Particulate air pollution is associated with an acute phase response in men

Results from the MONICA–Augsburg Study

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Aims Episodes of increased air pollution are associated with increases in hospital admissions for cardiovascular disease. Even modest acute phase responses are associated with increased risk of coronary heart disease. The study investigates whether induction of an acute phase response by exposure to air pollution may contribute to cardiovascular pathology.

Methods and Results A prospective cohort study based on a survey in 1984/85 with a 3-year follow-up was conducted in 631 randomly selected men aged 45 to 64 years free of cardiovascular disease at entry 1984/85. Serum C-reactive protein concentrations were determined by a high sensitivity immunoradiometric assay. C-reactive protein concentration was increased in association with the 1985 air pollution episode. In multivariate analyses, elevated concentrations were independently associated with concentrations of total suspended particles and the sulphur dioxide episode. At ambient concentrations of pollution, as noted during the 1985 air pollution episode, the odds of observing C-reactive protein concentrations above 5·7 mg·l⁻¹ (>90th percentile) tripled, and increases of 26 µg·m⁻³ total suspended particles (mean of 5 days) raised the odds of C-reactive protein levels 50% above the 90th percentile.

Conclusions Exposure to current levels of particulate matter in the atmosphere elicits an acute phase response in randomly selected healthy middle-aged men, which may contribute to the increased cardiovascular risk caused by air pollution.

Key Words: Acute phase reaction, air pollution, cardiovascular disease, epidemiology, risk factors.

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Introduction

While air pollution has been largely declining over past decades, adverse health effects can be noted even under current conditions and particulate air pollution is still a major concern[1]. Hospital admissions for both respiratory and cardiovascular diseases increase in association with particulate air pollution[2–5]. The mechanisms underlying the association between inhalation of particles from the ambient air and acute exacerbations of cardiovascular disease, necessitating hospital care, are clearly of considerable interest. Seaton et al.[6] have hypothesized that pulmonary inflammation may trigger systemic hypercoagulability. C-reactive protein, the classical acute phase protein, is not directly involved in the coagulation process but is a sensitive marker of inflammation, tissue damage, and infection[7]. The important role of inflammation in the onset of acute ischemic syndromes is well established, with clear evidence of neutrophil activation and elevated levels of acute phase proteins in unstable angina pectoris and in initially healthy subjects who go on to suffer myocardial infarction in the future[8]. The close temporal relationship between acute and chronic infections and coronary events is also well documented[9–11].

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In January 1985, an air pollution episode occurred throughout Central Europe resulting in an increase in hospital admissions for cardiovascular diseases, such as acute coronary syndromes and arrhythmias. The first MONICA survey (MONItoring of trends and determinants in CArdiovascular disease) was carried out in Augsburg (Southern Germany) during the winter 1984/85 and included the days of the episode. This survey provides a unique opportunity to study the impact of an air pollution episode on markers of early biological effects or altered function of the heart in a random sample of the adult population. An increase in plasma viscosity during the 1985 air pollution episode in Central Europe provided the first evidence of a systemic response to exposure to air pollution. Here we report on the impact of air pollution on serum C-reactive protein levels measured by a high sensitivity assay in a sample of 631 men aged 45 to 64 years from the MONICA Augsburg Cohort Study.

**Methods**

**Population and design**

The first Augsburg MONICA survey was carried out in 1984/85. Of the 5069 randomly sampled eligible subjects 4022, aged 25–64 years, took part, a 79.3% response rate. All survey methods were as in the MONICA protocol. We report here on a subsample of men aged 45 to 64 years, who had no history of myocardial infarction or diseases possibly associated with an acute phase reaction at entry into the study; those with evidence of acute infections were excluded. In 1987/88, participants in the first MONICA survey were re-examined using the same protocol as 3 years before. Age and sex distribution over time was uniform for both examinations. Of the 936 subjects with C-reactive protein measurements during the first examination, valid C-reactive protein measurements were obtained in 631 subjects during re-examination. Losses were due to: (a) follow-up (n=90), (b) no blood samples taken at the re-examination (n=41), (c) samples had been used for other determinations (n=95), (d) no date was recorded (n=12), (e) no valid C-reactive protein measurement (n=26), and (f) evidence of an acute infection at the time of examination (n=41). Baseline characteristics of the cohort are presented in Table 1.

