Effects of Particulate Air Pollution on Blood Pressure and Heart Rate in Subjects with Cardiovascular Disease: A Multicenter Approach

Angela Ibald-Mulli,[1,2] Kirsi L. Timonen,[3,4] Annette Peters,[1] Joachim Heinrich,[1] Gabriele Wölke,[1,2] Timo Lanki,[4] Gintautas Buzorius,[5] Wolfgang G. Kreyling,[6,7] Jeroen de Hartog,[8] Gerard Hoek,[8] Harry M. ten Brink,[9] and Juha Pekkanen[4]

[1]Institute of Epidemiology, GSF–National Research Centre for Environment and Health, Neuherberg, Germany; [2]IBE Department of Epidemiology, Ludwig-Maximilians-University, Munich, Germany; [3]Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland; [4]Unit of Environmental Epidemiology, National Public Health Institute, Kuopio, Finland; [5]Department of Physical Science, Helsinki University, Helsinki, Finland; [6]Institute of Inhalation Biology, GSF–National Research Centre for Environment and Health, Neuherberg, Germany; [7]Focus Network Aerosols and Health, GSF–National Research Centre for Environment and Health, Neuherberg/Munich, Germany; [8]Environmental and Occupational Health Unit, Institute for Risk Assessment Sciences University of Utrecht, Utrecht, the Netherlands; [9]Energy Research Centre of the Netherlands, Petten, the Netherlands

Given the hypothesis that air pollution is associated with elevated blood pressure and heart rate, the effect of daily concentrations of air pollution on blood pressure and heart rate was assessed in 131 adults with coronary heart disease in Helsinki, Finland; Erfurt, Germany; and Amsterdam, the Netherlands. Blood pressure was measured by a digital monitor, and heart rate was calculated as beats per minute from an electrocardiogram recording with the patient in supine position. Particle concentrations were measured at central measuring sites. Linear regression was used to model the association between 24-hr mean concentrations of particles and blood pressure and heart rate. Estimates were adjusted for trend, day of week, temperature, barometric pressure, relative humidity, and medication use. Pooled effect estimates showed a small significant decrease in diastolic and systolic blood pressure in association with particulate air pollution; a slight decrease in heart rate was found. Of the three centers, Erfurt revealed the most consistent particle effects. The results do not support findings from previous studies that had shown an increase in blood pressure and heart rate in healthy individuals in association with particles. However, particle effects might differ in cardiac patients because of medication intake and disease status, both affecting the autonomic control of the heart. *Key words:* **autonomic control, blood pressure, cardiovascular disease, fine and ultrafine particles, heart rate.** *Environ Health Perspect* **112:369–377 (2004). doi:10.1289/ehp.6523 available via** *http://dx.doi.org/* **[Online 1 December 2003]**

Particulate air pollution has been linked to increased mortality and morbidity. Several reviews summarizing and evaluating health effects of particulate air pollution have been published (ATS 1996; Pope 2000; Pope et al. 1995). Adverse effects of air pollution include an increase in cardiovascular and respiratory deaths among elderly people as well as increased hospital admissions for heart and respiratory diseases (Borja-Aburto et al. 1998; Burnett et al. 1999; Dab et al. 1996; Delfino et al. 1994; Prescott et al. 1998; Schwartz 1994, 1999; Sheppard et al. 1999; Spix and Wichmann 1996; Thurston 1996; Zanobetti et al. 2000; Zmirou et al. 1998). With the improvement of measurement techniques, clearer effects were observed with smaller particle size fractions. In studies where both PM_{10} (particulate matter < 10 μm in diameter) and $PM_{2.5}$ (particulate matter < 2.5 μm in diameter) data were available to characterize the ambient concentrations of particle mass, there were indications that $PM_{2.5}$ was more strongly associated with mortality than was PM_{10} (Dockery et al. 1992; Schwartz et al. 1996). Recent studies on subjects with respiratory diseases showed effects of ultrafine particles (UFP) on peak expiratory flow, symptoms, and medication use (Klot et al. 2002; Pekkanen et al. 1997; Peters et al. 1997b). A study on daily mortality from Erfurt, Germany, found comparable effects of fine particles and UFP in all size classes considered. However, effects of fine particles were more immediate, whereas UFP showed rather delayed effects on mortality (Wichmann et al. 2000).

There is only a moderate body of evidence from epidemiologic studies on effects of particles on the cardiovascular system. Although mortality studies and hospital admission data show the largest effects among people with cardiovascular and respiratory diseases, most of the evidence on cardiovascular effects was derived from studies in healthy subjects. Recently published literature suggests that potential mechanisms of particulate matter toxicity affecting cardiovascular health include the alteration of the autonomic nervous system (Dockery 2001), systemic and local inflammatory events (Liao et al. 1999; Seaton et al. 1995), and alterations in blood coagulability (Peters et al. 2000b; Pekkanen et al. 2000).

Studies on the daily variation of particulate air pollution and heart rate variability, a marker of autonomic function of the heart, in elderly subjects showed a decrease in heart rate variability associated with particulate air pollution (Creason et al. 2001; Gold et al. 2000; Liao et al. 1999; Pope et al. 1999a). Further, results of a study by Pope et al. (1999b) indicated an increase in pulse rate in association with PM_{10}, and an increase in heart rate was observed during an air pollution episode in Germany (Peters et al. 1999). Blood pressure and heart rate are physiologic parameters that can be used to assess changes in the autonomic control of the heart and vascular tone (Grassi et al. 1998; Noll et al. 1998). Elevated blood pressure is a well-established risk factor for cardiovascular morbidity and mortality (Welin et al. 1993). Recent analyses of air pollution effects on blood pressure in a population-based sample as well as in a panel of asthmatic subjects found an increase in systolic blood pressure with elevated concentrations of particulates (Ibald-Mulli et al. 2001; Linn et al. 1999). Given previous study results, the purpose of this analysis was to assess whether fine particles and UFP in ambient air are associated with elevated blood pressure as well as heart rate in subjects with preexisting heart disease. The analyses have been conducted as part of ULTRA, the European multicenter study on exposure and risk assessment for fine particles and UFP in ambient air.

