Particulate matter air pollution and respiratory symptoms in subjects having either asthma or chronic obstructive pulmonary disease: a European multicentre panel study

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Abstract

Background

The RUPIOH study, an EU-funded multicentre study, was designed to examine the distribution of various ambient particle metrics in four European cities (Helsinki, Athens, Amsterdam, Birmingham) and assess their health effects in subjects with asthma or COPD, based on a more detailed exposure assessment.

Methods

At each centre a panel of subjects with either asthma or COPD recorded respiratory symptoms and restriction of activities in a diary for six months. Exposure assessment included simultaneous measurements of coarse, fine, and ultrafine particles at a central site. In this paper the association of central site measurements with respiratory symptoms and restriction of activities is examined.

Results

A 10 $\mu g/m^3$ increase of coarse particles concentrations was consistently associated with most symptoms (an increase of 0.6 to 0.7% in average) and limitation in walking at lag 1. Ozone was positively associated with cough at lags 1 and 2. No consistent associations were observed between fine and ultrafine particle number concentrations, nitrogen dioxide and respiratory health effects.

Conclusions

The observed associations with coarse particles are in agreement with the findings of toxicological studies. Together they suggest it is prudent to regulate also coarse particles in addition to fine particles.

Keywords

air pollution, asthma, chronic obstructive pulmonary disease, coarse particles, particle

number concentration, respiratory health

Background

Over the last decades numerous epidemiological studies have clearly shown that urban air pollution can produce a variety of adverse health effects [1,2]. Ambient particulate matter (PM) either characterized as the mass concentration of particles less than 10 μm (PM_{10}) or less than 2.5 μm ($PM_{2.5}$) are considered to be the major culprit so that current air quality standards or guidelines are expressed as PM_{10} and/or $PM_{2.5}$ [3,4]. However, in reality ambient PM is a mixture of coarse (2.5-10 μm), fine (<2.5 μm) and ultrafine (<0.1 μm) particles generated from different processes, having variable chemical composition and atmospheric behavior. It should also be noted that although the ultrafine fraction accounts for less than 1% of the mass of particulate matter, it represents the greatest proportion in terms of number of particles (typically >80%) [5-7]. Furthermore, the mechanism and the fraction of PM that are mainly responsible for the observed health effects is a matter of controversy [1]. In 1995 Seaton hypothesized that the number of ultrafine particles may be a more health relevant property than the usually measured mass of inhaled particles smaller than 2.5 or 10 μm [8]. This is because of the greater surface area available to react with epithelial and inflammatory cells in the lung and because of the capacity of ultrafine particles to penetrate deeper in the lung parenchyma, potentially reaching the circulation and exerting adverse biological effects by releasing toxic free radicals [8-11]. On the other hand, the only systematic review of studies that have analysed fine and coarse PM jointly demonstrates that the health effects of coarse particles are significant and should not be overlooked [12]. Thus, special consideration should be given to each fraction of the particles and their effects on health. Better

characterization of the health relevant particle fraction will have major implications for air quality policy since it will determine which sources should be controlled.

The RUPIOH (Relationship between Ultrafine and fine Particulate matter in Indoor and Outdoor air and respiratory Health) is an EU-funded multicentre study designed to examine the distribution of various particle metrics both indoors and outdoors in four European cities and assess their health effects in subjects with asthma or COPD, based on a more detailed exposure assessment. The study consisted of two parts: i) the diary study in which subjects were asked to complete a daily diary for six months while exposure was assessed based on a central site measurements and ii) the intensive week measurements during which, for each subject, more intensive health and exposure measurements were conducted. In this paper, we report the association of ambient $PM_{10,}$ $PM_{2.5}$, coarse particle mass ($PM_{10-2.5}$) and particle number concentrations (PNC), measured at the central site, with respiratory symptoms in subjects having either asthma or COPD who have been followed for six months. The relationships between central site outdoor, residential outdoor and indoor concentrations, as well as the association between outdoor and indoor exposure to fine and ultrafine particles and lung function in the same subjects but based on the intensive week measurements have been published before [13-17].

Methods

Study design

In the context of RUPIOH, a multicentre study was conducted from October 2002 to March 2004 in four European metropolitan areas, namely, Amsterdam (The Netherlands), Athens (Greece), Birmingham (United Kingdom) and Helsinki (Finland). During the whole study period a central site in each city was used to

monitor particle mass and particle number concentrations on a daily basis. At various locations covering the entire metropolitan area, homes of subjects with either asthma or COPD were selected. The criteria for the central site and homes selection have been described in detail in a previous publication [14]. Respiratory health status of each participant was monitored for six months by a daily symptom diary. We used a staged entry of the subjects in order to increase the period of data collection and thus, decrease the likelihood for uncontrolled factors or unexpected events to influence the associations between air pollution and health [18].

Study population

Subject inclusion criteria and recruitment procedures have been described in detail before [16]. Briefly, in each city participants were aged 35 or more, had a doctor diagnosis of either asthma or COPD and had experienced respiratory symptoms in the past 12 months. Especially, in the Netherlands some patients who had a diagnosis of chronic non-specific lung disease (CNSLD) as a relic of tradition (term previously used to indicate either asthma or COPD) were also included [19]. Severe patients defined as those using relief bronchodilating medications more than three times per day or using nebulised bronchodilators or long-term oxygen therapy as well as subjects unable to perform a satisfactory spirometry test were excluded from the study. An attempt was made to select non-working, non-smoking patients living in a non-smoking household to eliminate potential confounding by occupational exposures to airborne particles and by environmental tobacco smoke. The same screening questionnaire was used across the four centres to ascertain eligibility. However, each centre was allowed to choose the optimal subject recruitment method.

