overview and critique of the air pollution and health: a european approach (APHEA) project

Prepared by:

L. Rushton
Institute for Environment and Health
University of Leicester

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SUMMARY

The relationship between air pollution and adverse health outcomes is a subject of current concern in the area of environmental health. The Air Pollution and Health: a European Approach (APHEA) project is a co-ordinated study of the short-term effects of air pollution on mortality and hospital admissions in sixteen cities in eleven European countries. The Institute for Environment and Health have been requested by CONCAWE to carry out an independent review and critique of the APHEA project. Twenty-three published papers were identified and reviewed.

Methodology

A standardised protocol was developed and adopted by all centres in the APHEA project for the collection of air pollutant data, health outcome data and information on potential confounders, such as temperature, relative humidity and unusual events. Poisson regression, allowing for autocorrelation and overdispersion was used by each centre to analyse their own data and the procedure for the building statistical models was specified in detail. Each city fitted the model of 'best fit' to their data, so that the city-specific models differed in the number of variables they included and the transformations and lag times used for the time-dependant variables. The meta-analyses combined the relative risks obtained from the best fitting models for the individual cities to give overall summary estimates. A fixed effects model was first fitted and a test of heterogeneity was carried out. If heterogeneity was significant, a random effects model was then fitted, with explanatory variables.

Results

- Small increases in the relative risks were consistently found in the individual cities and in the combined analyses for several air pollutants and health outcomes
- The relative risks for total mortality ranged from 0.98 to 1.13, most being between 1.01 and 1.03.
- The strongest effect for total mortality was found for sulphur dioxide (SO_2), with particulates showing a slightly weaker association.
- Consistently elevated relative risks were found for both nitrogen dioxide (NO_2) and ozone (O_3) and the estimates from the combined analyses were statistically significant.
- The results for mortality attributable to respiratory disease and cardiovascular disease were less consistent with a wider variation in risk estimates between cities and few being significantly elevated.
- Similar patterns were found for digestive system diseases, chosen as a control group, although risk estimates tended to be lower.
- Increased risk of hospital admissions for respiratory disease was found for SO_2 in the elderly (aged 65 and over), and for black smoke (BS) in the 15-64 age group.
- Results for NO_2 and respiratory disease admissions were inconsistent.
- A significantly positive association was found for respiratory admissions in London with O_3, and the combined estimate was significantly raised and was larger in the elderly.

- A combined analysis from four cities for emergency hospital admissions for asthma found associations with NO_2 in both children under the age of 15 years and adults aged from 15-64 years, and for SO_2 in children that were significantly raised.
- Emergency admissions for chronic obstructive pulmonary disease were significantly associated with all pollutants using the combined estimates, with the strongest and most consistent effect being found for O_3.
- The effects of temperature and season varied between cities and by pollutant and health outcome. There was a tendency for effects to be stronger in the summer.
- Correlations between pollutants within cities and the extent to which synergy between pollutants existed also varied considerably.

Critique

The systematic and co-ordinated approach is one of the strengths of the APHEA project, and the results have contributed to the previous lack of meaningful information in Europe. The results support those found in many other studies of the adverse effects of air pollution. There was a tendency, however, for there to be a stronger association with SO_2, than studies, for example from the USA, and risk estimates for particles were generally lower than those obtained in the American studies.

However, the project was limited by the quality of some of the data, in particular the exposure information. There were variations in the numbers of monitors per geographical area and per population, the location of the monitors, the measurement and sampling techniques, and the correlations between values from the monitors. Ecological studies such as this are subject to a high degree of misclassification due to the use of ambient air exposure data as a surrogate for personal exposure. There were also problems of completeness of diagnosis for some of the hospital admission data, and it was not possible to separate emergency from planned admissions in some centres.

The published papers do not report the results in a standardized format. Information important for the interpretation and comparison of the results between the cities was not consistently presented. For example, it would have been useful to know, for all the cities, the values of the correlations between pollutants measured in order to assess potential collinearity, the risk estimates for all the covariates included in the models, changes in the values of the coefficients of the pollutants as variables were added to or removed from models, and an indication of the fit of the models. The correct adjustment for potentially strong confounders, such as those relating to climatic conditions, is particularly important when elevation of the relative risk estimates is so small. Variables, such as population size, age structure, migration patterns and proportion of smokers, which might have undergone change over the study periods and influenced either health or pollution or both, were described for some cities but were not considered as variables for inclusion in the models. Other time-varying factors, such as pollen, which might influence respiratory diseases such as asthma, were not included in the analyses.

The lack of homogeneity in some of the data and the use of risk estimates derived from the ‘best fit’ models, with varying choice of variables, lag times and transformations, necessitates caution when evaluating the summary estimates obtained from the meta-analyses.

Recommendations

Although the results from the APHEA project concur with many other studies in showing an association between a range of airborne pollutants and adverse health outcomes, they have also helped to emphasise the wide variation in both the magnitude and direction of the estimates and the predominant pollutants.

Clarification of the relationship between levels of air pollution measured by outdoor fixed-site monitoring, levels indoor and personal exposures is required. The role of each pollutant, both as an individual risk factor and in its contribution to a synergistic effect, the importance of different sources and mixtures of pollution, the interrelationships of pollution and climate and the influence of microenvironments are all areas which require further research. The development of a European air pollution monitoring network, which uses the same method of sampling and analysis and is more evenly distributed by area and population is also essential.

In view of the lack of consistency of reporting of the results from the APHEA project, a paper summarising these in a standard format, as suggested earlier, for all cities, pollutants and health outcomes, would be useful. The result for diseases of the digestive system should also be given for all cities to assist comparisons. Although there are limitations in the APHEA data, reanalyses of the combined data sets using the raw data from all the relevant centres, would be helpful. Lag times, transformations and weights could be fitted, and explanatory variables and interaction terms characterising the individual centres could also be included.

Ecological study designs are limited in their inherent assumption that individual risk can be estimated using group data. Spurious associations may be identified through an unobserved variable or by incomplete adjustment for confounding. Collinearity between pollutants may make it difficult to identify exactly which pollutant is important and there may be incomplete knowledge about the time-exposure-response relationship. The regression coefficients obtained from the models used cannot be used to quantify the effect of pollution. A Cohort study approach is needed to assess causality and also estimate the potential public health benefit of a reduction in pollution.

1. INTRODUCTION

The Air Pollution and Health: a European Approach (APHEA) project is a co-ordinated study of the short term effects of air pollution on mortality and hospital admissions in eleven European countries. Twenty-three papers have been published in the scientific literature concerning the methodology and results, and include combined analyses from several of the centres. The Institute for Environment and Health (IEH) have been requested by CONCAWE, the oil companies' European organisation for environmental health and safety, to carry out an independent review and critique of the APHEA project, including the design, data quality, analytical methodology and interpretation of the results.

The review presented in this report is divided into two main parts:

(i) In section 3 a description of the overall design and methodology of the project and a summary of the results for each individual city is given. Differences in methodology between countries are highlighted and the results compared and contrasted. An evaluation and critique of these studies is then given.

(ii) Section 4 gives an outline of some of the general issues pertinent to the design of a prospective meta-analysis, followed by a description and critique of the pooled APHEA analyses.

The last section (5) of the report presents a summary of the findings from the project and suggests potential future research strategies.

2. LITERATURE SEARCH STRATEGY

A literature search of appropriate databases, including MEDLINE and EMBASE, was carried out by IEH staff. Only papers published in the scientific literature have been reviewed. Copies of the study protocol and unpublished reports were not obtained. Three papers describe the background, objectives, design and analytical methodology of the project (Katsouyanni et al, 1996; Katsouyanni et al, 1995; Schwartz et al, 1996). Fourteen papers present analyses for the separate cities in the study, ten reporting mortality results (Anderson et al, 1996; Bacharova et al, 1996; Ballester et al, 1996; Bogdan et al, 1996; Dab et al, 1996; Spix et al, 1996; Sunyer et al, 1996; Touloumi et al, 1996; Vigotti et al, 1996; Zmirou et al, 1996), and six reporting hospital admissions results (Dab et al, 1996; Poloniecki et al, 1997; Ponce de Leon et al, 1996; Ponka et al, 1996; Schouten et al, 1996; Vigotti et al, 1996). Five further papers (Anderson et al, 1997; Katsouyanni et al, 1997; Spix et al, 1998; Sunyer et al, 1997; Touloumi et al, 1997) give results of pooled analyses, and one gives an overall summary of selected results (Katsouyanni et al, 1997).

The APHEA studies represent only a small proportion of the many studies which have been carried out world-wide to investigate the relationship between outdoor air pollution and adverse health outcomes. No attempt has been made in this report to review these in full, but some are referred to in the discussion sections, in order to set the APHEA studies in context with the wider literature. Previous critiques and overviews are also referred to.

3. THE INDIVIDUAL CITIES

3.1. BACKGROUND AND OBJECTIVES OF THE APHEA PROJECT.

Sections 3.1 - 3.5 present the design of the APHEA project as described in the protocol. A copy of the actual protocol was not obtained, but two papers by Katsouyanni et al (1995,1996) describe the overall design, and a paper by Schwartz et al (1996) discusses some of the methodological issues. Deviations from the protocol occur for some cities, and these are highlighted in the text.

Katsouyanni et al (1995) states that the overall aim of the APHEA project was to quantify the health effects of exposure to moderate or low pollution levels, and to identify the relevant pollutants and their possible synergistic effects.

The objectives of the APHEA programme were:

- To provide quantitative estimates of the short-term health effects (using total and cause - specific daily numbers of deaths and emergency hospital admissions) of air pollution, taking into consideration interactions between different pollutants and between pollutants and other environmental factors.
- To further develop and standardise the methodology for the detection of short term effects in the analysis of epidemiological time-series data.
- To select and develop a meta-analytical approach for epidemiological time series studies.
- To assess the feasibility of creating a European data base of air pollution measurements and of health indicators, recorded on a daily basis.

The programme involved sixteen cities (although Katsouyanni et al (1995) lists only fifteen) from eleven European countries. **Table 1** lists these cities, the study period for each one and the population covered by the data collection. It should be noted that it was not possible in all cities to separate emergency from planned hospital admissions, and not all countries were able to provide monitoring on a daily basis for all pollutants. These issues are discussed in more detail in later sections.

3.2. MEASUREMENTS OF AIR POLLUTION

Air pollution measurements were obtained from public monitoring networks in each city but not all the pollutants of interest were available and not all were measured over the same period. **Table 1** summarises, for each city, the main sources of pollution as reported in the papers, the pollutants measured, the number of monitors used for each pollutant and the monitoring method. Specific points about the monitoring are given briefly for each city in the comments column of **Table 1**, but are described in more detail in section 3.4.

In general, the protocol required that only urban stations located near roads with busy traffic and/or background urban stations were used (preferably at least one of each). Only the French groups used solely background sites. The height of measurement points varied from 2-10 m. As can be seen from **Table 1**, the number of monitoring sites was generally greater than 3. No quality assurance programme for monitoring was organised within APHEA, but Katsouyanni et al (1995) state that all the monitoring networks run their own quality assurance programmes, most of

which conform to European legal requirements. However, as indicated in **Table 1** and section 3.4, some countries reported that they did not have any quality assurance system in place during the period of data collection.

The arithmetic mean of measurements from all stations fulfilling the completeness criteria was used to give a daily figure. For the calculation of 24 hour nitrogen dioxide (NO_2) and sulphur dioxide (SO_2) and maximum one hour NO_2 values, at least 75% of the one hour values on a particular day had to be available. For the maximum one hour ozone (O_3) values, 75% of the hourly values from 6 am to 7 pm had to be available, and for the 8 hour value of O_3 the 9 am to 5 pm average was used, providing at least 6 hourly values were available. Monitoring stations with more than 25% of values missing for the whole study period were excluded. Where days in the time-series for one site had missing values, these were estimated using data from the other monitoring sites, and the estimation method depended on the total number of sites available. Where a city used three or fewer monitoring sites in total, missing values for one particular station were predicted from a regression equation. The mean of all stations on days when all measurements were available (the dependent variable) was regressed on the measurements of the sites except that with missing values (the independent variables), adjusting for season. This was then used to predict the mean daily level for missing values. When more than three stations were available, missing values were estimated by calculating the mean level of the remaining stations and multiplying by a factor equal to the ratio of the seasonal (three month) mean for the missing station over the corresponding mean from the stations available on that particular day (Katsouyanni et al, 1996).

There were considerable differences between cities in the air pollution mixtures, seasonal effects and mean levels of the various pollutants between cities (see **Table 2**). For example, mean levels of black smoke ranged from 11 $\mu g/m^3$ in Amsterdam to 84 $\mu g/m^3$ in Athens. In some cities there was also considerable variation between the levels recorded at the different monitoring stations utilised, with a wide range of mean values being obtained. Katsouyanni et al (1995) comment that this probably reflects the geographical location of the stations, for example, the proximity to emission sources, such as traffic, rather than the pollutant dispersion.

3.3. HEALTH DATA

The APHEA study focused on (i) daily counts of deaths and (ii) the daily number of hospital admissions, for certain causes. Mortality data were obtained for all causes of death, except external causes, such as accidents, although not all cities were able to exclude accidental deaths. Diseases of the respiratory system and cardiovascular disease were selected as the outcomes most relevant to air pollution exposure. Deaths from diseases of the digestive system were used as a 'control' cause. The study protocol specified the International Classification of Disease (9th revision) codes used for each disease group. Hospital admissions from all respiratory diseases, chronic obstructive pulmonary disease (COPD) and asthma were considered. **Table 3** gives details of the health endpoints, disease groups and age groups for which results are reported for the 16 cities. Thirteen cities present results for mortality data for all causes of death, and fewer for specific causes. Only six cities report results for hospital admissions.

The sources of mortality were the national death registration systems for all cities, except Athens where the researchers collected and coded the data. Hospital admission data were provided by government operated national registers or

municipality operated local registers. Discharge diagnosis was used, and was complete for over 70% of the diagnostic categories used in the project. Katsouyanni et al (1995) comment that in some areas it was impossible to distinguish between planned and emergency admissions. The impact of missing diagnostic information and the impossibility of separating planned from emergency admissions for some cities on the interpretation of the results is addressed in later sections.

3.4. DATA ON POTENTIAL CONFOUNDING FACTORS

Time series data on daily temperature (°C) and relative humidity were used to control for the potential effects of weather. Wind velocity and direction were considered as exposure correlates, not as confounders, and other meteorological variables were not considered important. Data for daily pollen levels were not included as they were not available in all centres. The participating cities had a wide diversity of climatic conditions. Day of the week, holidays, influenza epidemics and other unusual events, such as strikes or a heat wave were also modelled (Katsouyanni et al, 1996).

3.5. STATISTICAL ANALYSIS

The procedure for the statistical analysis was specified in detail in the project protocol to ensure a standardised and uniform method of analysis in all centres. In modelling this type of time-series data a Poisson process is assumed, i.e. that the counts of deaths or hospital admissions are an independent and random occurrence over a set period (a day). In the Poisson process the mean is equal to the variance. However, in many actual count processes the variance is larger than the mean, defined as overdispersion. Daily counts of deaths are also correlated day-to-day, (autocorrelation), due to the day-to-day correlation of the determinants of death, such as weather patterns and air pollution concentrations. Adjustment for both autocorrelation and overdispersion, was used in the APHEA analysis.

A systematic approach to the building of the models was adopted. Initially a ‘core’ model was constructed fitting the daily number of deaths (or hospital admissions) (log transformed), as the dependent variable, with all the potential confounders. Firstly, sinusoidal terms were used to control for seasonal and other long-term cyclical patterns. Long-term trends were controlled by introducing a linear or quadratic term in the model and/or dummy variables (coded as 0 or 1 for each level of the variable) for years as appropriate. After removal of seasonal and long-term patterns from the mortality data, the short-term effects of temperature and humidity on mortality were fitted using transformations where appropriate. The association of adverse health and air pollution or climate has been shown in some studies to be lagged, i.e. the health effect occurs up to a week after the exposure occurs. Lag times of 0-2 days were considered for temperature and relative humidity in the APHEA analyses. The effect of the day of the week, holidays, and unusual events were fitted using dummy variables. Influenza epidemics were fitted, where possible, using a case-count, although daily figures were not available in all cities.

The contribution of each variable on the model was assessed by using goodness of fit statistics, such as the F-test or χ^2 test. Time-series plots of the dependent variable, predicted variable and residuals (random variation remaining after a model has been fitted) were also used to check if cyclical and long-term patterns had been removed. Air pollution variables were then entered one at a time using the best fitting transformation and time lags (0,1,2 and averages of different consecutive

lags) for each centre, for every pollutant. However, in some cases, for example in Amsterdam, Athens, Barcelona, Lyon, Rotterdam and Valencia, longer lags were used. At the final stage, Poisson autoregressive models allowing also for overdispersion were applied. Effect modification by season was investigated by introducing a dummy variable for season and also including an interaction term with the pollutant. In some analyses, interactions among pollutants were examined. The data for each city were analysed separately following the above procedure. Each analysis resulted in a final model which the authors considered gave the 'best fit' for that city. These inevitably differed between cities depending on the transformations chosen and variables included. Most of the papers do not report the statistical software package used to carry out the analyses, although one or two mention SAS (Bogdan et al, 1996; SAS Institute Inc, 1989).

3.6. METHODOLOGY USED IN THE INDIVIDUAL CITIES

Before summarising the results for the sixteen cities it is appropriate to highlight areas of methodology which may differ from the standard protocol as described in the above sections.

Amsterdam and Rotterdam (Schouten et al, 1996)

Only one monitoring station was available in each of Amsterdam and Rotterdam. Data from these city stations were used as much as possible for all pollutants measured, except for O_3, for which a suburban site was selected. The authors state that this was chosen so as to be more representative of fluctuations in O_3 exposure rather than central sites where O_3 concentrations tend to be lower as a result of higher NO_2 levels. Missing data were estimated using data from stations (a variable number depending on pollutant) within 25 km of the city station. Data on hospital admissions for all patients whose place of residence was Amsterdam or Rotterdam were obtained from the National Medical Register, which the authors state was 'almost complete' for the Netherlands. However, they do not say whether all hospitals in the two cities were included.

Athens (Touloumi et al, 1996)

The average daily measurements from three monitoring stations were used (not the same for each pollutant, four stations in all, from different regions in the city) but the paper does not say how many stations there were in total. During the study period the overall mean levels from three monitoring stations were 49.1, 80 and 124 $\mu g/m^3$ for black smoke (BS), 23.6, 54.6 and 75 $\mu g/m^3$ for SO_2 and 2.7 6.1 and 11 $\mu g/m^3$ for carbon monoxide (CO). Pearson correlation coefficients between the daily measurements at different stations ranged from 0.4 to 0.7. During the study period BS exceeded the WHO air quality guidelines on 42% of the days, SO_2 on 12% and CO on 54% in the centre of Athens where the highest levels were observed.

