends need to be adequately accounted for. A strength of our study was the ability to conduct individual-level analysis by incorporating spatially-resolved time-dependent concentrations of ambient NO_2 and O_3.

Although we had tens of thousands of deaths and we used a large number of referents, the confidence intervals were in some instances relatively wide, and this is likely due to lower than optimal spatial and/or temporal variability. Notably, the inverse-distance weighting method yielded wider confidence intervals likely because it generated a smoother surface of concentrations, thus constraining between-person exposure variability. In general, confidence intervals from our nested case-control analysis were wider as compared to the time-stratified case-crossover analysis despite using a greater number of referents (100 controls per risk set in the nested case-control design versus 3-4 control days in the case-crossover design), and this was probably due to reduced spatial variability in exposure at each failure time as compared to the case-crossover design which had greater temporal variation at a given location.

Another key strength of this study was the application of DLNMs to individual level data (Gasparrini, 2014). The application of these flexible statistical models can substantially improve the characterization of relationships between mortality and air pollution and weather. We

consider that these models are the most appropriate for time series analyses and are clearly an essential method for characterizing delayed effects in cohort studies.

The present study also adds to the limited literature comparing the influence of different methods to predict daily exposures on the magnitude of the acute mortality or morbidity of air pollution (Sarnat et al., 2013). Because NO_2 and O_3 exhibit a substantial degree of spatial variability within Montreal (Crouse et al., 2009; Deville Cavellin et al., 2016), the expectation is that enhancing the spatial resolution of our ambient air concentration data should contribute in reducing exposure measurement errors as compared to assuming that the daily mean concentration of air pollutant is spatially homogeneous over the study area. However, the spatiotemporal methods used to predict exposures have limitations (Buteau et al., 2017) and these may in part explain the observed differences in the estimated associations. In particluar, in the back-extrapolation method it is assumed that the surface derived from a land use regression model would change from day to day in proportion to what was observed at fixed-site monitoring stations in the study area. Therefore, the accuracy of the predictions from this method depends first on the land use regression model, but also on the number and spatial distribution of available historical monitors. The nearest station and inverse-distance weighting interpolation both depended entirely on the density of the monitoring network and ignored sources (e.g., road traffic) and other factors (e.g., meteorological, built environment, topography) that potentially influence daily concentrations. Of note is that the monitors are situated in areas to assess compliance to regulations (many monitors in high air pollution areas) as well as some are placed in residential areas, thus providing an over representation of high or low concentrations relative to that of population exposure (Sheppard et al., 2012). The Bayesian maximum entropy model developed for O_3 (Adam-Poupart et al., 2014) was also highly depended on the monitoring network, as the model used measurements at fixed-site monitors and incorporated a land use regression model developed from only the fixed-site monitors. The predictive ability of a LUR derived from a fixed-site network will be constrained by the number of monitoring stations and the variability in the land use characteristics surrounding the monitoring sites (Jerrett et al., 2005).

Another limitation was that residential postal codes of subjects, although time-varying, were not updated on a daily basis. Daily mobility or activity patterns were also not available, but because of the age and compromised health conditions of participants, it is plausible that many spent a

greater amount of time near their homes.

Potential misclassification of congestive heart failure due to inaccurate diagnostic or coding on the medical records is another potential limitation. Our definitions of congestive heart failure were based on knowledge of clinical practice in Quebec but have not been validated against patient charts and other clinical data. Also, before August 1996 prescriptions for persons age 65 years and over were covered entirely by the Quebec Health Insurance Plan; however, this has changed through time and the public drug insurance program was estimated to cover 96.6% of persons aged 65 and over in 1998 and 89.6% in 2003(Goldberg et al., 2013). Thus, it is unlikely that there were large errors in characterizing these subjects as having heart failure.

5. CONCLUSIONS

In this population-based cohort study of persons having congestive heart failure in Montreal, 1991-2003, non-accidental mortality was found to be associated with spatially-resolved exposures to daily ambient concentrations of NO_2 and O_3 predicted from a back-extrapolation method using a land use regression model from dense sampling surveys. We showed that the method used to assess daily exposures of individuals influenced the estimates of risk. Notably, this study suggests that more effort is needed to improve exposure models for estimating daily exposures at the individual level. Additional cohort studies making use of subject-specific information (including residential history) and of refined spatiotemporal exposure models are needed to further elucidate how air pollution exposures (both daily and historical) and individual factors, notably physiological conditions, disease processes (e.g., heart failure severity) and changes in a person's health, contribute to the underlying personal risk profile.

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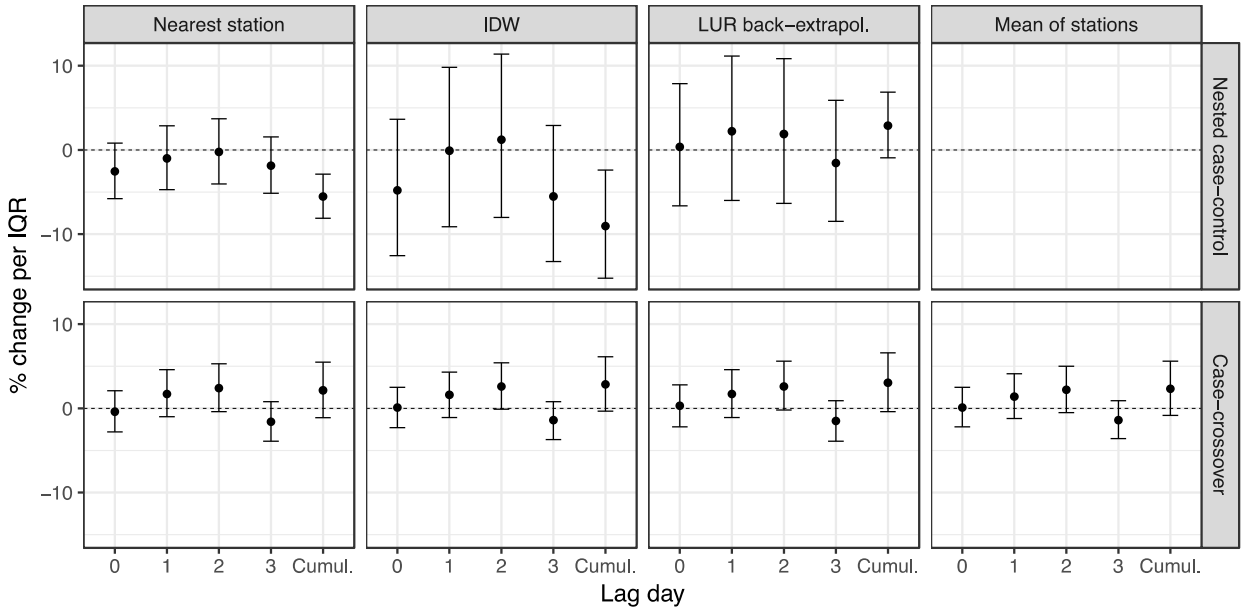

Figure 1. Estimated percentage change in daily non-accidental mortality among subjects 65 years of age and over with congestive heart failure according to the interquartile range in daily 24-hour mean exposures to ambient NO_2 (all year) from different spatiotemporal methods to predict concentrations and type of analysis, Montreal, 1991–2003. Interquartile ranges (IQRs) were 13.6, 10.0, 8.8 and 9.6 ppb for the nearest station approach ("Nearest station"), inverse-distance weighting ("IDW"), back-extrapolation from a land use regression ("LUR back-extrapol."), and the daily mean across all stations ("Mean of stations"), respectively. Numbers on the horizontal axis denote single day lags (0 to 3) and the cumulative for these lags ("cumul."). Dots represent maximum likelihood estimates and bars represent 95% confidence intervals. In both type of analysis NO_2 was fitted from a distributed lag non-linear model accumulated over lags 0 to 3 days using a linear structure for NO_2 and an unconstrained structure for lags. In the case-crossover analyses, time invariant factors and temporal trends were controlled by design and we statistically adjusted for maximum temperature (natural cubic spline with 3 df), and relative humidity (linear), from a distributed lag non-linear model accumulated over lags 0 to 3 days. In the nested case-control analyses, we adjusted for age (natural cubic splines with 3 df), sex, and area-based indicators of socio-economic status including median household income (natural cubic splines with 3 df), unemployment rate among adults (natural cubic splines with 3 df), and percent of adults without high school diploma (linear). We could not in the nested case-control analyses estimate the mean of all stations, as this metric does not have any variability between individuals.

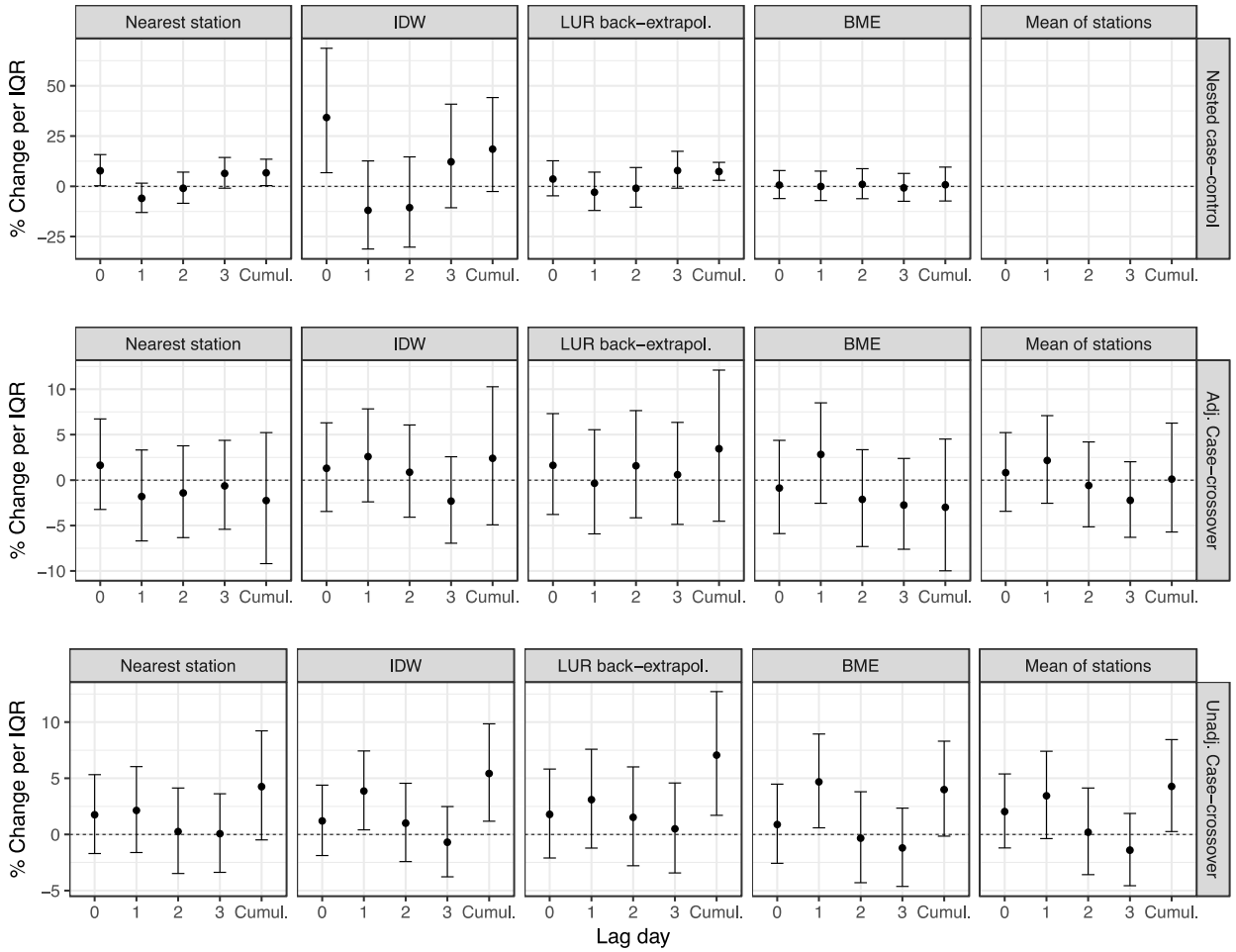

Figure 2. Estimated percentage change in daily non-accidental mortality among subjects 65 years of age and over with congestive heart failure according to the interquartile range in daily 8-hour mean exposures to ambient O_3 (May-September) from different spatiotemporal methods to predict concentrations and type of analysis, Montreal, 1991–2003. Interquartile ranges (IQRs) were 19.6, 16.6, 16.4, 11.6 and 11.8 ppb for the nearest station approach ("Nearest station"), inverse-distance weighting ("IDW"), back-extrapolation from a land use regression ("LUR back-extrapol."), Bayesian maximum entropy model ("BME") and the daily mean across all stations ("Mean of stations"), respectively. We present results for the case-crossover adjusting ("Adj. Case-crossover") and not adjusting for weather ("Unadj. Case-crossover"). Numbers on the horizontal axis denote single day lags (0 to 3) and the cumulative for these lags ("cumul."). Dots represent maximum likelihood estimates and bars represent 95% confidence intervals. In both types of analyses, O_3 was fitted from a distributed lag non-linear model accumulated over lags 0 to 3 days using a linear function for O_3 and an unconstrained structure for lags. In the nested case-control analysis, we adjusted for age (natural cubic splines with 3 df), sex, and area-based indicators of socio-economic status including: median household income (natural cubic splines with 3 df; unemployment rate among adults (natural cubic splines with 3 df); and percent of adults without high school diploma (linear). The case-crossover controlled for time invariant factors and temporal trend by design and in the adjusted model ("Adj. Case-crossover") we statistically adjusted for maximum temperature (natural cubic spline with 3 df), and relative humidity (linear), from a distributed lag non-linear model accumulated over lags 0 to 3 days. We could not in the nested case-control analyses estimate the mean of all stations, as this metric does not have any variability between individuals.

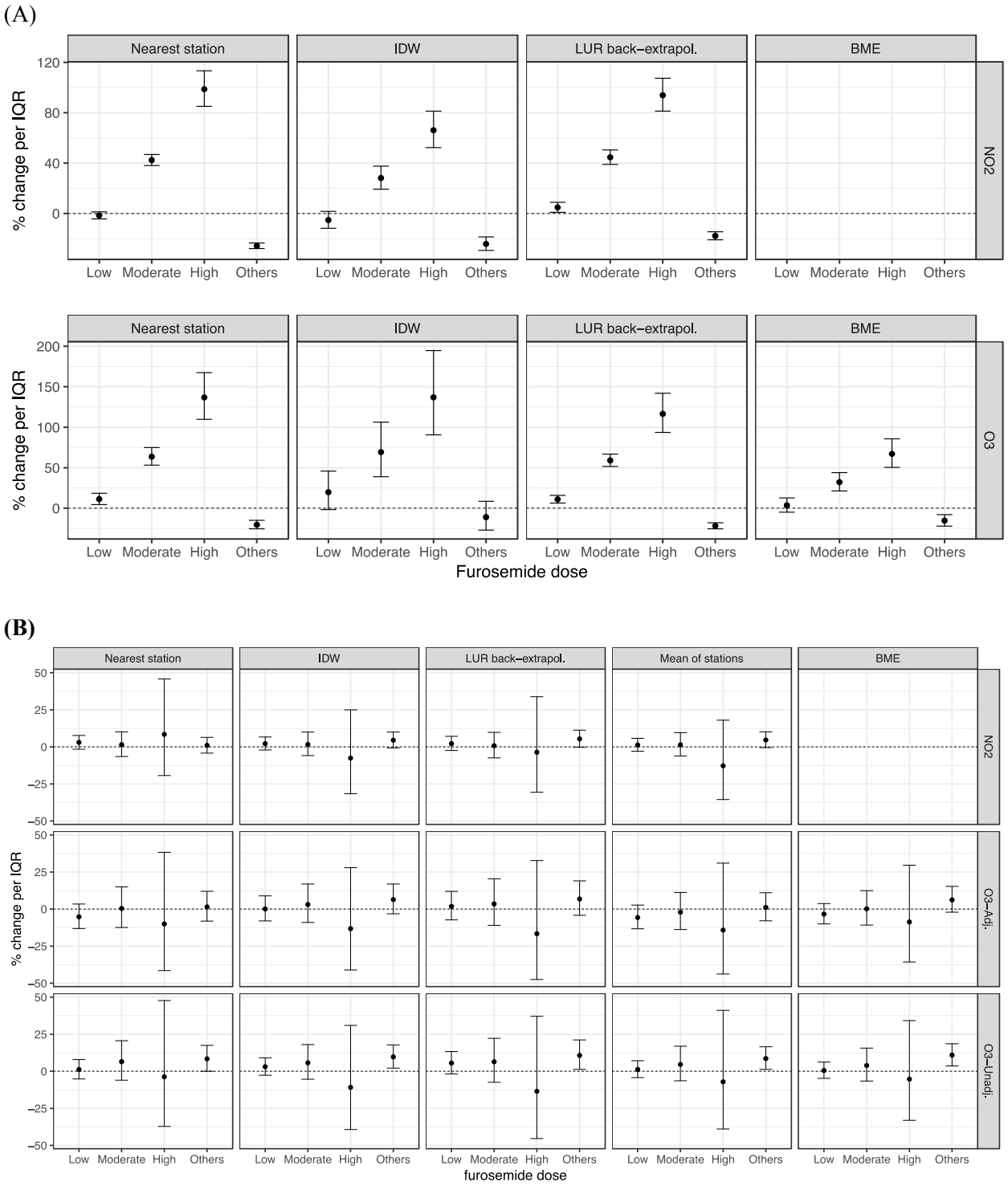

Figure 3. Estimated cumulative percentage change in the (A) nested case-control and, (B) case-crossover analysis on the risks of non-accidental mortality per interquartile range increase in daily 24-hour mean exposures to ambient NO_2 (all year) and, daily 8-hour mean exposures to ambient O_3 (May-September), according to the prescribed dose of furosemide. Dots represent maximum likelihood estimates and bars represent 95% confidence intervals. For O_3, we present results adjusting

("O3-Adj.") and not adjusting for weather ("O3-Unadj."). The horizontal axis indicates the different categories based on the dose of furosemide, with "Others" defining people who were not taking furosemide. We did not develop the BME model for NO_2. For NO_2, interquartile ranges (IQRs) were 13.6, 10.0, 8.8 and 9.6 ppb for the nearest station approach ("Nearest station"), inverse-distance weighting ("IDW"), back-extrapolation from a land use regression ("LUR back-extrapol."), and the daily mean across all stations ("Mean of stations"), respectively. For O_3, IQRs were 19.6, 16.6, 16.4, 11.6 and 11.8 ppb for the nearest station, IDW, LUR back-extrapol., BME and mean of stations, respectively.