Medical ethical clearance was acquired from the relevant local medical ethics

committees in all centers before the start of the recruitment. Written informed consent was obtained from each subject.

Symptom diary

The diary was based upon diaries used in previous studies of acute effects of air pollution such as the PEACE study [18]. Subjects were instructed to complete a daily record about respiratory symptoms and medication taken "as needed" for six months, grading shortness of breath, wheeze, cough, phlegm production and being awakened by breathing problems as absent (0), slight (1), or moderate/severe (2). In addition, subjects were asked about limitation in daily life activities (vigorous, moderate, walking one block/climbing one flight of stairs and leaving one's home) because of breathing problems. This limitation could be reported in three grades: no limitation (0), yes, did activity slowly (1) and yes, avoided activity completely (2). Questions on whether they have been outside the house or town and for how long have also been included.

During the study period there was personal contact with the subjects once a month to collect the completed diary forms, discuss potential problems and keep the motivation at a good level.

Air pollution exposure

Exposure assessment has been described in previous publications [13-15,17]. In brief, during the entire study period in each city, measurements of $PM_{2.5}$, PM_{10} and PNC were performed continuously at a central site representing urban background levels [14]. The same type of condensation particle counter (TSI 3022A, TSI Inc., St. Paul, MN, USA) was used in each city to monitor PNC. 24-hour average particle mass

concentration was measured with Harvard impactors for particulate matter with a 50% size cut-off at 2.5 μm ($PM_{2.5}$) and for particulate matter with a 50% size cut-off at 10 μm (PM_{10}). Coarse particles concentrations were calculated by subtracting $PM_{2.5}$ from PM_{10}. After weighing, the absorbance of the $PM_{2.5}$ filters (a good surrogate for elemental carbon/soot) was determined using reflectometry. Data on concentrations of other air pollutants (ozone, sulfur dioxide, nitrogen dioxide, nitrogen oxide, carbon monoxide) and meteorology (ambient temperature, relative humidity) were collected from existing national monitoring networks in each country.

Confounder data

Time trend in health endpoints (e.g. fatigue in reporting), weather (outdoor temperature, relative humidity), medication use and day of the week were taken into account as potential confounders. Because of the staged entry of subjects, we evaluated two time variables: calendar date (proxy for unmeasured confounders) and day of study for a specific subject (possibly related to fatigue).

QA/QC

Air pollution and health measurements were performed according to standard operating procedures (SOPs). A training workshop was organized before the start of the fieldwork and site visits were implemented during the fieldwork to identify any deviations from SOPs.

Statistical analysis

Data analysis was done according to a predefined analysis plan. The symptom variables initially coded as 0 for no symptoms, 1 for moderate symptoms and 2 for

severe symptoms were dichotomised for the analysis by setting 0 for no symptoms and 1 for moderate/severe symptoms. Each symptom was analysed separately either as prevalent (irrespective of its occurrence on the previous day) or incident (when that symptom was reported to be absent on the previous day). Medication use was coded as 0 (no medication) versus 1 (intake of one or more doses) by medication group on the basis of Anatomical-Therapeutical-Chemical codes.

For every pollutant the following lags were evaluated: lag 0, 1, 2 and the average of lag 0-6 days. Lag 0 was defined as the 24-hour period starting from noon of the calendar day before the health response.

A hierarchical modelling approach was used. First, regression models were fitted in each city separately to allow specific control for seasonal effects, weather and other potential confounders. Results of the individual city analysis were used in a second stage analysis to provide overall estimates.

We applied logistic regression to obtain centre-specific effect estimates. A smooth function (natural splines with 6 degrees of freedom per year) of time was used to remove the seasonal patterns and long time trends for the data. Afterwards, same-day (lag0) and previous-day (lag1) mean daily temperatures were introduced into the model. For both lags of temperature, a linear term was compared with a smoothed function (natural splines) with 2, 3 and 4 degrees of freedom and the model with the lowest Akaike's Information Criterion (AIC) was selected. A linear term of relative humidity was added to the model as another indicator of weather. Finally, indicator variables for day of the week, medication use and individual differences in frequency of symptoms, were added to the model. After setting up the baseline model, the effects of the various lags of the pollutants were evaluated.

In the city specific analysis we fitted fixed effects as well as random intercept logistic

regression models using "glmmPQL" function from MASS library in R software, to take into account the correlation among each subject's measurements. Results from the random effects analysis were very similar to those derived from fixed effects and the same exposure significant associations between exposure and outcome effects were identified. In a few cases though, we faced convergence issues. This was even more the case when we tested a first order autoregressive correlation structure. The significance of the associations was similar between random intercept models and the models incorporating an autoregressive term.

The robustness of the findings was evaluated by fitting two pollutant models in a sensitivity analysis.

Effect estimates are expressed as odds ratios for an increase of 10μg/m^3 in PM_{10}, 10μg/m^3 in $PM_{2.5}$, 10μg/m^3 in $PM_{10-2.5}$, 10,000 particles/cm^3 for PNC and $1 \cdot 10^{-5}$ m^{-1} for absorbance, in order to be comparable with other studies.

All analyses were performed using R software [20].

Results

Panel characteristics

A brief description of the study population is presented in Table 1. In Amsterdam a large group was reported to have CNSLD. Medication use was high in the panels. Seventy seven per cent of the subjects (77%) used reliever medication. Use of "as needed medication" was recorded in 26.5% of total person days in Helsinki, 13.9% in Athens, 37.9% in Amsterdam and 59.7% in Birmingham.

