Increased plasma viscosity during an air pollution episode: a link to mortality?

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Summary

Background Air pollution episodes have been consistently associated with increased mortality, and most strikingly with mortality due to cardiovascular disease. One hypothesis to explain this association is that inflammation of the peripheral airways caused by pollution might increase blood coagulability. We have tested this hypothesis in a cross-sectional study by comparing measurements of plasma viscosity during a severe episode of air pollution during 1985 with those made on less polluted days.

Methods Plasma viscosity was measured as part of the MONICA Augsburg survey during the winter of 1984–85 in 3256 randomly selected men and women aged 25–64 years. Daily mean concentrations of air pollutants and meteorological variables were measured in Augsburg as part of the automated Bavarian air-quality network. We compared measurements of plasma viscosity made in 324 people who attended for screening during the pollution episode and in 2932 people screened during the remainder of the survey period.

Findings In January, 1985, high concentrations of sulphur dioxide (mean 200 $\mu g/m^3$) and total suspended particles (mean 98 $\mu g/m^3$) were recorded during a 13-day period in Augsburg. In men, the odds ratio for plasma viscosity above the 95th percentile of the distribution (1·38 mPa s) was 3·6 (95% CI 1·6–8·1) comparing measurements during the air pollution episode with non-episode measurements after adjustment for cardiovascular risk factors and meteorological variables. The corresponding odds ratio for women (95th percentile of plasma viscosity 1·37 mPa s) was 2·3 (1·0–5·3). High concentrations of carbon monoxide were also associated with increased plasma viscosity in women.

Interpretation During the 1985 air pollution episode, an increased risk of extreme values of plasma viscosity was observed in both men and women. Altered blood rheology due to inflammatory processes in the lung that induce an acute-phase reaction might therefore be part of the pathological mechanisms linking air pollution to mortality.

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Introduction

Increased mortality in the general population has been observed at times when concentrations of ambient air pollutants are raised.[1–3] The excess deaths were attributable to cardiovascular as well as respiratory causes. The involvement of the cardiovascular system was strongly supported by analyses showing an association between concentrations of particulate matter and hospital admissions for ischaemic heart disease and congestive heart failure.[4,5] In addition, evidence from seven large cities in the USA showed that high concentrations of carbon monoxide were associated with hospital admission for congestive heart failure.[6] Although the link between air pollutants and exacerbation of pre-existing respiratory impairment has been well established and seems biologically plausible,[7] little is known about the biological mechanisms linking ambient air pollution with exacerbation of cardiovascular diseases. Seaton and colleagues[8] postulated that inflammation in the peripheral airways caused by air pollutants might increase the coagulability of the blood, and thereby lead to an increased number of deaths.

Our aim was to test this hypothesis in the data collected in the first MONICA survey in Augsburg, Germany, between October, 1984, and June, 1985. We investigated whether plasma viscosity (which is determined by fibrinogen and other large asymmetrical plasma proteins such as immunoglobulin M and α_2-macroglobulin) was higher on days with increased air pollution than on less polluted days in a random sample of the population. In January, 1985, there was an air pollution episode all over Europe, which led to high concentrations of sulphur dioxide and total suspended particles (TSP) throughout western and central Europe.[9] Increased mortality, hospital admissions, and ambulance requests were reported during this episode compared with a control period in the Ruhr area of Germany.[10] These effects were more pronounced for cardiovascular diseases (19% increase in hospital admissions) than for respiratory diseases (7% increase in hospital admissions). The analyses presented here focus on the question: was plasma viscosity higher than normal in a random sample of the population in Augsburg during the days of the 1985 air pollution episode?

Methods

MONICA survey Augsburg

The first MONICA survey in Augsburg (southern Germany) was carried out in 1984–85. 4022 (79%) of the 5069 randomly selected eligible individuals, aged 25–64 years, took part.[11] This report is based on a subsample of 3256 men and women in whom plasma viscosity was measured,[12] whose blood samples were obtained on the day of the interview, and who had no acute infections. There were no differences in conventional cardiovascular risk variables between the subgroup and the total sample.[11,12] All survey methods were as in the MONICA protocol.[13] After a standard interview, blood pressure was measured according to the recommendations of the MONICA manual. Height, bodyweight, body-mass index, and smoking behaviour were recorded.

