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Short term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project

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Abstract

Objectives: To carry out a prospective combined quantitative analysis of the associations between all cause mortality and ambient particulate matter and sulphur dioxide.
Design: Analysis of time series data on daily number of deaths from all causes and concentrations of sulphur dioxide and particulate matter (measured as black smoke or particles smaller than 10 μm in diameter (PM_{10})) and potential confounders.
Setting: 12 European cities in the APHEA project (Air Pollution and Health: a European Approach).
Main outcome measure: Relative risk of death.
Results: In western European cities it was found that an increase of 50 μg/m³ in sulphur dioxide or black smoke was associated with a 3% (95% confidence interval 2% to 4%) increase in daily mortality and the corresponding figure for PM_{10} was 2% (1% to 3%). In central eastern European cities the increase in mortality associated with a 50 μg/m³ change in sulphur dioxide was 0.8% (−0.1% to 2.4%) and in black smoke 0.6% (0.1% to 1.1%). Cumulative effects of prolonged (two to four days) exposure to air pollutants resulted in estimates comparable with the one day effects. The effects of both pollutants were stronger during the summer and were mutually independent.
Conclusions: The internal consistency of the results in western European cities with wide differences in climate and environmental conditions suggest that these associations may be causal. The long term health impact of these effects is uncertain, but today's relatively low levels of sulphur dioxide and particles still have detectable short term effects on health and further reductions in air pollution are advisable.

Introduction

The adverse health effects of episodes of severe air pollution were established over 40 years ago by investigations in Europe and North America.[1] Since then the levels of particles and sulphur dioxide, which characterised these episodes, have fallen below the limits considered safe for human health in the 1980s.[2]

More recent studies, mainly from the United States,[3,4] have found associations between mortality and other health indicators and levels of outdoor suspended particulate matter that are well within existing air quality guidelines and standards. These studies have had a considerable impact on scientific dialogue and standards.[5,6] However, little information exists about the possible effects of the current concentrations of sulphur dioxide.

Apart from data from a few European studies which used various methodological approaches,[6-10] little is known about the short term effects of air pollution on mortality in Europe. There are many differences between Europe and the United States, and within Europe itself, which might influence the health effects of air pollution; these include emission sources, pollution mixes, climate, lifestyle, and the underlying health of the population.

A multicity analysis of the short term health effects of air pollution on mortality and hospital emergency admissions was initiated within the European Union Environment 1991-94 Programme (Air Pollution and Health: a European Approach: the APHEA project). The study investigated the effects of several air pollutants in 15 European cities in 10 countries.[11] This paper reports the combined results from the 12 cities which had data available for investigating the effects of sulphur dioxide and particulate matter on daily mortality.

Methods

Table 1 shows the cities studied, the size of populations, the concentrations of the available pollutants, the length of study, and the mean daily number of deaths. Particulate matter was measured either as black smoke (determining the intensity of the black stain produced mainly by particles below 4 μm in diameter) or as particles below 10 μm in diameter (PM_{10}). Under the protocol the data for each city were analysed separately but with a standardised approach to data eligibility and statistical analysis.[12,13] About half of the data from individual cities used in this paper have been published previously.[14,15]

The daily data from the cities were analysed by time series methods.[13] A specific standardised method was applied to control for confounding while at the same time allowing the flexibility to take account of local characteristics. This procedure included modelling all potential confounders (seasonal and long term patterns, daily temperature, humidity, day of the week, holidays, influenza epidemics, and other unusual events), choosing the "best" air pollution models, and applying diagnostic tools to check the adequacy of the models. For each pollutant the best one day measurement chosen from lags 0 (same day) to 3 and the best average indicating cumulative exposure (up to four consecutive days) were selected by each centre.