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Table 1. Description of the cohort of persons 65 years of age and older having congestive heart failure in Montreal, 1991-2003

	Women	Men	All
Number of persons included in the cohort	37,587	25,947	63,534
Mean (SD) age at entry in the cohort	75.8 (6.9)	78.1 (7.4)	77.2 (7.3)
No. of deaths	14,062	17,645	31,707
Mean (SD) age at death (in years)	79.9 (7.2)	83.2 (7.6)	81.7 (7.6)
Furosemide (Lasix) usage at time of death			
Not taking furosemide	6,560 (60%)	4,394 (40%)	10,954
Mild dose (0-40 mg)	8,843 (55%)	7,203 (45%)	16,046
Moderate dose (41-80 mg)	2,094 (48%)	2,274 (52%)	4,368
High dose (>80 mg or intravenous or oral solution)	148 (44%)	191 (56%)	339

	Percentiles					
	5th	**25th**	**50th**	**75th**	**95th**	**99th**
Number of selected important health conditions at entry in the cohort[1]	0	1	1	2	4	6
Number of hospitalisations and emergency department visits during follow-up						
No. of hospitalisation and emergency visits in the last 3 months	0	0	1	2	5	8
No. of hospitalisation and emergency visits in the last 6 months	0	0	1	2	6	10
No. of hospitalisation during the whole follow-up	0	0	1	2	6	11

Abbreviation: SD, standard deviation.

[1]Refer to Appendix Table C2 for the list of selected important comorbidities and the algorithms used for each condition.

Table 2. Prevalence of selected important comorbidities at time of entry in the cohort among persons 65 years of age and older having congestive heart failure in Montreal, 1991-2003[1]

Comorbidities	**Prevalence (%)**
Myocardial infarction	19.0%
Chronic pulmonary disease	18.9%
Diabetes without chronic complication	17.3%
Cerebrovascular disease	13.3%
Peripheral vascular disease	11.4%
Renal disease	10.5%
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	7.3%
Peptic ulcer disease	4.4%
Diabetes with chronic complication	4.1%
Dementia	3.5%
Hemiplegia or paraplegia	3.0%
Mild liver disease	2.2%
Rheumatic disease	1.7%
Metastatic solid tumor	1.5%
Moderate or severe liver disease	0.4%
AIDS/HIV	<0.1%

[1]Comorbidities were identified from primary and secondary diagnoses from hospital discharge data based on the Enhanced ICD-9-CM diagnosis coding algorithms. Please refer to Appendix Table C2 for the coding algorithms used to define each comorbid condition.

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

Appendices

Stephane Buteau, Mark S. Goldberg, Richard T. Burnett, Antonio Gasparrini, Marie-France Valois, James M. Brophy, Dan L. Crouse, Marianne Hatzopoulou

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Figure E2. Adjusted cumulative response functions fitted as natural cubic splines with 3 degrees of freedom in the case-crossover analyses over lags 0 to 3 days between the odds of non-accidental mortality among subjects 65 years of age and over with congestive heart failure in Montreal, 1991-2003, and the spatially-resolved daily mean 8-hour exposures to ambient O_3 predicted from the following methods: (A) nearest station; (B) inverse-distance weighting ("IDW"); (C) back-extrapolation from a land use regression model ("LUR-back-extrapolated"); (D) combined LUR and Bayesian maximum entropy model ("BME"); (E) mean of all stations.

Figure E3. Adjusted cumulative response functions fitted as natural cubic spline with 3 degrees of freedom in the nested case-control analyses over lags 0 to 3 days between the hazards of non-accidental mortality among subjects 65 years of age and over with congestive heart failure in Montreal, 1991-2003, and the spatially-resolved daily 24-hour mean exposures to ambient NO_2 predicted from the following methods: A) nearest station; B) inverse-distance weighting ("IDW"); C) back-extrapolation from a land use regression model ("LUR-back-extrapolated").

Figure E4. Adjusted cumulative response functions fitted as natural cubic spline with 3 degrees of freedom in the nested case-control analyses over lags 0 to 3 days between the hazards of non-accidental mortality among subjects 65 years of age and over with congestive heart failure in Montreal, 1991-2003, and the spatially-resolved daily 8-hour mean exposures to ambient O_3 predicted from the following methods: A) nearest station; B) inverse-distance weighting ("IDW"); C) back-extrapolation from a land use regression model ("LUR-back-extrapolated"); D) combined LUR and Bayesian maximum entropy model ("BME").

Figure E5. Unadjusted cumulative response function for maximum temperature and relative humidity in the case-crossover analyses over lags 0 to 3 days for the odds of non-accidental mortality among subjects 65 years of age and over with congestive heart failure, all year and the warm season (May-September), Montreal, 1991-2003.

Figure E6. Unadjusted cumulative response functions in the nested case-control analyses of the hazards of non-accidental mortality among subjects 65 years of age and over with congestive heart failure, Montreal, 1991-2003, for: (A) age and the following time-varying area-based contextual covariates: (B) unemployment rate; (C) percentage of adults that did not complete high school; D) median household income.

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Figure E9. Estimated cumulative percentage change, over lag 0-3 day, in non-accidental daily mortality per interquartile range increase in (A) daily mean 24-hour mean exposures to ambient NO_2 (all year) and, (B) daily 8-hour mean exposures to ambient O_3 (May-September), according to the number of hospitalisations and emergency room visits in the past six months.

Figure E10. Estimated cumulative percentage change in non-accidental daily mortality over lag 0-3 day per interquartile range increase in (A) daily 24-hour mean exposures to ambient NO_2 (all year) and, (B) daily 8-hour mean exposures to ambient O_3 (May-September), according to the number of hospitalisations since the beginning of the follow-up.

Figure E11. Estimated cumulative percentage change, over lag 0-3 day, in non-accidental daily mortality per interquartile range increase in (A) daily mean 24-hour mean exposures to ambient NO_2 (all year) and, (B) daily 8-hour mean exposures to ambient O_3 (May-September), by gender.

Appendix F. Example of R code

Appendix A. Parameters estimated by the nested case-control and case-crossover designs

In both models that we used in this study (nested case-control, and case-crossover), we made use of the Cox proportional hazards model, which is essentially equivalent to a conditional logistic model.

The regression coefficients (or smoothed functions) in each design are estimated consistently with alternative definitions of the risk sets, thus providing two parameters of effects with distinct inferential interpretation. To see this explicitly, we appeal to the partial likelihood function of the Cox model.

Let $Y_i = I(x_i \geq u)$, for i^{th} individual at risk at time=u.

For one covariate that is assumed to be either a linear or a categorical variable, the partial log-likelihood is

$$l(\beta) = \Sigma_{\{\text{all grid points } u\}} [dN(u) \{ z_{I(u)} \beta - \log [\Sigma_I \exp(z_i \beta) Y_i(u)] \}]$$

where β is the parameter being estimated and z_i is the exposure for subject i.

In the nested case-control study, i in the last sum represents different subjects in each risk set, which implies that the parameter β that is being estimated represents the log rate ratio for an increase in exposure, across subjects in each risk sets, summed across all failures. It is assumed that the underlying rate ratio is invariant in time (proportional hazards assumption) and assumes independent censoring.

In the case-crossover design, the risk set at each failure now comprises only the case. Thus, z_I represents the exposure of the case at two sets of times; one at the time of the event and the other at the set of selected reference times. The last sum is therefore over the failure time of the case and his own exposure reference times. This is then summed over all failures. Thus, β represents an estimate of the within-subject log rate ratio, assuming that there exists a common log rate ratio for each failure. Thus, this is an estimate of the within-subject log rate ratio for a change in exposure.

Appendix B. Addition information about the construct of the cohort of congestive heart failure, Montreal, 1991-2003

This is an open cohort of men and women, 65 years of age and older, residing in Montreal and classified as having congestive heart failure during the study period of January 1st, 1991 to December 31st, 2002. The date of initiating the cohort was January 1, 1991. The cohort was constructed as follows. Individuals were considered as having congestive heart failure at baseline if they met our definitions (see Table B1 for the algorithms used to define congestive heart failure) in the two years prior to January 1, 1991. Persons who were resident of Montreal and age 65 years and older, who were identified as having congestive heart failure, and who were not censored (due to death or moving outside of the Montreal area) during the definition period were entered into the cohort. The same pattern was repeated every two years, i.e., new subjects entered the cohort on January 1 every two years if they were classified as having congestive heart failure sometime in the two preceding years and met the study inclusion criteria. The last sub-cohort was entered on January 1, 2001, thus leaving a potential of two years of follow-up for this last sub-cohort, 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.

Figure A1 shows the Island of Montreal, the boundaries of the three-character postal code districts from the 2001 Census Boundary Files, as well as the distribution of the number of death among persons 65 years and older during the study period of 1991-2002, inclusively. Figure A2 shows the schematic of the study design.

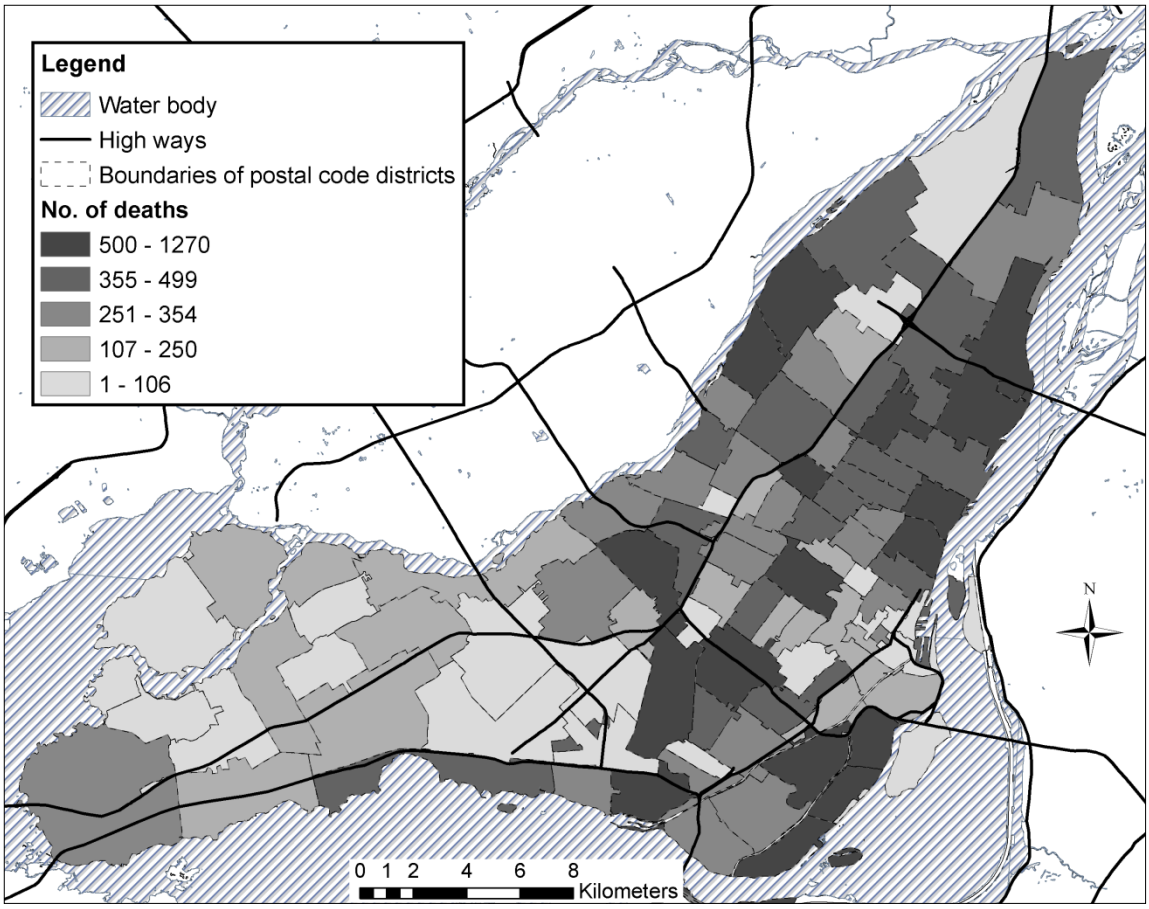


Figure B1. Map of Montreal showing the boundaries of the geographic units designated by the first three characters of the postal code, location of highways (bold black lines), and the spatial distribution of deaths among persons age 65 years and older having congestive heart failure, 1991-2003.

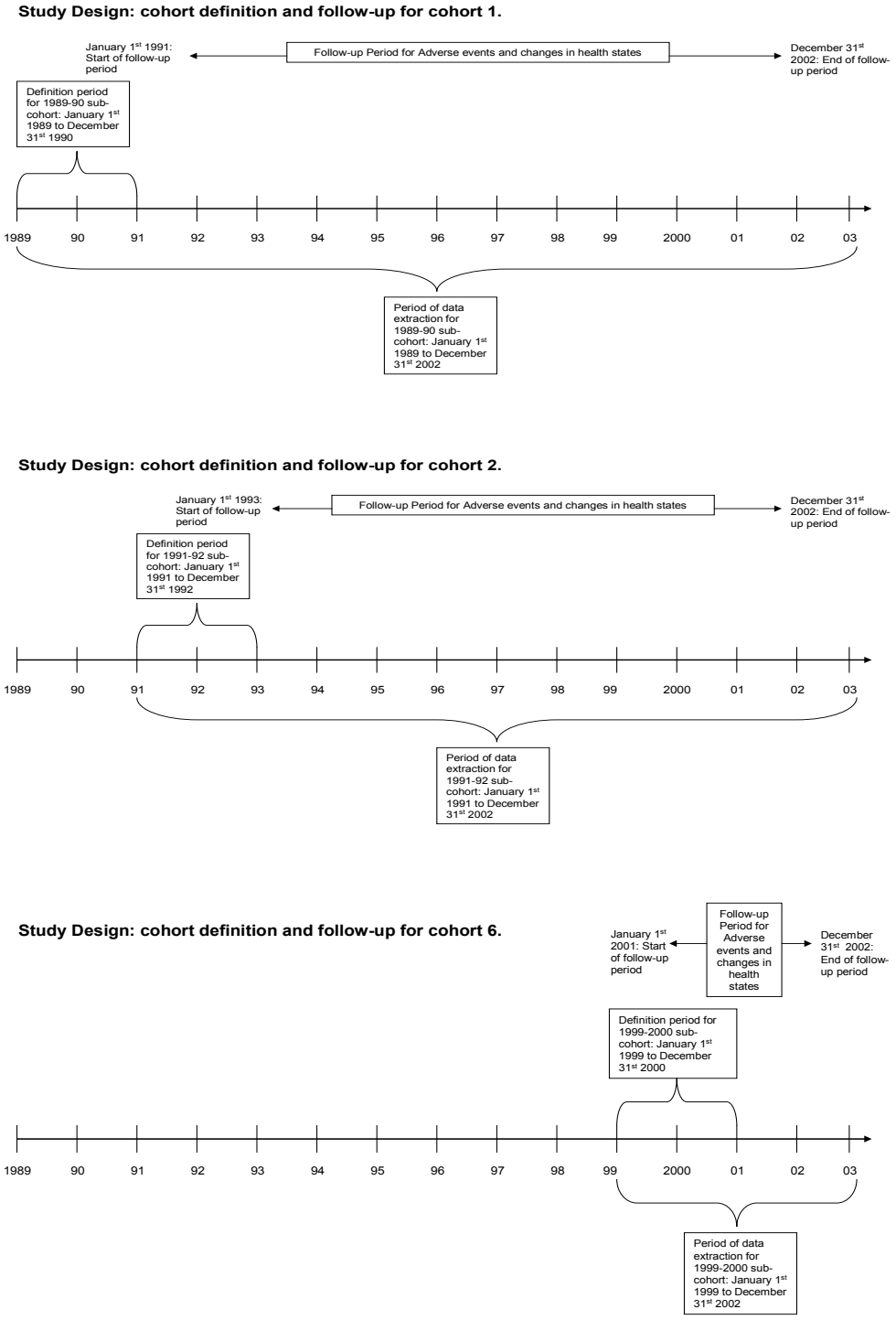


Figure B2. Schematic of the cohort study design of congestive heart failure, Montreal, 1991-2002.