Blood samples were drawn with only short-term venous occlusion and minimal suction. Blood was taken into edetic acid (4·0 mmol/L), centrifuged at 3000 *g* for 15 min, and stored at 4°C for a maximum of 4 days. Plasma viscosity was measured at 37°C in a Coulter-Harkness capillary viscometer (Coulter Electronics, Luton, UK).

Measurement procedures and sample preparations met the criteria of the International Committee for Standardisation in Haematology.[14] Plasma viscosity tests were done in triplicate. For quality control, continuous comparisons with a water control were made. The coefficient of variation was 1·0%. There was no baseline shift during the data collection period. At irregular times duplicates were measured in a single-blind way. Their coefficient of variation was 2·0%, and 93% of the duplicates agreed within 5%.[12] Total and high-density-lipoprotein (HDL) cholesterol were measured by enzymatic methods.[11] Lipid analyses were standardised in all studies on the WHO lipid quality control reference laboratory in Prague.

Air pollution

Sulphur dioxide, carbon monoxide, and TSP were measured as part of the automated Bavarian air-quality network operated by Bayerisches Landesamt für Umweltschutz. The monitoring station was located in the centre of Augsburg. 24 h mean concentrations (midnight to midnight) were provided. Air pollution measurements were available on more than 85% of days between Oct 1, 1984, and May 30, 1985. 24 h mean temperature, relative humidity, and air pressure (midnight to midnight) were measured on the outskirts of the city, and the data were complete. A period of 3 or more consecutive days with sulphur dioxide concentrations above 150 μg/m³ is defined as a pollution episode.

Statistical methods

The MONICA survey was carried out between Oct 9, 1984, and May 24, 1985 in the city of Augsburg and surrounding communities. On average 23 (range 1–52) participants were interviewed on each of 144 days. A detailed description of the MONICA survey as regards plasma viscosity and cardiovascular risk factors has been published previously.[12] Average plasma viscosities were calculated each day and plotted over time, but no seasonal variation in plasma viscosity was detected. A uniform age and sex distribution over time was preserved by design.

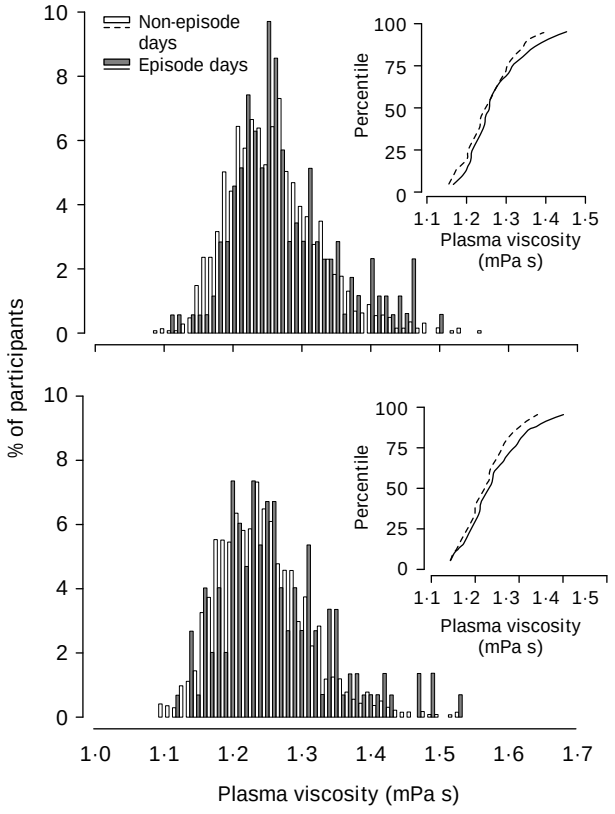

Figure 1: **Distribution of plasma viscosity in men (upper panel) and women (lower panel) stratified for air pollution episode**
Insets=cumulative distributions.