Mortality data were obtained from Athens Town Registry and the registries of nineteen towns contiguous to Athens. In July 1987 the total number of deaths more than doubled due to a heat wave and this month was excluded as a climate outlier. The temperature and mortality relationship was shown to be U shaped, i.e. a higher number of deaths during very cold or very hot days, but with a steeper slope at high temperatures.

Barcelona (Sunyer et al, 1996)

Air pollution in Barcelona is primarily caused by vehicle exhausts, with levels of BS, particles and NO_2 being in the highest range for western cities participating in the APHEA project. Twenty four hour BS measurements were averaged from seven manual samplers, only one of which gave missing values for more than 5% of days. SO_2, NO_2 and O_3 were averaged from three automatic samplers, each representing a different type of urban pollution (industrial, residential, and residential with high traffic). For all pollutants missing observations were replaced by the city's average value. Data on daily deaths were supplied by the regional mortality register.

Bratislava (Bacharova et al, 1996)

Nine monitoring stations were operating during the study period in Bratislava, two being located near roads with frequent traffic, four near chemical factories and three in suburban areas. The four stations selected were those which recorded the highest concentration of pollutants in the city, and where the percentage of missing data was less than 15 % for whole study period and less than 25 % for each year. The study period covered a period of political and economic change characterised by an increase in traffic, intermittent reduction of industrial production, and the introduction of new technologies. In 1991, after the study period, new automated monitoring systems were installed. Before this only limited data on mean daily concentration of SO_2 and total suspended particles (TSP) were available.

The daily number of deaths classified according to ICD 9 and the place of residence were provided by the Statistical Office. Although the number of deaths occurring daily ranged from 3 to 22 for total causes, the ranges for respiratory disease and diseases of the digestive system were 0 - 4 or 5, with means of under 1.

Cologne (Spix et al, 1996)

SO_2 values were available from five stations, three just on the outside of the inner city and two in the suburbs. 48 daily half-hour values were sampled, daily means or maxima being accepted if 75% of the values were available. TSP values were available from 1975-84 from five stations in a state run network. This was gradually replaced in the 1980's by a modern telemetric network. Only data from the modern ones were used. Continuous data were not available, so samples were taken on Tuesdays, Thursdays and Saturdays. The system provided only daily means and about 17% of the data were missing. Two of the five stations used were within the urban ring and three were in the suburbs. Daily mean PM_7 data were also obtained from a research institute in Dusseldorf, 40 km north of Cologne, although 12% were missing. Recalibration took place every eighth day, resulting in a missing value. NO_2 values came from two background stations. Half hour data were available with fewer than 10% missing. Daily total mortality data were obtained from state authorities. In some places and years there was an artificially high number of deaths on January 1 because 'forgotten' certificates were assigned to this date. A variable for this was fitted in the model. No systematic data on influenza incidence were available but the Dutch data (from APHEA) had a weekly count and this was used. Temperature showed a U effect. Dew point temperature was used as a proxy for relative humidity.

Cracow, Lodz, Poznan, and Wroclaw (Bogdan et al, 1996)

Three manually-operated fixed sampling units were used in different parts of each city. The numbers of monitors available in each city varied over time and differed between cities, but figures are not given in the paper. The authors state that there was no system of quality control in place for the monitoring at the time of the study. The three monitors in Cracow and Wroclaw were more widespread than those for Lodz and Poznan. Correlation coefficients for the measurements between the monitoring sites are not given, but the authors report that they were higher for BS in Cracow and Lodz than in Poznan and Wroclaw, although there was no difference for SO_2. The proportions of days with measurements from all three monitors were in the ranges 77-83% for SO_2 and 75-79% for BS, and under 5% of days had no measurements at all. Days with missing values for air pollution and meteorological conditions were omitted from the analysis. The authors also discuss the potential inadequate characterisation of air pollution mixtures present in the cities using SO_2 and BS as indicator pollutants. There was considerable difference in the sources of the pollutants. For example, SO_2 makes up 10% of gaseous pollutants in Cracow compared to 85% in Lodz. Data on deaths were obtained from the central statistical office for permanent residents in each city or surrounding region (confidentiality issues concerning geographical place of death prevented the exclusion of residents in the region surrounding each city).

Helsinki (Ponka et al, 1996)

Eight stations were used altogether, six for TSP, one for O_3, four for SO_2, two for NO_2. Instruments for SO_2 and NO_2 were calibrated monthly, and bimonthly for O_3. TSP was collected by high volume samplers every second day at six stations, and every third day at two stations. Data for TSP were missing for 375 out of 1096 days, but data for NO_2 and SO_2 were only missing for 13 and 4 days, respectively. Missing observations were imputed from regression analyses.

The authors comment that the modelling was problematic, with difficulties experienced in correction for cyclical patterns and autocorrelation, and the choice of appropriate transformations.

London (Anderson et al, 1996; Poloniecki et al, 1997; Ponce de Leon et al, 1996)

There is some confusion over the study period in the paper reporting hospital admissions for respiratory disease (Ponce de Leon et al, 1996). The title implies that years 1989 and 1990 were omitted from the analyses. However, both health and air pollution data appear to have been collected throughout the period 1987 to 1992. There was an influenza epidemic in the winter of 1989/1990, but this was allowed for in the analyses by the use of a dummy variable corresponding to the 6 week period of the epidemic.

Only one monitoring site was used for O_3, but levels correlated highly ($r>0.95$) with monitoring subsequently set up in another inner London site and an outer London site. For the studies reporting results for respiratory admissions (Ponce de Leon et al, 1996) and daily mortality (Anderson et al, 1996) additional monitors were also used for the other pollutants. The levels of NO_2 concentration from the two monitors used were highly correlated. Daily levels of BS and SO_2 were obtained from four monitors, with data for more than 75% of days. Missing values were replaced by a regression technique, for days on which only one or two monitors had missing values. Days for which data were missing for more than two stations were

considered missing. The values between the four monitors for BS and SO_2 were highly correlated. For the study of cardiovascular hospital admissions (Poloniecki et al, 1997) measurements of NO_2 and SO_2 were only used from the central London site used for O_3 in the other two studies, and CO measurements were also taken from this monitor.

Emergency admissions for respiratory diagnoses to hospitals in the London health districts were obtained from the Hospital Episode System for 1987-1992. March 1992 was discarded because of a deficit associated with data recording. Area of residence was incomplete in the earlier years so the hospital district was used. Diagnosis was recorded at discharge and was available in 73%, 76%, 85%, 88%, and 95% of records for the years 1987/88 - 1991/92 respectively. Hospital Episode statistics data from 1987 - 1994 were used for cardiovascular disease admissions (Poloniecki et al, 1997).

Lyon (Zmirou et al, 1996)

Lyon has had an air pollution monitoring network for a long time and air pollution is higher than many other French cities, and other cities involved in the APHEA project. All relevant monitoring stations available within the limits of the city were used, although, as shown in **Table 1**, these varied in number. They were chosen in order to represent the background air quality levels. One monitor, situated in a location with very high traffic density, had very high values of particulate matter (PM), NO_2 and SO_2, and was excluded so the average values were not distorted. Estimation was used for missing values by averaging the measurements of the other available stations, and correcting this by using the ratio of the mean value for the missing station and the mean values of the other stations for the same year and season. For NO_2 the discarded station's values were used. No missing values for O_3 were estimated. The O_3 monitor was located within the centre of Lyon and the authors raise the question of its relevance to O_3 population exposure, due to scavenging by NO. Daily counts of deaths were obtained for residents of the city of Lyon, excluding the Lyon metropolitan area. Lyon is the smallest APHEA city and there were no deaths on an appreciable proportion of days for some causes (e.g. 65%, 68% for respiratory and digestive conditions).

Milan (Vigotti et al, 1996)

During the study period the proportion of children aged 14 and younger dropped from 4.1% to 3.2% and the proportion of elderly (65+) rose from 14.1% to 16.2%. The area of high industry situated to the north of the city was not included.

Four monitoring stations (located in school yards) were used in different quadrants of the city, about 100 m within the Milan ring avenues. 24 hour averages were calculated if at least 75% of the hourly measurements were available. The APHEA protocol was followed to estimate days with missing values. The correlation between measurements from the two TSP monitors was 0.81 and the correlations between the four stations monitoring SO_2 ranged from 0.89 to 0.91. TSP values increased slightly over the study period and SO_2 fell from 157 to 87 $\mu g/m^3$, mainly because of legislation requiring the use of lower sulphur fuel, the conversion of home heating in about half the residences to natural gas, and the transfer of industries outside of the city.

The hospital data were restricted to residents of Milan, admitted to hospitals in Milan or to hospitals in neighbouring local health units. This represented 92% of the admissions of Milan citizens during the period. Death data were also limited to those who died within the city.

Paris (Dab et al, 1996)

There are three monitoring networks in Paris (i) for background levels (ii) for automobile exhaust and (iii) in areas of high population density. Stations in the background pollution network whose location had remained 'stable' between 1987 and 1992 were chosen. Different numbers of stations were used, fifteen for 24 hour BS, and four stations for SO_2, NO_2, PM_{13}, O_3 (the same four).

These are linked to a computer and provide data every 15 minutes. Missing data (if data from at least 18 hours were not available) for the daily mean were estimated using the average of the stations available for that day if the correlation was above 0.7. If data for an entire day were missing, the mean concentrations at the other stations were used, weighted by the ratio of the mean value of the missing station over the three month season to the mean value of the other stations for the same period. After this procedure, the percentages of missing values were 0%, 3%, 5%, 5% and 6% for BS, O_3, SO_2, NO_2, and PM_{13} respectively. The levels of the pollutants were similar at all stations. Hospital admission data were obtained from 27 public hospitals, which admit patients on short term care (all university teaching hospitals).

Valencia (Ballester et al, 1996)

There were thirteen fixed monitoring stations, five of which were considered for the study, being 'weekly' stations which allowed collection of sequenced samples for up to eight days at a time. The other stations were 'daily' stations, in which a change of filter and capture solution had to be carried out manually each day. Two weekly stations were excluded because one had approximately 35% missing values for the study period and the other was in a location 'considered to be inadequate'. The percentage of days with missing values for the three stations used in the study varied from 6% and 13 % for BS and between 8% and 13% for SO_2. The monitoring sites were located within the urban area of Valencia, with a medium to intense level of vehicular traffic. The correlation between the three monitors was between 0.63 and 0.76 for BS and between 0.14 and 0.63 for SO_2. The correlation between the mean of the three stations for BS and SO_2 was low (r=0.24).

3.7. RESULTS

The use of regression models allows the calculation of relative risks, i.e. the risk among a high exposed group relative to a group exposed to some lower level. A relative risk above 1 indicates an elevated risk. Confidence intervals around the relative risk can also be calculated, i.e. assuming no bias or confounding, the interval within which one has a certain confidence that the true relative risk will lie. A 95% confidence interval which excludes the value 1.0 indicates statistical significance at the 5% level (either raised or reduced). **Tables 4 - 7** present, for each city, relative risks per 100 $\mu g/m^3$ increase in pollutant, 95% confidence intervals for the relative risks and lag time for different health effects and pollutants.

Mortality

Table 4 summarises the results for all cause mortality and **Figure 1** illustrates the results for SO_2 and particulates. Almost all the relative risks are slightly elevated. Two cities, Athens and Barcelona, in which three or four pollutants were measured, show statistically significantly elevated risks for all of them, the strongest effect being for SO_2. Cracow and Lodz also show significantly elevated risks for both SO_2 and BS. Nine of the eleven relative risks for SO_2 are elevated, six significantly so, and two are significantly reduced. All eight relative risks for BS are elevated, six significantly so, with a weakly significant result for PM_7 in Cologne and the risks for PM_{13} and TSP being non-significantly elevated. All the relative risks reported for NO_2 and O_3 are greater than 1, with one being significant for NO_2 and two for O_3. There was a significantly elevated risk associated with CO in Athens.

Table 5 presents the mortality results for respiratory disease, cardiovascular disease and the control, diseases of the digestive system for SO_2 and particulates, and these are illustrated in **Figures 2 - 4**. There is more variation in the results for these diseases. Six of the relative risks for respiratory disease and SO_2 are elevated, but only two statistically significant, (Lyon and Milan), with these two cities also being the only ones showing a significantly elevated risk with particulates. It should be noted that PM_{10} was measured in Lyon and TSP in Milan. The results for Barcelona and Paris for both SO_2 and particulates approach significance. London, Lyon and Barcelona reported results investigating the relationship between exposure to NO_2 and O_3 and respiratory disease (not tabulated). Only one relative risk was elevated for NO_2 but not significantly. All the relevant risks were greater than 1 for O_3 with a significantly elevated relative risk (RR) of 1.06 (95% confidence interval (CI) 1.02-1.10) reported in London.

Six of the nine relative risks presented for cardiovascular disease in relation to exposure to SO_2 and seven of the nine for particulates are greater than 1, with three being statistically significant for SO_2 and one for particulates. All the relative risks for cardiovascular disease with exposure to NO_2 and O_3 were 1 or more. Barcelona reported significant associations for cardiovascular disease mortality and exposure to both NO_2 (RR = 1.04, 95% CI 1.00-1.07) and O_3 (RR = 1.06, 95% CI 1.01-1.11). A significant association in relation to O_3 was only found in the warm season for London (RR = 1.04, 95% CI 1.01-1.06). Only six cities reported results for the control disease group, diseases of the digestive system. The patterns follow that of the other two disease groups and all causes of death, with three relative risks being above and three below 1, (not the same cities for SO_2 and particulates) with, two, for SO_2 in Bratislava and particulates in Cracow, being significantly elevated.

Hospital admissions

The results for hospital admissions are summarised in **Table 6** and illustrated in **Figure 5**. Five cities reported results for hospital admissions for respiratory disease. A pattern of generally elevated risk can be seen for total respiratory disease admissions, for all the four pollutants measured. SO_2 appears to have the strongest effect, with Milan and Paris reporting statistically significant elevated risks. Significantly elevated risks were only found in association with exposure to NO_2 in London, for all ages and the over 65 year old group. London was also the only city to report significantly elevated risks for O_3. Milan, Paris and Rotterdam all found a significantly elevated risk in relation to exposure to particulates, two of these being in patients aged between 15 and 64 years. Each of the three cities took different measures of particulate exposure.

Three cities analysed hospital admissions for asthma. Two of the three found significantly elevated risks in association with SO_2 exposure but a significantly reduced risk was found in Amsterdam. In Helsinki, admissions for asthma among 0-14 year olds were related to 8 hour O_3 levels, but admissions for digestive tract disorders, used as a control were also significantly associated with this pollutant. There was only one significantly elevated relative risk found for COPD, in Paris, associated with exposure to SO_2.

A recent paper reports an analysis, following the APHEA protocol, for cardiovascular hospital admissions in relation to the previous day's air pollution in London (Poloniecki et al, 1997). In addition to all diseases of the circulatory system, separate analyses were carried out for acute myocardial infarction, angina pectoris, other ischaemic heart disease, arrythmia, heart failure, cerebrovascular disease, and all remaining circulatory diseases. **Table 7** presents the results for each pollutant and disease group. All circulatory diseases and acute myocardial infarction were significantly associated with all pollutants except O_3. In addition CO was significantly associated with other circulatory diseases, NO_2 with arrhythmia, and BS with angina. O_3 was negatively associated with all disease subgroups except arrythmia. The authors note that correlations between pollutants were all positive, with the exception of O_3 which was negatively correlated with all other pollutants. The majority were also significantly correlated. The authors were concerned that significant associations found in full models might have arisen as an artefact of the complex modelling. They therefore tested for the presence of an association in a partial model i.e. a model without sine and cosine terms and without the Poisson assumption. Only the associations with acute myocardial infarction were significant in both the full and partial models.

Analyses by temperature, season and co-pollutants

Several of the papers investigated the potential modification effects of temperature and season on the risk estimates. In Athens, SO_2, but not BS or CO, significantly interacted with season with the strongest effect being observed in the winter. A stronger effect of SO_2 on mortality was observed when BS was at higher levels, which occurred in the winter.

In Barcelona, mortality, SO_2, and BS levels were higher in the winter but O_3 levels were higher in the summer. BS and SO_2 were highly correlated whereas the other correlations were low. O_3 gave the highest correlation with temperature (0.415). The association of BS with mortality in the elderly (greater than 70 years) did not vary by season, whereas the association between SO_2 and respiratory mortality was higher in the summer, in contrast to the findings in Athens. The relationship between oxidant pollutants and cardiovascular mortality varied by season, being positive and significant in the summer, but negative and non-significant in the winter.

Two explanations suggested by the authors for the increase due to SO_2 and oxidants in summer are (i) during winter people are less exposed to outdoor air, hence there may be higher misclassification in the exposure measurement (ii) competing causes of death e.g. respiratory infections have a lower impact in summer. They suggest that the toxicity of the pollution mixture varies by season and may be more toxic in summer.

Similar results were found in Cologne and Valencia. In Cologne, where the SO_2 daily mean was highly correlated with PM_7 (r=0.68) and TSP (r=0.60), there were somewhat stronger effects for all pollutants in summer. SO_2 in relation to particulates gave no indication of a synergism. In fact, SO_2 effects were stronger

when TSP was below 100 $\mu g/m^3$ or PM_7 was below 60 $\mu g/m^3$, which both occur in summer. In general, particle effects tended to be stronger at an SO_2 daily mean below 100 $\mu g/m^3$. In Valencia, as in Barcelona, no variation was found with season for BS, but the relative risks associated with SO_2 were greater during the warm months for total mortality and for mortality from both respiratory and cardiovascular diseases.

In Lyon the association of particulates with respiratory and cardiovascular deaths were of borderline significance with a slightly larger effect in the cold season. SO_2 did not show a seasonal effect. The data suggested an interaction between particulates and SO_2, with the risk of respiratory deaths associated with a 50 $\mu g/m^3$ increase in the daily mean of SO_2 being greater when particulates were high e.g. PM_{13} greater than 60 $\mu g/m^3$.

In Milan, hot summer days were associated with an increased risk of deaths when the 24 hour mean temperature reached 24^oC and this risk increased to 2.58 as temperature increased to 29^oC and over. Daily mean temperature of 29^oC and above was associated with an increased risk of respiratory hospital admissions in the older age group. SO_2 was significantly associated with deaths occurring the same day but there was no interaction with seasons. There was a marginal seasonal effect for TSP suggesting a stronger effect in the warm season.

The paper reporting results for respiratory admissions in London (Ponce de Leon et al, 1996) presents the correlation coefficients between pairs of air pollutant indicators and meteorological variables for the whole year and the warm and cool seasons. Strong positive relationships were found between temperature and O_3 and between any two of NO_2, BS and SO_2. O_3 and NO_2 had a positive association in the warm season and negative in the cool season. O_3 and BS, and O_3 and SO_2 were negatively associated in the cool season as well as for the whole year.