Materials and Methods

Study population. The ULTRA study was a multicenter study with centers in Amsterdam (the Netherlands), Erfurt (Germany), and Helsinki (Finland). In each center, a panel of subjects with coronary heart disease was studied for 6 months during the winter of 1998–1999. The study protocol consisted of

Address correspondence to A. Ibald-Mulli, GSF–National Research Centre for Environment and Health, Institute of Epidemiology, Ingolstädter Landstraße 1, 85764 Neuherberg, Germany. Telephone: 49-89-3187-3512. Fax: 49-89-3187-3380. E-mail: ibald@gsf.de

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clinical visits once every 2 weeks and daily recording of symptoms and medication use. Subjects who were included in the study had to be free-dwelling nonsmokers and ≥ 50 years of age with doctor-diagnosed coronary heart disease. Subjects with a recent (< 3 months) cardiac event such as myocardial infarction, stroke, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty (PTCA) were excluded from the panels. Other exclusion criteria were unstable angina pectoris and type 1 diabetes mellitus. Subjects were examined by a physician to exclude persons who were too ill, unable to perform the exercise challenge, or likely to have problems with the study for other reasons. The subjects were characterized by a questionnaire and a recording of a 12-lead standard resting electrocardiogram (ECG).

In Amsterdam, panelists were recruited by sending out information letters and screening questionnaires to retirement homes. Because the response was low, a newspaper advertisement was used and letters were distributed in areas mainly inhabited by senior citizens to enroll more subjects. Finally, 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 by an advertisement in the journal of a patient organization of the Finnish Heart Association. Furthermore, information letters were distributed to members of the association with the postal code of the study area of Helsinki and to physical rehabilitation groups of the association. In addition, subjects were recruited by an advertisement in a local newspaper.

From each subject, a written consent was obtained. In each study center the study protocol was approved by the responsible review board.

Blood pressure and heart rate measurements. All methods used in the ULTRA study were conducted according to standard operating procedures (SOPs) developed for the ULTRA study (Pekkanen and Timonen 2000). The clinical visit included the recording of a five-lead ECG during a standardized protocol, which consisted of 5-min periods of rest in supine position, rest in supine position with paced breathing, and standing in upright position. Further, a 6-min light exercise challenge with a bicycle ergometer and a 10-min rest in supine position were included. For each subject, the visit was always scheduled for the same weekday and at the same time of the day. The daily medication of the subjects was recorded and not changed for the clinical visit. The ambulatory ECG was recorded with an Oxford MR-63 tape recorder (Oxford Instruments, Abington, UK). Two-channel recordings were performed with standard electrode position recommended by the manufacturer. The ECG recordings were analyzed with the Oxford Exel Medilog II V 7.5 system (Oxford Instruments) at Kuopio University Hospital. Trained research assistants reviewed and, when necessary, interactively edited the automatically predetermined beat-to-beat intervals. During the ECG recording, blood pressure was measured with a digitalized monitor (Omron M4; OMRON Medizintechnik Handelsgesellschaft GmbH, Mannheim, Germany) according to the instruction manual. Blood pressure was measured twice in supine position with 45 sec between measurements. For the analyses, systolic and diastolic blood pressure in supine position was calculated as the mean from the two measurements in supine position. After postural change from supine to standing position, blood pressure was measured again after 3 min of standing. Heart rate was calculated as beats per minute from the total number of corrected normal-to-normal beat intervals during the 5 min of rest in supine position.

Air pollution monitoring. In each city, concentrations of ambient air pollutants were measured at a fixed monitoring site representing urban background levels according to the ULTRA SOPs (Pekkanen and Timonen 2000). Size distributions of particle number concentrations were measured with aerosol spectrometers, which had been compared thoroughly in previous side-by-side ambient air measurements (Khlystov et al. 2001; Mirme et al. 2002; Tuch et al. 2000). Fractions of number concentrations in different size classes were determined to form one size class for UFP, (particles in the size range of 0.01–0.1 μm) and one for accumulation mode particles (ACP), (particles in the size range of 0.1–1.0 μm). $PM_{2.5}$ was measured with Harvard impactors (Air Diagnostics and Engineering Inc., Harrison, ME, USA).

Data on meteorologic variables as well as PM_{10}, oxides of nitrogen, carbon monoxide, sulfur dioxide, and ozone were collected from

Table 1. Description of the study population and heart rate and blood pressure variables during resting in supine position.

	Amsterdam	Erfurt	Helsinki	Difference[a] between centers
No. of subjects	37	47	47	
No. of clinical visits	429	491	511	
No. of ECG recordings	413	472	509	
No. of heart rate measurements	366	417	460	
No. of blood pressure readings	414	471	495	
Sex [*n* (%)]				
Female	13 (35)	4 (9)	23 (45)	1
Male	24 (65)	43 (9)	24 (55)	
Age [years, mean (range)]	71.5 (54–84)	64.6 (40–78)	68.3 (54–83)	2
Body mass index [mean (range)]	27.4 (19–34)	27.2 (22–33)	28.8 (20–36)	NS
Medical history [*n* (%)]				
Myocardial infarction	26 (70)	33 (30)	27 (57)	NS
Coronary bypass or PTCA	17 (46)	34 (72)	23 (49)	1
Hypertension	18 (49)	31 (66)	29 (62)	NS
Type 2 diabetes mellitus	2 (5)	8 (7)	5 (11)	NS
Smoking [*n* (%)]				
Never-smoker	7 (19)	10 (21)	21 (45)	1
Ex-smoker	30 (81)	37 (79)	26 (55)	
Environmental tobacco smoke at home [*n* (%)]	4 (11)	8 (17)	0 (0)	1
Daily medication use [*n* (%)]				
Beta-blockers	13 (35)	35 (74)	31 (66)	1
ACE inhibitors or AT_2 blockers	12 (32)	25 (53)	10 (21)	1
Ca^{2+} blockers	11 (30)	18 (38)	13 (28)	NS
Diuretics	6 (16)	20 (43)	13 (28)	1
Combined blood medication[b]	9 (24)	28 (58)	13 (28)	1
Digitalis	2 (5)	9 (19)	7 (15)	1
Nitrates	7 (19)	17 (36)	19 (40)	1
Any cardiac medication	27 (73)	45 (96)	45 (96)	1
Heart rate (beats/min)	62 ± 11	66 ± 11	60 ± 8	2
Systolic blood pressure in supine position (mm/Hg; mean ± SD)	140 ± 19	133 ± 18	142 ± 22	2
Diastolic blood pressure in supine position (mm/Hg; mean ± SD)	84 ± 11	80 ± 8	77 ± 12	3
Systolic blood pressure in standing position (mm/Hg; mean ± SD)	144 ± 22	138 ± 20	150 ± 26	2
Diastolic blood pressure in standing position (mm/Hg; mean ± SD)	86 ± 12	84 ± 10	87 ± 11	NS

NS, nonsignificant.
[a]1 = chi squared test, $p < 0.05$; 2 = difference between Erfurt and Amsterdam and between Erfurt and Helsinki, Tukey's test, $p < 0.05$; 3 = All centers different, Tukey's test, $p < 0.05$. [b]Any combination of beta-blockers, ACE inhibitors, Ca^{2+} blockers, and diuretics.

existing networks. All variables are 24-hr means from 1200 hr to 1200 hr.

