International Journal of Cardiology 255 (2018) 231–236

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

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

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ARTICLE INFO

Article history:
Received 10 July 2017
Received in revised form 22 November 2017
Accepted 19 December 2017
Available online 24 December 2017

Keywords:
Cardiovascular disease
Air pollution
Myocardial infarction
Stroke
Arrhythmia

ABSTRACT

Many studies have shown a short-term association between NO_2 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_2 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_2 and cardiovascular disease. Apart from haemorrhagic stroke, the strongest association between NO_2 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_2 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.

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_2) and the onset of an acute coronary disorder has been described on numerous occasions [3,7]. Unlike fine particles, NO_2 does not appear to have a direct effect on cardiovascular pathologies [8]. Conversely, this pollutant is a good proxy for particulate pollution (PM_{10} and $PM_{2.5}$) generated by road traffic [9]. Stronger associations are observed between cardiovascular disease and NO_2 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_{10} and NO_2 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_2 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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https://doi.org/10.1016/j.ijcard.2017.12.058
0167-5273/

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^2 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_2 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_2 concentrations were recorded by 10 monitoring stations spread across the study area. The daily concentrations of NO_2 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_2 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_2 and CVD stratified over age and for the association between NO_2 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 artial 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 $\mu g/m^3$ of NO_2 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_2 is stable for the period of analysis with 21.1, 20.3, 21.2 and 19.3 $\mu g/m^3$ in 2008, 2009, 2010 and 2011 respectively. However, the monthly averages are subject to a seasonal effect with a minimum of 13.1 $\mu g/m^3$ in July and a maximum of 26.9 $\mu g/m^3$ in January. NO_2 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_2 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_2 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_2 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_2 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_2. 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_2 and hospital admissions for CVD as well as on heart rhythm disorders and myocardial infarction. For these pathologies, the effect of NO_2 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_2 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 $\mu g/m^3$ increase of NO_2 concentration, the ERR [$CI_{95\%}$] 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_2 is positively associated with daily hospital admissions for heart rhythm disorders, myocardial infarction and ischemic or haemorrhagic stroke. NO_2 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_{10} and $PM_{2.5}$), i.e. the most toxic, caused by road traffic [9]. Stronger associations between cardiovascular disease and NO_2 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 [$CI_{95\%}$: 2.1; 3.9] for an increase of one IQR in NO_2 against 1.3% [$CI_{95\%}$: 0.6; 2.0] for $PM_{2.5}$

Table 1
Number of hospital admission stratified by gender, age group, season and temperature.

	CVD	Arrhythmia	AMI	Ischemic stroke	Haemorrhagic stroke
Overall	113,147 (100%)	52,937 (46.8%)	21,491 (19.0%)	32,902 (29.1%)	5817 (5.1%)
Gender					
Female	50,691 (44.8%)	24,286 (45.9%)	7110 (33.1%)	16,283 (49.5%)	3012 (51.8%)
Male	62,456 (55.2%)	28,651 (54.1%)	14,381 (66.9%)	16,619 (50.5%)	2805 (48.2%)
Age group, year					
25–54	17,903 (15.8%)	8291 (15.7%)	5136 (23.9%)	3345 (10.2%)	1131 (19.4%)
55–64	20,039 (17.7%)	9177 (17.3%)	5006 (23.3%)	4956 (15.1%)	900 (15. 5%)
≥65	75,205 (66.5%)	35,469 (67.0%)	11,349 (52.8%)	24,601 (74.8%)	3786 (65.1%)
Season					
Warm	27,164 (24.0%)	12,791 (24.2%)	5017 (23.3%)	7947 (24.2%)	1409 (24.2%)
Cold	28,204 (24.9%)	12,919 (24.4%)	5545 (25.8%)	8285 (25.2%)	1455 (25.0%)
Temperature					
High	29,577 (26.1%)	14,036 (26.5%)	5471 (25.5%)	8601 (26.1%)	1469 (25.3%)
Low	29,798 (26.3%)	13,769 (26.0%)	5747 (26.7%)	8706 (26.5%)	1576 (27.1%)

Warm period: June–August; cold period: December–February.
High temperature: >P75 (16.3 °C); low temperature: <P25 (5.8 °C).
CVD: cardiovascular diseases; AMI: acute myocardial infarction.

