Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Air Pollution and Health: a European

Acute Effects of Particulate Air Pollution on Respiratory Admissions

Results from APHEA 2 Project

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The APHEA 2 project investigated short-term health effects of particles in eight European cities. In each city associations between particles with an aerodynamic diameter of less than 10 μm (PM_{10}) and black smoke and daily counts of emergency hospital admissions for asthma (0–14 and 15–64 yr), chronic obstructive pulmonary disease (COPD), and all-respiratory disease (65+ yr) controlling for environmental factors and temporal patterns were investigated. Summary PM_{10} effect estimates (percentage change in mean number of daily admissions per 10 $\mu g/m^3$ increase) were asthma (0–14 yr) 1.2% (95% CI: 0.2, 2.3), asthma (15–64 yr) 1.1% (0.3, 1.8), and COPD plus asthma and all-respiratory (65+ yr) 1.0% (0.4, 1.5) and 0.9% (0.6, 1.3). The combined estimates for Black Smoke tended to be smaller and less precisely estimated than for PM_{10}. Variability in the sizes of the PM_{10} effect estimates between cities was also investigated. In the 65+ groups PM_{10} estimates were positively associated with annual mean concentrations of ozone in the cities. For asthma admissions (0–14 yr) a number of city-specific factors, including smoking prevalence, explained some of their variability. This study confirms that particle concentrations in European cities are positively associated with increased numbers of admissions for respiratory diseases and that some of the variation in PM_{10} effect estimates between cities can be explained by city characteristics.

Keywords: particles; respiratory admissions; heterogeneity; APHEA 2

The APHEA (Air Pollution and Health: a European Approach) project was initiated in 1993 with the aim of investigating whether there was epidemiological evidence for an adverse short-term effect of air pollution on health (1–2). In the six cities studied there were small, significant effects of particles and gases on daily hospital admissions and emergency room visits for respiratory disease (3–5). This large and comprehensive study together with evidence from other epidemiological studies provided substantial evidence that historically low levels of air pollution were associated with adverse health effects (6–8). However, there is still debate about the causal nature and importance of these small effects (9, 10). There remain unanswered questions concerning the biological mechanisms involved, the identification of the causal pollutant(s), and, not least, the interpretation and public health significance of the results (11).

One approach to addressing some of these questions is to standardize the analytical method and apply it to locations that differ in environmental and meteorological conditions as well as in the health status of their populations. In this way, the consistency of the pollution effect estimates across locations can be examined, and reasons for any substantial variability or heterogeneity in the size of the effect estimates can be investigated. The APHEA 2 project was initiated in 1998 with one of its aims being to tackle these issues. New, more recent datasets containing particles with an aerodynamic diameter of less than 10 μm (PM_{10}) measurements were available. This paper presents the results of the analysis of the associations between PM_{10} and Black Smoke (BS) and daily numbers of emergency admissions to hospital for respiratory disease, chronic obstructive pulmonary disease (COPD), and asthma in eight European cities. A second-stage investigation into possible causes of variability in PM_{10} effect estimates is also presented. Other papers from the APHEA 2 group will report findings for mortality, hospital admissions for cardiovascular causes, other pollutants, and a detailed examination of exposure–response relationships.

METHODS

Eight cities in the APHEA 2 group were able to provide hospital admissions data. They were Barcelona, Birmingham, London, Milan, The Netherlands (considered as a city because of its relatively small size and dense population), Paris, Rome, and Stockholm. Time series of daily counts of admissions were constructed for four groups of admissions: asthma (International Classification of Diseases, Revision 9 [ICD9] 493) ages 0–14 yr and 15–64 yr, COPD and asthma (ICD9 490–496) ages 65+ yr, and all-respiratory disease admissions (ICD9 460–519) ages 65+ yr. Where possible, emergency admissions resulting in an overnight hospital stay were specified to exclude elective admissions and those resulting only in an emergency room visit. The minimum time period for each series was 3 yr.

Daily 24-h average background concentrations of PM_{10} or total suspended particles (TSP), BS, and sulfur dioxide (SO_2) were used. For ozone (O_3) and carbon monoxide (CO) an 8-h average was used, and for nitrogen dioxide (NO_2) the daily maximum 1-h measure was used. All monitoring stations providing data were subject to criteria governing data completeness and location. Other environmental (daily temperature and humidity measures) and social (school and public holiday dates) data were also collected.

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See the Appendix for members of the APHEA 2 collaborative group.

