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## Short-term effects of nitrogen dioxide on hospital admissions for cardiovascular disease in Wallonia, Belgium

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## ABSTRACT

Many studies have shown a short-term association between NO<sub>2</sub> and cardiovascular disease. However, few data are available on the delay between exposure and a health-related event. The aim of the present study is to determine the strength of association between NO<sub>2</sub> and cardiovascular health in Wallonia for the period 2008–2011. This study also seeks to evaluate the effects of age, gender, season and temperature on this association. The effect of the delay between exposure and health-related event was also investigated. The daily numbers of hospital admissions for arrhythmia, acute myocardial infarction, ischemic and haemorrhagic stroke were taken from a register kept by Belgian hospitals. Analyses were performed using the quasi-Poisson regression model adjusted for seasonality, long-term trend, day of the week, and temperature.

Our study confirms the existence of an association between NO<sub>2</sub> and cardiovascular disease. Apart from haemorrhagic stroke, the strongest association between NO<sub>2</sub> concentrations and number of hospital admissions is observed at lag 0. For haemorrhagic stroke, the association is strongest with a delay of 2 days. All associations calculated without stratification are statistically significant and range from an excess relative risk of 2.8% for myocardial infarction to 4.9% for haemorrhagic strokes. The results of this study reinforce the evidence of the short-term effects of NO<sub>2</sub> on hospital admissions for cardiovascular disease. The different delay between exposure and health-related event for haemorrhagic stroke compared to ischemic stroke suggests different mechanisms of action.

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## 1. Introduction

Numerous epidemiological studies have shown that short-term variations in atmospheric pollution may be associated with health problems, such as cardiovascular morbidity or mortality [1,2,3,4]. Temperature is also a direct risk factor but may also have a modifying and/or confounding effect on the association between air pollution and non-traumatic mortality [5,6].

The association between exposure to fine particles or nitrogen dioxide (NO<sub>2</sub>) and the onset of an acute coronary disorder has been described on numerous occasions [3,7]. Unlike fine particles, NO<sub>2</sub> does not appear to have a direct effect on cardiovascular pathologies [8]. Conversely, this pollutant is a good proxy for particulate pollution (PM<sub>10</sub> and PM<sub>2.5</sub>) generated by road traffic [9]. Stronger associations are observed between cardiovascular disease and NO<sub>2</sub> compared to fine particles [10].

The associations between air pollution and myocardial infarction are far more pronounced during warm periods of the year compared to cold

periods [11]. However, the effects of air pollution on other cardiovascular diseases such as heart rhythm disorders or strokes have been less studied. Moreover, very few data are available on the modifying effect of the seasons or temperature on the association between air pollution and these two pathologies. Strokes can be ischemic or haemorrhagic. Since the mechanisms leading to the onset of these pathologies are different, it seems important to analyse them separately.

The impact of air pollution on health has mostly been studied in Europe and the United States [4], in Asia [12] and in Latin America [13]. While some studies on the effect of PM<sub>10</sub> and NO<sub>2</sub> on the onset of myocardial infarction have been conducted in Belgium [11,14], none have been carried out on the impact of pollution on heart rhythm disorders or strokes.

This study was carried out in Wallonia, the region in the south of Belgium. Given that it is a particularly polluted industrial region of Europe, it seems important to determine the impact of this air pollution on cardiovascular health and to compare the results obtained with those available for other geographical areas.

Our study aims to determine the strength of association between NO<sub>2</sub> and cardiovascular health in Wallonia. It also seeks to evaluate the effects of age, gender, season, and temperature on this association.

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## 2. Material and methods

### 2.1. Geographical area

The present study was conducted in Wallonia from 1 January 2008 to 31 December 2011. Wallonia is the southern region of Belgium, with an area of 16,844 km<sup>2</sup> and 3,525,000 inhabitants in 2011.

