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Lung function and indicators of exposure to indoor and outdoor particulate matter among asthma and COPD patients

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ABSTRACT

Objectives: Misclassification of exposure related to the use of central sites may be larger for ultrafine particles than for particulate matter $\leqslant 2.5$ μm and $\leqslant 10$ μm ($PM_{2.5}$ and PM_{10}) and may result in underestimation of health effects. This paper describes the relative strength of the association between outdoor and indoor exposure to ultrafine particles, $PM_{2.5}$ and PM_{10} and lung function.

Methods: In four European cities (Helsinki, Athens, Amsterdam and Birmingham), lung function (forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1) and peak expiratory flow (PEF)) was measured three times a day for 1 week in 135 patients with asthma or chronic obstructive pulmonary disease (COPD), covering study periods of >1 year. Daily concentrations of particle number, $PM_{2.5}$ and PM_{10} were measured at a central site in each city and both inside and outside the subjects' homes.

Results: Daily average particle number concentrations ranged between 2100 and 66 100 particles/cm^3. We found no association between 24 h average particle number or particle mass concentrations and FVC, FEV_1 and PEF. Substituting home outdoor or home indoor concentrations of particulate air pollution instead of the central site measurements did not change the observed associations. Analyses restricted to asthmatics also showed no associations.

Conclusions: No consistent associations between lung function and 24 h average particle number or particle mass concentrations were found in panels of patients with mild to moderate COPD or asthma. More detailed exposure assessment did not change the observed associations. The lack of association could be due to the high prevalence of medication use, limited ability to assess lagged effects over several days or absence of an effect.

What this paper adds

- Short-term increases in particulate matter air pollution have been associated with decreased lung function in children and adults.
- Some epidemiological studies found stronger associations between central site measurements of ultrafine particles and lung function decrements than with particulate matter $\leqslant 10$ μg (PM_{10}) but other studies reported similar or smaller effects.
- Some of these inconsistencies may be due to more exposure misclassification for ultrafine particles than for PM_{10}/particulate matter $\leqslant 2.5$ μg ($PM_{2.5}$), related to using a central site.
- No consistent associations between lung function and 24 h average particle number or particle mass concentrations were found in panels of patients with mild to moderate chronic obstructive pulmonary disease or asthma.
- More detailed exposure assessment by using home outdoor and home indoor concentration levels of ultrafine particles, PM_{10} and $PM_{2.5}$ instead of central site measurements did not change the lack of associations.

Numerous studies have reported short-term effects of outdoor air pollution on mortality, hospital admissions for cardiopulmonary disease, respiratory symptoms, lung function and changes in cardiac function.[1] Particulate matter, usually that $\leqslant 10$ μm in aerodynamic diameter (PM_{10}) is the main driver of the observed health effects. Toxicological studies have shown that ultrafine particles (<100 nm in aerodynamic diameter) may be most toxic.[2 3] The ultrafine fraction accounts for <1% of the mass of particulate matter, but the greater proportion in terms of numbers.[2 4 5] Ultrafine particles may be harmful because of the large numbers, the large (reactive) surface area, more effective deposition in the lungs[6] and their ability to penetrate into the interstitium of the lungs.[7]

There are few epidemiological studies on the effects of ultrafine particles on respiratory health.[8–13] Some studies suggested that ultrafine particles were more strongly associated with lung function decrements than PM_{10}[11 13] but other studies reported similar[8 9 12] and even smaller effects of ultrafine particles compared with PM_{10}.[10]

Some of these inconsistencies may be due to differences in exposure assessment which usually relied on central site measurements of air pollution. While there is evidence that central site concentrations of $PM_{2.5}$ and PM_{10} are a good approximation of personal exposure[14] it is largely unknown how well ultrafine particle measurements at a fixed outdoor site represent personal exposure.[5] If exposure misclassification is larger for ultrafine particles than for PM_{10}/$PM_{2.5}$, more underestimation of potential health effects in epidemiological studies for ultrafine particles may occur.

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The Relationship between Ultrafine and fine Particulate matter in Indoor and Outdoor air and respiratory Health (RUPIOH) study was designed to assess the impact of more detailed exposure assessment, by comparing the health effects related to simultaneous measurements of fine and ultrafine particles at a central site, inside and directly outside study participants' homes. In this paper, the relative strength of the association between outdoor and indoor exposure to fine and ultrafine particles and lung function in subjects with asthma or chronic obstructive pulmonary disease (COPD) is described. Relationships between central site outdoor, residential outdoor and indoor concentrations have been published previously.[15 16]

MATERIALS AND METHODS

Study design

A multicentre study was conducted from October 2002 to March 2004 in Helsinki (Finland), Athens (Greece), Amsterdam (the Netherlands) and Birmingham (UK). During the whole study period a reference site in each city was used to monitor particle mass and particle number concentration on a daily basis. At various locations covering the entire metropolitan area, homes of subjects with either asthma or COPD were selected. Air pollution monitoring was successively performed for 1 week in the selected homes indoors (living room) and directly outdoors. During this week, respiratory health was characterised by spirometry, a symptom diary, collection of exhaled breath condensate and urine sample for CC16 determination. This paper focuses on lung function. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1) and peak expiratory flow (PEF) were measured three times per day with data storage spirometers. Mixed models were used to assess the association between 24 h average particle concentrations from the central site, home outdoor and home indoor locations and lung function.

Study population

The inclusion criteria were age ⩾35 years, a doctor diagnosis of asthma or COPD and having experienced chronic respiratory symptoms in the previous 12 months. Subjects unable to perform a satisfactory spirometry test and severe patients, defined as using bronchodilating reliever medications for >3 times a day or using nebulised bronchodilators or long-term oxygen treatment, were excluded. Preference was given to non-working subjects to eliminate potential confounding by occupational exposures to airborne particles and to approximate personal exposure closer by the indoor measurements. We attempted to select non-smokers living in a non-smoking household to avoid confounding by environmental tobacco smoke. Although recruitment methods differed across the four centres, the same screening questionnaire was used to check eligibility.