Appendix C. Algorithms used to define congestive heart failure and other important comorbidities

Table C1. Algorithm used to define congestive heart failure from administrative health data[1].

CHF (specialists only)	Diagnoses (ICD-9 code 428) in billings, in specified time interval	Diagnoses (ICD-9 code 428) in hospitalization (primary or secondary), in specified time interval	Prescriptions in specified time interval	Services / tests / procedures in the specified time interval
Definition 1:	None	None	≥ 1 prescription for diuretics **AND** ≥ 1 prescription for Digoxine	≥ 1 CHF
Definition 2:	None	None	≥ 1 prescription for diuretics **AND** ≥ 1 prescription for ACE-inhibitors	≥ 1 CHF
Definition 3:	None	≥ 1 CHF (Any MD)	None	None

[1]We identified congestive heart failure diagnoses and procedures using the *International Classification of Diseases* (ICD)*, 9th Revision* codes, specifically ICD-9 428 for diagnosis and codes 8303, 8305, 8307, and 8670 for procedures.

Table C2. Coding Algorithms and weights used for defining comorbidity from hospital discharge data using International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM).

Comorbidities	**Enhanced ICD-9-CM coding used to define comorbidity[1]**
Myocardial infarction	410, 412
Congestive heart failure	428 (see Table A1 for the exact algorithms used)
Peripheral vascular disease	0930, 4373, 440, 441, 4431, 4432, 4438, 4439, 4471, 5571, 5579, V434
Cerebrovascular disease	430, 431, 432, 433, 434, 435, 436, 437, 438
Dementia	290, 2941, 3312
Chronic pulmonary disease	4168, 4169, 490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505, 5064, 5081, 5088
Rheumatic disease	4465, 7100, 7101, 7102, 7103, 7104, 7140, 7141, 7142, 7148, 725
Peptic ulcer disease	531, 532, 533, 534
Mild liver disease	570, 571, 5733, 5734, 5738, 5739, V427
Diabetes without chronic complication	2500, 2501, 2502, 2503, 2508, 2509
Diabetes with chronic complication	2504, 2505, 2506, 2507
Hemiplegia or paraplegia	3341, 342, 343, 3440, 3441, 3442, 3443, 3444, 3445, 3446, 3449
Renal disease	582, 5830, 5831, 5832, 5834, 5836, 5837, 585, 586, 5880, V420, V451, V56
Cancer	140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 170, 171, 172, 174, 175, 176, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 200, 201, 202, 203, 204, 205, 206, 207, 208, 2386
Moderate or severe liver disease	4560, 4561, 4562, 5722, 5723, 5724, 5728
Metastatic solid tumor	196, 197, 198, 199
AIDS/HIV	042, 043, 044

[1] Based on Quan, H., et al., 2005. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 43**,** 1130-9.

Appendix D. Development of indicators if health in older adults with congestive heart failure

Individuals having congestive heart failure have different natural histories. We presumed that exogenous insults interfere in the potential causal pathway linking air pollution and mortality by either "triggering" declines in health or causing exacerbations of concurrent conditions. As there is no gold standard by which to define indicators of "health", we have developed a series of possible indices that may reflect the underlying construct of "declining health" from the administrative health data, including hospital discharge, billings, pharmaceutical prescriptions. The following describe four indicators that we developed from the administrative health data.

Indicators of hospitalisations and emergency department visits

First we used the combined number of hospitalisations and emergency department visits. We created two indices reflecting the cumulative number in the three months and in the six months before an event. (Events refer to either a death of the subject or being included in a risk set for other deaths.) The underlying assumption was that each hospitalisation and emergency department visit potentially reflected a complication or worsening in a person's health. If a patient's record included more than one hospitalisation or emergency room visit on a single day, these were counted as one event. Because the distributions were highly skewed to the right and we were concerns that some very high values may be wrong (see Table D1 for the distributions) the indicators were treated as ordinal, with all cumulative counts greater than the 99th percentile of the marginal distribution (i.e., 8 and 10 for the indicator based in the prior three and six months, respectively) rounded to this value. Therefore, the indicators based on number of hospitalisations and emergency department visits in the past three and six months had nine (taking values from 0 to 8) and eleven (taking values from 0 to 10) categories, respectively.

The third indicator was the time-varying cumulative number of hospitalisations from time of entry into the study until an event. The rationale for using only hospitalisations, rather than hospitalisations and emergency department visits combined, was that a hospitalisation plausibly reflects a greater complication or worsening in a person's health of greater severity than an emergency department visit. This indicator was treated as ordinal, with all cumulative counts

greater than the 99th percentile (i.e., 11 hospitalisations) rounded to this value. Therefore, the indicator based on the number of hospitalisations since entry in the cohort had twelve categories with value ranging from 0-11.

Table D1. Distribution of the number of hospitalisations and emergency department visits in persons 65 years of age and older who were diagnosed with congestive heart failure in Montreal, 1991-2003.

Indicator of health based on hospitalisations and emergency department visits	**Percentiles**						
	Min	**25th**	**50th**	**75th**	**95th**	**99th**	**Max**
No. of hospitalisations and emergency department visits in the last 3 months	0	0	1	2	5	8	60
No. of hospitalisations and emergency department visits in the last 6 months	0	0	1	2	6	10	63
No. of hospitalisations since beginning of follow-up	0	0	1	2	6	11	111

Indicators of pharmaceutical usage

The fourth indicator was constructed from the pharmaceutical data. Based on expert judgement (Dr. James M. Brophy), the indicator relies on the prescribed dose of furosemide (Lasix), which is a loop diuretic commonly used in the treatment of heart failure to prevent the body from absorbing too much salt and thus relieves congestion. Furosemide is not specific to the treatment of congestive heart failure, and may be prescribed to those having liver disease, a kidney disorder such as nephrotic syndrome, or to treat hypertension. Typically, furosemide is taken as an oral tablet at doses of 20, 40, 80 or 500 mg. Other forms include oral solution and intravenous injection, which are generally reserved for in-hospital usage. The indicator was defined considering a tablet dosage of 40 mg or less as a "low dose" of furosemide, 41 to 80 mg as a "moderate dose" and greater than 80 mg as a "high dose". Oral solution and intravenous injection of furosemide were considered in the latter category (i.e., "high dose") as they are generally administrated to in-patients or out-patients. Those not taking furosemide were considered as a separate category. Table D2 describes prescribed usage of furosemide at time of death for persons included in the cohort of residents of Montreal, 1991-2003, 65 years of age and older, who were diagnosed with congestive heart failure.

Table D2. Description of furosemide prescribed usage among persons 65 years of age and older who were diagnosed with congestive heart failure and died in Montreal, 1991-2003.

Furosemide (Lasix) usage at time of death	Women	Men	All
Not taking furosemide	6,560 (60%)	4,394 (40%)	10,954
Mild dose (0-40 mg)	8,843 (55%)	7,203 (45%)	16,046
Moderate dose (41-80 mg)	2,094 (48%)	2,274 (52%)	4,368
High dose (>80 mg or intravenous or oral solution)	148 (44%)	191 (56%)	339

Appendix E. Additional Results

Table E1. Distribution of the indicators of health for all cases and controls included in the nested case-control analyses for NO_2 (all year).

Furosemide (Lasix) usage	**Controls**	**Cases**
Not taking furosemide	50.9%	34.6%
Mild dose (0-40 mg)	42.7%	50.7%
Moderate dose (41-80 mg)	6.1%	13.8%
High dose (>80 mg or intravenous or oral solution)	0.3%	0.9%

Indicator of health based on hospitalisations and emergency department visits [1]	**Percentiles**						
	Min	**25th**	**50th**	**75th**	**95th**	**99th**	**Max**
No. of hospitalisations and emergency department visits in the past 3 months							
Controls	0	0	1	2	5	8	8
Cases	0	1	2	4	7	8	8
No. of hospitalisations and emergency department visits in the past 6 months							
Controls	0	0	1	2	6	10	10
Cases	0	1	3	5	10	10	10
No. of hospitalisations since beginning of follow-up							
Controls	0	0	1	2	6	11	11
Cases	0	1	2	4	10	11	11

[1]The indicators of health based on hospitalisations and emergency department visits were treated as ordinal with all cumulative counts greater than the 99th percentile of their marginal distribution rounded to this value (i.e., 8 and 10 for the indicator based in the number of hospitalisations and emergency department visits in the past three and six months, and 11 for the indicator based on the number of hospitalisations since the begging of the follow-up).

Table E2. Distributions of exposure of the different metrics used for daily 8-hour (9 a.m. to 5 p.m. from May-September) mean concentrations (ppb) of O_3 and daily 24-hour mean concentrations (ppb) of NO_2, assigned to participants of the case-crossover design, Montreal, 1991-2003.

Methods	Daily mean concentration (ppb)								
	Mean	Standard deviation	Percentiles						
			Minimum	5th	25th	50th	75th	95th	Maximum
8-hour O_3 (May-September)									
Nearest station	28.7	15.2	0	7.5	17.7	27.2	37.4	57.2	108.8
Inverse-distance weighting	29.0	13.2	0.2	10.2	19.6	27.3	36.1	53.7	91.4
Back-extrapolation from a current LUR	21.1	14.0	0	4.6	11.1	18.1	27.6	47.9	148.5
Bayesian maximum entropy	30.7	9.3	0	16.9	24.4	30.3	35.9	46.9	83.7
Mean of all stations	21.6	10.0	1.1	7.6	14.7	19.8	26.5	39.3	66.6
24-hour NO_2 (entire year)									
Nearest station	21.5	10.7	0	6.7	13.9	20.3	27.5	40.4	169.5
Inverse-distance weighting	21.1	8.1	1.5	8.6	15.4	20.1	25.4	33.9	121.8
Back-extrapolation from a current LUR	16.6	7.1	0.7	6.5	11.5	15.5	20.3	28.7	121.5
Mean of all stations	20.1	7.8	4.0	5.7	14.6	19.1	24.2	30.0	90.6

Abbreviations: ppb, parts per billion; LUR, land use regression model

Table E3. Distributions of exposure of the different metrics used for daily 8-hour (9 a.m. to 5 p.m. from May-September) mean concentrations (ppb) of O_3 and daily 24-hour mean concentrations (ppb) of NO_2, assigned to participants of the nested case-control design, Montreal, 1991-2003.

Methods	Daily mean concentration (ppb)								
	Mean	Standard deviation	Percentiles						
			Minimum	5th	25th	50th	75th	95th	Maximum
8-hour O_3 (May-September)									
Nearest station	28.9	15.3	0	7.5	17.8	27.3	37.5	57.5	108.8
Inverse- distance weighting	29.2	13.3	0.1	10.3	19.7	27.5	36.4	54.2	91.4
Back-extrapolation from a current LUR	21.3	13.9	0	4.8	11.4	18.3	27.8	47.9	174.3
Bayesian maximum entropy	30.8	9.4	0	16.8	24.4	30.3	36.0	47.2	83.7
24-hour NO_2 (entire year)									
Nearest station	21.6	10.9	0	6.7	14.0	20.4	27.7	40.9	169.5
Inverse-distance weighting	21.2	8.2	1.5	8.7	15.4	20.2	25.5	34.2	138.6
Back-extrapolation from a current LUR	16.6	7.2	0.7	6.5	11.5	15.4	20.3	28.9	131.5

Abbreviations: ppb, parts per billion; LUR, land use regression model

Table E4. Distribution of selected weather variables for all years and summers (May-September, inclusive), 1991-2003, Montreal, Canada

Environmental variables	Mean	Standard deviation	Percentiles				
			Minimum	25th	50th	75th	Maximum
All year							
Daily Temperature (ºC)							
Mean	7.2	11.7	-27.6	-1.5	7.9	17.7	29.2
Minimum	2.7	11.5	-31.2	-5.1	3.2	12.6	25.8
Maximum	11.3	12.2	-24.0	1.6	12.0	22.2	35.4
Average relative humidity (%)	70.2	12.4	28.54	61.8	70.5	79.3	100
May-September							
Daily Temperature (ºC)							
Mean	18.1	4.6	3.3	15.2	18.7	21.4	29.2
Minimum	13.2	4.9	-1.2	10.0	13.7	16.7	25.8
Maximum	22.7	5.0	4.9	19.5	23.3	26.3	35.4
Average relative humidity (%)	68.7	11.7	28.5	60.9	69.0	76.9	97.8

Table E5: Spearman correlation coefficients of same-day daily mean concentrations of air pollutants for the different metrics, and mean values of maximum temperature, Montreal, 1991-2003. [1]

				NO_2				O_3				
		Maximum temperature	Relative humidity	Nearest station	IDW	Back-extrapol.	Mean of stations	Nearest station	IDW	BME	Back-extrapol.	Mean of stations
	Maximum temperature	1										
	Relative humidity	-0.14	1									
NO_2	Nearest station	0.10	-0.02	1								
NO_2	IDW	0.18	-0.01	0.79	1							
NO_2	Back-extrapol.	0.17	-0.01	0.73	0.90	1						
NO_2	Mean of stations	0.18	-0.01	0.63	0.94	0.83	1					
O_3	Nearest station	0.51	-0.38	-0.12	0.09	0.07	0.18	1				
O_3	IDW	0.61	-0.43	0.08	0.20	0.17	0.24	0.89	1			
O_3	BME	0.59	-0.37	0.11	0.22	0.19	0.24	0.73	0.85	1		
O_3	Back-extrapol.	0.44	-0.33	-0.09	0.01	-0.12	0.12	0.76	0.78	0.63	1	
O_3	Mean of stations	0.49	-0.32	0.03	0.08	0.08	0.07	0.71	0.84	0.81	0.62	1

[1] Spearman correlation coefficients for O_3 were computed using data limited to the period of May-September, inclusively. Abbreviations: O_3, ozone; NO_2, nitrogen dioxide; IDW, inverse-distance weighting; back-extrapol., back-extrapolation from a land use regression surface; BME, Bayesian maximum entropy model.

Table E6. Model fit of the adjusted cumulative response functions for air pollutants fitted using linear and non-linear structures in the case-crossover analyses over lags 0 to 3 days for the odds of non-accidental mortality among subjects 65 years of age and over with congestive heart failure, Montreal, 1991-2003.

Metric of exposure and functional form for air pollutant	**Akaike information criterion (AIC)**			
	Case-crossover		**Nested case-control**	
	24-hour NO_2 (all year)	**8-hour O_3 (May-Sep.)**	**24-hour NO_2 (all year)**	**8-hour O_3 (May-Sep.)**
Nearest station				
Linear	93,152	33,791	286,209	104,725
Natural cubic splines, 2df	93,159	33,794	286,212	104,727
Natural cubic splines, 3df	93,161	33,799	296,216	104,727
Inverse-distance weighting				
Linear	93,151	33,790	286,218	104,727
Natural cubic splines, 2df	93,157	33,795	286,222	104,727
Natural cubic splines, 3df	93,161	33,803	286,227	106,733
Back-extrapolation from LUR				
Linear	92,640	33,791	284,623	104,723
Natural cubic splines, 2df	92,647	33,796	284,628	104,727
Natural cubic splines, 3df	92,652	33,803	284,633	104,731
Bayesian maximum entropy model				
Linear	N/A	33,789	N/A	104,735
Natural cubic splines, 2df	N/A	33,796	N/A	104,742
Natural cubic splines, 3df	N/A	33,798	N/A	104,747
Mean of all stations				
Linear	93,153	33,793	N/A	N/A
Natural cubic splines, 2df	93,159	33,794	N/A	N/A
Natural cubic splines, 3df	93,162	33,799	N/A	N/A

Abbreviations: df, degrees of freedom, LUR, land use regression model, N/A, not available (the Bayesian maximum entropy model for NO_2 was not developed and the nested case-control analysis requires variation in the daily exposure across individuals; thus cannot be performed using the mean of all stations).