Several previously decided pollutant transformations were tested. Generally, in cleaner cities linear terms for the pollutants fitted the data best. When log transformations had the best fit, additional models were fitted with linear pollutant terms, restricting the analysis to days when the pollutant did not exceed 200 μg/m³. The final analysis was done with autoregressive Poisson models, allowing for overdispersion and autocorrelation where necessary. Modification of the effect by season and the levels of other pollutants was also tested by appropriate models. Effects were reported by each city as partial regression coefficients, standard errors, and covariances (where needed) from the final Poisson models. Details of the analytical methods used for each city's data have been published.[12,13]

The city specific estimates of effect for each model were combined quantitatively. The summary estimates were weighted means of the regression coefficients, with weights inversely proportional to local variances (fixed effects model).[16] All available coefficients were included in the analysis. Homogeneity of the coefficients was tested with a χ^2 test under the fixed effects hypothesis. If significant heterogeneity was present ($P<0.05$), its determinants were investigated by using a predefined list of explanatory variables which included the levels of the pollutant evaluated and the levels of other pollutants (annual mean or seasonal mean and correlations between pollutants); meteorological factors (annual mean or seasonal temperature and humidity); accuracy of measurements of air pollutants (number of monitoring sites, correlations between measurements from different sites); health of the population (age standardised mortality, proportion of elderly people); smoking prevalence; geographical differences (north-south, east-west). A random effects model was also applied in case of significant unexplained heterogeneity. Under this model the between cities variance is added to the estimates of the local variances as a way of quantifying the inherent greater uncertainty of heterogeneous results.

Table 1 Duration of analysis, population, and pollutant data for cities contributing to analysis of total daily mortality

Town	Length of study	Population* (x 1000)	No of deaths/day (SD)	Black smoke (μg/m³) percentiles 50	Black smoke (μg/m³) percentiles 90	Sulphur dioxide (μg/m³) percentiles 50	Sulphur dioxide (μg/m³) percentiles 90	Particulate matter† (μg/m³) percentiles 50	Particulate matter† (μg/m³) percentiles 90
Athens	1987-91	2000	35 (6)	73	146	45	86	—	—
Barcelona	1986-92	1700	46 (9)	40	76	41	77	85	116
Bratislava	1987-91	443	11 (3)	—	—	13	50	39	95
Cracow	1977-89	740	18 (5)‡	73	247	74	170	—	—
Cologne	1975-85	977	30 (6)	—	—	44	96	34	69
Lodz	1977-90	848	28 (6)‡	57	151	46	123	—	—
London	1987-91	7200	199 (21)‡	13	23	29	45	—	—
Lyons	1985-90	410	8 (3)‡	—	—	37	86	33	64
Milan	1980-89	1500	32 (7)‡	—	—	66	293	66	137
Paris	1987-92	6140	128 (15)‡	26	56	23	59	47	81
Poznan	1983-90	575	18 (4)‡	34	92	41	131	—	—
Wroclaw	1979-89	637	14 (4)‡	54	141	29	83	—	—

*Numbers refer to the populations covered by the data collection. †Particles <13 μm for Paris and Lyons and <7 μm for Cologne; total suspended particles (TSP) for the other cities, converted to particles <10 μm (PM_{10}) with the formula: PM_{10}=TSP*0.55. ‡Excluding deaths from external causes.

Results

The participating cities showed substantial variation in air pollution mixtures and concentrations and in geographical distribution, seasonal patterns, and meteorological and climatic conditions.[11] Mean winter concentrations of sulphur dioxide varied from 30 to 330 μg/m³ and of black smoke from 10 to 290 μg/m³; the mean summer concentrations of nitrogen dioxide varied from 60 to 205 μg/m³ and of ozone from 55 to 165 μg/m³. Typical patterns of winter and summer type smog were observed, with some cities having particularly high winter type smog, dominated either by sulphur dioxide (for example, Milan) or particles (for example, Cracow) while others had relatively high air pollution of both types (for example, Athens). The average temperature and humidity in the winter ranged from −2°C to 10°C and from 67% to 89% respectively and in the summer from 17°C to 26°C and from 50% to 76%.[11]