In Finland, subjects were selected from the Helsinki Metropolitan Area through advertisements in the respiratory patient association magazine, newspapers and notice boards of pulmonary disease clinics of four major hospitals. Eligible subjects were interviewed by telephone and invited to an information session.

In Greece, patients from the Athens greater area were recruited through local chest physicians. Eligible subjects were contacted by phone. Those willing to participate were visited by investigators to check inclusion criteria.

In the Netherlands, subjects across the city of Amsterdam were approached by distributing 10 000 information letters and through a call for participation in a local newspaper. Eligible subjects were visited by investigators to check inclusion criteria.

In the UK, subjects living in the greater area of Birmingham were selected from the Chest Research Institute database of respiratory patients at Birmingham Heartlands Hospital, restricted to those who had given written consent to be approached for research studies. Local general practices were approached as well as targeted recruitment from the Birmingham Chest Clinic. Finally, an advertisement was placed in a local newspaper.

Medical ethical clearance was acquired from the local medical ethics committees in all centres before the start of the recruitment. Written informed consent was obtained from each subject.

Lung function

The Diary Card (Micro Medical Ltd., Rochester, UK) was used for lung function monitoring. This device is a compact, battery-operated and portable data-recording spirometer measuring FVC, FEV_1 and PEF. The spirometer uses a turbine to measure flows, so no adjustment to volumes at body temperature and pressure saturated (BTPS) is necessary. The instrument fulfils American Thoracic Society requirements[17] and has been tested in previous studies.[18 19] Advantages compared with the frequently used Mini Wright meters (Clement Clarke International Ltd, London, UK) are that the subject does not have to record data and that FVC and FEV_1 data are obtained.

During the first home visit the subjects were instructed on how to perform the forced expiratory manoeuvre. The subjects were asked to perform three tests a day (morning, lunch and evening) during the monitoring week. The spirometer was programmed for a morning test between 7:00 and 10:00, a lunch test between 12:00 and 14:00, and an evening test between 20:00 and 24:00. One test outside these time windows was allowed. At two check visits, feedback was given to the subjects. A test consisted of two acceptable manoeuvres. The system was programmed to give instructive messages after every manoeuvre. The device was programmed to reject manoeuvres without a peak (peak expiratory flow time >120 ms), with a slow start (back extrapolated volume >150 ml) or with cough or an early termination. A warning message was also given if any of these occurred and the subject was instructed to repeat the manoeuvre. Before and after every monitoring week, five syringe checks and two spirometric manoeuvres by a field technician were performed. The syringe check had to be within 3.5% for all five checks. FVC and FEV_1 of the technician had to be within 6% and PEF within 15% of the mean value of the technician.

Baseline characteristics were collected with a questionnaire, including subject biometry and daily medication use. Height and age were used to calculate predicted values for FEV_1, FVC and PEF, using sex-specific equations.[20] Information on reliever medication use was collected with a daily questionnaire. In this questionnaire, participants recorded the use of medication and occurrence of symptoms before the lung function tests. The focus is on FEV_1, since this is the least effort dependent variable from the available indices, has good reproducibility and is linearly related to the severity of airways obstruction.[21]

Air pollution exposure

Procedures of air pollution measurements have been reported before.[15 16] Briefly, we measured mass and number concentration at an urban background central site in each city, near the subject's home outdoors and in the subject's home. Outdoor

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and indoor monitoring was successively carried out at each subject's home for a week, whereas the central site monitoring was running continuously during the whole study period. Particle number concentration (PNC) was continuously monitored with condensation particle counters (TSI 3022A, TSI Inc., St. Paul, Minnesota, USA). Twenty-four-hour average particle mass concentration was measured with Harvard impactors with a 50% size cut-off at 2.5 μm ($PM_{2.5}$) and at 10 μm (PM_{10}). After weighing, the absorbance of the $PM_{2.5}$ filters was determined using reflectometry. The same instruments and standard operating procedures (SOP) were used at the central site and the home measurements in the four cities. PNC was transformed to "noon-to-noon" 24 h means, to coincide with the $PM_{2.5}$ measurements. Meteorological data (ambient temperature, relative humidity) and data on gaseous air pollution (nitric oxide, nitrogen dioxide, carbon monoxide, sulphur dioxide and ozone) were obtained from existing national monitoring networks.

Quality assurance/quality control

Air pollution and health measurements were conducted according to common SOPs. A training workshop was organised before the start of the fieldwork and site visits were implemented during the fieldwork to identify aberrations from SOP.

Data analysis

All analyses were performed per city to allow for differences in associations of, for example, weather variables with lung function between the four cities. Linear regression was used to obtain centre-specific effect estimates, controlling for between-subject differences in lung function using a random-effect approach. The confounder model further consisted of supervision of the test (yes/no), an indicator variable for season (spring, summer, autumn, winter), time of day (morning, lunch, evening), ambient temperature and humidity. Adjustment for autocorrelation was performed by including a first order autoregressive term (AR-1) in the covariance. For every centre, the best confounder model for temperature and relative humidity was identified for FEV_1 starting with a model that included the other indicator variables in the model, but not air pollution. Shape of the association was explored using non-parametric loess functions[22] with spans from 0.6 to 1. Previous day (lag 0) and the successive previous days (lag 1, lag 2 and lag 3) for temperature and relative humidity were evaluated. Based on the lowest Akaike's Information Criterion and the FEV_1 covariate plot, an adequate fit was chosen.