Table E7. Estimated percentage change in non-accidental mortality among subjects 65 years of age and over with congestive heart failure according to an interquartile range increase in the daily 24-hour mean concentrations (ppb) of NO_2 (all year) and the daily 8-hour mean concentrations (ppb) of O_3 (May-September), Montreal, 1991–2003.[1]

Lagged effect	**NO_2 - % Change (95% CI)**		**O_3 - % Change (95% CI)**		
(in days)	Nested case-control	Case-crossover	Nested case-control	Case-crossover, adjusted for weather	Case-crossover, unadjusted
Nearest station					
Lag 0	-2.5 (-5.8, 0.8)	-0.4 (-2.8, 2.1)	7.7 (0.3, 15.7)	1.6 (-3.2, 6.7)	1.8 (-1.7, 5.3)
Lag 1	-1.0 (-4.7, 2.9)	1.7 (-1.0, 4.6)	-6.0 (-13.0, 1.6)	-1.8 (-6.7, 3.3)	2.1 (-1.6, 6.0)
Lag 2	-0.2 (-4.0, 3.7)	2.4 (-0.4, 5.3)	-1.0 (-8.5, 7.1)	-1.4 (-6.3, 3.8)	0.3 (-3.5, 4.1)
Lag 3	-1.9 (-5.2, 1.5)	-1.6 (-3.9, 0.8)	6.4 (-0.9, 14.3)	-0.6 (-5.4, 4.4)	0.1 (-3.4, 3.6)
Cumulative	-5.5 (-8.1, -2.9)	2.1 (-1.1, 5.5)	6.7 (0.3, 13.5)	-2.2 (-9.2, 5.2)	4.3 (-0.5, 9.2)
Inverse-distance weighting					
Lag 0	-4.8 (-12.6, 3.6)	0.1 (-2.3, 2.5)	34.2 (6.8, 68.6)	1.2 (-3.5, 6.3)	1.2 (-1.9, 4.4)
Lag 1	-0.1 (-9.1, 9.8)	1.6 (-1.1, 4.3)	-11.9 (-31.2, 12.7)	2.6 (-2.4, 7.8)	3.9 (0.4, 7.4)
Lag 2	1.2 (-8.0, 11.4)	2.6 (-0.1, 5.4)	-10.6 (-30.3, 14.6)	0.9 (-4.1, 6.1)	1.0 (-2.4, 4.6)
Lag 3	-5.5 (-13.2, 2.9)	-1.4 (-3.7, 0.8)	12.2 (-10.7, 40.8)	-2.3 (-7.0, 2.6)	-0.7 (-3.8, 2.5)
Cumulative	-9.0 (-15.2, -2.4)	2.8 (-0.3, 6.1)	18.5 (-2.6, 44.1)	2.4 (-4.9, 10.3)	5.4 (1.2, 9.8)
Back-extrapolation from LUR					
Lag 0	0.4 (-6.6, 7.9)	0.3 (-2.2, 2.8)	3.6 (-4.8, 12.7)	1.6 (-3.8, 7.3)	1.8 (-2.1, 5.8)
Lag 1	2.2 (-6.0, 11.2)	1.7 (-1.1, 4.6)	-3.0 (-12.0, 7.0)	-0.4 (-5.9, 5.5)	3.1 (-1.2, 7.6)
Lag 2	1.9 (-6.4, 10.9)	2.6 (-0.2, 5.6)	-1.0 (-10.4, 9.4)	1.6 (-4.2, 7.7)	1.5 (-2.8, 6.0)
Lag 3	-1.6 (-8.5, 5.9)	-1.5 (-3.9, 0.9)	7.8 (-1.0, 17.4)	0.6 (-4.9, 6.4)	0.5 (-3.4, 4.6)
Cumulative	2.9 (-0.9, 6.9)	3.0 (-0.4, 6.6)	7.3 (3.0, 11.9)	3.5 (-4.5, 12.1)	7.1 (1.7, 12.7)
Bayesian maximum entropy model					
Lag 0	N/A	N/A	0.6 (-6.1, 7.9)	-0.9 (-5.9, 4.4)	0.9 (-2.6, 4.5)
Lag 1	N/A	N/A	-0.1 (-7.1, 7.5)	2.8 (-2.6, 8.5)	4.7 (0.6, 8.9)
Lag 2	N/A	N/A	1.0 (-6.2, 8.7)	-2.1 (-7.3, 3.3)	-0.3 (-4.3, 3.8)
Lag 3	N/A	N/A	-0.8 (-7.5, 6.4)	-2.7 (-7.6, 2.4)	-1.2 (-4.6, 2.3)
Cumulative	N/A	N/A	0.8 (-7.3, 9.5)	-3.0 (-10.0, 4.5)	4.0 (-0.1, 8.3)
Mean of all stations					
Lag 0	N/A	0.1 (-2.2, 2.5)	N/A	0.8 (-3.4, 5.2)	2.0 (-1.2, 5.4)
Lag 1	N/A	1.4 (-1.2, 4.1)	N/A	2.2 (-2.5, 7.1)	3.4 (-0.4, 7.4)
Lag 2	N/A	2.2 (-0.5, 5.0)	N/A	-0.6 (-5.1, 4.2)	0.2 (-3.6, 4.1)
Lag 3	N/A	-1.4 (-3.6, 0.9)	N/A	-2.2 (-6.3, 2.0)	-1.4 (-4.6, 1.9)
Cumulative	N/A	2.3 (-0.8, 5.6)	N/A	0.1 (-5.7, 6.3)	4.3 (0.3, 8.5)

Abbreviations: LUR, land use regression, N/A, not applicable (the Bayesian maximum entropy model for NO_2 was not developed and the nested case-control analysis requires variation in the daily exposure across individuals; thus cannot be performed using the mean of all stations).

[1]For NO_2, interquartile ranges (IQRs) were 13.6, 10.0, 8.8 and 9.6 ppb for the nearest station approach, inverse-distance weighting, back-extrapolation from a land use regression (LUR), and the daily mean across all stations ("Mean of stations"), respectively. For O_3, IQRs were 19.6, 16.6, 16.4, 11.6 and 11.8 ppb for nearest station approach, inverse-distance weighting, back-extrapolation from a land use regression (LUR), Bayesian maximum entropy model and the daily mean across all stations, respectively.

Table E8. Effect of adjustments for weather (maximum temperature and relative humidity) in the case-crossover analyses on the odds of non-accidental mortality among subjects 65 years of age and over with congestive heart failure, per interquartile range increase in each air pollutant, Montreal, 1991–2003.[1]

	24-hour mean NO_2 (all year)		**8-hour mean O_3 (May-Sep.)**	
	AIC	% Change (95%CI)	AIC	% Change (95%CI)
Nearest station				
Unadjusted for weather	93338	2.9 (-0.2, 6.1)	33797	4.3 (-0.5, 9.2)
Adjusted for weather	93152	2.1 (-1.1, 5.5)	33791	-2.2 (-9.2, 5.2)
Inverse-distance weighting				
Unadjusted for weather	93335	3.5 (0.5, 6.6)	33790	5.4 (1.2, 9.8)
Adjusted for weather	93151	2.8 (-0.3, 6.1)	33790	2.4 (-4.9, 10.3)
LUR back-extrapolated				
Unadjusted for weather	92823	3.7 (0.5, 7.0)	33793	7.1 (1.7, 12.7)
Adjusted for weather	92640	3.0 (-0.4, 6.6)	33791	3.5 (-4.5, 12.1)
Bayesian maximum entropy				
Unadjusted for weather	N/A	N/A	33792	4.0 (-0.1, 8.3)
Adjusted for weather	N/A	N/A	33789	-3.0 (-10.0, 4.5)
Mean of all stations				
Unadjusted for weather	93338	3.1 (0.1, 6.1)	33790	4.3 (0.3, 8.5)
Adjusted for weather	93153	2.3 (-0.8, 5.6)	33789	0.1 (-5.7, 6.3)

Abbreviations: LUR, land use regression, N/A, not applicable

[1] Effect estimates are from the case-crossover analysis that controlled for time invariant factors and temporal trend by design. The model adjusted for weather included maximum temperature (natural cubic spline with 3 df), and relative humidity (linear), from a distributed lag non-linear model using an unconstrained lag structure over lags 0 to 3 days. For NO_2, interquartile ranges (IQRs) were 13.6, 10.0, 8.8 and 9.6 ppb for the nearest station, inverse-distance weighting, LUR back-extrapolated and the daily mean of all stations, respectively. For O_3, IQRs were 19.6, 16.6, 16.4, 11.6 and 11.8 ppb for the nearest station, inverse-distance weighting, LUR back-extrapolated, Bayesian maximum entropy and the daily mean of all stations, respectively.

Table E9. Effects of adjustments for the indicators of health in the nested case-control analyses on the hazards of non-accidental mortality among subjects 65 years of age and over with congestive heart failure per interquartile range increase in air pollutant, Montreal, 1991–2003.[1]

	24-hour mean NO_2 (all year)		**8-hour mean O_3 (May-Sep.)**	
	AIC	% Change (95% CI)	AIC	% Change (95% CI)
Nearest station				
Model without any indicator of health	286,209	-5.5 (-8.1, -2.9)	104,726	6.7 (0.3, 13.5)
Model adjusting for Hosp + ER in past 3 months	266,811	-4.8 (-7.4, -2.1)	97,362	3.9 (-2.3, 10.5)
Model adjusting for Hosp + ER in past 6 months	267,138	-5.5 (-7.7, -2.5)	97,211	4.0 (-2.2, 10.6)
Model adjusting for Hosp over whole follow-up	267,764	-7.3 (-9.8, -4.7)	97,656	10.5 (3.8, 17.5)
Model adjusting for furosemide	281,502	-5,2 (-7.8, -2.5)	102,792	5.9 (-0.5, 12.6)
Inverse-distance weighting				
Model without any indicator of health	286,218	-9.0 (-15.2, -2.4)	104,727	18.5 (-2.6, 44.1)
Model adjusting for Hosp + ER in past 3 months	266,814	-9.5 (-15.7, -2.9)	97,361	17.1 (-3.9, 42.6)
Model adjusting for Hosp + ER in past 6 months	267,141	-10.7 (-16.8, -4.2)	97,210	19.2 (-2.1, 45.2)
Model adjusting for Hosp over whole follow-up	267,767	-16.4 (-22.1, -10.3)	97,652	45.6 (19.6, 77.2)
Model adjusting for furosemide	281,511	-8.1 (-14.4, -1.4)	102,791	15.7 (-5.0, 40.8)
LUR back-extrapolated				
Model without any indicator of health	284,623	2.9 (-0.9, 6.9)	104,723	7.3 (3.0, 11.9)
Model adjusting for Hosp + ER in past 3 months	265,347	1.7 (-2.2, 5.6)	97,361	5.6 (1.3, 10.1)
Model adjusting for Hosp + ER in past 6 months	265,672	1.0 (-2.8, 4.9)	97,209	6.1 (1.8, 10.6)
Model adjusting for Hosp over whole follow-up	266,279	-0.6 (-4.3, 3.3)	97,641	12.2 (7.6, 17.0)
Model adjusting for furosemide	279,918	2.0 (-1.8, 5.9)	102,789	6.7 (2.3, 11.2)
Bayesian maximum entropy				
Model without any indicator of health	N/A	N/A	104,736	0.8 (-7.3, 9.5)
Model adjusting for Hosp + ER in past 3 months	N/A	N/A	97,370	-0.6 (-8.6, 8.1)
Model adjusting for Hosp + ER in past 6 months	N/A	N/A	97,219	-0.2 (-8.2, 8.6)
Model adjusting for Hosp over whole follow-up	N/A	N/A	97,672	1.7 (-6.5, 10.6)
Model adjusting for furosemide	N/A	N/A	102,800	0.8 (-7.3, 9.6)

Abbreviations: AIC, Akaike information criterion; ER, emergency room visits; Hosp, hospitalisation; LUR, land use regression; N/A, not applicable.

[1] Effect estimates are from the nested case-control analysis that controlled for temporal factor and gender by design. The model adjusted for weather included maximum temperature (natural cubic spline with 3 df), and relative humidity (linear), from a distributed lag non-linear model using an unconstrained lag structure over lags 0 to 3 days. For NO_2, interquartile ranges (IQRs) were 13.6, 10.0 and 8.8 ppb for the nearest station, inverse-distance weighting and LUR back-extrapolated methods, respectively. For O_3, IQRs were 19.6, 16.6, 16.4 and 11.6 ppb for the nearest station, inverse-distance weighting, LUR back-extrapolated and Bayesian maximum entropy methods, respectively.

Table E10. Cumulative percentage change (and 95% confidence interval) in non-accidental mortality among subjects 65 years of age and over with congestive heart failure according to an interquartile range increase in the daily 24-hour mean concentrations (ppb) of NO_2 for all year and the warm season (May-September), Montreal, 1991–2003.

	% Change (95% CI)			
	Case-crossover		**Nested case-control**	
	All year	May-September	All year	May-September
Nearest station	2.1 (-1.1, 5.5)	1.3 (-4.0, 6.9)	-5.5 (-8.1, -2.9)	-5.2 (-8.8, -1.5)
Inverse-distance weighting	2.8 (-0.3, 6.1)	1.3 (-4.1, 6.9)	-9.0 (-15.2, -2.4)	-9.4 (-17.7, -0.3)
LUR back-extrapolated	3.0 (-0.4, 6.6)	1.6 (-4.1, 7.7)	2.9 (-0.9, 6.9)	-0.2 (-5.8, 5.8)
Mean of stations	2.3 (-0.8, 5.6)	-0.7 (-5.9, 4.9)	N/A	N/A

Abbreviations: N/A, not applicable; LUR, land use regression.

[1] For the case-crossover, the results are from the model adjusting for weather. For all year, interquartile ranges were 13.6, 10.0, 8.8 and 9.6 ppb for the nearest station approach, inverse-distance weighting, LUR back-extrapolated, and the daily mean across all stations ("Mean of stations"), respectively. For the warm season, interquartile ranges were 12.7, 8.5, 7.3, 7.8 ppb for the nearest station approach, inverse-distance weighting, LUR back-extrapolated, and the daily mean across all stations ("Mean of stations"), respectively.

Table E11. Cumulative percent change (and 95% confidence interval) in the case-crossover analyses on the odds of non-accidental mortality among subjects 65 years of age and over with congestive heart failure per interquartile range increase in air pollutant, Montreal, 1991–2003, according to level of agreement in the exposure assigned to postal areas by the different metrics.[1]

	% Change (95% CI)		
	24-hour mean NO_2 (all year)	8-hour mean O_3 (May-Sep.)	
		Adjusted for weather	Unadjusted For weather
Nearest station			
Postal districts of higher agreement	3.1 (-1.6, 8.0)	-3.7 (-12.4, 5.9)	2.2 (-3.7, 8.5)
Postal districts of lower agreement	1.1 (-3.3, 5.7)	-0.2 (-11.1, 12.2)	7.6 (-0.1, 15.9)
Inverse-distance weighting			
Postal districts of higher agreement	3.8 (-0.5, 8.3)	0.4 (-8.9, 10.6)	3.5 (-2.0, 9.2)
Postal districts of lower agreement	1.6 (-3.0, 6.4)	5.2 (-6.3, 18.2)	8.4 (1.7, 15.6)
LUR back-extrapolated			
Postal districts of higher agreement	3.4 (-1.0, 7.9)	2.6 (-7.4, 13.7)	4.6 (-1.5, 11.1)
Postal districts of lower agreement	2.9 (-2.6, 8.7)	8.7 (-5.7, 25.3)	14.4 (-0.4, 13.2)
Mean of all stations			
Postal districts of higher agreement	3.1 (-1.2, 7.5)	-2.0 (-9.5, 6.0)	2.5 (-2.7, 7.9)
Postal districts of lower agreement	1.3 (-3.4, 6.1)	2.7 (-46.3, 12.5)	6.8 (0.6, 13.3)
Bayesian maximum entropy			
Postal districts of higher agreement	N/A	-3.2 (-12.0, 6.5)	2.6 (-2.7, 8.1)
Postal districts of lower agreement	N/A	-2.7 (-13.7, 9.8)	6.2 (-0.4, 13.2)

Abbreviations: N/A, not applicable; LUR, land use regression.