[10]. A study conducted in Belgium by Argacha et al. [18] shows similar results with higher associations for STEMI-type infarction with NO_2 (OR = 1.051 [$CI_{95\%}$: 1.018; 1084]) compared to PM_{10} (OR = 1.026 [$CI_{95\%}$: 1.005; 1.048]) and to $PM_{2.5}$ (OR = 1.028 [$CI_{95\%}$: 1.003; 1.054]), these results being calculated for a 10 μg/m^3 increase in NO_2. Compared to fine particles, NO_2 also displays a better correlation with other potentially toxic but more difficult to measure pollutants (for example: volatile organic compounds or polycyclic aromatic hydrocarbons) [9,19]. For these reasons, we have chosen to consider concentrations of NO_2 rather than of fine particles.

A number of potential mechanisms have been suggested to explain the short-term effect of particulate pollution on cardiovascular diseases, including the inflammatory process, oxidative stress and the alteration of the autonomic nervous control of the heart [20]. Studies have shown an increase in levels in the blood of such inflammation markers as interleukin-12 and C-reactive protein in subjects exposed to air pollution

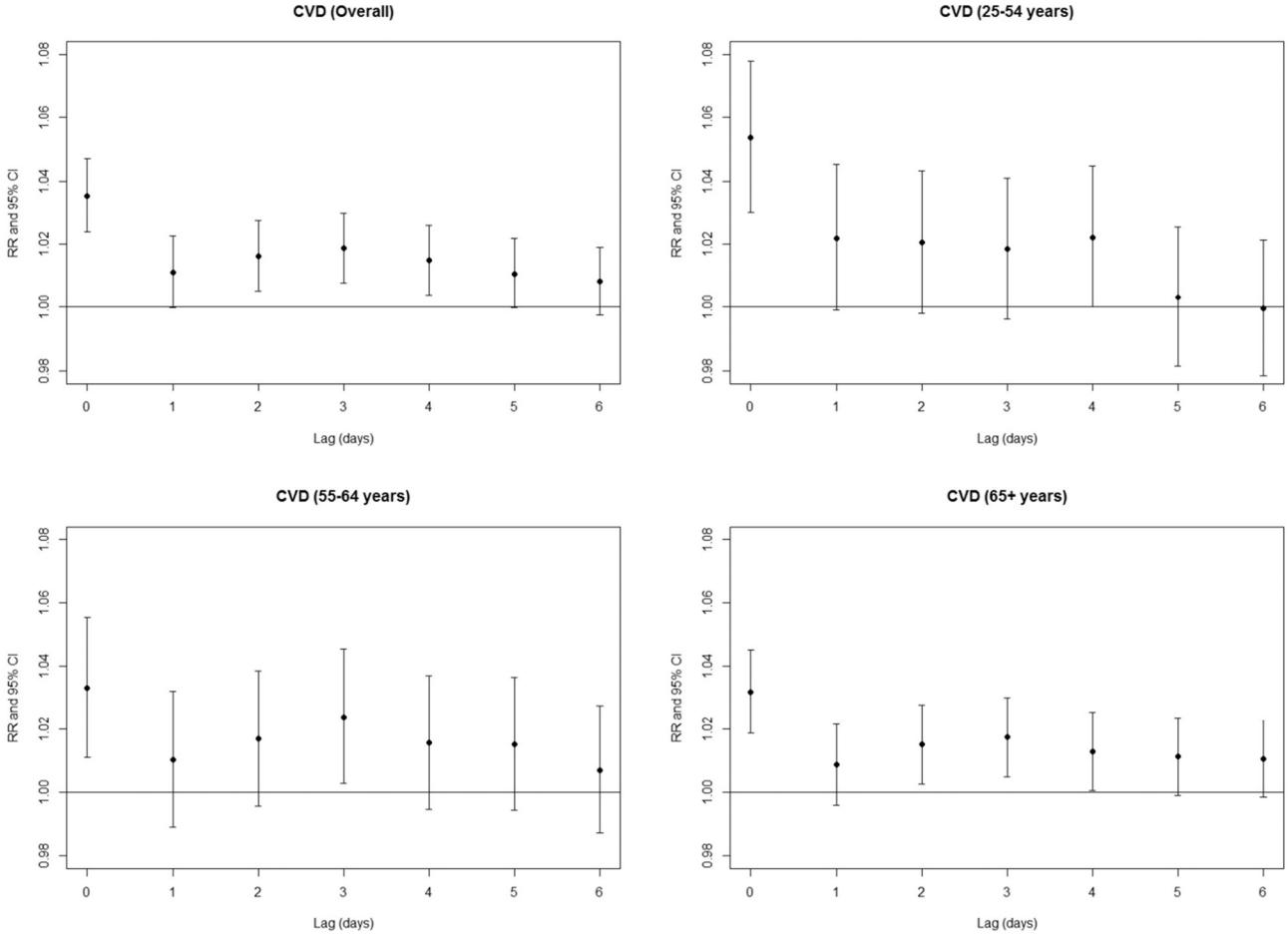

Fig. 1. Relative risks (RR with 95% confidence intervals) for the association between NO_2 and CVD per 10 μg/m^3 increase of NO_2 concentration obtained with the single lag model. Analysis performed for different age groups.

