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Effects of Fine and Ultrafine Particles on Cardiorespiratory Symptoms in Elderly Subjects with Coronary Heart Disease

The ULTRA Study

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The ULTRA Study, a study investigating the association between fine and ultrafine particulate air pollution and cardiorespiratory health, was conducted during the winter of 1998–1999 in Amsterdam, the Netherlands; Erfurt, Germany; and Helsinki, Finland. At each study center, a panel of elderly subjects with coronary heart disease recorded cardiac and respiratory symptoms in a diary. Exposure to ambient air pollution was characterized by measuring daily mass concentrations of particles smaller than 10 µm (PM_{10}) and 2.5 µm ($PM_{2.5}$), number concentrations of ultrafine particles ($NC_{0.01–0.1}$), and gases. Odds ratios for the relation of symptoms to air pollution, adjusted for time trend, respiratory infections, and meteorologic variables, were mostly homogeneous across the centers. No association was found between air pollution and chest pain. A 10-µg/m^3 increase in $PM_{2.5}$ was positively associated with the incidence of shortness of breath (odds ratio (OR) = 1.12, 95% confidence interval (CI): 1.02, 1.24) and with avoidance of activities (OR = 1.09, 95% CI: 0.97, 1.22). $NC_{0.01–0.1}$ was only associated with the prevalence of avoidance of activities (OR = 1.10, 95% CI: 1.01, 1.19). In conclusion, $PM_{2.5}$ was associated with some cardiac symptoms in three panels of elderly subjects. $PM_{2.5}$ was more strongly related to cardiorespiratory symptoms than ultrafine particles were.

aged; air pollution; cardiovascular diseases; coronary disease; environmental exposure; particle size; pathological conditions, signs and symptoms; respiration disorders

Abbreviations: CI, confidence interval; CPC, condensation particle counter; NC, number concentration; $NC_{0.01–0.1}$, number concentrations of particles with a size range of 0.01–0.1 µm; PM_{10}, mass concentration of particles less than 10 µm in diameter; $PM_{2.5}$, mass concentration of particles less than 2.5 µm in diameter; ULTRA, Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air.

Daily mortality has been associated with daily variation in air pollution in several epidemiologic studies. The associations observed have been strongest for respiratory and cardiovascular disorders (1). The plausibility of these associations has been increased by studies that have reported associations of air pollution with respiratory and cardiovascular hospital admissions, respiratory symptoms, and pulmonary function (1, 2).

In most epidemiologic studies, particulate matter has been characterized as the mass concentration of particles less than 10 µm in diameter (PM_{10}). However, it is not clear which fraction of particulate matter is responsible for the observed

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health effects. In addition, a plausible mechanism for cardiovascular effects cannot yet be established.

One hypothesis is that ultrafine particles (smaller than 0.1 µm in diameter) deposited in the alveoli lead to increased blood coagulation. This mechanism operates either via pulmonary inflammation or via a direct action of those ultrafine particles on red blood cells, leading to the sequestration of erythrocytes (3, 4). An alternative hypothesis is that the cardiovascular effects are caused by alteration of the autonomic control of the heart. This theory is supported by epidemiologic studies on heart rate, heart rate variability, and arrhythmia. Peters et al. (6) found increases in heart rate in association with air pollution (5), and in another study they found increased arrhythmias on high air pollution days among patients with implanted cardioverter defibrillators. In three recent US studies (7–9), changes in heart rate and heart rate variability were found among elderly subjects on days with elevated levels of particulate matter. These findings are supported by the results of several toxicologic studies. Changes in respiratory and cardiac parameters, such as an increase in the S-T segment, were observed in dogs with coronary occlusion and rats after exposure to particulate matter (10, 11).

Because of these studies, one would anticipate that air pollution would be associated with cardiac symptoms as well. However, to our knowledge, there have been no published articles from panel studies reporting on the association between cardiovascular symptoms and air pollution, except for one older study (12).

The aim of the ULTRA Study (Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air) was to investigate the effects of different fractions of particulate matter (mass and number concentration) and gaseous air pollutants on the cardiovascular system in panels of elderly subjects with a history of coronary heart disease. In this paper, we report the effects of air pollution on the presence of cardiorespiratory symptoms.

MATERIALS AND METHODS

Study population

The ULTRA Study was a multicenter study conducted in Amsterdam, the Netherlands; Erfurt, Germany; and Helsinki, Finland. During the winter of 1998–1999, three panels of subjects were followed for 6 months with biweekly clinic visits and daily symptom diaries. Subjects who were selected were aged 50 years or more, had been diagnosed with coronary heart disease by a physician, and were nonsmokers. Subjects with a recent (<3 months) cardiac event, such as myocardial infarction, stroke, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty, were excluded. Other exclusion criteria were: unstable angina pectoris (New York Heart Association grade 4), type 1 diabetes mellitus, and a physician's evaluation that the person was too sick to participate, was unable to perform the exercise challenge, or was likely to have other problems with the study.

In Amsterdam, the panelists were recruited through distribution of screening questionnaires in homes for the elderly (senior residences). Letters were distributed in residential areas populated by a relatively high number of elderly persons, and an advertisement was placed in a local newspaper after an initially low response. Finally, additional subjects were recruited via the Department of Cardiology of the Academic Medical Center. In Erfurt, the study population was recruited through a local cardiologist. In Helsinki, subjects were recruited through the placement of advertisements in the journal of a Finnish Heart Association patient organization and a local newspaper. Furthermore, informational letters were distributed to members of the heart association who had the postal code of the study area in Helsinki and to gymnastic groups affiliated with the association. Written informed consent was obtained from each subject. The study protocol was approved by a medical ethical committee at each study center. Detailed information on the study methods has been reported elsewhere (13) and is available at the ULTRA Study website (http://www.ktl.fi/ultra).

Symptom diary

Subjects were instructed to report the presence of several selected cardiovascular and respiratory symptoms in the daily diary (13). Respiratory symptoms were selected from previous diary studies (14, 15). The cardiac symptoms were selected on the basis of angina pectoris quality-of-life questionnaires (16). The symptoms included in the diary were: chest pain, chest pain at physical exertion, shortness of breath, feeling tired or weak, tripping or racing heart, cold hands or feet, cough, phlegm, being awakened by breathing problems, wheezing, and common cold or flu and fever; symptoms were reported as absent (0), mild (1), or moderate/severe (2). In addition, subjects were asked about the avoidance of physically demanding activities because of symptoms (hereafter called avoidance of activities), as well as the question, "How would you rate your overall health today?". This perceived health could be reported in five grades, ranging from "very bad" to "good." Finally, the use of respiratory or cardiovascular medication could be reported (13). During each clinic visit, the completed diary was checked and replaced by a new diary. Assistants at each center manually keyed in the diary data. To ensure data quality, checks on impossible values and decision rules for coding were applied, as described in the ULTRA manual (13).

