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Short-term effects of air pollution on health: a European approach using epidemiological time-series data

The APHEA project: background, objectives, design

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ABSTRACT: Recent studies investigating the adverse health effects of air pollution indicate that effects exist around and below the current national and international air quality guidelines and standards. However, the difficult methodological issues involved, and the diversity of analytical techniques so far applied, hinder direct between-study comparability and the drawing of clear conclusions.

The APHEA (Air Pollution on Health: European Approach) project is an attempt to provide quantitative estimates of the short-term health effects of air pollution, using an extensive data base from 10 different European countries, which represent various social, environmental and air pollution situations. Within the framework of the project, the methodology of analysing epidemiological time series data, as well as that of performing meta-analysis, are further developed and standardized.

Data have been collected from 15 European cities with a total population exceeding 25 million. The exposure data consist of daily measurements of black smoke, sulphur dioxide, suspended particles, nitrogen dioxide and ozone (each available in several, though not all, cities) from already existing monitoring networks. There is substantial variability in air pollution mixtures and air pollutant levels in participating cities. The mean (24 h) levels of SO_2 range 27–327 $\mu g \cdot m^{-3}$ in the winter season, and those of black smoke range 15–292 $\mu g \cdot m^{-3}$. The mean (1 h) levels of ozone in the summer season range 32–166 $\mu g \cdot m^{-3}$. The outcome data are daily counts of total and cause-specific deaths and hospital emergency admissions. Data on potential confounders (mainly meteorological and chronological variables) are also used. There is large diversity in the climatic conditions in the different cities. Thus, the mean winter temperature ranges -4 to 10°C (minimum -1 to -37°C) and the mean summer temperature 16° to 26°C (maximum 26° to 35°C). Poisson regression allowing for autocorrelation and overdispersion is used in the analysis, after careful control of seasonality and other periodic patterns, and other confounding effects.

The protocol and procedures followed are described, and the advantages and expectations from such an extensive European collaborative effort are presented and discussed.

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Background. Short-term effects of air pollution on health: recent results focus attention on an old issue

The well-known severe episodes of air pollution in Europe and North America before 1960 provided indisputable evidence that high levels of air pollution have important short-term effects on human health, including a significant increase in mortality [1]. Since then, legal and other corrective measures have contributed to a decrease in air pollution to moderate or low levels in many, though not all, of these areas [2]. Also, in Europe and elsewhere, a change in the emission sources was followed by changes in the air pollution mixtures. Air quality guidelines and standards set by national and international organizations have, so far, been based on studies of the early, severe air pollution episodes [3]. However, recent publications indicate that moderate and low levels of air pollution have short-term effects on mortality and morbidity, and that these effects are measurable at

levels of air pollutants which do not exceed the set safety limits. These new findings are consistent in demonstrating small but statistically significant increases in mortality and hospital emergency visits and admissions, in association with small elevations of air pollution. In addition, there is evidence - limited so far - that air pollutants may interact between one another as well as with other environmental factors, resulting in different effect estimates depending on local or regional conditions.

Until 1992, when the APHEA (short-term effects of Air Pollution on Health: a European Approach) proposal was submitted, several studies using more advanced analytical methods had already indicated health effects at relatively low levels of pollutants. These results were derived, in part, by exploring old data more thoroughly. Analyses of the London epidemiological time-series data on daily mortality for the years 1958–1971, when smoke and SO_2 measurements rarely exceeded 500 $\mu g \cdot m^{-3}$, showed that an association of air pollution with mortality persisted. OSTRO [4] showed that no threshold of effects could be identified; on the contrary, the slope of the regression line increased at lower air pollution levels. SCHWARTZ and MARCUS [5] applied a time-series analytical technique to the London data and confirmed the relationship of black smoke to mortality, thus showing that it was not due to inappropriate previous analytical approaches. In another study of the same London time-series, THURSTON *et al.* [6] found that acid aerosol levels were also associated with mortality. A time-series analysis of cause-specific mortality data from Lyon and Marseille in France, where the mean annual average of SO_2 was 66 and 51 $\mu g \cdot m^{-3}$, respectively, showed a statistically significant association of daily air pollution levels (as indicated by SO_2) to mortality from respiratory causes [7]. In Athens, an analysis of mortality data over the period 1975–1982 [8], when the levels of smoke and SO_2 were higher, resulted in a statistically significant effect of air pollution, which was shown to be mainly attributable to deaths from respiratory causes among the elderly [9].

Analyses using data after 1983, when the "traditional" pollutants (*e.g.* smoke) were mixed with increasing levels of photochemical smog, indicated that the effects on mortality persist during the winters, whilst there is possible synergy between air pollution levels and extremely high temperatures during the summers [10]. An analysis of air pollution and mortality in Los Angeles also showed a statistically significant effect of several indicator pollutants, including ozone, to daily mortality [11]. Analysis of mortality and morbidity data during an air pollution episode in West Germany in 1985, when air pollution levels (daily mean) reached values as high as 600 $\mu g \cdot m^{-3}$ for suspended particulates and 830 $\mu g \cdot m^{-3}$ for SO_2, showed a moderate effect both on mortality and morbidity indices [12]. In Helsinki, a city with low air pollution levels, an effect of air pollution on the daily asthma emergency admissions was detected, and the possibility of synergy between the levels of air pollution and extremely low temperatures was discussed [13]. In the Mediterranean region, analyses of emergency admissions for chronic obstructive pulmonary disease (COPD) in Barcelona showed an increase of 17% in the daily number of admissions during high air pollution days [14]. Similarly, in Athens an analysis of emergency admissions for respiratory and cardiovascular causes showed a 16 and 13% increase, respectively [15].