**Analytical methods**

Laboratory procedures were as described earlier. Briefly, non-fasting blood samples were taken at baseline and 3 years later and stored at −70 °C until analysis. Serum concentrations of C-reactive protein were measured by means of a sensitive immunoradiometric assay (range 0.05 to 10 mg l−1) and calibrated with the WHO International Reference Standard for C-reactive protein Immunoassay, standard 85/506, produced at the Immunological Medicine Unit, Royal Postgraduate Medical School (London, U.K.). Recovery >100% pure C-reactive protein spiked into serum was 100%. Coefficients of variation within assays were 4%, and between assays were 12% across the whole range. Samples with values >10 mg l−1 were remeasured at appropriately higher dilution. All samples were measured in triplicate and values were averaged for analysis. Sulphur dioxide (SO2), carbon monoxide (CO) and total suspended particulates were measured daily at one central site as part of the automated Bavarian air quality network. The monitoring station was located in the centre of the city while temperature, relative humidity and air pressure were measured south of the city.

**Statistical analysis**

The distribution of C-reactive protein values was markedly skewed to the right (Table 2). Therefore, C-reactive protein concentrations were dichotomized at the 80th (values >4.1 mg l−1), 90th (values >5.7 mg l−1) and 95th (values >8.7 mg l−1) percentiles. Logistic regression models were used taking into account repeated measurements. Air pollution was considered in two ways in the analyses: (a) as an indicator for the 1985 episode or (b) as a continuous measure of SO2, total suspended particulates and CO concentrations. Categorical variables were constructed to control for age (10 year categories), body mass index (25 to 30 kg m−2, and >30 kg m−2, compared to <25 kg m−2 as a reference category) and current smoking. Systolic blood pressure, total and high density lipoprotein (HDL) cholesterol were entered into the models as continuous variables. Meteorological parameters were considered as possible confounders in the regression analyses; temperature was entered into the final model as a quadratic function and relative humidity was considered linearly.

**Results**

Sulphur dioxide (SO2) concentrations decreased substantially during the 3 year period of follow-up, but total...
suspended particles as well as carbon monoxide concentrations remained unchanged (Table 2). Peak concentrations of air pollutants were observed during the 1985 air pollution episode between 7 January and 19 January 1985\(^{14}\). At that time, the average SO\(_2\) concentration was 200 \(\mu g \cdot m^{-3}\) (average excluding the episode: 48 \(\mu g \cdot m^{-3}\)) and the average total suspended particulate concentration was 98 \(\mu g \cdot m^{-3}\) (average outside the episode: 47 \(\mu g \cdot m^{-3}\))\(^{19}\). The episode was characterized by low temperatures, stable relative humidity and easterly winds\(^{15}\). Excluding the 1985 air pollution episode, average SO\(_2\) concentrations were 48-1 \(\mu g \cdot m^{-3}\), average total suspended particulate concentrations were 47-4 \(\mu g \cdot m^{-3}\) and CO concentrations remained unchanged\(^{19}\).

During the air pollution episode, a higher proportion of men had elevated levels of C-reactive protein compared to the remaining days of the first survey and to the re-examination (Fig. 1). Results of multivariate analyses for the air pollutants SO\(_2\), total suspended particulates and CO adjusted for age, body mass index, systolic blood pressure, total and HDL-cholesterol, current smoking, treatment with cardiac medication, and meteorology are shown in Table 3. C-reactive protein values were elevated in older men, men with a high body mass index, current smokers, men with high systolic blood pressure and men treated with cardiac medication. High levels of HDL cholesterol were associated with decreased concentrations of C-reactive protein, while the total cholesterol concentration had no association with high C-reactive protein concentration. Temperature as a quadratic function and relative humidity changed the estimates of the air pollutants for more than 10%, but had no strong associations with C-reactive protein concentrations themselves.