We assessed same-day (lag 0, from yesterday noon to today noon) and previous-day (air pollution and weather) exposures (lag 1–3 days). For indoor and outdoor home environments, exposures up to lag 2 were analysed since longer lags involved too many missing data. Coarse particle concentrations (PM_{coarse}) were calculated by subtracting $PM_{2.5}$ from PM_{10}. Effect estimates were calculated for an increase of 20 $\mu g/m^{-3}$ PM_{10}, 20 $\mu g/m^{-3}$ $PM_{2.5}$, 10 000 particles/cm^{-3} PNC, $2x10^{-5}/m^{-1}$ absorbance and 20 $\mu g/m^{-3}$ coarse particles based on the interquartile ranges of the central site air pollution levels.

For PNC we also analysed hourly data. We assessed the average concentration of 1, 4, 8 and 12 h before the test.

To obtain combined effect estimates, the inverse of the variances of the city-specific estimates were used as weights to calculate a weighted mean of the city-specific slopes.

Sensitivity analyses were performed by excluding tests with a high (>10%) coefficient of variation within the test, subjects with <10 tests, smokers, and subjects with low variation in exposure during the measurement week (less than the 5th percentile: 3.98 $\mu g/m^{-3}$ for $PM_{2.5}$, 4200 particles/cm^{-3} for PNC and 0.54 $\mu g/m^{-3}$ for coarse particles). Furthermore, we excluded observations below the 5th and above the 95th percentile per city for the weather variables and above the 95th percentile for air pollution. Analyses were also performed separately for the three test times of the day to account for different time activity patterns before these time points. Exploratory analysis was performed with S-plus 2000 (Professional Edition for Windows, Release 1; Mathsoft Engineering & Education, Inc. Cambridge, Massachusetts, USA) while the final analysis of the air pollution effects was performed using mixed-effects models (PROC MIXED) in SAS V.8.02 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Panel characteristics

Data from 135 subjects were used in the analysis (table 1). Overall, 69% of the participants were female. Mean age and age range were about the same in all cities. Three subjects in Athens were slightly below the recruitment criterion of ≥35 years. Overall, more subjects had doctor-diagnosed asthma (69%), especially in Helsinki and Birmingham, than COPD (27%).

About half of the panel consisted of ex-smokers. Four subjects were currently smokers and six subjects were exposed to smoke in their home. The majority of the panel (77%) used reliever medication. Of the 22 subjects who were prescribed oral steroids, five of them were prescribed oral steroids for regular use. Inhaled glucocorticosteroids were used by 113 (83%) of the subjects. Of those, seven subjects were prescribed a daily dose of ≥1500 μg (750 μg for the more potent fluticasone). These seven subjects and the five subjects using oral steroids for regular use were considered as having severe disease. About 30% of the panel used glucocorticosteroids as needed (and therefore considered as mild), but only very few subjects (7.4%) actually used glucocorticosteroids during the measurement week.

Twenty-nine subjects (22%) worked outside their home, especially from Amsterdam and Birmingham. Those who worked outside their home, worked on average 19 h/week.

Lung function

A mean of 17.8 tests per person out of a possible 21 tests (85%) was available for analysis. Failure to perform the test and store test results occasionally, resulted in 14 subjects with <10 tests, of which two subjects were excluded because of only one available test. In 131 cases two consecutive tests were performed within 30 minutes. Since 90% were within 7 minutes, these tests were considered repetitions and treated as one test. In 240 cases subjects performed the test outside the predefined time windows. Since most of these tests (n = 171) were just outside the predefined time windows, we included tests performed within 1 h of the original time window.

The mean percentage of the predicted FEV_1 was lower in Athens and Birmingham compared with Helsinki and Amsterdam. This was also true for PEF and FVC, especially in Athens (table 2). For 16 subjects (three in Helsinki, six in Athens, four in Amsterdam and three in Birmingham) measured FEV_1 was between 30 and 50% of the predicted FEV_1. One subject's FEV_1 was below 30% of the predicted value. Hence, 17 subjects would be classified as severe or moderate/severe according to the global initiative for chronic obstructive lung disease criteria for COPD.

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Table 1 Characteristics of four European panels of patients with chronic respiratory disease

	Helsinki	Athens	Amsterdam	Birmingham
	(n = 36*)	(n = 34*)	(n = 36*)	(n = 29*)
Male/female	6/30	19/15	10/26	7/22
Age†	63.5 (36–85)	62.2 (33–84)	63.3 (46–77)	60.1 (37–76)
Body mass index†	24.8 (19–32)	27.9 (19–44)	26.8 (19–41)	27.5 (19–46)
Asthma, n (%)	32 (89)	18 (53)	15 (42)	28 (97)
COPD, n (%)	4 (11)	16 (47)	13 (36)	2 (6.9)
Other respiratory disease, n (%)‡	0 (0)	0 (0)	17 (47)	0 (0)
Smoking status				
Never smoker, n (%)	26 (72)	14 (41)	13 (36)	15 (52)
Current, n (%)	0 (0)	1 (3)	0 (0)	3 (10)
Ex-smoker, n (%)	10 (28)	20 (59)	23 (64)	14 (48)
ETS§ exposure at home, n (%)	0 (0)	5 (14.7)	0 (0)	1 (3.4)
Medication use				
Short-acting β_2 agonist, n (%)	24 (67)	9 (26)	16 (44)	28 (97)
Reliever medication, n (%)¶	29 (81)	21 (62)	25 (69)	29 (100)
Inhaled glucocorticosteroids, n (%)	34 (94)	28 (82)	27 (75)	24 (83)
Oral glucocorticosteroids, n (%)	5 (14)	5 (15)	6 (17)	6 (21)
On need medication use				
Short-acting β_2 agonist, n (%)	18 (50)	8 (24)	14 (39)	28 (97)
Reliever medication, n (%)¶	22 (61)	21 (62)	18 (50)	29 (100)
Inhaled glucocorticosteroids, n (%)	6 (17)	18 (53)	7 (19)	5 (17)
Oral glucocorticosteroids, n (%)	3 (8)	5 (15)	4 (11)	5 (17)

*Total subjects in panel.
†Given as mean and (range), body mass index (BMI) is calculated as weight (kg) × height $(m)^{-2}$.
‡Mainly defined as chronic non-specific lung disease in the Netherlands (a diagnosis that was formerly used for both asthma and chronic obstructive pulmonary disease).
§Environmental tobacco smoke.
¶Includes short-acting β_2 agonist, long-acting β_2 agonist, anticholinergic drugs and combination of an anticholinergic drug and a β_2 agonist.