Table 2 shows the pooled estimates of relative risk associated with a 50 μg/m³ change in 24 hour pollutant levels and the tests for heterogeneity for black smoke, PM_{10}, and sulphur dioxide for one day and cumulative effects. Significant heterogeneity was found for the effects of sulphur dioxide and black smoke. The attempt to explain this heterogeneity by the variables described in the Methods section showed that only the separation between western and central eastern European cities resulted uniformly in more homogeneous subgroups. However, significant heterogeneity still remained for the effect of sulphur dioxide in western cities. Overall, an increase of 50 μg/m³ in the one day pollutant levels was associated with an increase in the daily mortality of 3% for sulphur dioxide, 3% for

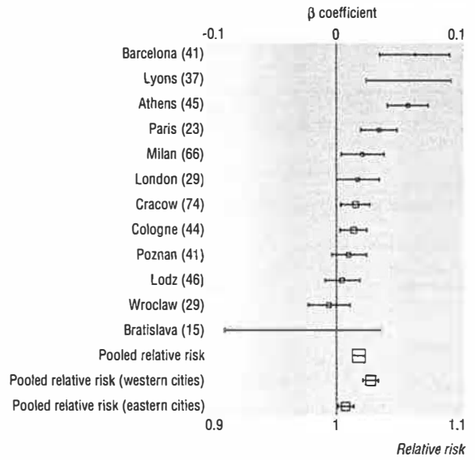

Fig 1 Estimated individual city and pooled relative risks of mortality associated with increase of 50 μg/m³ in sulphur dioxide concentration. Numbers in parentheses are median value of pollutant, and the size of the point representing each relative risk is inversely proportional to its variance

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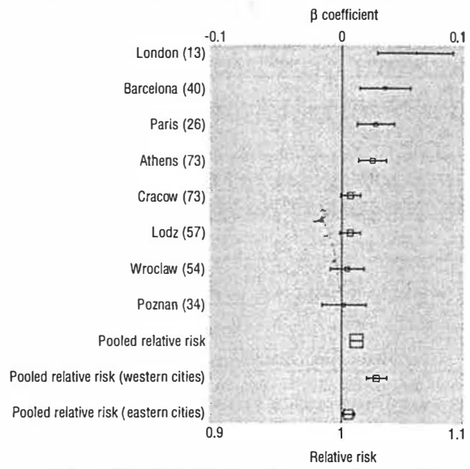

Fig 2 Estimated individual city and pooled relative risks of mortality associated with increase of 50 μg/m³ in black smoke levels. Numbers in parentheses are median value of pollutant, and the size of the point representing each relative risk is inversely proportional to its variance

black smoke, and 2% for PM_{10} in the western European cities. The corresponding figures for central eastern cities were 1% for sulphur dioxide and black smoke (4% for PM_{10} in Bratislava, the only city with results available). The cumulative effects were consistent with the one day estimates but the relative risks were larger, as would be expected since they reflect the same day and the lagged effects of air pollution.

Figures 1-3 show the relative risks for 50 μg/m³ change in the pollutant levels for each city as well as the pooled estimates (also separately for central eastern and western European cities). When two pollutant models were fitted, including both sulphur dioxide and black smoke or PM_{10}, the regression coefficients for the effects of sulphur dioxide and black smoke both decreased by 32%. The relative risks (95% confidence intervals) became 1.023 (1.007 to 1.039) and 1.020 (1.000 to 1.040) for an increase of 50 μg/m³ for sulphur dioxide and black smoke respectively.

Table 3 shows the pooled estimates separately for summer and winter for western and central eastern European cities. The effects were stronger in the summer per unit increase in the pollutant in the western cities. The difference between seasons was significant for PM_{10}. All the pollutants analysed had highest concentrations during winter.