Since 1992, the number of papers published on the subject of short-term effects of air pollution on health has considerably increased. Several studies from the USA indicated small, statistically significant increases in mortality as a result of short-term exposure to air pollution, especially to "inhalable" particulate matter (particles with an aerodynamic diameter of less than 10 µm, *i.e.* PM10). These studies use data from cities and areas with different socioeconomic, geographic and climatic characteristics, and different levels and mixtures of air pollutants. The areas include Utah Valley [16], Philadelphia, Pennsylvania [17], Steubenville, Ohio [18], St. Louis, Missouri and Eastern Tennessee [19] and Birmingham, Alabama [20]. In a 10 year study in East Germany (Erfurt), using data from before the unification, a significant logarithmic relationship was found between SO_2 or particulates and daily mortality. The logarithmic shape means that most of the effect is seen in the lower concentration range. Comparing the 5th percentile to the 95th percentile, an increase of 23 to 929 $\mu g \cdot m^{-3}$ SO_2 leads to an increase in mortality of 10%, whilst 15 to 331 $\mu g \cdot m^{-3}$ suspended particulates causes a 22% increase [21].

In Philadelphia, a study of cause-specific mortality revealed a pattern of increase in causes of death on high air pollution days similar to that observed in the 1952 London air pollution episode [22]. A study from Southern Europe indicated a possible interaction between air pollution and extremely high temperature in their effect on mortality [23]. A meta-analysis using predominantly data from the USA has also been conducted, and concluded that a 6% increase in the relative risk of dying accompanied a 100 $\mu g \cdot m^{-3}$ rise in total suspended particulate (TSP) concentration [24]. The volume and public health importance of these results is reflected in reviews and editorials, which followed their publication [25, 26].

Results from other studies during the same period indicated that air pollution also has short-term effects on morbidity. The Barcelona study on emergency admission for COPD was extended to a 5 year period, and the results confirmed those of the previous analyses [27]. An increase in asthma emergency visits for persons under 65 yrs of age was reported for Seattle, Washington, with an associated relative risk of 1.12 for a 30 $\mu g \cdot m^{-3}$ increase in PM10, the levels of which remained below the US ambient air quality standards during the study period [28]. A similar increase was associated with high ozone levels in New Jersey [29]. Several other reports have shown effects on symptoms and lung function [30–34].

This evidence indicates that adverse health effects of air pollution occur at air pollution levels currently observed in Europe and the USA. Therefore, the challenge today is to adequately quantify the smaller, but probably important at the public health level, effects of moderate and lower air pollution levels, and to identify the pollutants responsible and their possible synergistic effects.

The methodological approaches used in the papers published vary. Some analyses are based on time-series methodology and others on linear or nonlinear regression, although all apply modelling. Furthermore, although the role of particulate matter has been extensively investigated, less attention has been paid to other pollutants (*e.g.* SO_2, ozone); their effects at current ambient levels are largely unknown. There is a need for standardization and better in-depth understanding of methodological issues.

The APHEA project: purpose and objectives

The project proposal was submitted to the Commission of the European Communities (CEC), Directorate General for Science, Research and Development (DGXII), Environment 1991–1994 Programme first call in 1992. The objectives of the programme are:

1. To provide quantitative estimates of the short-term health effects (using total and cause-specific daily number of deaths and emergency hospital admissions) of air pollution, taking into consideration interactions between different pollutants and between pollutants and other environmental factors. This objective will be realized with the use of a very extensive data base from 10 different European countries, which represent various social, environmental and air pollution situations.
2. To further develop and standardize the methodology for the detection of short-term effects in the analysis of epidemiological time-series data. This will involve detailed consideration of the methods used so far, and suggestions for new approaches as well as standardization of the exposure (air pollution) measurements and confounding factors to be controlled.
3. To select and develop a meta-analytical approach for epidemiological time-series studies.
4. To assess the feasibility of creating a European data base of air pollution measurements and of health indicators, recorded on a daily basis. This will allow a continuous surveillance of short-term effects of air pollution in the future.

Eight groups contributing data from: Amsterdam and Rotterdam, The Netherlands; Athens, Greece; Barcelona, Spain; Helsinki, Finland; Cologne, Germany; London, UK; Lyon and Paris, France; participated in the first proposal. Later, three more groups were added with data from: Milan, Italy; Lódz, Poznan, Cracow and Wroclaw, Poland; and Bratislava, Slovakia. Thus, recent data from 15 cities are being analysed, which concern an exposed population of over 25,000,000 (table 1).