Symptoms

In total between 4,764 and 5,920 person days were available for analysis in the four

cities. Consistent with the composition of the panel, fairly high symptom prevalence occurred during the study period. Person days with severe symptoms were low, except for cough and phlegm. There were small differences between the cities (Table 2).

Air pollution concentrations

Helsinki had the lowest median concentrations for all components whilst Athens had the highest. However, maximum concentrations of $PM_{2.5}$ were observed in Amsterdam (103.4 μg/m^3) and of $PM_{10-2.5}$ (152.6 μg/m^3) in Helsinki (Table 3).

Air pollution effects on symptoms-restriction of activities

Prevalence analyses

In Tables 4 and 5 combined odds ratios for the association of particulate matter indices, NO_2, ozone and prevalence of symptoms and limitation in activities are presented, using random effects models adjusting for the above mentioned confounders and "as needed" medication. A 10μg/m^3 increase in PM_{10} was significantly associated with shortness of breath in the lag 1 whilst the association in the lags 2 and 0 to 6 was of borderline significance. Significant associations were also observed for wheezing (lag 1) and limited in walking (lag 1). The association was driven by the $PM_{10-2.5}$ component of PM_{10} and much less by $PM_{2.5}$. Coarse PM concentrations were positively associated with most symptom and restriction of activities variables in lag1. Furthermore, the magnitude of the associations increased when we applied a two-pollutant model for $PM_{10-2.5}$ and $PM_{2.5}$ in lag 1 (data not shown).

Ozone was also positively associated with cough at lag 0, lag 1, lag 2 and with woken with breathing problems at lag 0. No association with other symptoms was found.

The above-mentioned positive associations remained after restriction of the analysis to the asthmatic only subjects, although not all of them remained statistically significant probably due to the smaller number of observations (data not shown). Neither $PM_{2.5}$ nor NO_2 were consistently associated with any symptom or limitation in activities variable. As for PNC a (statistically mostly non-significant) negative association was observed with most symptoms whilst the positive association with restriction of activities did not reach the nominal level of significance.

Centre specific and overall effect estimates with 95 percent confidence intervals (95% CI) for the association of each symptom and air pollutant in lag1 are presented in Figure 1. Odds ratios (OR) for the effect of $PM_{10-2.5}$ were consistently above one in almost every city as well as in the pooled data using random effects models.

Incidence analyses

Patterns similar to those in the combined prevalence analyses were observed for the associations of incident symptoms and particles especially the coarse fraction. Shortness of breath was consistently associated with PM_{10} and $PM_{10-2.5}$ in lag 1 with no indication of heterogeneity between the centres (OR= 1.045, 95% CI: 1.008, 1.083 and OR= 1.065, 95% CI: 1.009, 1.124 respectively). There was also a tendency towards positive associations between $PM_{10-2.5}$ and incidence of wheezing, cough and limitation in walking but none of the associations were statistically significant. Additionally, ozone was positively associated with cough in lags 1 and 2 (Table 6).

Discussion

In this multicentre study we found consistent positive associations between coarse particles central sites concentrations and prevalence of respiratory symptoms, as

recorded in a 6-month diary, in four panels of subjects with predominantly mild to moderate asthma or COPD in four European cities participating in the RUPIOH study. We also found a significant association of ozone with cough and woken with breathing problems, but not with other symptoms. One particularity of the RUPIOH study is the in depth assessment of particulate air pollution by measuring PM_{10}, $PM_{2.5}$ (then deriving coarse particles), filters absorbance as well as the number of ultrafine particles.

Previous work from RUPIOH that included air pollution monitoring for one week inside and directly outside participant's homes reported no association with lung function [16]. As the authors stated a potential explanation could be the high prevalence of medication use, the short period of measurements (one-week) that limited the ability to assess lagged effects over several days or absence of an effect. Our coarse particle findings are however consistent with the observation that in the RUPIOH study only the coarse particle concentration at central sites was significantly associated with increased nitrate and nitrite concentrations in the exhaled breath condensate collected during the same week as the spirometry (unpublished results). Nitrate and nitrite concentrations in exhaled breath condensate are a marker of oxidative stress. The link between coarse particles with oxidative stress and airway inflammation may explain the increase in respiratory symptoms we found.

In the last two decades a substantial body of literature has focused on the harmful health effects of PM_{10} and $PM_{2.5}$. As a result guideline values have been recommended by the U.S. Environmental Protection Agency and World Health Organization for both indicators of PM pollution to protect public health [2,3]. However, from recent studies there is increasing evidence that the health effects of coarse particles should not be underestimated. In a systematic review of epidemiological studies that have analyzed

fine and coarse PM jointly, Brunekreef and Forsberg examined the epidemiological evidence for effects of coarse particles on health [12]. They concluded that the effects of $PM_{10-2.5}$ were stronger than or as strong as $PM_{2.5}$ on short-term respiratory morbidity. Furthermore, in a national, multicity study, Zanobetti and Schwartz found a strong association of both fine and coarse particles with daily deaths in 112 U.S. cities [21]. A 10 $\mu g/m^3$ increase in $PM_{10-2.5}$ was significantly associated with total mortality, stroke, cardiovascular, and respiratory mortality, the latter of which showing the largest effect (a 1.2% increase). Mechanistically, these effects may be due either to biogenic factors or to metals carried by coarse particles by activation of inflammatory and oxidative stress pathways [22-24]. The findings of our study support previous epidemiological and toxicological evidence that health effects due to the coarse fraction may be substantial [25].