Air pollution exposure

In each city, concentrations of ambient air pollutants were measured at a fixed monitoring site representing urban background levels. Size distributions of particle number concentrations were measured with aerosol spectrometers. Previous side-by-side measurements showed that these spectrometers were comparable (17–19). Number concentrations (NC) in different size classes were determined to form one size class for particles with a size range of 0.01–0.1 µm, referred to as ultrafine particles ($NC_{0.01-0.1}$). A condensation particle counter (CPC) with a lower detection limit of 0.007 µm (TSI 3022A; TSI, Inc., St. Paul, Minnesota) was used at all centers to measure continuously the total number concentration of particles (hereafter called CPC count). Mass concentration of particles less than 2.5 μm in diameter ($PM_{2.5}$) was measured with Harvard impactors (20). All air pollution measurements were taken according to standard operating procedures that are described in the ULTRA manual (13).

PM_{10} measurements, as well as measures of gaseous air pollution (nitrogen oxide, nitrogen dioxide, carbon monoxide, sulfur dioxide, and ozone), were obtained from the National Quality Monitoring Network, which is operated by the National Institute of Public Health and the Environment (21) in the Netherlands. In Finland, these data came from the network measurement site of the Helsinki Metropolitan Area Council. In Germany, carbon monoxide data were collected by the state (Thüringer Landesanstalt für Umwelt). All other measurements were performed by the National Research Center for Health and Environment at the ULTRA site. All variables were transformed to 24-hour means, noon-to-noon, to coincide with the $PM_{2.5}$ measurements.

Confounder data

Hourly data on ambient temperature, relative humidity, and atmospheric pressure were obtained from national meteorologic network sites in or near the study area (the Royal Dutch Meteorological Institute in Amsterdam, the Thüringer Landesanstalt für Umwelt und Geologie in Erfurt, and the Helsinki Metropolitan Area Council in Helsinki). Data on the incidence of influenza-like illness were obtained per center from a sentinel system. Regional influenza data were used in both the Netherlands (cases/10,000 in northwestern Netherlands) (22) and Finland (total number of influenza cases reported in Helsinki). In Germany, regional respiratory infection data (weekly counts of patients in Thuringia who had to stay home because of acute respiratory infection) were used. Data on influenza-like illness were recoded from the weekly registrations into 0- to 6-day and 7- to 13-day averages.

Data analysis

All symptom variables were recoded as binary variables, with 0 representing no symptoms and 1 representing moderate/severe symptoms. Chest pain and chest pain upon physical exertion were interpreted as mutually exclusive symptoms by the subjects, especially in Finland and the Netherlands. Therefore, chest pain was recoded to 1 (present) when chest pain upon physical exertion was reported. Perceived health was recoded as 0 (good, quite good, or average) versus 1 (bad or very bad). We analyzed all symptoms separately instead of grouping them, since each symptom might be a reflection of a different mechanistic response. We analyzed the daily occurrence of a

TABLE 1. Characteristics of three panels of elderly subjects with a history of coronary heart disease, ULTRA Study, winter 1998–1999

	Amsterdam, the Netherlands (*n* = 37)		Erfurt, Germany (*n* = 47)		Helsinki, Finland (*n* = 47)	
	No.	%	No.	%	No.	%
Sex						
Female	13	35	4	9	23	49
Male	24	65	43	91	24	51
Mean age (years)	71.5 (54–84)*		64.6 (40–78)		68.3 (54–83)	
Past myocardial infarction	25	68	33	70	27	57
Angina pectoris	24	65	26	55	30	64
CABG†/PTCA†	17	46	34	72	23	49
Diabetes mellitus	2	5	7	15	5	11
COPD† or asthma	9	24	1	2	9	19
ETS† exposure at home	4	11	8	17	0	0
Daily medication use						
Beta blocker	13	35	35	74	31	66
ACE† inhibitor + AT† blocker	12	32	25	53	10	21
Calcium antagonist	11	30	18	38	13	28
Aspirin	22	59	36	77	36	77
Digitalis	2	5	9	19	7	15
Inhaled beta-agonist	2	5	1	2	3	6
Nitroglycerin	7	19	17	36	19	40

* Numbers in parentheses, range.

† CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; COPD, chronic obstructive pulmonary disease; ETS, environmental tobacco smoke; ACE, angiotensin-converting enzyme; AT, angiotensin receptor.

TABLE 2. Mean incidence and prevalence of cardiorespiratory symptoms in three panels of elderly subjects with a history of coronary heart disease, ULTRA Study, winter 1998–1999

	Incidence (%)			Prevalence (%)		
	Amsterdam, the Netherlands	Erfurt, Germany	Helsinki, Finland	Amsterdam, the Netherlands	Erfurt, Germany	Helsinki, Finland
Chest pain	2.1	7.7	5.5	8.9	34.3	11.9
Chest pain upon physical exertion	1.2	4.8	3.8	6.7	21.5	9.0
Shortness of breath	3.4	6.1	5.9	15.7	24.1	17.6
Being awakened by breathing problems	0.7	2.8	2.2	4.8	8.0	6.6
Wheezing	1.7	1.7	2.1	6.7	6.5	7.6
Coughing	2.8	2.4	2.9	24.0	9.7	21.8
Phlegm	3.5	2.3	1.9	34.1	13.9	22.4
Avoidance of activities	2.5	2.3	1.9	13.5	15.2	11.0
Perceived health	0.6	1.7	2.8	1.2	3.3	5.7

symptom when that symptom was reported to be absent on the previous day (incident symptom). We also analyzed the occurrence of symptoms irrespective of the occurrence of symptoms on the previous day (prevalent symptoms). In the diary, subjects only recorded "as needed" medication. Medication use was recoded as 0 (no medication) versus 1 (intake of one or more doses) by medication group on the basis of Anatomical-Therapeutical-Chemical codes (table 1).

Exposure variables were 24-hour average concentrations of particulate matter (PM_{10}, $PM_{2.5}$, $NC_{0.01–0.1}$, CPC count), and gaseous components (carbon monoxide, nitrogen oxide, nitrogen dioxide, ozone, and sulfur dioxide). For all components, same-day concentration (lag 0), previous-day concentration (lag 1), concentrations 2 (lag 2) and 3 (lag 3) days before, and 5-day average concentration were analyzed. Lag 0 was defined as the 24-hour period from noon on the same day to noon the next day. The 5-day average was calculated as the mean of values from lag 0 to lag 4. Missing values for $NC_{0.01–0.1}$ were estimated using a regression model with CPC count as the independent variable. The Spearman correlation coefficient for the correlation between $NC_{0.01–0.1}$ and CPC count was above 0.91 for all centers.