O_3 was consistently associated with respiratory admissions, especially among 15-64 year olds, with warm season effects being much larger than cool season. Statistically significant health effects of NO_2 lagged by 2 days were obtained for the elderly and were greater in the warm season. The authors note that NO_2 and O_3 are highly positively correlated in the warm period so that the health effects of these two pollutants might be confounded.

O_3 was also significantly associated with the warm season, but not the cold season, for both all cause and cardiovascular mortality in London (Anderson et al, 1996), and relative risks were significantly elevated for both seasons for respiratory mortality, that for the cold season being slightly higher than that of the warm season. Significant effects of BS were found for all cause mortality for both seasons. Inclusion of both O_3 and BS in a model made little difference to the effect obtained in the single pollutant model in the warm season. However, for the cool season, the effects of BS on all cause mortality were doubled when O_3 was included in the model. The effects of both BS and O_3 remained significant after inclusion of NO_2 or SO_2 in the model.

In the analysis of admissions for cardiovascular diseases in London, acute myocardial infarction was significantly associated with four pollutants, NO_2, SO_2, BS and CO, but not O_3. However these relationships were only significant in the cool season and not the warm season. All pollutants remained significant when O_3 was introduced into the model. However, only SO_2 remained significant when a pollutant other than O_3 was introduced, but again only in the cool season.

3.8. DISCUSSION

3.8.1. Results from the APHEA project in the context of findings from other studies

The APHEA project has made a major contribution to the area of air pollution research through the adoption of systematic and standardised procedures for data management and analysis. There was previously a lack of meaningful information in Europe relating to this issue. Although there are differences in the lag times fitted in the models and problems with some of the data quality, particularly pertaining to the pollutant data, the results from the individual cities are remarkably consistent, with, for example, the relative risks for total mortality ranging from 0.98 to 1.13, with most being between 1.01 and 1.03 (see figures). The strongest effect for total mortality is found for SO_2, with particulates, generally measured as BS, showing a slightly weaker association. This pattern is also observed for mortality related to respiratory and cardiovascular diseases, although less consistently. However, an interesting finding is that the range and pattern of relative risks for diseases of the digestive system, chosen as a 'control' group is similar to that of the other disease groups, although very few of the results are statistically significant. It should be noted that only six cities reported the results for digestive system diseases, although the intention of the original protocol was to include this disease group. The pattern of the results may thus be biased, for example if only reduced relative risks are reported.

There have been many other studies, mainly in the US, reporting small but significant increases in mortality in association with elevation of air pollution concentrations. As with the APHEA project, consistency has been shown across a range of geographical regions, climates and populations. In many early studies it is difficult to separate out the effects of the various pollutants, particularly SO_2 and particulates. In contrast to the results from the APHEA project, many other studies have found that the principal association with daily mortality is exposure to particulates, and not to SO_2. For example, increased daily mortality has been reported to be associated with particulate air pollution in Steubenville, Ohio (Schwartz et al (b), 1992), Detroit (Schwartz, 1991), Philadelphia (Schwartz et al (a), 1992), Utah Valley (Pope et al, 1992), Birmingham, Alabama (Schwartz, 1993), Cincinnati (Schwartz, 1994) (a), Los Angeles (Kinney et al, 1995), Amsterdam (Verhoeff et al, 1996), Beijing (Xu et al, 1994) and Erfurt, Germany (Spix et al, 1993). In some European studies, however, a significant effect with both particulates and SO_2 has been shown (Derrienic et al, 1989; Hatzakis et al, 1986; Verhoeff et al, 1996).

Control for confounding by other pollutants can be obtained most easily when one pollutant is dominant. Mortality associated with particulates in the absence of other pollutants was found in two US studies in Santa Clara (Fairley, 1990) and in Utah (Pope et al, 1992). It should be noted that, in many of the US studies, levels of SO_2 were lower than those found in Europe, and that the measurement of particulates in the APHEA project was mostly black smoke, which is a measure of finer particles than, for example, PM_{10}, which is often measured in the US. In many of the APHEA studies particles and SO_2 were often highly correlated (Hoek, 1997). Katsouyanni et al (1997) suggest several reasons for the differences between the APHEA and USA studies including more complex mixtures in the APHEA study, differences in the size and toxicity of the particles, or the proportion of susceptible individuals. Lee (1972) showed that particulate matter suspended in the USA and Great Britain was fairly uniform in distribution and that aerosols in the vicinity of highways tended to have

larger particles than those some distance away. The location of the monitors may thus influence the results.

The composition and sources of the particles may also differ. Ultrafine particles, aerosol acidity and surface complexed transition metals may all influence health outcomes (Utell, 1995). Particle acidity has been implicated as a causal factor by Lipman and Thuston (1996) but not in two studies of six Eastern US cities (Dockery et al, 1992; Schwartz, 1997).

Katsouyanni et al (1995) suggest that either or both SO_2 and particulates may be surrogates for other unmeasured pollutants and perhaps should be considered as proxies for personal exposure to primary combustion related pollution.

An association of daily mortality with air pollution would also be expected to extend to specific causes of death. Respiratory disease and cardiovascular disease have been reported as being associated with air pollution, for example, with particulates (Dockery et al, 1993; Pope, 3rd et al, 1995; Schwartz, 1994 (a); Schwartz, 1993), although there is considerable variation between studies, and these mainly focus on the elderly. This is also reflected in the results from the APHEA study, which are less consistent than the results for total mortality.

The association of pollutants other than particulates and SO_2 was investigated in only a few of the APHEA studies, with inconsistent results. The study in Athens was the only one to report results for carbon monoxide in relation to total mortality and found a significantly increased risk. CO concentrations have been found in other studies to be associated with hospital admissions for myocardial infarction (Cohen et al, 1969; Hexter et al, 1971), as was the case in the London study (Poloniecki et al, 1997) .

There are fewer studies reporting results for O_3, in relation to mortality. Kinney and Ozkaynak (1991,1992) report a positive association for total mortality, excluding injuries, and cardiovascular mortality in New York City and Los Angeles, whereas studies in St Louis and Tennessee (Dockery et al, 1992) found no association. No association was found with respiratory mortality among infants in Sao Paolo (Saldiva, 1994). There was a suggestion that there may be an interdependence between ozone and other pollutants, particularly with NO_2, due to the mechanisms of O_3 formation.

Only six of the APHEA cities reported results for hospital admissions. SO_2 again appeared to show the strongest effect for total respiratory disease and asthma, although some cities also reported associations with particulates, and O_3 was significantly associated with respiratory disease in London. Increased total respiratory hospital admissions have been reported associated with increased sulphate concentrations (Burnett et al, 1995; Thurston et al, 1992), with $PM_{2.5}$ (Thurston et al, 1994), and TSP (Samet et al, 1981), and for asthma associated with PM_{10} (Schwartz 1994 (b); Schwartz 1993). Two studies have found an association during the summer months between SO_2 and hospital admissions (Bates et al, 1990; Walters et al, 1994).

Ozone has been shown to have a consistently adverse effect on respiratory health particularly in summer when concentrations are higher. Associations between O_3 and respiratory admissions have been reported in various parts of North America (Bates et al, 1987; Burnett et al, 1994; Schwartz, 1994 (b); Schwartz, 1994 (c); Thurston et al, 1994; Thurston et al, 1992). A meta-analysis of six studies from North America (Schwartz, 1995) found a weighted average relative risk of 1.06 for a

50 ppb increase in the hourly maximum O_3 level. The London study (Ponce de Leon et al, 1996) found that admissions for respiratory disease did not increase until the 8 hour O_3 average was above 50 ppb and that the relationship for levels above this was linear. This level approximates to recommended guidelines from the WHO, the EU and the UK Expert Panel on Air Quality Standards. The authors suggest that there is little or no safety margin in a 50 ppb standard. There was no suggestion of an association between O_3 and hospital admissions for cardiovascular disease in London (Poloniecki et al, 1997).

The authors of the paper reporting hospital admissions for cardiovascular disease in London state that is hard to reconcile the positive association found for BS, NO_2 and SO_2 with a lack of association with circulatory deaths in the same city (Ponce de Leon et al, 1996). They suggest that the significant associations might arise because factors which affect air pollution, such as the weather and driving motor vehicles, also have an effect on human behaviour and on acute health outcomes.

3.8.2. Data Quality

Mortality Data

In all countries in the APHEA project death registration is mandatory and well established. Under-registration should not, therefore, be a major concern. However, although standard procedures exist for the recording of cause of death information this may be subject to inaccuracies and incompleteness. The state of medical knowledge and availability of diagnostic facilities may influence the precision of the clinical and autopsy diagnoses and these may vary between countries and between cities and rural communities. Alderson (1988) discusses and reviews this topic. Although these issues should be considered in any study using mortality data across several countries, they may not be of serious concern given the broad diagnostic categories used in the APHEA project.

Morbidity Data

In contrast to mortality data, hospital admissions data may have more problems of comparability and completeness. In the APHEA project data were obtained from national or local hospital registers. Data from the Netherlands (Amsterdam and Rotterdam) were reported as being ‘almost complete’. Only the twenty-seven public hospitals were included in the Paris study and no indication was given of the proportion of total admissions that this represented. In the study from Milan, hospital discharge records for 92% of Milan citizens were included. The Helsinki study included emergency admissions for asthma and the data were reported as being ‘comprehensive’. Only the paper from London reporting results for respiratory admissions (Ponce de Leon et al, 1996) gave figures on completeness of diagnoses which increased from 73% to 95% over the study period. Alderson (1988) outlines the potential problems of completeness and accuracy relating to hospital admission data. He points out that a minimum data set for these records was recommended for the EU countries as early as 1981. Missing and inaccurate diagnosis data may lead to misleading estimates of the risks from potential causative factors such as air pollution. It has also been noted previously that for two cities, Paris and Milan, it was not possible to separate emergency admissions from planned admissions, although the latter were thought to represent only a small proportion of the total.

Exposure Data

Several of the APHEA publications discuss the limitations of the project in relation to exposure data. Ecological studies of this type are subject to a high degree of misclassification, due largely to the use of ambient air concentration data from fixed site monitors as a surrogate for personal exposure. The relationship between measurements of outdoor and indoor air quality and personal exposure is not sufficiently quantified to assess the suitability of proxy measures. Ecological studies do not generally attempt to control for indoor exposures nor for differing patterns of exposure, for example, the varying proportion of time spent outside over time, or by different subsets of the population, or changing ventilation between seasons. Outdoor air may relate more closely to personal exposure during a warm season than a cold one but this is difficult to assess. The pollutant being measured, the type of housing, and traffic density are among other factors which will influence the relationship.

Although the APHEA study has largely succeeded in standardising its approach to the collection of health data, it has been less successful with regard to the exposure data. **Table 1** and section 3.6 draw attention to some of the differences that exist between the cities. These highlight the lack of a truly uniform European wide air pollution monitoring system. The number of monitors varied as did the population sizes and geographical areas covered by them. For example, in London, there were only four monitors for a large area and a population of 7 million. Not all the papers reported the correlations between values for different monitors, but these were low for some pollutants and cities. This highlights the potential for greater misclassification when averages are then calculated and applied uniformly to overall health data. Some cities, such as Amsterdam, used monitors which gave background levels of pollution. Others, such as Cologne, used a mixture of background stations and stations near roads, whilst one, Bratislava, selected stations which measured the highest concentrations of pollutants. A further area of concern is the difference in monitoring methodology, including the frequency of sampling and calibration, and the techniques used to analyse the samples (**Table 1**). Many of the above issues need to be taken into consideration when comparing results between the cities and in the use of these data for combined analyses, (see section 4).

Data on Confounders Adjusted for in the APHEA Studies

Adjustment for several potential confounding variables was carried out for all cities in the APHEA project. Time-series data on daily temperature and relative humidity were used to control for the potential confounding effects of weather. These data were obtained from well established meteorological recording systems within the cities. Dew point temperature was used as a proxy for relative humidity in Cologne. Information on influenza events from daily counts was used where possible, but was not available in all cities. Day of the week, holidays and unusual events, such as a strike or heat wave, were also used as variables in the models. In Athens, data for one very unusually hot July, in which double the expected number of deaths occurred, were excluded. It would have been appropriate to report analyses with and without the data for this month to assess the sensitivity of the results to this type of outlier. The quality of the above confounders could be expected to be fairly uniform across all countries.

3.8.3. Statistical Methodology and Presentation of Results

The basic steps incorporated into the method of analysis and building of models has been described in section 3.5. All the published papers describe their statistical methodology in great detail, and all seem to have rigidly adhered to the protocol. This aspect of the APHEA project is one of its major strengths.

Unfortunately, this standardisation does not extend to the reporting of the results and the papers differ greatly, both in the way the results are presented and the detail given. For example, some papers report full models while others report only summary results, such as relative risks, although even these are sometimes left as regression coefficients or may be presented for different increases in pollutant. Comparison of the results between studies is thus unnecessarily difficult. It would have been appropriate for all papers to present as a minimum:

(i) correlations between the exposure levels from the monitors used and correlations between the pollutants measured, in addition to summary data on air pollution levels. The latter would facilitate assessment of potential collinearity between pollutants.

(ii) summary data on health outcomes including ranges

(iii) data on the proportion of missing values and how and if these were estimated

(iv) regression coefficients, relative risks and confidence intervals for the final models, to facilitate assessment of the relative contribution of all the variables, for example, temperature

(v) some indication of how the coefficients (or relative risks) for the pollutants changed as variables were added to or removed from the models

(vi) some indication of the fit of the models. This was not really addressed in any of the papers but is fundamental to the reader in assessing the success of the modelling.

Although the statistical methodology used a standardised approach, there was no co-ordination for the assessment of the influence of the various potentially important confounding factors. Each city fitted the 'best' model to their data and the final choice of variables to be included and appropriate transformations and lag times was left to the authors. For example, the risk estimates are presented for different lag times, as can be seen in **Tables 4-6**. A more informative approach would have been to make an assessment of the risks for different lags, and present these, together with a measure of the goodness of fit, for each city. This would have facilitated both the interpretation of the potential lagged effects of the pollutants on health and comparisons between cities.

Time-series studies have the advantage that many causes of increased mortality such as smoking and hypertension, cannot confound the observed associations with air pollutants, because these factors do not vary with daily pollution exposures. The responses may, of course, differ by some of these factors. For example, the APHEA study in Lyon found that people dying on days with high SO_2 levels were slightly older on average than those who died on other days. It can be seen from **Table 1** that several of the studies covered a time period of 10 years or more. No attempt was made to model changes which might have occurred during this time and which might have influenced either air pollution or health, for example, changes in

population numbers or age distribution, long-term population migration or shorter term movements between different environments, such as commuting to work, or the proportion of the population who smoke. Several of the papers do comment on this sort of change, including the influence of clean air acts on the reduction of certain type of air pollutants. Differences in the sources and mixtures of pollutants are referred to, but not adjusted for. As indicated in section 3.8.2 ecological studies are limited in their estimation of potentially important micro-variations in exposure and in the range of contrast of exposure limits.

Weather and seasonal factors have been consistently found to be strong predictors of daily mortality, and in the US have been shown to explain between 11% and 70% of the variability in mortality (Kalkstein et al, 1989). Correct adjustment for such a potentially strong confounder is thus important, as this could impact on the very low relative risks associated with air pollutants.

The relationship between mortality and temperature often follows a J or U shaped pattern, with increasing numbers of deaths at both low and high temperatures, although the slopes may differ. This relationship was reported in several of the APHEA papers. One approach to adjusting for the confounding effect of weather, which has been adopted in the APHEA project, is to use primary variables such as daily mean temperature and relative humidity, that are likely to be associated with daily mortality. A study by Mackenbach et al (1993) in the Netherlands found that controlling for temperature by using deviations from the threshold and varying the lag period for temperature significantly reduced the association of SO_2 with mortality. An alternative approach used in a study by Pope (1996) is to use statistical methods such as factor analysis to group data on several meteorological variables into 'synoptic' weather categories or patterns.

Differences in patterns of mortality and morbidity were found between seasons and hot and cold weather as described in section 3.7, although these were not consistent. Few of the APHEA papers report sufficient detail to assess the relative contribution to the overall risk of temperature compared with air pollution. Sunyer et al (1996), in reporting the study from Barcelona, assessed whether the extensive parametrisation or their models (72 variables were included) affected the inferences and stability of the associations obtained. They present the changes in the coefficients for BS and SO_2 for total mortality as each parameter is included. BS was more sensitive than SO_2, but variables representing season and weather reduced the coefficients for both pollutants. Similar results were found for Cologne (Spix et al, 1996). A earlier study in Barcelona by Saez (1995) showed that relative risks for temperature were generally higher than for pollutants. Meteorological effects were found to be statistically significant in all age groups except 15 - 64 year olds in the London study of respiratory admissions (Ponce de Leon et al, 1996).

A time-varying factor which might have potential importance in the study of the cause of asthma is the level of pollen exposure. This was not included as a variable in the APHEA project as data were not available in all cities (Katsouyanni et al, 1995).

In assessing the risk from a specific air pollutant the potential for confounding by co-pollutants must be considered. In the APHEA project, models were developed for each pollutant separately. However, interaction between pollutants was investigated for some cities by introducing dummy variables to distinguish between 'high' and 'low' levels of potential co-pollutants. The cut-off points for the co-pollutants were different for each pollutant (Katsouyanni et al, 1996). The results were inconsistent. For example, in Lyon and Athens an interaction between particulates and SO_2 was

found, with respiratory mortality relative risks being higher when particulates were higher. In contrast, in Cologne, where SO_2 was highly correlated with PM_7 and TSP, the effects for SO_2 were stronger at a lower level of particulates. A synergistic effect of pollutants was not found in the Netherlands, Milan or Valencia. Dockery and Pope (1997) tabulate the results from several studies which have examined the effect of confounding by various co-pollutants on risk for particulates. In most there was some reduction in the effect estimates for particulates, although a positive association was found even after adjustment for each of the co-pollutants. In the study reporting respiratory admissions in London, co-pollutants were only investigated in association with O_3, as this was not strongly correlated with other pollutants. The inclusion of either SO_2 or BS hardly affected the magnitude and precision of the estimated O_3 effect, but the estimated effect for the second pollutant increased over that for the second single pollutant model. O_3 is known to bind with SO_2 to give ‘acid particles’, which were not measured.

4. COMBINED ANALYSES

4.1. META-ANALYSIS - GENERAL ISSUES

The third objective of the APHEA project (see section 3.1) was to 'select and develop a meta-analytical approach for epidemiological time series studies'. Meta-analysis has come to refer to the integration of results from several independent studies. It is an approach which has been particularly successful in the area of clinical trials, which because of their 'experimental' nature can be expected to be reasonably uniform in design and execution. The use of meta-analysis in observational studies is more controversial but Greenland (1994) suggests that the technique should be used as an aid for comparing studies and identifying patterns among study results. He agrees with critics, however, that there are problems if heterogeneity is ignored and only single fixed-effects summaries are reported.