The large number of calculations we have done could have given some statistically significant associations by chance. However, this is not likely since the associations of $PM_{10-2.5}$ with symptoms, that we report, were consistent across lag times and odds ratios were mainly homogeneous across centers. Furthermore, $PM_{10-2.5}$ remained the best predictor for symptoms when we restricted the analysis to the asthmatic only subjects. An analysis restricted to COPD patients was not possible due to the small number of COPD patients participating in Helsinki and Birmingham.

The majority of studies that investigated health effects of particulate pollutants have expressed results on a mass basis. It has been suggested that when taking into consideration particle number or surface area, the pulmonary dose of toxic material related to $PM_{2.5}$ may be much larger than the dose related to $PM_{10-2.5}$ that for this reason alone, comparison on a mass basis may be less informative [12]. In our study we separately investigated the mass and the number effect. Neither central site $PM_{2.5}$

nor PNC were consistently associated with symptoms. The analysis of RUPIOH data by Puustinen et al showed generally high correlations between 24 hour average central site and residential outdoor concentrations for $PM_{2.5}$ and soot with a lesser median correlation for PM_{10} and a lower correlation for PNC and $PM_{10-2.5}$ [14]. For $PM_{10-2.5}$ correlations between central site and home outdoor measurements were 0.66, 0.74, 0.89 and 0.64 in Helsinki, Athens, Amsterdam and Birmingham respectively. A central site thus provides a reasonably good estimate of more local exposures even for coarse particles.

The relatively high divergence of $PM_{10-2.5}$ concentrations between proximate sites in the UK has recently been confirmed by Liu and Harrison [26]. Consequently, for both PNC and $PM_{10-2.5}$, there is a higher probability of exposure misclassification than for $PM_{2.5}$ or soot. The finding of significant associations with respiratory health outcomes for $PM_{10-2.5}$ but not for PNC is therefore quite striking but appears consistent with the recent findings of a time series study in London which found significant associations between PNC and cardiovascular health outcomes whilst PM mass metrics were associated with respiratory outcomes [27].

In summary, the results of our study are in agreement with the findings of recent epidemiological and toxicological studies and provide enough evidence to conclude that it is prudent to keep $PM_{10-2.5}$ regulated in addition to fine particles.

Conclusions

Our study adds to the limited existing evidence of recent epidemiological and toxicological studies that health effects due to the coarse fraction of ambient PM may be substantial. Furthermore, the observed associations suggest it is prudent to regulate also coarse particles in addition to fine particles.

Abbreviations

AIC, Akaike's information criterion; CNSLD, Chronic non-specific lung disease; COPD, Chronic obstructive pulmonary disease; OR, Odds ratio; PM, Particulate matter; $PM_{10-2.5}$, Coarse particle mass; PM_{10}, Mass concentration of particles less than 10 μm; $PM_{2.5}$, Mass concentration of particles less than 2.5 μm; PNC, Particle number concentrations; RUPIOH, Relationship between Ultrafine and fine Particulate matter in Indoor and Outdoor air and respiratory Health; SOPs, Standard operating procedures; 95% CI, 95% confidence interval

Competing interests

The authors declare that they have no competing interests

Authors' contributions

All authors of this paper have critically read and approved the final version submitted. They have also made substantive intellectual contributions by directly participating either in the planning, execution, or analysis of the study. AK contributed to the development of the study design, acquisition and interpretation of data and drafted the paper. AA did the analysis, contributed to the interpretation of data and wrote the statistical analysis section of the paper. DP, IGK, JdeH contributed substantially to acquisition and interpretation of data. JGA, RMH, AK, JP, KH, GPAK, KK contributed to the study design, interpretation of data and have been involved in drafting the manuscript. GH conceived and developed the study design, contributed to the interpretation of data and was involved in drafting the paper. All authors have

revised drafts and contributed to the revisions.

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Table 1 Characteristics of four European panels of asthmatic/COPD patients

	Helsinki n=36[a]		Athens n=35[a]		Amsterdam n=36[a]		Birmingham n=29[a]	
Male / Female	6 / 30		19 / 15		10 / 26		7 / 22	
Age[b]	63.5	[36-85]	62.2	[33-84]	63.3	[46-77]	60.1	[37-76]
Asthma	31	(86%)	19	(54%)	11	(31%)	27	(93%)
COPD	4	(11%)	15	(43%)	9	(25%)	1	(3.5%)
Asthma+COPD	1	(3%)	1	(3%)	4	(11%)	1	(3.5%)
CNSLD[c]	0	(0%)	0	(0%)	12	(33%)	0	(0%)
Smoking status								
Never smoker	26	(72%)	15	(43%)	13	(36%)	15	(52%)
Current	0	(0%)	1	(3%)	0	(0%)	3	(10%)
Ex-smoker	10	(28%)	19	(54%)	23	(64%)	11	(48%)
ETS [d] exposure at home	0	(0%)	5	(14.7%)	0	(0%)	1	(3.4%)
Medication use								
Short acting β2-agonist	24	(67%)	9	(26%)	16	(44%)	28	(97%)
Reliever medication [e]	29	(81%)	21	(62%)	25	(69%)	29	(100%)
Inhaled glucocorticosteroids	34	(94%)	28	(82%)	27	(75%)	24	(83%)
Oral glucocorticosteroids	5	(14%)	5	(15%)	6	(17%)	6	(21%)
On need medication use								
Short acting β2-agonist	18	(50%)	8	(24%)	14	(39%)	28	(97%)
Reliever medication [e]	22	(61%)	21	(62%)	18	(50%)	29	(100%)
Inhaled glucocorticosteroids	6	(17%)	18	(53%)	7	(19%)	5	(17%)
Oral glucocorticosteroids	3	(8%)	5	(15%)	4	(11%)	5	(17%)

[a] Total subjects in panel

[b] Given as mean and [range]

[c] chronic non-specific lung disease

[d] Environmental tobacco smoke

[e] includes short acting β2-agonist, long acting β2-agonist, anticholinergic drugs and combination of an anticholinergic drug and a β2-agonist.

