The association of daily sulfur dioxide air pollution levels with hospital admissions for cardiovascular diseases in Europe (The Aphea-II study)

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The objective of this study is to assess the short-term effect of sulfur dioxide (SO₂) air pollution levels on hospital admissions for cardiovascular diseases. Daily mean hospital admissions for cardiovascular diseases, ischemic heart diseases (IHDs), and stroke in seven European areas (the cities of Birmingham, London, Milan, Paris, Rome, and Stockholm, and in The Netherlands) participating in the multicenter European study of air pollution (Aphea-II), were measured. Time series analysis of daily hospital admission counts was performed using poison autoregressive models. A summary regression coefficient for all cities was provided. Daily numbers of all cardiovascular admissions except stroke, and particularly IHDs, rose significantly with an increase of daily SO₂ levels of the same day and day before. After adjusting for PM₁₀ (i.e. particles with size <10 µm), the association of SO₂ with IHD admissions remained significant (i.e. an increase of 0.7%; 95% confidence interval=0.1–1.3, per each 10 µg/m³ increase of SO₂) among subjects younger than 65 years, but not among subjects older than 65. In the older group the increase was only significant for particles (1.3%; CI 0.7–1.8, per each increase in 10 µg/m³ of PM₁₀). This study provides new evidence for the effects of urban air pollution on cardiac diseases in Europe, and suggests that SO₂ pollution may play an independent role in triggering ischemic cardiac events. From a Public Health perspective...
Introduction

In the fog episode in London in 1952 deaths due to heart diseases more than doubled (although less than deaths due to bronchitis).\(^1\) Hospital admissions for heart disease were also increased. The London fog was characterized by very high concentrations of black smoke and sulfur dioxide (SO\(_2\)) in the atmosphere, largely released by domestic coal combustion. In other episodes of air pollution involving the same pollutants, as in the Meuse Valley in 1930\(^2\) and in Donora, Pennsylvania in 1948,\(^3\) many of the people admitted to hospital suffered from chronic cardiac disease. In the last decade, a number of epidemiological studies have reported an acute association between daily counts of hospital deaths and hospital admissions for cardiovascular diseases and levels of air pollution of the preceding days at levels close to or even lower than current national standards, specially in North America,\(^3\)–\(^13\) in Europe,\(^14\)–\(^20\) and in other parts of the world, such as Sydney, Australia,\(^21\) and Hong Kong, China.\(^22\)

In the first multicities European Air Pollution Health Effects Approach (APHEA) study, that covered the period 1985–1990, an association between cardiovascular mortality and both particles (measured as black smoke) and SO\(_2\) was observed.\(^23\) In the second APHEA study, which includes more European cities and covers the period 1990–1996, the association between air pollution and hospital admissions due to cardiovascular causes was measured. Hospital admission is a more sensitive marker than mortality of the environmental effects. An association between particles and admission for ischemic heart diseases (IHDs) in people older than 65 years was reported.\(^24\) The objective of this paper is to study the short-term effect of SO\(_2\), after adjusting for particles and other air pollutants, on hospital admissions for cardiovascular diseases (i.e. what fraction of daily counts of hospital admissions was associated with SO\(_2\) pollution levels of the preceding days).

Data and methods

Table 1 shows daily mean numbers of hospital admissions for cardiovascular diseases (International Classification of Diseases (ICD), 9th revision, 390–429), IHD (ICD-9, 410–413), and stroke (ICD-9, 430–438) by age groups in seven European areas (all the European cities participating in the hospital admissions project within APHEA-II, with the exception of Barcelona, which was excluded because the detection limit for SO\(_2\) was set at an arbitrary cut-off of 10 µg/m\(^3\), a value close to the median). Daily admission data was provided by routine registers. Emergency admissions were used in every city except in Milan, Paris, and Rome where only general admissions data was available. The Netherlands was not able to provide information for all cardiac causes.

