Investigation of factors which might indicate susceptibility to particulate air pollution

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Abstract

***Objectives*—To determine whether previous symptoms or recognised risk factors of cardiovascular ill health, are associated with an increased likelihood of adverse health effects related to particulate air pollution.**

***Methods*—Cardiovascular event rates were studied relative to urban concentrations of particulate air pollution and baseline risk factors. The Edinburgh artery study consisted of a cohort of 1592 subjects aged 55–74 and was followed up to the end of March 1998 for a median of 10 years resulting in about 5 million person-days of observation. Baseline measurements included plasma fibrinogen and blood and plasma viscosity. A nested case-control approach was used to investigate a possible interaction between effects of these selected baseline risk factors and particulate air pollution, on subsequent event rates.**

***Results*—During the follow up period there were 343 fatal and non-fatal myocardial infarctions or strokes. Trends in adverse cardiovascular outcomes related to pollution were identified among subjects belonging to the highest baseline quintile of plasma fibrinogen. Evidence for interactions between concentrations of particulate pollution and fibrinogen was not established at conventional levels of significance.**

***Conclusions*—People with high concentrations of plasma fibrinogen might be more susceptible to adverse cardiovascular effects of particulate air pollution, but limitations of power mean that evidence relating to such an interaction is not conclusive. A range of cardiopulmonary risk factors warrant investigation in relation to possible susceptibility to air pollution.**

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There is an increasing body of evidence associating urban particulate air pollution with adverse cardiovascular[1] and respiratory[2 3] outcomes. The consistency of many of the epidemiological reports, corroborated by experimental evidence from other sources,[4] suggests that, at least in part, the association is causal. However, the estimated percentage contribution of urban outdoor particulate air pollution to ill health and day to day mortality in the general population is small (0.6%–1.5% increase in all cause mortality,[5 6] and 4% increase in respiratory mortality in elderly people for a 10 μg/m^3 increment in black smoke[6]).

Because most of the adverse outcomes occur in the elderly population and against the background of ischaemic heart disease or chronic obstructive lung disease, it has been assumed that these subgroups are susceptible[7] and that public policy should reduce their health risks, collectively and individually. However, epidemiological evidence identifying specific subgroups as more susceptible to the ambient levels of air pollution in cities of developed countries is lacking. Suitable methods need to be developed to consider the hypothesis that possible risk factors may be associated with a subsequent increased risk of adverse outcomes in relation to particulate air pollution.

The aim of this study was to investigate whether the association between the likelihood of cardiovascular events and the urban concentration of particulate air pollution was influenced by other variables—notably plasma fibrinogen concentration—at recruitment into the cohort.

Methods

STUDY POPULATION

The study was based on a random population survey based cohort in the Edinburgh artery study of 1592 men and women aged 55–74 years at recruitment in 1987–8, and spread geographically and socioeconomically across the city of Edinburgh.[8] Subsequent follow up provided a total of over 5 million person-days of observation up to 31 March 1998. Baseline variables examined in this cohort included age, sex, smoking habit, symptoms of angina (with the World Health Organisation (WHO) angina questionnaire[9]), low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, systolic and diastolic blood pressure, plasma fibrinogen, whole blood viscosity, and plasma viscosity. Fibrinogen was measured in citrated plasma by a thrombin clotting turbidometric method in a centrifugal analyser.[10] Blood and plasma viscosity were measured from a blood sample anticoagulated with dry dipotassium edetate (EDTA 1.5 mg/ml) at high shear rates (over 300/s) in a Coulter-Harkness viscometer at 37°C.