Table 2 Person days with symptoms in the diary (n = number of person days)

	Helsinki		Athens		Amsterdam		Birmingham	
	n	%	n	%	n	%	n	%
Woken with Breathing Problems								
No	4759	82.9	5334	88.9	4897	83.6	3953	83.0
Yes	978	17.1	667	11.1	958	16.4	808	17.0
Short Of Breath								
No	3987	67.6	4891	81.5	3410	58.1	3111	65.4
Slight symptoms	1774	30.1	1015	16.9	2179	37.1	1443	30.3
severe symptoms	140	2.4	96	1.6	284	4.8	206	4.3
Wheeze								
No	4932	83.5	4325	72.0	4554	78.7	3182	66.8
Slight symptoms	923	15.6	1627	27.1	1102	19.0	1383	29.0
severe symptoms	49	0.8	51	0.8	134	2.3	196	4.1
Cough								
No	3418	57.9	4303	71.7	3251	56.3	2189	46.0
Slight symptoms	2305	39.0	1583	26.4	2234	38.7	2026	42.6
severe symptoms	184	3.1	116	1.9	289	5.0	546	11.5
Phlegm								
No	1973	33.3	3291	54.8	2957	51.3	2087	43.8
Slight symptoms	3462	58.5	2448	40.8	2597	45.1	2137	44.9
severe symptoms	485	8.2	264	4.4	206	3.6	537	11.3
Limitation of vigorous activities due to breathing problems								
No	3837	67.3	2716	45.5	3714	67.5	2663	55.9
did activity slowly	1259	22.1	2661	44.6	897	16.3	988	20.7

Avoided activity completely	603	10.6	587	9.8	891	16.2	1113	23.4
Limitation of moderate activities due to breathing problems								
No	3775	64.1	3928	65.6	4237	75.2	3420	71.8
did activity slowly	2030	34.4	1874	31.3	1266	22.5	1211	25.4
Avoided activity completely	88	1.5	184	3.1	135	2.4	131	2.8
Limitation of walking due to breathing problems								
No	4867	84.6	3455	58	4449	77.6	3472	72.9
did activity slowly	795	13.8	2438	40.9	1132	19.7	1228	25.8
Avoided activity completely	94	1.6	62	1	152	2.7	63	1.3

Table 3 Daily (24 hours noon-to-noon, central site) median air pollution concentration and meteorology in the four cities

		Helsinki		**Athens**		**Amsterdam**		**Birmingham**	
		Median	Range	Median	Range	Median	Range	Median	Range
PNC	10,000·cm^{-3}	1.3	(0.2, 4.4)	2.0	(0.3, 6.6)	1.8	(0.8, 4.4)	1.9	(0.2, 5.1)
PM_{10}	µg·m^{-3}	12.4	(0.2, 156.4)	51.7	(8.5, 158.7)	26.6	(7.4, 126.0)	16.6	(2.8, 126.2)
$PM_{2.5}$	µg·m^{-3}	7.4	(0.3, 33.2)	22.7	(2.4, 79.1)	16.7	(4.0, 103.4)	8.4	(0.7, 71.9)
PM_{coarse}	µg·m^{-3}	4.6	(0.0, 152.6)	28.8	(0.7, 126.4)	9.4	(0.9, 24.2)	6.9	(0.3, 118.9)
Absorbance	10^{-5}·m^{-1}	1.2	(0.2, 3.8)	3.5	(0.9, 8.4)	1.9	(0.5, 7.2)	1.3	(0.2, 4.9)
NO_2	µg·m^{-3}	22.7	(4.5, 77.9)	39.9	(11.8, 110.9)	38.4	(10.4, 97.3)	34.4	(7.3, 83.3)
Ozone	µg·m^{-3}	42.5	(4.1, 93.2)	46.9	(4.7, 108.2)	33.1	(0.9, 104.3)	37.3	(0.9, 106.6)
Temperature	ºC	2.0	(-22.8, 25.6)	15.0	(-3.1, 33.2)	9.1	(-6.1, 25.3)	9.2	(-1.4, 26.9)
Rel. humidity	%	80.7	(36.5, 100)	66.1	(21.8, 93.2)	80.8	(38.5, 98.7)	79.3	(45.8, 97.9)

Table 4 Associations of particulate matter indices, NO_2 and O_3 with prevalence of symptoms in the four panels (random effects pooled estimate). Bold are significant pooled effects