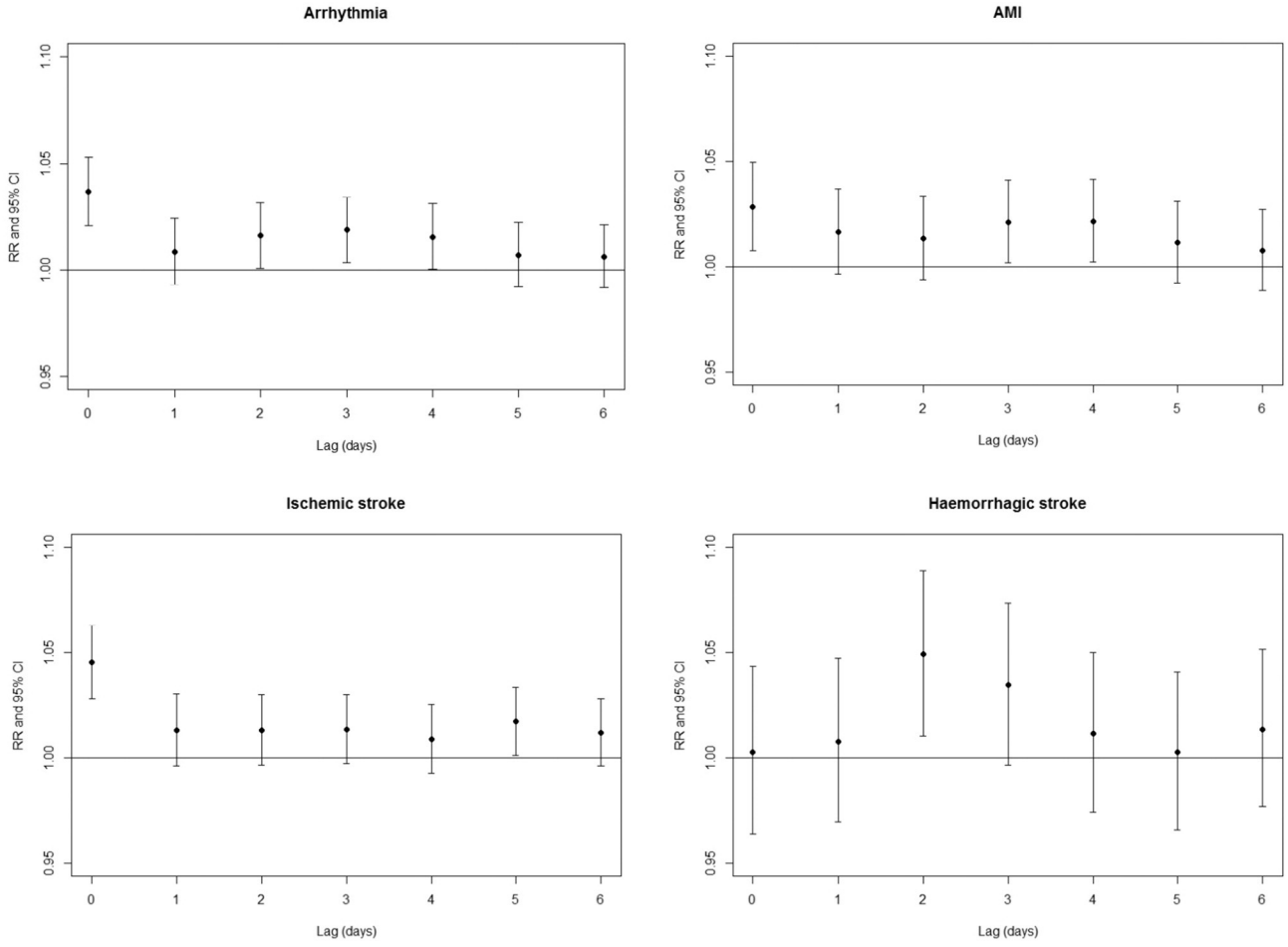

Fig. 2. Relative risks (RR with 95% confidence intervals) for the association between NO_2 and different cardiovascular diseases per 10 μg/m^3 increase of NO_2 concentration obtained with the single lag model. Analysis performed for all age groups.

[21]. These inflammatory processes can lead to the destabilization and rupture of the atheromatous plaque, to vasoconstriction of the arteries causing increased blood pressure, and finally to an increase in the viscosity of the blood that may enhance the formation of a thrombus [20]. For brain pathologies, even slight increases in $PM_{2.5}$ have been associated with changes in cerebral haemodynamics, increasing cerebrovascular resistance and decreasing cerebral blood circulation [22]. Another potential effect of air pollution is the increased risk of heart rhythm disorders [21,22,23]. The biological mechanisms of the onset of heart rhythm disorders caused by air pollution disorders may be, for example, an alteration of the autonomic nervous system causing repolarization disorders. Another involves the pollutants passing into the bloodstream

Table 2