The APHEA Project: design and implementation

Data

Within the framework of the project, epidemiological time-series data are being used, which were either collected routinely by public administrative organizations or were collected by the researchers participating in the study. The data consist of:

Table 1. – APHEA cities

City	Time period	Population
Amsterdam	1977–1989	694,700
Athens	1987–1991	3,096,775
Barcelona	1986–1992	1,700,000
Bratislava	1987–1991	442,999
Cologne	1975–1985	977,000
Cracow	1977–1989	740,000
Helsinki	1987–1989	491,148
Lodz	1977–1990	848,000
London	1987–1991	7,200,000
Lyon	1985–1990	410,000
Milan	1980–1989	1,500,000
Paris	1987–1992	6,140,000
Poznan	1983–1990	575,000
Rotterdam	1977–1989	576,200
Wroclaw	1979–1989	637,000

APHEA: Air Pollution on Health, European Approach.

Air pollution measurements. All air pollution measurements were made available by public monitoring networks established in each city.

Table 2 shows the pollutants used and the number of cities where they are available. The study protocol includes detailed criteria for completeness of measurements and methods to be used for filling in missing data. In order to maximize the comparability of the data sources in terms of the geographical location of the monitoring stations, and since the project is a study of urban air pollution effects, it was decided to use only urban stations located either near traffic roads (but not on limited access highways) and/or "background" urban stations for all pollutants, except ozone, for which a suburban moitoring station may be used (since ozone levels are lower in city centres, in the presence of primary pollutants, due to scavenging). The height of the measurement points was in most stations 2–10 m. Measurements from all stations fulfilling the completeness criteria were averaged. The number of monitoring sites used for each pollutant was ≥3 in the large majority of cases, and included one station near an urban traffic road and at least one urban background station. Although a quality assurance

Table 2. – Air pollutants used in the APHEA data analysis

Pollutant $\mu g \cdot m^{-3}$	Reference time	Availability Cities n
SO_2	24 h	15
SO_2	1 h	8
TSP	24 h	6
BS	24 h	10
PM_{10}	24 h	3
NO_2	24 h	10
NO_2	1 h	9
Ozone	8 h	6
Ozone	1 h	6

TSP: total suspended particulates; BS: black smoke; PM_{10}: particulate matter with an aerodynamic diameter ≤10 µm; APHEA: Air Pollution on Health, European Approach.

programme was not organized within the framework of APHEA, all monitoring networks included in the study run their own quality assurance programmes, most of them to conform to European Union legal requirements. The methods of measurement for each pollutant were either identical or broadly comparable.

One advantage of the study is the variability observed across the participating areas, in air pollution mixtures and pollutant levels. This is shown in tables 3 and 4 for selected pollutants during the winter (December, January, February) and summer (June, July, August) season. To illustrate the dispersion and range of pollution levels observed in each city, both tables report the seasonal values measured by those monitoring stations showing the highest (Stmax) and the lowest (Stmin) annual mean levels. Typical patterns of "winter" and "summer" type smog are observed, with some cities characterized by particularly high "winter" type smog, either dominated by SO_2 (*e.g.* Milan) or particles (*e.g.* Cracow), and some by "summer" type smog (*e.g.* Rotterdam), whilst some cities have relatively high air pollution of both types (*e.g.* Athens). In table 5, the ratio of pollutant value during the season with the maximum level to the value during the season with the minimum level is shown for every city. A large ratio indicates pronounced seasonal patterns, probably arising from sources operating during

Table 3. – Levels of air pollutants in each city for the winter season (December-January-February) during the study period

			Particulate matter 24 h							
	SO_2 24 h µg·m^{-3}		Black smoke µg·m^{-3}		TSP or PMx µg·m^{-3}		NO_2 1 h µg·m^{-3}		O_3 1 h µg·m^{-3}	
City	Stmax	Stmin	Stmax	Stmin	Stmax	Stmin	Stmax	Stmin	Stmax	Stmin
Amsterdam	27 (28)	19 (26)	15 (17)				85 (23)	60 (26)	52 (27)	35 (23)
Athens	106 (61)	31 (31)	141 (90)	64 (34)			170 (67)	64 (57)	82 (36)	34 (18)
Barcelona	60 (30)	35 (22)	137 (24)	40 (25)	233 (82)	138 (44)	114 (50)	92 (38)	43 (21)	46 (25)
Bratislava	67 (53)	31 (48)			113 (105)	85 (64)				
Cologne	88 (61)	71 (50)			84 (46)	70 (42)	72 (38)	82 (48)		
Cracow	181 (102)	124 (81)	292 (180)	120 (116)						
Helsinki	30 (21)	17 (12)			122 (130)	33 (21)	74 (44)	48 (26)	28 (14)	
Lodz	150 (73)	95 (61)	178 (86)	95 (57)						
London	42 (21)	28 (22)	24 (18)	11 (9)			108 (67)	106 (63)	27 (19)	
Lyon	110 (40)	66 (38)			88 (30)#	49 (40)#	74 (42)	70 (53)		
Milan	327 (216)	182 (110)			200 (95)	188 (95)				
Paris	53 (42)	34 (30)	49 (24)	31 (25)	67 (47)#	36 (17)#	83 (46)	62 (35)	23 (15)	19 (15)
Poznan	129 (101)	91 (74)	97 (86)	62 (50)						
Rotterdam	48 (36)	19 (24)	29 (22)	16 (13)			80 (28)	59 (18)	46 (25)	31 (22)
Wroclaw	99(76)	66 (58)	160 (126)	88 (75)						

Data are presented as mean and SD in parenthesis; Stmax/Stmin: measurements from the station giving the maximum/minimum annual levels for each city; TSP: total suspended particulates; PMx: particulate matter with an aerodynamic diameter ≤ χ µm. #: PM13, a fraction of TSP.