Symptom	Pollutant	Lag0		Lag1		Lag2		Lag06	
		OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Woken breathing problems	PM_{10}	1.001	0.966-1.037	1.010	0.964-1.059	0.978	0.928-1.030	1.009	0.881-1.155
	$PM_{2.5}$	0.997	0.952-1.044	0.980	0.915-1.049	0.953	0.886-1.025	0.889	0.682-1.160
	$PM_{10-2.5}$	1.020	0.883-1.179	1.047	0.989-1.109	0.996	0.935-1.062	1.019	0.860-1.208
	PNC	0.971	0.865-1.090	1.027	0.952-1.109	0.958	0.863-1.064	0.910	0.638-1.298
	Absorbance	1.014	0.952-1.079	1.018	0.966-1.073	0.971	0.922-1.022	0.929	0.777-1.111
	NO_2	0.980	0.940-1.021	0.983	0.943-1.026	0.970	0.926-1.016	0.969	0.856-1.098
	O_3	**1.063**	**1.020-1.108**	1.023	0.957-1.094	1.010	0.959-1.064	1.037	0.896-1.200
Shortness of breath	PM_{10}	0.998	0.970-1.026	**1.037**	**1.002-1.074**	1.014	0.986-1.042	1.050	0.998-1.106
	$PM_{2.5}$	1.001	0.942-1.063	1.035	0.974-1.099	1.026	0.984-1.070	1.027	0.944-1.117
	$PM_{10-2.5}$	0.995	0.949-1.042	**1.060**	**1.015-1.107**	1.002	0.949-1.057	1.044	0.947-1.151
	PNC	0.972	0.901-1.048	0.910	0.844-0.982	0.919	0.860-0.982	0.908	0.770-1.071
	Absorbance	1.019	0.936-1.109	1.042	0.954-1.138	1.026	0.978-1.077	1.064	0.929-1.218
	NO_2	1.011	0.934-1.094	0.996	0.915-1.085	0.985	0.940-1.032	1.011	0.874-1.170
	O_3	0.988	0.957-1.021	0.961	0.921-1.003	0.975	0.946-1.004	0.962	0.914-1.014
Wheezing	PM_{10}	1.026	0.980-1.074	**1.027**	**1.000-1.055**	1.011	0.981-1.041	0.989	0.869-1.125
	$PM_{2.5}$	0.998	0.925-1.077	1.004	0.931-1.082	0.982	0.882-1.094	0.873	0.629-1.213
	$PM_{10-2.5}$	1.041	0.990-1.094	**1.073**	**1.028-1.120**	1.023	0.980-1.068	1.053	0.966-1.147
	PNC	0.934	0.791-1.104	0.947	0.816-1.099	0.985	0.841-1.154	1.092	0.639-1.865
	Absorbance	0.980	0.910-1.055	1.000	0.930-1.075	0.999	0.888-1.123	0.926	0.644-1.332
	NO_2	0.995	0.922-1.074	0.983	0.923-1.047	1.003	0.933-1.078	1.004	0.828-1.217
	O_3	1.008	0.966-1.051	1.012	0.965-1.061	1.009	0.949-1.073	1.031	0.933-1.138
Cough	PM_{10}	1.001	0.975-1.027	1.014	0.985-1.045	0.999	0.957-1.043	1.007	0.913-1.110
	$PM_{2.5}$	0.960	0.922-0.999	0.971	0.933-1.011	0.962	0.919-1.008	0.901	0.753-1.079
	$PM_{10-2.5}$	1.099	0.943-1.282	1.089	0.956-1.240	1.043	0.958-1.137	1.210	0.772-1.896
	PNC	0.981	0.916-1.051	1.009	0.944-1.079	0.968	0.895-1.047	0.894	0.714-1.119
	Absorbance	0.939	0.898-0.982	0.976	0.932-1.022	0.959	0.917-1.003	1.083	0.797-1.472
	NO_2	0.971	0.937-1.007	0.981	0.945-1.017	0.965	0.931-1.000	0.959	0.899-1.024
	O_3	**1.061**	**1.013-1.111**	**1.049**	**1.016-1.083**	**1.059**	**1.027-1.091**	1.066	0.982-1.157

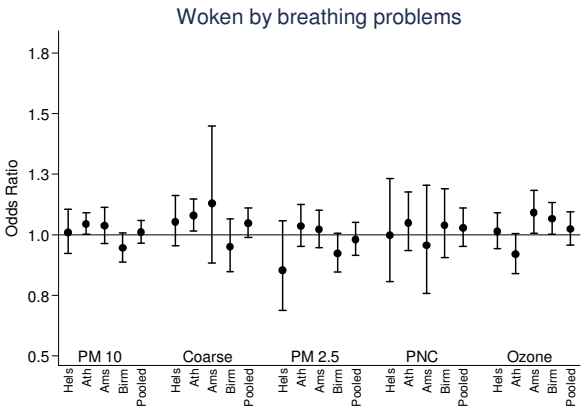
Table 5 Associations of particulate matter indices, NO_2 and O_3 with limitation of activities due to breathing problems in the four panels (random effects pooled estimate). Bold are significant pooled effects