NO_2 effects (risk excess and 95% confidence intervals).

Parameters	CVD (n = 113,147)		Arrhythmia (n = 52,937)		AMI (n = 21,491)		Ischemic stroke (n = 32,902)		Haemorrhagic stroke (5817)	
	ERR (%)	[95% IC]	ERR (%)	[95% IC]	ERR (%)	[95% IC]	ERR (%)	[95% IC]	ERR (%)	[95% IC]
Overall	3.5	[2.4; 4.7]	3.7	[2.1; 5.3]	2.8	[0.8; 4.9]	4.5	[2.8; 6.3]	4.9	[1.1; 8.9]
Gender										
Female	3.4	[1.9; 5.0]	3.4	[1.4; 5.6]	2.8	[−0.1; 6.4]	4.5	[2.0; 7.0]	7.3	[2.1; 12.8]
Male	3.6	[2.2; 5.1]	3.9	[1.9; 5.9]	2.9	[0.3; 5.5]	4.6	[2.3; 7.0]	2.3	[−3.2; 8.0]
Age group, year										
25–54	5.4	[3.0; 7.8]	7.6	[4.1; 11.1]	1.0	[−3.0; 5.0]	6.6	[1.1; 12.4]	3.8	[−4.6; 12.9]
55–64	3.3	[1.1; 5.5]	2.5	[−0.1; 5.8]	4.5	[0.3; 8.8]	4.6	[0.4; 9.0]	−0.1	[−9.0; 9.8]
≥65	3.2	[1.9; 4.5]	3.1	[1.3; 4.9]	3.0	[0.3; 5.8]	4.2	[2.3; 6.2]	6.5	[1.7; 11.5]
Season										
Warm	7.0	[3.1; 10.9]	11.0	[5.5; 16.7]	0.0	[−6.5; 6.9]	5.5	[−0.1;11.4]	5.2	[−7.4; 19.6]
Cold	1.8	[0.0; 3.6]	0.7	[−1.7; 3.2]	0.9	[−2.2; 4.0]	4.6	[2.0; 7.3]	1.1	[−4.6; 7.4]
Temperature										
High	6.1	[3.2; 9.2]	7.5	[3.4; 11.7]	6.2	[0.9; 11.8]	4.6	[0.2; 9.1]	2.8	[−6.9; 13.7]
Low	3.0	[1.1; 4.8]	2.2	[−0.3; 4.8]	3.0	[−0.2; 6.3]	4.7	[2.0; 7.5]	1.8	[−4.5; 5.1]