The pollutants were those generally measured in European cities and have been described in detail elsewhere.\(^23,24\) Pollution levels were assessed at fixed monitoring sites. Particles were measured mostly as PM\(_{10}\) (i.e. particles with size <10 µm), except in Paris (PM\(_{13}\)), and in Milan and Rome (total suspended particulate, TSP). Four areas (Birmingham, London, The Netherlands, and Paris) were also able to provide black smoke data (BS) as a measure of particles. Sulfur dioxide (24-h average), nitrogen dioxide (hourly values and 24-h average), and ozone (hourly value and maximum 8-h average) measurements were available in all cities. Carbon monoxide (8-h average) was also available in all cities except Paris. Stations were chosen to represent background inner-city air quality levels, except for ozone. Thus, stations located in highways were excluded.

Time series analysis was used, the unit of observation being the day and not the individual. The analysis assessed what fraction of the daily variations in hospital admission counts was explained by the daily variations in air pollution of the preceding days, after controlling for other variables that varied in time (such as trend, seasonal patterns, or meteorological factors). Usual risk factors of cardiovascular diseases (such as smoking, diet, or exercise) are not cofactors since they did not vary in the short-term time window analyzed in relation to air pollution daily variations. A Poisson autoregressive model of the hospital admissions time series was constructed which included terms to describe the seasonal patterns in the admissions, their dependence on temperature and humidity, their association with holiday periods and influenza episodes, and finally air pollution measures.\(^23\) These models provided estimates of the effect of air pollution on hospital admissions.
<table>
<thead>
<tr>
<th>City</th>
<th>Cardiovascular (390–429)</th>
<th>Ischemic heart disease (410–413)</th>
<th>Stroke (430–438)</th>
<th>Air pollutants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All ages</td>
<td>&gt;65 years</td>
<td>&lt;65 years</td>
<td>&gt;65 years</td>
</tr>
<tr>
<td>Birmingham</td>
<td>47</td>
<td>30</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>London</td>
<td>121</td>
<td>81</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>Milan</td>
<td>38</td>
<td>25</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Netherlands</td>
<td>–</td>
<td>–</td>
<td>60</td>
<td>74</td>
</tr>
<tr>
<td>Paris</td>
<td>138</td>
<td>67</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Rome</td>
<td>87</td>
<td>55</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Stockholm</td>
<td>36</td>
<td>28</td>
<td>4</td>
<td>12</td>
</tr>
</tbody>
</table>

*a PM₁₀ (particles of size <10 µg)=TSP (total suspended particles)×0.75 (originally measured on TSP).

b PM₁₃.
pollution on the mean number of admissions per day. Generalized Additive Models were used to study non-linear relationships between confounders and morbidity,\textsuperscript{24} thus temperature and humidity were included as a smooth function on the same day of admission or lagged up to 3 preceding days. In every city, the air pollution indicator (i.e. SO\textsubscript{2}) was introduced as a linear term representing the average of the same and the preceding day’s levels. Finally, two pollutant-models were fitted to assess the changes in the SO\textsubscript{2} estimates after the inclusion of the other pollutants.

In a second step, the heterogeneity of the associations between air pollution levels and daily admission levels among cities was assessed using the chi-square test for heterogeneity. A significant result indicated that the variation in the effect estimates was greater than expected by chance. However, a summary estimate for all the cities that accounted for this additional variation was calculated (random-effects estimate). Where there was significant heterogeneity between estimates further analyses were carried out to investigate possible reasons for this. In this second stage of the analyses, regression models were used to investigate associations between the seven SO\textsubscript{2} effect estimates (one for each city) and variables describing the health and environmental conditions in each city. In this way factors which may affect the toxicity of the pollutants or the vulnerability of the exposed population (effect modifiers) were examined (such as prevalence of smoking or social class average).