Logistic regression with an indicator variable for each subject was used to obtain center-specific effect estimates controlled for individual differences in frequency of symptom reporting. A confounder model was built for each symptom and for each center separately, without air pollution in the model. All models contained data on time trend, temperature, relative humidity, and ambient pressure independently of the direction of the association, as well as indicator variables for day of the week and subject. Influenza was only included when a relation in the expected direction appeared in the exploratory analyses. For temperature and relative humidity, lags of 0, 1, 2, and 3 days were evaluated. The shapes and lags of the covariates were explored using LOESS functions (23). A linear term was compared with nonparametric functions with spans that ranged from 0.3 to 1 for trend and from 0.6 to 1 for other covariates, with steps of 0.1. In principle, the model with the lowest Akaike's Information Criterion was selected. However, a less detailed model was selected when the response-trend plot showed too much detail (patterns with a period of less than 1

TABLE 3. Mean 24-hour averages and ranges of air pollutant concentrations and temperature in three European cities, ULTRA Study, winter 1998–1999

	Amsterdam, the Netherlands		Erfurt, Germany		Helsinki, Finland	
	Mean	Range	Mean	Range	Mean	Range
PM_{10}* (µg/m³)	36.5	13.6–112.0	27.1	5.2–104.2	19.6	6.4–67.4
$PM_{2.5}$* (µg/m³)	20.0	3.8–82.2	23.4	4.5–118.1	12.8	3.1–39.8
$NC_{0.01–0.1}$* (per cm³)	17,309	5,699–37,195	21,228	3,867–96,678†	17,078	2,305–50,306
Carbon monoxide (mg/m³)	0.6	0.4–1.6	0.4	0.1–2.5	0.4	0.1–1.0
Nitrogen dioxide (µg/m³)	43.1	8.5–93.5	29.2	6.7–81.7	31.2	10.7–67.5
Sulfur dioxide (µg/m³)	6.8	0.2–32.8	5.6	0.5–46.7	5.8	0.2–35.0
Temperature (°C)	7.7	–4.0 to 20.1	3.5	–7.8 to 13.6	–1.8	–24.3 to 11.5

* PM_{10}, mass concentration of particles less than 10 µm in diameter; $PM_{2.5}$, mass concentration of particles less than 2.5 µm in diameter; $NC_{0.01–0.1}$, number concentrations of particles with a size range of 0.01–0.1 µm.

† 99th percentile value: 54,479.

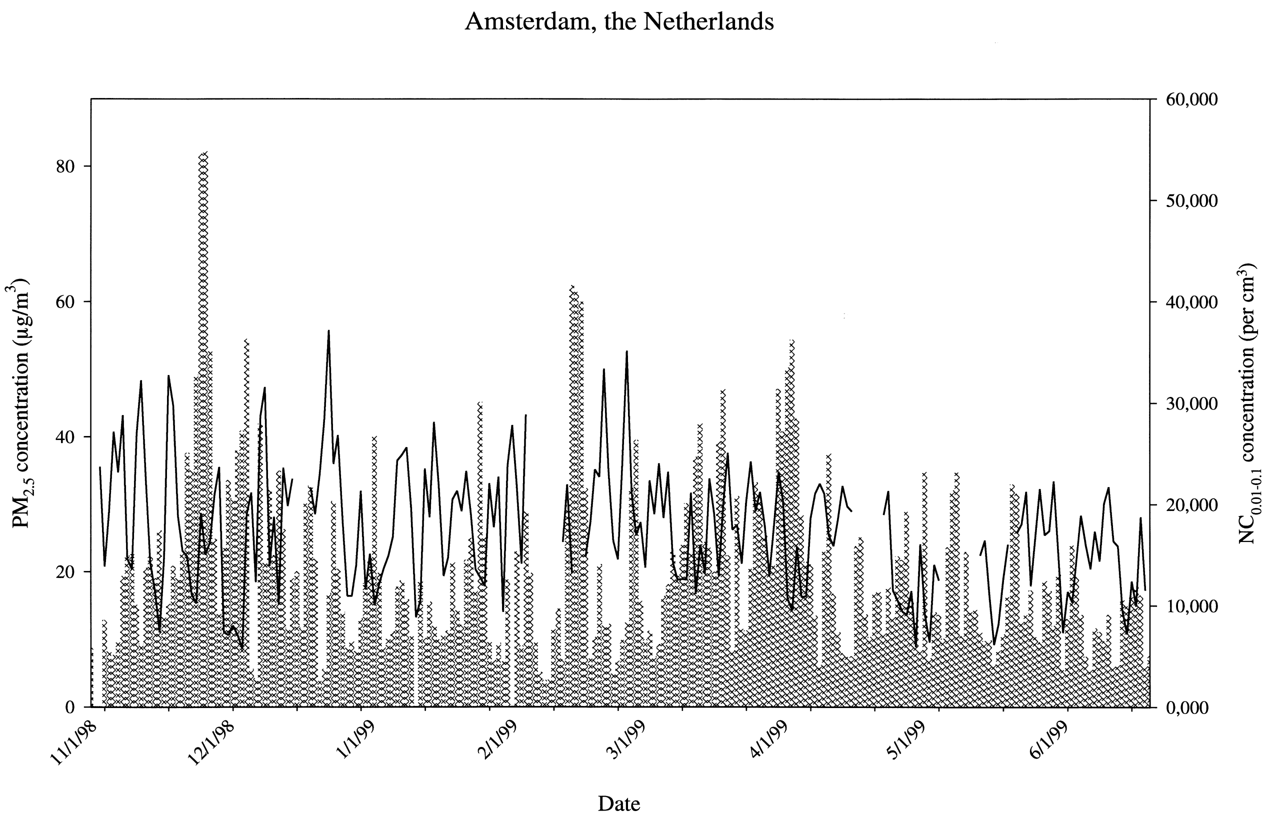

FIGURE 1. Daily concentrations of particles less than 2.5 µm in diameter ($PM_{2.5}$) and number concentrations of particles in the size range of 0.01–0.1 µm ($NC_{0.01–0.1}$), Amsterdam, the Netherlands, ULTRA Study, winter 1998–1999. $PM_{2.5}$ data are shown as a bar chart and $NC_{0.01–0.1}$ data are shown as a solid line.

month) or if, at lags from 1 day to 10 days, consistent negative autocorrelation coefficients occurred in the residuals. Model-building started with long-term confounders (time trend) and moved towards short-term confounders (weather).