Table 4. – Levels of air pollutants in each city for the summer season (June-July-August) during the study period

			Particulate matter 24 h							
	SO_2 24 h µg·m^{-3}		Black smoke µg·m^{-3}		TSP or PMx µg·m^{-3}		NO_2 1 h µg·m^{-3}		O_3 1 h µg·m^{-3}	
City	Stmax	Stmin	Stmax	Stmin	Stmax	Stmin	Stmax	Stmin	Stmax	Stmin
Amsterdam	12 (9)	7 (5)	5 (4)				81 (31)	48 (26)	105 (33)	83 (37)
Athens	48 (26)	23 (15)	102 (60)	42 (23)			206 (85)	96 (55)	166 (59)	95 (33)
Barcelona	29 (16)	24 (16)	65 (33)	24 (12)	178 (73)	117 (46)	127 (66)	85 (36)	111 (42)	88 (37)
Bratislava	29 (24)	16 (14)			62 (60)	64 (33)				
Cologne	43 (24)	30 (19)			83 (35)	72 (32)	85 (39)	70 (33)		
Cracow	47 (40)	60 (47)	35 (18)	27 (17)						
Helsinki	19 (15)	8 (7)			92 (42)	42 (19)	79 (27)	57 (19)	32 (18)	
Lodz	24 (13)	15 (16)	49 (27)	19 (12)						
London	38 (18)	26 (17)	16 (8)	7 (5)			108 (62)	102 (41)	57 (35)	
Lyon	67 (31)	32 (13)			56 (21)#	30 (16)#	89 (51)	64 (37)		
Milan	34 (23)	25 (17)			85 (41)	82 (36)				
Paris	22 (18)	15 (10)	36 (19)	15 (11)	48 (21)#	38 (16)#	94 (62)	61 (45)	74 (41)	57 (33)
Poznan	25 (23)	19 (17)	29 (29)	13 (13)						
Rotterdam	27 (17)	9 (6)	20 (11)	9 (5)			93 (34)	51 (20)	122 (43)	86 (38)
Wroclaw	20 (16)	17 (14)	40 (23)	30 (21)						

Data are presented as mean and SD in parenthesis; #: PM13, a fraction of TSP. For abbreviations see legend to table 3.

Table 5. – Magnitude of seasonality: ratio of pollutant value at season with maximum level over value at season with minimum level*

City	SO_2 1 h	SO_2 24 h	BS	TSP	PMx**	NO_2 1 h	NO_2 24 h	O_3 1 h	O_3 8 h
Amsterdam	1.66	2.25	2.87			1.10	1.33	2.04	2.10
Athens		2.23	1.38			1.21		2.04	
Barcelona	1.93	2.09	2.13	1.35		1.19	1.21	2.57	3.12
Bratislava		3.50		1.80					
Cologne	1.57	2.05		1.04	1.32	1.18	1.08		
Cracow		3.87	8.46						
Helsinki	1.60	1.59		2.10		1.24	1.28	2.15	2.07
Lodz		3.63	6.29						
London		1.11	1.52			1.13	1.14	2.13	2.21
Lyon	1.52	3.15			1.58	1.38	1.36		
Milan		9.49		2.35			1.83		
Paris	2.20	2.37	1.49	1.40	1.35	1.20	1.34	3.33	4.31
Poznan		3.33	5.08						
Rotterdam	1.38	1.84	1.54			1.22	1.23	2.69	2.86
Wroclaw		5.00	3.98						

*: the monitoring station with maximum levels has been used; **: PM_{13} for Lyon and Paris, PM_7 for Cologne. For abbreviations see legends to tables 2 and 3.

Table 6. – Ratio of level of pollutant measured at the station giving the maximum values to that measured at the station giving the minimum values

City	SO_2 1 h	SO_2 24 h	BS	TSP	PMx**	NO_2 1 h	NO_2 24 h	O_3 1 h	O_3 8 h
Amsterdam	1.33	1.49				1.49	1.92	1.36	1.49
Athens		3.20	2.55			2.45		2.29	
Barcelona	1.59	1.44	3.15	1.64		1.38	1.57	1.11	1.18
Bratislava		2.25		1.13					
Cologne	1.35	1.30		1.17		1.22	1.05		
Cracow		1.24	1.89						
Helsinki	1.77	1.94		2.78		1.42	1.48		
Lodz		1.73	2.18						
London		1.57	2.11			1.05	1.03		
Lyon	1.71	2.27			1.93	1.25	1.33		
Milan		1.52		1.12			1.33		
Paris	1.29	1.48	1.71		1.56	1.35	1.41	1.38	1.57
Poznan		1.50	1.73						
Rotterdam	2.64	2.79	2.10			1.63	1.80	1.38	1.48
Wroclaw		1.34	1.59						

*: PM_{13} for Lyon and Paris. For abbreviations see legends to tables 2 and 3.

particular times of the year (*e.g.* heating or prolonged sunlight). A small seasonality ratio indicates relatively constant levels of air pollution exposure for the population across the year.