Data analysis. Data were analyzed using the statistical package SAS (version 8; SAS Institute Inc., Cary, NC, USA) and S-Plus 2000 (professional release 1; Insightful Corp., Seattle, WA, USA). Blood pressure and heart rate measurements were checked for autocorrelation within each subject for the repeated measurements. Because of different climatic and topographic conditions of each location, basic model building was done for each panel separately. Nonparametric smooth functions based on locally weighted least squares in S-Plus were applied to explore the shape of the association between confounders and the dependent variable. The following covariates were considered: an indicator variable for each subject, long-term time trend, temperature (lags 0–3), relative humidity (lags 0–3), barometric pressure (lags 0–3), blood pressure active medication, and day of the week of the visit. Criteria for building the basic model were Akaike's Information Criterion and exposure–response plots. Because there was no autocorrelation for within-subject measurements, no adjustment for autocorrelation was necessary. In general, the model with the lowest Akaike's Information Criterion was selected (Pekkanen and Timonen 2000).

For the blood pressure analyses, the basic model for the Amsterdam panel included a smooth function for time trend, a quadratic term for temperature, a smooth function for relative humidity, and a linear term for barometric pressure. The basic model for Erfurt included a quadratic term for time trend and smooth functions for temperature, relative humidity, and barometric pressure. The basic model for Helsinki included a quadratic term for time trend, smooth functions for temperature and barometric pressure, and a linear term for relative humidity. Use of any blood pressure active medication was included as categorical variable in all three models to control for individual medication intake. Further, day of the week was included as categorical variable to adjust for a potential cluster effect because of examining the same groups of subjects on the same days of the week. The confounder models for heart rate were as follows: for Amsterdam, linear terms for time trend, temperature, relative humidity, and barometric pressure; for Erfurt, a smooth function for time trend and barometric pressure and quadratic terms for temperature and relative humidity; for Helsinki, smooth functions for time trend, temperature, and barometric pressure and a linear term for relative humidity. Based on the model selection criteria, day of the week and medication intake were added to all three models as categorical variables. Subgroup analyses were conducted by disease status.

For the calculation of the effect estimates in S-Plus, the default setting of the convergence criteria was reset to $\varepsilon = 10 \times 10^{-15}$, and the maximum iterations was increased to 1,000 to avoid iterations being prematurely halted at something other than the maximum likelihood solution. In addition to the S-Plus models with nonparametric confounder adjustment, effects were also estimated using the mixed procedure in SAS with parametric terms to adjust for trend, temperature, barometric pressure, and relative humidity. The effects were more conservative using S-Plus software compared with SAS. Therefore, the results based on the nonparametric adjustment for confounders using S-Plus are presented.

Pooled effect estimates were calculated as a weighted average of the center-specific estimates using the inverse of the center-specific variances as weights. The heterogeneity between centers was tested with chi-squared test. For heterogeneous estimates, random effect models were applied to calculate pooled effects (Spix et al. 1998).

Table 2. Summary statistics of daily concentrations of air pollutants, temperature, relative humidity, and barometric pressure during the study period.[a]

	No.	Mean	Minimum	25th[b]	50th[b]	75th[b]	Maximum
UFP (n/cm^3)							
Amsterdam	216	17,338	5,699	12,614	17,147	21,322	37,195
Erfurt	177	21,124	3,867	12,401	19,198	27,933	96,678
Helsinki	182	17,041	2,305	11,052	14,886	20,879	50,306
ACP (n/cm^3)							
Amsterdam	202	2,131	413	1,212	1,874	2,795	6,413
Erfurt	177	1,829	303	964	1,492	2,237	6,848
Helsinki	176	1,390	344	909	1,200	1,672	3,782
$PM_{2.5}$ (μg/m^3)							
Amsterdam	228	20.0	3.8	10.4	16.9	23.9	82.2
Erfurt	161	23.1	4.5	10.5	16.3	27.4	118.1
Helsinki	181	12.7	3.1	8.1	10.6	16.0	39.8
CO (mg/m^3)							
Amsterdam	237	0.6	0.4	0.5	0.6	0.7	1.6
Erfurt	176	0.4	0.1	0.2	0.3	0.5	2.5
Helsinki	173	0.4	0.1	0.3	0.4	0.6	1.0
NO_2 (μg/m^3)							
Amsterdam	237	42.7	8.5	30.8	42.2	53.9	93.5
Erfurt	177	28.9	6.7	18.5	26.5	36.8	81.7
Helsinki	182	31.1	10.7	22.8	29.7	35.5	67.5
SO_2 (μg/m^3)							
Amsterdam	237	6.7	0.2	3.5	5.5	8.8	32.8
Erfurt	177	5.6	0.5	2.7	3.8	6.0	46.7
Helsinki	180	5.8	0.2	2.8	4.6	7.5	35.0
Temperature (°C)							
Amsterdam	237	7.8	–4.0	4.6	7.5	11.6	20.1
Erfurt	177	3.7	–7.8	0.8	4.4	6.7	13.6
Helsinki	182	–1.7	–24.3	–4.6	–0.4	2.2	11.5
Barometric pressure (mbar)							
Amsterdam	237	1,014	988	1,008	1,014	1,021	1,041
Erfurt	176	1,016	992	1,008	1,016	1,023	1,040
Helsinki	181	1,012	961	1,001	1,011	1,022	1,040
Relative humidity (%)							
Amsterdam	237	86	48	81	87	92	100
Erfurt	177	86	64	82	86	90	99
Helsinki	182	86	51	82	88	92	98

[a]Amsterdam, 3 November 1998–18 June 1999; Erfurt, 14 October 1998–31 March 1999; Helsinki, 2 November 1998–30 April 1999. [b]Percentiles.

Results

Descriptive characteristics of the study populations and the physiologic variables blood pressure and heart rate during the resting period in supine position are given in Table 1. Overall, there were 131 subjects and 1,431 clinical visits. Subjects in the Erfurt panel were younger, their blood pressure was lower, and their heart rate was higher than those of subjects from the Amsterdam and Helsinki panels. History of coronary bypass or PTCA and use of blood pressure medication such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and diuretics differed significantly between centers. Subjects in Erfurt took significantly more combinations of blood pressure active medication than did participants in the other two centers. Overall, cardiac medication intake was > 70% in all three centers.