Univariate and multivariate logistic regression models were used to estimate the association between air pollution and increased plasma viscosity. Air pollution was considered in two ways in the analyses—an indicator for the 1985 episode was used, and the continuous concentrations of sulphur dioxide, carbon monoxide, and TSP were used to assess the dose-response. Logistic regression rather than linear regression analyses were chosen, because a comparison of the distributions of plasma viscosity on non-episode days and episode days did not reveal a shift in the distribution, but a tendency towards higher values of plasma viscosity (figure 1). The analyses were done separately for men (n=1663) and women (n=1593) to allow different associations with the covariants as observed previously.[12] Plasma viscosity was treated as a binary variable—whether or not the plasma viscosity exceeded the 80th percentile (1·30 mPa s for men [n=379] and 1·29 mPa s for women [n=331]), the 90th percentile (1·35 mPa s for men [n=176]) and 1·33 mPa s for women [n=144]), or the 95th percentile (1·38 mPa s for men [n=83]) and 1·37 mPa s for women [n=68]). Categorical variables were constructed to control for known risk factors such as age, body-mass index, systolic and diastolic blood pressure, total and HDL cholesterol, and current smoking as well as passive smoking: 10-year categories for age; body-mass index below 25 kg/m², 25–30 kg/m², and above 30 kg/m²; and quartiles for total and HDL cholesterol and systolic and diastolic blood pressure. Evidence for an association between meteorological variables and plasma viscosity was examined. Temperature, relative humidity, and air pressure were therefore investigated as possible confounders in the regression analyses. Temperature was included in categories below 0°C, 0–10°C, above 10°C; an indicator for relative humidity was 1 if the relative humidity exceeded 85%; and an indicator for high air pressure was 1 if the air pressure exceeded 1020 mbar. Odds ratios and 95% CI summarise the results of the logistic regression analyses.

Results

Between Jan 4 and Jan 7, 1985, there was a steep increase in daily mean sulphur dioxide concentrations from 43 μg/m³ to 181 μg/m³. Until Jan 19, sulphur dioxide concentrations above 150 μg/m³ were recorded (figure 2). Table 1 gives the average concentrations of the air pollutants restricted to the days of the MONICA survey. During the air pollution episode in Augsburg, average sulphur dioxide concentrations of 200 μg/m³ were recorded, whereas on all other days of the MONICA survey the concentrations were near or below 100 μg/m³ (table 1, figure 2). TSP concentrations were also raised during this episode, and particularly accumulated towards the end of the episode (figure 2). The episode was characterised by low temperatures, stable relative humidity (figure 2), and easterly winds. No differences in carbon monoxide concentrations were observed between episode and non-episode days. TSP concentrations exceeded 100 μg/m³ repeatedly between the end of February and March, whereas sulphur dioxide concentrations generally remained below 100 μg/m³ on the days of the MONICA survey. As a result, TSP and sulphur dioxide concentrations showed a moderate correlation (r=0·42). Carbon monoxide concentrations were weakly associated with those of sulphur dioxide (r=0·28) and showed no correlation with TSP (r=0·05).

