Daily concentrations of air pollution and plasma fibrinogen in London


Abstract

Objectives—The reason for the association between air pollution and risk of cardiovascular diseases is unknown. The hypothesis was examined that daily concentrations of air pollution are associated with daily concentrations of fibrinogen, a risk factor for cardiovascular disease.

Methods—Data on concentrations of plasma fibrinogen for 4982 male and 2223 female office workers, collected in a cross sectional survey in London between September 1991 and May 1993, were combined with data on concentrations of air pollution during the day of blood sampling and during the 3 preceding days.

Results—After adjustment for weather and other confounding factors, an increase in the 24 hour mean NO₂ during the previous day from the 10th to the 90th percentile (61.7 µg/m³) was associated with a 1.5% (95% confidence interval (95% CI) 0.4% to 2.5%) higher fibrinogen concentration. The respective increase for CO (1.6 mg/m³) was 1.5% (95% CI 0.5%, 2.5%). These associations tended to be stronger in the warm season (April to September). Significant associations were found for black smoke and particulate matter of diameter 10 µm (PM₁₀) only in the warm season. No association with fibrinogen was found for SO₂ or ozone.

Conclusions—The short term association between air pollution, possibly from traffic, and risk of cardiovascular events may be at least partly mediated through increased concentrations of plasma fibrinogen, possibly due to an inflammatory reaction caused by air pollution.

Keywords: air pollution; fibrinogen; haemostatic factors

Associations between air pollution and daily cardiovascular mortality and morbidity have been reported from several cities, including London. Two cohort studies have also reported associations of particulate air pollution with long term risk of cardiovascular death. The reasons for these associations are, however, unknown. It has been suggested that air pollutants, especially particulate matter, may induce inflammation, which would increase the concentrations of acute phase reactants, including fibrinogen. Fibrinogen is an important risk factor for cardiovascular diseases, especially ischaemic heart disease, but also stroke and peripheral arterial disease. In support of this inflammation hypothesis, it was recently reported that plasma viscosity increased during an air pollution episode in Germany.

We therefore examined the association between daily concentrations of air pollution and concentrations of plasma fibrinogen measured among 4982 male and 2223 female office workers in Whitehall, London between September 1991 and May 1993.

Methods

The demographic characteristics, health, and risk factors of the 10 308 subjects (6895 men and 3413 women) in the Whitehall II study at baseline are published elsewhere. Subjects were recruited in 1985–8 by inviting all employees aged 35–55 from 20 London based civil service departments. The response rate was 73%, but detailed investigation in one department showed that 4% of those on the list of employees had moved before recruitment, and so the true response rate was somewhat higher. The haemostatic data analysed here were measured at the second screening examination (1991–3) when 5616 men and 2488 women aged 39–63 years participated.

Venepuncture of the left antecubital vein was performed with tourniquet and blood was collected into Sarstedt citrate monovettes. After centrifugation samples were immediately frozen at −80 °C and stored until assay. Fibrinogen was measured by an automated modification of the Clauss method. Technical error was estimated by assaying blinded duplicate samples for 5% of subjects. The coefficient of variation was 7.7%.

The air pollution data were obtained from AEA Technology, NETCEN, Culham, Abingdon, Oxfordshire. We used 24 hour averages of NO₂, particulate matter of diameter 10 µm (PM₁₀), and CO and maximum 8 hour means of O₃ all measured in central London. Black smoke and SO₂ are 24 hour imputed averages for London from measurements at five sites: London City, Croydon in South London, Enfield in North London, Acton in West London, and Ilford in East London. Daily maximum and minimum temperature and 0600 and 1500 relative humidity measures at Holburn, central London, were obtained from the Meteorological Office.

In the analyses, fibrinogen was modelled in two ways. Firstly, in the linear regression models, fibrinogen was regressed on the air pollutants. Logarithmic transformation was indicated because of the log normal distribution of fibrinogen. We also tried a linear first order autoregressive model, but there was no evidence of autocorrelation. Secondly, in the
logistic regression models, those 10% of the subjects with the highest fibrinogen (above 3.19 g/l) concentrations were defined as having high concentrations and the rest low concentrations. This binary variable was then re- adjusted for age, sex, employment grade (six categories),21 ethnicity (four categories: European, South Asian, Afro-Caribbean, other), smoking (three categories: never, ex, current), body mass index, alcohol consumption, month of examination (21 categories) to model seasonality in fibrinogen concentrations, minimum temperature, and relative humidity. Body mass index, alcohol, temperature, and humidity were entered as continuous variables, all other variables were treated as categorical. The adjustments made very little difference and only adjusted analyses are reported here. Further adjustments for the type of building, where the person worked, for maximum temperature, or for weekday, had little effect on the results.