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The statistical analyses of these time series data involved two steps. First, for each time series, a statistical model was constructed that included terms to describe the seasonal patterns in the admissions, their dependence on temperature and humidity, their association with holiday periods and influenza episodes, and finally air pollution measures. These models provided estimates of the effect of air pollution on the mean number of admissions per day. The variability or heterogeneity between the city-specific particle estimates within each outcome group was assessed using the chi-square test for heterogeneity. A significant result indicated that the variation in the effect estimates was greater than expected by chance and a summary estimate that accounted for this additional variation was calculated (random-effects estimate). Otherwise a simple, weighted average of the estimates or fixed-effects estimate was calculated. Where there was significant heterogeneity between estimates, further analyses were carried out to investigate possible reasons for this. In this second stage of the analyses, regression models were used to investigate associations between the eight particle effect estimates (for an outcome group) and variables describing the health and environmental conditions in each city. In this way factors that may affect the toxicity of the particles or the vulnerability of the exposed population (effect modifiers) could be explored. The details of these second-stage regressions and a fuller description of the time series methods used are available in a supplementary methods section on the Journal's web site.

The effects on particle estimates of adding a second pollutant were also investigated in each city, using a series of two-pollutant models. For each outcome studied, NO_2, SO_2, and O_3 were added, in turn, to the models for PM_{10}. Summary PM_{10} estimates adjusted for the second pollutants were also calculated.

RESULTS

The combined population in the eight cities totalled 38 million. Table 1 gives descriptive statistics for the respiratory outcomes studied in each city. The median daily number of respiratory admissions in the 65+ age group ranged from 11 to 55. The corresponding figures for asthma admissions in the 0–14 and 15–64 yr age groups were 0 to 18 and 0 to 13, respectively. Table 1 presents statistics for the whole period for which ad-

TABLE 1. DESCRIPTIVE STATISTICS FOR ADMISSION AND PARTICLE MEASURES FOR THE EIGHT CITIES STUDIED

City	Data Availability	Disease Outcome (*n/day*)/ Particle Measure ($\mu g/m^3$)	N	Minimum	Median	Maximum
Barcelona	1/1/94–31/12/96	Respiratory, 65+ yr	1096	1	11	36
		Asthma, 0–14 yr	1096	0	0	4
		Asthma, 15–64 yr	1096	0	1	8
		COPD + asthma, 65+ yr	1096	0	5	20
	1/1/94–31/12/96	PM_{10}	1096	17.1	53.3	131.7
	1/1/94–31/12/96	Black Smoke	1096	14.1	36.2	116.0
Birmingham	1/1/92–31/12/94	Respiratory, 65+ yr	1096	1	18	58
		Asthma, 0–14 yr	1096	0	7	39
		Asthma, 15–64 yr	1096	0	5	16
		COPD + asthma, 65+ yr	1096	0	6	20
	20/3/92–31/12/94	PM_{10}	1017	6.5	21.5	115
	1/1/92–31/12/94	Black Smoke	1096	1.5	11.5	57.1
London	1/1/92–31/12/94	Respiratory, 65+ yr	1096	13	55	150
		Asthma, 0–14 yr	1096	2	18	80
		Asthma, 15–64 yr	1096	2	13	85
		COPD + asthma, 65+ yr	1096	7	22	63
	25/1/92–31/12/94	PM_{10}	1072	7.8	24.9	80.4
	1/1/92–31/12/94	Black Smoke	1096	2.3	11.3	55.9
Milan	1/1/90–31/12/97	Respiratory, 65+ yr	2922	0	8	38
		Asthma, 0–14 yr	2922	0	0	6
		Asthma, 15–64 yr	2922	0	0	5
		COPD + asthma, 65+ yr	2922	0	2	16
	19/1/90–31/12/97	TSP	2904	18.3	60.5	149.2
Netherlands	1/1/88–30/9/95	Respiratory, 65+ yr	2830	11	51	206
		Asthma, 0–14 yr	2830	0	5	24
		Asthma, 15–64 yr	2830	0	5	17
		COPD + asthma, 65+ yr	2830	2	26	99
	1/1/92–30/9/95	PM_{10}	1369	11.3	33.4	130.8
	1/1/89–30/9/95	Black Smoke	2464	1.2	9.1	116.6
Paris	1/1/92–30/9/96	Respiratory, 65+ yr	1735	1	23	64
		Asthma, 0–14 yr	1735	0	5	23
		Asthma, 15–64 yr	1735	0	7	28
		COPD + asthma, 65+ yr	1735	0	5	21
	1/1/92–30/9/96	PM_{13}	1735	5.8	20.1	80.9
	1/1/92–30/9/96	Black Smoke	1735	4.5	18.6	142.2
Rome	1/1/95–31/10/97	Respiratory, 65+ yr	1035	3	19	52
		Asthma, 0–14 yr	1035	0	1	11
		Asthma, 15–64 yr	1035	0	2	11
		COPD + asthma, 65+ yr	1035	0	9	24
	1/1/95–18/7/97	TSP	930	19.7	69.2	132.6
Stockholm	1/1/88–31/12/96	Respiratory, 65+ yr	3288	0	10	35
		Asthma, 0–14 yr	3288	0	1	9
		Asthma, 15–64 yr	3288	0	1	8
		COPD + asthma, 65+ yr	3288	0	5	17
	9/3/94–8/12/96	PM_{10}	1006	4.3	13.6	43.3

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; PM_{10}, PM_{13} = particles with an aerodynamic diameter of less than 10 and 13 μm; TSP = total suspended particles.

missions data were available; the series analyzed, however, varied according to availability of individual pollutants.