The odds of observing high C-reactive protein levels increased in association both with total suspended particulates and SO\(_2\) but not with CO concentration (Table 3). Regression coefficients of each pollutant are expressed for increases from the 25th to the 75th percentile (inter-quartile range) and therefore direct comparisons between the estimates are possible. The odds ratio for observing high C-reactive protein values in association with particulate air pollution grew stronger the more extreme C-reactive protein concentrations were considered as outcomes. Evidence was found for an immediate effect as indicated by the positive association between high C-reactive protein levels and total suspended particulate or SO\(_2\) concentrations on the day of the examination. In addition, a slightly stronger, cumulative effect appeared to be present, as suggested by the estimates for the 5 days mean. The odds for observing high C-reactive protein values might increase linearly in association with total suspended particulates, as suggested by quintile plots (Fig. 2). C-reactive protein concentrations above 10 mg \(\cdot l^{-1}\) exceed the 99th centile of the distribution observed in all published studies of ostensibly healthy normal subjects\(^{19}\) and are generally considered abnormal\(^{1-21}\). The odds ratio for observing a C-reactive protein concentration above 10 mg \(\cdot l^{-1}\) for a 5 day mean of total suspended particulate (increase of 26 \(\mu g \cdot m^{-3}\)) was 2.06 (95% confidence interval (CI): 1.46 to 2.90) and was therefore even stronger than the estimates for the three extreme percentiles chosen. Alternatively, the change in C-reactive protein concentrations was evaluated using multivariate linear regression models. C-reactive protein concentrations increased 0.88 mg \(\cdot l^{-1}\) (95% CI: 0.34 to 1.42 mg \(\cdot l^{-1}\)) in association with 26 \(\mu g \cdot m^{-3}\) total suspended particulates (5 day mean), 0.41 mg \(\cdot l^{-1}\) (95% CI: -0.17 to 0.98 mg \(\cdot l^{-1}\)) in association with 30 \(\mu g \cdot m^{-3}\) SO\(_2\) (5 day mean) and 0.19 mg \(\cdot l^{-1}\) (95% CI: -0.25 to 0.64 mg \(\cdot l^{-1}\)) in association with 1.5 mg \(\cdot m^{-3}\) CO (5 day mean).

The effects for total suspended particulates were generally more consistent than those for SO\(_2\). Total suspended particulates and SO\(_2\) were only moderately correlated during the two winters (\(r=0.42\) in 1984/85 and \(r=0.45\) in 1987/88). Two pollutant models estimated an odds ratio of 1.12 (95% CI: 0.92 to 1.47) for the 5 day mean of SO\(_2\) (30 \(\mu g \cdot m^{-3}\)) and odds ratio of

### Table 2 C-reactive protein (CRP) concentrations, air pollution concentrations, and meteorological parameters during the 1984/85 study period and the re-examination in 1987/88

<table>
<thead>
<tr>
<th>Time period</th>
<th>n</th>
<th>Mean (SD)</th>
<th>Min</th>
<th>Q1</th>
<th>Median</th>
<th>Q3</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg (\cdot l^{-1}))</td>
<td>1984/85</td>
<td>631</td>
<td>3.01 (5.20)</td>
<td>0.05</td>
<td>0.70</td>
<td>1.59</td>
<td>3.63</td>
</tr>
<tr>
<td>1987/88</td>
<td>631</td>
<td>2.88 (5.08)</td>
<td>0.02</td>
<td>0.78</td>
<td>1.65</td>
<td>3.50</td>
<td>83.2</td>
</tr>
<tr>
<td>SO(_2) ((\mu g \cdot m^{-3}))</td>
<td>1984/85</td>
<td>117 (89%)</td>
<td>60.8 (48.8)</td>
<td>13</td>
<td>29</td>
<td>53</td>
<td>68</td>
</tr>
<tr>
<td>1987/88</td>
<td>144 (100%)</td>
<td>24.3 (12.5)</td>
<td>6</td>
<td>17</td>
<td>22</td>
<td>28</td>
<td>71</td>
</tr>
<tr>
<td>TSP ((\mu g \cdot m^{-3}))</td>
<td>1984/85</td>
<td>113 (86%)</td>
<td>54.0 (32.6)</td>
<td>7</td>
<td>30</td>
<td>44</td>
<td>69</td>
</tr>
<tr>
<td>1987/88</td>
<td>118 (82%)</td>
<td>47.8 (22.1)</td>
<td>12</td>
<td>32</td>
<td>44</td>
<td>59</td>
<td>134</td>
</tr>
<tr>
<td>CO ((\mu g \cdot m^{-3}))</td>
<td>1984/85</td>
<td>116 (88%)</td>
<td>4.5 (1.8)</td>
<td>1.3</td>
<td>3.2</td>
<td>4.3</td>
<td>5.5</td>
</tr>
<tr>
<td>1987/88</td>
<td>114 (100%)</td>
<td>4.1 (1.3)</td>
<td>1.7</td>
<td>3.2</td>
<td>4.0</td>
<td>4.8</td>
<td>8.2</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>1984/85</td>
<td>132 (100%)</td>
<td>1.6 (7.8)</td>
<td>-24.8</td>
<td>-1.4</td>
<td>2.5</td>
<td>6.4</td>
</tr>
<tr>
<td>1987/88</td>
<td>139 (97%)</td>
<td>5.5 (6.3)</td>
<td>-11.3</td>
<td>0.3</td>
<td>5.2</td>
<td>11.1</td>
<td>18.7</td>
</tr>
<tr>
<td>Relative humidity (%)</td>
<td>1984/85</td>
<td>132 (100%)</td>
<td>81.9 (9.4)</td>
<td>58</td>
<td>76</td>
<td>83</td>
<td>90</td>
</tr>
<tr>
<td>1987/88</td>
<td>139 (97%)</td>
<td>80.7 (12.5)</td>
<td>48</td>
<td>72</td>
<td>85</td>
<td>91</td>
<td>96</td>
</tr>
</tbody>
</table>