Many meta-analyses are carried out on previously reported studies and depend on (i) a systematic literature search to ascertain all studies, both published and unpublished, (ii) inclusion and exclusion criteria, (iii) extraction of study specific data on health outcomes, exposure and other variables. Problems can include the possibility of bias, (e.g., in study selection and publication), study heterogeneity, (e.g., different protocols, varying outcomes and data quality), and incomplete access to the databases of individual studies.

The APHEA project is an example of a prospective meta-analysis which, with careful procedural methodology, enables many of the above sources of bias to be eliminated. However, it is still important to ensure assessment of any heterogeneity, i.e. systematic variation in individual effect estimates, that may be present. Potential areas of concern in the APHEA project included variations in the sources of exposure and pollution mixtures, imprecision in the exposure estimates, and the nature of the weather patterns between each country. Differences due to such factors as geographical location, population structure, and socioeconomic and cultural patterns were not explored in the APHEA project.

Models for combining study estimates include:

(i) fixed effects models

The assumption is made that all the studies estimate the same underlying effect, i.e. the true relative risk is constant across all studies. This model assumes no heterogeneity between the study results which are to be combined. An overall average of the observed effects is obtained by weighting each individual result by some measure of its precision i.e. the weights are inversely proportional to the variance.

(ii) random effects model

In this model, both a between study and within study variance are acknowledged. The studies are regarded as a sample drawn from a wider population of studies, each estimating different underlying effect sizes i.e. varying at random. This involves the assumption of a specific statistical distribution of effects. The random effects model acknowledges the possibility of heterogeneity.

Confidence intervals estimated in the random effects model will be wider than those from a fixed effects assumption.

A common approach to meta-analysis, adopted in the first of the APHEA combined analyses described below, is to first use a fixed effects model and assess heterogeneity. If significant heterogeneity is found then a random effects model is used to assess the robustness of the initial conclusions.

4.2. COMBINED ANALYSIS OF THE EFFECTS OF SO_2 AND PARTICULATES ON MORTALITY (Katsouyanni et al, 1997)

Katsouyanni et al used the data from twelve cities to give a combined estimate for mortality from all causes of death from exposure to SO_2, BS and particulates (converted to PM_{10} where necessary). A fixed effects model was first used to calculate a summary estimate from the weighted means of the regression coefficients, with weights inversely proportional to local variances. All available coefficients were used in the analysis. The authors do not give the individual relative risks for each city nor any detail of the models from which these were taken and how they differed, for example, in transformations and lag times used or explanatory factors included. Homogeneity of the coefficients was tested and if significant heterogeneity was found its determinants were investigated using a predefined list of explanatory variables. The authors do not say how these variables were selected, nor how the cut off points were determined for the categorical variables. Overall, an increase of 50 $\mu g/m^3$ in the one day pollutant levels was associated with a relative risk of 1.02 (95% CI 1.015-1.024) for SO_2 , 1.01 for BS (95% CI 1.009-1.017), and 1.02 (95% CI 1.013-1.031) for PM_{10}. Significant heterogeneity was found for the effects of SO_2 and BS. Only an explanatory variable categorising the cities into western and eastern gave more homogeneous subgroups, although significant heterogeneity remained for SO_2. The relative risks associated with an increase of 50 µg/m3 in western cities were 1.03 for SO_2, 1.03 for BS and 1.02 for PM_{10}, with the corresponding figures for eastern cities being 1.01, 1.01, and 1.04 (only one eastern city, Bratislava measured PM_{10}) respectively. When SO_2 was fitted together with either BS or PM_{10} the relative risks for both pollutants decreased slightly. The effects of all three pollutants were stronger in the summer. There was no synergistic effect of SO_2, with the other pollutants with the effects being similar for days with low and high levels of the other pollutant. An additional analysis, including estimates from five additional European cities (Ballester et al, 1996; Verhoeff et al, 1996; Wietlisbach et al, 1996) gave similar results, with relative risks associated with 50 $\mu g/m^3$ change of SO_2, BS and PM_{10} being 1.028, 1.03 and 1.025 respectively.

The authors suggest that differences between the eastern and western cities may have been because the pollution measurements were unrepresentative of the population exposure, differences existed in the health of the population, for example, different proportions of susceptible groups, cities had a different pollutant toxicity or mix, or the control for season may be less successful in eastern cities if there is a more variable rate of illness. A letter to the journal (Bobak et al, 1997) following this paper, however, showed a positive relation between the relative risk of death in the twelve cities and average winter temperature, with risks rising from eastern European cities through western cities to southern cities having the highest relative risks and temperatures. The authors speculate that there may be an interaction between air pollution and climate, i.e. an identical increase in air pollution may not be equally harmful in different climatic conditions, ambient concentrations may reflect personal exposures more closely in warmer cities or there may be residual confounding by climatic factors. The APHEA study found that daily concentrations of SO_2 and particulates are lower in warmer weather. The slope of association between low temperatures and mortality is steeper in places with warmer winters, maybe because of inadequate protection against the cold. This may

lead to stronger residual confounding in warmer cities, hence higher estimates of pollution effects. It may be important to include other aspects of climate such as daily minima in models to take account of this.

4.3. COMBINED ANALYSIS OF OXIDANT EXPOSURE ON MORTALITY (Touloumi et al, 1997)

The same statistical methodology was used to combine the results relating to exposure to NO_2 and O_3 with mortality. Only six cities in the APHEA project contributed to this analysis, namely Athens, Barcelona, Cologne, London, Lyon and Paris, and the results for Athens have not been published separately. In all cities, except Athens and Barcelona, deaths from external causes were excluded from the total daily numbers of deaths. External causes contribute 4-5% of total deaths. For inclusion in the meta-analyses, additional analyses were carried out where necessary, for the separate cities restricting pollution data to days with concentrations less than 200 $\mu g/m^3$ and using linear pollution terms. For the meta-analyses of the main effects of NO_2 and O_3 on total daily mortality the paper states that four additional cities, Amsterdam (Verhoeff et al, 1996), Basel, Geneva and Zurich (Wietlisbach et al, 1996) contributed data, their reported regression coefficients being based on comparable statistical analyses. The individual results, neither numerical nor graphical, for these four cities are not presented in this paper and only the APHEA cities are referred to. It is thus not possible to assess the influence of these four cities on the combined estimates.

All risk estimates from the six APHEA studies for NO_2 were positive, although only three just reached statistical significance (Athens, Barcelona and Paris). The test for heterogeneity was non-significant. The pooled relative risk for NO_2 was 1.01 (95% CI 1.009-1.018) using the 1-hour maximum value and 1.02 (95% CI 1.017-1026) using cumulative NO_2. Significant adverse effects of O_3 on total daily mortality were found for all four APHEA cities for which data were available, with London having the largest effect. The pooled relative risk for 1-hour maximum O_3 was 1.02 (95% CI 1.014-1.033) and for cumulative O_3 was 1.023 (95% CI 1.012-1.037). Due to the extreme estimate in London heterogeneity was significant. The random effects estimate for 1-hour maximum O_3 was slightly higher, 1.029, but its 95% confidence interval was wide, 1.010-1.049. Relative risks were slightly higher during the warm season but not significantly so. There was a tendency for there to be larger effects of NO_2, but not O_3, in cities with higher levels of BS. The inclusion of BS in a model with NO_2 substantially reduced the risk estimate for NO_2, although this remained significant. The authors suggest that NO_2 may act as a proxy variable for particulates, and that the issue of independent effects of NO_2 requires further investigation. A model including both BS and O_3 also reduced the risk estimate for O_3 but to a much lesser extent. Including both NO_2 and O_3 in the same model did not significantly change their risk estimates. The authors do not report the results of exploration of potential explanatory variables on the heterogeneity found for O_3.

4.4. COMBINED ANALYSIS OF AIR POLLUTION ON HOSPITAL ADMISSIONS OF RESPIRATORY DISEASE (Spix et al, 1998)

A pooled analysis was carried out using the results for five cities, Amsterdam, London, Milan, Paris and Rotterdam. In an attempt to standardise the statistical methodology utilised in the five cities, models were refitted, where necessary, to the original data using untransformed pollution values (rather than log-transformed) and omitting all days on which pollution levels exceeded 200 $\mu g/m^3$. The meta-analysis

thus focused on relatively low levels of exposure. A similar approach to the analysis was used as in the studies reported in 4.2 and 4.3. An iterative maximum likelihood approach was used to estimate the between cities variance for use in any random effects models. When heterogeneity was present and coefficients from at least five cities were available, weighted linear regressions were carried out on city specific coefficients of non-time dependent factors. These included indicators of general population health status, climate, health and pollution data quality and air pollution situation.

Table 8, combined from the two tables in the paper, summarises the results for all the pollutants considered, separately for age groups 15-64 years and 65 years and over, and for warm and cold seasons. The authors state that heterogeneity was often significant and that a random effects model was therefore necessary. However, they do not indicate in the tables from which model the relative risks were obtained, although this can sometimes be obtained from the text. Heterogeneity between cities for SO_2 was explained either by the number of stations measuring SO_2 or mean winter temperature or by the mean life expectancy. Amsterdam and Rotterdam had only one measuring station, the lowest mean winter temperature and the highest life expectancy, and no adverse effect of SO_2 could be detected. Results were homogeneous for the elderly age group, and the pooled estimate was significant.

Most results for BS for the 15-64 age group were positive and the pooled estimate was significant. The pooled estimate for the elderly was non significant for BS as were the results for TSP for both age groups. There was no effect of an association with NO_2 in either age group. Most of the cities found a positive effect with O_3, particularly in London. The pooled estimates were all significantly positive, especially in the elderly. The commonest lag was with the same or previous day.

Random effects models were required for almost all the by-season models. Only one seasonal difference was significant (not specified in the paper), but effects were generally slightly higher in the warm season for the elderly age group, particularly for O_3. In the 15-64 age group there was an indication that the effect of SO_2 might be higher at higher levels of particles, but there were no differences in the effect of BS at different levels of SO_2. There was a significant difference, especially for the 15-64 age group, in the effect of BS by level of NO_2 on the same day, being stronger when NO_2 levels were higher. However, there were no differences in the effect of NO_2 by different same-day levels of either BS or O_3.

The authors discuss the problem of data comparability between cities. In Paris and Milan it was not possible to distinguish between emergency and non-emergency admissions. Examination of the data from London revealed that the majority of the admissions for the elderly age group were emergencies, whereas only 50-70% of the admissions in the 15-64 age group were emergency admissions. This might have influenced some of the differences found between the two age groups. The authors also draw attention to the problems of combining data on particles when different measurements methods were used between cities. The authors do not appear to believe that the differences in risk estimates between seasons can be explained by the existence of a threshold. They suggest that the dependence of the BS effect on NO_2 levels might indicate different effects of particles by source of emission or composition of the particles.

4.5. COMBINED ANALYSIS OF URBAN AIR POLLUTION ON EMERGENCY ADMISSIONS FOR ASTHMA (Sunyer et al, 1997)

Data from four cities, Barcelona, Helsinki, London and Paris, were combined. The health outcome data were not strictly the same for all cities, being emergency room visits in Barcelona, emergency hospital admissions in Helsinki and London, and total admissions in Paris. Completeness of diagnosis was over 90% in all cities except London, where it rose from 73% to 95% during the 4 years of the study period. To simplify the meta-analysis each centre fitted a linear relationship between the pollutant and asthma admissions for days below 200 $\mu g/m^3$. Separate regressions were fitted for the whole period, for the 'cold' season (October to March) and for the 'warm' period (April to September). As in all the APHEA analyses, the most sensitive lag time for each centre was fitted i.e. these could differ between cities. This was justified as being necessary because the lag time could be influenced by local factors, such as wind direction, size of the city or location of the monitoring sites (Katsouyanni et al, 1996). The same type of analysis was carried out as in the previous meta-analyses, i.e. using a fixed effects model, testing for heterogeneity, and the fitting a random effects model if appropriate. Only O_3 required a random effects model.

Table 9 gives the results for each city and the combined estimate for adults aged 15-64 years of age and children aged under 15 years (combined from two tables in the paper). The elderly, aged 65 or more years, were not considered in this paper. For adults, admissions were positively associated with BS, NO_2 and O_3, but of the combined estimates only those for NO_2 were significant. The relative risks for BS were positive for all cities but not significant. An analysis for BS, restricting to a 0 lag in all cities, gave a similar combined estimate, but the result restricting to lag 1 was lower (RR= 1.007, 95%CI 0.972-1.045). For NO_2 the association was consistently greater at greater time exposures. The results for O_3 in London and Barcelona were statistically significant. The patterns for Helsinki were rather different from the other cities although not significantly so. Neither NO_2 nor SO_2 showed any effect with season. Overall the association with BS was higher in winter, although this was not consistent among cities, being stronger in the warm season in Barcelona and in the cold season in London and Paris. There was no seasonal effect for O_3 in the combined analysis but the association was significantly higher during the warm season in London and lower in Barcelona and Paris.

In children positive associations were observed for SO_2, BS and NO_2, with several being significant. There was again an increasing risk for NO_2 as time exposures increased. The patterns in Helsinki were again somewhat different. There was no variation in results by season for SO_2 or O_3. The association with BS and NO_2 was higher in the winter. Adjustment for particles increased the association for NO_2 in adults relative to the model with a single pollutant. Similar results were found for the association with SO_2 levels in children. Adjustment for NO_2 for BS or SO_2 in children increased the association with NO_2 and decreased the association with BS or SO_2 in London, with the opposite pattern being found in Paris.

The authors discuss the difficulties in identifying the separate roles of each pollutant. They suggest that a single pollutant could act as a marker of a pollution mixture. For example, NO_2 could be a marker of other pollutants generated by vehicle exhausts such as particles. There is often collinearity among pollutants, i.e. high correlations between them. They suggest that further research is required on exposure mixtures including NO_2, SO_2 and particles in volunteers in ambient air and in the laboratory although the latter might be difficult to implement. The authors consider that potential confounding by pollen, which was not measured, is unlikely as the

association when NO_2 occurred more strongly in the winter, when pollen levels are low. They also consider that indoor air pollution is unlikely to confound their findings as 'day to day variations in indoor emissions are not correlated with outdoor pollution'. However, Vahlberg and Watson (1996) suggest that varying levels of outdoor air pollutants, for example, particulates, may be correlated to conditions that directly modify morbidity and mortality rates i.e. the same factors that causes fluctuations in air pollution may also signal changes in physiologic factors, such as stress, and exposures, such as to indoor air, which may be causally linked to morbidity and mortality. They suggest that weather fluctuations leading to cold or heat stress may result in an increasing fraction of time spent indoors, (particularly important for those residing with smokers) and the increased use of climate-control systems at times of inclement weather which can generate increased indoor levels of potentially toxic airborne particles. Weather stress tends also to increase air pollutants, such as particulates, through increased use of vehicles and increased demand for electric power.

4.6. COMBINED ANALYSIS OF AIR POLLUTION AND ADMISSIONS FOR COPD (Anderson et al, 1997)

Data from six cities, Amsterdam, Barcelona, London, Milan, Paris and Rotterdam, were combined, but only results from Amsterdam, Paris and Rotterdam have so far been published in separate papers. Emergency hospital admissions for bronchitis (chronic and unspecified), emphysema and chronic airways obstruction, comprising COPD, were used. All hospitals admitting medical emergencies were included in each city, except Barcelona where six hospitals, covering 90% of emergencies, were used. In Milan and Paris, emergency admissions could not be separated from total admissions but the authors suggest, that based on an analysis of the London data, the proportion of planned admissions were likely to be about 5%. A similar procedure for the analysis was carried out as in the combined analysis for asthma (see 4.5), in that each centre fitted a linear relationship between pollutant and COPD for days below 200 $\mu g/m^3$, and coefficients were estimated separately for cold and warm seasons. The procedure for estimating the summary effects was also the same.

The cities varied considerably in size, environmental characteristics and daily number of COPD admissions (1 to 20). **Table 10**, reproduced from the paper, summarises the combined estimates associated with a 50 $\mu g/m^3$ increase in each pollutant. The relative risks for the separate cities are represented graphically in the paper and the actual figures are not given. The risk estimates for SO_2 vary, with two below 1 and four above, and the respective lags also vary, but the summary estimates for cumulative SO_2 are significant. Heterogeneity was largely caused by the data from the two cities in the Netherlands, with this being associated with the use of only one monitoring station compared with three or more in other cities, and relatively low temperatures.

Estimates for BS were more consistent across cities, with summary estimates being significant. Similarly, results for NO_2 tended to be consistent across cities (with the exception of Amsterdam for which the relative risk was below 1), and three of the four summary estimates were significant. All the city specific relative risks associated with O_3 were greater than 1 and all summary estimates were statistically significant. Lags for particles and NO_2 varied from 0 to 2 days, and all but one city (Rotterdam) had either a 0 or 1 day lag for O_3. In the warm season, significant or borderline significant effects were found for SO_2, NO_2 and O_3, with marginally significant effects for BS and O_3 in the cold season. Only O_3 showed a significant

effect between warm and cold seasons, with a much stronger effect in the warm season. A meta-analysis was not carried out for 65+ age group as only three cities analysed this age group separately. However, effects of SO_2 were higher in this age group than all ages together for all three cities, with a similar effect for BS in two of the cities.

The authors draw attention to the fact that interpretation of the results of this meta-analysis needs to take into account that each centre selected the lag which gave the greatest effect rather than *a priori*. They also point out that the diagnosis of COPD is known to vary between countries. This, together with the inclusion of a small proportion of non-emergency admissions, might lead to variation in the risk estimate depending on how misclassification affected the average sensitivity of the diagnostic group. Similar results have been found for emergency admissions for COPD associated with O_3 in studies in North America, particularly in the elderly (Burnett et al, 1995; Schwartz, 1994 (b); Schwartz, 1994 (c); Schwartz, 1993). The relative risks for particles in the APHEA study are considerably smaller than those in the American studies. The authors suggest that differences between the two continents may be explained by differences in the chemical nature and size of the particle mixture, and the composition of the pollution mixture as a whole.

4.7. ISSUES OF CONCERN IN THE META-ANALYSES

Section 3.8 drew attention to some of the potential problems relating to the quality of data in the sixteen cities. The differences highlighted between cities pertaining to the exposure data necessitate caution when comparing the results from the different cities and different study periods, and when combining the information in a meta-analysis. The acknowledgement of a potential lack of homogeneity is implicit in some of the meta-analyses, in the use of variables characterising pollution data quality, such as number of monitoring stations, inhabitants represented per station and correlation between stations, as explanatory variables in the random effects models. Some problems with homogeneity of the hospital admissions data was also experienced.