Table 1 also summarizes the distributions of the particle measures for each city. The duration of the particle series ranged from 930 to 2904 d. For five cities the median daily levels of PM_{10} ranged from 14 to 53 $\mu g/m^3$. Two cities (Milan and Rome) recorded median daily TSP levels of 61 and 69 $\mu g/m^3$ and one city (Paris) reported median daily levels of PM_{13} of 20 $\mu g/m^3$. Five cities provided measures of BS. Correlation coefficients between daily PM_{10}/PM_{13}/TSP and BS measures ranged from 0.5 to 0.8 and the number of monitoring stations in each city ranged between 1 and 12 (data not shown).

City-specific variables that may account for heterogeneity in the particle effect estimates are shown in Table 2. Between cities there was a 4.5- and 3.5-fold variation in average daily PM_{10} and BS levels, respectively. The corresponding figures for SO_2, O_3, NO_2, and CO were 7.6, 2.6, 4.1, and 11.3. Daily O_3 concentrations were the least correlated with daily PM_{10} measures, the correlation coefficients ranging from −0.28 to 0.4. The correlation between daily levels of PM_{10} and SO_2 and NO_2 were positive in all cities, ranging from 0.15 (Rome) to 0.77 (Birmingham) for SO_2 and from 0.3 (Stockholm) to 0.72 (Milan) for NO_2. Average daily temperature and humidity levels also varied substantially between cities.

Table 3 tabulates city-specific results for PM_{10}, PM_{13}, or TSP for each outcome studied. Fixed-effect and, where appropriate, random-effect estimates are also given.

Asthma Admissions, Age 0–14 yr

Particle-effect estimates varied substantially between centers, chi-square statistic for test for heterogeneity (χ^2) = 21.3, and degrees of freedom (df) = 7. For cities recording PM_{10} or PM_{13} measures, the associations ranged from a decrease in admissions, −0.9% (95% CI: −2.1, 0.4) to an increase of 2.8% (95% CI: 0.8, 4.8). The overall random-effects estimate was 1.2% (95% CI: 0.2, 2.3) indicating a positive association between admissions in children and PM_{10} levels. Results for BS were homogeneous, χ^2 = 3.5, df = 4. The fixed-effects estimate for BS was 1.3% (95% CI: 0.3, 2.4).

Asthma Admissions, Age 15–64 yr

Associations with both particle measures were consistently positive with no evidence of heterogeneity. The fixed-effect PM_{10} estimate was similar to that for children, 1.1% (95% CI: 0.3, 1.8). The corresponding BS estimate was 0.7% (95% CI: −0.3, 1.8).

Admissions for COPD and Asthma, Age 65+ yr

In all but one city, associations between PM_{10}/PM_{10}/TSP and admissions for COPD and asthma were positive. There was weak evidence of heterogeneity, χ^2 = 9.2, df = 7, and, unsurprisingly, the fixed and random-effect estimates were very similar, 1.0% (95% CI: 0.4, 1.5). Results for BS for this subgroup were also heterogeneous, ranging from −2.1% to 2.2%. The summary estimate for BS was 0.2% (−0.7, 1.1).

Admissions for All-respiratory Disease, Age 65+ yr

Associations between PM_{10} and admissions for respiratory disease were mostly positive and confidence intervals were generally smaller than for other subgroups reflecting the larger number of admissions for respiratory disease. For respiratory admissions the summary random-effects model estimate was 0.9% (95% CI: 0.6, 1.3). The BS associations for the all-respiratory group were more variable, but overall showed no statistically significant association.

Two-pollutant Models

Summary estimates for two-pollutant models are presented in Table 4 for each of the four outcome groups. The purpose of these analyses was to assess the sensitivity of the size, direction, and precision of the PM_{10} effect estimates to the inclusion of other pollutants in the models. NO_2, O_3, CO, and SO_2 were investigated.