On 11 of the 13 days of the air pollution episode, totals

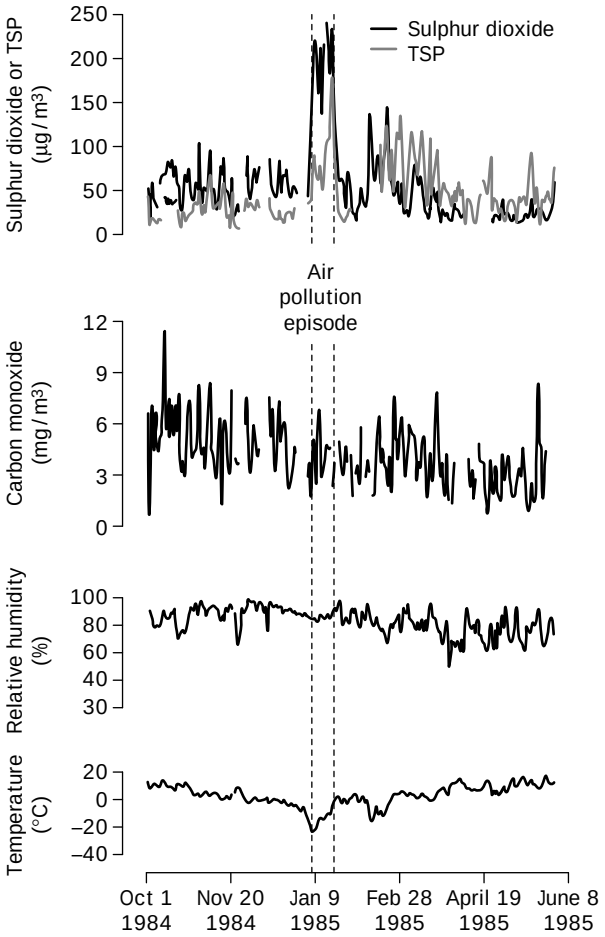

Figure 2: **Daily mean concentrations of sulphur dioxide, TSP, and carbon monoxide, temperature, and relative humidity between Oct 1, 1984, and May 31, 1985, in Augsburg**

of 175 men and 149 women were interviewed, and blood samples were obtained. Plasma viscosity was on average 0·013 mPa s higher on episode days than on non-episode days in men (p=0·015, table 1). Similarly, there was a difference of 0·017 mPa s in plasma viscosity between episode days and non-episode days in women (p=0·002, table 1). A comparison of the distributions of plasma viscosity on non-episode days and episode days showed no shift in the distribution, but a tendency towards high values of plasma viscosity on episode days (figure 1).

In logistic regression analyses the odds ratios for high plasma viscosity (comparing episode and non-episode days) were approximately two (table 2). The odds ratios increased after adjustment for conventional cardiovascular risk factors and meteorological variables in men and remained at about two in women. The results of the multivariate logistic regression analyses with high plasma viscosity defined as above the 95th percentile are shown in table 3. In men, plasma viscosity above this value was associated with older age, total cholesterol, and systolic blood pressure; HDL cholesterol above 1·0 mmol/L and low environmental temperatures were associated with decreased risks of high plasma viscosity (table 3). In women, high plasma viscosity was associated with greater body-mass index and total cholesterol and with low environmental temperatures, but only total cholesterol above 5·8 mmol/L achieved statistical significance; HDL cholesterol above 1·3 mmol/L and age over 34 years were associated with reduced risks of high plasma viscosity (table 3).

Analysis of data only for people who lived in the city of Augsburg gave similar results for the comparison of non-episode and episode days. The associations between high plasma viscosity and the air pollution episode were slightly stronger when the analyses were restricted to non-smokers. The odds ratio for plasma viscosity above the 95th percentile during the air pollution episode was 4·3 (95% CI 1·4–13·2) in non-smoking men (n=1032) and 2·5 (1·0–5·9) in non-smoking women (n=1244).

Influenza virus was detectable in serum samples from people in Munich (50 km southeast of Augsburg) in February and March (H-O Habermehl, Institut für Virologie, Berlin). Although people with acute infections were excluded from our analyses, an indicator for February and March showed slightly increased risks for plasma viscosity above the 95th percentile (odds ratio 1·3 [0·7–2·4] in men and 1·9 [1·0–3·5] in women), whereas the estimates for the cardiovascular risk factors remained unchanged. Odds ratios for the risk of high plasma viscosity associated with the air pollution episode even increased slightly when this indicator was included in the model (4·4 [1·8–10·9] in men and 3·4 [1·3–8·5] in women).