The study period in Amsterdam was from 3 November 1998 until 18 June 1999, in Erfurt from 14 October 1998 until 31 March 1999, and in Helsinki from 2 November until 30 April 1999. Particulate and gaseous air pollutants and meteorologic variables are given in Table 2. Mean and maximum number concentrations of UFP (0.01–0.1 μm) were highest in Erfurt; Amsterdam and Helsinki had similar concentrations of UFP. The mean number concentration of ACP (0.1–1.0 μm) was

slightly higher in Amsterdam than in Erfurt; Helsinki had considerably lower number concentrations in this size fraction. The mean and maximum mass concentrations of $PM_{2.5}$ were lowest in Helsinki and comparable in Erfurt and Amsterdam. Because of the longer study period in Amsterdam, the mean temperature there varied between –4.0°C and 20.1°C. Erfurt had a maximum of 13.6°C, and Helsinki a maximum of 11.5°C, reflecting the colder season. Concentrations of gaseous air pollutants were highest in Amsterdam; Erfurt and Helsinki had rather similar concentrations.

Figure 1A–C shows UFP and $PM_{2.5}$ concentrations and temperature during the study periods. UFP concentrations were not strongly correlated with ACP and $PM_{2.5}$, whereas ACP concentrations were highly correlated with $PM_{2.5}$ (Table 3). The correlation between gaseous and particulate air pollutants was highest for ACP in all three centers (Table 3).

Blood pressure. Center-specific and pooled estimates for blood pressure in supine position in association with UFP, ACP, and $PM_{2.5}$ are given in Table 4. Pooled effect estimates suggest a decrease in systolic as well as diastolic blood pressure with UFP. Effects were homogeneous for the 5-day average and showed a decrease in systolic blood pressure by 0.72 mm Hg [95% confidence interval (CI), –1.92 to 0.49] and diastolic blood pressure by 0.70 mm Hg (95% CI, –1.38 to –0.02) in association with an increase of 10,000 UFP per cubic centimeter. However, results for same-day effects of UFP were heterogeneous and showed a decrease in blood pressure for Erfurt and Helsinki, but a significant increase for Amsterdam. ACP is also associated with a decrease in systolic and diastolic blood pressure. Homogeneous significant effects were seen with same-day and with 5-day average pollutant concentrations. $PM_{2.5}$ was associated with a small decrease in blood pressure, with significant effect estimates for diastolic blood pressure on the same day of exposure, 1-day lag, and the 5-day average concentrations of $PM_{2.5}$.

Figure 2 illustrates center-specific and pooled effect estimates of particulate as well as gaseous air pollutants on diastolic blood pressure. Estimates are given per increase in pollutant as shown in the legend. In Amsterdam, effect estimates for UFP and ACP point in the opposite directions; all the other pollutants do not seem to have a significant effect on diastolic blood pressure. Erfurt shows an immediate as well as cumulative decrease of diastolic blood pressure in association with all pollutants, with the highest effects for particles in the UFP range at lag 0 and in the 5-day average. In Helsinki, effect estimates scatter around zero for all pollutants.

Results of the effects of particulate air pollutants on blood pressure in standing position are shown in Table 5. Pooled effect estimates are mainly consistent with those seen in supine position. Significant effect estimates for systolic blood pressure in standing position are higher than those for supine position. Significant effects on diastolic blood pressure are mostly comparable with those observed in supine position. Center-specific estimates show a higher decrease of systolic blood pressure for UFP and ACP in Erfurt. Results for Amsterdam are also comparable in the UFP range, but less so for ACP and $PM_{2.5}$. Helsinki does not show any significant associations between particles and blood pressure in standing position.

Heart rate. Center-specific and pooled effect estimates of particulate air pollution on

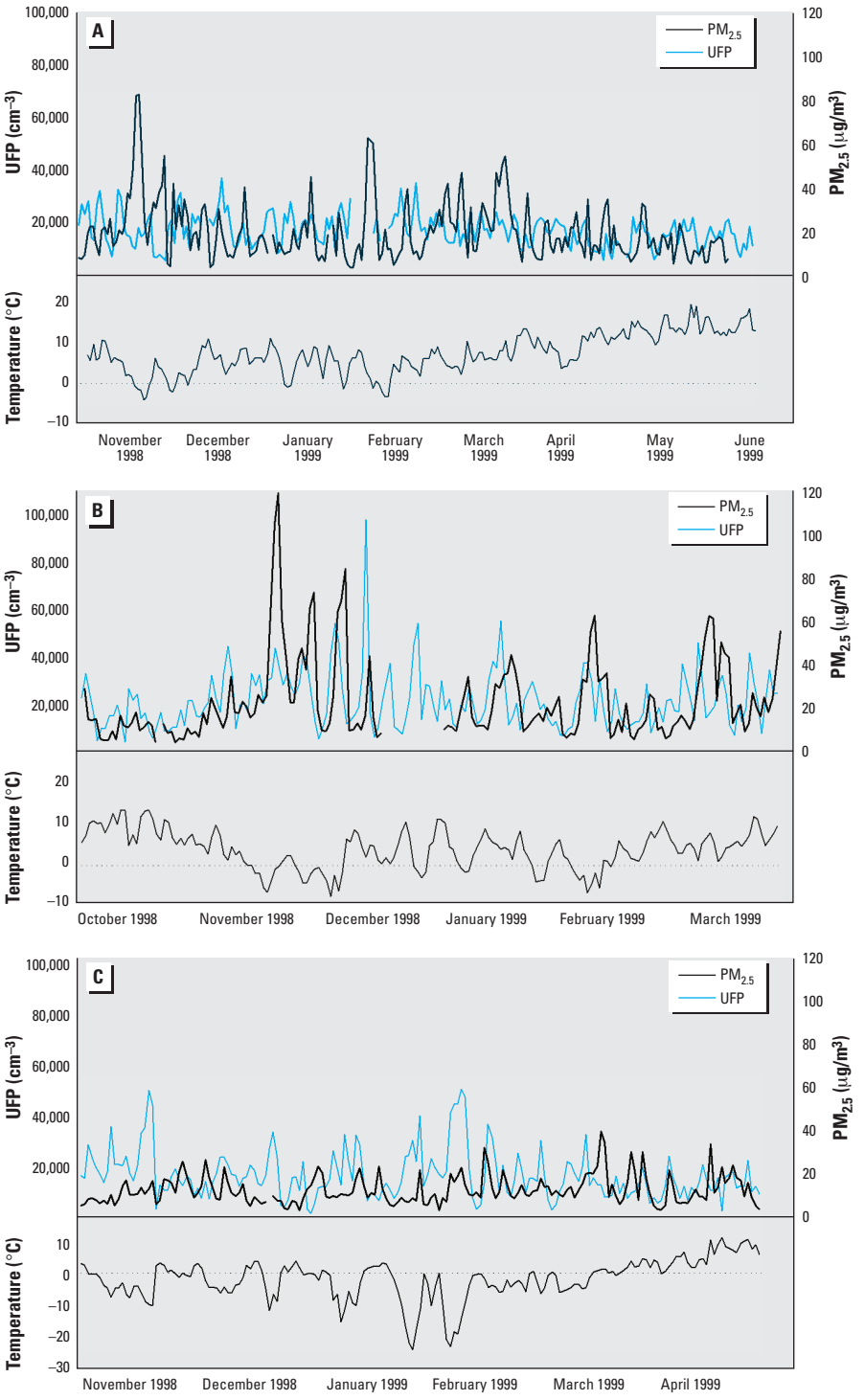

Figure 1. Time series of 24-hr mean number concentrations of UFP, $PM_{2.5}$, and temperature for (*A*) Amsterdam, (*B*) Erfurt, and (*C*) Helsinki [note that the temperature scale in (*C*) differs from those in (*A*) and (*B*)].