A diurnal pattern for lung function was observed with highest FEV_1 during lunch. The within-test coefficient of variation (CV_{within}) was low (<5%) for FEV_1, FVC and PEF in all cities (table 2), indicating that the tests were performed satisfactorily. For FEV_1, 103 (4.3%) tests had a CV_{within} of >10%, 13 had a CV_{within} of >20%. The median within-person variability of FEV_1 across the approximately 18 test moments ($CV_{between}$) was 7.4% and ranged from 1.8% to 25.9% between subjects. There was no significant difference between unsupervised tests and tests that were supervised by a technician.

Air pollution concentrations

Median air pollution concentrations at the central site were lowest in Helsinki and highest in Athens (table 3). The median particle number concentrations were highest at the central site, followed by home outdoor and home indoor concentration, except for Amsterdam. For the central site, home outdoor and home indoor locations 0.5, 1.3 and 1.6% of the coarse PM concentrations were negative. Most of these values were close to zero. The small number of negative concentrations is likely due to the subtraction of $PM_{2.5}$ from PM_{10}. Limits of detection and duplicates showed good quality of PM measurements.[15] Detection limits for $PM_{2.5}$ and PM_{10} ranged from 1.1 to 4.7 $\mu g/m^3$ between the four cities. The relative standard deviation calculated from field duplicates ranged from 6 to 9% for $PM_{2.5}$ and PM_{10}; 9 to 24% for coarse particles across the four cities.

The within-subject exposure variation was smaller than reported in table 3, as subjects participated for 1 week. For most subjects, there was a considerable range in concentration. On average, the within-subject range of central site $PM_{2.5}$ concentrations was between 94% (Athens) and 130% (Birmingham) of the individual mean $PM_{2.5}$ concentration. For central site PNC, the average percentage within-subject range was between 63% (Amsterdam) and 100% (Helsinki).

City-specific Spearman correlations between particle number and mass at the central site were weak to moderate (range 0.20–0.55 for PM_{10}, 0.21–0.47 for $PM_{2.5}$ and 0.00–0.39 for PM_{coarse}). City-specific Spearman correlations between concentrations measured at the central site and near the home outdoors ranged from 0.6 to 0.7 (particle number) and 0.8 to 1.0 ($PM_{2.5}$).[15] City-specific Spearman correlation between concentrations measured at the central site and in the home ranged from 0.1 to 0.4 for particle number and 0.3 to 0.8 for $PM_{2.5}$.[16]

Air pollution effects on lung function

There was no consistent association between particulate air pollution and lung function (FEV_1, PEF and FVC) (table 4, fig 1). There was a positive significant association between FEV_1 and home outdoor $PM_{2.5}$ at lag 0 and lag 1, but no relationship with central site $PM_{2.5}$ and indoor $PM_{2.5}$. There was a significant negative association between central site $PM_{2.5}$ and lung function at lag 3. Concentrations measured inside or outside the home were not more strongly related to lung function than concentrations measured at the central site. Although city-specific effect estimates ranged from negative to positive, confidence intervals overlapped for PNC and $PM_{2.5}$ (fig 2) and other air pollutants (data not shown).

The lack of an association between lung function and air pollution was robust for various modifications in the model. Removing smoking subjects (n = 4), subjects with <10 tests (n = 14), tests with a >10% coefficient of variation (n = 103) or subjects with a low variation in exposure did not change the observed associations meaningfully. The basic model, with subject as a fixed or random effect but without confounders showed practically the same associations as the model with confounders. Removing high air pollution and high and low temperature and relative humidity days did not change the observed associations: effect estimates for the lag 0 concentrations at the central site of PNC and $PM_{2.5}$ on FEV_1 were 11 (−3 to 24) and 23 (−4 to 49) ml/s^{-1}, respectively.

Negative associations between lung function and air pollution could be masked by increased medication use on high air pollution days. However, adding the "as needed" use of β_2 agonist in the model did not reveal such an effect. No consistent associations between FEV_1 at different times of day and air pollution were found (data not shown).

When the analysis was restricted to the 93 asthmatic subjects in the panel, no association between air pollution and FEV_1 was found. The combined effect estimate at central site lag 0 for FEV_1 and $PM_{2.5}$ was 17 (−10 to 43) and for PNC 13 (−1 to 27).