All results are reported for an increase in the pollutant concentration from its 10th to its 90th percentile. Therefore, the odds ratios derived from logistic regression can be interpreted as the relative risk for having a high concentration of fibrinogen in a high pollution day (90th percentile) compared with a low pollution day (10th percentile). As fibrinogen was logarithmically transformed for the linear regression analyses, the analyses give the relative difference in fibrinogen for a given change in the pollutant. The results are reported as the mean (SEM) of % difference in fibrinogen associated with increase in the pollutant concentration from 10th to 90th percentile, which were calculated by multiplying the original coefficient (SEM) by number of units of air pollution between the 10th and 90th percentiles, taking the exponent of this, then subtracting one, and multiplying by 100.

Results

Haemostatic data were collected from September 1991 to May 1993. Except for PM$_{10}$ and O$_3$, and six missing days of NO$_2$, air pollutant data were available for 349 days during which blood was collected (table 1). The analyses focus on the 7205 office workers examined on those days who had non-missing data on the confounders needed for the multivariate models.

Correlations between all pollutants, except O$_3$, were high and positive (table 2). Lowest correlations, around 0.6, were found for PM$_{10}$ with black smoke and with CO. Highest correlations, around 0.8–0.9, were found for CO with NO$_2$ and with black smoke. Ozone correlated negatively with all other pollutants, but especially with CO and black smoke (−0.45).

In the linear regression analyses, fibrinogen concentrations were significantly and positively associated with all lags of CO and NO$_2$, but not with other pollutants. The findings from the logistic regression analyses were generally in the same direction, but less significant (table 3).

The consistency of the associations found at lag 1 was then analysed in subgroups defined by season, sex, and smoking. The association of NO$_2$ and ozone with fibrinogen tended to be stronger among women than men (table 4).
Black smoke, PM$_{10}$, CO, and NO$_2$ tended to be more strongly associated with fibrinogen in the warm season. The results among non-smokers were in general similar to the results among all subjects. These subgroup analyses were repeated for CO and NO$_2$ at lag 3, as they showed a significant association also in the logistic regression models (table 3). The results from these subgroup analyses were similar to the results obtained for both CO and NO$_2$ at lag 1 (table 4).

Logistic regression analyses were also done in subgroups defined by season, sex, and smoking (data not shown). In these analyses, the direction of the associations between air pollutants and fibrinogen were in general consistent with the linear regression analyses (table 4), but associations were less significant. There were, however, two exceptions. Firstly, the direction of the associations between PM$_{10}$ and fibrinogen were not consistent between the linear and logistic regression analyses. Secondly, significant associations for SO$_2$ were found in the logistic regression analyses only in the cool season and among non-smokers.

Multipollutant models were then run separately for the cool and warm season. During the warm season, the associations of black smoke, PM$_{10}$, NO$_2$, and CO at lag 1 all became non-significant with simultaneous adjustment. This was generally the case also in two pollutant models. The strength of the association of black smoke was little affected by adjustment for other pollutants. The coefficients for PM$_{10}$ was reduced from 3.2% to 1.7%, when adjusting for black smoke, but adjusting for other pollutants had little effect. The coefficients for NO$_2$ and CO varied from model to model. During the cool season, both NO$_2$ (lag 3) and CO (lag 3) lost their significance when adjusted for the effect of other pollutants.

**Discussion**

In the present study of office workers in London, daily concentrations of NO$_2$ and CO were associated with increased plasma fibrinogen concentration in both seasons, with similar associations for black smoke and PM$_{10}$ in the warm season. These results support the proposal that the association between air pollution and cardiovascular events may at least partly be mediated by haemostatic or inflammatory mechanisms.

Several studies have reported associations of daily variations in CO, particulates, O$_3$, NO$_x$, and SO$_2$ with daily changes in cardiovascular mortality and morbidity. The results seem to be most consistent for particulate air pollution and probably CO. Although the relative risks of cardiovascular mortality are usually smaller than respiratory mortality, the largest number of excess deaths due to particulate air pollution are attributable to cardiovascular diseases, as the absolute risk of cardiovascular disease in western societies is high.

It has been suggested that the many ultrafine particles in urban air may promote inflammation of lung epithelium, which would increase the concentrations of acute phase proteins—like fibrinogen—which in turn have been shown to be risk factors for cardiovascular diseases. Also NO$_2$, O$_3$, and SO$_2$ are capable of producing inflammatory reactions in the lungs, and could thereby also increase fibrinogen.
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26 27 Several recent studies have shown carboxyhaemoglobin decreases the exercise other mechanisms probably also exist. This has ing air pollution to cardiovascular disease, but than in the logistic regression analyses.

28 29 and CO was associated with a 1.5% di the same di...

30 There is some coherence between our results and those of two time series studies of daily cardiovascular events in London over the same period, and with the same pollutant indicators (except that PM10 was not measured). A study of cardiovascular mortality 10 found significant associations with NOx and SO2, but not black smoke, in the warm season. A study of emergency admissions for acute myocardial infarction 2 found associations with NO2, SO2, CO and black smoke, but for reasons we cannot reconcile with our study or the mortality study, these were found mainly in the cool sea.

31 In the present analyses, a difference between the lowest and the highest decile of both NOx and CO was associated with a 1.5% difference in fibrinogen. The same difference in NOx and CO was associated with a 2.8% and a...
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