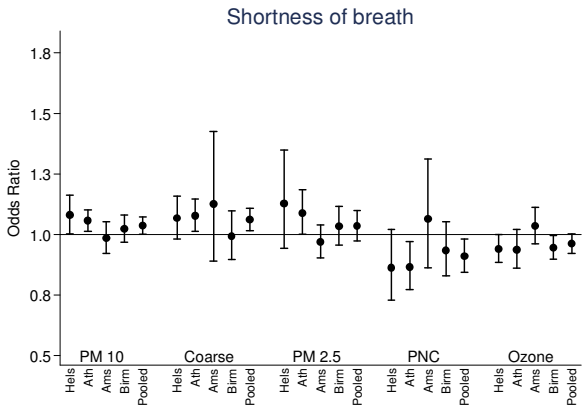
Symptom	Pollutant	Lag0		Lag1		Lag2		Lag06	
		OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Vigorous activities	PM_{10}	1.018	0.950-1.092	1.028	0.957-1.103	1.026	0.956-1.102	0.989	0.854-1.146
	$PM_{2.5}$	1.016	0.910-1.135	1.016	0.892-1.158	1.039	0.922-1.169	1.005	0.831-1.216
	$PM_{10 - 2.5}$	1.093	0.933-1.281	1.114	0.949-1.308	1.049	0.948-1.160	1.230	0.851-1.779
	PNC	1.001	0.888-1.129	1.018	0.916-1.133	1.054	0.985-1.129	0.906	0.778-1.054
	Absorbance	0.999	0.894-1.117	1.021	0.917-1.137	1.010	0.885-1.152	0.994	0.691-1.432
	NO_2	0.988	0.940-1.038	1.010	0.971-1.051	1.037	0.979-1.097	1.007	0.844-1.202
	O_3	1.033	0.935-1.141	1.031	0.946-1.124	1.024	0.932-1.125	1.107	0.879-1.394
Moderate activities	PM_{10}	0.973	0.888-1.067	0.973	0.923-1.026	0.973	0.907-1.044	0.904	0.729-1.122
	$PM_{2.5}$	0.922	0.749-1.136	0.950	0.848-1.065	0.963	0.862-1.077	0.953	0.808-1.124
	$PM_{10 - 2.5}$	1.068	0.913-1.249	1.023	0.932-1.122	1.014	0.966-1.064	0.912	0.667-1.248
	PNC	1.077	0.937-1.239	1.034	0.899-1.189	1.010	0.927-1.100	0.935	0.762-1.146
	Absorbance	0.973	0.891-1.062	0.973	0.869-1.088	0.974	0.851-1.116	1.036	0.740-1.451
	NO_2	1.004	0.917-1.100	0.991	0.915-1.074	1.007	0.932-1.088	1.064	0.873-1.296
	O_3	0.970	0.899-1.046	1.000	0.916-1.091	1.002	0.939-1.070	1.022	0.879-1.189
Walking	PM_{10}	1.010	0.924-1.104	**1.039**	**1.007-1.073**	1.012	0.976-1.049	1.074	0.966-1.194
	$PM_{2.5}$	1.000	0.917-1.091	1.019	0.953-1.088	0.963	0.850-1.090	0.839	0.574-1.225
	$PM_{10 - 2.5}$	1.072	0.904-1.273	**1.076**	**1.026-1.128**	1.044	0.997-1.092	1.079	0.819-1.420
	PNC	0.978	0.797-1.199	0.986	0.915-1.063	1.007	0.937-1.083	0.975	0.670-1.418
	Absorbance	1.014	0.915-1.124	1.038	0.956-1.128	1.013	0.942-1.089	0.852	0.544-1.333
	NO_2	0.979	0.940-1.019	1.011	0.959-1.065	1.034	0.993-1.077	1.075	0.931-1.241
	O_3	1.012	0.975-1.050	1.004	0.961-1.048	1.020	0.983-1.059	1.038	0.971-1.109

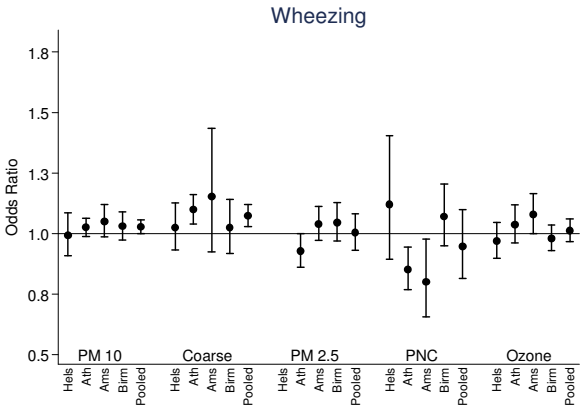
Table 6 Associations of particulate matter indices, NO_2 and O_3 with incidence of symptoms in the four panels (pooled random effects). Bold are significant pooled effects.