Warm period: June–August; cold period: December–February; high temperature: >P75 (16.3 °C); low temperature: <P25 (5.8 °C).
CVD: cardiovascular diseases; AMI: acute myocardial infarction.
The analysis were performed at lag 0 for CVD, arrhythmia, AMI, ischemic stroke and at lag 2 for haemorrhagic stroke.

causing high blood pressure and endothelial dysfunction. This latter mechanism has been especially shown for ultrafine particles [24]. Some mechanisms, such as oxidative stress, have been demonstrated by experimental studies in humans [25].

Our study has revealed statistically significant associations between NO_2 concentrations and hospital admissions for heart rhythm disorders. These results are in accordance with several studies conducted according to variable protocols in terms of the measurement of exposure or the evaluation of the pathology. For example, a study carried out in Brazil showed that there was an association between NO_2 levels and ER consultations for cardiac arrhythmias [26]. Several studies have shown an association between air pollution and heart rhythm disorders in subjects with an implantable automatic defibrillator [27,28]. Our study analyses the impact of pollution on atrial and ventricular arrhythmias. Atrial fibrillation is the most common rhythm-related disorder and it has the particular trait of increasing the risk of intra-cardiac blood clots that can get into the bloodstream and cause an ischemic stroke [22,29]. To refine the results of the effect of air pollution on heart rhythm disorders, further investigations that distinguish between ventricular and supra-ventricular arrhythmias would be necessary [30].

Our study also suggests that NO_2 concentrations are positively associated with myocardial infarction. These results are in accordance with earlier studies in Belgium 11, 18]. An association between this pollutant and myocardial infarction is reported in a recent meta-analysis. Based on the results collected in 34 studies, the overall relative risk for an increase of 10 mg/m^3 of NO_2 is 1.011 [CI 95%: 1.006; 1.029] [3].

Concerning stroke, a distinction should be made between ischemic and haemorrhagic stroke. According to a recent study [22], associations between air pollution and ischemic stroke appear to be reproducible. However, the results for haemorrhagic stroke are less precise and more controversial. This lack of precision may be due to the fact that the number of hospital admissions for haemorrhagic stroke is lower compared to those for ischemic stroke. As discussed above, air pollution could cause ischemic stroke due to an increase in inflammatory processes or the production of a blood clot during atrial fibrillation. Vasoconstriction and increased blood pressure could lead to a haemorrhagic stroke. An association between air pollution and hospital admissions for these two types of stroke is therefore likely. This is what we observe in our study. However the delay between exposure and health-related event is different for these two diseases. We observe an immediate effect for ischemic stroke while a delayed effect is observed for haemorrhagic stroke. This last finding is in keeping with the different physiopathologies. Overall, our study has allowed observing statistically significant associations between air pollution and the number of hospital admissions for ischemic stroke. A statistically positive association with NO_2 was also observed after meta-analysis (ERR = 1.024 [$CI_{95\%}$: 1.010; 1.038]), this measure of association being two times lower than that observed in Wallonia [22].

4.1. Age effect

Most studies on myocardial infarction show greater sensitivity of the elderly to air pollution [31,32,33]. This phenomenon is less well described for other cardiovascular diseases. In general, the possible causes of this increased sensitivity of seniors to air pollution are a prevalence of higher co-morbidities and reduced pulmonary elimination of pollutants [33].

A recent study has highlighted a link between air pollution and the first episode of the onset of atrial fibrillation in young adults (≤ 65 years) with NO_2 (OR = 1.08; $p = 0.025$), whereas no association was found with this pollutant when parsing on the population all ages combined [29]. These data are in line with our results. Indeed, we observed a much higher sensitivity of persons aged 25 to 54 years compared with persons aged 55 or over.