The summary relative risks were estimated by weighting the risks obtained from the best fitting models in individual cities. These models, although similar in structure, differed in the number of variables included, and the transformations and the lag times used for some of the time dependent variables, including the pollutants. As previously noted it is difficult to assess exactly how different the models were as they were not consistently reported in the papers. This has been addressed to some extent in several of the meta-analysis in the refitting of models with the same transformation (or not) for the pollutant and in the asthma meta-analysis presenting summary estimates when the lag was restricted to zero. However, the appropriateness of carrying out a meta-analysis of estimates derived in this way must be questioned.

The five meta-analyses followed the same procedure. Firstly a fixed effects model was fitted to provide an overall estimate, and a test of heterogeneity was carried out. If heterogeneity was significant a random effects model was then fitted, with explanatory variables. The justification for the choice of variables and how the cut offs for the categorical variables were chosen is not discussed in the papers and few of the results are presented.

The test used for heterogeneity is of relatively low power, so a non-significant result does not necessarily mean that the individual results are homogeneous. The results from the APHEA studies and from studies in the USA and elsewhere do not give a completely consistent relationship between air pollution and adverse health outcomes, and there is quite a lot of variation in both magnitude and direction of risk estimates and predominance of the different pollutants. For example, SO_2 seem to be of more importance in Europe than in the USA, where particulates seem more dominant. An appropriate approach to a meta-analysis would therefore be to fit a random effects model with relevant covariates. However, given that the emphasis in the APHEA project is on collaboration, and all cities appear to have adhered to the protocol, an obvious approach would be to carry out a reanalysis of the combined data sets using the raw data. Lag times, transformations and weights could be fitted appropriately and variables and interaction terms characterising the individual centres could also be fitted. In addition it would be interesting to carry out an appropriate meta-analysis for diseases of the digestive system which, although chosen as a control disease group, showed very similar patterns to the other diseases.

5. CONCLUSIONS AND FUTURE RESEARCH

The APHEA project has made a major contribution to research into the potential effects of air pollution on health, through adoption of systematic and standardised procedures for data management and analysis of data from several European cities.

A fairly consistent, though small, increase in the relative risk was shown in the results from the individual cities and from the combined analyses for several air pollutants and health outcomes. The strongest effect for total mortality was found for SO_2, with particulates, mainly measured as BS, showing a slightly weaker association. The relative risks from the combined analyses for both these pollutants were significantly raised. Fewer cities analysed total mortality in relation to exposure to NO_2 and O_3 but consistently elevated relative risks were found for both pollutants, and the estimates from the combined analyses were statistically significant. The results for respiratory disease and cardiovascular disease mortality were less consistent with a wider variation in risk estimates between cities and few estimates being significantly elevated.

SO_2 was associated with increased risk of hospital admissions for respiratory disease, particularly in the elderly (aged 65 and over). In contrast, BS was associated with increased admissions in the 15-64 age group. Results for NO_2 and respiratory disease admissions were inconsistent. A significantly positive association was found in London with O_3, and other cities also showed a positive tendency. The combined estimate was significantly raised for all O_3 indicators, and both age groups, but larger in the elderly.

A lack of association of air pollution with cardiovascular deaths was shown in London, although significantly elevated risks for hospital admissions for myocardial infarction were found for SO_2, NO_2, CO and BS in the same city. Interestingly the pattern of results for digestive diseases chosen as a control group was similar to that of the other diseases, although relative risks tended to be lower.

NO_2 was significantly associated with increased emergency hospital admissions for asthma in both children under the age of 15 years and adults aged from 15-64 years, and risk increased as time exposures increased. There was also a consistently significantly raised risk associated with exposure to SO_2 on asthma admissions in children. Daily emergency admissions for COPD, available from six cities, were significantly associated with all pollutants using the combined estimates, with the strongest and most consistent effect being found for O_3.

The effects of temperature and season on the risk estimates varied between cities and by pollutant and health outcome. There was a tendency overall for the effects of several of the pollutants to be stronger in the summer months, but some cities showed no difference between seasons and Athens, for example, found an increased risk for total mortality in winter. Correlations between pollutants within cities and the extent to which synergy between pollutants existed also varied considerably, with some single study or combined estimates finding stronger effects for some pollutants in association with high levels of other pollutants, and others finding quite different relationships.

The results from the APHEA project support those found in many other studies of the adverse effects of air pollution. There was a tendency, however, for there to be a stronger association with SO_2, than studies, for example from the USA, and risk estimates for particles were generally lower than those obtained in the American studies.

Although a standardised approach was used for data management and statistical analysis the project was limited by the quality of some of the data, in particular the exposure information. There were variations in the numbers of monitors per geographical area and per population, the location of the monitors, the measurement and sampling techniques, the quality control procedures and the correlations between values from the monitors. Ecological studies such as this are also subject to a high degree of misclassification due to the use of ambient air exposure data as a surrogate for personal exposure.

There was no co-ordination in the reporting of the results in the published papers, and information which is important for the interpretation of the impact of the results was not consistently presented. For example, correlations between pollutants measured which can cause collinearity in the models, risk estimates for the covariates included in the models, an indication of the change in pollutant coefficients as variables were added to or removed from models and an indication of the fit of the models. Results for each city were also presented for the 'best fit' model, with varying choice of variables, lag times and transformations. Analyses in each city for the risks of different lags, together with a measure of the goodness of fit, would have facilitated both the interpretation of the potential lagged effects of pollutants on health and comparisons between cities. Variables which might have undergone change over the study periods and influenced both health and pollution were described for some cities but were not considered as variables for inclusion in the models. Other time-varying factors, such as pollen, which might influence respiratory diseases such as asthma , were not included in the analyses.

The meta-analyses were carried out following a standardised procedure combining the relative risks obtained from the models for the individual cities to give summary estimates. As pointed out above, the city specific models differed in their structure. There was also a lack of homogeneity in some of the data, particularly the air pollution data. Caution is therefore necessary when evaluating the summary estimates obtained from these meta-analyses.

Future work

The results from the APHEA project concur with many other studies in showing an association between air pollution and adverse health outcomes. However, they have also helped to emphasise the wide variation in both the magnitude and direction of the estimates and the predominant pollutants. Ecological study designs are limited in their inherent assumption that individual risk can be estimated using group data. Clarification of the relationship between levels of air pollution measured by outdoor, fixed-site monitoring, levels indoors and personal exposures is required and might also enable surrogate measures of personal exposure to be evaluated. The role of each pollutant, both as an individual risk factor and in its contribution to a synergistic effect, the importance of different sources and mixtures of pollution, the interrelationships of pollution and climate and the influence of microenvironments are all areas which require further research.

Problems associated with the comparison of data collected using different monitoring techniques have not been explored in detail in this critique, but should be considered when evaluating all studies of air pollution, including APHEA. The development of a European air pollution monitoring network, which uses the same method of sampling and analysis and is more evenly distributed by area and population is essential.

Considerable effort has been expended in the APHEA project on ensuring the standardisation of data collection. Although there are limitations in the data, it would be appropriate to carry out reanalyses of the combined data sets using the raw data from all the relevant centres, for the different pollutants and for all the health outcomes, including the control disease groups. Appropriate lag times, transformations and weights could be fitted and explanatory variables and interaction terms characterising the individual centres could also be included.

Spurious associations may be identified through an unobserved variable or by incomplete adjustment for confounding. Collinearity between pollutants may make it difficult to identify exactly which pollutant is important, as does incomplete knowledge about the time-exposure-response relationship. The regression coefficients obtained from the models used cannot be used to quantify the effect of pollution. A cohort study approach is needed to assess causality and also estimate the potential public health benefit of a reduction in pollution.

Table 1 Air Pollution measured in APHEA study

City	Monitoring Period	Population covered by data collection (x1000)	Main sources of Air Pollution	Pollutants Measured	Number of Monitors	Monitoring Method	Comment
Amsterdam	1977-89	69.5	Not given	SO_2	1	Gas-phase fluorescence	Monitor located in street with <2750 vehicles per 24 hours in circle of 35 metres around station. Represent city background concentrations. BS data only available 1986-89
				BS	1	OECD method	
				NO_2	1	Chemiluminescence	
				O_3	1	Chemiluminescence	
Athens	1987-91	3100	Vehicle exhaust	SO_2	3	Pulsed fluorescence	Not same 3 stations for each pollutant. Two of the stations used for BS closer together than those used for SO_2 and CO
				BS	3	OECD method	
				CO	3	Infrared, non-dispersive method	
Barcelona	1985-91	1700	Vehicle exhaust	SO_2	3	Fluorescence	Manual samplers used for BS. Data for 1985 not used for SO_2, NO_2 and O_3 because of quality problems at the start of automatic sampling.
				BS	7	OECD method	
				NO_2	3	Chemiluminescence	
				O_3	3	Chemiluminescence	

Table 1 *continued*

City	Monitoring Period	Population covered by data collection (x1000)	Main sources of Air Pollution	Pollutants Measured	Number of Monitors	Monitoring Method	Comment
Bratislava	1987-91	443	Chemical industry, Oil refinery	SO_2	4	Not given	Automated monitoring systems introduced in 1991. Only mean daily concentrations available pre 1991. 4 out of 9 stations selected so that they had the highest concentration and % missing data did not exceed 15%.
				TSP	4	Not given	
Cologne	1975-85	977	Chemical industry, vehicle exhaust	SO_2	5	4 fluorescence 1 conductometric device	Measurements of SO_2 taken every 30 minutes. Continuous measurements of TSP not available . Samples taken on Tuesday, Thursday and Saturday. 2 stations inner city, 3 in suburbs.
				TSP	5	Semiautomated gravimetric method	
				PM_7	1	Daily means at Dusseldorf. Every eight day missing for calibration	
				NO_2	2	Chemiluminescence	
Cracow	1977-89	740	Industry, coal fired power plants and domestic heating	SO_2	3	Titration with Sodium tetraborate after absorption in hydrogen peroxide	Manually operated units. No system of quality control. About 60% of emitted dust is ashes. SO_2 contributes 10% of gaseous pollutants and 25% metallurgic dust.
				BS	3	Reflectometric method	

Table 1 *continued*

City	Monitoring Period	Population covered by data collection (x1000)	Main sources of Air Pollution	Pollutants Measured	Number of Monitors	Monitoring Method	Comment
Helsinki	1987-89	491	Coal and oil fired power plants, industry, road traffic	SO_2	4	Coulometric automatic instruments	Calibration monthly for SO_2 and NO_2 biomonthly for O_3. TSP samples collected every 2nd day at 4 stations and every 3rd day at 2 stations. 4 stations in town centre, 4 in suburbs.
				NO_2	2	Chemiluminescence	
				O_3	1	Ultraviolet absorption	
				TSP	6	High volume samplers	
Lodz	1977-90	848	Industry, coal fired power plants and domestic heating	SO_2	3	Colorometric method with p-rosaniline	Manually operated units. No system of quality control. About 90% of emitted dust is ashes. SO_2 contributes 85% of gaseous pollutants.
				BS	3	Reflectometric method	
London	1987-92	7300	Motor vehicles, power generation industry	SO_2	4	Acidimetric bubbler system	O_3 monitor near Victoria Station. NO_2 at Victoria and Earls Court BS and SO_2 at 4 more scattered sites.
				BS	4	Smoke stain method	
				NO_2	2	Chemiluminescence	
				O_3	1	Ultraviolet absorption	
				CO	1	Gas filter correlation	
Lyon	1985-90	410	Chemical industry	SO_2	5	Ultraviolet fluorescence	Stations chosen to represent background levels. O_3 monitor in urban centre of Lyon.
				NO_2	1	Chemiluminescence	
				O_3	1	Ultraviolet absorption	
				PM_{13}	3	β-ray atomic absorption	

Table 1 *continued*

City	Monitoring Period	Population covered by data collection (x1000)	Main sources of Air Pollution	Pollutants Measured	Number of Monitors	Monitoring Method	Comment
Milan	1980-89	1500	Not given but industry transferred outside city and half residents heating converted to gas from solid fuel during study period and legislation passed requiring use of low sulphur fuel	SO_2	4	Coulometric method	Study areas included central urban area. Most industries are north of the city. 4 monitors for SO_2 in different quadrants of the city.
				TSP	2	β Attenuation method	
Paris	1987-92	6140	Not given specifically but "heavily polluted"	BS	15	Reflectrometric technique	Includes Paris and inner suburbs. Stations linked to computer – gives data every 15 minutes. Calibrated every 2 weeks.
				SO_2	4	Ultraviolet fluoresence	
				NO_2	4	Chemiluminescence	
				O_3	4	Ultraviolet absorption	
				PM_{13}	4	Radiometry	
Poznan	1983-90	575	Industry, coal fired power plants and domestic heating	SO_2	3	Colorometric method with p-rosaniline	Manually operated units. No system of quality control. About 90% of ashes. SO_2 contributes emitted dust is 60% of gaseous pollutants.
				BS	3	Reflectometric method	
Rotterdam	1977-1989	576	Not given	SO_2	1	Gas-phase fluorescence	Same as Amsterdam. Monitor located in street with <2750 vehicles per 24 hours in circle of 35 metres around station. Represent city background concentrations. BS data only available 1986-89.
				BS	1	OECD method	
				NO_2	1	Chemiluminescence	
				O_3	1	Chemiluminescence	

Table 1 *continued*

City	Monitoring Period	Population covered by data collection (x1000)	Main sources of Air Pollution	Pollutants Measured	Number of Monitors	Monitoring Method	Comment
Valencia	1991-93	750	Motor Vehicles	BS	3	Reflectometry	"Weekly" stations used ie sequenced samples collected for up to 8 days at a time. Monitors located in urban area.
Wroclaw	1979-89	637	Industry, coal fired power plants and domestic heating	SO_2	3	Colorometric method with p-rosaniline	Manually operated units. No system of quality control. About 90% of emitted dust is ashes. SO_2 contributes 60% of gaseous pollutants.
				BS	3	Reflectometric method	

Table 2 General Levels of Pollution (mean µg/m^3) in Participating Cities during the study periods for each city

Pollutant	Sulphur Dioxide (24 hour)	Nitrogen Dioxide (24 hour)	Ozone (24 hour)	Carbon Monoxide (8 hour)	Black Smoke (8 hour)	PM_7 (24 hour)	PM_{13} (24 hour)	TST (24 hour)
City								
Amsterdam	28	50	69	-	11	-	-	-
Athens	51	-	-	7	84	-	-	-
Barcelona[b]	46[a]	88[a]	55[a]	-	50[a]	-	-	-
Bratislava	24	-	-	-	-	-	-	89
Cologne	44[a]	45[a]	-	-	-	34	-	68
Cracow	74[a]	-	-	-	73[a]	-	-	-
Helsinki	19	39	22	-	-	-	-	77
Lodz	46[a]	-	-	-	57[a]	-	-	-
London	31[a]	35[a]	14[a]	-	13[a]	-	-	-
Lyon	47	70	10	-	-	-	38	-
Milan	118[c]	-	-	-	-	-	-	139
Paris	30	45	28	-	32	-	51	-
Poznan	41[a]	-	-	-	34[a]	-	-	-
Rotterdam	40	54	64	-	26	-	-	-
Valencia	40	-	-	-	68	-	-	-
Wroclaw	29[a]	-	-	-	54[a]	-	-	-

[a] Median

[b] Figures for Barcelona are for winter. Summer medians 35.36.97, 87 respectively. O_3 maximum daily value per hour

[c] The median for Milan was 66 indicating some very extreme values

Figures taken from the publications for individual cities, rounded to whole numbers

Table 3 Health Effects Investigated in the 16 cities

City	Health Endpoint	Disease Group	Age Group
Amsterdam	Emergency hospital admissions	Respiratory disease	15-64, 65+
		Chronic obstructive pulmonary disease	All
		Asthma	All
Athens	Mortality	All causes	All
Barcelona	Mortality	All causes	All, 70+
		Cardiovascular disease	All
		Respiratory disease	All
Bratislava	Mortality	All causes	All
		All causes minus external causes*	All
		Respiratory disease*	All
		Respiratory infections*	All
		Obstructive lung disease*	All
		Cardiovascular disease	All
		Ischaemic heart disease*	All
		Lung cancer*	All
		Digestive system disease	All
Cologne	Mortality	All causes	All
Cracow	Mortality	All causes minus external causes	All
		Circulatory system diseases	All
		Respiratory disease	All
		Digestive system disease	All

Table 3 *continued*

City	Health Endpoint	Disease Group	Age Group
Helsinki	Emergency hospital admissions	Asthma	0-14
			15-64
			65+
		Digestive system disease	All
Lodz	Mortality	All causes minus external causes	All
		Circulatory system disease	All
		Respiratory disease	All
		Digestive system disease	All
London	Mortality	All causes minus external causes	All
		Respiratory disease	All
		Circulatory system disease	All
	Emergency hospital admissions	Respiratory disease	0-14
			15-64
			65+
		Circulatory system disease	All
Lyon	Mortality	All causes minus external causes	All
		Cardiovascular disease	All
		Respiratory disease	All
		Digestive system disease	All

Table 3 *continued*

City	Health Endpoint	Disease Group	Age Group
Milan	Mortality	Respiratory disease	All
	General hospital admissions	Respiratory disease	15-64
			65+
Paris	Mortality	Respiratory disease	All
	General hospital admissions	Respiratory disease	All
		Chronic obstruction	All
		Pulmanory disease	All
		Asthma	All
Poznan	Mortality	All causes minus external causes	All
		Circulatory system disease	All
		Respiratory disease	All
		Digestive system disease	All
Rotterdam	Emergency hospital admissions	Respiratory disease	15-64, 65+
		Chronic obstructive pulmonary disease	All
		Asthma	All
Valencia	Mortality	All causes	All, 70+
		Circulatory system disease	All
		Respiratory disease	All
Wroclaw	Mortality	All causes minus external causes	All
		Circulatory system disease	All
		Respiratory disease	All
		Digestive system disease	All

* results not presented for these diseases

Table 4 Summary of Relative Risks per each 100 μg/m^3 increase in pollutant and 95% Confidence Intervals, and Lag Time for All Cause Mortality by Pollutant (figures as published)