The partial autocorrelation plot of the prevalence of symptoms showed autocorrelation from the previous 2 days. Therefore, an autoregressive structure for the previous 2 days was included in the model. No autocorrelation was present for incidence.

Effect estimates are expressed as odds ratios for an increase of 10 µg/m^3 in $PM_{2.5}$, 10,000 particles/cm^3 for $NC_{0.01–0.1}$, 0.25 mg/m^3 for carbon monoxide, and 15 µg/m^3 for nitrogen dioxide, based on the interquartile ranges of the air pollution levels at the three centers. To obtain combined effect estimates, we used the inverse of the variances of the center-specific estimates as weights to calculate weighted means of the panel-specific slopes. The heterogeneity of effect estimates between centers was tested with a χ^2 test (24). Sensitivity analyses changing time trend and temperature function, excluding high air pollution days, high influenza days, and high temperature days, and adding pollen counts were carried out to evaluate robustness of the effect estimates. In addition, two-pollutant models were explored. All analyses were performed with S-PLUS 2000 (25).

RESULTS

Panel characteristics

Subjects in the Dutch panel were slightly older than those in the other panels (table 1). The fraction of males was higher in the German panel than in the Dutch and Finnish panels. The prevalence of past myocardial infarction was slightly lower in the Helsinki panel than in the other panels. Angina pectoris was less prevalent and coronary artery bypass graft and percutaneous transluminal coronary angioplasty were more prevalent in the German panel than in the other panels. Doctor-diagnosed asthma and chronic obstructive pulmonary disease were less prevalent in the German panel than in the Helsinki and Amsterdam panels. In the Netherlands, 78.4 percent of the study population used one or more cardiovascular medicines on a daily basis. This figure was 100 percent for the study populations in Erfurt and Helsinki. Medication use was mostly stable. Only in 14 of the 131 cases (five in Amsterdam, five in Erfurt, and four in Helsinki) was the subject's medication changed or stopped during the study period.

The dates of the study periods were as follows: in Amsterdam, from November 2, 1998, to June 18, 1999 (229 days); in Erfurt, from October 12, 1998, to April 4, 1999 (171 days); and in Helsinki, from November 2, 1998, to April 30, 1999 (175 days). Because of recruitment problems,

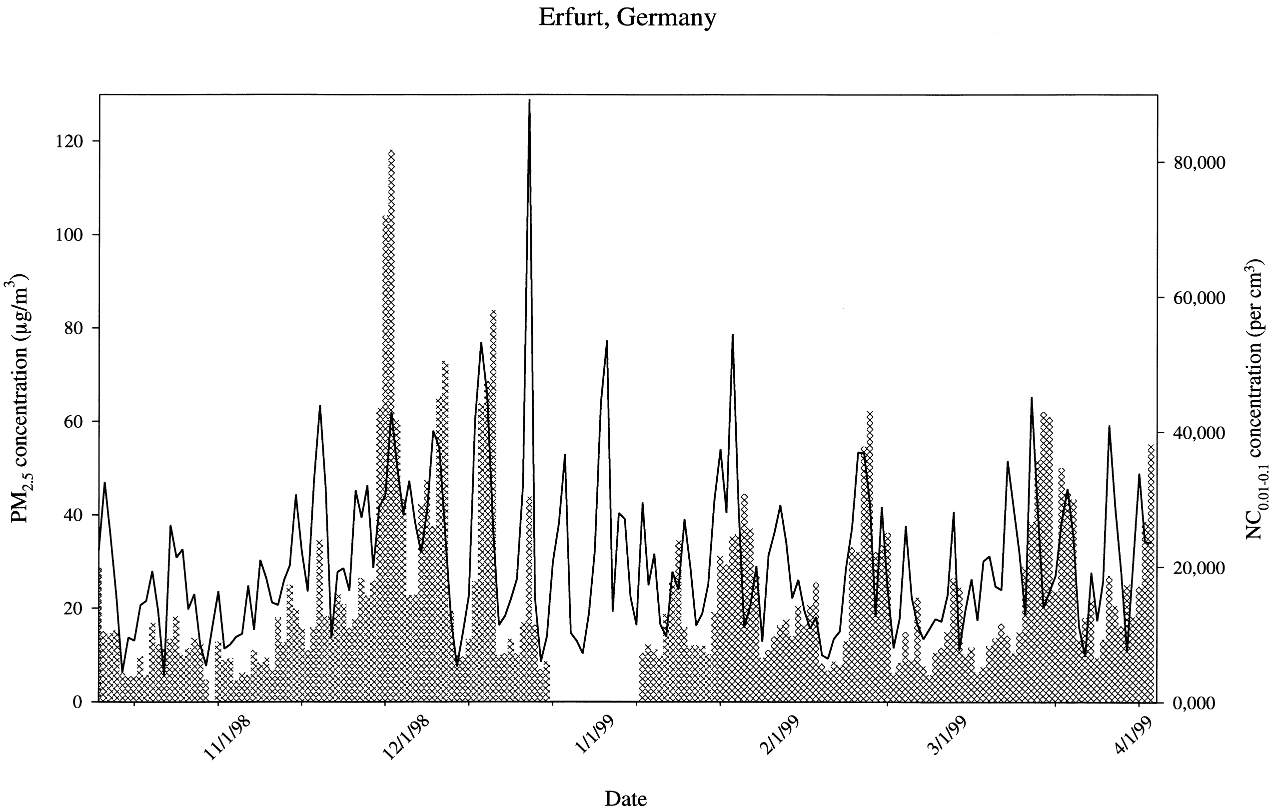

FIGURE 2. Daily concentrations of particles less than 2.5 µm in diameter ($PM_{2.5}$) and number concentrations of particles in the size range of 0.01–0.1 µm ($NC_{0.01–0.1}$), Erfurt, Germany, ULTRA Study, winter 1998–1999. $PM_{2.5}$ data are shown as a bar chart and $NC_{0.01–0.1}$ data are shown as a solid line.

we extended the study period towards the summer in the Netherlands to obtain a sufficient number of observations. In total, 6,228, 7,491, and 7,828 observations were obtained in Amsterdam, Erfurt, and Helsinki, respectively. For some of the observations (12.5 percent in Amsterdam, 5.9 percent in Erfurt, and 9.1 percent in Helsinki), there were one or more missing values because a subject reported having been out of town for more than 8 hours that day or failed to complete the diary. In both Amsterdam (1.8 percent) and Helsinki (0.9 percent), the item on which data were missing most frequently was the avoidance of activities. All other symptoms had less than 0.6 percent missing values, except for perceived health in Amsterdam (1.6 percent). In Germany, none of the symptoms had missing values.