In additional analyses, the measured air-pollutant concentrations were treated as continuous variables (table 4). The regression coefficients were expressed as odds ratios for an increase in the concentration of air pollutant from the 5th to the 95th percentile of the respective distribution so that direct comparisons between the risk estimates of each pollutant and between the risk estimates of the episode and the pollutants were possible. Positive associations similar to those for the episode were observed for sulphur dioxide and TSP in men; those in women were even stronger. Both effects were clearly reduced when the indicator for the air pollution episode

	Pollution episode (Jan 7–19, 1985)		Remainder of MONICA survey period	
	Number of days	Mean (SE; range) value	Number of days	Mean (SE; range) value
Air pollution				
Sulphur dioxide (µg/m³)	10	200·3 (8·4; 160–238)	116	48·2 (2·1; 13–103)
TSP (µg/m³)	11	97·7 (9·4; 62–176)	112	47·4 (2·7; 7–135)
Carbon monoxide (µg/m³)	10	4535 (466; 2385–6852)	116	4512 (181; 914–11 508)
Meteorology				
Temperature (°C)	11	−15·5 (6·1; −24·8 to −5·1)	133	3·4 (5·9; −18·0 to 14·5)
Relative humidity (%)	11	83·3 (1·8; 81–86)	133	81·8 (9·7; 58–97)
Air pressure (mbar)	11	1012 (6; 1004–1023)	133	1015 (8; 997–1031)
Plasma viscosity	**Number of participants**		**Number of participants**	
Men	175	1·273 (0·074; 1·11–1·50)	1488	1·260 (0·066; 1·09–1·56)
Women	149	1·263 (0·078; 1·12–1·53)	1444	1·246 (0·065; 1·10–1·53)

Table 1: **Air pollution (24 h averages), meteorology (24 h averages), and plasma viscosity on days of MONICA survey (October, 1984, to June, 1985)**

Plasma viscosity above:	Odds ratio (95% CI) for raised plasma viscosity	
	Men (n=1663)	Women (n=1593)
Crude data		
>80th percentile	1·41 (0·99–2·00)	1·63 (1·12–2·37)
>90th percentile	1·72 (1·11–2·67)	2·38 (1·49–3·77)
>95th percentile	2·32 (1·33–4·05)	2·41 (1·29–4·53)
Adjusted for cardiovascular risk factors*		
>80th percentile	1·32 (0·90–1·94)	1·56 (1·03–2·34)
>90th percentile	1·57 (0·97–2·54)	2·29 (1·39–3·77)
>95th percentile	2·28 (1·25–4·17)	2·07 (1·05–4·06)
Adjusted for cardiovascular risk factors* and meteorology†		
>80th percentile	1·42 (0·91–2·23)	1·27 (0·79–2·03)
>90th percentile	1·99 (1·10–3·60)	2·26 (1·23–4·16)
>95th percentile	3·62 (1·61–8·13)	2·26 (0·97–5·26)

*Age, body-mass index, total cholesterol, HDL cholesterol, systolic blood pressure, diastolic blood pressure, passive smoking, and smoking.
†Temperature, relative humidity, and air pressure.

Table 2: **Associations between raised plasma viscosity and 1985 air pollution episode**

was included in the model. No association between high carbon monoxide concentrations and raised plasma viscosity was found in men, but in women plasma viscosity was high on days with high carbon monoxide concentrations. Models that included both carbon monoxide and the indicator for the air pollution episode showed that the two factors predicted high plasma viscosity independently (odds ratio for the episode 2·6 [1·0–6·6], odds ratio for an increase of carbon monoxide of 6·0 mg/m^3 2·9 [1·1–7·4]).

Discussion

During the 1985 air pollution episode, plasma viscosity was high in a random sample of the population of Augsburg. The raised values persisted after adjustment for known cardiovascular risk factors and for meteorological features associated with high plasma viscosity. In addition, there appeared to be an independent association between carbon monoxide and high plasma viscosity in women.

The design of the study was cross-sectional, so the variability in plasma viscosity was determined mainly by factors such as age, sex, and cardiovascular risk factors as reported previously.[12] No evidence of a seasonal variation in plasma viscosity was found in this cross-sectional survey. Comparison of the crude and the adjusted odds ratios showed that the observed association was not confounded by cardiovascular risk factors or meteorological variables. Although some cardiovascular risk factors and temperature had different effects on the risk of high plasma viscosity between men and women, the estimates for the air pollution episode were similar in both sexes. A close correlation between individual cardiovascular risk factors and the coincidence of low temperatures and high air-pollutant concentrations might have resulted in some variation of the effect estimates for men and women. The distributions of plasma viscosity were not shifted upwards on episode days, but there was a tendency towards high values of plasma viscosity on episode days. This observation might suggest that a particular group of individuals in the population of Augsburg were susceptible to air pollution.