City	Pollutant			
	Sulphur Dioxide (24 hour)	Nitrogen Dioxide (24 hour)	Ozone (8 hour)	Carbon Monoxide (maximum 8 hour)
Athens	1.12 (1.07, 1.16) [1]	-	-	1.10[a] (1.05, 1.15) [0]
Barcelona	1.127 (1.068, 1.189) [1]	1.034 (1.013, 1.055) [1]	1.048 (1.012, 1.086) [0]	-
Bratislava[e]	0.978 (0.96, 0.99)	-	-	-
Cologne[c]	1.03 (1.007, 1.052) [1]	1.01 (0.988, 1.035) [1]	-	-
Cracow[b]	1.026 (1.007, 1.044) [1]	-	-	-
Lodz[b]	1.022 (1.005, 1.038) [2]	-	-	-
London[c]	1.0095 (0.9999, 1.0191) [1]	1.0075 (0.9992, 1.0160) [1]	1.0243 (1.0111, 1.0376) [0]	-
Lyon[g]	1.06 (1.02, 1.09) [0]	1.02 (0.98, 1.06) [1]	1.03 (0.95, 1.12) [0]	-
Poznan[b]	1.007 (0.996, 1.019) [1]	-	-	-
Valencia[f]	1.0007 (0.9999, 1.0015) [2]	-	-	-
Wroclaw[b]	0.989 (0.980, 0.999) [2]	-	-	-

Table 4 *continued*

City	Particulates		
	Black Smoke (24 hour)	PM_7 (24 hour)	PM_{13} (24 hour)	Total Suspended Particles (24 hour)
Athens	1.05 (1.03, 1.08) [1]	-	-	-
Barcelona	1.070 (1.029, 1.112) [1]	-	-	-
Bratislava[e]	-	-	-	1.008 (0.96, 1.04)
Cologne[c]	-	1.02[d] [1]	-	1.02[d] [1]
Cracow[b]	1.018 (1.001, 1.036) [2]	-	-	-
Lodz[b]	1.018 (1.003, 1.032) [3]	-	-	-
London[c]	1.0170 (1.0082, 1.0258) [1]	-	-	-
Lyon[g]	-	-	1.01 (0.97, 1.05) [0]	-
Poznan[b]	1.009 (0.993, 1.024) [0]	-	-	-
Valencia[f]	1.0009 (1.0003, 1.0015) [3]	-	-	-
Wroclaw[b]	1.006 (0.986 1.026) [1]	-	-	-

[a] per 10 $\mu g/m^3$ increase
[b] Relative risks not given in paper. Calculated by taking exponential or regression estimate and 95% confidence intervals. Associated with two fold increase in daily concentration.
[c] 95^{th} centile compared with 5^{th} centile, at least 20 $\mu g/m^3$
[d] 95% confidence intervals not given in papers, coefficients and standard errors for daily mean log. PM_7 significant at 10% level.
[e] lag not specified but probably 0
[f] per 1 $\mu g/m^3$
[g] per 50 $\mu g/m^3$ increase

Table 5 Summary of Relative Risks per each 100 μg/m^3 Increase in Pollutant and 95% Confidence Intervals for Respiratory, Cardiovascular and Digestive Mortality, for Sulphur Dioxide and Particulates

	RESPIRATORY DISEASE		CARDIOVASCULAR DISEASE		DIGESTIVE SYSTEM DISEASE	
	Sulphur Dioxide	Particulates (24 hour)	Sulphur Dioxide (24 hour)	Particulates (24 hour)	Sulphur Dioxide (24 hour)	Particulates (24 hour)
City						
Barcelona[a]	1.128(0.991, 1.281)[0]	1.097(0.990, 1.215) [3]	1.145(1.063, 1.232)[1]	1.093(1.036, 1.153)[1]	-	-
Bratislava[be]	-	-	0.986(0.94, 1.00)	0.989 (0.93, 1.02)	1.035 (1.01, 1.05)	0.999 (0.95, 1.01)
Cracow[af]	0.966(0.883, 1.057)[1]	0.985(0.906, 1.071)[1]	1.039(1.013, 1.066) [0]	1.011(0.986, 1.035)[0]	1.050 (0.965, 1.142)[1]	1.087 (1.012, 1.167)[1]
Lodz[af]	0.988(0.919, 1.061)[1]	0.953(0.897, 1.012)[1]	1.020(0.999, 1.041) [2]	1.007(0.989, 1.026)[2]	0.991 (0.925, 1.062)[1]	0.976(0.920, 1.036)[1]
London[a]	1.0168(0.9869, 1.0476)[1]	1.0066(0.9838, 1.0299)[1]	1.0022(0.9865, 1.0181)[1]	1.0058(0.9932, 1.0185)[1]	-	-
Lyon[cg]	1.05(1.02, 1.09)[3]	1.04(1.00, 1.09)[0]	1.08(1.03, 1.12)[0-3]	1.04(0.99, 1.10)[2]	0.98 (0.85, 1.13)[0]	1.51(0.27, 8.50)[0]
Milan[b]	1.12(1.03, 1.23)[0]	1.12(1.02, 1.23)[0]	-	-	-	-
Paris[a]	1.082(0.970, 1.206)[1]	1.071[d](0.975, 1.177)[1]	-	-	-	-
Poznan[af]	0.975(0.932, 1.019)[2]	0.967(0.910, 1.028)[0]	0.998(0.983, 1.012)[0]	0.993(0.974, 1.013)[2]	1.030 (0.970, 1.093)[1]	1.072(0.991, 1.161)[1]
Valencia[ah]	0.9971(0.9937, 1.0006)[2]	0.9993(0.9975, 1.0010)[1]	1.0012(0.9995, 1.0025)[2]	1.0012(1.0003, 1.0022)[4]	-	-
Wroclaw[af]	1.024(0.980, 1.070)[0]	0.902(0.829, 0.982)[1]	0.987(0.974, 0.999)[2]	1.007(0.981, 1.034)[1]	0.988 (0.946, 1.032)[2]	0.990(0.907, 1.081)[1]

[a] BS
[b] TSP
[c] PM_{10}
[d] BS, RR for PM_{13} 1.17, 95% confidence interval (1.04, 1.31)
[e] lag not given
[f] relative risks not given in paper, calculated by taking exponential of regression estimates and 95% confidence intervals. Associated with twofold increase in daily concentration.
[g] per 50μg/m^3 increase
[h] per 1μg/m^3 increase

Table 6 Summary of Relative Risks and 95% Confidence Intervals for Emergency Hospital Admissions (Figures as published)

			Respiratory Disease			
City	Age		Sulphur Dioxide (daily mean)	Nitrogen Dioxide (daily mean)	Ozone (8 hour)	Particulates
Amsterdam[a]	15-64		0.944(0.864, 1.032)[2]	0.890(0.783, 1.012)[1]	1.001(0.903, 1.111)[1]	0.869[c](0.579, 1.304)[2]
	65+		1.046(0.965, 1.134)[2]	1.023(0.907, 1.154)[2]	1.060(0.059, 1.172)[1]	1.081[c](0.757, 1.543)[2]
London[b]	0-14		1.0093(0.9837, 1.0356)[1]	1.0104(0.9943, 1.0267)[2]	1.0269(0.9995, 1.0551)[2]	0.9815[c](0.9641, 0.9993)[1]
	15-64		1.0223(0.9942, 1.0511)[1]	1.0113(0.9920, 1.0309)[1]	1.0536(1.0232, 1.0849)[1]	1.0166[c](0.9959, 1.0378)[2]
	65+		1.0221(0.9970, 1.0478)[2]	1.0216(1.0049, 1.0386)[2]	1.0455(1.0172, 1.0746)[1]	1.0114[c](0.9932, 1.0298)[2]
	All		1.0092(0.9926, 1.0261)[1]	1.0114(1.0006, 1.0222)[2]	1.0293(1.0113, 1.0477)[1]	0.9974[c](0.9958, 1.0091)[1]
Milan[ag]	15-64		1.05(1.00, 1.10)[0]	-	-	1.05[d](1.00, 1.10)[2]
	65+		1.04(1.00, 1.09)[0]	-	-	1.05[d](0.99, 1.10)[1]
Paris[ag]	All		1.042(1.005, 1.080)[0-2]	1.043(0.997, 1.090)[0]	1.024(0.975, 1.074)[0]	1.041[c](1.007, 1.075)[0]
						1.045[e](1.004, 1.087)[0]
Rotterdam[a]	15-64		0.941(0.855, 1.036)[1]	0.965(0.833, 1.118)[1]	0.998(0.888, 1.122)[0]	1.374[c](1.091, 1.730)[0]
	65+	1977-81	1.027(0.904, 1.165)[2]	1.342(0.998, 1.805)[0]	1.248(1.039, 1.499)[2]	-
		1982-84	1.087(0.890, 1.328)[0]	1.232(0.945, 1.606)[0]	0.927(0.745, 1.154)[1]	-
		1985-89	1.045(0.908, 1.204)[0]	1.172(0.990, 1.387)[0]	1.044(0.882, 1.235)[0]	0.969[a](0.787, 1.193)[2]

Table 6 Summary of Relative Risks and 95% Confidence Intervals from Studies Reporting Hospital Admissions

		Asthma			
City	Age	Sulphur Dioxide (daily mean)	Nitrogen Dioxide (daily mean)	Ozone (8 hour)	Particulates
Amsterdam[a]	All	0.802(0.696, 0.924)[1]	1.062(0.887, 1.271)[2]	1.090(0.934, 1.272)[1]	0.802[c](0.435, 1.478)[0]
Helsinki[af]	0-14	non significant	non significant	1.17(1.004, 1.371)[0]	non significant
	15-64	1.24(1.001, 1.543)[2]	non significant	non significant	non significant
	65+	1.27(1.051, 1.541)[2]	non significant	non significant	non significant
Paris[ag]	All	1.070(1.004, 1.141)[2]	1.175(1.059, 1.304)[0-1]	0.878(0.792, 0.974)[0]	1.043[c](0.975, 1.116)[0]
					0.975[e](0.902, 1.054)[2]

Table 6 Summary of Relative Risks and 95% Confidence Intervals from Studies Reporting Hospital Admissions

		Chronic Obstructive Airway Disease			
City	Age	Sulphur Dioxide (daily mean)	Nitrogen Dioxide (daily mean)	Ozone (8 hour maximum)	Particulates
Amsterdam[a]	All	0.907(0.814, 1.011)[0]	0.937(0.814, 1.079)[1]	1.039(0.924, 1.168)[0]	1.131[c](0.734, 1.744)[0]
Paris[ag]	All	1.099(1.023, 1.180)[0]	0.974(0.898, 1.058)[2]	1.121(0.991, 1.267)[0-1]	0.955[c](0.899, 1.026)[2] 0.954 (0.873, 1.043)[2]
Rotterdam[a]	All	0.963(0.874, 1.059)[2]	1.051(0.903, 1.223)[2]	1.039(0.921, 1.171)[2]	0.929[c](0.724, 1.192)[2]

a Relative risks are per 100µg/m^3
b Relative risks from 10th to 90th centile c Black Smoke
c Black Smoke
d TSP
e PM_{13}
f Only significant results reported. Relative risks and confidence intervals calculated from regression coefficients and standard errors. Assumed to be for 1µg/m^3 increase.
g All admissions included, ie emergency plus planned

Table 7 Poisson model results for significance of association of emergency admissions with previous day's air pollutant (% increase in admission/unit of pollutant, and relative risk for an increase in concentration from the 10^{th} to 90^{th} percentile (RR80)

	P Value	Admissions % / Unit	Relative risk (RR80) (95% CI)
Acute myocardial infarction ICD-9 410:			
O_3	0.2638	-0.07	0.9825 (0.9534 to 1.0142)
NO_2	0.0024*	0.09	1.0274 (1.0084 to 1.0479)
SO_2	0.0006*	0.17	1.0326 (1.0133 to 1.0511
CO	0.0010*	2.26	1.0275 (1.0096 to 1.0457)
Black Smoke	0.0033	0.19	1.0303 (1.0092 to 1.0528)
Angina pectoris ICD-9 413:			
O_3	0.4887	-0.06	0.9850 (0.9469 to 1.0256)
NO_2	0.0948	0.07	1.0212 (0.9950 to 1.0457)
SO_2	0.2291	0.07	1.0133 (0.9907 to 1.0383)
CO	0.2202	1.15	1.0140 (0.9904 to 1.0381)
Black Smoke	0.0220*	0.19	1.0303 (1.0030 to 1.0593)
Other ischaemic heart disease ICD-9 414:			
O_3	0.2230	-0.11	0.9726 (0.9270 to 1.0214)
NO_2	0.8019	-0.01	0.9970 (0.9667 to 1.0289)
SO_2	0.6495	-0.03	0.9944 (0.9651 to 1.0239)
CO	0.2676	-1.07	0.9870 (0.9588 to 1.0158)
Black Smoke	0.1074	-0.16	0.9752 (0.9418 to 1.0090)

Table 7 *continued*

	P Value	Admissions % / Unit	Relative risk (RR80) (95% CI)
Cardiac arrhythmia ICD-9 427:			
O_3	0.5562	0.06	1.0153 (0.9704 to 1.0598)
NO_2	0.0382*	0.09	1.0274 (1.0006 to 1.0984)
SO_2	0.2024	0.10	1.0181 (1.0000 to 1.0448)
CO	0.0755	0.16	1.0020 (0.9997 to 1.0043)
Black Smoke	0.0755	0.16	1.0254 (0.9958 to 1.0570)
Heart failure ICD-9 428:			
O_3	0.6708	-0.02	0.9940 (0.9604 to 1.0287)
NO_2	0.8311	-0.01	0.9970 (0.9769 to 1.0194)
SO_2	0.5194	0.03	1.0057 (0.9846 to 1.0258)
CO	0.2780	0.69	1.0084 (0.9885 to 1.0287)
Black Smoke	0.4463	0.05	1.0079 (0.9846 to 1.0309)
Cerebrovascular diseases ICD-9 430-8:			
O_3	0.3055	-0.06	0.9850 (0.9560 to 1.0127)
NO_2	0.1234	-0.05	0.9851 (0.9684 to 1.0045)
SO_2	0.9146	0.01	1.0019 (0.9837 to 1.0189)
CO	0.3667	-0.66	0.9920 (0.9735 to 1.0091)
Black Smoke	0.7972	-0.02	0.9969 (0.9772 to 1.0176)

Table 7 *continued*

	P Value	Admissions % / Unit	Relative risk (RR80) (95% CI)
Other circulatory disease:			
O_3	0.4496	-0.04	0.9900 (0.9614 to 1.0220)
NO_2	0.1763	0.06	1.0182 (1.0000 to 1.0398)
SO_2	0.0621	0.10	1.0190 (0.9994 to 1.0383)
CO	0.0040*	2.56	1.0313 (1.0126 to 1.0503)
Black Smoke	0.1130	0.10	1.0158 (0.9942 to 1.0386)
Combined circulatory diseases ICD-9 390-459:			
O_3	0.0686	-0.11	0.9726 (0.9436 to 1.0046)
NO_2	0.0034*	0.08	1.0243 (1.0054 to 1.0448)
SO_2	0.0031*	0.13	1.0248 (1.0062 to 1.0444)
CO	0.0012*	2.31	1.0281 (1.0100 to 1.0466)
Black Smoke	0.0083*	0.15	1.0238 (1.0028 to 1.0464)

* $P<0.05$

Table 8 Summary Effects of Pollutants on Daily Respiratory Admissions as Relative Risk (RR) per 50µg/m^3 Increase in Pollutant by age group and season - from Spix et al (Spix et al, 1998)

Pollutant	Cities	Age Group	Warm[c]		Cold[c]		All Year	
			RR	95%CI	RR	95%CI	RR	95%CI
SO_2 daily mean	L, A, R, P, M	15-64	1.01	(0.98, 1.04)	1.01	(0.97, 1.07)	1.009	(0.992, 1.025)
		65+	1.06[a]	(1.01, 1.11)	1.02	(0.99, 1.04)	1.020[a]	(1.005, 1.046)
BS daily mean	L, A, R, P	15-64	0.99	(0.90, 1.09)	1.04[a]	(1.02, 1.07)	1.028[a]	(1.006, 1.051)
		65+	1.07[a]	(1.00, 1.15)	1.00	(0.95, 1.04)	1.020	(0.996, 1.046)
TSP daily mean	A, R, M	15-64	1.03[b]	(1.00, 1.06)	0.97	(0.93, 1.02)	1.010	(0.989, 1.031)
		65+	1.01	(0.98, 1.04)	1.02[b]	(1.00, 1.05)	1.016	(0.994, 1.039)
NO_2 daily mean	L, A, R, P	15-64	1.00	(0.96, 1.04)	1.01	(0.98, 1.04)	1.010	(0.985, 1.036)
		65+	1.02	(0.99, 1.06)	1.00	(0.98, 1.03)	1.019	(0.982, 1.060)
NO_2 daily maximum		15-64	1.00	(0.99, 1.02)	1.00	(0.98, 1.01)	1.004	(0.996, 1.011)
		65+	1.00	(0.98, 1.02)	1.00	(0.98, 1.03)	1.005	(0.977, 1.033)
O_3 8-h average	L, A, R, P	15-64	1.02	(0.99, 1.05)	1.03	(0.98, 1.08)	1.031[a]	(1.013, 1.049)
		65+	1.04[a]	(1.02, 1.07)	1.02	(0.99, 1.05)	1.038[a]	(1.018, 1.058)
O_3 1-h maximum		15-64	1.01	(0.99, 1.05)	1.02	(0.99, 1.05)	1.019[a]	(1.005, 1.033)
		65+	1.04[a]	(1.02, 1.05)	1.03[b]	(1.00, 1.06)	1.031[a]	(1.015, 1.047)

RR = relative risk, CI = confidence interval, SO_2 = sulphur dioxide, BS =black smoke, TSP = total suspended particulates, O_3 = ozone

A = Amsterdam, L = London, M = Milano, P = Paris, and R = Rotterdam.