Table 4 shows the pooled estimated effects for sulphur dioxide for days with high or low particle levels and the corresponding black smoke effects for days with high or low sulphur dioxide concentrations in western European cities. The effects of sulphur dioxide and black smoke were similar for days with low or high levels of the other pollutant and the same as their overall effect.

Discussion

Air Pollution and Health: a European Approach is a systematic attempt to analyse time series data on air pollution and health in a standardised way on a large scale. The cities included in the project covered over 23 million people and represented various environmental and climatic conditions, offering an important opportunity for assessing the consistency of the association between air pollution and mortality. The estimated effects are for moderate and low levels of pollution (particulate matter and sulphur dioxide below 200 μg/m³), which are the most relevant exposures in current situations.

Table 2 Estimated pooled relative risks and 95% confidence intervals for 50 μg/m³ change in 24 hour pollutant levels* from Poisson autoregressive models of sulphur dioxide, particulate matter (PM_{10}), and black smoke on total mortality

	All cities			Western cities			Central eastern cities		
Pollutant	**No of cities**	**Relative risk (95% CI)**	**P value†**	**No of cities**	**Relative risk (95%CI)**	**P value†**	**No of cities**	**Relative risk (95% CI)**	**P value†**
Sulphur dioxide									
1 Day:									
Fixed effects model	12	1.020 (1.015 to 1.024)	<0.0001	7	1.029 (1.023 to 1.035)	<0.001	5	1.008 (0.993 to 1.024)	0.25
Random effects model‡	—	—	—	7	1.035 (1.020 to 1.050)	—	—	—	—
Cumulative§:									
Fixed effects model	12	1.023 (1.017 to 1.028)	<0.0001	7	1.032 (1.024 to 1.040)	<0.0001	5	1.011 (1.002 to 1.019)	0.04
Random effects model‡	—	—	—	7	1.040 (1.018 to 1.062)	—	5	1.008 (0.993 to 1.023)	—
Black smoke									
1 Day	8	1.013 (1.009 to 1.017)	0.08	4	1.029 (1.021 to 1.037)	0.34	4	1.006 (1.001 to 1.011)	0.99
Cumulative§	8	1.014 (1.009 to 1.020)	<0.001	4	1.031 (1.022 to 1.040)	0.08	4	1.004 (0.997 to 1.011)	0.40
PM_{10}¶									
1 Day	6	1.022 (1.013 to 1.031)	0.53	5	1.021 (1.012 to 1.030)	0.58	1	1.043 (1.003 to 1.085)	—
Cumulative§	6	1.021 (1.012 to 1.031)	0.43	5	1.031 (1.022 to 1.040)	0.08	1	1.049 (0.996 to 1.105)	—

*Averaging time.
†P value from χ^2 for heterogeneity.
‡Used only when there was significant heterogeneity.
§Average of 2 to 4 consecutive days, including the day of recorded mortality
¶PM_{10}: PM_{13} for Paris and Lyon and PM_7 for Cologne; total suspended particles (TSP) for other cities were converted to PM_{10} by the formula PM_{10} = TSP*0.55.

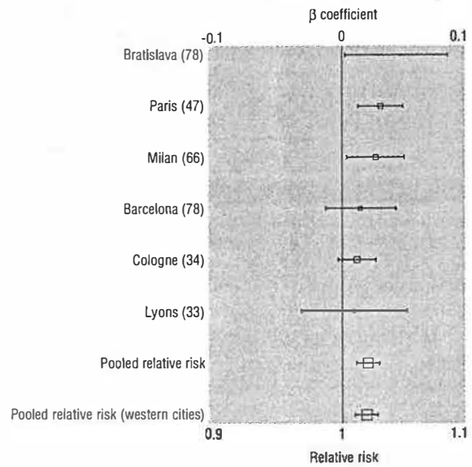

Fig 3 Estimated individual city and pooled relative risks of mortality associated with an increase of 50 μg/m³ in particulate matter (PM_{10}) levels. Numbers in parentheses are median value of pollutant, and the size of the point representing each relative risk is inversely proportional to its variance

The project planned a combined quantitative summary of results from all the cities. In this respect it differs from most meta-analyses, which are started only after a substantial number of papers on a specific hypothesis have been published. It follows that several common problems affecting meta-analyses do not apply here: there was no publication bias (all the results were included), no selection bias (in the sense that all cities which could provide data and enter the project were included long before the results were known), and all the necessary coefficients were available.