In general, the incidence and prevalence of cardiovascular symptoms were lowest in Amsterdam and highest in Erfurt (table 2). There were small differences in the incidence of the respiratory symptoms coughing and wheezing, whereas the incidence of phlegm was highest in Amsterdam. Symptoms were weakly correlated, supporting the analysis of individual symptoms. All kappa values were below 0.4, except for chest pain during exercise and shortness of breath in Erfurt ($\kappa = 0.429$).

Although concentrations of $NC_{0.01–0.1}$ between the study centers were similar, concentrations of $PM_{2.5}$ differed substantially between the centers (table 3). The correlation between $PM_{2.5}$ and $NC_{0.01–0.1}$ was low in Amsterdam and Helsinki and moderately high in Erfurt (figures 1, 2, and 3). Spearman correlation coefficients were –0.15, 0.14, and 0.62 in these cities, respectively. PM_{10} and $PM_{2.5}$ were correlated in Amsterdam (r = 0.78) and Helsinki (r = 0.76) and were highly correlated in Erfurt (r = 0.95). Concentrations of gaseous air pollutants were more highly correlated with particulate air pollution in Erfurt than in Amsterdam and Helsinki.

Incidence analyses

In the combined and center-specific analyses, no consistent associations were present between air pollution and chest pain (data not presented) or between air pollution and chest pain upon physical exertion (table 4). Because the vast majority of effect estimates were homogeneous across centers, we present only combined odds ratios in the tables (full tables are available at http://www.ktl.fi/ultra/). Associations between $PM_{2.5}$ and shortness of breath were consistently positive at all study centers (figure 4) and for all lags, resulting in combined odds ratios above unity for all lags. No clear associations were observed between shortness of breath and $NC_{0.01–0.1}$. Being awakened by breathing problems was associated with $PM_{2.5}$ at lag 1 and with $NC_{0.01–0.1}$ at lag 3

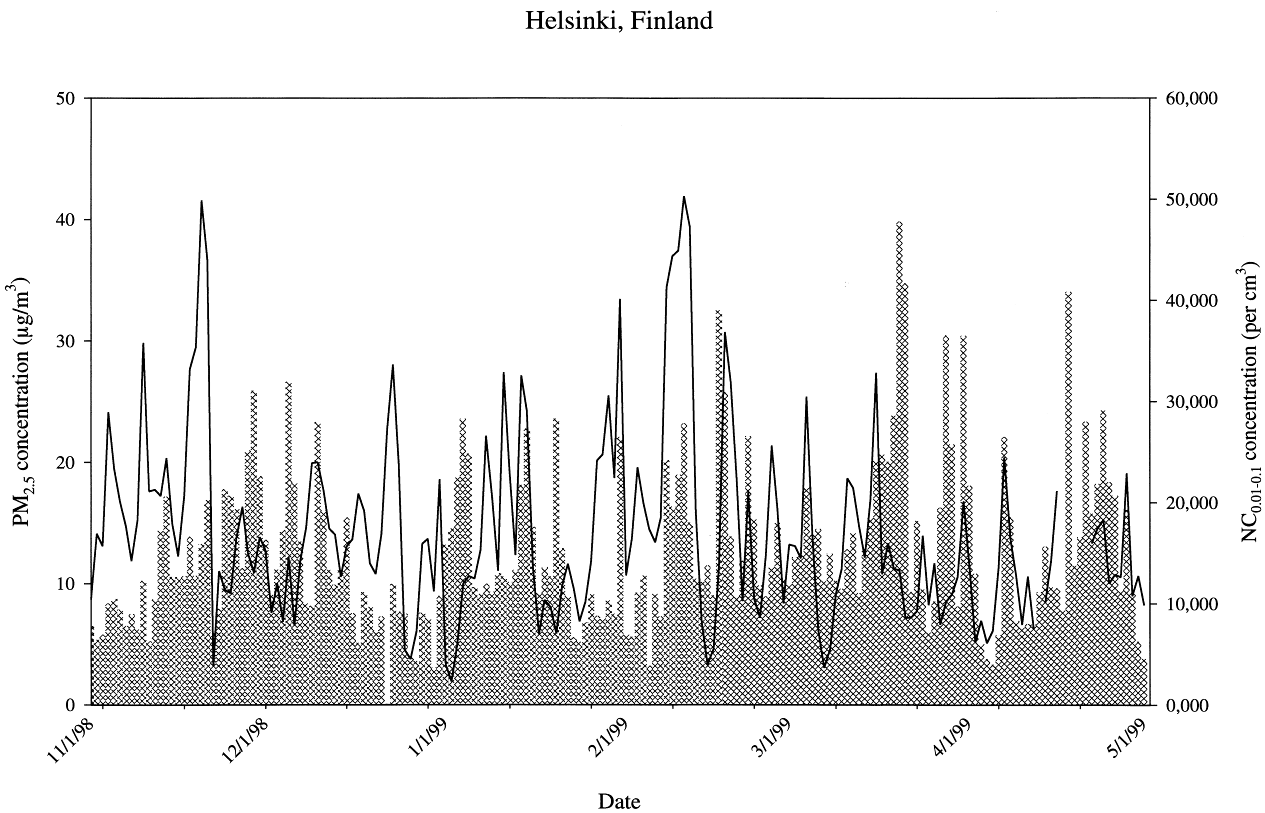

FIGURE 3. Daily concentrations of particles less than 2.5 μm in diameter ($PM_{2.5}$) and number concentrations of particles in the size range of 0.01–0.1 μm ($NC_{0.01-0.1}$), Helsinki, Finland, ULTRA Study, winter 1998–1999. $PM_{2.5}$ data are shown as a bar chart and $NC_{0.01-0.1}$ data are shown as a solid line.

only. For carbon monoxide and nitrogen dioxide, positive associations were seen mainly at higher lags. The incidence of the respiratory symptoms wheezing and coughing was not associated with any of the air pollutants (data not shown). Phlegm showed consistent associations with $PM_{2.5}$ in the combined analyses for all analyzed lags (table 4), but not with $NC_{0.01-0.1}$. There was a tendency toward positive associations between avoidance of activities and both particulate air pollution (PM_{10}, $PM_{2.5}$, $NC_{0.01-0.1}$) and gases (carbon monoxide, nitrogen dioxide), but none of the associations were statically significant. There were no clear associations between incidence of perceived health and air pollution (data not shown).