When the 29 working subjects were excluded, associations between air pollution and lung function were unchanged. The

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Table 2 Descriptive statistics of the lung function variables in the four Relationship between Ultrafine and fine Particulate matter in Indoor and Outdoor air and respiratory Health centres

		Helsinki	Athens	Amsterdam	Birmingham
		(n = 645*)	(n = 604*)	(n = 600*)	(n = 562*)
		Mean	Mean	Mean	Mean
FEV_1	l	2.09	1.85	2.21	1.93
PRED.† FEV_1	l	2.42	2.60	2.62	2.58
%PRED. FEV_1	%	86.4	71.0	84.4	74.9
CV_{within}‡ FEV_1	%	3.0	3.7	3.6	3.2
$CV_{between}$§ FEV_1	%	5.7	8.6	7.0	8.3
PEF	l/s^{-1}	6.00	5.09	5.87	5.42
PRED. PEF	l/s^{-1}	6.34	6.90	6.72	6.62
%PRED. PEF	%	94.6	73.8	87.4	81.9
CV_{within} PEF	%	3.5	4.9	4.3	4.1
$CV_{between}$ PEF	%	6.6	11.4	8.5	9.6
FVC	l	2.65	2.40	2.92	2.60
PRED. FVC	l	2.93	3.24	3.20	3.13
%PRED. FVC	%	90.4	74.0	91.3	83.2
CV_{within} FVC	%	3.7	4.1	3.8	4.0
$CV_{between}$ FVC	%	6.4	8.1	7.8	10.4

*Total amount of tests.
†PRED is predicted value using subjects' height and age.
‡Mean coefficient of variation between two consecutive blows within test.
§Mean coefficient of variation of best value between tests.
CV, coefficient of variation; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow.

combined effect estimate at central site lag 0 for FEV_1 and $PM_{2.5}$ was 23 (−4 to 49) and for PNC 11 (−3 to 24).

Hourly particle number concentrations

Combined effect estimates were essentially zero for 1 h, 4 h, 8 h and 12 h average PNC concentrations preceding the test for central site and indoor. For home outdoor PNC, small significant positive associations were found, consistent with the association observed for the concurrent 24 h average concentration. For FEV_1, combined effect estimates for the average PNC of the previous 4 h were 0.3 (−6 to 6), 6.5 (0.4 to 13) and 0.5 (−3 to 4) ml/s^{-1} per 10 000 particles/cm^3 for the central site, home outdoor and indoor location.

DISCUSSION

No consistent associations between lung function and particulate matter air pollution were found in four panels of subjects with predominantly mild to moderate asthma or COPD.

Table 3 Daily (24 h noon-to-noon) median 24 h average air pollution concentration and meteorology in the four Relationship between Ultrafine and fine Particulate matter in Indoor and Outdoor air and respiratory Health centres

		Helsinki	Athens	Amsterdam	Birmingham
		Median (range)	Median (range)	Median (range)	Median (range)
Central site					
PNC	1000 cm^{-3}	12.5 (2.1 to 44.5)	20.2 (3.3 to 66.1)	18.3 (8.5 to 44.4)	19.2 (2.2 to 50.8)
PM_{10}	$\mu g/m^{-3}$	12.4 (0 to 156.4)	51.7 (8.5 to 158.7)	26.6 (7.4 to 126)	16.6 (2.8 to 126.2)
$PM_{2.5}$	$\mu g/m^{-3}$	7.4 (0 to 33.2)	22.7 (2.4 to 79.1)	16.7 (4.0 to 103.4)	8.4 (0.7 to 71.9)
PM_{coarse}	$\mu g/m^{-3}$	4.3 (−1.7 to 152.6)	28.8 (0.7 to 126.4)	9.2 (−6.4 to 24.2)	7.0 (−3.7 to 118.9)
Absorbance	$10^{-5}/m^{-1}$	1.2 (0.2 to 3.8)	3.5 (0.9 to 8.4)	1.9 (0.5 to 7.2)	1.3 (0.2 to 4.9)
Home outdoor					
PNC	1000 cm^{-3}	4.6 (1.2 to 22.2)	15.5 (1.0 to 64.2)	24.8 (10 to 114.4)	15.7 (6.5 to 42.4)
PM_{10}	$\mu g/m^{-3}$	12.2 (1.9 to 51.5)	44.9 (9.9 to 165.1)	28.8 (9.4 to 121.3)	17.2 (4.6 to 71.6)
$PM_{2.5}$	$\mu g/m^{-3}$	8.4 (1.4 to 33)	20.3 (5.5 to 103.2)	17.2 (4.6 to 105.3)	9.8 (1.7 to 58)
PM_{coarse}	$\mu g/m^{-3}$	3.5 (−3.7 to 28.5)	21.3 (−7.7 to 105.1)	10.7 (−0.1 to 23.8)	7.6 (−3.5 to 52)
Absorbance	$10^{-5}/m^{-1}$	1.2 (0.3 to 5.6)	2.9 (0.8 to 9.2)	2.2 (0.6 to 7.9)	1.3 (0.4 to 5.5)
Home indoor					
PNC	1000/cm^{-3}	3.7 (0.4 to 58.9)	11.9 (0.8 to 156.3)	12.6 (4.1 to 152.1)	10.4 (2.1 to 97.4)
PM_{10}	$\mu g/m^{-3}$	11.1 (2.7 to 40.6)	32.6 (5.5 to 77.2)	20.9 (6.1 to 106.8)	14.2 (4.3 to 509.1)
$PM_{2.5}$	$\mu g/m^{-3}$	6.5 (1.5 to 35.1)	20.3 (3.3 to 51.5)	12.9 (4.0 to 98.5)	7.3 (1.4 to 512.3)
PM_{coarse}	$\mu g/m^{-3}$	4.2 (−4.2 to 31.1)	11.8 (−0.9 to 56.8)	6.9 (−1.7 to 55.5)	6.1 (−3.2 to 86.2)
Absorbance	$10^{-5}/m^{-1}$	0.8 (0.1 to 7.5)	2.7 (0.7 to 8.6)	1.8 (0.3 to 11)	0.9 (0.1 to 5.4)
Network					
Temperature	°C	2.0 (−22.8 to 25.6)	15.0 (−3.1 to 33.2)	9.1 (−6.1 to 25.3)	9.2 (−1.4 to 26.9)
Relative humidity	%	80.7 (36.5 to 100)	66.1 (21.8 to 93.2)	80.8 (38.5 to 98.7)	79.3 (45.8 to 97.9)

$PM_{2.5}$, particulate matter of $\leqslant 2.5$ μg; PM_{10}, particulate matter of $\leqslant 10$ μg; PNC, particle number concentration.