We found a clear significant effect of moderate to low levels of sulphur dioxide and particles (<200 μg/m³) in western European cities which seems independent for the two pollutants. In the United States meta-analyses focusing on the effects of particles (using total suspended particles and PM_{10} as indicators) estimated that an increase of 100 μg/m³ total suspended particles (about 50 μg/m³ PM_{10}) is associated with a relative risk of daily deaths of 1.05 to 1.06.[3,4] The relative risks for PM_{10} in the individual studies (for about 50 μg/m³ change) ranged from 1.03 to 1.08; the largest estimates were in the areas with the lowest sulphur dioxide concentrations (Utah Valley; Kingston, Tennessee; St Louis, Missouri). In Philadelphia, where there are moderate sulphur dioxide concentrations, detailed recent analyses indicate that both total suspended particles and sulphur dioxide affect death rates.[17] These results have been shown to be insensitive to different methods of analysis.[18]

In Europe, two earlier studies indicated that the effect of sulphur dioxide is more pronounced than that of particles (measured as black smoke), but these results cannot be readily interpreted as relative risks.[6,7] Analyses of daily mortality and air pollution in the Netherlands showed no effect of sulphur dioxide (which was at very low concentrations) on mortality but reported a significant association with black smoke.[19] Data from Athens for the five years before this study indicated independent effects of both sulphur dioxide and black smoke on total mortality.[20]

The size of the effect of particles (either PM_{10} or black smoke) that we found is compatible with those reported in the United States and in other studies, although at the lower end of the range of relative risks. We found, however, that the effect of sulphur dioxide on mortality, which has not been so thoroughly studied elsewhere, was consistent with and of a similar size to the effect of particles. Furthermore, inclusion of estimates from recent analyses in five additional western European cities[19,21,22] results in a pooled relative risk associated with a 50 μg/m³ change in the pollutant level of 1.028, 1.025, and 1.030 for sulphur dioxide, PM_{10}, and black smoke respectively. These values are similar to our original estimates.

The reason for our results for particles being on the lower side of the range reported in the United States may be the more complex mixtures of pollutants that we observed. Thus, in a place where there are high levels of particles in the absence of sulphur dioxide the particle effect may be higher because there is no competing pollutant to deplete the pool of people at high risk. Alternatively, the distribution of the size and toxicity of the particles may differ or the proportion of susceptible individuals may be larger in the American cities studied.

Table 3 Estimated pooled relative risks and 95% confidence intervals for 50 μg/m³ change in 24 hour pollutant levels from Poisson autoregressive models of sulphur dioxide, particulate matter (PM_{10}), and black smoke on total mortality by season

	Warm season		Cold season	
Pollutant	**Relative risk (95% CI)**	**P value***	**Relative risk (95% CI)**	**P value***
Sulphur dioxide				
Western:				
Fixed effects model	1.040 (1.028 to 1.053)	0.35	1.024 (1.071 to 1.031)	<0.001
Random effects model†	—	—	1.033 (1.015 to 1.051)	—
Central eastern:				
Fixed effects model	1.011 (0.999 to 1.023)	0.003	1.008 (1.002 to 1.015)	0.05
Random effects model†	1.008 (0.979 to 1.037)		1.009 (0.997 to 1.020)	—
PM_{10}‡				
Western	1.043 (1.027 to 1.060)	0.31	1.010 (0.998 to 1.022)	0.81
Central eastern	1.053 (0.994 to 1.116)	—	1.019 (0.941 to 1.107)	—
Black smoke				
Western	1.040 (1.024 to 1.057)	0.27	1.024 (1.016 to 1.032)	0.50
Central eastern	1.013 (1.002 to 1.024)	0.40	1.005 (0.998 to 1.011)	0.96

*P value from χ^2 for heterogeneity.
†Given only when there was significant heterogeneity.
‡PM_{10}: PM_{13} for Paris and Lyon and PM_7 for Cologne; total suspended particles (TSP) for the other cities were converted to PM_{10} by the formula: PM_{10} = TSP*0.55.