[1] Effect estimates for NO_2 are from the case-crossover that controlled for time invariant factors and temporal trend by design and we statistically adjusted for maximum temperature (natural cubic spline with 3 df), and relative humidity (linear), from a distributed lag non-linear model accumulated over lags 0 to 3 days. For O_3 we presented the results adjusting ("Adjusted for weather") and unadjusting for weather ("Unadjusted for weather") as we were concerned with possible overadjustment. Threshold value used to distinguish postal districts of higher agreement from lower agreement was the median of the mean intraclass correlation coefficient (ICC) across pairs of methods by postal code area (ICC=0.75 for NO_2, ICC = 0.65 for O_3). For NO_2, there were 17,389 cases in postal code districts of higher agreement and 14,152 cases in postal districts of lower agreement. For O_3 there were 6,751 and 5,061 cases that were residents of postal district of higher and lower agreement, respectively. For NO_2, interquartile ranges (IQRs) were 13.6, 10.0, 8.8, 9.6 ppb for the nearest station, inverse-distance weighting, LUR back-extrapolated and mean of all stations, respectively. For O_3, IQRs were 19.6, 16.6, 16.4, 11.8, 11.6 ppb for the nearest station, inverse-distance weighting, LUR back-extrapolated, mean of all stations and Bayesian maximum entropy, respectively.

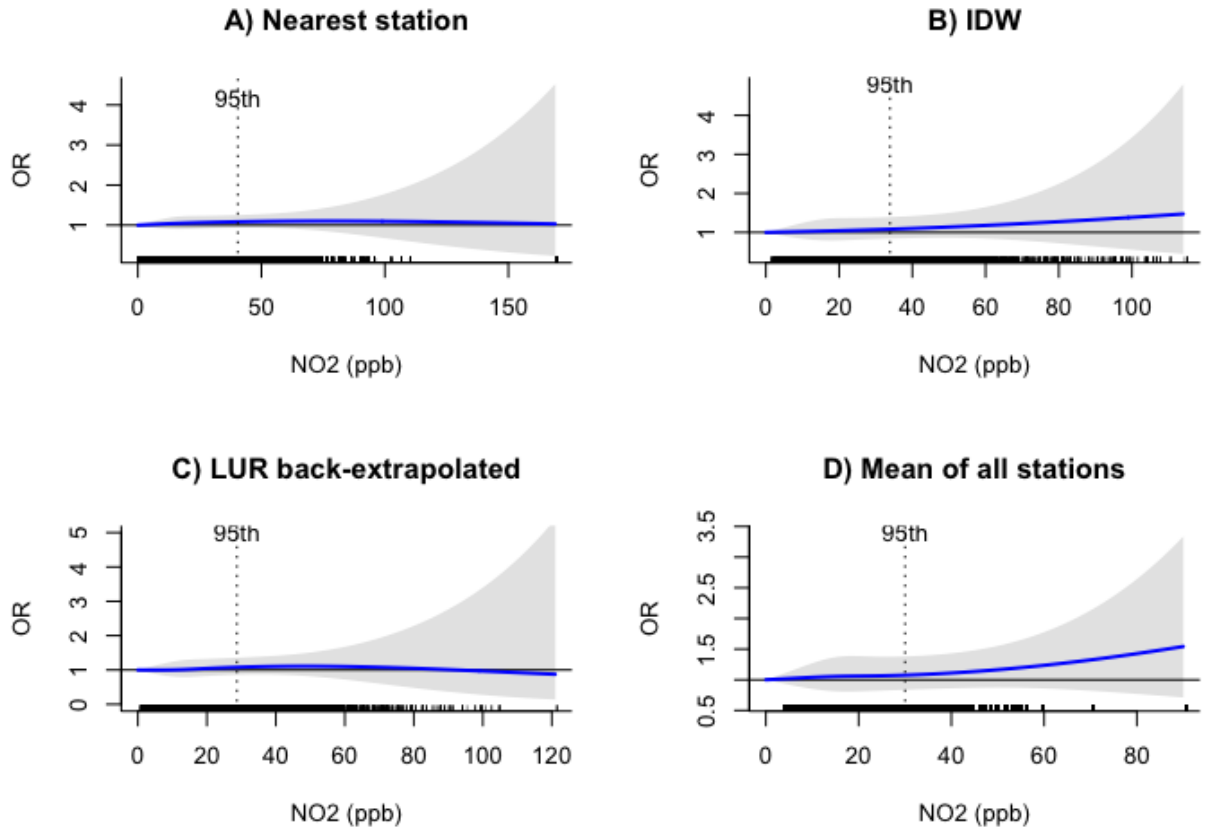


Figure E1. Adjusted cumulative response functions fitted as natural cubic splines with 3 degrees of freedom in the case-crossover analyses over lags 0 to 3 days between the odds of non-accidental mortality among subjects 65 years of age and over with congestive heart failure in Montreal, 1991-2003, and the spatially-resolved daily 24-hour mean exposures to ambient NO_2 predicted from the following methods: (A) nearest station; (B) inverse-distance weighting ("IDW"); (C) back-extrapolation from a land use regression model ("LUR-back-extrapolated"); (D) mean of all stations. We statistically adjusted for maximum temperature (natural cubic splines with 3 df), and relative humidity (linear), from a distributed lag non-linear model accumulated over lags 0 to 3 days. An unconstrained lag structure was always used. The odds ratios (OR) are relative to the minimum value of the exposure distribution. The solid line in blue represents the mean OR from the non-linear function fitted using natural cubic splines with 3 df, with shaded grey representing the 95% confidence interval. The rug plot over the horizontal axis shows the distribution of NO_2 exposures of cases and controls, whereas the vertical line (dotted) indicates the 95^{th} percentile.

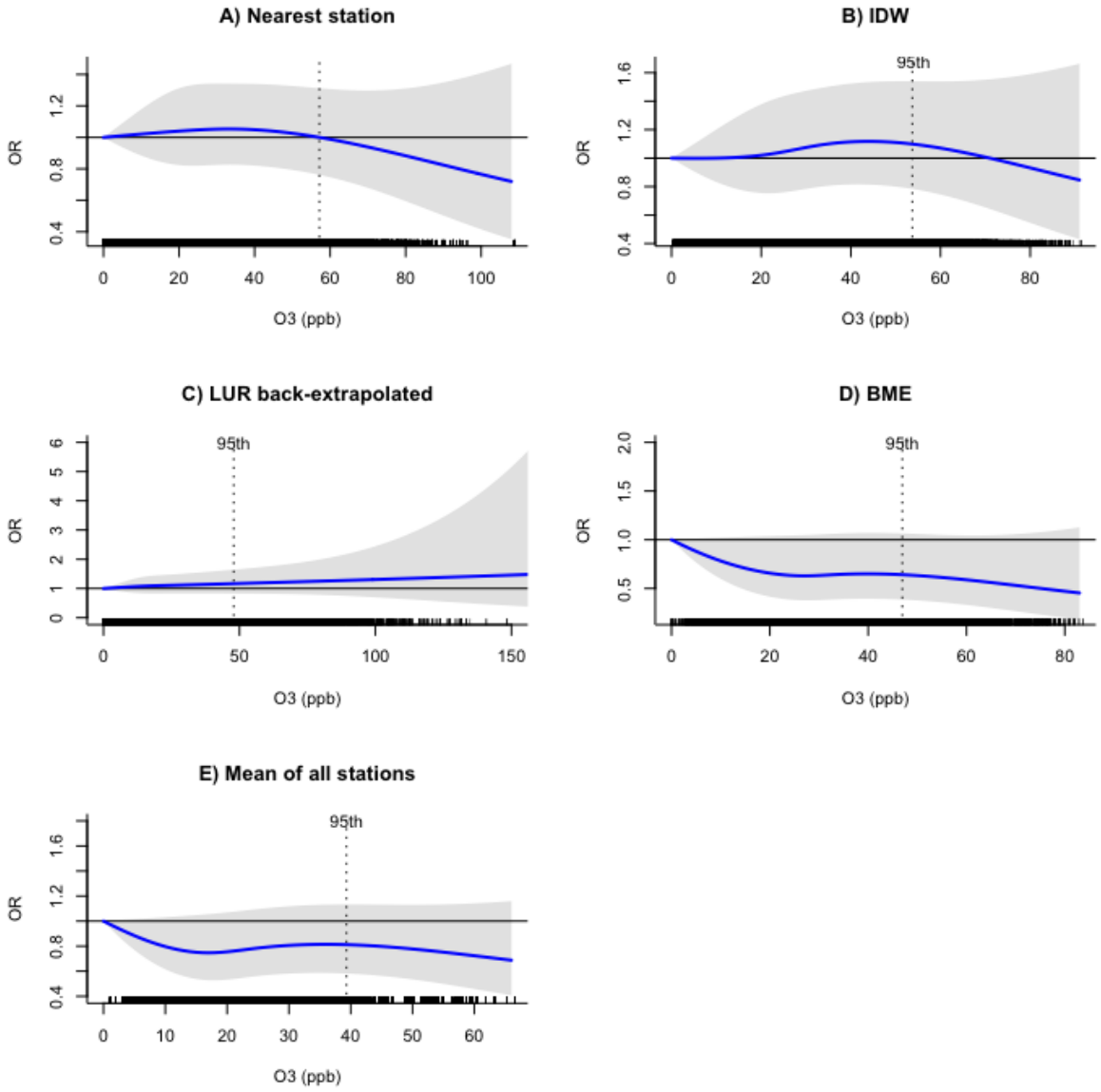


Figure E2. Adjusted cumulative response functions fitted as natural cubic splines with 3 degrees of freedom in the case-crossover analyses over lags 0 to 3 days between the odds of non-accidental mortality among subjects 65 years of age and over with congestive heart failure in Montreal, 1991-2003, and the spatially-resolved daily mean 8-hour exposures to ambient O_3 predicted from the following methods: (A) nearest station; (B) inverse-distance weighting ("IDW"); (C) back-extrapolation from a land use regression model ("LUR-back-extrapolated"); (D) combined LUR and Bayesian maximum entropy model ("BME"); (E) mean of all stations. We statistically adjusted for maximum temperature (natural cubic splines with 3 df), and relative humidity (linear), from a distributed lag non-linear model accumulated over lags 0 to 3 days. An unconstrained lag structure was always used. The odds ratios (OR) are relative to the minimum value of the exposure distribution. The solid line in blue represents the mean OR from the non-linear function fitted using natural cubic splines with 3 df, with shaded grey representing the 95% confidence interval. The rug plot over the horizontal axis shows the distribution of O_3 exposures of cases and controls, whereas the vertical line (dotted) indicates the 95th percentile.

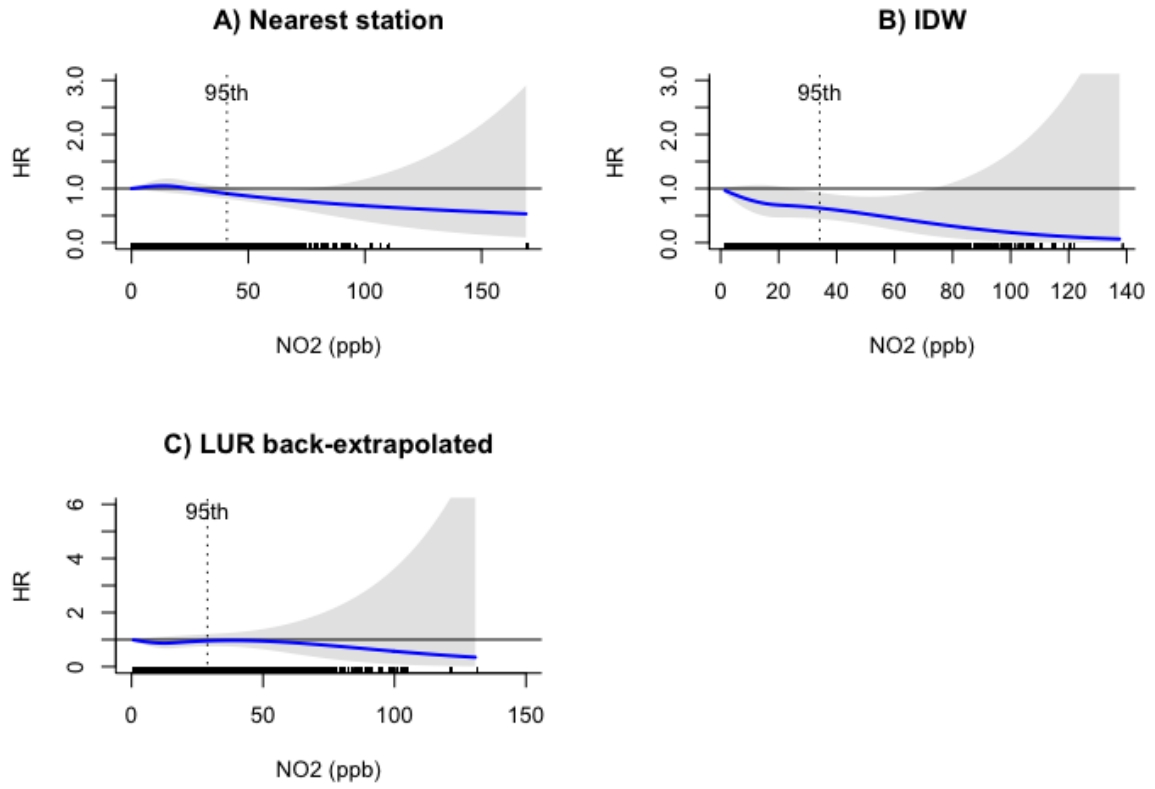


Figure E3. Adjusted cumulative response functions fitted as natural cubic spline with 3 degrees of freedom in the nested case-control analyses over lags 0 to 3 days between the hazards of non-accidental mortality among subjects 65 years of age and over with congestive heart failure in Montreal, 1991-2003, and the spatially-resolved daily 24-hour mean exposures to ambient NO_2 predicted from the following methods: A) nearest station; B) inverse-distance weighting ("IDW"); C) back-extrapolation from a land use regression model ("LUR-back-extrapolated"). An unconstrained lag structure was always used. The hazard ratios (HR) are relative to the minimum value of the exposure distribution. The solid line in blue represents the mean HR from the non-linear function fitted using natural cubic splines with 3 degrees of freedom, with shaded grey representing the 95% confidence interval. The rug plot over the horizontal axis shows the distribution of NO_2 exposures of cases and controls, whereas the vertical line (dotted) indicates the 95^{th} percentile.

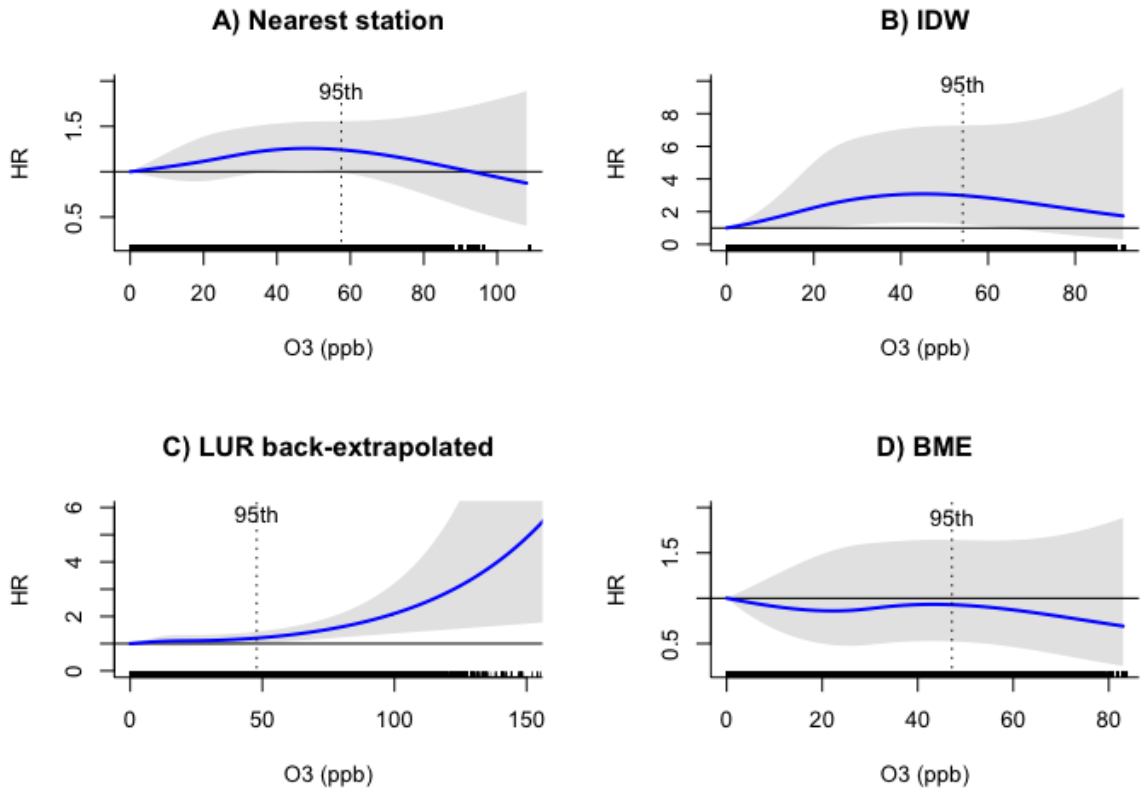


Figure E4. Adjusted cumulative response functions fitted as natural cubic spline with 3 degrees of freedom in the nested case-control analyses over lags 0 to 3 days between the hazards of non-accidental mortality among subjects 65 years of age and over with congestive heart failure in Montreal, 1991-2003, and the spatially-resolved daily 8-hour mean exposures to ambient O_3 predicted from the following methods: A) nearest station; B) inverse-distance weighting ("IDW"); C) back-extrapolation from a land use regression model ("LUR-back-extrapolated"); D) combined LUR and Bayesian maximum entropy model ("BME"). An unconstrained lag structure was always used. The hazard ratios (HR) are relative to the minimum value of the exposure distribution. The solid line in blue represents the mean HR from the non-linear function fitted using natural cubic splines with 3 degrees of freedom, with shaded grey representing the 95% confidence interval. The solid and dashed lines in green represent the mean HR and the 95% confidence interval of linear response function, respectively. The rug plot over the horizontal axis shows the distribution of O_3 exposures of cases and controls, whereas the vertical line (dotted) indicates the 95th percentile.