POLLUTION MEASUREMENTS AND OUTCOME VARIABLES

The exposure metric for particulates was daily concentration of black smoke, expressed in mg/m^3, measured with volumetric apparatus and a stain method at a city centre site, and

expressed as the moving average of the 3 days before the day of the adverse health event.[6] For the purposes of this study, all fatal and non-fatal myocardial infarctions (MI) and strokes (henceforth collectively referred to as cardiovascular events) were included if they occurred between recruitment (3 August 1987) and 31 March 1998 and met specified criteria[8] adapted from the American Heart Association

STATISTICAL ANALYSIS

In the initial statistical analysis, which we called the "person-day approach", cohort members were divided into subgroups according to the previous risk factor of interest. Thus, for fibrinogen, whole blood, and plasma viscosity, risk factor subgroups were defined according to the quintiles of baseline measurements. Within each subgroup the person-days of exposure over the study period were divided into five categories according to the quintile of black smoke pollution. Thus cardiovascular adverse event rates (events per person-day of exposure) were calculated for each cell of 5x5 tables. The trends of these cardiovascular event rates with concentrations of pollution at each risk factor level were examined; however statistical modelling of these trends is not presented owing to the difficulty of controlling simultaneously for many potential baseline risk factors. The relation between the cardiovascular event rate on each day during the Edinburgh artery study follow up period, 3 August 1987 to 31 March 1998, and the average of the previous 3 days black smoke was examined with Poisson regression.

For modelling purposes we used a nested case-control analysis in which the case was not a specific individual, but a person-day on which an event had occurred. Controls were randomly selected from the other people at risk on that day (the matching variable) who did not have a cardiovascular event. This allowed us to compare different distributions of possible risk factors between the cases and controls and hence obtain a viable method of investigating possible interactions. With this approach we could estimate the interaction of pollution level with individual risk factors, but not the main effects of daily pollution, as on a given day only a single centrally recorded pollution measurement was available for both cases and controls.

Choosing the number of random controls to select for each case required a balance between improved precision of estimation obtainable with a larger number of controls and a possible lack of true independence resulting from too many controls. With too many controls the same people would be selected as controls on many different days, and so the contrasts between cases and controls contributed by each day might not be regarded as independent (although to the extent that each person-day is regarded as an independent trial this objection would be reduced). Results are presented for 10 random controls per case.

A conditional logistic regression model was used to analyse the nested case-control data. The terms in the core model for the odds of an adverse cardiovascular event were: age at event, sex, pack-years of smoking, systolic blood pressure, and HDL and LDL cholesterol. To this model we first added each of the continuous haematological variables (fibrinogen, whole blood viscosity, and plasma viscosity) separately and then considered terms for interaction of the effects of these variables with pollution.

A simple way to express such interaction, for a specific risk factor such as fibrinogen, was as follows. Firstly, define a binary variable for each day as 0 or 1 according to whether black smoke pollution was below or above the median. Then for each person-day create an interaction term by multiplying the individual baseline fibrinogen concentration by this binary pollution variable. Adding this interaction term to the regression model, the magnitude and significance of its coefficient gives an indication whether the effect of high fibrinogen on risk was greater on high pollution days (above median) than on low pollution days (below median). The results of this analysis were compared with the difference between the coefficients of fibrinogen obtained when separate regression models were fitted to the high and low pollution days. (This strategy was less satisfactory because the coefficients of all the other variables would also differ between the two models.)

Another way to define interaction was to create the product variable by multiplying the actual daily pollution measurements by the fibrinogen measurement. Significance tests on the coefficient for the product variable gave an indication of whether there was any evidence that the effects of the haematological factors on the risk of cardiovascular events were modified by the acute effects of pollution. The advantage of greater statistical power with this approach was offset by the difficulty in interpreting the coefficient, as the product variable was on an unusual scale, combining units of exposure (black smoke) with units of a clinical index (fibrinogen). The other risk factors were considered in a similar manner to fibrinogen.

Results

There were 343 cardiovascular events for 273 people, comprising 226 non-fatal events and 117 deaths. Eight of the events were experienced by patients for whom there was no fibrinogen measurement and another one of these events was experienced on a day for which the average of the previous 3 days black smoke was not available. Thus there were 5 271 882 person-days of exposure, but 132 072 of these were for patients for whom there was no fibrinogen measurement and another 61 529 of these person-days were days for which the average of the previous 3 days black smoke was not available. Therefore the person-day analysis was based on 334 (97.4%) cardiovascular events and 5 078 281 (96.3%) person-days of exposure. Subjects with cardiovascular events had significantly higher age, pack-years of smoking, systolic blood pressure, LDL cholesterol, plasma fibrinogen, plasma viscosity, and blood viscosity, and lower HDL