Given that the observed associations between air pollution and mortality are small, the odds ratios we calculated appear to be large. On the other hand, if plasma viscosity is a biomarker associated with disease, larger associations with the exposure can be expected. Plasma viscosity was positively associated with the risk of

	Odds ratio (95% CI) for raised plasma viscosity >95th percentile*	
	Men (n=1663)	Women (n=1593)
Age (years)		
25–34	1·00	1·00
35–44	3·55 (0·98–12·8)	0·35 (0·14–0·33)
45–54	4·68 (1·35–16·2)	0·35 (0·14–0·87)
55–64	7·84 (2·30–26·8)	0·56 (0·22–1·38)
Body-mass index (kg/m^2)		
<25	1·00	1·00
25–30	1·13 (0·58–2·21)	1·38 (0·70–2·70)
>30	1·32 (0·62–2·83)	1·82 (0·85–3·88)
Quantities of HDL cholesterol (mmol/L) in men/women		
<1·04/<1·34	1·00	1·00
1·04–1·27/1·34–1·60	0·38 (0·20–0·72)	0·52 (0·26–1·06)
1·28–1·53/1·61–1·89	0·36 (0·18–0·69)	0·58 (0·29–1·18)
>1·53/>1·89	0·38 (0·20–0·73)	0·53 (0·26–1·09)
Quartiles of total cholesterol (mmol/L) in men/women		
<5·23/<5·08	1·00	1·00
5·23–5·99/5·08–5·79	0·75 (0·30–1·86)	1·02 (0·35–3·01)
6·00–6·85/5·80–6·62	1·33 (0·60–2·96)	2·86 (1·13–7·24)
>6·85/>6·62	2·34 (1·11–4·92)	3·52 (1·38–8·99)
Quartiles of systolic blood pressure (mm Hg) in men/women		
<122/<113	1·00	1·00
122–130/113–123	1·19 (0·49–2·89)	0·96 (0·34–2·68)
131–142/124–136	1·64 (0·68–3·97)	0·99 (0·33–2·98)
>142/>136	3·20 (1·32–7·78)	1·73 (0·54–5·51)
Quartiles of diastolic blood pressure (mm Hg) in men/women		
<75/<71	1·00	1·00
75–82/71–77	1·01 (0·46–2·20)	1·30 (0·46–3·72)
83–90/78–86	0·91 (0·39–2·10)	2·13 (0·74–6·12)
>90/>86	0·99 (0·42–2·31)	1·97 (0·61–6·30)
Smoking		
Current smoker	1·39 (0·85–2·25)	0·64 (0·30–1·37)
Passive smoking	1·11 (0·67–1·86)	1·03 (0·60–1·78)
Environmental temperature (°C)		
>10	1·00	1·00
10–0	0·58 (0·27–1·22)	1·44 (0·59–3·52)
<0	0·37 (0·16–0·87)	1·26 (0·48–3·33)
Meteorology		
Relative humidity >85%	1·14 (0·66–1·97)	0·95 (0·54–1·68)
Pressure >1020 mbar	1·01 (0·60–1·72)	1·39 (0·81–2·40)
Episode	3·62 (1·61–8·13)	2·26 (0·97–5·26)

*Men >1·38 mPa s, women >1·37 mPa s.