The association between asthma admissions and PM_{10} was removed with the inclusion of NO_2. For example, in children aged 0–14 yr, the change in daily number of admissions associated with 10 $\mu g/m^3$ increases in daily PM_{10} levels was reduced from 1.2% (95% CI: 0.2, 2.3) to 0.1% (95% CI: −0.8, 1.0) after the inclusion of NO_2 in the city-specific models. In the two 65+ age groups the inclusion of NO_2 decreased the precision of the PM_{10} effect estimates but their magnitudes were largely unchanged. The inclusion of SO_2 in the models only modified PM_{10} associations in the 0–14 yr age group and the inclusion of O_3 only affected those associations found in admissions for COPD and asthma in the 65+ age group. For CO only particle effects in the asthma 0–14 yr group were reduced.

Factors Explaining Variability in the PM_{10} Effect Estimates

The three groups showing evidence of heterogeneity in PM_{10} effect estimates (asthma admissions in 0–14 yr, admissions for COPD plus asthma, and all-respiratory admissions in the 65+

TABLE 2. VARIABLES DESCRIBING THE ENVIRONMENTAL CONDITIONS AND HEALTH STATUS OF THE POPULATION IN EACH CITY

	Pollutant Level* ($\mu g/m^3$)				Temperature*	Humidity*	Correlation Coefficient with PM_{10}					Number	Number of Lung Cancer		Smoking Prevalence	
City	SO_2	O_3	NO_2	CO	(° C)	(%)	SO_2	O_3	NO_2	Temperature	Humidity	of Deaths†	Deaths‡	> 65 yr§	(%)	Area‖
Barcelona	NA¶	59.3	94.4	7.9	16.8	77.0	0.32	0.03	0.48	−0.02	0.11	740	48	17	36	156
Birmingham	24.3	44.3	75.8	1.1	10.0	78.3	0.77	−0.28	0.68	−0.13	0.11	895	49	15	29	900
London	23.6	34.9	95.9	1.5	12.0	70.5	0.72	0.00	0.70	0.20	0.04	851	50	14	34	1600
Milan	29.1	43.3	147.0	5.0	14.0	68.4	0.64	−0.25	0.72	−0.21	0.17	632	41	21	25	182
Netherlands	8.5	57.7	50.1	0.7	10.4	83.1	0.67	−0.01	0.64	−0.07	−0.08	757	52	13	36	41526
Paris	17.7	36.3	87.2	NA¶	12.3	75.3	0.63	−0.11	0.44	−0.17	0.12	640	42	9	30	657
Rome	9.8	26.0	139.7	3.9	16.2	60.3	0.15	0.12	0.32	0.21	0.03	585	47	15	35	1283
Stockholm	3.8	66.6	35.6	0.7	8.0	71.1	0.36	0.40	0.30	0.06	−0.13	666	31	17	22	500

Definition of abbreviations: PM_{10} = particles with an aerodynamic diameter of less than 10 μm.
* Mean daily level.
† Standardized number of deaths due to all causes.
‡ Standardized number of deaths due to lung cancer.
§ Percentage of population over 65 yr old.
‖ Area of city covered by health statistics.
¶ NA = not available, pollutant not measured.