No consistent associations were present between the use of "as needed" nitroglycerin and particulate and gaseous air pollution components. For instance, the combined odds ratios for $PM_{2.5}$ and the incidence of "as needed" nitroglycerin use ranged from 0.91 (95 percent confidence interval (CI): 0.80, 1.02) for the 5-day average to 0.99 (95 percent CI: 0.91, 1.08) for lag 1. The underlying center-specific odds ratios were homogeneous for most of the combined odds ratios. Other "as needed" medications had very low incidences, which made an analysis impossible.

Prevalence analyses

Patterns similar to those in the combined incidence analyses were observed for the symptoms chest pain, wheezing, coughing, phlegm (data not shown), and chest pain upon physical exertion (table 5). The combined odds ratios for $PM_{2.5}$ and phlegm ranged from 1.05 (95 percent CI: 0.98, 1.12) for lag 0 to 1.15 (95 percent CI: 1.06, 1.25) for the 5-day average, with no indication of heterogeneity between the three centers. No association with $NC_{0.01-0.1}$ was found. In contrast to the incidence analysis, the prevalence of shortness of breath was not associated with any of the air pollutants (table 5). Moreover, for some lags there was highly significant heterogeneity between the centers. Being awakened by breathing problems was consistently associated with $PM_{2.5}$, with no indication of heterogeneity between the centers (table 5). Perceived health was associated with $PM_{2.5}$, carbon monoxide, and nitrogen dioxide, especially at the 2- and 3-day lags and the 5-day average (table 5). However, these results were fairly heterogeneous, except those for carbon monoxide. Avoidance of activities was homogeneously associated with $NC_{0.01-0.1}$ but was not clearly associated with $PM_{2.5}$, carbon monoxide, or nitrogen dioxide.

In both incidence analyses and prevalence analyses, odds ratios for PM_{10} were generally similar to the corresponding

TABLE 4. Combined odds ratios for the association of air pollution and incidence of symptoms in three panels of elderly subjects with a history of coronary heart disease, ULTRA Study, winter 1998–1999

	Chest pain upon physical exertion		Shortness of breath		Being awakened by breathing problems		Avoidance of activities		Phlegm	
	OR*,†	95% CI*	OR†	95% CI	OR†	95% CI	OR†	95% CI	OR†	95% CI
$PM_{2.5}$*										
Lag 0	1.04	0.96, 1.13	1.04	0.96, 1.12	NA*,‡		1.04	0.96, 1.14	1.03	0.93, 1.13
Lag 1	1.01	0.93, 1.09	1.06	0.99, 1.14	1.09	1.00, 1.20	1.03	0.95, 1.12	1.10	1.01, 1.19
Lag 2	0.98	0.90, 1.05	1.05	0.98, 1.12	1.04	0.95, 1.14	1.05	0.97, 1.14	1.08	1.00, 1.18
Lag 3	1.00	0.93, 1.08	1.08	1.01, 1.15	0.99	0.91, 1.08	1.06	0.98, 1.14	1.10	1.01, 1.19
5-day	1.02	0.91, 1.13	1.12	1.02, 1.24	1.03	0.90, 1.18	1.09	0.97, 1.22	1.16	1.03, 1.32
$NC_{0.01–0.1}$*										
Lag 0	0.98§	0.87, 1.11	0.97	0.88, 1.07	NA‡		1.12	0.98, 1.28	0.98	0.84, 1.14
Lag 1	0.94	0.84, 1.05	0.87	0.79, 0.97	0.92	0.80, 1.06	1.01	0.88, 1.16	0.92	0.79, 1.08
Lag 2	0.92	0.82, 1.03	0.99	0.89, 1.09	1.01	0.88, 1.16	1.11	0.96, 1.27	1.06	0.92, 1.23
Lag 3	0.99	0.89, 1.11	1.09	0.99, 1.21	1.14	1.01, 1.30	1.06	0.92, 1.21	1.07	0.93, 1.24
5-day	0.93	0.77, 1.12	0.93	0.77, 1.13	1.18	0.92, 1.52	1.17	0.91, 1.49	1.08	0.82, 1.41
Carbon monoxide										
Lag 0	1.01	0.91, 1.12	1.00	0.92, 1.10	NA‡		1.06	0.94, 1.19	1.05	0.93, 1.19
Lag 1	0.97	0.88, 1.08	0.96	0.88, 1.05	1.02	0.92, 1.14	1.03	0.91, 1.15	1.02	0.91, 1.14
Lag 2	0.94	0.86, 1.04	1.00	0.92, 1.09	1.03	0.93, 1.15	1.08	0.97, 1.21	1.08	0.96, 1.22
Lag 3	1.02	0.94, 1.12	1.07	0.98, 1.16	1.11	1.00, 1.22	1.05	0.94, 1.17	1.09	0.97, 1.22
5-day	0.99§	0.86, 1.15	1.03	0.90, 1.18	1.16	0.98, 1.37	1.12	0.94, 1.34	1.13	0.94, 1.35
Nitrogen dioxide										
Lag 0	1.02	0.89, 1.17	0.94§	0.85, 1.05	NA‡		1.04	0.90, 1.20	0.99	0.85, 1.15
Lag 1	0.95	0.83, 1.08	0.89	0.80, 0.99	1.00	0.86, 1.17	1.01§	0.88, 1.17	0.99	0.86, 1.14
Lag 2	0.94	0.83, 1.07	1.02	0.92, 1.14	1.11	0.96, 1.30	1.08	0.94, 1.24	1.14	0.99, 1.32
Lag 3	1.04	0.93, 1.18	1.11	1.00, 1.24	1.08§	0.94, 1.25	1.12	0.99, 1.28	1.12	0.97, 1.30
5-day	0.99	0.81, 1.21	1.00	0.84, 1.20	1.14	0.90, 1.46	1.16	0.93, 1.45	1.18	0.94, 1.48

* OR, odds ratio; CI, confidence interval; $PM_{2.5}$, mass concentration of particles less than 2.5 µm in diameter; $NC_{0.01–0.1}$, number concentrations of particles with a size range of 0.01–0.1 µm; NA, not applicable.

† Odds ratio for an increase of 10 µg/m^3 for $PM_{2.5}$, 10,000 particles/cm^3 for $NC_{0.01–0.1}$, 0.25 mg/m^3 for carbon monoxide, and 15 µg/m^3 for nitrogen dioxide.

‡ Exposure and symptom have no overlap. Being awakened by breathing problems will only be experienced in the morning, but diaries were filled out in the evening of that day. The air pollution measurement started at noon on that same day (lag 0). Therefore, data for lag 0 are not presented, and data for lag 1 will be indicative of immediate effects.