Table 3: **Multivariate logistic regression analyses for plasma viscosity above 95th percentile**

a first myocardial infarction in the Augsburg MONICA survey[15] and with the incidence of coronary heart disease in the Caerphilly and Speedwell studies.[16] Fibrinogen, an important determinant of plasma viscosity and an independent risk factor for cardiovascular disease,[17] was not measured as part of the first MONICA project in Augsburg. A meta-analysis of six prospective cohort studies in initially healthy individuals estimated a summary odds ratio of 2·3 (95% CI 1·9–2·8) for the association between high fibrinogen concentrations and subsequent myocardial infarction or stroke.[18] In patients with pre-existing coronary heart disease, high plasma fibrinogen concentrations were also positively associated with mortality.[19]

Time-series analyses have shown that a large proportion of the deaths in association with high air pollution levels are attributable to cardiovascular disorders.[1–3] The risk of being affected by high concentrations of air pollutants increases with age.[20] These observations were made in association with the 1952 smog in London, UK, as well as in Philadelphia, USA, during the 1970s.[20] In two prospective cohort studies[21,22] linking the yearly average of particulate air pollution to mortality with adjustment for individual risk factors, the strongest associations between

Pollutant (numerical increase from 5th to 95th percentile)	Odds ratio for raised plasma viscosity (95% CI)	
	Men	Women
TSP (100 μg/m³)		
Same day as plasma viscosity measurement	1·75 (0·79–3·89)	2·30 (0·92–5·79)
1 day before	1·72 (0·77–3·81)	2·33 (0·93–5·86)
2 days before	1·82 (0·84–3·96)	2·17 (0·87–5·44)
3 days before	1·71 (0·78–3·73)	2·20 (0·88–5·50)
Sulphur dioxide (165 μg/m³)		
Same day as plasma viscosity measurement	1·97 (0·85–4·58)	2·49 (1·04–5·99)
1 day before	2·02 (0·87–4·64)	2·52 (1·05–6·03)
2 days before	2·15 (0·94–4·91)	2·56 (1·07–6·11)
3 days before	2·13 (0·93–4·86)	2·55 (1·07–6·08)
Carbon monoxide (6060 μg/m³)		
Same day as plasma viscosity measurement	1·08 (0·45–2·61)	3·27 (1·29–8·29)
1 day before	1·07 (0·45–2·57)	3·27 (1·28–8·35)
2 days before	1·30 (0·55–3·08)	3·96 (1·54–10·2)
3 days before	1·12 (0·47–2·71)	3·91 (1·52–10·1)

*Calculated based on estimated regression coefficients for an increase in air pollutant from 5th to 95th percentile.

Table 4: **Associations between plasma viscosity above 95th percentile and measures of air pollution treated as continuous variables**

particulate air pollution and mortality were for cardiopulmonary disorders. Since the relation between heart and lung disease is extremely complex, the cardiopulmonary deaths observed during air pollution episodes may be attributable to a compromised respiratory system.[7] Acute bronchiolitis or pneumonia induced by air pollutants may precipitate congestive heart failure in the presence of pre-existing heart disease.[7] In addition, symptoms of chronic bronchitis predict the risk of coronary disease independently from known major cardiovascular risk factors.[23] However, Seaton and colleagues[8] put forward a hypothesis linking inflammatory responses in peripheral airways directly to both congestive heart failure and ischaemic heart disease. They suggested that low-grade inflammation caused by ultra-fine particles deposited in the alveoli might lead to increased blood coagulability.

Air masses from eastern Europe influenced air quality throughout western and central Europe during the 1985 air pollution episode. These meteorological conditions led to unusually high sulphur dioxide concentrations in Augsburg. Models for long-range transport of air pollution suggest that sulphur dioxide and respirable particulate matter had been transported to Augsburg in addition to local sources. Later in January, 1985, the same air masses originating from the industrial centres of the former German Democratic Republic, where sulphur-rich coal had been used, reached the Ruhr area,[10] the Netherlands,[24] and the UK,[25] and much higher values of air pollutants were recorded. Evidence for inflammatory responses to sulphur dioxide and particulate air pollution has been found in experiments in animals.[3] Godleski and colleagues[26] showed inflammatory responses, cytokine production, and increased mortality in compromised animals exposed to particulate matter from Boston air.

Fibrinogen concentrations were strongly related to inflammatory markers such as neutrophil count and acute-phase proteins (C-reactive protein and α_1-antichymotrypsin) and to self-reported respiratory infections in a cohort study of elderly men and women.[27] There is evidence for a thrombogenic state in patients at increased risk of acute ischaemic events. A prospective multicentre study found that baseline concentrations of fibrinogen and C-reactive protein were highly correlated in patients with angina pectoris, and that these variables were independently associated with an increased risk of myocardial infarction.[28,29] Our additional analyses, however, excluded an influenza epidemic coinciding with the air pollution episode as an alternative explanation for our results.