TSP=total suspended particulates; CO=carbon monoxide; SO\(_2\)=sulphur dioxide.
1·37 (95% CI: 1·08 to 1·73) for the 5 day mean of total suspended particulates (26 µg · m⁻³) for C-reactive protein values above the 90th percentile. Including an indicator for the episode together with the measured air pollutant, demonstrated that the effect of total suspended particulates was independent of the episode (Table 4) while the SO₂ effect was not. With total suspended particulates in the multivariate model, increased, but statistically non-significant, odds ratios were observed for an indicator of the air pollution episode, e.g. C-reactive protein values above the 90th percentile: OR 3·57 (95% CI: 0·68 to 18·7). Two pollutant models with SO₂ and the episode estimated the following odds ratios for C-reactive protein values above the 90th percentile: OR 1·18 (95% CI: 0·92 to 1·51) for a 5 day mean of SO₂ and OR 1·64 (95% CI: 0·25 to 10·7) for the episode. Based on the results presented in Table 3, the effect of the 1985 episode can be estimated based on the change in SO₂ concentrations. The 1985 air pollution episode was
characterized by an elevation of SO$_2$ of 150 $\mu$g. m$^{-3}$, which would result in an OR of 3.01 (95% CI: 1.18 to 7.66) for the 90th percentile. Excluding the episode did not reduce the associations between total suspended particulates and C-reactive protein (Table 4). Estimates for the 5 day mean of total suspended particulates were slightly larger for subjects living within the city limits. While non-smokers showed a stronger response when C-reactive protein values above the 80th were considered, weaker effects were observed with more extreme C-reactive protein concentrations. Increases in C-reactive protein concentrations in association with the particulate air pollution were observed both in patients with and without cardiac medication.

**Discussion**

Elevated concentrations of C-reactive protein were consistently associated with particulate air pollution. Increases in C-reactive protein concentrations were noted during the 1985 air pollution episode, but even after exclusion of the air pollution episode, increases in C-reactive protein concentrations were observed in

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*Models did not converge due to small numbers.*

### Figure 2
Multivariate regression results for quintiles of total suspended particulates (TSP) on C-reactive protein concentrations above 5.7 mg. l$^{-1}$ (90th percentile).

### Table 4
Effect of ambient total suspended particulate concentrations (5 day means) on high C-reactive protein (CRP) concentrations in 631 men adjusted for age, body mass index, blood pressure, cholesterol, smoking, treatment of cardiac diseases, and meteorology