TABLE 3. SINGLE POLLUTANT MODEL RESULTS AND POOLED ESTIMATES FOR PARTICLE MEASURE*

Disease Group	City	Measure	Estimate (*95% CI*)	Measure	Estimate (*95% CI*)
Asthma, 0–14 yr	Barcelona	PM_{10}	2.7 (−4.9, 10.9)	BS	10.4 (0.4, 21.4)
	Birmingham	PM_{10}	2.8 (0.8, 4.8)	BS	2.0 (−1.9, 6.0)
	London	PM_{10}	0.6 (−0.8, 2.0)	BS	1.1 (−1.3, 3.6)
	Milan	TSP	3.0 (1.3, 4.8)	NA	
	Netherlands	PM_{10}	−0.9 (−2.1, 0.4)	BS	1.4 (−0.4, 3.3)
	Paris	PM_{13}	0.7 (−1.5, 3.0)	BS	0.9 (−0.8, 2.7)
	Rome	TSP	1.0 (−2.4, 4.6)	NA	
	Stockholm	PM_{10}	1.7 (−6.0, 10.2)	NA	
	Summary estimate	PM_{10} (RE)	1.2 (0.2, 2.3)	BS (FE)	1.3 (0.3, 2.4)
	Heterogeneity		$\chi^2 = 21.3$, df = 7		$\chi^2 = 3.5$, df = 4
Asthma, 15–64 yr	Barcelona	PM_{10}	0.4 (−3.5, 4.4)	BS	2.1 (−3.0, 7.5)
	Birmingham	PM_{10}	2.5 (0.1, 4.9)	BS	2.8 (−1.9, 7.7)
	London	PM_{10}	1.4 (−0.1, 3.0)	BS	1.8 (−0.9, 4.5)
	Milan	TSP	0.3 (−1.6, 2.3)	NA	
	Netherlands	PM_{10}	0.4 (−0.9, 1.8)	BS	−0.4 (−2.2. 1.5)
	Paris	PM_{13}	1.2 (−0.7, 3.2)	BS	0.8 (−0.7, 2.3)
	Rome	TSP	1.1 (−2.2, 4.4)	NA	
	Stockholm	PM_{10}	5.4 (−4.0, 15.7)	NA	
	Summary estimate	PM_{10} (FE)	1.1 (0.3, 1.8)	BS (FE)	0.7 (−0.3, 1.8)
	Heterogeneity		$\chi^2 = 3.6$, df = 7		$\chi^2 = 2.9$, df = 4
COPD + asthma, 65+ yr	Barcelona	PM_{10}	2.6 (1.0, 4.3)	BS	−2.1 (−4.3, 0.0)
	Birmingham	PM_{10}	0.5 (−1.4, 2.6)	BS	2.2 (−1.7, 6.2)
	London	PM_{10}	0.3 (−0.8, 1.5)	BS	0.4 (−1.6, 2.5)
	Milan	TSP	0.9 (0.0, 1.7)	NA	
	Netherlands	PM_{10}	1.1 (0.5, 1.7)	BS	0.7 (−0.2, 1.6)
	Paris	PM_{13}	−0.6 (−2.5, 1.3)	BS	0.2 (−1.3, 1.6)
	Rome	TSP	0.5 (−0.8, 1.9)	NA	
	Stockholm	PM_{10}	2.7 (−1.5, 7.1)	NA	
	Summary estimate	PM_{10} (RE)	1.0 (0.4, 1.5)	BS (RE)	0.2 (−0.7, 1.1)
	Heterogeneity		$\chi^2 = 9.2$, df = 7		$\chi^2 = 6.6$, df = 4
All respiratory, 65+ yr	Barcelona	PM_{10}	2.0 (0.8, 3.1)	BS	−0.7(−2.3, 0.9)
	Birmingham	PM_{10}	0.9 (−0.3, 2.2)	BS	2.9 (0.6, 5.4)
	London	PM_{10}	0.4 (−0.3, 1.2)	BS	−1.1 (−2.4, 0.3)
	Milan	TSP	0.8 (0.3, 1.3)	NA	
	Netherlands	PM_{10}	1.2 (0.7, 1.6)	BS	0.0 (−0.7, 0.7)
	Paris	PM_{13}	−0.1 (−1.3, 1.0)	BS	0.5 (−0.4, 1.4)
	Rome	TSP	0.5 (−0.4, 1.5)	NA	
	Stockholm	PM_{10}	1.7 (−1.2, 4.7)	NA	
	Summary estimate	PM_{10} (RE)	0.9 (0.6, 1.3)	BS (RE)	0.1 (−0.7, 0.9)
	Heterogeneity		$\chi^2 = 9.6$, df = 7		$\chi^2 = 10.3$, df = 4

Definition of abbreviations: BS = Black Smoke; COPD = chronic obstructive pulmonary disease; df = degrees of freedom; FE = fixed-effects estimates; NA = not available; PM_{10}, PM_{13} = particles with an aerodynamic diameter of less than 10 and 13 μm; RE = random-effects estimates; TSP = total suspended particles; χ^2 = chi-square test for heterogeneity.

* Table gives the associations as percentage change in mean number of admissions associated with 10 $\mu g/m^3$ increases in particle measures. Only TSP measures were available in Milan and Rome. TSP estimates for Milan and Rome are scaled (PM_{10} = TSP/0.75) for inclusion in fixed (FE) and random-effects (RE) estimates. PM_{13} estimates for Paris are assumed to equate to PM_{10} measures. No BS measurements were available from Stockholm, Milan, or Rome.

yr age groups) were investigated using the 16 potential explanatory factors in Table 2. Table 5 gives standardized, second-stage regression estimates and their standard errors for those modifiers that reduced the χ^2 statistic by at least 40%. These estimates and standard errors indicate the direction, magnitude, and precision of the (linear) associations between the city-specific PM_{10} estimates and the city-specific levels of the explanatory factors. The TSP estimates have been scaled to make them comparable with the PM_{10}/PM_{13} estimates prior to these analyses.