heart rate are shown in Figure 3. Only at lag 2, a borderline significant decrease in heart rate can be seen in association with fine particles and UFP looking at pooled effect estimates. This decrease is mainly driven by Amsterdam, which shows a significant decrease in heart rate in association with ACP. SO_2 had a borderline significant negative effect on heart rate in association with pollutant concentrations on the day before the clinical visit (1-day lag), with a pooled effect estimate of –0.40 (95% CI, –0.82 to 0.01) beats/min for an increase of 5 μg/m^3 SO_2. CO and NO_2 were not associated significantly with changes in heart rate (data not shown).

Subgroup analyses. Because of a lack of a clear effect on heart rate, subgroup analyses were conducted only for blood pressure. Figure 4 illustrates the effects of all particle fractions on systolic and diastolic blood pressure stratified by myocardial infarction status. The decrease of systolic blood pressure seems to be more pronounced in subjects with prior myocardial infarction in terms of same-day exposure and the 5-day average concentration of particles. With regard to diastolic blood pressure, effects for the same day of exposure to particles and the 5-day average exposure were also more significant in subjects with prior myocardial infarction. However, estimates for 2-day lagged exposure were heterogeneous between centers. Further subgroup analyses by intake of blood pressure active medication or by NYHA criteria did not disentangle the differences seen for center-specific estimates.

Table 3. Center-specific correlation coefficients of daily concentrations of air pollutants.

	ACP	$PM_{2.5}$	NO_2	CO	SO_2
UFP (*n*/cm^3)					
Amsterdam	0.16	–0.15	0.49	0.22	0.48
Erfurt	0.67	0.62	0.82	0.72	0.56
Helsinki	0.53	0.14	0.72	0.35	0.49
ACP (*n*/cm^3)					
Amsterdam		0.80	0.67	0.60	0.67
Erfurt		0.84	0.82	0.78	0.57
Helsinki		0.80	0.72	0.51	0.49
$PM_{2.5}$ (μg/m^3)					
Amsterdam			0.49	0.58	0.48
Erfurt			0.82	0.77	0.69
Helsinki			0.35	0.40	0.44
NO_2 (μg/m^3)					
Amsterdam				0.76	0.72
Erfurt				0.86	0.63
Helsinki				0.32	0.41
CO (mg/m^3)					
Amsterdam					0.50
Erfurt					0.68
Helsinki					0.19

Discussion

The results of this multicenter study suggest a small decrease in diastolic as well as systolic blood pressure in association with fine particles and gaseous air pollution in cardiac patients. This decrease seems to be mostly driven by patients with prior myocardial infarction. Further, the results suggest a slight decrease of heart rate in association with a 2-day lagged exposure to ambient particle concentrations. Particles in the UFP range did not show homogeneous effects across centers. However, effects of UFP on blood pressure in supine as well as in standing position were

Table 4. Association between particulate air pollution and blood pressure in supine position adjusted for trend, temperature, barometric pressure, relative humidity, medication, and day of the week [β (95% CI)].

	Amsterdam	Erfurt	Helsinki	Pooled
Systolic blood pressure				
UFP (10,000/cm^3)				
Lag 0	1.87 (–0.33 to 4.07)	–0.62 (–1.40 to 0.16)	–1.06 (–2.57 to 0.45)	–0.47 (–1.16 to 0.22)*
Lag 1	1.69 (–0.66 to 4.04)	–0.52 (–1.48 to 0.44)	–0.36 (–1.73 to 1.01)	–0.25 (–1.00 to 0.50)
Lag 2	0.35 (–1.86 to 2.56)	–0.33 (–1.45 to 0.79)	–0.52 (–1.85 to 0.81)	–0.31 (–1.11 to 0.49)
5-Day average	0.56 (–3.24 to 4.36)	–0.84 (–2.43 to 0.75)	–0.89 (–3.01 to 1.23)	–0.72 (–1.92 to 0.49)
ACP (1,000/cm^3)				
Lag 0	–0.43 (–1.67 to 0.82)	–0.71 (–1.55 to 0.13)	–0.88 (–2.61 to 0.85)	–0.66 (–1.3 to –0.01)
Lag 1	0.84 (–0.38 to 2.05)	–0.59 (–1.55 to 0.36)	–0.17 (–1.84 to 1.50)	–0.07 (–0.75 to 0.62)
Lag 2	1.12 (–0.02 to 2.26)	–1.34 (–2.2 to –0.47)	–1.35 (–2.86 to 0.16)	–0.51 (–1.85 to 0.83)*
5-Day average	0.37 (–1.47 to 2.20)	–1.68 (–3.04 to –0.32)	–2.06 (–4.81 to 0.69)	–1.11 (–2.12 to –0.09)
$PM_{2.5}$ (10 μg/m^3)				
Lag 0	–0.06 (–0.95 to 0.84)	–0.36 (–0.83 to 0.11)	–0.44 (–2.27 to 1.40)	–0.30 (–0.71 to 0.11)
Lag 1	0.18 (–0.74 to 1.10)	–0.40 (–0.91 to 0.11)	–0.17 (–1.69 to 1.35)	–0.25 (–0.68 to 0.18)
Lag 2	0.93 (0.01 to 1.85)	–0.68 (–1.20 to –0.17)	–1.14 (–2.51 to 0.23)	–0.26 (–1.22 to 0.70)*
5-day average	0.49 (–0.74 to 1.72)	–0.68 (–1.44 to 0.09)	–0.59 (–3.08 to 1.90)	–0.36 (–0.99 to 0.27)
Diastolic blood pressure				
UFP (10,000/cm^3)				
Lag 0	1.26 (–0.01 to 2.53)	–0.61 (–1.06 to –0.16)	–0.28 (–1.10 to 0.54)	–0.12 (–0.84 to 0.60)*
Lag 1	1.52 (0.17 to 2.87)	–0.61 (–1.16 to –0.06)	–0.05 (–0.79 to 0.69)	0.06 (–0.77 to 0.89)*
Lag 2	–0.19 (–1.50 to 1.12)	–0.35 (–0.98 to 0.28)	–0.36 (–1.09 to 0.37)	–0.34 (–0.78 to 0.11)
5-Day average	0.65 (–1.58 to 2.88)	–1.17 (–2.07 to –0.27)	–0.28 (–1.46 to 0.90)	–0.70 (–1.38 to –0.02)
ACP (1,000/cm^3)				
Lag 0	–0.50 (–1.23 to 0.23)	–0.57 (–1.05 to –0.09)	–0.08 (–1.04 to 0.88)	–0.48 (–0.85 to –0.11)
Lag 1	0.09 (–0.62 to 0.79)	–0.57 (–1.11 to –0.03)	–0.14 (–1.07 to 0.79)	–0.29 (–0.68 to 0.10)
Lag 2	0.08 (–0.61 to 0.76)	–0.72 (–1.21 to –0.23)	–0.52 (–1.35 to 0.32)	–0.46 (–0.82 to –0.10)
5-Day average	–0.34 (–1.43 to 0.75)	–1.24 (–2.01 to –0.47)	–1.00 (–2.52 to 0.51)	–0.95 (–1.53 to –0.37)
$PM_{2.5}$ (10 μg/m^3)				
Lag 0	–0.29 (–0.34 to 0.22)	–0.29 (–0.56 to –0.02)	0.22 (–0.79 to 1.23)	–0.27 (–0.5 to –0.03)
Lag 1	–0.36 (–0.89 to 0.17)	–0.31 (–0.61 to –0.02)	–0.08 (–0.92 to 0.75)	–0.30 (–0.55 to –0.05)
Lag 2	0.10 (–0.44 to 0.64)	–0.27 (–0.56 to 0.03)	–0.38 (–1.13 to 0.38)	–0.20 (–0.45 to 0.05)
5-Day average	–0.27 (–0.98 to 0.44)	–0.42 (–0.86 to 0.02)	–0.52 (–1.88 to 0.85)	–0.39 (–0.75 to –0.03)