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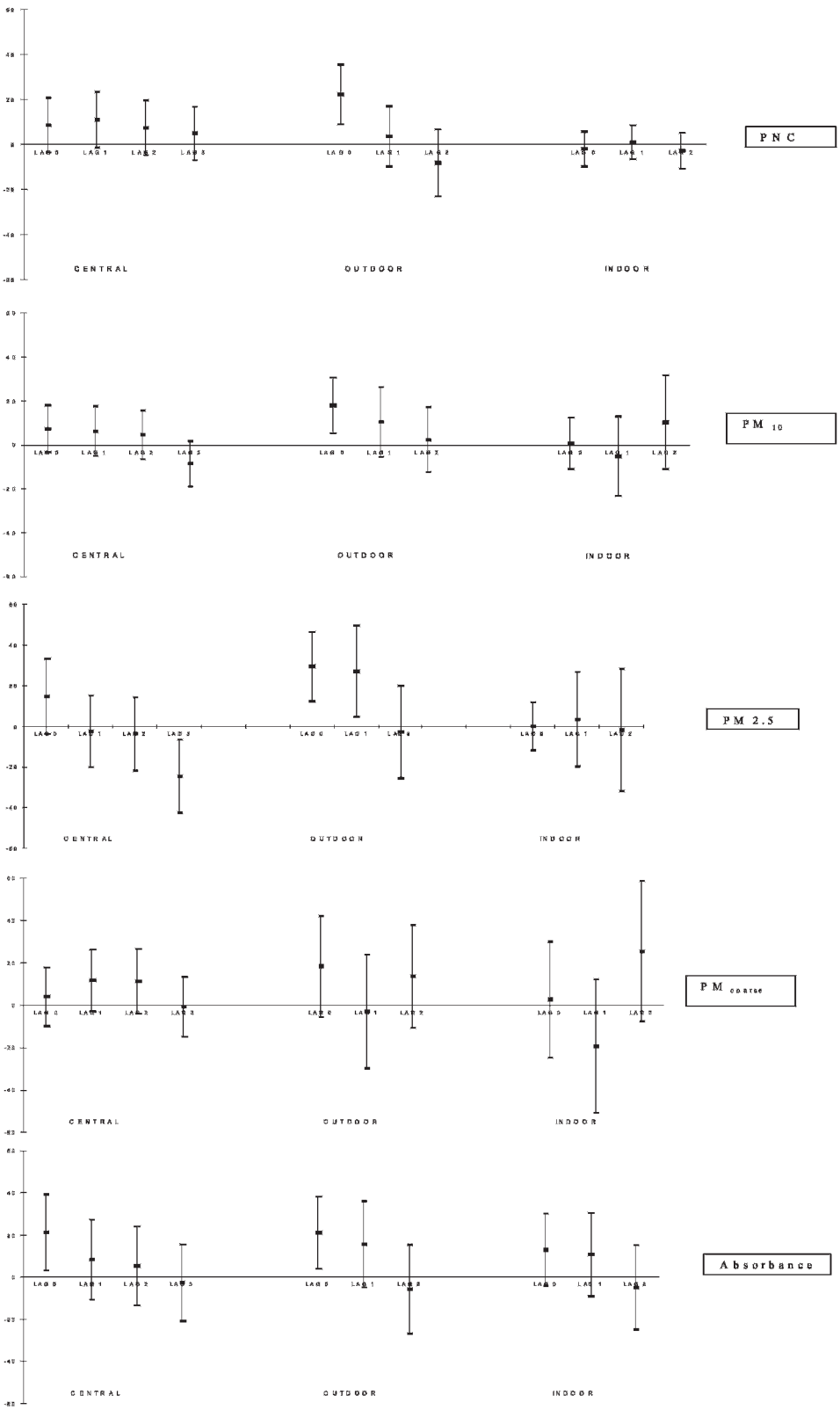

Figure 1 Combined effect estimates (Δ in ml/s^{-1}) with 95% CI for the association of forced expiratory volume in 1 second and air pollution components at central site, home outdoors and home indoors. $PM_{2.5}$, particulate matter $\leqslant 2.5$ μm; PM_{10}, particulate matter $\leqslant 10$ μm; PNC, particle number concentration.

Associations did not become stronger when exposure was characterised using concentrations measured near/in the home of study participants instead of at a central site.

This study is not in agreement with earlier studies, since no effect from particle mass or number was observed. However, in previous studies that measured both particle mass and number, the observed effects on spirometry varied substantially. A German study in 27 asthmatic adults in Erfurt found associations of both PM_{10} and particle number with daily PEF, but the associations for ultrafine particle numbers were stronger than those of PM_{10}.[13] In a Finnish study associations were stronger for particle number when using daily peak-flow measurements[11] and stronger for accumulation mode particles when using PEF measured biweekly with a spirometer in the same panel of

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Table 4 Combined effect estimates (Δ) with 95% CI for the association of air pollution and forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF) and forced vital capacity (FVC) in four panels of symptomatic subjects