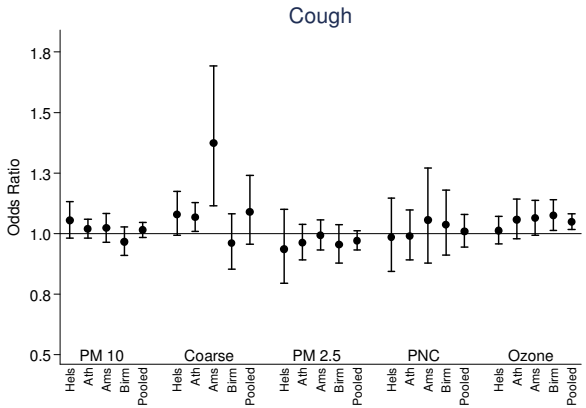
Symptom	Pollutant	Lag0		Lag1		Lag2		Lag06	
		OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Woken breathing problems	PM_{10}	0.994	0.951-1.038	0.992	0.950-1.037	0.920	0.877-0.966	0.925	0.852-1.004
	$PM_{2.5}$	0.995	0.931-1.064	0.965	0.903-1.033	0.919	0.857-0.984	0.878	0.784-0.983
	$PM_{10-2.5}$	0.994	0.928-1.065	1.016	0.950-1.088	0.823	0.701-0.967	0.882	0.654-1.189
	PNC	0.878	0.736-1.048	1.041	0.934-1.160	0.887	0.716-1.099	0.816	0.563-1.181
	Absorbance	1.003	0.930-1.082	0.998	0.924-1.077	0.909	0.815-1.012	0.861	0.729-1.016
	NO_2	1.013	0.936-1.096	1.015	0.953-1.082	0.956	0.900-1.016	0.923	0.817-1.043
	O_3	1.016	0.912-1.131	0.988	0.937-1.041	0.994	0.945-1.045	1.069	0.980-1.165
Shortness of breath	PM_{10}	1.008	0.958-1.060	**1.045**	**1.008-1.083**	0.992	0.954-1.031	1.048	0.974-1.127
	$PM_{2.5}$	1.019	0.963-1.079	1.039	0.982-1.098	0.999	0.941-1.061	1.069	0.976-1.171
	$PM_{10-2.5}$	0.993	0.929-1.062	**1.065**	**1.009-1.124**	0.977	0.906-1.054	1.101	0.883-1.373
	PNC	0.963	0.871-1.066	0.871	0.785-0.966	0.968	0.861-1.088	0.992	0.767-1.283
	Absorbance	1.017	0.949-1.091	0.995	0.931-1.064	0.988	0.925-1.055	1.372	0.756-2.490
	NO_2	1.022	0.970-1.076	0.969	0.918-1.022	0.998	0.947-1.052	1.036	0.921-1.165
	O_3	0.989	0.945-1.035	0.987	0.944-1.031	1.021	0.980-1.065	1.021	0.950-1.097
Wheezing	PM_{10}	1.009	0.963-1.057	0.997	0.903-1.100	1.000	0.930-1.076	1.025	0.838-1.254
	$PM_{2.5}$	1.009	0.949-1.073	0.989	0.884-1.106	1.023	0.925-1.132	1.065	0.839-1.351
	$PM_{10-2.5}$	1.010	0.946-1.079	1.044	0.763-1.427	0.970	0.872-1.079	1.065	0.910-1.246
	PNC	0.968	0.832-1.127	1.060	0.938-1.198	1.051	0.950-1.163	1.207	0.877-1.660
	Absorbance	0.991	0.925-1.061	1.018	0.950-1.091	1.025	0.957-1.099	1.106	0.922-1.328
	NO_2	1.009	0.951-1.071	0.986	0.932-1.043	1.028	0.974-1.086	1.089	0.988-1.199
	O_3	0.968	0.921-1.017	0.978	0.899-1.064	0.975	0.931-1.022	0.940	0.861-1.026
Cough	PM_{10}	1.014	0.961-1.070	1.005	0.966-1.045	0.982	0.943-1.024	1.017	0.948-1.092
	$PM_{2.5}$	0.976	0.891-1.069	0.969	0.912-1.030	0.990	0.932-1.052	0.991	0.898-1.094
	$PM_{10-2.5}$	1.060	0.938-1.198	1.037	0.975-1.104	0.972	0.909-1.040	1.160	0.875-1.538
	PNC	0.956	0.834-1.095	1.024	0.924-1.135	0.983	0.888-1.089	1.109	0.819-1.500
	Absorbance	0.991	0.879-1.116	0.980	0.911-1.054	0.942	0.877-1.012	1.029	0.828-1.279
	NO_2	0.994	0.942-1.049	0.968	0.884-1.061	0.975	0.923-1.030	0.999	0.844-1.182
	O_3	0.984	0.939-1.032	1.027	0.950-1.109	**1.044**	**1.000-1.090**	1.030	0.938-1.132

Figure 1 Odds ratio (95% CI) for prevalence of symptoms and limitation of activities associated with an increase of 10μg/m^3 in previous day (lag1) concentrations of each pollutant (10,000/cm3 for PNC) in each participating city and overall estimate (random effects).


Woken by breathing problems
Odds Ratio
1.8
1.5
1.3
1.0
0.8
0.5
PM 10
Coarse
PM 2.5
PNC
Ozone
Hels
Ath
Ams
Birm
Pooled


Shortness of breath
Odds Ratio
1.8
1.5
1.3
1.0
0.8
0.5
PM 10
Coarse
PM 2.5
PNC
Ozone
Hels
Ath
Ams
Birm
Pooled


Wheezing
Odds Ratio
1.8
1.5
1.3
1.0
0.8
0.5
PM 10
Coarse
PM 2.5
PNC
Ozone
Hels
Ath
Ams
Birm
Pooled


Cough
Odds Ratio
1.8
1.5
1.3
1.0
0.8
0.5
PM 10
Coarse
PM 2.5
PNC
Ozone
Hels
Ath
Ams
Birm
Pooled

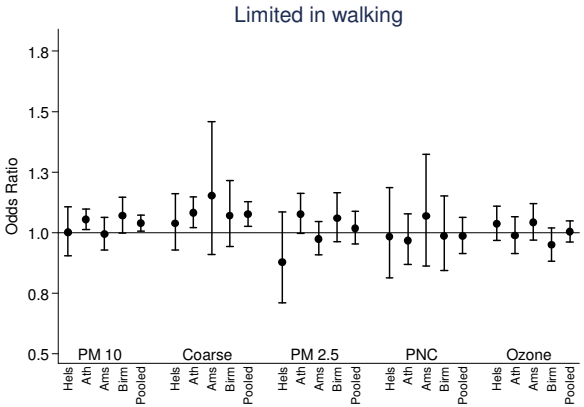

Limited in walking
Odds Ratio
1.8
1.5
1.3
1.0
0.8
0.5
PM 10
Coarse
PM 2.5
PNC
Ozone
Hels
Ath
Ams
Birm
Pooled

Figure 1