Table 1 Description of baseline risk factors by cardiovascular events

	Cardiovascular events			
	All subjects (n=1592) mean (SD)	*Yes (n=273) mean (SD)*	*No (n=1319) mean (SD)*	*p Value*
Age (y)	64.9 (5.7)	66.9 (5.5)	64.4 (5.6)	<0.0001
Sex, male (%)	51	68	47	<0.0001
Smoking (pack-years)	17.2 (22.0)	23.1 (23.4)	15.9 (21.5)	0.0001
Systolic BP (mm Hg)	144 (24)	152 (27)	143 (23)	<0.0001
LDL Cholesterol (mmol/l)	5.28 (1.22)	5.42 (1.22)	5.25 (1.22)	0.037
HDL Cholesterol (mmol/l)	1.44 (0.41)	1.31 (0.38)	1.47 (0.41)	<0.0001
Fibrinogen (g/l)	2.72 (0.69)	2.94 (0.74)	2.67 (0.67)	<0.0001
Plasma viscosity (mPa.s)	1.33 (0.09)	1.36 (0.09)	1.33 (0.09)	<0.0001
Whole blood viscosity (mPa.s)	3.58 (0.58)	3.75 (0.60)	3.55 (0.57)	<0.0001
Angina (%)	16	30	13	<0.0001

The p values presented are for two sample *t* tests comparing means or χ^2 tests comparing percentages for those subjects who did and did not experience any cardiovascular events, except for pack–years of smoking where the p value is from the Wilcoxon rank sum test.

cholesterol than subjects without (table 1). Higher percentages of males, lifetime smoking history, and subjects with symptoms of angina were found in the group who had cardiovascular events.

PERSON-DAY ANALYSES

Table 2 shows the numbers of cardiovascular events and event rates when the 334 events were cross classified by quintiles of black smoke and fibrinogen. There was a clear increase in the cardiovascular event rate with increasing baseline fibrinogen. Within fibrinogen categories, there was little sign of any trend of increasing cardiovascular event rate with increasing black smoke. However, it was notable that the highest event rate was found in the bottom right hand cell of the table 2, corresponding to the highest fibrinogen quintile and the highest black smoke quintile.

A similar inspection of event rates for categories defined by black smoke pollution and plasma viscosity and blood viscosity showed that the highest event rate corresponded to the highest levels of the risk factors and highest quintile of black smoke. Cardiovascular event rates increased with increasing baseline plasma and blood viscosity, but there was no indication of trends with black smoke within categories of plasma viscosity and blood viscosity.

Table 2 Cardiovascular event rates per million person-days (number of events), by quintile of average of previous 3 days black smoke and quintile of baseline fibrinogen

Black smoke quintiles: mean values (μg/m³)	*Fibrinogen quintiles : mean values (g/l)*				
	1.87	*2.31*	*2.64*	*3*	*3.76*
2.63	47 (10)	38 (8)	44 (9)	57 (11)	97 (18)
4.94	33 (7)	39 (8)	63 (13)	98 (19)	107 (20)
6.97	51 (11)	47 (10)	38 (8)	96 (19)	105 (20)
9.94	60 (13)	52 (11)	67 (14)	111 (22)	83 (16)
19.29	47 (10)	14 (3)	53 (11)	71 (14)	152 (29)

Table 3 Unadjusted and adjusted estimates of effects (95% CIs) of 1SD increments in fibrinogen, plasma viscosity, and whole blood viscosity on odds of cardiovascular event*

	Unadjusted OR (95% CI) p value	*Adjusted† OR (95% CI) p value*
Fibrinogen	1.40 (1.27 to 1.56) <0.0001	1.23 (1.09 to 1.38) 0.0006
Plasma viscosity	1.38 (1.23 to 1.53) <0.0001	1.20 (1.05 to 1.36) 0.005
Whole blood viscosity	1.38 (1.24 to 1.54) <0.0001	1.09 (0.96 to 1.24) 0.17

*Fibrinogen SD=0.69 g/l; plasma viscosity SD=0.09 mPa.s; whole blood viscosity SD=0.58 mPa.s.
†Adjusted for age, sex, pack-years of smoking, systolic blood pressure, and HDL and LDL cholesterol.