	FEV_1	PEF	FVC
	Δ† (95% CI)	Δ† (95% CI)	Δ† (95% CI)
Central site			
PNC lag 0	9 (−3 to 21)	22 (−16 to 60)	1 (−17 to 18)
PNC lag 1	11 (−1 to 24)	14 (−25 to 53)	13 (−5 to 31)
PNC lag 2	8 (−4 to 20)	4 (−34 to 42)	12 (−5 to 30)
PNC lag 3	5 (−7 to 17)	−4 (−40 to 33)	11 (−6 to 28)
$PM_{2.5}$ lag 0	15 (−3 to 34)	25 (−32 to 81)	20 (−7 to 48)
$PM_{2.5}$ lag 1	−2 (−20 to 16)	−23 (−79 to 32)	−16 (−43 to 11)
$PM_{2.5}$ lag 2	−4 (−22 to 15)	−14 (−70 to 41)	−16 (−42 to 10)
$PM_{2.5}$ lag 3	−24 (−42 to −6)	−53 (−108 to 1)	−28 (−53 to −3)
Home outdoor			
PNC lag 0	22 (9 to 36)	44 (5 to 83)	19 (0 to 38)
PNC lag 1	4 (−10 to 17)	17 (−28 to 62)	−7 (−27 to 13)
PNC lag 2	−8 (−23 to 7)	−29 (−77 to 19)	−13 (−34 to 7)
$PM_{2.5}$ lag 0	30 (13 to 47)	48 (−6 to 101)	16 (−10 to 41)
$PM_{2.5}$ lag 1	27 (5 to 50)	32 (−34 to 99)	16 (−15 to 48)
$PM_{2.5}$ lag 2	−3 (−25 to 20)	−7 (−77 to 63)	−13 (−44 to 18)
Home indoor			
PNC lag 0	−2 (−10 to 6)	−4 (−27 to 20)	−7 (−18 to 4)
PNC lag 1	1 (−6 to 9)	−5 (−29 to 19)	−1 (−12 to 9)
PNC lag 2	−3 (−11 to 5)	5 (−20 to 29)	−5 (−15 to 5)
$PM_{2.5}$ lag 0	0 (−12 to 12)	−12 (−45 to 20)	0 (−19 to 19)
$PM_{2.5}$ lag 1	4 (−20 to 27)	−13 (−83 to 57)	−3 (−34 to 29)
$PM_{2.5}$ lag 2	−2 (−32 to 29)	0 (−96 to 95)	−13 (−53 to 28)

†Absolute change (Δ) in ml (FVC), ml/s^{-1} (PEF, FEV_1) for an increase of 10 000 particles/cm^{-3} for PNC and 20 μg/m^{-3} for $PM_{2.5}$, based on the interquartile ranges of the central site air pollution levels in the four cities.
$PM_{2.5}$, particulate matter ⩽2.5 μg; PNC, particle number concentration.

57 asthmatic adults.[12] Another study in 44 adult patients with COPD found borderline significant associations of PEF with PM_{10} only.[10] Statistically significant associations with PM_{10}, but not with particle number, were observed in a Finnish panel of 39 asthmatic schoolchildren.[8] In another study with 49 Finnish schoolchildren associations varied by lag.[9]

Many panel studies of short-term effects of outdoor air pollution relied on measurement of peak flow using Mini Wright Peak Flow meters. In the current study, we used a home spirometer allowing data storage so that the subjects did not have to record test results in a diary. As recording of peak flow in diaries may be unreliable[23 24] and compliance with paper diaries poor,[25] the use of a spirometer that stored lung function data is a major advantage of this study. Furthermore, portable spirometers allow monitoring of FEV_1 and FVC next to PEF. PEF, FEV_1 and FVC measure different aspects with PEF being more a measure of large airway flow. Home spirometry has been shown to be feasible, even in 5–10-year-old asthmatic children: 94% compliance and 85% reproducible lung function tests.[26] In the current study, compliance was good and coefficients of variation low, suggesting that the tests have been performed properly. The majority of tests were not supervised, but we did not find a significant difference between supervised and non-supervised tests. A disadvantage of the use of a home spirometer is the smaller number of observations per subject compared with diary studies using the cheaper Mini Wright meter. Compared with the published single city panel studies, our study included a larger number of subjects.

Lack of statistical power is an unlikely explanation of the null findings in this study. The standard error of the combined effect estimates was small, for example, for $PM_{2.5}$ the standard errors were 9, 13 and 39 ml/s^{-1} per 20 μg/m^3 for FEV_1, FVC and PEF, respectively (between 0.5 and 0.7% of the population mean lung function). The few (positive and negative) significant effect estimates were about 1% of the population mean. We cannot exclude the possibility that smaller effects occurred, but the biological significance of short-term changes <1% seems unclear.

The panel included both asthma and COPD patients, in varying ratios in the different cities. This may have contributed to heterogeneity in effect estimates and may potentially have masked an association. However, all panels included a large fraction of asthmatic subjects. Overall, 93 of the 135 subjects were asthmatic. An analysis restricted to the asthmatic subjects also showed no negative association with lung function. An analysis restricted to COPD patients was not possible, because in Helsinki and Birmingham only four and two COPD patients participated. Hence, the power to assess the health effects of air pollution in this group was limited.

The analysis restricted to asthmatics has taken care of one of the main differences between the four panels that may have resulted in heterogeneity in effect estimates. Further, in none of the individual cities, there was evidence of a negative association with lung function. Effect estimates amounted to a change of typically <1% of the population mean lung function in individual city analyses (fig 2), with the exception of the positive effect estimates for $PM_{2.5}$ in Helsinki where a low variability in exposure resulted in wide confidence limits.

Concentrations measured at the central site tended to be higher than in the Finnish studies[8 11 12] that did find negative associations with lung function, so low exposure levels are an unlikely explanation. Although we measured both particle mass and number, it is possible that other characteristics of particulate matter were important, for example, surface area.

As people spend most of their time indoors, the characterisation of exposure to air pollution using data obtained at a central site, may result in substantial exposure misclassification. However, indoor and home outdoor particle concentrations were not more strongly associated with lung function than central site air pollution. Exposure misclassification seems an unlikely explanation for the lack of effect of air pollution.