**Results**

Daily counts of cardiovascular admissions, and particularly IHD over 65 years, increased in a statistically significant way in association with an increase of daily SO\textsubscript{2} levels of the same and the preceding day. Hence, an increase in 10 µg/m\textsuperscript{3} of daily average of SO\textsubscript{2} was associated with an increase of 0.7%; 95% confidence interval=0.1–1.3, of all cardiovascular admissions of the same and the next day. No such pattern was seen for stroke (Table 2). The association with IHD over 65 was homogenous (i.e. positive in all cities except Stockholm, and statistically significant in four of the seven cities) (Fig. 1).

The association for all cardiovascular admissions was less homogeneous between cities (it was positive for all cities except for Birmingham, but the magnitude of the positive effect varied widely). Most of this heterogeneity of the association with cardiovascular admissions was explained by the average level of humidity of each city. The association of SO\textsubscript{2} with cardiovascular admissions (both at all ages and over 65) was stronger at lower levels of humidity (percent increase of all cardiovascular admissions at all ages was 1.67, CI=0.65–2.71, per 10 µg/m\textsuperscript{3} of SO\textsubscript{2} at the lowest levels of humidity and 0.81, CI=0.43–1.19 at the highest).

None of the other variables examined (such as climatic, socio-economic variables, and others such as prevalence of smoking) helped to explain the heterogeneity between cities.

To analyze if the association with SO\textsubscript{2} was explained by the levels of other pollutants usually present in urban air such as particles, a second analysis was done fitting two-pollutant models (i.e. adjusting the effect of SO\textsubscript{2} for a second pollutant). The association with all cardiovascular admissions (both at all ages and above 65 years) weakened and became non-significant after adjusting for CO, NO\textsubscript{2}, black smoke, and PM\textsubscript{10}. In contrast, the association of IHD –65 years showed little change after controlling for the other pollutants. For IHD over 65 years of age, the association weakened and became non-significant after adjusting for NO\textsubscript{2}, black smoke, and PM\textsubscript{10} (Table 3). Among subjects older than 65 years, the association with IHD was stronger for particles than for SO\textsubscript{2}, while among subjects younger than 65, the association appeared stronger for SO\textsubscript{2} (Table 3). A sub-analysis with cities using strictly the same data on PM\textsubscript{10} (almost the same cities as for the analysis of black smoke) provided the same results.

**Discussion**

This combined analysis summarizes the results from seven European cities concerning the short-term effects of SO\textsubscript{2} air pollution on hospital admissions for cardiovascular causes. It represents the first multicenter epidemiological study examining the impact of SO\textsubscript{2} on cardiovascular morbidity in Europe, where the association between air pollution involving SO\textsubscript{2} and mortality for cardiovascular

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**Table 2** Percentage increase in the daily number of hospital admissions per each increase of 10 µg/m\textsuperscript{3} in SO\textsubscript{2} levels of the same and preceding day

<table>
<thead>
<tr>
<th>Outcome (ICD-9)</th>
<th>SO\textsubscript{2}</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular (390–429)</td>
<td>0.7</td>
<td>0.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Cardiovascular over 65 years</td>
<td>0.7</td>
<td>0.3</td>
<td>1.2</td>
</tr>
<tr>
<td>IHD (410–413) below 65 years</td>
<td>0.6</td>
<td>0.2</td>
<td>1.1</td>
</tr>
<tr>
<td>IHD over 65 years</td>
<td>1.2</td>
<td>0.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Stroke (430–438) over 65 years</td>
<td>0.0</td>
<td>–0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
causes has been consistently shown.\textsuperscript{23,25} We found a significant effect of SO\textsubscript{2} on admissions for cardiac causes and IHD for all ages. The percentage increase associated with a 10 µg/m\textsuperscript{3} increase in SO\textsubscript{2} was similar to the effect found for particles (between 0.5 and 1%) in the APHEA study.\textsuperscript{24} The association was larger for IHD over 65 years old. Given that everyone is exposed to urban air pollutants, for a city such as London with more than 100 admissions per day an increase in 10 µg/m\textsuperscript{3} in SO\textsubscript{2} (its standard deviation was 23 µg/m\textsuperscript{3}) would result in an impact of at least one additional