In table 6, the ratio of the measurement in the monitoring station giving highest levels over the station giving lowest levels is presented (mean for four seasons for every city). This probably reflects more the geographical placement of the monitoring stations (*e.g.* the proximity to emission sources, such as traffic), more than the pollutant dispersion. Most ratios are below 2. However, in some instances (*e.g.* Athens) these ratios for all or some pollutants are above 2. On the other hand, the uniformity in some cases is remarkable (*e.g.* London for NO_2).

Correlations between pollutants measured at the same locations are generally positive. Negative coefficients are only noted between ozone and other pollutants, but this is easily explained by inverse seasonal pattern and the chemical behaviour of ozone, which is exclusively a secondary pollutant.

Health data. Table 7 presents a summary description of the daily number of deaths and hospital admissions data to be used in the project. Deaths and admissions must relate to the defined study area. Emergency hospital admissions are considered most suitable. However, in some areas, due to the recording system or other problems in health care, it is impossible to distinguish between planned and emergency admissions.

Table 7. – Mortality and morbidity indices available in the APHEA data analysis: total and cause-specific daily number of deaths and daily number of hospital (emergency) admissions by cause

Mortality or morbidity index	ICD-9	Availability Cities n
All deaths (except deaths from external causes if possible) (all ages and ages ≥70 yrs)	All (except ≥800)	12
Respiratory deaths	460–519	8
Cardiovascular deaths	390–459	8
Digestive system deaths ("control" cause)	520–579	8
Hospital admissions	All (except ≥800)	3
Respiratory admissions (age groups: 15–64 yrs, >65 yrs)	460–519	5
Asthma admissions (age groups: 0–14 and 15–64 yrs)	493	5
COPD admissions (all ages and only >65 yrs)	490–496	5
Digestive admissions ("control" cause)	520–579	4

APHEA: Air Pollution on Health, European Approach; COPD: chronic obstructive pulmonary disease; ICD-9: International Classification of Disease (9th revision).

Specific causes of death and admission, mainly diseases of the respiratory system, have been chosen as the most "relevant" outcomes of air pollution exposure. This was based on biological plausibility, as well as on results from previous studies.

The total number of deaths and total number of emergency admissions have been considered suitable health outcomes, even though it may be argued that they include a substantial proportion of "irrelevant" causes. They are completely recorded and avoid the problem of misclassification of diagnosis or cause of death. Control conditions or causes of death (digestive system diseases), are also studied, in order to check the absence of association with air pollution levels.

Table 8 shows the mean daily number of deaths from all causes, by season, for all cities providing mortality data (Dutch cities and Helsinki are only analysing admission data). It can be seen that the mean daily numbers of deaths are high, which reflects the large populations covered, and there is a consistent seasonal pattern in all centres.

Table 8. – Total daily number of deaths by city

City	Winter	Spring	Summer	Autumn
Amsterdam				
Athens	41 (7)	37 (7)	26 (3)	34 (7)
Barcelona	52 (10)	43 (8)	42 (9)	46 (9)
Bratislava	11 (3)	11 (3)	10 (3)	10 (3)
Cologne	32 (6)	31 (6)	28 (6)	29 (6)
Cracow	19 (5)	18 (5)	16 (5)	17 (4)
Helsinki				
Lodz	29 (6)	29 (6)	26 (6)	27 (6)
London	231 (31)	196 (18)	179 (16)	191 (20)
Lyon	9 (3)	7 (3)	7 (3)	7 (3)
Milan	37 (7)	33 (7)	28 (7)	31 (7)
Paris	144 (17)	128 (13)	116 (16)	124 (15)
Poznan	19 (5)	18 (4)	16 (4)	17 (4)
Rotterdam				
Wroclaw	15 (4)	14 (4)	13 (4)	13 (4)

Data are presented as mean and SD in parenthesis.

Data on potential confounders

Meteorological variables. Temperature (24 h) has been shown to be a very important predictor of mortality and morbidity patterns [22, 35], and it is probably the most important (together with seasonality, a related phenomenon) confounder in this analysis. Humidity (24 h relative humidity) has often been defined *a priori* as a potential confounder, although results often show an insignificant effect of humidity on health (at the ranges observed in the study locations). It has, therefore, been decided to use temperature and humidity measurements in all analyses. Among routinely recorded meteorological variables, wind velocity and direction was considered an exposure correlate, not a confounder, whilst there is no evidence that other meteorological variables may be important. An interesting and challenging feature of the APHEA project is the diversity of climatic conditions characterizing participating cities. This is illustrated in table 9.