Table 4 Estimated pooled relative risks of deaths from all causes (95% confidence intervals) for 50 μg/m³ change in 24 hour pollutant levels from Poisson autoregressive models of sulphur dioxide and black smoke by high and low levels of other pollutant in western European cities

	Days with lower level of other pollutant		Days with high level of other pollutant*	
Pollutant	**Relative risk (95% CI)**	**P value†**	**Relative risk (95% CI)**	**P value†**
Sulphur dioxide				
Fixed effects model	1.029 (1.016 to 1.043)	0.11	1.030 (1.022 to 1.038)	0.002
Random effects model‡	—	—	1.034 (1.019 to 1.050)	—
Black smoke				
Fixed effects model	1.028 (1.013 to 1.043)	0.10	1.027 (1.019 to 1.035)	0.15

*Above the city's median level.†P value from χ^2 for heterogeneity. ‡Random effects model, only when there is significant heterogeneity.

Independent effects

There is evidence from three different approaches that the effects of the two pollutants investigated are independent. Firstly, if the effect of one pollutant was a surrogate of the other, then ranking the effects estimated for one pollutant by the mean level of the other—for example, plotting the sulphur dioxide coefficient for all cities ranked by their black smoke level—should show a monotonic trend in the size of the effect. This was not found for either sulphur dioxide or any particle measurement. Secondly, models for the two pollutants during days with low and high levels of the other pollutant were fitted, and the pooled results indicated independent effects. Thirdly, the results of the two pollutant models showed a similar moderate decrease in the effects of both pollutants, which remained significant.

It is possible, however, that either or both these pollutants may be surrogates for other unmeasured substances. In fact, the exposure variables that we used are proxies for personal exposure correlated with day to day differences in personal exposure to particles and sulphur dioxide or, generally, to primary combustion related pollution. If the responsible pollutants must be those to which individuals are exposed for longer periods during a day, then the pollutants which penetrate and remain suspended indoors are strong candidates. Fine particles (with a diameter <2.5 μm), and in particular sulphates, have been found suspended indoors in the absence of indoor sources.[23] The stronger correlation of mortality with black smoke rather than PM_{10} found in this study may reflect the fact that black smoke consists only of fine particles or may reflect a relatively greater toxicity of diesel related pollution, which is the major source of black particles in many cities. The effects of both pollutants studied are not likely to be confounded by ozone or nitrogen dioxide concentrations as their correlation with ozone is low and the observed effects of nitrogen dioxide on mortality were relatively weak and largely confounded by particle levels.[24]

How health is affected

Our results are consistent with the effects of particles and sulphur dioxide on cardiovascular and respiratory mortality found within the APHEA project. Specifically, in five western European cities an increase in sulphur dioxide concentrations of 50 μg/m³ was associated with a 4% and 5% rise in cardiovascular and respiratory mortality respectively; the corresponding figures for black smoke were 2% and 4% (unpublished data).

The biological mechanism by which exposure to particulate matter may increase mortality is not well understood but has received considerable attention.[25] Acidic ultrafine particles may provoke alveolar inflammation causing acute changes in blood coagulability and release of mediators able to provoke attacks of acute respiratory illness in susceptible individuals.[26] Other potential mechanisms include impairment of lung defences and physiological disturbances of gas transfer. Fine particles do penetrate into the respiratory region, and recent studies have shown that exposure to 288 μg/m³ of fine urban particles for six hours a day for three days resulted in 37% mortality in bronchitic rats compared with 0% in control rats.[27] Bronchoconstriction was found in the exposed bronchitic rats, and inflammatory cytokines were detected in both the lung and the heart.