Conversely, for myocardial infarction, the effect of age observed in our study does not confirm the results generally published, i.e., greater sensitivity of the elderly to air pollution. However, a recent study in Belgium showed greater sensitivity of the younger groups [18].

A recent study highlights the risk in young adults and observes a statistically significant association between admissions for ischemic stroke and an increase of the interquartile range (IQR) of PM_{10} (OR = 1.11 [1.02–1.20]) and $PM_{2.5}$ (OR = 1.10 [1.00–1.21]) in persons under 55 years of age. They have not noted an association in persons aged 55 to 65, nor over 65 [34].

Among seniors, atherosclerosis is the main risk factor for ischemic stroke. It is suggested that atherosclerosis and the consumption of medications such as vasodilators and statins (anti-cholesterol drugs) would decrease the contractility of the vessels and would therefore protect against the vasoconstrictor effect of pollutants from the air in this often older population [34]. Other risk factors should affect the 25–64 age group. In younger people, atherosclerosis remains a significant risk factor for ischemic stroke but cardiometabolic causes are more likely, giving rise to hypercoagulation sending a blood clot to the brain [34].

4.2. Gender effect

Various gender effects are reported in the literature. As for many other parameters, the socio-economic context of the target country must be taken into consideration [35,36]. For example, a study conducted in China shows greater susceptibility to air pollution in women than in men. The authors explain that this difference is due to the lower socio-economic level of women in said country [37]. Other authors also show that women are more susceptible than men to air pollution [38]. These differences could be due, for example, to pulmonary absorption or a different hormonal status. A recent meta-analysis [39] showed that from 14 studies based on data on hospital admissions for respiratory and cardiovascular causes, 13 studies showed no significant modifying effect of gender. Finally, according to Colais et al. [40], the difference in male/female sensitivity to air pollution would be dependent on the pathology studied, with men being more sensitive to the onset of arrhythmias and women to heart failure.

4.3. Temperature effect

The effect of the season and/or temperature is well described for the association between air pollution and mortality. In this context, most studies show greater sensitivity during the warmer months, or periods when the temperature is high [5].

For Europe and North America, these effects have been less studied for the various cardiovascular diseases. Regarding ischemic stroke, we find increased susceptibility to air pollution during the warm months in Canada [41]. This increased sensitivity during the hot months is also highlighted for myocardial infarction in Belgium [14]. However, in a study conducted in Spain [42], the association between NO_2 and heart rhythm disorders is especially marked during the cold period. In the present study, the temperature has an effect on the association between pollution and myocardial infarction while the season has no effect. This may be due to the fact that the stratification on the temperature is more precise than stratification on the season.

During the warmer months, people spend more time outdoors and it is highly likely that the concentrations measured by fixed stations are more representative of 'individual' exposure to air pollution [41]. Outdoor activities are most often related to a physical activity that could act as an independent trigger or increase the exposure to pollution by increasing respiratory rate [43]. In addition, high outdoor temperatures would contribute to the increase of blood viscosity and of cholesterolaemia, secondarily promoting thromboembolic events [41].

4.4. Strengths

The present study is the first to explore the lag effect across age groups and different CVD. Another advantage of this study is that it more

precisely assesses season and temperature effect for different CVD in the same study. In addition, this study is the first conducted in Wallonia, a region in the south of Belgium, to analyse the impact of air pollution on CVD and especially on arrhythmias and ischemic and haemorrhagic stroke.

4.5. Limitations

As in many studies of this type, data on individual exposure were not available, so the average outdoor concentrations of NO_2 were collected from fixed sites. Socioeconomic factors were not considered. The study was only conducted in Wallonia, and therefore the results of this study can only be generalized to countries with the same environmental and socioeconomic characteristics.

4.6. Conclusions

The results of this study reinforce the evidence of the short-term effects of NO_2 on hospital admissions for cardiovascular disease. This study shows that young people are also sensitive to air pollution. The effect of NO_2 is immediate for ischemic stroke and delayed by two days for haemorrhagic stroke. This difference suggests that their mechanisms of action are different.

Conflict of interest statement.

The authors declare no competing financial interests.

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