<table>
<thead>
<tr>
<th></th>
<th>80th percentile</th>
<th>90th percentile</th>
<th>95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRP &gt;4.1 mg. l$^{-1}$</td>
<td>CRP &gt;5.7 mg. l$^{-1}$</td>
<td>CRP &gt;8.7 mg. l$^{-1}$</td>
</tr>
<tr>
<td>Adjusted for the 1985 episode</td>
<td>1.26 1.05 to 1.52</td>
<td>1.41 1.12 to 1.77</td>
<td>1.62 1.17 to 2.25</td>
</tr>
<tr>
<td>Excluding the 1985 episode</td>
<td>1.33 1.11 to 1.59</td>
<td>1.41 1.12 to 1.78</td>
<td>1.68 1.21 to 2.34</td>
</tr>
<tr>
<td>Living within the city limits</td>
<td>1.37 1.01 to 1.85</td>
<td>1.86 1.30 to 2.65</td>
<td>—*</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>1.36 1.08 to 1.70</td>
<td>1.37 1.04 to 1.79</td>
<td>1.32 0.88 to 1.98</td>
</tr>
<tr>
<td>No cardiac medication</td>
<td>1.16 0.93 to 1.43</td>
<td>1.45 1.12 to 1.88</td>
<td>1.54 1.06 to 2.24</td>
</tr>
</tbody>
</table>

*Models did not converge due to small numbers.*

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association with elevated concentrations of particulate air pollution. In two pollutant models, both the 1985 air pollution episode and total suspended particulates, concentrations were independent predictors of high C-reactive protein concentrations. Unfortunately, no data on the concentrations of fine and ultra-fine particles were available, so that SO₂ and total suspended particulates serve as surrogates for the levels of inhalable particles. However, the multivariate modelling allows for tight control of cardiovascular risk factors as well as meteorological factors which might potentially confound the association between ambient air pollution and C-reactive protein concentrations.

C-reactive protein is clearly a cardiovascular risk factor in healthy subjects[17,21,22] as well as in individuals with coronary heart disease[23]. A recent review estimated a combined risk ratio of 2.0 (95% CI: 1.6 to 2.5) comparing the lowest to the highest tertile of its distributions[8]. In the MONICA study, men with C-reactive protein concentrations in the highest quintile had a 2.6-fold risk of a subsequent first major coronary heart disease event compared to the men in the lowest quintile[17]. The increases in association with air pollution thus indicate an increased risk of cardiac events on a population basis.

C-reactive protein is a tightly regulated protein, the plasma concentration of which can increase by more than 1000-fold during an acute phase response[24]. Its plasma half-life is only 19 h and is constant regardless of the clinical condition, so that the synthesis rate is the sole determinant of the plasma concentration. It is upregulated rapidly, within hours, during an acute phase response[24]. This makes C-reactive protein a sensitive, robust and uniquely quantitative marker of the acute phase response. It is produced in response to most forms of tissue injury, infection, and inflammation and regulated by cytokines including interleukin-6, interleukin-1, and tumour necrosis factor-α[25]. Possible mechanisms by which air pollution may induce C-reactive protein synthesis include deposition of particles in the alveoli, leading to activation of, and cytokine production by, alveolar macrophages[26] and epithelial cells[27], recruitment of inflammatory cells[28] and mobilization of leukocytes from the bone marrow[29,30].

During the 1985 air pollution episode there was an increased prevalence of raised plasma viscosity[15]. The changes reported here for C-reactive protein are even more pronounced; the odds for C-reactive protein concentrations above the 90th percentile tripled while the odds for plasma viscosity levels above the 90th percentile had only doubled[15]. This result is consistent with the fact that both plasma viscosity and C-reactive protein are markers of the acute phase response[25], and that plasma viscosity is largely determined by the concentration of fibrinogen which, although an acute phase reactant, responds much more slowly and over a much smaller dynamic range than C-reactive protein. Several mechanisms have been postulated to link inhalation of particulate matter with cardiac responses. Besides a systemic reaction, evidence has been found that the automatic control of the heart might be altered after exposure to particulate air pollution. Studies evaluating heart rates and heart rate variability in association with air pollution in elderly persons[21,34] support this hypothesis. In the MONICA Cohort Study, evidence has been found for increasing heart rates in association with the 1985 air pollution episode and particulate matter concentrations[39]. Furthermore, heart rates were three times higher observed in subjects with elevated plasma viscosity concentrations[35]. The increases in plasma viscosity and C-reactive protein as well as the elevation in heart rates were observed in association with the same-day concentrations of ambient pollution, indicating that both mechanisms might change the risk factor profiles acutely. Both mechanisms might potentially increase the likelihood of ischaemic events and arrhythmias, especially in person with manifest atherosclerotic disease.

In conclusion, the data presented here indicate that current levels of particulate matter induce an acute phase response in healthy middle-aged men randomly selected from the general population. This finding is of considerable clinical significance in view of the powerful association between the systemic acute phase response and future cardiac events.

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References