*p-Value for test of heterogeneity < 0.1.

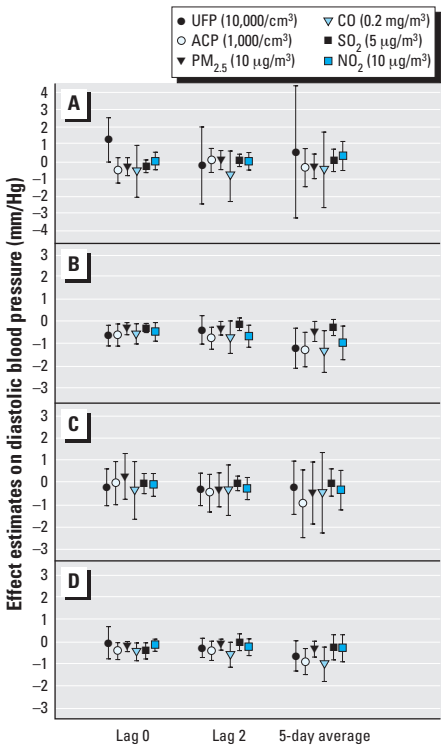

Figure 2. Center-specific and pooled effects of particulate and gaseous air pollutants on diastolic blood pressure in supine position. (*A*) Amsterdam. (*B*) Erfurt. (*C*) Helsinki. (*D*) Pooled (the effect scale differs for Amsterdam). Error bars indicate 95% CIs.

significant for the Erfurt panel and consistent across all exposure variables.

Blood pressure and heart rate are physiologic parameters that can be used to assess changes in autonomic control of the heart and vascular tone (Grassi et al. 1998; Noll et al. 1998). Evidence has been provided that the activation of the sympathetic nervous system plays an important role in the regulation of blood pressure (Grassi 1998). Previous and recent study results showed increases in systolic as well as diastolic blood pressure with elevated concentrations of ambient particle pollution (Ibald-Mulli et al. 2001; Linn et al. 1999; Zanobetti et al. 2002). An increase of sympathetic tone in association with particulate air pollution and/or the modulation of basal systemic vascular tone due to increased concentrations of endothelin associated with particulate air pollution were suggested as potential mechanisms for this increase in blood pressure (Ibald-Mulli et al. 2001). The findings on the association of particulate air pollution on blood pressure also complement results on the alteration of heart rate variability and arrhythmia seen in association with exposure to higher particle concentrations in ambient air (Gold et al. 2000; Peters et al. 2000a, 2000b; Pope et al. 1999a). However, in a recent chamber exposure study conducted by a group from the University of Southern California (Gong et al. 2002), a decrease in systolic blood pressure after exposure to concentrated air particles relative to filtered air in asthmatics was reported.

There is some evidence that short-term variations in particulate air pollution are associated with an increase in heart rate (Peters et al. 1999; Pope et al. 1999b). However, Gold et al. (2000) observed a decrease in heart rate in association with $PM_{2.5}$ in a panel of elderly. Including the findings of the presented study, overall evidence on the effects of particulate air pollution on blood pressure and heart rate seems challenging. A decrease in blood pressure in association with fine particles cannot be explained by the underlying mechanisms that were suggested in previous studies.

Although the effects seen in this analysis are very small, they seem to be more pronounced after postural change from supine to standing position with respect to systolic blood pressure, which might indicate autonomic imbalance in association with particle concentrations. Further, the decrease in diastolic blood pressure was higher in individuals with prior myocardial infarction, which might indicate that they are more likely to respond to particle exposure. One possible mechanism for the decrease in blood pressure could be a shift in sympathovagal balance due to an increase in vagal tone (Laitinen et al. 1999).

Table 5. Association between particulate air pollution and blood pressure in standing position adjusted for trend, temperature, barometric pressure, relative humidity, medication, and day of the week [β (95% CI)].