Seasonal or other chronological variables. Seasonality and other time-related patterns (*i.e.* cycles with periods from 2 years to 2 months) in the time-series will be controlled. Also, day of the week and holidays, as well as any unusual event (*e.g.* a strike in the health services, a heat wave) will be modelled.

Other variables. Influenza events will be identified when possible. Data for pollen levels on a daily basis is not available in all centres, and is not being included.

Analysis

Poisson regression, allowing for autocorrelation and overdispersion, is used for the data analysis [16–20]. Each centre will analyse its own data. The procedure of model building has been specified in detail to ensure a standardized and uniform method of analysis in all centres. Sinusoidal terms up to the 6th order will be introduced to control for periodic patterns in the time series. Long-term trends will be controlled by introducing a

Table 9. – Meteorological data: 24 h temperature and relative humidity

City	Winter		Spring		Summer		Autumn	
	Temp. °C	Humidity %	Temp. °C	Humidity %	Temp. °C	Humidity %	Temp. °C	Humidity %
Amsterdam	2.5 (5)	87 (8)	8.6 (4)	77 (11)	16.2 (3)	78 (8)	10.5 (5)	85 (7)
Athens	9.8 (3)	71 (10)	15.5 (4)	62 (11)	26.4 (3)	50 (8)	18.6 (5)	65 (11)
Barcelona	9.6 (3)	74 (12)	15.5 (5)	77 (9)	23.1 (2)	76 (7)	12.8 (4)	78 (10)
Bratislava	0.9 (5)	81 (10)	10.3 (6)	68 (11)	20.0 (3)	65 (10)	10.0 (6)	77 (9)
Cologne	3.7 (4)	80 (9)	10.7 (5)	70 (12)	18.5 (4)	70 (11)	11.7 (5)	78 (8)
Cracow	-1.9 (5)	84 (7)	7.9 (6)	75 (11)	16.8 (3)	76 (8)	8.2 (6)	83 (8)
Helsinki	-4.3 (8)	89 (7)	4.0 (6)	79 (16)	15.8 (4)	75 (11)	5.8 (6)	86 (8)
Lodz	-1.6 (5)	87 (7)	7.9 (6)	74 (12)	16.7 (3)	75 (11)	8.2 (5)	84 (9)
London	7.1 (3)	77 (9)	11.3 (4)	69 (10)	17.0 (3)	69 (10)	12.7 (4)	75 (9)
Lyon	3.3 (5)	83 (9)	10.9 (5)	72 (11)	20.1 (3)	66 (11)	12.3 (6)	78 (10)
Milan	4.3 (3)	67 (21)	13.4 (5)	56 (17)	23.7 (3)	56 (12)	14.4 (6)	70 (14)
Paris	5.1 (4)	84 (9)	11.7 (5)	70 (11)	19.0 (4)	71 (12)	12.3 (5)	83 (10)
Poznan	-0.3 (6)	85 (7)	8.5 (6)	72 (12)	17.0 (3)	72 (11)	8.5 (5)	83 (9)
Rotterdam	2.5 (5)	87 (8)	8.6 (4)	77 (11)	16.2 (3)	78 (8)	10.5 (5)	85 (7)
Wroclaw	-0.8 (6)	85 (7)	8.3 (6)	75 (11)	17.1 (3)	75 (9)	8.9 (6)	82 (8)

Data are presented as mean and SD in parenthesis.

linear or quadratic (as appropriate) term in the model and/ or dummy variables for years, as appropriate. Temperature and relative humidity will be subsequently introduced with possible transformations, which will depend on the specific time-series data analysed (possible effects of local climatic conditions). Meteorological variables may be lagged by up to 2 days. Holidays, day of the week and other unusual events will be controlled, with the introduction of appropriate dummy variables. Influenza epidemics will be fitted where possible, through the introduction of a case count. At each step of model building, the residuals will be checked for remaining patterns.

Air pollution variables will be entered into the models one-at-a-time at the initial stages of analysis. The best fitting transformations and time lags (lag 0, 1 and 2, and averages of different consecutive lags) will be used by each centre, for every pollutant. However, all centres will choose at least one average of consecutive days and one 1 day measurement for each pollutant at the final stage, for reasons of comparability. Autocorrelation will be taken into account using autoregressive models. Interaction of pollution indicators and season will be investigated through modelling the effects of each pollutant separately by season (winter, summer) including appropriate interaction terms and a dummy variable for season in the models. The application of Poisson regression will allow calculation of relative risks. If appropriate, synergy between pollutants will be estimated through modelling (*i.e.* by evaluating the effects of one pollutant on days when the other pollutant is either "low" or "high", using a predefined cut-off). Every centre will report results at every stage of the analysis (including residual plots) to allow evaluation of the procedure and the choice of core variables.

A meta-analysis will follow, taking as input the relative risks calculated as a result of the analysis by centre. At this stage, heterogeneity of relative risk estimates across cities will be evaluated and the distribution of predictive variables, such as age structure, smoking habits, or general climatological features, will be assessed in order to address their possible synergy with air pollutant levels.

The statistical procedures applied will not be used blindly, but will take into account biomedical hypotheses and biological plausibility.