TABLE 4. SUMMARY PM_{10} ESTIMATES FROM TWO-POLLUTANT MODELS*

Outcome	PM_{10} Only	+ NO_2	+ O_3	PM_{10} Only‡	+ SO_2	PM_{10} Only§	+ CO
Asthma, 0–14 yr	1.2 (0.2, 2.3)	0.1 (−0.8, 1.0)	1.3 (0.1, 2.5)†	1.3 (0.2, 2.5)	0.8 (−3.7, 5.6)†	1.5 (0.2, 2.7)	0.7 (−0.3, 1.7)†
Asthma, 15–64 yr	1.1 (0.3, 1.8)	0.4 (−0.5, 1.3)	1.1 (0.1, 2.1)†	1.1 (0.3, 1.9)	1.6 (0.6, 2.6)	1.0 (0.2, 1.9)	0.8 (0.2, 1.4)†
COPD + asthma, 65+ yr	1.0 (0.4, 1.5)	0.8 (−0.6, 2.1)†	0.4 (−1.5, 2.2)†	0.9 (0.5, 1.3)	1.3 (0.7, 1.8)	1.1 (0.7, 1.5)	1.0 (0.4, 1.5)†
All respiratory, 65+ yr	0.9 (0.6, 1.3)	0.7 (−0.3, 1.7)†	0.8 (0.2, 1.4)†	0.9 (0.6, 1.2)	1.1 (0.7, 1.4)	1.1 (0.8, 1.4)	1.0 (0.7, 1.3)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; PM_{10} = particles with an aerodynamic diameter of less than 10 μm.

* Table gives the percentage change in the mean daily number of admissions associated with 10 $\mu g/m^3$ increases in PM_{10}. The estimates are fixed or random-effect (†) estimates for all eight cities derived using a second-stage regression of results from city-specific two-pollutant models.

‡ Summary PM_{10} estimates derived from single-pollutant models excluding Barcelona (no SO_2 data available).

§ Summary PM_{10} estimates derived from single-pollutant models excluding Paris (no CO data available).

TABLE 5. REGRESSION ESTIMATES (STANDARD ERRORS) FOR EFFECT MODIFIERS IN A SECOND-STAGE ANALYSIS OF PARTICLE (PM_{10}) EFFECT ESTIMATES*

Effect Modifier	EM Regression Estimate	SE	χ^2, df	Reduction in χ^2 (%)	EM IQR	Standard Regression Estimate	SE
Asthma, 0–14 yr							
Humidity, daily mean	−0.000141	0.000079	12.2, 6	43	7.4	−0.001043	0.000585
Smoking prevalence	−0.000176	0.000075	10.5, 6	51	7.3	−0.001285	0.000548
Population over 65, %	0.000367	0.000106	9.4, 6	56	3.3	0.001211	0.000350
COPD + asthma, 65+ yr							
Ozone, daily mean	0.000040	0.000020	5.2, 6	43	22.2	0.000888	0.000444
All-respiratory, 65+ yr							
Ozone, daily mean	0.000033	0.000014	3.9, 6	59	22.2	0.000733	0.000311

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; df = degrees of freedom; EM = effect modifier; IQR = interquartile range; PM_{10} = particles with an aerodynamic diameter of less than 10 μm; χ^2 = chi-square test.

* Regression estimates are from a second-stage linear regression of PM_{10} coefficients on the effect modifier. The regression coefficients indicate the change in the PM_{10} effect estimate on hospital admissions for unit changes in the effect modifiers. Only factors giving at least a 40% reduction in the χ^2 statistic are shown. Standardized regression estimates are calculated by multiplying the effect modifier regression estimate by the interquartile range of the effect modifier. It enables the impact of each effect modifier on the particle effect estimate to be compared.

Mean daily O_3 levels were positively associated with the size of the PM_{10} effect estimates in both the 65+ age groups. Figure 1 illustrates the results for all-respiratory disease and mean daily O_3 levels. It shows the city-specific PM_{10} regression coefficients plotted against O_3 levels in each center, together with the estimated regression equation from the second-stage analysis. There were no such associations with the daily PM_{10}/O_3 correlation coefficients within each center. Mean daily humidity levels, the number of PM_{10} monitoring stations providing data, smoking prevalence in each city, the standardized number of lung cancer deaths, and the proportion of the population over the age of 65 were all associated with the magnitude of the PM_{10} regression coefficients for asthma, 0–14 yr. A scatterplot of these data (not shown) suggested that the relationships between regression estimates and values for mean daily humidity levels and number of monitoring stations were not convincing and may have been unduly influenced by outliers. Within-city correlation coefficients between daily PM_{10} and humidity levels were not associated with the size of the particle estimates.

DISCUSSION

In this study we have found small, positive associations between daily levels of particles and admissions for respiratory diseases. Summary estimates for PM_{10} were typically increases of 1% in mean daily admissions for 10 $\mu g/m^3$ increases in PM_{10}. Estimates for BS were generally smaller. There was evidence to suggest that large proportions of the between-city variability in PM_{10} effect estimates in the two 65+ yr age groups could be explained by average levels of ozone. We have also shown that, in some instances, the summary particle effect estimates were either removed or moderated by the inclusion of a second pollutant.