Table 3  Percentage increases (and 95% CI) in hospital admissions for IHDs (ICD-9, 410-413) per 10 µg/m\textsuperscript{3} increase in the average of SO\textsubscript{2}, after adjusting for particles (either PM\textsubscript{10} or black smoke)

<table>
<thead>
<tr>
<th>Age</th>
<th>Including seven cities</th>
<th>Including four cities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude\textsuperscript{a}</td>
<td>Adjusted</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SO\textsubscript{2}</td>
<td>0.6 (0.1–1.1)*</td>
<td>0.7 (0.1–1.3)*</td>
</tr>
<tr>
<td>PM\textsubscript{10}</td>
<td>0.2 (−0.2–0.5)</td>
<td>0.0 (−0.4–0.3)</td>
</tr>
<tr>
<td>Black smoke</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SO\textsubscript{2}</td>
<td>1.2 (0.8–1.6)*</td>
<td>−1.4 (−8.0–6.0)</td>
</tr>
<tr>
<td>PM\textsubscript{10}</td>
<td>0.7 (0.3–1.1)*</td>
<td>1.3 (−1.8–4.5)</td>
</tr>
<tr>
<td>Black smoke</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

\textsuperscript{a}A single pollutant was fitted in each model.

\textsuperscript{*}p<0.05.

Fig. 1  Estimated percentage increase in admissions for IHD among subjects aged over 65 years in each city as well as pooled fixed and random-effect estimates associated with a 10 µg/m\textsuperscript{3} increase in the average of SO\textsubscript{2} for 0 and 1 day average lag. Average values of SO\textsubscript{2}, daily mean in µg/m\textsuperscript{3}, were 24.3, 23.6, 21.1, 8.5, 17.7, 9.8, and 3.8, respectively, for the cities (in alphabetic order).
admission per day due to this pollutant, which if translated to all the European cities would result in a considerable public health impact.

The acute effect of air pollution on cardiovascular disease has already been observed, mainly outside Europe. Table 4 summarizes the results from studies examining the relationship between hospital admissions for cardiovascular diseases and both, SO2 and particles, using a systematic review.26 There were 34 reports including particulates, and all except one (97%) found a positive and significant association between particle levels and cardiovascular admissions. For studies including SO2, 17 of the 24 (71%) found positive and significant associations with at least one of the indicators of cardiovascular admissions. Among the 24 reports including SO2, only 12 analyzed both SO2 and particles and these are included in Table 4. We have also included a more recent article30 published after completion of the review. An association between cardiovascular hospital admissions and SO2 was found in nine out of the 13 studies (Table 4).

The present study refers to the assessment of air pollution as a trigger of cardiovascular disease admissions, and mainly of IHD. The underlying hypothesis was that frail individuals were at higher risk of having an attack on days with higher air pollution levels. This study, then, did not refer to the classical risk factors that mainly ascertain cumulative or chronic relationships. While epidemiological findings, such as the present study, are very consistent, the issue of the biological plausibility is weak since the underlying mechanisms of an acute heart effect of air pollution are unknown. Several physiopathological pathways have been proposed for the relationship between particulate air pollution and cardiovascular health.31–33 One of the major hypotheses is that particles induce activation of some mediators/indicators of alterations in blood coagulability.33 Another kind of mechanism examined includes those indicative of cardiac autonomic control, such as heart rate and various indices of its variability.34 The lack of an association with stroke is an intriguing finding since effects of air pollution on hemostatic profile would be expected to increase the number of stroke events.