[a] Significant at 5% level
[b] Significant at 10 % level
[c] Cold season mainly October- March; warm season mainly April-September

Table 9 Adjusted[e] relative risk of asthma admissions under age 15 and 15-64 per 50 µg/m^3 increase in air pollutants (and lag)[ab]

Air pollutant	Barcelona	Helsinki	London	Paris	Total (95% CI)
Admissions under age 15					
Sulphur dioxide					
24 h average	-	0.791[0]	1.089[1][c]	1.070[2][c]	1.075 (1.026 to 1.126)[d]
Cumulative	-	0.709[3]	1.113[2][d]	1.022[2]	1.061 (0.996 to 1.131)
Black smoke					
24h average	-	-	1.031[0]	1.030[2]	1.030 (0.979 to 1.084)
Cumulative	-	-	1.046[3]	1.046[2]	1.046 (0.978 to 1.120)
Nitrogen dioxide					
Hourly maximum	-	0.958[0]	1.011[2]	1.008[1]	1.011 (0.999 to 1.022)
24h average	-	0.758[0]	1.027[2][c]	1.026[2]	1.026 (1.006 to 1.049)[c]
Cumulative	-	0.903[1]	1.034[3][d]	1.062[3]	1.037 (1.004 to 1.067)[d]
Ozone					
Hourly maximum	-	1.352[1]	1.009[1]	0.920[2]	1.006 (0.976 to 1.037)
8 hour maximum	-	1.235[1]	1.011[2]	0.957[1]	0.989 (0.941 to 1.038)
Admissions under age 15-64					
Sulphur dioxide					
24 h average	0.968[3]	1.365[2]	0.968[2]	1.012[2]	0.997 (0.961 to 1.034)
Cumulative	0.999[3]	1.647[3]	0.971[2]	1.007[3]	1.003 (0.959 to 1.050)
Black smoke					
24h average	1.036[3]	-	1.035[0]	1.012[0]	1.021 (0.985 to 1.059)
Cumulative	1.027[3]	-	1.026[1]	1.032[3]	1.030 (0.981 to 1.081)
Nitrogen dioxide					
Hourly maximum	1.023[0]	1.065[0]	1.008[0]	1.017[0]	1.012 (0.999 to 1.024)
24h average	1.048[0]	0.900[1]	1.024[0]	1.041[1]	1.029 (1.003 to 1.055)[d]
Cumulative	1.087[3]	0.905[1]	1.025[1]	1.078[1]	1.038 (1.008 to 1.068)[d]
Ozone					
Hourly maximum	1.048[0][d]	0.779[0]	1.071[1][d]	0.937[1]	1.015 (0.955 to 1.078)
8 hour maximum	1.058[0]	1.183[2]	1.086[1][d]	0.986[1]	1.035 (0.937 to 1.144)

[a] Single day lag: effects may be on the same day [0] or lagged up to three days [3]

[b] Cumulative: effects of mean of same day and up to three previous days

[c] p<0.025

[d] p<0.05

[e] Adjusted for trend, seasonality, day of the week, temperature and influenza epidemics

Table 10 Summary effects of pollutants on daily emergency hospital admissions for chronic obstructive lung diseases (expressed as relative risk (RR) per 50 µg/m^3 increased in pollutant)

Pollutant	Cities	lag	RR[a]	95%CL
SO_2 24h	A, B, L, M, P, R	One day	1.022	(0.981, 1.055)
		Cumulative	1.021[c]	(0.998, 1.045)
SO_2 1h	A, B, P, R	One day	1.011	(0.994, 1.029)
		Cumulative	1.015[b]	(1.003, 1.027)
BS 24h	A, B, L, P, R	One day	1.035[b]	(1.010, 1.060)
		Cumulative	1.038[b]	(1.008, 1.070)
TSP 24h	A, B, M, R	One day	1.022[c]	(0.998, 1.047)
		Cumulative	1.033	(0.994, 1.074)
NO_2 24h	A, B, L, P, R	One day	1.019[b]	(1.002, 1.047)
		Cumulative	1.026[b]	(1.004, 1.036)
NO_2 1h	A, B, L, P, R	One day	1.013[b]	(1.003, 1.022)
		Cumulative	1.014	(0.976, 1.054)
Ozone 8h	A, B, L, P, R	One day	1.043[b]	(1.022, 1.065)
		Cumulative	1.056[b]	(1.027, 1.086)
Ozone 1h	A, B, L, P, R	One day	1.029[b]	(1.011, 1.047)
		Cumulative	1.049[b]	(1.024, 1.075)

[a] The original Poisson regression coefficient may be calculated by diving the natural logarithm of the RR by 50.

[b] $p<0.05$

[c] $p=0.05$-0.1

A = Amsterdam, B = Barcelona, L = London, M = Milan, P = Paris, R = Rotterdam; one day lag: effects may be on the same day or lagged up to 3 days (ozone 5 days); Cumulative: effects of mean on the same day and up to 3 previous days (ozone up to 5 previous days); 95% CL: 95% confidence limits; BS: black smoke; TSP: total suspended particles.

Figure 1 Relative risks and 95 % confidence intervals (from Table 4) for total mortality for sulphur dioxide and particulates

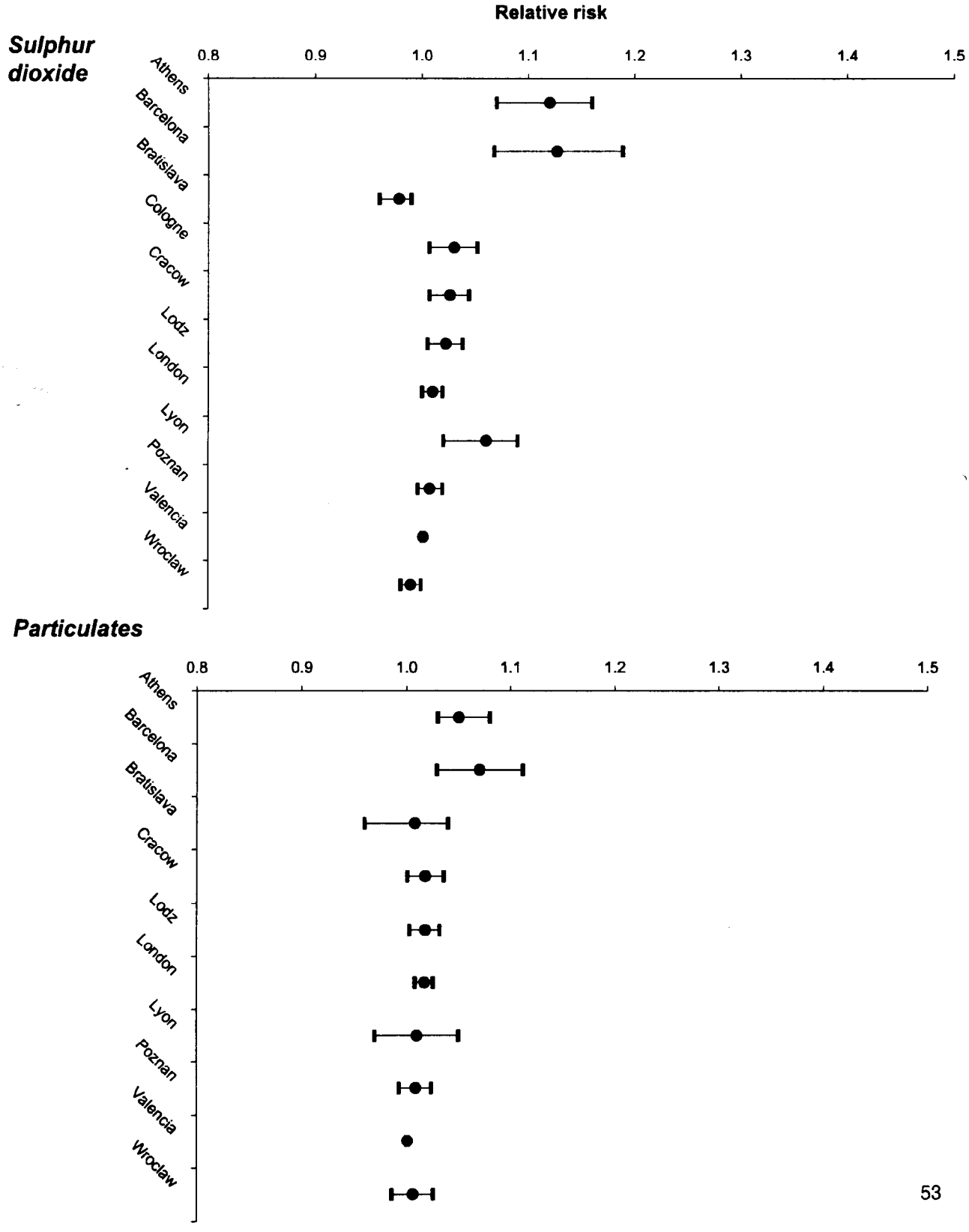


Figure 2 Relative risks and 95% confidence intervals (from Table 5) for mortality from respiratory disease for sulphur dioxide and particulates

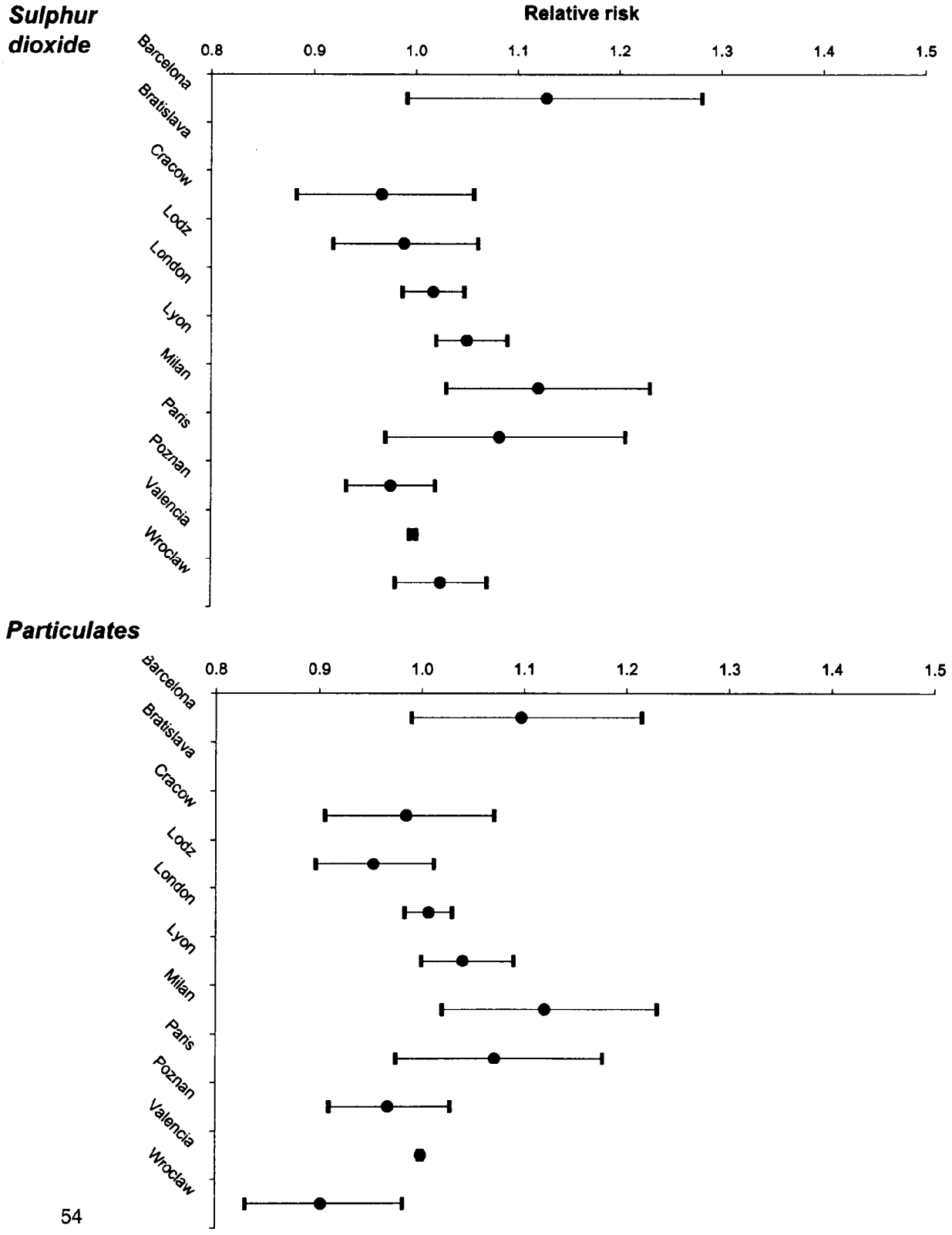


Figure 3 Relative risks and 95% confidence intervals (from Table 5) for mortality from cardiovascular disease for sulphur dioxide and particulates

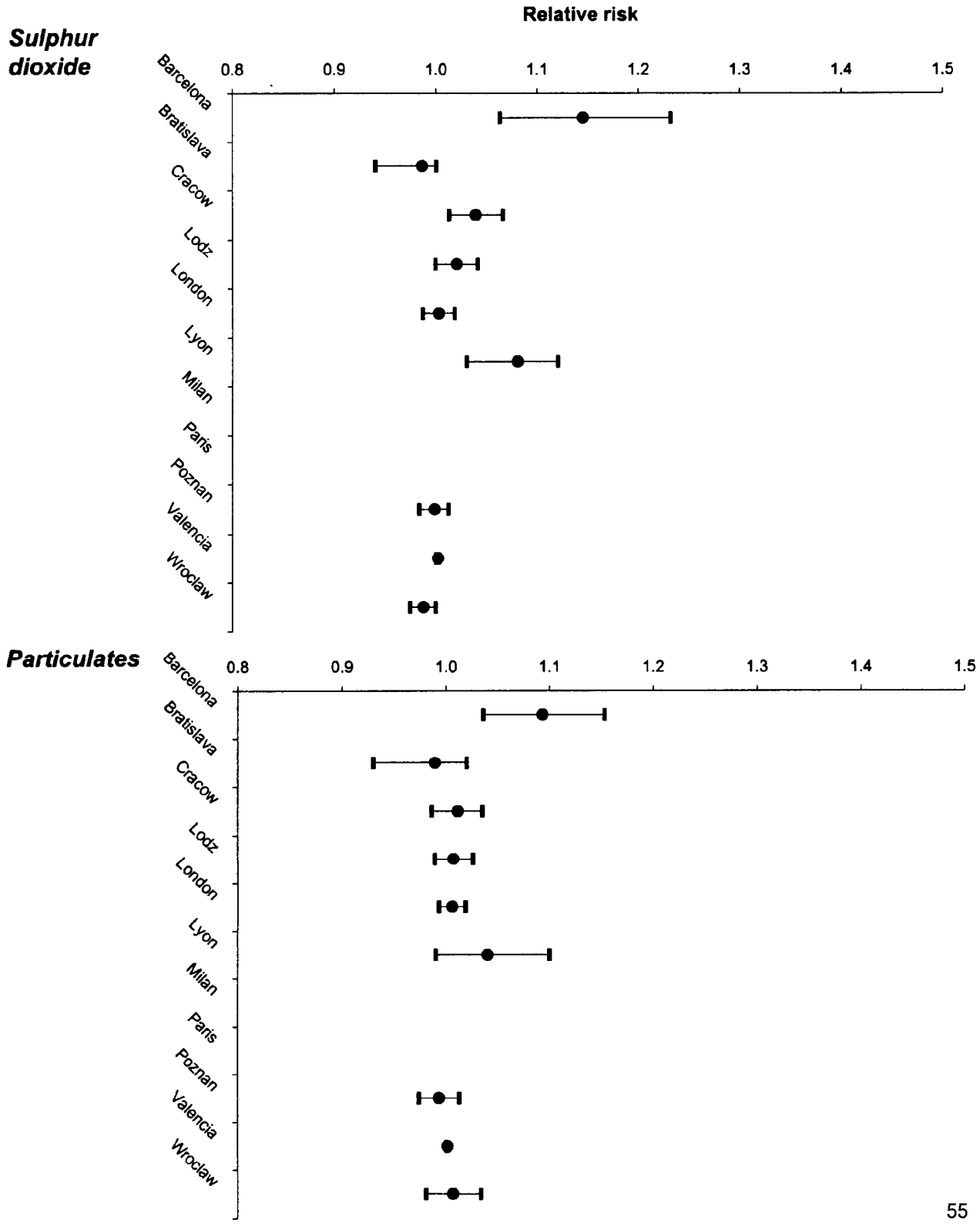


Figure 4 Relative risks and 95% confidence intervals (from Table 5) for mortality from digestive system disease for sulphur dioxide and particulates