The increased plasma viscosity observed in these analyses of a cross-sectional survey might therefore represent a part of the pathophysiological chain linking high ambient air pollution to increased mortality and hospital admissions for cardiovascular diseases. Our findings suggest that plasma viscosity may be an intermediate step for both particulate air pollution and carbon monoxide, which have been found to be associated with hospital admissions for cardiovascular diseases.[4–6]

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Offspring recurrence rates and clinical characteristics of conjugal multiple sclerosis

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Summary

Background There has been no previous systematic study of conjugal multiple sclerosis. This study of conjugal pairs with complex traits investigated disease transmissibility and the genetic contribution to frequency and clinical course.

Methods We studied 45 conjugal pairs concordant for multiple sclerosis from 58 pairs recorded in a national register of familial disease. 86 offspring of the 45 pairs were individually assessed for clinical evidence of neurological disease; those over age 16 underwent cranial magnetic resonance imaging. Clinical features were compared in 33 pairs in whom neither member had symptoms before they met.

Findings Of the 86 offspring, five (6%) had clinically definite multiple sclerosis. A further five children had either characteristic imaging abnormalities or clinical symptoms consistent with demyelination, but did not meet the criteria for clinically definite disease. There was no evidence of clinical concordance, clustering at year of onset, or distortion of the expected pattern of age of onset in the second affected spouse from 33 pairs. The crude recurrence in children of conjugal pairs (1 in 17) is significantly higher than previously reported population-based risks for offspring of single affected parents (1 in 200).

Interpretation Taken with the low prevalence of multiple sclerosis in the spouses of affected individuals, and the lack of concordance for age at onset in these families, the disparity in crude recurrence between children of conjugal pairs and those of single affected parents shows that the recurrence risk in children is determined by genetic factors inherited from both parents.

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Introduction

Despite an apparent increase in the prevalence of multiple sclerosis over the past 20 years, reports of conjugal disease remain rare. This study examined the genetic and environmental factors that contribute to the frequency and distribution of conjugal multiple sclerosis.

Conjugal pairs with multiple sclerosis who have children can be studied to assess the contribution of genetic factors to disease susceptibility. Comparison of the population frequency for multiple sclerosis in northern Europeans (1 in 800)[1,2] with the crude recurrence risks for twins (1 in 3),[3,4] siblings (1 in 30), children (1 in 200), other first-degree relatives (1 in 100),[5,6] half siblings (1 in 100), [7] and adoptees (1 in 800),[8] shows that familial clustering is best explained by a polygenic inheritance model. The inheritance of risk factors from both parents might produce a higher disease frequency in the offspring of conjugal pairs than in the children of single affected parents, and lead to distinctive clinical phenotypes.

If a transmissible agent is involved in the aetiology of multiple sclerosis, spouses of affected individuals—who share the same environment over a long period—might have a higher frequency of disease than the general population. If an infective agent were contracted from the first affected spouse, age of onset in the second affected partner would be distorted when compared with the general population; if the disease in both partners results from common exposure, year of onset would tend to cluster. In either situation, however, aetiological heterogeneity in multiple sclerosis would distort the potential for concordant age at onset and clinical course between affected spouses.

Methods

We identified probands of families that contained conjugal pairs concordant for multiple sclerosis from the Cambridgeshire register, and also from requests for notification sent to practising members of the Association of British Neurologists. Some cases were identified through the Multiple Sclerosis Society of Great Britain and Northern Ireland. There were a few self-referrals also. After obtaining permission from the referral source, we contacted all families and arranged a domestic visit. Clinical histories and demographic details were taken from each partner (if possible) and all children by standard questionnaire, and a neurological examination was done. We obtained an extended pedigree, and when other affected family members were identified, we confirmed the diagnosis by personal review, supplemented by