A growing number of studies35–37 support the hypothesis that composition of ultrafine particles38 (those with size less than 100 nm in diameter) and transition metals39 could explain, in a substantial part, these harmful effects of air pollution on the cardiovascular system. However, an additive role of SO2 or other gaseous pollutants such as CO, could not be discarded.7,40 Particles and SO2 may act via a different mechanism rather than interacting with each other through the same mechanistic route. In a recent study, a change in heart rate variability in humans on exposure to SO2 (200 ppb for 1 h) was attributed to stimulation of receptors in the upper respiratory tract.31 Such a mechanism of SO2 may be operating in patients with IHD. Among the studies on cardiovascular admissions (Table 4), after adjusting for particles, the association of SO2 remained significant only in three studies,7,20,28 while the association of particles is less affected by the adjustment for SO2. However, in a recent study in Hong Kong, abatement of SO2 levels had a notable impact in reducing adverse health effects, although particle levels remained stable.41 The fact that PM10, black smoke, CO, and NO2 reduce the association of SO2 with cardiovascular admissions in the present study may be because these pollutants probably come from the same source (i.e. diesel exhaust or fossil fuel combustion) or may increase together due to the meteorological conditions. To disentangle the specific effect of each of the pollutants in the urban atmospheres is not possible in the present study. Only the association of SO2 with IHD in individuals aged under 65 was not confirmed by particles or CO, although it was slightly reduced after adjusting for NO2 levels. This suggests that SO2 may play an independent role in triggering ischemic cardiac events. A different question is why SO2 is associated with IHD in the younger but not in the older age group, after adjusting for particles. One explanation could be that the daily activity pattern of the young group could result in a lower measurement error, using ambient measurements as surrogates for personal measurements, than in the older group.

A problem of the present study refers to lack of checking of diagnosis labels. This problem could affect present results if variation in coding occurs within the same city on a daily basis. However, given that this error, if it occurs, is unlikely to be related with time variations in air pollution levels, the consequent bias would reduce the magnitude of the associations estimated. One problem encountered with data comparability on health outcome was that Paris and Milan were not able to provide emergency admissions only. However, a sub-analysis excluding these cities yielded very similar results, suggesting that the error produced by including both hospital admissions and emergency admissions was small. In a sub-analysis of the London data, emergency admissions accounted for the majority of hospital admissions for cardiovascular causes. On the other hand, the potential problem of using routinely collected
<table>
<thead>
<tr>
<th>Author/s (year of publication)</th>
<th>Site/period of study</th>
<th>Outcome</th>
<th>Age group</th>
<th>Estimates of the association a SO₂</th>
<th>PM₁₀b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz and Morris (1995)⁴</td>
<td>Detroit, USA/1986–1989</td>
<td>Ischemic heart disease (ICD-9, 410–414)</td>
<td>&gt;65 years</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Burnett et al. (1997)⁹</td>
<td>Toronto, Canada/1992–1994 (summer)</td>
<td>Cardiac disease (ICD-9, 410–414, 427,428)</td>
<td>&gt;65 years</td>
<td>SO₂-l h: 2.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Wong et al. (1999)²²</td>
<td>Hong Kong, China/1994–1995</td>
<td>Cardiovascular diseases (ICD-9, 410–414,427,428,434–440)</td>
<td>All ages</td>
<td>1.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Atkinson et al. (1999)²⁷</td>
<td>London, UK/1992–1994</td>
<td>Ischemic heart disease (ICD-9, 410–414)</td>
<td>All ages</td>
<td>2.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Burnett et al. (1999)⁷</td>
<td>Toronto, Canada/1980–1994</td>
<td>Ischemic heart disease (ICD-9, 410–414)</td>
<td>&gt;65 years</td>
<td>1.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Moolgavkar (2000)²⁸</td>
<td>Three counties: Los Angeles (LA), Cook, Maricopa, USA/1987–1995</td>
<td>Ischemic heart disease (ICD-9, 410–414)</td>
<td>&gt;65 years</td>
<td>LA, 4.8; Cook, 1.4; Maricopa, 2.5</td>
<td>LA, 0.6; Cook, 0.8; Maricopa, NS</td>
</tr>
<tr>
<td>Lipmann et al. (2000)¹³</td>
<td>Detroit, USA</td>
<td>Ischemic heart disease (ICD-9, 410–414)</td>
<td>&gt;65 years</td>
<td>NS</td>
<td>1.2</td>
</tr>
<tr>
<td>Ballester et al. (2001)²⁰</td>
<td>Valencia, Spain/1994–1996</td>
<td>Ischemic heart disease (ICD-9, 410–414)</td>
<td>All ages</td>
<td>3.0</td>
<td>BS: 1.5 (only significant in summer)</td>
</tr>
<tr>
<td>Biggeri et al. (2001)²⁹</td>
<td>Six Italian cities (Turin, Milano, Bologna, Firenze, Rome, and Palermo)/1995–1999</td>
<td>Ischemic heart disease (ICD-9, 410–414)</td>
<td>All ages</td>
<td>3.6</td>
<td>BS: 1.5 (only significant in summer)</td>
</tr>
<tr>
<td>Anderson et al. (2001)³⁰</td>
<td>West Midlands (Birmingham), UK/1994–1996</td>
<td>Cardiovascular disease (ICD-9, 390–429)</td>
<td>All ages</td>
<td>2.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Sunyer et al. (this paper)</td>
<td>APHEA2: Birmingham, London, Milan, Netherlands, Paris, Rome, and Stockholm</td>
<td>Cardiovascular disease (ICD-9, 390–429)</td>
<td>&gt;65 years</td>
<td>0.7</td>
<td>0.4</td>
</tr>
</tbody>
</table>