	Amsterdam	Erfurt	Helsinki	Pooled
Systolic blood pressure				
UFP (10,000/cm^3)				
Lag 0	2.38 (–0.46 to 5.22)	–0.88 (–2.00 to 0.24)	–0.18 (–2.36 to 2.00)	–0.39 (–1.33 to 0.54)
Lag 1	3.33 (0.21 to 6.45)	–1.43 (–2.8 to –0.06)	–0.50 (–2.48 to 1.48)	–0.04 (–1.94 to 1.86)*
Lag 2	0.81 (–2.11 to 3.73)	–1.86 (–3.43 to –0.29)	–0.87 (–2.79 to 1.05)	–1.13 (–2.25 to –0.01)
5-Day average	2.68 (–2.36 to 7.72)	–2.75 (–4.98 to –0.52)	–0.86 (–3.92 to 2.20)	–1.55 (–3.25 to 0.15)
ACP (1,000/cm^3)				
Lag 0	–0.60 (–2.23 to 1.03)	–0.62 (–1.81 to 0.57)	0.83 (–1.67 to 3.34)	–0.42 (–1.32 to 0.47)
Lag 1	1.01 (–0.57 to 2.58)	–1.02 (–2.37 to 0.34)	0.38 (–2.03 to 2.80)	–0.08 (–1.02 to 0.87)
Lag 2	0.29 (–1.18 to 1.76)	–2.11 (–3.34 to –0.89)	–1.07 (–3.23 to 1.09)	–1.02 (–2.29 to 0.27)*
5-Day average	–0.07 (–2.42 to 2.28)	–1.84 (–3.76 to 0.08)	–2.19 (–6.13 to 1.75)	–1.27 (–2.66 to 0.13)
$PM_{2.5}$ (10 μg/m^3)				
Lag 0	–0.44 (–1.6 to 0.72)	–0.59 (–1.24 to 0.06)	1.17 (–1.46 to 3.80)	–0.48 (–1.03 to 0.07)
Lag 1	–0.61 (–1.8 to 0.59)	–0.70 (–1.42 to 0.03)	0.01 (–2.17 to 2.19)	–0.62 (–1.21 to –0.03)
Lag 2	0.32 (–0.88 to 1.51)	–0.65 (–1.37 to 0.07)	–0.63 (–2.60 to 1.34)	–0.41 (–1.00 to 0.17)
5-Day average	–0.55 (–2.15 to 1.04)	–0.68 (–1.74 to 0.39)	–1.96 (–5.51 to 1.60)	–0.72 (–1.57 to 0.14)
Diastolic blood pressure				
UFP (10,000/cm^3)				
Lag 0	1.69 (0.18 to 3.20)	–0.52 (–1.13 to 0.09)	–0.72 (–1.94 to 0.50)	0.03 (–1.05 to 0.21)*
Lag 1	1.29 (–0.42 to 3.00)	–0.51 (–1.25 to 0.23)	0.32 (–0.80 to 1.44)	–0.07 (–0.66 to 0.51)
Lag 2	0.77 (–0.84 to 2.38)	–0.67 (–1.53 to 0.19)	–0.35 (–1.43 to 0.73)	–0.35 (–0.97 to 0.27)
5-Day average	2.42 (–0.27 to 5.11)	–1.12 (–2.34 to 0.10)	–0.28 (–2.00 to 1.44)	–0.21 (–1.47 to 1.05)*
ACP (1,000/cm^3)				
Lag 0	0.28 (–0.62 to 1.18)	–0.63 (–1.28 to 0.02)	–1.09 (–2.48 to 0.30)	–0.41 (–0.91 to 0.08)
Lag 1	–0.16 (–1.04 to 0.71)	–0.64 (–1.38 to 0.10)	–0.05 (–1.39 to 1.29)	–0.38 (–0.9 to 0.14)
Lag 2	–0.20 (–1.02 to 0.62)	–0.93 (–1.6 to –0.26)	–0.63 (–1.83 to 0.57)	–0.63 (–1.11 to –0.16)
5-Day average	–0.38 (–1.68 to 0.92)	–0.86 (–1.91 to 0.19)	–1.31 (–3.49 to 0.88)	–0.75 (–1.51 to 0.01)
$PM_{2.5}$ (10 μg/m^3)				
Lag 0	–0.14 (–0.76 to 0.48)	–0.51 (–0.86 to –0.15)	–0.81 (–2.29 to 0.67)	–0.44 (–0.74 to –0.14)
Lag 1	–0.41 (–1.05 to 0.22)	–0.35 (–0.75 to 0.04)	–0.44 (–1.66 to 0.79)	–0.37 (–0.70 to –0.05)
Lag 2	–0.24 (–0.88 to 0.40)	–0.15 (–0.55 to 0.25)	–0.18 (–1.29 to 0.93)	–0.18 (–0.50 to 0.15)
5-Day average	–0.58 (–1.43 to 0.27)	–0.27 (–0.85 to 0.32)	–0.46 (–2.47 to 1.54)	–0.37 (–0.84 to 0.10)

*p-Value for test of heterogeneity < 0.1.

The results of the heart rate variability analyses within the same study (Timonen KL et al., unpublished data) found a slight increase in high-frequency power, a frequency domain parameter of heart rate variability mainly influenced by vagal tone. Further, a decrease in the ratio between low- and high-frequency power reflecting a shift in sympathovagal balance toward vagal tone was observed. These findings agree with the observed decrease of blood pressure and heart rate.

The ULTRA study used a time-series approach comparable with other panel studies. All procedures were standardized, and panels were selected based on the same inclusion and exclusion criteria in all three centers. The results are suggestive of particle effects and are homogeneous for ACP and $PM_{2.5}$; only for particles in the UFP range do they not show consistent patterns between centers. Looking at effect estimates within each center (Figure 2), mainly the Erfurt panel shows a consistent decrease in blood pressure across all exposure variables. Previous studies in Erfurt have shown particle effects on lung function and mortality with a similar relation between the effects of UFP and ACP (Ibald-Mulli et al. 2002; Klot et al. 2002; Wichmann et al. 2000).

To discuss the differences seen in the effect estimates between centers and differences compared with other study results, two major questions need to be addressed. First, how can differences or measurement error in the assessment of exposure affect the results? Time-series studies of acute air pollution effects are subject to limitations because of available measurements of pollution levels. It has been shown that the particle-measuring devices in all three centers are comparable (Khlystov et al. 2001; Ruuskanen et al. 2001; Tuch et al. 2000). However, factors such as wind direction, climatic conditions, long-range transport, and distances from sources affect exposure patterns between pollutants (Croxford et al. 1996; Cyrys et al. 1998; Pakkanen et al. 2001; Vignati et al. 1996). Table 3 shows the variation in correlation patterns within the different particle size fractions between the three centers. Figure 2 shows that the effect estimates for UFP and $PM_{2.5}$ in association with diastolic blood pressure point in opposite directions for Amsterdam, where the ratio between ACP and UFP is very different compared with Erfurt and Helsinki (Tables 2 and 3). Furthermore, although considerable effort was made to measure new physical parameters of the ambient urban aerosol beyond the classical mass-derived data, the effect of the chemical composition of the aerosols was not assessed in the present analyses. It is very likely that the chemical composition of the aerosol differed between the three cities, which may have affected the different response patterns indicated in Figure 2.