Discussion

In recent years, the need for European collaborative biomedical projects has been widely recognized, and this fact has been expressed in the numerous European Community calls for joint research proposals and concerted actions. There are some obvious advantages in these multicentre projects: they concern larger populations or can recruit a larger number of cases, and they usually represent a wider variability in the distribution of risk factors. An important positive result of such collaborations is also the transfer of know-how and the "assimilation" of research procedures and approaches among the involved groups. The need to pull together data and results from similar protocols has also been expressed in many recent attempts to apply meta-analysis. The results of meta-analysis are inherently more powerful than the individual results, and are useful and informative when the requirements for comparability across the original studies are fulfilled [36]. The alternative procedure of performing a joint analysis of all the data in one centre may offer a potential for a more thorough insight into the data, but its advantages over meta-analysis based on the same data are questionable [37]. Furthermore, it has two important disadvantages: firstly, it would pose major computational problems, due to the size of the joint database; and secondly it would remove from the programme one of its significant features, *i.e.* the standardization of methodology used by various European

Groups and the transfer of knowledge among participants.

In air pollution epidemiology, an approach based on such a large and diverse geographical area is particularly suitable for many reasons. Levels of air pollution observed in Europe today are, in most instances, below what used to be considered safe levels as reflected in most standards, either national or international. It is, therefore, difficult and requires powerful techniques to identify and quantify the possible health effects of these air pollution levels. Furthermore, the expected relatively weak associations to be observed under these conditions can often be a result of confounding effects. The observation of the same relationship under different circumstances and populations makes causality a more plausible interpretation of any possible association. Even a "weak" effect of air pollution on health will constitute an important public health problem, since a unique characteristic of air pollution exposure is the ubiquity of exposure for large populations [36]. Important efforts were made to ensure reasonable comparability of air pollution data, through careful selection of relevant monitoring stations and consideration of measurement methods in each city.

The temporal studies using aggregated data (or time-series studies) are an old design, which has been used in other disciplines and has now been adapted and developed in epidemiology, especially in air pollution studies [5, 11, 14, 17–22, 24]. The main drawbacks of a time-series design are the lack of individual measurements in exposure and outcome (*i.e.* its "ecological" nature), and the possible presence of unmeasured confounders. However, time-series studies of short-term effects, like the ones used in this project, which use long series of small units (days), tend to minimize such errors. An important feature in such study designs is that the population under investigation serves also as its own control over time and, thus, possible confounders can only be factors varying according to the small time-units, *i.e.* from day to day. Such factors can only be meteorological and chronological factors, which are accurately measured and easily recorded.

It is the first time, within the framework of the APHEA project, that an attempt to standardize the methodology of analysing epidemiological time-series data has been made, bringing together a lot of expertise recently developed in and outside Europe. The analysis of data in every city is performed using a strictly comparable procedure, which at the same time incorporates local specificities in climate and air pollution mixtures. It provides a unique opportunity for a meta-analysis based on state-of-the-art inclusion criteria. The results will be very helpful in assessing whether current air pollution levels in Europe are harmful to human health - as far as short-term effects are concerned - and under what specific conditions. The APHEA conclusions will also contribute to the revisions of air quality guidelines, which are currently underway. Within the framework of the project, the possibility of routinely recording the appropriate data to form the basis of "air pollution health effects surveillance" in European countries will be addressed.

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References

1. Ware JH, Thribodeau LA, Speizer FE, Colome S, Ferris BG. Assessment of the health effects of atmospheric sulfur oxides and particulate matter: evidence from observational studies. *Environ Health Perspect* 1981; 41: 255–276.
2. Waller RE. Control of air pollution: present success and future prospects. *In*: Bennett AE, ed. Recent Advances in Community Medicine. London, Churchill Livingstone, 1978.
3. Air Quality Guidelines for Europe. World Health Organization. Regional Office for Europe. Copenhagen, WHO Regional Publications, European Series No. 23, 1987.
4. Ostro BD. A search for a threshold in the relationship of air pollution to mortality: a reanalysis of data on London winters. *Environ Health Perspect* 1984; 58: 397–399.
5. Schwartz J, Marcus A. Mortality and air pollution in London: a time series analysis. *Am J Epidemiol* 1990; 131: 185–194.
6. Thurston GD, Kazuhito I, Lippmann M, Hayes C. Re-examination of London, England, mortality in relation to exposure to acidic aerosols during 1963–1972 winters. *Environ Health Perspect* 1989; 79: 73–82.
7. Derrienic F, Richardson S, Mollie A, Lellouch J. Short-term effects of sulphur dioxide pollution on mortality in two French cities. *Int J Epidemiol* 1989; 18: 186–197.
8. Hatzakis A, Katsouyanni K, Kalandidi A, Day N, Trichopoulos D. Short-term effects of air pollution on mortality in Athens. *Int J Epidemiol* 1986; 15: 73–81.
9. Katsouyanni K, Karakatsani A, Messari I, *et al.* Air pollution and cause-specific mortality in Athens. *J Epidemiol Commun Health* 1990; 44: 321–324.
10. Katsouyanni K, Hatzakis A, Kalandidi A, Trichopoulos D. Short-term effects of atmospheric pollution on mortality in Athens. *Arch Hellen Med* 1990; 7: 126–132 (In Greek with an English summary).
11. Kinney PL, Ozkaynak H. Associations of daily mortality and air pollution in Los Angles county. *Environ Res* 1991; 54: 99–120.
12. Wichmann HE, Mueller W, Allhoff P, *et al.* Health effects during a smog episode in West Germany in 1985. *Environ Health Perspect* 1989; 79: 89–99.
13. Pönkä A. Asthma and low level air pollution in Helsinki. *Arch Environ Health* 1991; 46: 262–270.
14. Sunyer J, Anto J, Murillo C, Saez M. Effects of urban