The study was designed to examine short-term effects of particles on respiratory admissions and, in particular, to examine sources of variability between effect estimates. A number of potential problems faced in this type of analysis were taken into account in the design of the study. First, the analyses of each city's data were undertaken centrally using a standardized method. This approach reduced the potential for inconsistencies in the results that could have arisen from different analysts applying different methods. Second, by analyzing a priori lag intervals for each pollutant, the potential for reporting spurious relationships between particles and admissions was minimized. The agreed criteria for including monitoring stations, uniform treatment of missing pollutant data, standardized definitions for the daily measures of each pollutant, together with agreed definitions for each outcome ensured that the data were collected and processed in a consistent manner across cities. This further minimizes extraneous sources of variability in the particle effects. Three centers were unable to differentiate between emergency and elective admissions. However, an analysis of the London admissions data suggested that the *lower* respiratory series selected for analysis would contain relatively small numbers of elective admissions (data not shown).

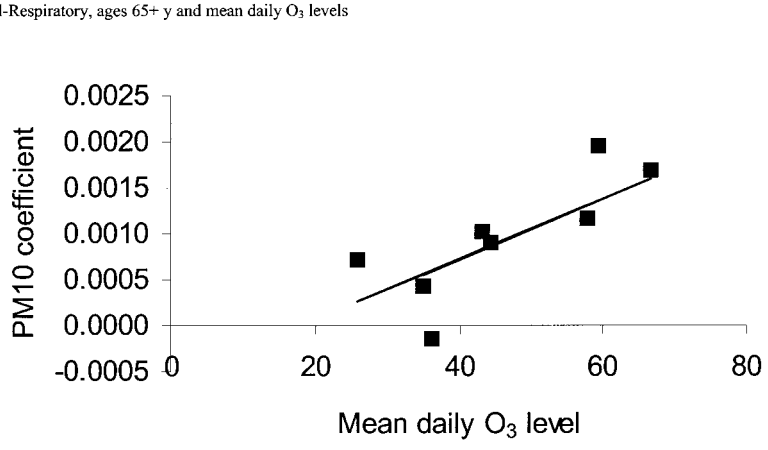

Figure 1. Plot of city-specific PM_{10} regression estimates against mean daily ozone levels in each city. Individual cities' PM_{10} effect estimates are plotted against mean daily ozone in each city. The straight line represents the estimated second-stage regression equation indicating the association between the magnitude of the PM_{10} effect estimates and mean ozone levels.

Hospital admissions data were available only from eight cities within the APHEA 2 group. Although this small number of cities does not pose a problem for the within-city analyses, it does limit the power of the study in the second-stage regression analyses. Furthermore, there were no a priori hypotheses for these analyses and because of the large number of statistical tests, the results of this second-stage analyses should be interpreted with some caution. As in all time series studies that rely upon exposure measurements from a small number of fixed site monitors, there is the potential for exposure misclassification. This type of error can produce a nondifferential bias and thus a conservative estimation of the effect. In some cases, however, this type of error can result in an overestimation of the effect (12). Exposure measurement error may be less of a problem for fine particles than for gases due to their more homogeneous geographical distribution (13).

In this analysis separate models were constructed for each disease outcome to provide the most appropriate control for confounding factors for each individual series. This approach was appropriate because the degree of smoothing required to model seasonal patterns adequately could differ between cities. Furthermore, this process was carried out prior to the inclusion of the particle measures in the statistical models. In this way potential bias during the model-building stages was averted.

PM_{10} data were unavailable to the original APHEA investigators, so comparisons with results of the original APHEA meta-analyses are not possible. However, it is possible to compare results from the two projects for BS (3–5). Also, there are a number of reviews of published studies that can be used for comparative purposes. For admissions for respiratory disease Schwartz summarized a selection of U.S. studies and reported approximate increases in respiratory admissions of 1.3% for 10 $\mu g/m^3$ increases in PM_{10} (8). This is comparable with the random-effects summary estimate of 0.9% from the present study. The U.S. Environmental Protection Agency (EPA) reviewed the evidence for health effects of particles, including admissions time-series studies, and tabulated results from a large number of studies (14). The EPA reports that particle effects ranged from approximately 1% to 5% for 10 $\mu g/m^3$ increases.

For COPD plus asthma admissions in the 65+ age group, the particle (PM_{10}) effect estimate from APHEA 2 was smaller (1.0% for 10 $\mu g/m^3$ increases in PM_{10}) than those found in five U.S. cities where increases in mean number of daily admissions ranged from 1.3 to 3.7% for 10 $\mu g/m^3$ increases in PM_{10} (15). The EPA review reported estimates of between 1% and 5% for 10 $\mu g/m^3$ increases in PM_{10} from their selection of (mainly U.S.) studies (14). The recent National Morbidity, Mortality and Air Pollution Study (NMMAPS) studied associations between hospital admissions for COPD and particles in 14 U.S. cities. They reported a small, significant summary effect of PM_{10} on COPD admissions in those aged 65+ yr, 1.98% (95% CI: 1.49, 2.47) per 10 $\mu g/m^3$ increase (16). Overall there is a tendency for estimates from European cities to be smaller than for U.S. cities. However, for BS and COPD admissions, the results from the APHEA 1 and 2 projects are not inconsistent, 0.7% (95% CI: 0.2, 1.4) and 0.2% (95% CI: −0.7, 1.1) for 10 $\mu g/m^3$ increases in BS, respectively, given the wide confidence intervals.