Second, how different is the panel composition between the three centers with respect to coronary heart disease status and medication use, and how do they compare with other study populations? Medication use differs significantly from one center to the others, and the Erfurt panel seems to have the highest medication intake, particularly with respect to blood pressure active medication (Table 1). As opposed to a population not taking blood pressure medication, as looked at in other studies (Ibald-Mulli et al. 2001; Linn et al. 1999), effects of medication might blunt or modify the autonomic response to air pollution exposure. This might partially explain the differences in findings by center. It has been shown that the effects of cardiovascular drugs on the sympathetic nervous system may be of great importance; depending on their pharmacologic profile, they can either activate or inhibit sympathetic activity (Noll et al. 1998). Therefore, the suggested mechanisms, such as an increase in sympathetic tone as a response to elevated particle concentrations, might not apply in patients with a high intake of cardiac medication.

Although it has been postulated that patients with cardiovascular disease are more susceptible to air pollution, most of the evidence with respect to heart rate, blood pressure, and heart rate variability has been found in populations without cardiovascular disease. Based on our results, the question arises how appropriate or powerful currently used parameters such as heart rate variability, heart rate, and blood pressure are assessing effects of air pollution in cardiac patients. As suggested by Zareba et al. (2001), a comprehensive analysis should be conducted of ECG parameters

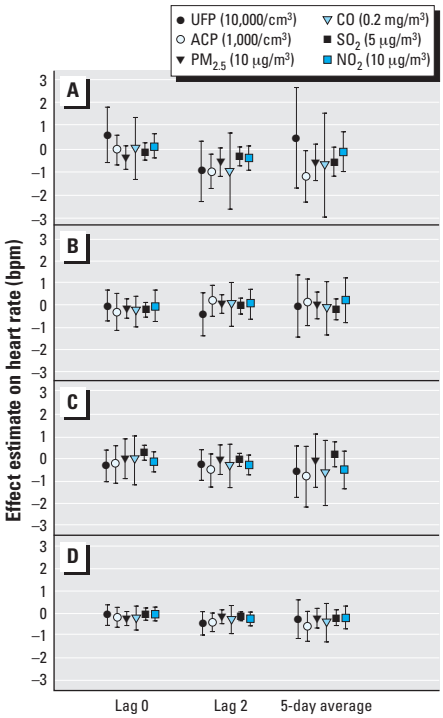

Figure 3. Center-specific and pooled effects of particulate and gaseous air pollutants on heart rate in supine position. (*A*) Amsterdam. (*B*) Erfurt. (*C*) Helsinki. (*D*) Pooled. Error bars indicate 95% CIs.

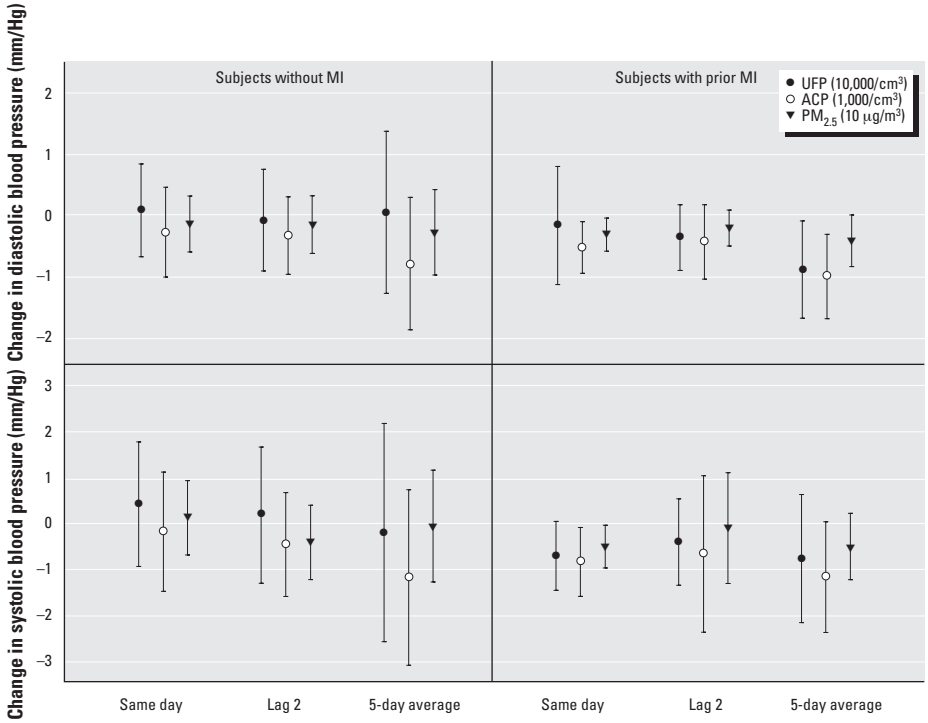

Figure 4. Effects of ambient particles on systolic and diastolic blood pressure in supine position of cardiac patients with and without myocardial infarction (MI). Error bars indicate 95% CIs.

describing not only the autonomic nervous system but also parameters reflecting myocardial repolarization such as QT-interval duration and T-wave morphology and parameters indicating cardiac arrhythmias and ischemia such as QT-interval synamics and ST-segment depressions. A preliminary analysis of arrhythmia within the same study showed an increase in ventricular ectopic beats in association with particulate air pollution in all three centers (Peters et al 2001b).

Pekkanen et al. (2002) did observe an association of particulate air pollution on ST-segment depression in the Finnish panel, suggesting that the particle effect is partly mediated through increased susceptibility to myocardial ischemia.

With respect to the effects on blood pressure and heart rate, it would not be appropriate to draw any conclusions regarding the clinical relevance of these findings because there is not enough epidemiologic evidence. However, it has been shown in animal studies that afferent nervous receptors in the lower respiratory tract are sensitive to irritants and pollutants and by reflex cause pronounced bradycardia and hypotension (Widdicombe and Lee 2002). Stone and Godleski (1999) hypothesized that inhaled environmental particles may promote a systemic sympathetic stress response as well as stimulate irritant receptors in the lung parenchyma and respiratory airways, which can lead to increased vagal responses of the heart, possibly causing bradyarrhythmias in appropriate settings. Therefore, the imbalance of the autonomic nervous system in either direction could lead to a decrease or an increase in blood pressure and may result in adverse cardiac events.

Overall, there is convincing evidence that particulate air pollution is associated with cardiovascular health (Gold et al. 2000; Liao et al. 1999; Pekkanen et al. 2000, 2002; Peters et al. 1997a, 2000a, 2001a; Pope et al. 1999a). More studies in patients with cardiovascular disease need to be conducted to establish further evidence on how particles affect the control of blood pressure and heart rate in a diseased population and how these effects contribute to adverse health outcomes.

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