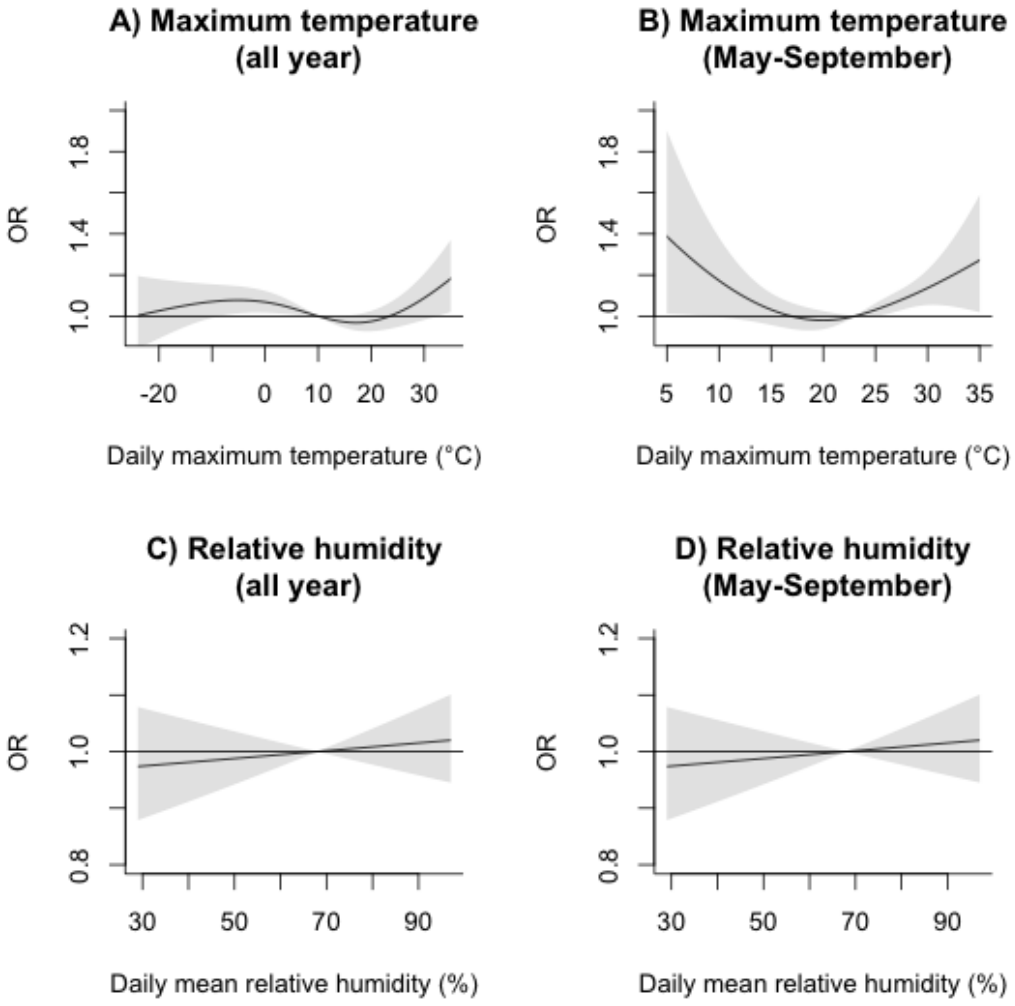


Figure E5. Unadjusted cumulative response function for maximum temperature and relative humidity in the case-crossover analyses over lags 0 to 3 days for the odds of non-accidental mortality among subjects 65 years of age and over with congestive heart failure, all year and the warm season (May-September), Montreal, 1991-2003. Daily maximum temperature and relative humidity were fitted from a distributed lag non-linear model over lag 0-3 day using natural cubic splines with 3 df and a linear function, respectively, and always using an unconstrained lag structure. The odds ratios (OR) and 95% confidence intervals are relative to A) 10°C, B) 23°C, C) 68%, D) 70%, which corresponded to the mean value of the weather variables over the different time periods.

Response functions for weather variables included in the case-crossover analyses and for contextual variables included in the nested case-control analyses.

Figure E5 shows below the unadjusted cumulative response function for maximum temperature and relative humidity in the case-crossover analyses over lags 0 to 3 days for the odds of non-accidental mortality among subjects 65 years of age and over with congestive heart failure, all year and the warm season (May-September), Montreal, 1991-2003. The odds of non-accidental showed a strong increase at higher maximum temperatures, starting at about 20°C, whereas when limited to the warm season the response function was "U"-shaped with the lowest risk at about 20°C. Relative humidity was positively associated with the odds of mortality, and the response-function was consistent with linearity for the entire year and in the warm season.

Figure E6 shows below the unadjusted cumulative response functions in the nested case-control analyses of the hazards of non-accidental mortality among subjects 65 years of age and over with congestive heart failure, Montreal, 1991-2003, for age and selected area-based contextual covariates. For age and unemployment the mortality response-functions were positive and monotonically increasing. For the percentage of adults who did not complete high school the relationship was positive and linear, whereas the risk of mortality decreased with increasing median household income until approximately the 97th percentile (approximately $Cdn60,000), above which daily mortality appears to increase but the confidence interval was wide.

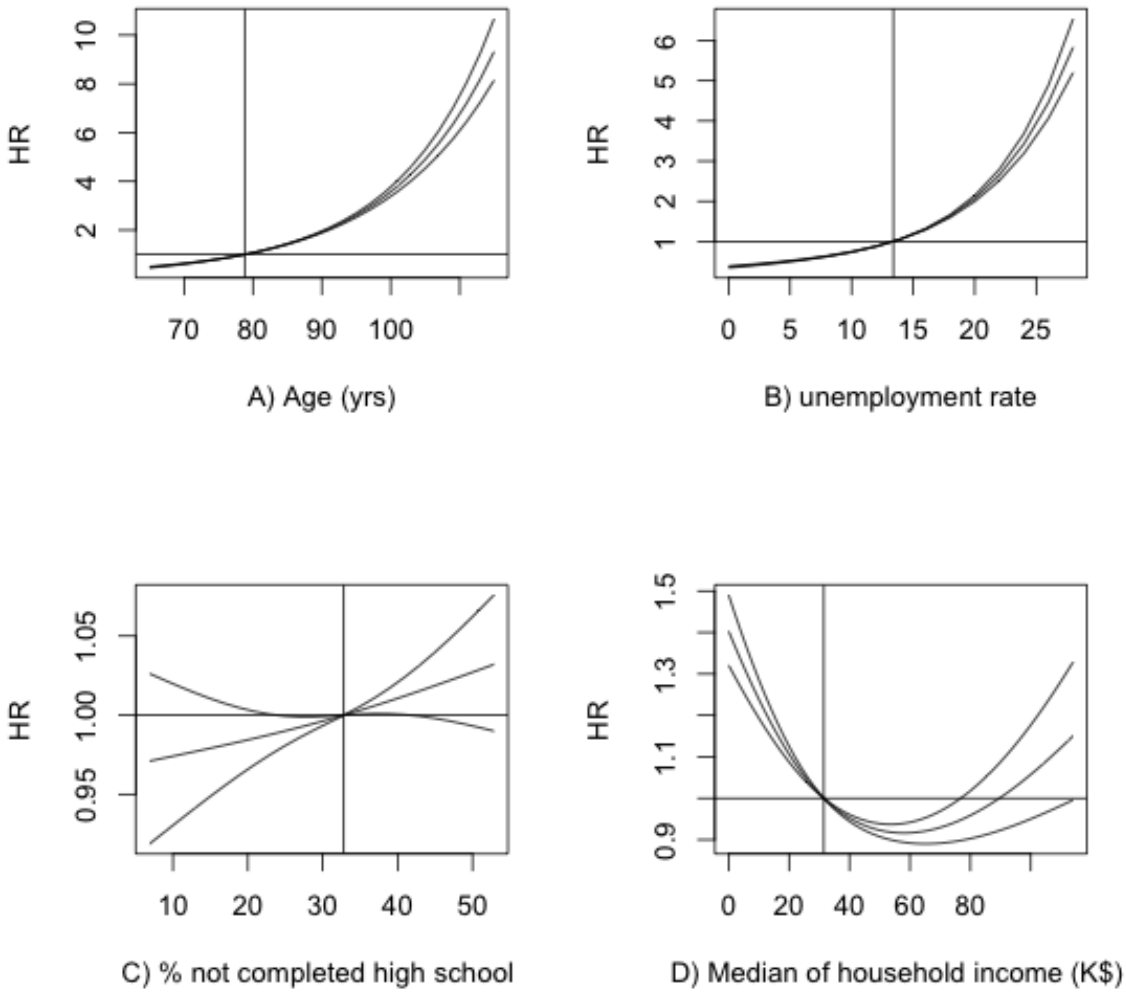


Figure E6. Unadjusted cumulative response functions in the nested case-control analyses of the hazards of non-accidental mortality among subjects 65 years of age and over with congestive heart failure, Montreal, 1991-2003, for: (A) age and the following time-varying area-based contextual covariates: (B) unemployment rate; (C) percentage of adults that did not complete high school; D) median household income. All response-functions were fitted using natural cubic splines with 3df, and the hazard ratios (HR) and 95% confidence intervals were expressed relative to the mean value of each variable (vertical line).

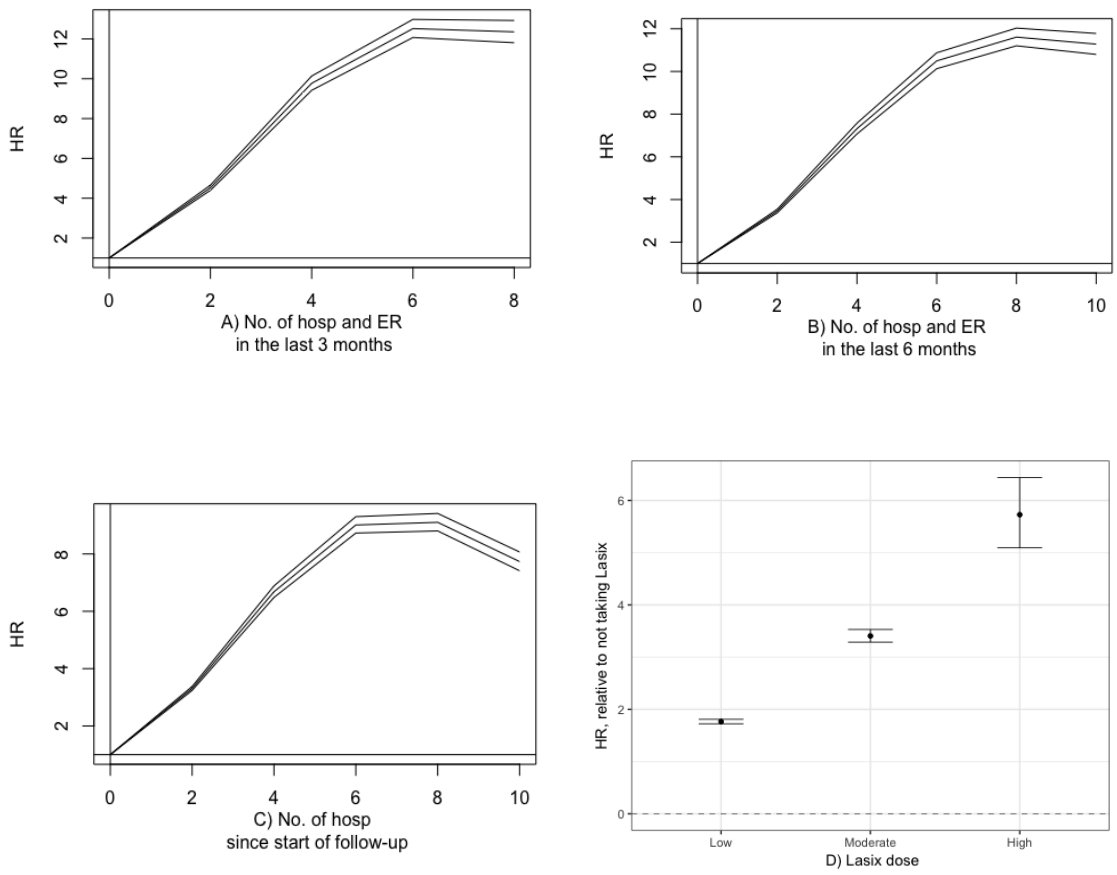


Figure E7. Unadjusted cumulative response functions in the nested case-control analyses of the hazards of non-accidental mortality among subjects 65 years of age and over with congestive heart failure, Montreal, 1991-2003, for: A) number of hospitalisations (hosp) and emergency room visits (ER) in the last 3 months; B) number of hospitalisation and emergency visits in the last 6 months; C) number of hospitalisations during the whole follow-up; D) furosemide (Lasix) usage. The hazard ratios (HR) and 95% confidence intervals were expressed relative to a value of zero for each variable (vertical line). For the indicator based on the prescribed dose of furosemide, the HR for the different categories of dose (low, moderate and high) are relative to those not taking furosemide.

Results of the assessment of effect modification according to the indicators of "declining health" based on the number of hospitalisations and emergency room in the past three and six months, and the cumulative number of hospitalisations since entry in the cohort

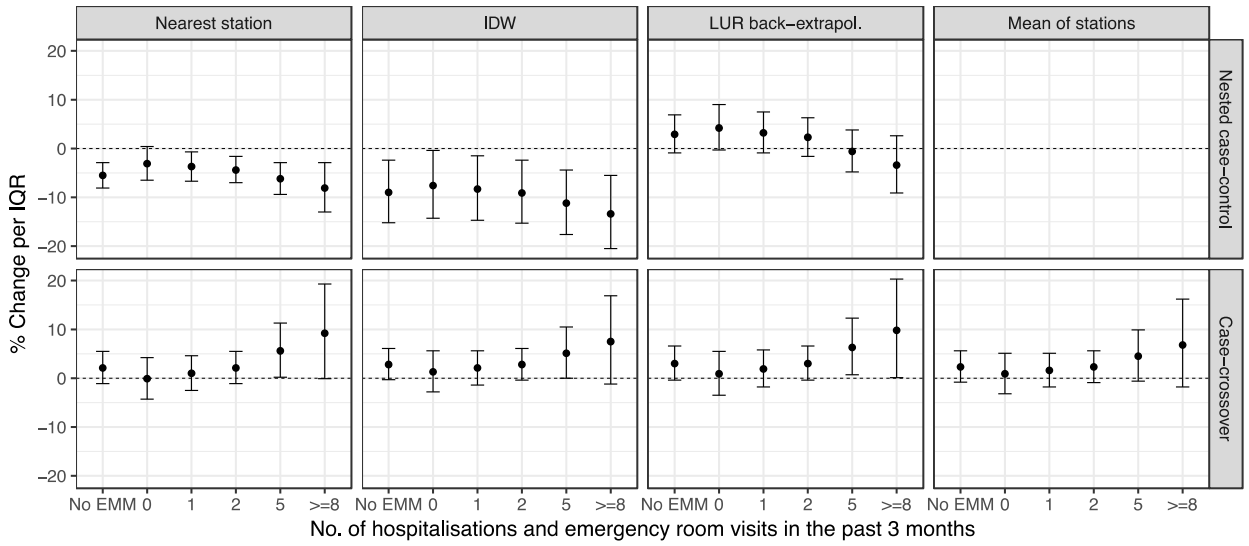
Figure E8, E9 and E10 shows below the results of the assessment of effect modification according to the indicators based on the number of hospitalisations and emergency room in the past three and six months, and the cumulative number of hospitalisations since entry in the cohort, respectively.