For admissions for asthma there are fewer studies with which to compare results, particularly so from the United States, where routine data collection on admissions is only for those aged 65 and over. Schwartz reported a 3.7% increase in admissions for asthma in the 0–64 age group in Seattle associated with a 10 $\mu g/m^3$ increase in PM_{10} (17). This compares with an increase in admissions in the 15–64 age group of 1.1% found in the present study. For BS, Sunyer and coworkers reported a summary estimate of 0.6% for four cities in APHEA I (5). This is comparable with the 0.7% summary estimate from five cities in APHEA 2 (three of which were included in the APHEA I analysis) with available BS data. Figures for children's asthma from the two APHEA studies were 0.9% and 1.3%.

Studying particle effects in different environments was one of the key motivations behind the APHEA 2 project. In this way environmental and social factors that explain variation between cities in the sizes of the particle estimates could be investigated. For hospitalizations for respiratory disease in the 65+ age group there was significant variability in the sizes of effect estimates. Mean daily ozone levels between cities explained a significant proportion of this variability (Table 5 and Figure 1). Daily correlation coefficients between PM_{10} and O_3, however, did not explain any of this heterogeneity. Furthermore, in two-pollutant models the PM_{10} summary regression estimate was largely unaltered by the inclusion of O_3. Therefore, these results suggest that it is the average levels of O_3 in each city rather than the day-to-day covariation between PM_{10} and O_3 that is important in determining the variation in the particle associations between cities.

It is known that secondary particle levels peak during summer months when the formation of secondary particles depends upon reactions involving hydroxy radical (OH), O_3, and H_2O_2 during the photochemical smog formation process (14, 18–20). This process is the same photochemical process that produces O_3. If secondary particle concentrations were more potent in producing respiratory effects than primary particles then average O_3 concentrations in each city would explain some of the variation in the PM_{10} effect estimates. A possible alternative explanation is that there is a biological interaction whereby exposure to O_3 increases an individual's sensitivity to particles. Such an interaction has been shown for ozone and aeroallergens (21, 22) and this may hold true for air pollution particles also. The results for all respiratory admissions were largely replicated in the other 65+ yr group studied—those admitted with COPD or asthma. However, the two-pollutant models suggested some confounding with O_3.

For admissions for asthma for children aged 0–14 yr, the PM_{10} regression estimates were confounded with day-to-day variations in NO_2 and SO_2 levels but not O_3 levels (Table 5). None of the average pollutant levels including NO_2 explained variation in the size of the particle effect estimates between cities. This day-to-day confounding with NO_2 suggests that the particle effects observed in this group may be due to particles derived from a source that is also correlated with the daily levels of NO_2, perhaps traffic-related sources. The mean annual levels of NO_2 were not associated with the city-specific particle effect sizes in the second-stage regressions, suggesting that NO_2 was not involved in the formation of the particles for which an association with asthma admissions was observed. However, this category of admissions has the smallest daily numbers of admissions (Table 1) and so the least power to detect associations with pollutants. The results should therefore be interpreted with some caution. Both smoking prevalence and the standardized number of deaths due to lung cancer in the cities were negatively associated with the PM_{10} effect estimates. The meaning of these associations is not clear. It may be that in cities with high smoking rates an individual's exposure to outdoor particles is a small proportion of their exposure to particles from all sources, indoor and outdoor. As a result the (small) effects of outdoor particles are not easily detected. Conversely, young individuals regularly exposed to tobacco smoke may be less sensitive to relatively low levels of

outdoor particle pollution. It is not possible to determine from this study which, if any, of these explanations are true.

In conclusion, this study has confirmed that particle air pollution was associated with daily admissions for respiratory disease in a selection of European cities. These associations were consistent with, though generally lower than, results from other studies, mainly from North America. Average daily ozone levels explained a large proportion of the between-city variability in the size of the particle effect estimates in the over 65 yr age group. These results suggest that secondary particles, formed by the same photochemistry that produces O_3, may have been responsible for the observed particle effects in the over 65 yr age group. In children, the particle effects were confounded with NO_2 on a day-to-day basis, suggesting that traffic-related particles could have been the relevant component of the PM_{10} particle fraction.

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APPENDIX

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