### 2.2. Hospital admissions data for cardiovascular diseases

The analyses presented below relate to patients between 25 and 104 years of age over time. The daily counts of hospital admissions for cardiovascular disease were taken from the 'Résumé Hospitalier Minimum' (RHM) for 42 hospitals within the study region. The RHM is a mandatory register kept by Belgian hospitals containing patient data (e.g.: year of birth, gender, place of residence) and stay data (e.g.: admission date). Clinical admission diagnoses were registered using the ICD-9 codes (International Classification of Disease, 9th version). The daily counts of hospital admissions for CVD were graded: arrhythmia (ICD9: 426 and 427), acute myocardial infarction (AMI, ICD9: 410), ischemic stroke (ICD9: 433, 434 and 435) and haemorrhagic stroke (ICD9: 430, 431 and 432).

### 2.3. Environmental data

Concentrations of NO<sub>2</sub> and temperature for the period between 2008 and 2011 were obtained from the ISSeP (Institut scientifique de service public). Temperature data were collected from five measuring stations while NO<sub>2</sub> concentrations were recorded by 10 monitoring stations spread across the study area. The daily concentrations of NO<sub>2</sub> were averaged from the data of the 10 stations. Averaged pollution data were used as surrogates of individual exposure. Correlation between monitoring stations was analysed using Spearman's rank correlation. >75% of the correlation coefficients between stations were higher than 0.75. There are no missing data for the daily averages of the two parameters studied.

### 2.4. Data analysis

A time-series design was used to assess the association between short-term exposure to air pollution and hospital admissions for CVD. The generalized additive model was applied to analyse the data with a quasi-Poisson regression to account for overdispersion [15]. The day of the week was modelled using an indicator variable. Adjustment for temperature was performed with a natural spline as a smoothing function with three degrees of freedom to overcome the non-linear effect of temperature [16]. Seasonality and long-term trend were also modelled using a natural spline with three degrees of freedom per year [15,16]. NO<sub>2</sub> was added in the model as a linear term without a delay (lag 0) and with a delay (lag 1 to 6). The lagged variables were introduced in the model separately. The effect of the delay was analysed for the association between NO<sub>2</sub> and CVD stratified over age and for the association between NO<sub>2</sub> and the various hospital admissions for cardiovascular pathologies. For each subgroup analysed, the lag giving the strongest association was selected. Residuals and partial autocorrelation were checked graphically to ensure the goodness of the model. The sum of the absolute values of the partial autocorrelation function was calculated for each degree of freedom. The analyses were performed without stratification (overall analysis) and with stratification on gender and age in three subgroups: 25–54, 55–64 and ≥65 years. Excess relative risk (ERR) and 95% confidence intervals (CI) were calculated using a Poisson regression model and R software 2.15.0 (The R Foundation for Statistical Computing) with the mgcv and spline packages. The excess relative risks for an increase of 10 µg/m<sup>3</sup> of NO<sub>2</sub> are presented in the tables.

### 2.5. Sensitivity analysis

Sensitivity analysis was performed to check the robustness of the model. Analysis using different degrees of freedom of the two natural splines was performed to estimate the effects on the strength of association. This sensitivity analysis was conducted using total daily admissions for CVD. The number of degrees of freedom giving the lowest sum of the absolute values of the partial autocorrelation function was selected.

## 3. Results

### 3.1. Environmental data

The average annual concentration of NO<sub>2</sub> is stable for the period of analysis with 21.1, 20.3, 21.2 and 19.3 µg/m<sup>3</sup> in 2008, 2009, 2010 and 2011 respectively. However, the monthly averages are subject to a seasonal effect with a minimum of 13.1 µg/m<sup>3</sup> in July and a maximum of 26.9 µg/m<sup>3</sup> in January. NO<sub>2</sub> concentration and temperature are negatively correlated ( $R = -0.59$ ,  $p < 0.001$ ) [17]. The coldest months are December (2.6 °C), January (2.5 °C) and February (4.2 °C) and the hottest months are June (17.0 °C), July (18.7 °C) and August (18.3 °C).