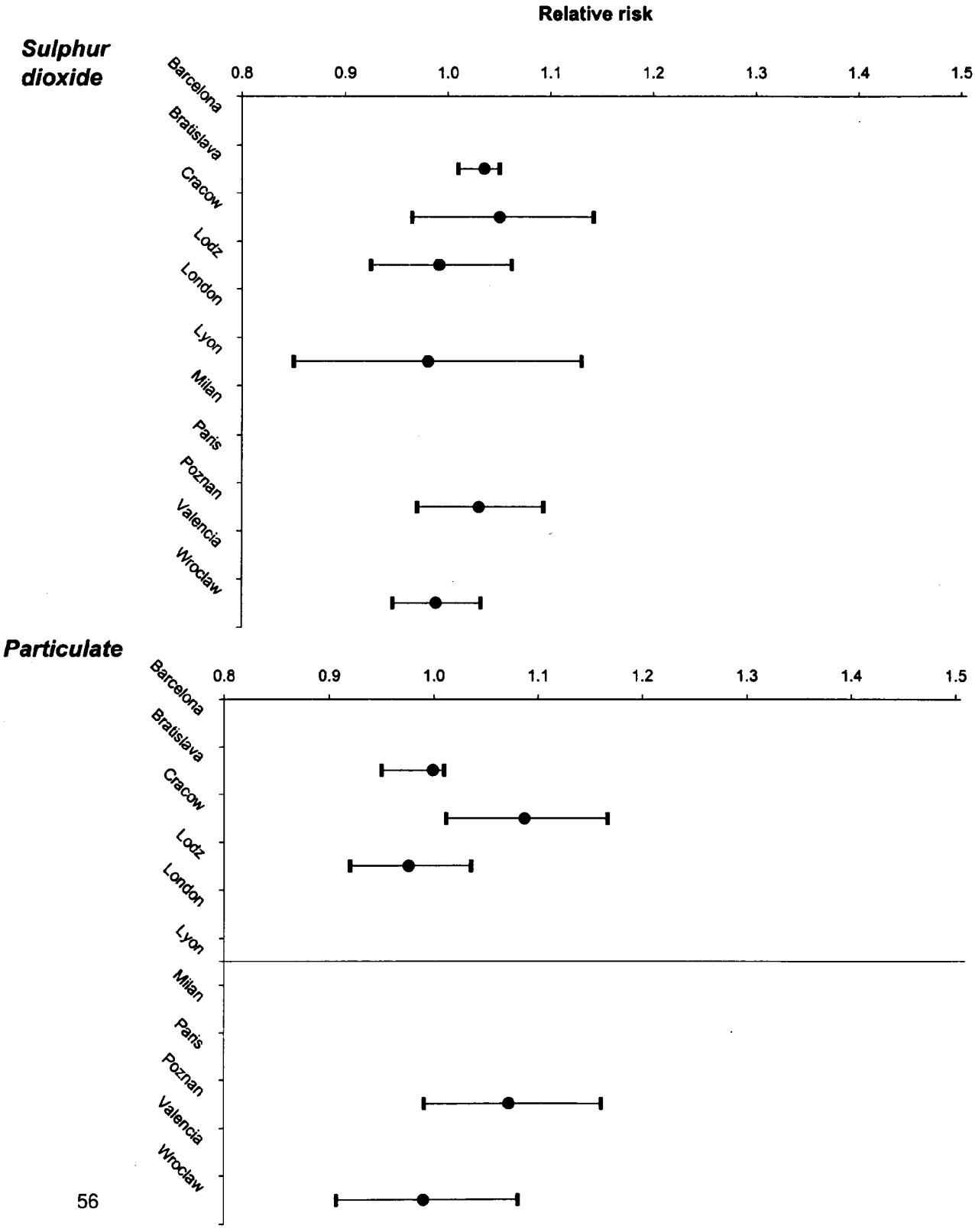
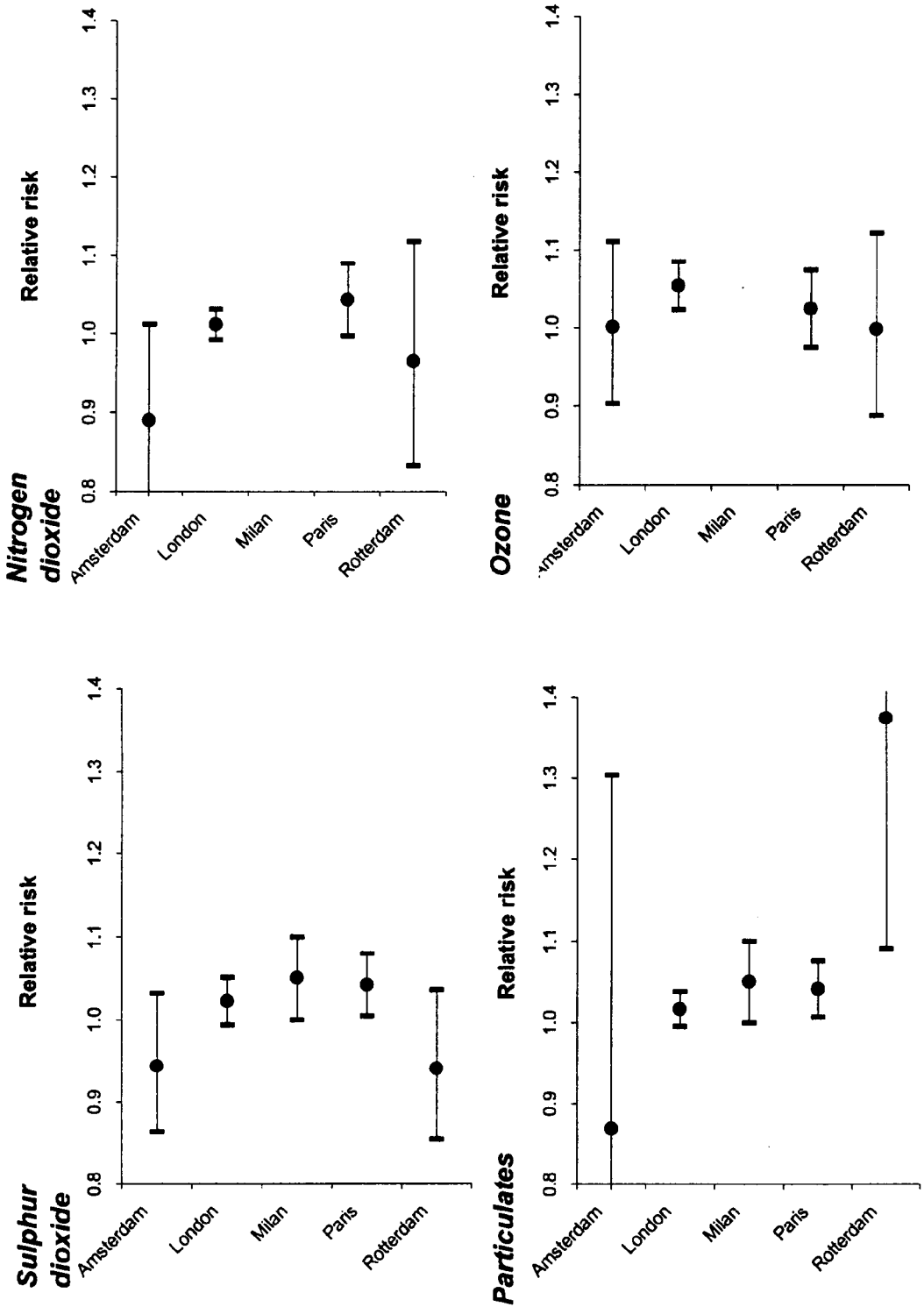


Figure 5 Relative risks and 95% confidence intervals (from Table 6) for emergency hospital admissions for adults aged 15-64 for respiratory disease



6. REFERENCES

1. Alderson MR (1988) *Mortality, morbidity and health statistics*, Basingstoke, UK, Macmillan Press

2. Anderson HR, Ponce de Leon A, Bland MJ, Bower JS & Strachan DP (1996) Air pollution and daily mortality in London:1987-92. *Br Med J, 312*, 665-669

3. Anderson HR, Spix C, Medina S, Schouten JP, Castellsague J, Rossi G, Zmirou D, Touloumi G, Wojtyniak B, Ponka A, Bacharova L, Schwartz J & Katsouyanni K (1997) Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. *Eur Resp J, 10*, 1064-1071

4. Bacharova L, Fandakova K, Bratinka J, Budunska M, Bachar J & Gudaba M (1996) The association between air pollution and the daily number of deaths: findings from the Slovak Republic contribution to the APHEA project. *J Epidemiol Community Health, 50*, S19-S21

5. Ballester F, Corella D, Pérez-Hoyos S & Hervás A (1996) Air pollution and mortality in Valencia, Spain: A study using the APHEA methodology. *J Epidemiol Community Health, 50*, 527-533

6. Bates DV, Baker-Anderson M & Sizto R (1990) Asthma attack periodicity: a study of hospital emergency visits in Vancouver. *Environ Res, 51*, 51-70

7. Bates DV & Sizto R (1987) Air pollution and hospital admissions in Southern Ontario: the acid summer haze effect. *Environ Res, 43*, 317-331

8. Bobak M & Roberts A (1997) Heterogeneity of air pollution effects is related to average temperature. *Br Med J, 315*, 1161

9. Bogdan, Wojtyniak B, Tomasz & Piekarski T (1996) Short term effect of air pollution on mortality in Polish urban populations - what is different? *J Epidemiol Community Health, 50*, S36-S41

10. Burnett R, Dales RE & Raizenne ME (1994) Effects of low ambient levels of ozone and sulphates on the frequency of respiratory admission to Ontario hospitals. *Environ Res, 65*, 172-194

11. Burnett RT, Krewski D & Vincent R (1995) Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory disease. *Am J Epidemiol, 142*, 15-22

12. Cohen S, Deane IM & Goldsmith JR (1969) Carbon monoxide and survival from myocardial infarction. *Arch Environ Health, 19*, 510-517

13. Dab W, Medina S, Quenel P, Le Moullec Y, Le Tertre A, Thelot B, Monteil C, Lameloise P, Pirard P, Monas I, Ferry R & Festy B (1996) Short term respiratory health effects of ambient air pollution: results of the APHEA project in Paris. *Journal Epidemiology and Community Health, 50*, S42-S46

14. Derrienic F, Richardson S, Mollie A & Lellouch J (1989) Short term effects of sulphur dioxide pollution on mortality in two French cities. *Inter J Epidemiol, 18*, 186-197

15. Dockery DW, Pope AC, 3d, Xu X, Spengler JD, Ware JH, Fay ME, Ferris, BG J & Speizer FE (1993 Dec 9) An association between air pollution and mortality in six U.S. cities [see comments]. *N Engl J Med, 329*, 1753-1759

16. Dockery DW & Pope CA, III (1997) Air Pollution I: Particulates. In: Steenland K & Savitz DA, eds, *Topics in environmental epidemiology*, Oxford, Oxford University Press

17. Dockery DW, Schwartz J & Spengler JD (1992) Air pollution and daily mortality: associations with particulates and acid aerosols. *Environ Res, 59*, 362-373

18. Fairley D (1990) The relationship of daily mortality to suspended particulates in Santa Clara County, 1980-1986. *Environ Health Perspect, 89*, 159-168

19. Greenland S (1994) Can meta-analysis be salvaged? *Am J Epidemiol, 140*, 783-787

20. Hatzakis A, Katsouyanni K, Kalandidi A, Day N & Trichopoulos D (1986) Short term effects of air pollution on mortality in Athens. *Inter J Epidemiol, 15*, 73-81

21. Hexter AC & Goldsmith JR (1971) Carbon monoxide association of community air pollution and mortality. *Science, 172*, 265-267

22. Hoek G, Schwarts JD, Groot B & Eilers P (1997) Effects of ambient particle matter and oxone on dialy mortality in Rotterdam, the Netherlands. *Archives of Enviromental Health, 52, 455-454*

23. Kalkstein LS & Davis RE (1989) Weather and human mortality: an evaluation of demographic and interregional responses in the United States. *Annals of the Association of American Geographers, 79*, 44-64

24. Katsouyanni K, Schwartz J, Spix C, Touloumi G, Zmirou D, Zanobetti A, Wojtyniak B, Vonk J, Tobias A, Ponka A, Medina S, Bacharova L & Anderson HR (1996) Short term effects of air pollution on health: a European approach using epidemiologic time series data: the APHEA protocol. *Journal Epidemiology and Community Health, 50*, S12-S18

25. Katsouyanni K, Touloumi G, Spix C, Schwartz J, Balducci F, Medina S, Rossi G, Wojtyniak B, Sunyer J, Bacharova L, Schouten JP, Ponka A & Anderson HR (1997) 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. *Br Med J, 314*, 1658-1663

26. Katsouyanni K, Zmirou D, Spix C, Sunyer J, Schouten JP, Ponka A, Anderson HR, Le Moullec Y, Wojtyniak B, Vigotti MA & Bacharova L (1995) Short term effects of air pollution on health: a european approach using epidemiological time-series data. *Eur Resp J, 8*, 1030-1038

27. Katsouyanni K, Zmirou D, Spix C, Sunyer J, Schouten JP, Ponka A, Anderson HR, Le Moullec Y, Wojtyniak B, Vigotti MA, Bacharova L & Schwartz J (1997) Short term effects of air pollution on health: A European approach using epidemiologic time series data. The APHEA project. *Publ Health Rev, 25*, 7-18

28. Kinney P & Ozkaynak H (1992) Associations between ozone and daily mortality and air pollution in Los Angeles and New York City. *American Review of Respiratory Disease, 145*, A95

29. Kinney PL, Ito K & Thurston GD (1995) A sensitivity analysis of mortality/PM10 association in Los Angeles. *Inhal Toxicol, 7*, 59-69

30. Kinney PL & Ozkaynak H (1991) Association of daily mortality and air pollution in Los Angeles County. *Environ Res, 54*, 99-120

31. Lippman M, Thuston GD (1996) Sulphate concentrations as an indicator of ambient particulate matter air pollution for health risk evaluations. *J Expos Anal Environ Epidemiol, 6, 123-146*

32. Mackenbach JP, Looman CWN & Kunst AE (1993) Air pollution, lagged effects of temperature, and mortality: The Netherlands 1979-87. *J Epidemiol Community Health, 47*, 121-126

33. Poloniecki JD, Atkinson RW, Ponce de Leon A & Anderson HR (1997) Daily time series for cardiovascular hospital admission and previous day's air pollution in London, UK. *Occupational and Environmental Health, 54*, 535-540

34. Ponce de Leon A, Anderson HR, Bland MJ, Strachan PD & Bower J (1996) Effects of air pollution on daily hospital admissions for respiratory disease in London between 1987-88 and 1991-92. *J Epidemiol Community Health, 33*, S63-S70

35. Ponka A & Virtanen M (1996) Asthma and ambient air pollution in Helsinki. *J Epidemiol Community Health, 50*, S59-S62

36. Pope CA, Schwartz J & Ramsom MR (1992) Daily mortality and PM10 pollution in Utah Valley. *Arch Environ Health, 47*, 211-217

37. Pope CA, 3rd, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer, FE & Heath CW, Jr. (1995Mar) Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *American Journal of Respiratory & Critical Care Medicine, 151*, 669-674

38. Pope CA, III & Kalkstein LS (1996) Synoptic weather modeling and estimates of the exposure -response relationship between daily mortality and particulate air pollution. *Environ Health Perspect, 104*, 414-420

39. Saez M (1995) Relationship between weather, temperature and mortality: a time series approach in Barcelona. *Inter J Epidemiol, 24*, 576-582

40. Saldiva PH (1994) Association between air pollution and mortality due to respiratory diseases in children in Sao Paulo Brazil: a preliminary report. *Environ Res, 65*, 218-225

41. Samet JM, Speizer FE, Bishop Y, Spengler JD & Ferris BG (1981) The relationship between air pollution and emergency room visits in an industrial community. *Journal of the air pollution control association, 31*, 236-240

42. SAS Institute Inc. (1989) *SAS/STAT User's guide version 6*, SAS Institute Inc

43. Schouten JP, Vonk J & De Graaf A (1996) Short term effects of air pollution on emergency hospital admissions for respiratory disease: results of the APHEA project in two major cities in The Netherlands 1997-89. *J Epidemiol Community Health, 50*, S22-S29

44. Schwartz J (1991) Particulate air pollution and daily mortality in Detroit. *Environ Res, 56*, 204-213

45. Schwartz J (1993) Air pollution and daily mortality in Birmingham, Alabama. *Am J Epidemiol, 137*, 1136-1147

46. Schwartz J (1994) (a) Particulate air pollution and daily mortality in Cincinnati, Ohio. *Environ Health Perspect, 102*, 186-189

47. Schwartz J (1994) (b) Air pollution and hospital admissions for the elderly in Detroit, Michigan. *American Journal of Respiratory Critical Care Medicine, 150*, 648-655

48. Schwartz J (1994) (c) PM10, ozone and hospital admissions for the elderly in Minneapolis-St Paul, Minnesota. *Arch Environ Health, 49*, 366-374

49. Schwartz J (1995) Health effects of air pollution from traffic: ozone and particulate matter. In: Fletcher AC & McMichael AJ, eds, *Health at the crossroads: transport policy and urban health*, London, London School of Hygiene and Tropical Medicine

50. Schwartz J & Dockery DW (1992) (a) Increased mortality in Philadelphia associated with daily air pollution concentrations. *American Review of Respiratory Disease, 145*, 600-604

51. Schwartz J & Dockery DW (1992) (b) Particulate air pollution and daily mortality in Steubenville, Ohio. *Am J Epidemiol, 135*, 12-19

52. Schwartz J, Spix C, Touloumi G, Bacharova L, Barumandzadeh T, LeTertre A, Piekarski T, Ponce de Leon A, Ponka A, Rossi G, Saez M & Schouten JP (1996) Methodological issues in studies of air pollution and daily counts of deaths or hospital admissions. *Journal Epidemiology and Community Health, 50*, S3-S11

53. Schwartz J, Dockery DW, Neas LM (1996) Is daily mortality associated specifically with fine particles? *J Air Waste. Manage. Assoc, 46, 927-939*

54. Spix C, Anderson HR, Schwartz J, Vigotti MA, LeTertre A, Vonk J, Touloumi G, Balducci F, Piekarski T, Bacharova L, Tobias A, Ponka A & Katsouyanni K (1998) Short term effects of air pollution on hospital admissions of respiratory diseases in Europe: A quantitative summary of APHEA study results. *Archieves of Enviromental Health*, 54-64

55. Spix C, Heinrich J, Dockery DW, Schwartz J, Volksch G, Schwinkowski K, Collen C & Wichmann HE (1993) Air pollution and daily mortality in Erfut, East Germany, 1980-1989. *Environ Health Perspect, 101*, 518-525

56. Spix C & Wichmann HE (1996) Daily mortality and air pollutants: findings from Koln, Germany. *J Epidemiol Community Health, 50*, S52-S58

57. Sunyer J, Castellsague J, Saez M, Tobias A & Anto JM (1996) Air pollution and mortality in Barcelona. *Journal Epidemiology and Community Health, 50*, S76-S80

58. Sunyer J, Spix C, Quenel P, Ponce de Leon A, Ponka A, Barumandzadeh T, Touloumi G, Bacharova L, Wojtyniak B, Vonk J, Schwartz J & Katsouyanni K (1997) Urban air pollution and emergency admissions for asthma in four European cities: the APHEA project. *Thorax, 52*, 760-765

59. Thurston GD, Ito K, Hayes CG, Bates DV & Lippmann M (1994) Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: Consideration of the role of acid aerosols. *Environ Res, 65*, 270-290

60. Thurston GD, Ito K, Kinney PL & Lippmann M (1992) A multi-year study of air pollution and respiratory hospital admissions in three New York state metropolitan areas: results for 1988 and 1989 summers. *Journal of exposure analysis and environmental epidemiology, 2*, 429-450

61. Touloumi G, Katsouyanni K, Zmirou D, Schwartz J, Spix C, Ponce de Leon A, Tobias A, Quennel P, Rabczenko D, Bisanti L, Vonk J & Ponka A (1997) Short term effects of ambient oxidant exposure on mortality: a combined analysis within the APHEA project. *Am J Epidemiol, 146*, 177-185

62. Touloumi G, Samoli E & Katsouyanni K (1996) Daily mortality and "winter type" air pollution in Athens, Greece - a time series analysis within the APHEA project. *J Epidemiol Community Health, 50*, S47-S51

63. Utell MJ, Frampton MW (1995) Particles and mortality: a clinical perspective. *In hal Toxicol, 7, 645-657*

64. Valberg PA & Watson AY (1996) Alternative hypotheses linking outdoor particulate matter (PM) with daily morbidity and mortality. In: Lee J & Phalen R, eds, *Proceedings of the Second Colloquium on Air Pollution and Human Health, Utah, USA*, Utah, The Second Colloquium on Air Pollution and Human Health, pp 4-573-4-589

65. Verhoeff AP, Hoek G, Schwartz J & Van Wijuen JH (1996) Air pollution and daily mortality in Amsterdam, the Netherlands. *Epidemiology, 7*, 225-230

66. Vigotti MA, Rossi G, Bisanti L, Zanobetti A & Schwartz J (1996) Short term effects of urban air pollution on respiratory health in Milan, Italy 1980-89. *J Epidemiol Community Health, 50*, S71-S75

67. Walters S, Griffiths RK & Ayres JG (1994) Temporal association between hospital admissions for asthma in Birmingham and ambient levels of sulfur dioxide and smoke. *Thorax, 49*, 133-140

68. Wietlisbach V, Pope CA & Ackermann-Lebrich U (1996) Air pollution and daily mortality in three Swiss urban areas. *Soz Preventivmed, 41*, 107-115

69. Xu X, Gao J, Dockery DW & Cheng Y (1994) Air pollution and daily mortality in residential areas of Beijing, China. *Arch Environ Health, 49*, 216-222

70. Zmirou D, Barumandzadeh T, Balducci F, Ritter P, Laham G & Ghilardi JP (1996) Short term effects of air pollution on mortality in the city of Lyon, France 1985-90. *J Epidemiol Community Health, 50*, S30-S35