*Table 4 Estimates of interaction of fibrinogen, plasma viscosity, and blood viscosity with a binary indicator of black smoke pollution**

	Odds ratio (95% CI)	*p Value*
Fibrinogen×black smoke*	1.15 (0.93 to 1.44)	0.2
Plasma viscosity×black smoke	0.93 (0.74 to 1.18)	0.56
Whole blood viscosity×black smoke	0.99 (0.78 to 1.25)	0.92

*Dichotomised at median=7 μg/m³.

The estimated effect, adjusting for year, month, daily minimum temperature, and daily mean wind speed, of a 10 μg/m³ increase in the average of the previous 3 days black smoke was an increase of 1% (95% confidence interval (95% CI) −15% to 20%, p=0.91) in the risk of a cardiovascular event.

NESTED CASE-CONTROL ANALYSES

Without any adjustment for confounders the main effects of fibrinogen, plasma viscosity, and whole blood viscosity on cardiovascular event rate were large and all highly significant (p<0.0001): the odds of an adverse cardiovascular event were estimated to increase by about 40% for a one SD increment in each factor considered separately. Higher baseline fibrinogen and plasma viscosity were still strongly associated with an increase in cardiovascular risk after adjustment for the effects of age, sex, pack-years of smoking, systolic blood pressure, and both HDL and LDL cholesterol. The estimated effects of a 0.69 g/l increment in fibrinogen or a 0.096 mPa.s increment in plasma viscosity were associated with increases in risk of >20%. However the adjusted effect of whole blood viscosity was smaller and not significant (table 3).

Table 4 shows estimates of the interaction of the haematological risk factors with a binary indicator of black smoke pollution. The odds ratio (OR) for interaction with fibrinogen suggested a possible trend towards greater risk on high pollution days among those with higher baseline fibrinogen, but the interaction was not significant. There was no evidence for such interaction in the case of plasma viscosity or whole blood viscosity. When the model was fitted separately to low and high black smoke days the coefficient of fibrinogen, adjusted for the other variables in the core model, was 1.18 on the low days (95% CI 1.00 to 1.38, p=0.048), and 1.31 on the high days (95% CI 1.10 to 1.55, p=0.002). This supported the analysis based on the interaction term in the model fitted to all days. With the more powerful technique which defined the interaction term as the product of the actual black smoke and fibrinogen measurements, the evidence for an interaction effect was stronger, with the coefficient attaining borderline significance (p=0.054).

Discussion

There is a consensus regarding the existence and order of magnitude of a causal association between urban air pollution and acute cardiac or pulmonary morbidity and mortality.[7] From day to day changes, most studies suggest that in

Table 5 Factors warranting study for possible association with susceptibility to adverse health effects of air pollution

Category	*Examples*
Genetic	Fibrinogen polymorphisms
Previous exposure	Tobacco smoking
Classic risk factors	Plasma fibrinogen, LDL cholesterol
Pre-existing symptoms	Angina (WHO), chronic bronchitis (MRC)
Impaired function	Reduced spirometric values
Confirmed disease	Myocardial infarction, bronchial asthma
Previous emergency admission	Ischaemic heart disease, obstructive lung disease
Other factors	Age, socioeconomic status

British urban populations the overall effect is of the order of up to 5% for increments in particulate pollution of about 10 μg/m^3.[14–18] In our time series study conducted in the population of Edinburgh, from whom this cohort was selected, significant associations were found between the concentration of particulate matter (expressed as black smoke averaged over the previous 3 days) and increased mortality from respiratory disease and between particulate matter with mean aerodynamic diameter 10 μm (PM_{10}, averaged over the 3 previous days) and increased cardiovascular morbidity in elderly people.[6] Others have shown significant associations between concentrations of particulate pollution and morbidity from respiratory causes,[19] but no significant association was shown in our population.