### 3.2. Number of hospital admissions

For the period of analysis there were 113,147 hospital admissions for cardiovascular disease (Table 1). Forty-five percent of patients were women and 66.5% were 65 and older. Heart rhythm disorders account for the majority of hospital admissions for cardiovascular disease, that is, >50,000 cases. Atrial fibrillation and flutter account for the majority (62.3%) of hospital admissions for heart rhythm disorders. Temperature and season have little effect on the number of hospital admissions. The number of hospital admissions for CVD is stable during the period of analysis with 28,403, 28,284, 28,073 and 28,387 hospital admissions for 2008, 2009, 2010 and 2011 respectively.

### 3.3. Modelling

#### 3.3.1. The lag effect

The effect of age on the lag pattern of the association between NO<sub>2</sub> concentrations and CVD is shown in Fig. 1. Regardless of age, the association is strongest taking into account the measurement of pollution on the day of the event (lag 0).

The lag patterns for the four cardiovascular diseases are presented in Fig. 2. For all ages combined, the strongest association between NO<sub>2</sub> concentrations and the number of hospital admissions is observed at lag 0 (Fig. 2), except for haemorrhagic stroke where the strongest association occurs at lag 2.

#### 3.3.2. Excess of risk

The associations between NO<sub>2</sub> concentrations and the various pathologies are presented in Table 2. All associations calculated without stratification are statistically significant and range from an ERR of 2.8% for myocardial infarction to 4.9% for haemorrhagic strokes. Apart from haemorrhagic stroke where excess relative risk is 7.3% for women and 2.3% for men, gender has very little effect on the association between NO<sub>2</sub> and cardiovascular disease. However, age has a more marked impact. For example, for heart rhythm disorders and haemorrhagic stroke, extreme age groups are the most susceptible to NO<sub>2</sub>. For myocardial infarction, the strongest association is found for the 55–64 years age group. Temperature has a modifying effect on the association between NO<sub>2</sub> and hospital admissions for CVD as well as on heart rhythm disorders and myocardial infarction. For these pathologies, the effect of NO<sub>2</sub> is far more pronounced when the temperature is above 16.3 °C (P75). The season has a similar effect on CVD and heart rhythm disorders but has no effect on myocardial infarction.

### 3.4. Sensitivity analysis

The association of NO<sub>2</sub> and AMI hospital admissions decreases slightly when the number of degrees of freedom (df) of the smoothing function used for seasonal adjustment increases. For a 10 µg/m<sup>3</sup> increase of NO<sub>2</sub> concentration, the ERR [CI<sub>95%</sub>] were 3.6 [2.5; 4.8], 3.6 [2.5; 4.8], 3.1 [1.9; 4.3], 2.3 [1.1; 3.5], 2.5 [1.3; 3.7] and 2.4 [1.1; 3.6] for df = 2, 3, 4, 5, 6 and 7 per year, respectively. The sum of the absolute values of the partial autocorrelation function was lowest for 3 df [17].

## 4. Discussion

This study shows that NO<sub>2</sub> is positively associated with daily hospital admissions for heart rhythm disorders, myocardial infarction and ischemic or haemorrhagic stroke. NO<sub>2</sub> does not appear to have a direct effect on cardiovascular diseases [8]. However, this pollutant is a good proxy for newly formed particulate pollution (PM<sub>10</sub> and PM<sub>2.5</sub>), i.e. the most toxic, caused by road traffic [9]. Stronger associations between cardiovascular disease and NO<sub>2</sub> compared to fine particles are observed in other studies. For example, data on hospital admissions for cardiovascular disease in Canada show an excess relative risk of 3.0 [CI<sub>95%</sub>: 2.1; 3.9] for an increase of one IQR in NO<sub>2</sub> against 1.3% [CI<sub>95%</sub>: 0.6; 2.0] for PM<sub>2.5</sub>.

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