§ The combined odds ratio reflects underlying heterogeneous center-specific odds ratios. The *p* value in the heterogeneity test was less than 0.10.

odds ratios for $PM_{2.5}$ but were somewhat less significant. The associations reported for $NC_{0.01–0.1}$ were essentially the same when nonimputed ultrafine number count or total number count (CPC count) was used as the exposure variable. For example, the combined odds ratio for the incidence of being awakened by breathing problems (at lag 3) was 1.14 (95 percent CI: 1.01, 1.29) for CPC count compared with 1.14 (95 percent CI: 1.01, 1.30) for $NC_{0.01–0.1}$. The combined odds ratio for the prevalence of avoidance of activities (at lag 0) was 1.08 (95 percent CI: 0.99, 1.11) for CPC count compared with 1.10 (95 percent CI: 1.01, 1.19) for $NC_{0.01–0.1}$.

Sensitivity analyses showed that effect estimates for incident symptoms were generally stable across different models. For phlegm only, substantial changes in the effect estimates occurred after exclusion of days with $PM_{2.5}$ concentrations above the 98th percentile (5 days in Amsterdam, 4 days in Erfurt and Helsinki). Combined effect estimates were 0.97, 1.00, 1.03, 1.08, and 1.07 for $PM_{2.5}$ lags of 0, 1, 2, and 3 days and the 5-day average, respectively. Although none of these odds ratios were statistically significant, odds ratios were still elevated for the 3-day lag and the 5-day average. This suggests that most, but not all, of the association was due to the highest $PM_{2.5}$ concentrations.

DISCUSSION

We found consistent positive associations of $PM_{2.5}$ with shortness of breath and phlegm. There were weak positive associations between $PM_{2.5}$ and being awakened by breathing problems and avoidance of activities. For the other symptoms, no consistent associations with $PM_{2.5}$ were present. In general, associations of cardiorespiratory symp-

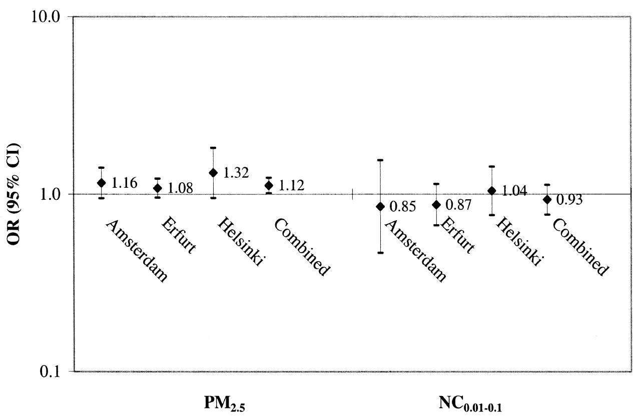

FIGURE 4. Odds ratios (OR) for the relation of incident shortness of breath to increases in particulate matter less than 2.5 μm in diameter ($PM_{2.5}$) and number concentrations of particles in the size range of 0.01–0.1 μm ($NC_{0.01-0.1}$) among elderly subjects with a history of coronary heart disease, ULTRA Study, winter 1998–1999. The odds ratios shown are for an increase of 10 μg/m^3 in $PM_{2.5}$ and an increase of 10,000 particles/cm^3 in $NC_{0.01-0.1}$ (5-day average). Bars, 95% confidence interval (CI).

toms were more consistent with $PM_{2.5}$ than with $NC_{0.01-0.1}$ or the gaseous pollutants carbon monoxide and nitrogen dioxide. The observed associations apply to a panel of medicated subjects with coronary heart disease.

Associations of $PM_{2.5}$ with shortness of breath, phlegm, being awakened by breathing problems, and avoidance of activities are not likely to have been due to chance, since associations were consistent across the different lag times evaluated. Furthermore, odds ratios for incidence were mainly homogeneous across centers. Odds ratios for prevalence were more often heterogeneous, which makes combined effect estimates more difficult to interpret. It is unlikely that the study design or data handling caused these differences, since all of the centers used standard operating procedures for the fieldwork and data management. Differences in age, sex, and lifestyle between subjects do not confound the results in panel studies. The use of fixed-effects models permitted each subject to serve as his or her own control, ruling out confounding. Medication use was stable for the study population during the study period, and the use of "as needed" medication showed no association with air pollution. All associations were adjusted for potentially confounding factors such as long-term time trends, respiratory infections, and meteorologic variables. A sensitivity analysis indicated that the estimates from the models were robust.

Apart from phlegm, respiratory symptoms (wheeze and cough) showed little association with air pollution, which may have been related to the composition of the panels (cardiovascular patients). Shortness of breath and being awakened by breathing problems have been considered respiratory symptoms in previous panel studies of asthmatic subjects or subjects with chronic obstructive pulmonary disease. It is plausible that in the current study, with cardiovascular patients, the presence of these symptoms was largely determined by cardiovascular conditions. This probably also holds for the avoidance of activities and perceived health.

Although chest pain showed no relation with air pollution, other cardiovascular symptoms such as shortness of breath, being awakened by breathing problems, and avoidance of activities were related to $PM_{2.5}$. One explanation for this might be that some patients have difficulty describing their angina as pain, feeling it more as a faint constriction in the chest (26). At the same time, reduced cardiac output leads to prolonged dyspnea even with minor exertion, which may influence a subject's decision to avoid physical activities. It is common for patients with left heart failure to be awakened from sleep by severe dyspnea resulting from pulmonary congestion (26). The observed associations were generally stronger for the higher lags, which contrasts with studies that showed daily and even hourly effects on the cardiovascular system (7–9). However, these studies examined variations in heart rhythm, and it is not obvious that mild changes in the heart are immediately reflected by symptoms.

One older panel study reported on the relation between air pollution and cardiovascular symptoms (12). In that study, symptoms of heart disease were related to total particulate levels, but no corrections for trend or other covariates were made. In a controlled exposure study, in which both heart disease patients and controls were exposed to ozone while walking on a treadmill, the onset of angina pain was not related to ozone exposure (27). The authors suggested that this could have been caused by the symptom-limited exercise of the patients (27).