The design of the study, with measurements within one subject performed in a 1-week period, limits the ability to assess lagged exposures. We therefore cannot exclude the possibility that exposures of averaging periods longer than a few days may have affected lung function. Some indication for an association with air pollution lagged 3 days was found in the current study, though this may have been a chance finding. Another disadvantage of the 1-week design is smaller exposure contrasts compared with measurements spread over a longer period. Most subjects, however, had sufficient variation and exclusion of those with small variation did not result in different effect estimates. The smaller contrast in exposure moreover does not result in bias, but in decreased precision.

We attempted to select subjects with moderately severe asthma/COPD, because we anticipated that severe patients might have chronically low lung function with relatively small temporal variation. An analysis of the regular use of oral and inhaled glucocorticosteroids showed that only 11 subjects with severe disease were included in the panel. Five subjects were prescribed oral steroids and seven subjects were on a high regular dose of inhaled steroids, with one of them also on oral steroids. Baseline lung function was <50% of predicted for

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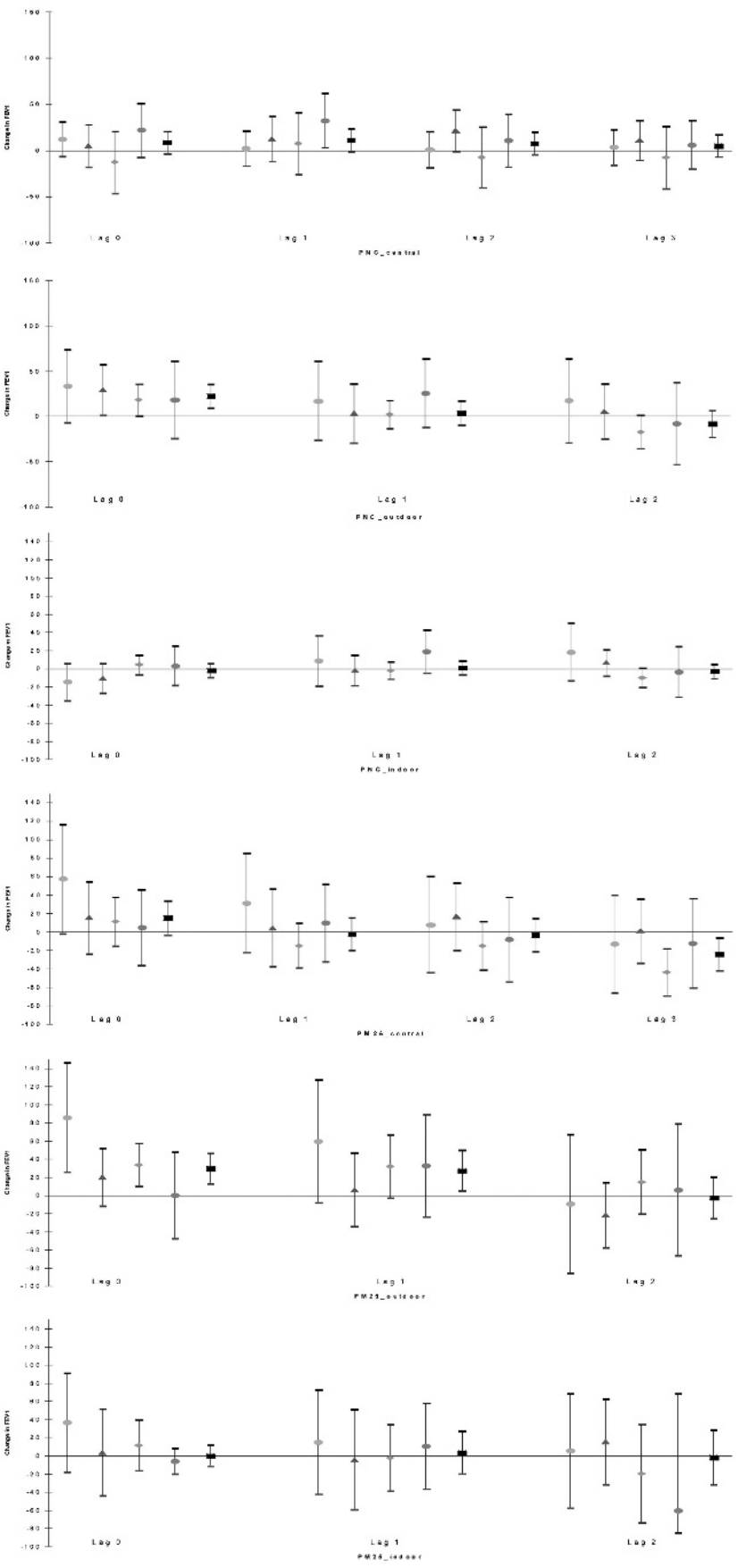

Figure 2 Combined and centre-specific effect estimates (Δ in ml/s^{-1}) with 95% CI for the association of forced expiratory volume in 1 second (FEV_1) and air pollution (particle number concentration (PNC) and particulate matter $\leqslant 2.5$ μg ($PM_{2.5}$)) components at central site, home outdoors and home indoors. From left to right: Helsinki, Athens, Amsterdam and Birmingham.

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17 subjects. Hence, the majority of subjects probably had mild/moderate disease.

A potential explanation could be the high use of respiratory medication (94%), which could have masked any effect of air pollution. Though we adjusted for as-needed medication using a binary variable, we cannot adjust for the potential masking effect of maintenance medication. We did not have daily data on dose of as-needed medication, but most panel studies have successfully evaluated binary variables as well.

In conclusion, no consistent associations between lung function and particulate matter air pollution were found in a group of patients with asthma or COPD across a range of severities. More detailed exposure assessment by using home outdoor and home indoor levels of particulate air pollution instead of central site measurements did not change the observed associations.

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