In the framework for assessment of the health effects of air pollution advocated by the Committee on the Health Effects of Air Pollutants[18] the final step is described as "a quantification of that (health) effect if applied to the overall population". However, we think that a further stage is necessary, namely the measurement of health effects in potentially susceptible subgroups of the population, as small or non-significant health effects in the population as a whole may hide important effects within these subgroups. To achieve this aim, several important research needs have to be fulfilled. The first is to develop methods to study possible susceptible subgroups relative to the influence of air pollution on health. Cohort studies are the methods of choice to investigate cumulative exposures and relate these to morbidity, mortality,[20] and longevity. However, the cohort approach may also be pursued to answer important questions regarding possible subgroups of the population with increased susceptibility to the short term effects of air pollution as illustrated by our person-day and nested case-control methods. Possible susceptible groups could be postulated as exemplified in table 5 and studied systematically. Finally, the effect of susceptibility needs to be measured in subgroups where susceptibility has been established, especially to determine whether the effects of previous risk factors and of pollution on health are multiplicative, or simply additive. Attention needs to be paid both to short term, and cumulative effects on longevity.[21] This paper considers some of the methodological issues, and provides preliminary estimates of the evidence for increased susceptibility in certain specific subgroups. The risk factors considered here include some known to influence cardiovascular outcomes,[22] and work is in progress with another data set exploring whether evidence of previous ill health might be associated with higher susceptibility to pollution (Cohen *et al*, personal communication).

A crude initial approach to consider possible susceptibility with patient linked hospital admission data[6] did not show an increased likelihood of pollution related emergency admissions among those subjects with a higher emergency admission rate (although further work exploiting record linkage is in progress). We therefore pursued a cohort approach. However, a compromise has to be found between the number of putative risk factors considered and the power of the study. Clearly, the larger the number of risk factors examined, the more tests that will need to be undertaken and hence the greater the likelihood of errors in interpretation due to multiple testing.

Fibrinogen and both plasma and blood viscosity are important predictors of cardiovascular events.[22–24] It is therefore also reasonable to investigate whether people with increased concentrations of fibrinogen or blood or plasma viscosity are at higher risk from subsequent exposure to pollution. Such information will be important as these analytes might be viewed both as previous risk factors or as mediators of the adverse effects under study, and can be reliably determined through the use of National[10] or International[25] fibrinogen standards. There is evidence to support the hypothesis that plasma fibrinogen mediates the cardiovascular consequences of exposure to particulate air pollution.[4] Peters *et al*[26] have shown an association between particulate pollution concentrations and plasma viscosity, although their study may have been constrained by residual confounding from low temperature. Some fibrinogen polymorphisms have been associated with plasma fibrinogen concentrations,[27] and independently of this, with the risk of peripheral atherosclerosis.[28]

With no individual exposure estimates available all members of the cohort are of necessity assumed to have the same pollution experience on a given day, as measured at a standard reference point in the city centre. This clearly increases problems due to misclassification of exposures.[29] There is also uncertainty over the appropriate time lag to use in assigning pollution exposures. As in our previously published work undertaken in Edinburgh, from where this cohort was derived,[6] we adopted the particulate metric of mean black smoke concentration over the previous 3 days as the best particulate exposure variable for this cohort. Over the period of our study, 1987–98, black smoke pollution showed a small, but non-significant decrease with time coupled with a small, but non-significant, increase in cardiovascular event rate, consistent with the aging of the cohort. Another important pollution metric—namely PM_{10}—has also been measured in relation to this cohort but for a lesser period of observation, and therefore this data set is not yet powerful enough for a comparable analysis.

The purpose of this study was not to consider the main effects of previous person specific risk factors (notably fibrinogen) on cardiovascular outcome, as this has already been done.[22] Moreover, this study was not intended to be powerful enough to show a main effect of particulate pollution on the general population and we have considered this issue in other ways.[6] However, this study presents methods for investigating potential susceptibility to general environmental air pollution within cohorts. The results suggest the possibility (of borderline significance) that the effect of increasing black smoke is greater for people with higher fibrinogen concentrations than for people with lower fibrinogen, despite the limitation of statistical power to show a main effect in the population as a whole. More work is needed, with larger and hence more powerful data sets, using methods such as these to establish whether an interaction exists between previous risk factors and subsequent exposure to atmospheric pollution. Such an interaction could have important implications for vulnerable people and for the public health.

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