NS=non-significant results. Results for pollutants other than SO₂ and PM₁₀/BS are not shown here. >65 years=persons aged 65 years and older; 0–64 years=persons aged under 65 years.

a Results expressed as the increase (%) in hospital admissions for an increase in the pollutant levels of 10 µg/m³.

b If PM₁₀ was not available we chose BS estimates.
data on air pollution has been extensively evaluated and, if anything, reduced the estimated coefficients.\textsuperscript{4,12,30}

The present study did not incorporate the classical risk factors for cardiovascular diseases even though these factors may change by season. However, the statistical procedure carried out here was adjusted for all the seasonal effects, and a residual confounding of these factors (such as seasonal variations on diet or exercise) is unlikely. A different question refers to the modification of the effect of air pollution by certain factors (such as age, sex, or smoking). Thus, the effect of air pollution could be more important in smokers than in non-smokers.\textsuperscript{37}

Time series analysis is not suitable for assessing susceptibility factors, which is beyond the present study. However, we performed a hierarchical analysis trying to ascertain which city variables could explain differences in the coefficients of the association between air pollution and cardiac admissions. Neither age and sex structure nor smoking prevalence explain these variations, but this analysis was only conducted with seven areas, and is of limited value.

It should be noted that certain frequently encountered problems of meta-analysis do not apply in our study. There was no selection bias in the sense that the participating cities were not selected by the results of the short-term analysis, but by their ability to provide data. All the city specific analyses were centralized in one place, giving more homogeneity in the application of the methodology defined within the APHEA-2 statistical group. We also set rules for exposures and confounding factor measurements. Similarly, problems due to the usual epidemiological design such as the lack of inclusion of classical risk factors of cardiovascular diseases do not apply to the present study since they did not vary from one day to the next.

Overall, this study provides new evidence for the effects of urban air pollution on cardiac diseases in Europe, suggesting that air pollutants could trigger a MI in subjects with vulnerable arteries. Mechanistically, most of the evidence refers to the hemodynamic and hemostatic effects of air pollutants, but solid evidence for the role of these possible physiological mechanisms is lacking. The present analysis shows that from a public health perspective, urban atmospheres in Europe are associated with admissions for IHD, and that SO\textsubscript{2} is a surrogate of these mixtures, in some cases (such as in IHD in younger than 65 years) in a stronger way than particles. Therefore, these results suggest that reduction in SO\textsubscript{2} levels in European cities could imply a reduction of admissions for IHDs.

Acknowledgements

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