Sulphur dioxide, on the other hand, is a highly reactive gas with short half life indoors. It is a known respiratory irritant and bronchoconstrictor, but its effects seem limited to patients with asthma and bronchitis, although sensitivity to exposure varies widely.[17 28] Exposure to sulphur dioxide may therefore not completely explain the observed increase in mortality; it may rather serve as a surrogate of other substances. Since sulphur dioxide is highly correlated with the levels of fine particles in some American cities, Schwartz *et al* postulated that sulphur dioxide may be a marker of fine particles.[21] However, the fact that we found a consistently significant effect of sulphur dioxide on mortality in all western European cities, whatever the level and composition of particles in each one, may suggest that sulphur dioxide has a direct effect. The role of outdoor peak exposures to sulphur dioxide in the increase of daily mortality should be further investigated.

Geographical differences

An intriguing finding was the difference observed in the effects of black smoke and sulphur dioxide on mortality in western and central eastern European cities. The estimates for the central eastern European cities were either similar to or lower than the ones estimated for sulphur dioxide in Erfurt, former East Germany, over the same concentration range (<200 μg/m³).[30] The variation between east and west may have been because the pollution measurements were unrepresentative of the population exposure, differences existed in the health of the population (smaller proportion of sensitive individuals), or cities had a different pollutant toxicity or mix, possibly because of the sources of pollutants. Furthermore, the model for seasonal control may fit the data less well in the central eastern cities because of a higher and more variable rate of respiratory illness.

In conclusion, the consistency of results from the western European cities with wide differences in topography, climate, environment, and air pollution sources supports a causal association between exposure to particulate matter and sulphur dioxide and mortality from all causes. The reported relative risks are small, but the short term effects of air pollution are not a trivial public health problem if the ubiquity of air pollution exposure is taken into account.

Key messages

- Evidence is accumulating that air pollution below the levels of national and international standards has adverse short term health effects
- In this study data from 12 European cities showed that increases in sulphur dioxide and particulate matter are associated with increased total mortality
- The effects of the two pollutants seem to be independent
- Associations were stronger and more consistent in western European cities
- Current low levels of sulphur dioxide and particles still affect health and further reductions in pollution are needed

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Simultaneous immunisation with influenza vaccine and pneumococcal polysaccharide vaccine in patients with chronic respiratory disease

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Pneumococcal disease is an important cause of morbidity and mortality in the United Kingdom.[1] The increasing numbers of elderly people and the development of drug resistant *Streptococcus pneumoniae* will exacerbate this problem. The safety, efficacy, and cost effectiveness of immunisation with pneumococcal polysaccharide vaccine is established,[2] and immunisation is now recommended for all patients aged over 2 years with chronic lung disease, a target group for influenza vaccination.[3] Coadministration of the vaccines is recommended, though the efficacy of pneumococcal polysaccharide vaccine given in this way has been questioned.[4] We examined whether an immunoresponsive interaction exists between 23 valent pneumococcal polysaccharide vaccine (Pnu-Imune 23) and influenza vaccine (Fluarix).

Patients, methods, and results

One hundred and fifty two adults with chronic respiratory disease were randomised to receive either pneumococcal vaccination and influenza vaccination on the same day (concurrent group; n=76) or influenza vaccination first, followed by pneumococcal vaccination one month later (interval group; n=76). The pneumococcal vaccine was given into the left deltoid muscle and the influenza vaccine into the right deltoid muscle. At the initial visit and one month after each injection venesection was performed for blinded analysis of pneumococcal antibody titres (serotypes 4, 6B, 14, 18C, 19F, 23F) by enzyme linked immunosorbent assay (ELISA) and influenza antibody titres (strains A (Taiwan), A (Johannesburg), B (Harbin)) by

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