air pollution on emergency room admissions for chronic obstructive pulmonary disease. *Am J Epidemiol* 1991; 134: 277–286.
15. Pantazopoulou A, Kremastinou T, Katsouyanni K. Short-term effects of atmospheric pollution on emergency hospital out-patient visits and admissions in the Greater Athens area. *Arch Hellen Med* 1990; 7: 139–144 (In Greek with an English summary).
16. Pope CA, Schwartz J, Ransom MR. Daily mortality and PM10 pollution in Utah Valley. *Arch Environ Health* 1992; 47: 211–217.
17. Schwartz J, Dockery DW. Increased mortality in Philadelphia associated with daily air pollution concentrations. *Am Rev Respir Dis* 1992; 145: 600–604.
18. Schwartz J, Dockery DW. Particulate air pollution and daily mortality in Steubenville, Ohio. *Am J Epidemiol* 1992; 135: 12–19.
19. Dockery DW, Schwartz J, Spengler JD. Air pollution and daily mortality: association with particulates and acid aerosols. *Environ Res* 1992; 59: 362–373.
20. Schwartz J. Air pollution and daily mortality in Birmingham, Alabama. *Am J Epidemiol* 1993; 137: 1136–1147.
21. Spix C, Heinrich J, Dockery D, Schwartz J, *et al.* Air pollution and daily mortality in Erfurt, East Germany, 1980–1989. *Environ Health Perspectives* 1993; 101: 518–526.
22. Schwartz J. What are people dying of on high air pollution days? *Environ Res* 1994; 64: 26–35.
23. Katsouyanni K, Pantazopoulou A, Touloumi G, *et al.* Evidence for interaction between air pollution and high temperature in the causation of excess mortality. *Arch Environ Health* 1993; 48: 235–242.
24. Schwartz J. Air pollution and daily mortality: a review and meta-analysis. *Environ Res* 1994; 64: 36–52.
25. Ostro B. The association of air pollution and mortality: examining the case for inference. *Arch Environ Health* 1993; 48: 336–342.
26. Utell MJ, Samet JM. Particulate air pollution and health: new evidence on an old problem. (Editorial). *Am Rev Respir Dis* 1993; 147: 1334–1335.
27. Sunyer J, Saez M, Murillo C, Castellsague J, Martinez F, Anto JM. Air pollution and emergency room admissions for chronic obstructive pulmonary disease: a 5 year study. *Am J Epidemiol* 1993; 137: 701–705.
28. Schwartz J, Slater D, Larson TV, Pierson WE, Koenig JQ. Particulate air pollution and hospital emergency visits for asthma in Seattle. *Am Rev Respir Dis* 1993; 147: 826–831.
29. Cody RP, Weisel CP, Birnbaum G, Lioy PJ. The effect of ozone associated with summertime photochemical smog on the frequency of asthma visits to hospital emergency departments. *Environ Res* 1992; 58: 184–194.
30. Romieu I, Corts Lugo M, Ruiz Velasco S, Sanchez S, Meneses F, Hernadez M. Air pollution and school absenteeism among children in Mexico City. *Am J Epidemiol* 1992; 136: 1524–1531.
31. Ransom MR, Pope CA. Elementary school absences and PM10 pollution in Utah Valley. *Environ Res* 1992; 58: 204–219.
32. Krzyzanowski M, Quackenboss JJ, Lebowitz MD. Relation of peak expiratory flow rates and symptoms to ambient ozone. *Arch Environ Health* 1992; 47: 107–115.
33. Hoek G, Brunekreef B. Acute effects of a winter air pollution episode on pulmonary function and respiratory symptoms of children. *Arch Environ Health* 1993; 48: 328–335.
34. Hoek G, Brunekreef B, Kosterink P, Van den Berg R, Hofschrender P. Effect of ambient ozone on peak expiratory flow of exercising children in the Netherlands. *Arch Environ Health* 1993; 48: 27–32.
35. Anonymous. Heat-related deaths: Philadelphia and United States, 1993–1994. *Morb and Mort Weekly Rep* 1994; 43: 453–455.
36. Katsouyanni K (Ed). Study designs. Commission of the European Communities, Air Pollution Epidemiology Report Series. Report No. 4. Luxembourg Office for Official Publications of the European Communities, 1993.
37. Greenland S. Can meta-analysis be salvaged? *Am J Epidemiol* 1994; 140: 783–787.