For NO_2, in the case-crossover the mean percentage change in the cumulative risk of non-accidental mortality showed a increasing trend according to the number of hospitalisations and emergency department visits in the past three months, whereas in the case-control there was an increasing trend. However, for both designs the confidence intervals were wide, particularly for the higher values of the indicators, and there was substantial overlap in the confidence intervals across the selected values of the indicator.

For O_3, in the nested case-control analysis for the nearest station and back-extrapolation methods from the LUR showed an increasing trend in the mean estimated effect according to the number of hospitalisations and emergency department visits in the past three (Figure E8) and six months (Figure E9). However, the confidence intervals were wide and overlapped between the different values of the indicator. Similarly, in the case-crossover analyses, the risk of non-accidental mortality increased with the number of hospitalisations and emergency department visits only for the back-extrapolation from the LUR, but the confidence intervals were wide and overlapped.

In Figure E10, for NO_2 there was a decreasing trend in non-accidental mortality according to the number of hospitalisations for both designs, but the decreasing trend was more modest in the case-crossover and there was substantial overlap in the confidence intervals. For O_3, the number of hospitalisations in the nested case-control analysis had practically no influence on the associations, whereas in the case-crossover analyses the odds of non-accidental mortality increased with the value of the indicator.

(A)



(B)

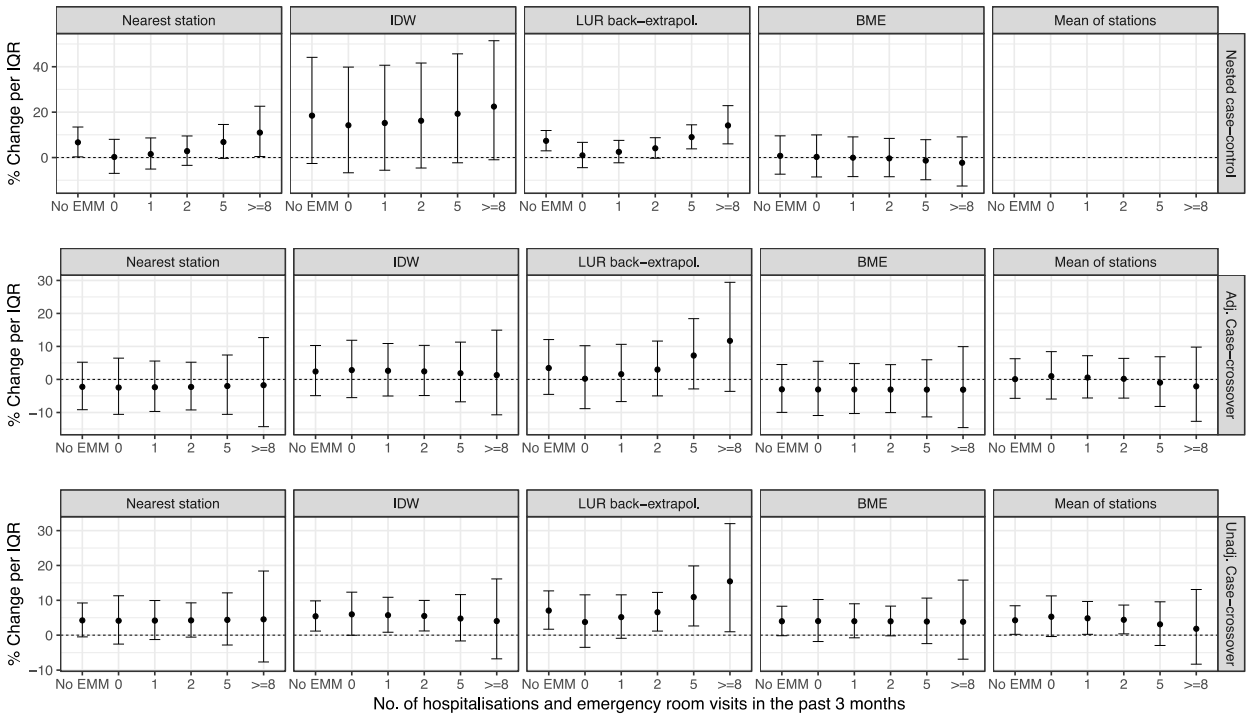


Figure E8. Estimated cumulative percentage change in non-accidental daily mortality over lag 0-3 day per interquartile range increase in (A) daily 24-hour mean exposures to ambient NO_2 (all year) and, (B) daily 8-hour mean exposures to ambient O_3 (May-September), according to the number of hospitalisations and emergency room visits in the past three months. For O_3, we present results for the case-crossover adjusting ("Adj. Case-crossover") and not adjusting for weather ("Unadj. Case-crossover"). Numbers on the horizontal axis are selected values of hospitalisation and emergency room visits, whereas "No EMM" represents the model without including the number of hospitalisations and

emergency room visits. Dots represent maximum likelihood estimates and bars represent 95% confidence intervals. We could not in the nested case-control analyses estimate the mean of all stations, as this metric does not have any variability between individuals. For NO_2, interquartile ranges (IQRs) were 13.6, 10.0, 8.8 and 9.6 ppb for the nearest station approach ("Nearest station"), inverse-distance weighting ("IDW"), back-extrapolation from a land use regression ("LUR back-extrapol."), and the daily mean across all stations ("Mean of stations"), respectively. For O_3, IQRs were 19.6, 16.6, 16.4, 11.6 and 11.8 ppb for the nearest station, IDW, LUR back-extrapol., BME and mean of stations, respectively.

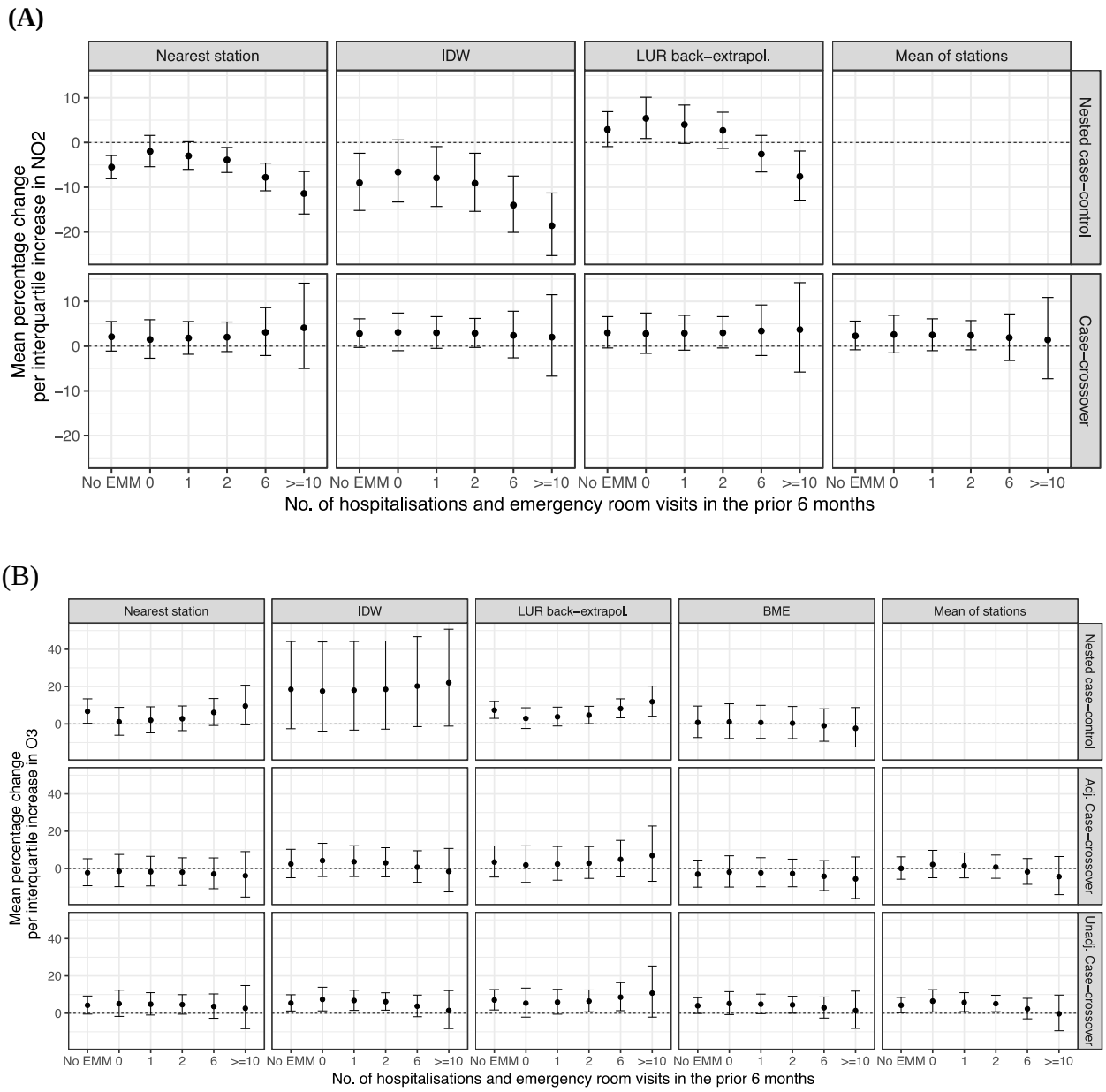
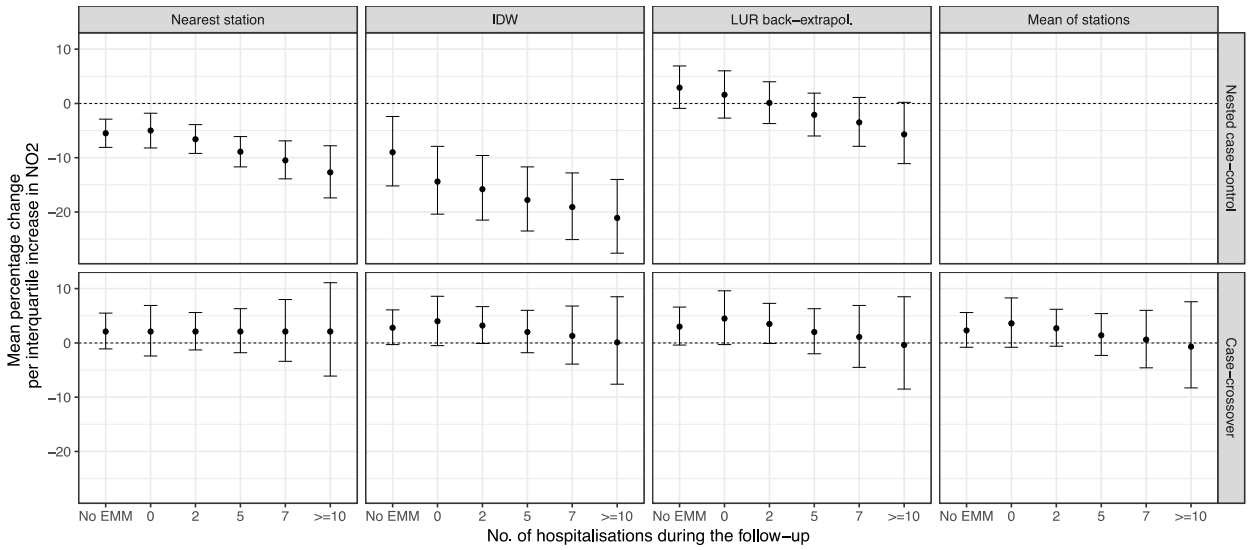


Figure E9. Estimated cumulative percentage change, over lag 0-3 day, in non-accidental daily mortality per interquartile range increase in (A) daily mean 24-hour mean exposures to ambient NO_2 (all year) and, (B) daily 8-hour mean exposures to ambient O_3 (May-September), according to the number of hospitalisations and emergency room visits in the past six months. Dots represent maximum likelihood estimates and bars represent 95% confidence intervals. Numbers on the horizontal axis are selected values of hospitalisation and emergency room visits, whereas "No EMM" represents the model without including the number of hospitalisations and emergency room visits. For O_3, we present the results from the case-crossover adjusting ("Adj. Case-crossover") and unadjusting for weather ("Unadj. Case-crossover") as we were concerned with possible overadjustment. For both air pollutants the nested case-control analysis could not be performed using the mean of all stations, as it requires some variability in the exposure between individuals. For NO_2, interquartile ranges (IQRs) were 13.6, 10.0, 8.8 and 9.6 ppb for the measurement at the nearest station ("Nearest station"), inverse-distance weighting interpolation ("IDW"), back-extrapolation from a land use regression ("LUR back-extrapol."), and the

daily mean across all stations ("Mean of stations"), respectively. For O_3, IQRs were 19.6, 16.6, 16.4, 11.6 and 11.8 ppb for the nearest station, IDW, LUR back-extrapolated, BME and mean of stations, respectively.

(A)



(B)

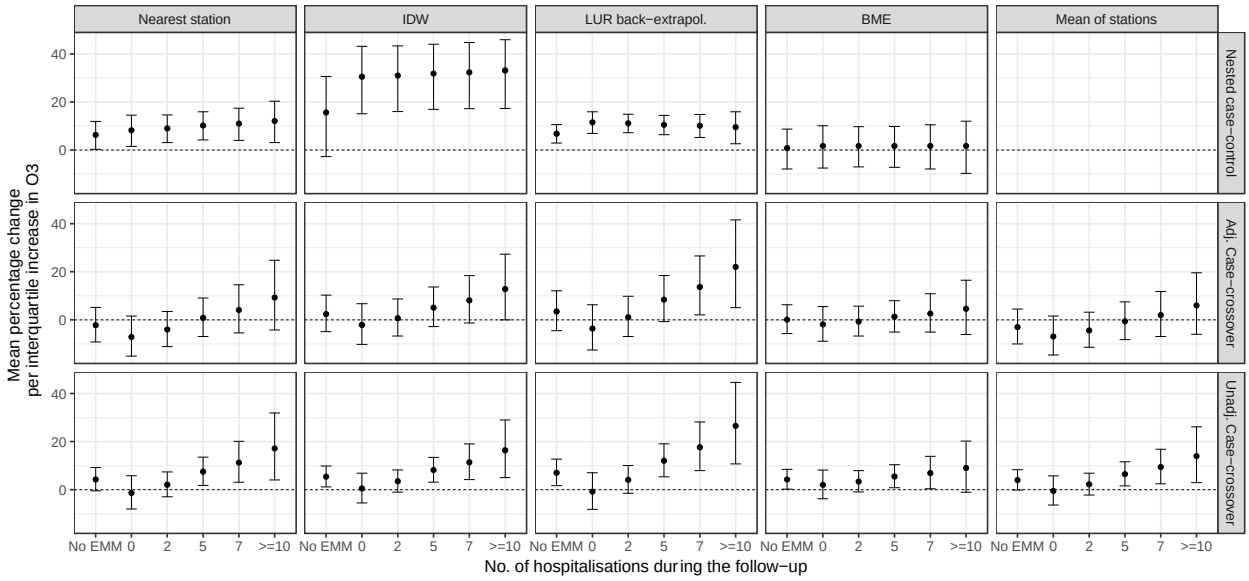


Figure E10. Estimated cumulative percentage change in non-accidental daily mortality over lag 0-3 day per interquartile range increase in (A) daily 24-hour mean exposures to ambient NO_2 (all year) and, (B) daily 8-hour mean exposures to ambient O_3 (May-September), according to the number of hospitalisations since the beginning of the follow-up. For O_3, we present results for the case-crossover adjusting ("Adj. Case-crossover") and not adjusting for weather ("Unadj. Case-crossover"). Numbers on the horizontal axis are specific values of hospitalisation, whereas "No EMM" represents the model without including the number of hospitalisations. Dots represent maximum likelihood estimates and bars represent 95% confidence intervals. We could not in the nested case-control analyses estimate the mean of all stations, as this metric does not have any variability between individuals. For NO_2, interquartile ranges (IQRs) were 13.6, 10.0, 8.8 and 9.6 ppb for the nearest station approach ("Nearest station"), inverse-distance weighting ("IDW"), back-extrapolation from a land use regression ("LUR back-extrapol."), and

the daily mean across all stations ("Mean of stations"), respectively. For O_3, IQRs were 19.6, 16.6, 16.4, 11.6 and 11.8 ppb for the nearest station, IDW, LUR back-extrapol., BME and mean of stations, respectively.