In contrast with some previous epidemiologic studies (28, 29) and several toxicologic studies (30–32), we found more consistent associations with $PM_{2.5}$ than with $NC_{0.01-0.1}$. Three Finnish studies found that respiratory health was not more strongly associated with ultrafine particles than with fine particles (33–35). Although few studies used $NC_{0.01-0.1}$ as an exposure variable, the levels of $NC_{0.01-0.1}$ were comparable to those of earlier studies (28). Thus, low levels of exposure cannot be the explanation for the weak associations found in this study. One possibility is that the use of concentrations in outdoor air measured at a fixed site is not a good proxy measure for the personal exposure of subjects, who spend most of their time indoors. This may be especially true for elderly subjects. For $PM_{2.5}$, there is evidence that ambient concentrations correlate well with the personal exposures of children (36) and the personal exposures of elderly adults in the current study in Amsterdam and Helsinki (20). Similar information is currently lacking for $NC_{0.01-0.1}$, but the short lifetime of $NC_{0.01-0.1}$ suggests that this correlation may be lower. Koponen et al. (37) showed that the indoor:outdoor ratio for particles smaller than 90 nm was approximately 0.2, but this was measured in an office building that had an effective filtration system, in contrast to most homes.

Associations of $NC_{0.01-0.1}$ and CPC count with the different symptoms were generally of the same magnitude and significance. This is consistent with the notion that ultrafine particles dominate outdoor particle number concentrations. This implies that in future epidemiologic studies, the less complicated CPC count could be used to study the effects of ultrafine number counts. However, the mean $NC_{0.01-0.1}$:CPC

TABLE 5. Combined odds ratios for the association of air pollution and prevalence of symptoms in three panels of elderly subjects with a history of coronary heart disease, ULTRA Study, winter 1998–1999

	Chest pain upon physical exertion		Shortness of breath		Being awakened by breathing problems		Avoidance of activities		Perceived health	
	OR*,†	95% CI*	OR†	95% CI	OR†	95% CI	OR†	95% CI	OR†	95% CI
$PM_{2.5}$*										
Lag 0	1.00§	0.94, 1.07	0.97	0.92, 1.02	NA*,‡		0.97	0.91, 1.04	1.05	0.97, 1.14
Lag 1	1.01§	0.95, 1.07	1.00	0.95, 1.05	1.10	1.03, 1.17	0.99	0.93, 1.05	1.05	0.98, 1.13
Lag 2	1.00§	0.94, 1.05	1.01	0.96, 1.05	1.06	0.99, 1.13	0.99	0.94, 1.05	1.03§	0.96, 1.10
Lag 3	0.99	0.94, 1.05	1.12§	1.07, 1.17	1.04	0.97, 1.11	1.02	0.97, 1.08	1.05	0.98, 1.12
5-day	1.00§	0.93, 1.09	1.00	0.93, 1.06	1.14	1.03, 1.25	1.02§	0.93, 1.11	1.11	1.00, 1.24
$NC_{0.01–0.1}$*										
Lag 0	0.99§	0.91, 1.08	0.97	0.91, 1.04	NA‡		1.10	1.01, 1.19	0.89§	0.79, 1.00
Lag 1	1.00	0.92, 1.08	0.94	0.88, 1.01	0.93§	0.84, 1.03	1.05	0.97, 1.14	1.01	0.91, 1.12
Lag 2	0.98	0.90, 1.07	0.97	0.91, 1.04	0.96	0.87, 1.06	1.01	0.93, 1.11	1.06§	0.96, 1.17
Lag 3	1.02	0.93, 1.11	0.98	0.92, 1.06	1.11	1.01, 1.22	1.02	0.93, 1.11	1.08	0.99, 1.19
5-day	1.02§	0.87, 1.20	0.85	0.75, 0.97	1.06§	0.89, 1.27	1.19	1.01, 1.42	1.07§	0.88, 1.29
Carbon monoxide										
Lag 0	1.00	0.93, 1.08	1.00	0.94, 1.06	NA‡		1.06	0.99, 1.15	0.97	0.87, 1.08
Lag 1	1.02	0.95, 1.10	0.99	0.94, 1.05	1.01	0.93, 1.10	1.02	0.95, 1.10	1.07	0.98, 1.17
Lag 2	0.98	0.92, 1.06	0.99	0.93, 1.05	0.99	0.91, 1.08	0.99	0.92, 1.07	1.11	1.02, 1.20
Lag 3	1.00§	0.93, 1.07	1.01§	0.95, 1.07	1.10	1.02, 1.19	1.01	0.94, 1.09	1.11	1.03, 1.20
5-day	1.03§	0.92, 1.15	0.98§	0.90, 1.07	1.13	1.00, 1.29	1.10	0.98, 1.25	1.24	1.08, 1.41
Nitrogen dioxide										
Lag 0	1.00	0.91, 1.11	0.95	0.88, 1.02	NA‡		1.00	0.91, 1.09	0.90§	0.79, 1.02
Lag 1	0.99	0.90, 1.09	0.95	0.88, 1.02	1.01§	0.90, 1.14	0.98§	0.90, 1.08	1.07	0.95, 1.20
Lag 2	0.98	0.89, 1.07	0.99	0.92, 1.06	1.05	0.94, 1.18	0.98	0.89, 1.07	1.07§	0.96, 1.20
Lag 3	1.03	0.94, 1.13	0.96	0.90, 1.03	1.09	0.98, 1.22	1.02	0.94, 1.12	1.11	1.00, 1.24
5-day	1.01	0.87, 1.18	0.87	0.77, 0.97	1.14	0.96, 1.36	1.01§	0.87, 1.17	1.13§	0.93, 1.36

* OR, odds ratio; CI, confidence interval; $PM_{2.5}$, mass concentration of particles less than 2.5 μm in diameter; $NC_{0.01–0.1}$, number concentrations of particles with a size range of 0.01–0.1 μm; NA, not applicable.

† Odds ratio for an increase of 10 μg/m^3 for $PM_{2.5}$, 10,000 particles/cm^3 for $NC_{0.01–0.1}$, 0.25 mg/m^3 for carbon monoxide, and 15 μg/m^3 for nitrogen dioxide.

‡ Exposure and symptom have no overlap. Being awakened by breathing problems will only be experienced in the morning, but diaries were filled out in the evening of that day. The air pollution measurement started at noon on that same day (lag 0). Therefore, data for lag 0 are not presented, and data for lag 1 will be indicative of immediate effects.

§ The combined odds ratio reflects underlying heterogeneous center-specific odds ratios. The *p* value in the heterogeneity test was less than 0.10.

count ratio differed for Amsterdam (0.71), Helsinki (0.75), and Erfurt (0.89), which emphasizes the need for calibration of the two instruments per study site.

In conclusion, these results from the ULTRA Study indicate that some cardiovascular and respiratory symptoms are related to levels of particulate air pollution among medicated subjects with coronary heart disease. The results indicate that the associations are stronger for $PM_{2.5}$ than for ultrafine particles and gaseous air pollutants.

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