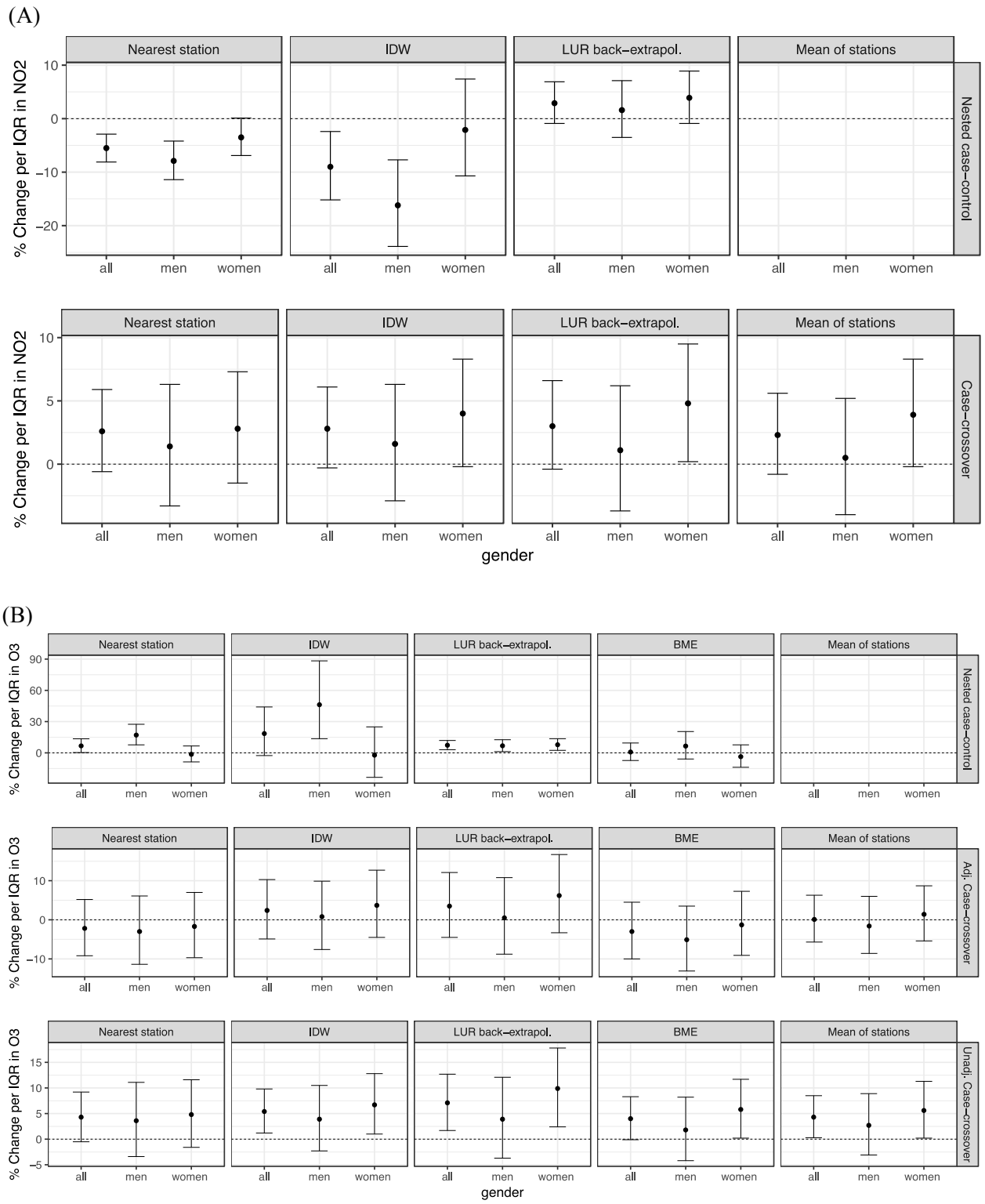


Figure E11. Estimated cumulative percentage change, over lag 0-3 day, in non-accidental daily mortality per interquartile range increase in (A) daily mean 24-hour mean exposures to ambient NO_2 (all year) and, (B) daily 8-hour mean exposures to ambient O_3 (May-September), by gender. For O3, we present results for the case-crossover adjusting ("Adj. Case-crossover") and not adjusting for weather ("Unadj. Case-crossover"). Numbers on the horizontal axis denote single day lags (0 to 3) and the

cumulative for these lags ("cumul."). Dots represent maximum likelihood estimates and bars represent 95% confidence intervals. We could not in the nested case-control analyses estimate the mean of all stations, as this metric does not have any variability between individuals. For NO_2, interquartile ranges (IQRs) were 13.6, 10.0, 8.8 and 9.6 ppb for the nearest station approach ("Nearest station"), inverse-distance weighting ("IDW"), back-extrapolation from a land use regression ("LUR back-extrapol."), and the daily mean across all stations ("Mean of stations"), respectively. For O_3, IQRs were 19.6, 16.6, 16.4, 11.6 and 11.8 ppb for the nearest station, IDW, LUR back-extrapolated, BME and mean of stations, respectively.

Appendix F. Example of R code

We performed our analyses in R, version 3.3.3 (R Foundation for Statistical Computing, 2016). For both type of analyses, i.e., time-stratified case-crossover and nested case-control, we used the Cox proportional hazards model for time-dependent variables (survival package, version 2.41-3) and we incorporated distributed lag non-linear models to simultaneously consider potential non-linear and delayed dependencies in the association between daily mortality and air pollution, accounting for possible non-linear effects of air pollution and other covariates (temperature and relative humidity) (dlnm package, version 2.3.2).

Traditionally, for both types of analyses the strata option is used in the code to specify that the models need to account for the matched nature of the selection of cases and controls. Rather than using this method we accounted for the matched nature of the selection of cases and controls by defining time intervals that were specific to each risk set and not overlapping. This method led to computational times that were approximately 300 times faster than the traditional approach. Below we show an example of the code used in R (see Stage 1) for this approach within the context of the nested case-control analysis between NO_2 and mortality. For simplicity we show an unadjusted model. Note that the exact same procedure and code can be used for a case-crossover analysis if time variables are defined according to each subject identification number.

Using the indicator based on the number of hospitalisations during the follow-up and the indicator based on furosemide (Lasix) usage as examples, we present in the second and third stage of the R code the procedure used to investigate potential effect modification in the associations between air pollution and mortality according to an ordinal and a categorical variable, respectively. Briefly, for the ordinal indicator of health and the cross-basis function for the air pollutant the procedure consisted into adding in the regression models an interaction term between the indicator of health and the cross-basis function for the air pollutant (Gasparrini et al., 2015; Gasparrini et al., 2016). The interaction term was centered at selected values of the indicator for which we computed estimates of association and their 95% confidence intervals for an interquartile increment in air pollutant. As for categorical variables, the DLNM can handle interaction only for binary variables, not for a multi-level categorical variable. Therefore for the indicator based on furosemide usage, which is a four-level categorical variable, we used a dummy parameterization to represent each category. An interaction term was created for each binary indicator and the cross-basis for air pollutant, centered accordingly to the selected values of the indicator for which we wanted to report the estimate of associations. All interaction terms were then included in the Cox regression model.

References:

Gasparrini, A., et al., 2015. Temporal Variation in Heat-Mortality Associations: A Multicountry Study. Environ Health Perspect. 123**,** 1200-7.

Gasparrini, A., et al., 2016. Changes in Susceptibility to Heat During the Summer: A Multicountry Analysis. American Journal of Epidemiology. 183**,** 1027-1036.

Example of R code:

```
#############################################################################################
# STAGE 1: EXAMPLE OF CODE FOR THE NESTED CASE-CONTROL BETWEEN AMBIENT NO2 AND MORTALITY      #
# INCPORATING DISTRIBUTED LAG NON-LINEAR MODELS FOR AIR POLLUTANT                             #
#############################################################################################

library(survival) ; library(dlnm)

#STEP 1: LOADING THE DATASET.
# This is the Dataset for the nested case-control analysis.
no2data<-read.table(file="NESTEDCC_NO2.csv", sep=",", header=TRUE)
head(no2data)

#STEP 2: DEFINE MATRIX OF EXPOSURE FOR NO2
# I am considering a lag period of 4 days, (i.e.,lag 0 (same-day) to lag 3-day)

#MATRIX FOR NO2
QNO2near <- as.matrix (no2data[,(6:9)])
colnames(QNO2near) <- paste("nearlag", 0:3, sep="")
QNO2near [1:3, 1:4]


#STEP 3: DEFINE CROSSBASIS FOR NO2, AND WEATHER VARIABLES

#CROSS-BASIS FOR NO2 (using concentrations from the nearest station)
# The selected function is linear with an unconstrained lag structure.
basisrefno2near<-crossbasis(QNO2near, lag=3, argvar=list(fun="lin"), arglag=list(fun="integer"))


#STEP 5: COX REGRESSION MODEL
# I am using cox regression, which is equivalent to conditional logistic.
# The variables included in the models are defined as following:
# cc, case/control status (1=case; 0=control);
# riskset_id, risk set identification number (defined as integer);
# basisrefno2near, cross-basis for NO2;

# DEFINE TIME VARIABLES IN A WAY THAT RISK SETS ARE AUTOMATICALLY DEFINED
# (NO STRATA NEEDED -> FASTER)
timeout <- as.numeric(factor(no2data$riskset_id))
timein <- timeout-0.1

# COX MODEL WITHOUT INTERACTION
modelref <- coxph(Surv(timein,timeout, cc)~ basisrefno2near,
                    no2data, method="breslow", x=T)

# STEP 6: GET CUMULATIVE ESTIMATE OF ASSOCIATION AS WELL AS SINGLE LAG DAY PREDICTIONS FOR AN
INTERQUARTILE RANGE IN NO2
summary(as.numeric(QNO2near))
iqr <- diff(quantile(as.numeric(QNO2near),c(25,75)/100,na.rm=T))
crosspred(basisrefno2near,modelref,cen=0,at=iqr)
```

```
##############################################################################################
# STAGE 2: INVESTIGATION OF EFFECT MODIFICATION BY AN INDICATOR OF HEALTH THAT IS ORDINAL       #
# IN THIS EXAMPLE THE SELECTED INDICATOR OF HEALTH IS THE NO. OF HOSPITALISATIONS (NHOSP)       #
# AND WE WANT TO OBTAIN THE CUMULATIVE ESTIMATES OF ASSOCIATION AND 95% CI                      #
# FOR AN INTERQUARTILE RANGE INCREASE IN NO2 AT NHOSP = 0 AND =5.                               #
##############################################################################################

# STEP 7: DEFINE INTERACTION TERMS BETWEEN NO2 AND HOSPITALISATION (NHOSP), CENTRED AT SELECTED
VALUES OF THE INDICATOR:
basisint0 <- basisrefno2near*(no2data$nhosp)
basisint5 <- basisrefno2near*(no2data$nhosp-5)

# STEP 8: COX MODELS WITH INTERACTION
modelint0 <- coxph(Surv(timein,timeout, cc)~ basisrefno2near + nhosp + basisint0,
              no2data, method="breslow", x=T)
modelint5 <- coxph(Surv(timein,timeout, cc)~ basisrefno2near + nhosp + basisint5,
              no2data, method="breslow", x=T)

# STEP 9: GENERATE PREDICTIONS FOR IQR INCREASE AT SELECTED VALUES OF THE INDICATOR FOR AN
INTERQUARTILE INCREASE IN NO2
predint0 <- crosspred(basisrefno2near,modelint0,cen=0,at=iqr)
predint5 <- crosspred(basisrefno2near,modelint5,cen=0,at=iqr)

# STEP 10: COMPARE OVERALL CUMULATIVE HR (CAN ALSO ACCESS CONFIDENCE INTERVALS)
# HR AT NHOSP =0
c(predint0$allRRfit,predint0$allRRlow,predint0$allRRhigh)
# HR AT NHOSP =5
c(predint5$allRRfit,predint5$allRRlow,predint5$allRRhigh)



##############################################################################################
# STAGE 3: INVESTIGATION OF EFFECT MODIFICATION BY AN INDICATOR OF HEALTH THAT IS CATEGORICAL   #
# IN THIS EXAMPLE THE INDICATOR OF HEALTH IS BASED ON FUROSEMIDE (LASIX) USAGE,                 #
# WHICH IS A FOUR-LEVEL CATEGORICAL VARIABLE                                                    #
# AND WE WANT TO OBTAIN THE CUMULATIVE ESTIMATES OF ASSOCIATION AND 95% CI                      #
# FOR AN INTERQUARTILE RANGE INCREASE IN NO2 SPECIFIC TO EACH CATEGORY                          #
#                                                                                               #
#                                                                                               #
# IN THE DATASET SET, FUROSEMIDE CATEGORIES ARE REPRESENTED USING THREE BINARY (CODED 0/1)      #
# INDICATOR VARIABLES DEFEINED AS FURO1, FURO2, FURO3,                                          #
# EACH OF THEM REPRESENTING A CATEGORY VS A REFERENCE IN A DUMMY PARAMETISATION                 #
##############################################################################################


# ESTIMATE THE ASSOCIATION FOR THE REFERENCE CATEGORY (I.E., ALL BINARY INDICATORS =0)

# STEP 11: CREATING INTEREACTION TERM BETWEEN EACH BINARY INDICATOR AND THE CROSS-BASIS FUNCTION
FOR AIR POLLUTANT

int_no2near_furo1 <- no2data$furo1* basisrefno2near
int_no2near_furo2 <- no2data$furo2* basisrefno2near
int_no2near_furo3 <- no2data$furo3* basisrefno2near

# STEP 12: COX MODEL WITH INTERACTIONS
cox_no2near_furo0<- coxph(Surv(timein,timeout, cc)~ basisrefno2near + int_no2near_furo1 +
int_no2near_furo2 + int_no2near_furo3, no2data, method="breslow", x=T)

# STEP 13: GET PREDICTIONS FOR AN IQR INCREASE IN NO2

predrefnear0 <- crosspred(basisrefno2near,cox_no2near_furo0,cen=0,at=iqrno2near)
c(predrefnear0$allRRfit,predrefnear0$allRRlow,predrefnear0$allRRhigh)


### TO OBTAIN ESTIMATES OF ASSOCIATIONS FOR THE OTHER CATEGORIES OF FUROSEMIDE, REPEAT THE
PROCEDURE (I.E., STEPS 11, 12 AND 13) BUT AT STEP 11 CENTER THE BINARY INDICATORS ON THE DESIRED
CATEGORY

# ESTIMATE FOR THE FIRST CATEGORY (I.E., FURO1=1, FURO2=0, FURO3=0)
int_no2near_furo1 <- (no2data$furo1-1)*basisrefno2near
```

```
int_no2near_furo2 <- no2data$furo2*basisrefno2near
int_no2near_furo3 <- no2data$furo3*basisrefno2near

cox_no2near_furo1<- coxph(Surv(timein,timeout, cc)~ basisrefno2near + int_no2near_furo1 +
int_no2near_furo2 + int_no2near_furo3, no2data, method="breslow", x=T)

predrefnear1 <- crosspred(basisrefno2near,cox_no2near_furo1,cen=0,at=iqrno2near)
c(predrefnear1$allRRfit,predrefnear1$allRRlow,predrefnear1$allRRhigh)


# ESTIMATE FOR THE SECOND CATEGORY (I.E., FURO1=0, FURO2=1, FURO3=0)
int_no2near_furo1 <- no2data$furo1*basisrefno2near
int_no2near_furo2 <- (no2data$furo2-1)*basisrefno2near
int_no2near_furo3 <- no2data$furo3*basisrefno2near

cox_no2near_furo2<- coxph(Surv(timein,timeout, cc)~ basisrefno2near + int_no2near_furo1 +
int_no2near_furo2 + int_no2near_furo3, no2data, method="breslow", x=T)

predrefnear2 <- crosspred(basisrefno2near,cox_no2near_furo2,cen=0,at=iqrno2near)
c(predrefnear2$allRRfit,predrefnear2$allRRlow,predrefnear2$allRRhigh)


# ESTIMATE FOR THE THIRD CATEGORY (I.E., FURO1=0, FURO2=0, FURO3=1)
int_no2near_furo1 <- no2data$furo1*basisrefno2near
int_no2near_furo2 <- no2data$furo2*basisrefno2near
int_no2near_furo3 <- (no2data$furo3-1)*basisrefno2near

cox_no2near_furo3<- coxph(Surv(timein,timeout, cc)~ basisrefno2near + int_no2near_furo1 +
int_no2near_furo2 + int_no2near_furo3, no2data, method="breslow", x=T)

predrefnear3 <- crosspred(basisrefno2near,cox_no2near_furo3,cen=0,at=iqrno2near)
c(predrefnear3$allRRfit,predrefnear3$allRRlow,predrefnear3$allRRhigh)
```