Ambient Air Pollution Is Associated With Increased Risk of Hospital Cardiac Readmissions of Myocardial Infarction Survivors in Five European Cities

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Background—Ambient air pollution has been associated with increases in acute morbidity and mortality. The objective of this study was to evaluate the short-term effects of urban air pollution on cardiac hospital readmissions in survivors of myocardial infarction, a potentially susceptible subpopulation.

Methods and Results—In this European multicenter cohort study, 22 006 survivors of a first myocardial infarction were recruited in Augsburg, Germany; Barcelona, Spain; Helsinki, Finland; Rome, Italy; and Stockholm, Sweden, from 1992 to 2000. Hospital readmissions were recorded in 1992 to 2001. Ambient nitrogen dioxide, carbon monoxide, ozone, and mass of particles <10 μm (PM_{10}) were measured. Particle number concentrations were estimated as a proxy for ultrafine particles. Short-term effects of air pollution on hospital readmissions for myocardial infarction, angina pectoris, and cardiac causes (myocardial infarction, angina pectoris, dysrhythmia, or heart failure) were studied in city-specific Poisson regression analyses with subsequent pooling. During follow-up, 6655 cardiac readmissions were observed. Cardiac readmissions increased in association with same-day concentrations of PM_{10} (rate ratio [RR] 1.021, 95% CI 1.004 to 1.039) per 10 μg/m^3) and estimated particle number concentrations (RR 1.026 [95% CI 1.005 to 1.048] per 10 000 particles/cm^3). Effects of similar strength were observed for carbon monoxide (RR 1.014 [95% CI 1.001 to 1.026] per 200 μg/m^3 [0.172 ppm]), nitrogen dioxide (RR 1.032 [95% CI 1.013 to 1.051] per 8 μg/m^3 [4.16 ppb]), and ozone (RR 1.026 [95% CI 1.001 to 1.051] per 15 μg/m^3 [7.5 ppb]). Pooled effect estimates for angina pectoris and myocardial infarction readmissions were comparable.

Conclusions—The results suggest that ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in 5 European cities. (***Circulation***. 2005;112:3073-3079.)

Key Words: air pollution ■ epidemiology ■ hospital readmission ■ myocardial infarction ■ multicenter study

Ambient air pollution has been associated with increases in acute morbidity and mortality.[1,2] Studies have suggested that patients with chronic obstructive pulmonary disease,[3] congestive heart disease,[4,5] or previous myocardial infarction or diabetes[6] are at higher risk of death on days with high concentrations of air pollution. Patients who have survived a myocardial infarction are at increased risk for recurrent ischemic events[7] and heart failure.[8] The association of acute hospitalization with air pollution, to the best of our knowledge, has not been specifically assessed in predefined cohorts of vulnerable myocardial infarction survivors.

The Health Effects of Particles on Susceptible Subpopulations (HEAPSS) Study followed cohorts of first myocardial infarction survivors in 5 European cities: Augsburg (Germany), Barcelona (Spain), Helsinki (Finland), Rome (Italy), and Stockholm (Sweden). For the same period, measurements of combustion-related air pollutant concentrations included mass of particles <10 μm (PM_{10}), nitrogen dioxide (NO_2), and carbon monoxide (CO). Moreover, the particle number concentration (PNC) was estimated as a proxy for ultrafine particles. The secondary pollutant ozone was also considered. The objective of the present work was to assess the associa-

TABLE 1. Characteristics of the City-Specific Cohorts and Recorded First Hospital Readmissions

	Augsburg*	Barcelona*	Helsinki†	Rome†	Stockholm†
Age range, y	35–74	35–79	≥35	≥35	≥35
Period of enrollment	1995–1999	1992–1995	1993–1999	1998–2000	1994–1999
Period of follow-up	1995–2000	1992–2000	1993–2000	1998–2001	1994–2000
Source population size, n	300 902	893 601	297 410	1 616 356	548 113
Persons followed up					
No.	1560	1134	4026	7384	7902
Men, %	75	79	54	70	59
Mean age, y	60	61	68	67	73
Maximum No. of follow-up days	2163	3168	2892	1432	2528
Recorded first hospital readmissions during follow-up, n					
Myocardial infarction	87	92	518	422	1202
Angina pectoris	168	168	630	1113	1462
Cardiac‡	286	296	1301	1916	2856

*Data source: myocardial infarction registry.

†Data source: administrative hospital discharge register.

‡First hospital readmissions for acute myocardial infarction, angina pectoris, dysrhythmia, or heart failure.

tion of cardiac hospital readmission with urban air pollution in this potentially susceptible subpopulation.

Methods

Study Population

Incident myocardial infarction survivors were recruited in the 5 cities during 1992 to 2000 (Table 1). Data sources were population-based myocardial infarction registries in Augsburg (Cooperative Health Research in the Augsburg Region[9]) and Barcelona and administrative hospital discharge registers in Helsinki, Rome, and Stockholm. Enrollment was restricted to residents of the above cities aged 35 years or more (Augsburg, 35 to 74 years; Barcelona, 35 to 79 years) who had their first myocardial infarction (index event) during the recruitment period. Diagnostic criteria were established for Augsburg and Barcelona within the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) framework.[10] Definite and possible myocardial infarctions and successfully resuscitated cardiac arrests according to the MONICA criteria were included.[9] Using the registers' databases, it was possible to exclude recurrent events. In Helsinki, Rome, and Stockholm, subjects with a primary myocardial infarction diagnosis in the hospital discharge record were included (International Classification of Diseases [ICD], 9th revision [ICD-9] code 410; ICD, 10th revision [ICD-10] codes I21 and I22) if they had no myocardial infarction during the 3 years preceding the index event and no diagnosis that indicated a previous myocardial infarction (ICD-9 412, ICD-10 I25.2). For all centers, the study was approved by the respective institutional review boards.

Follow-Up

Subsequent first cardiac rehospitalizations within the study area were recorded from the 29th day after the index event until the center-specific end of the follow-up period. Readmissions of interest were those with primary diagnoses of acute myocardial infarction (ICD-9: 410; ICD-10: I21, I22), angina pectoris (ICD-9: 411, 413; ICD-10: I20, I24), dysrhythmia (ICD-9: 427; ICD-10 I46.0, I46.9, I47–I49, R00.1, R00.8), and heart failure (ICD-9: 428; ICD-10: I50). Follow-up was performed by record linkage with the hospital admissions databases (Helsinki, Rome, and Stockholm), a telephone interview (Barcelona), or a mailed questionnaire sent to all cohort members or their relatives after the end of follow-up, followed by a search in the Central Clinic and in the Myocardial Infarction Registry (Augsburg). Vital status and place of residence at the end of the follow-up period were ascertained via comprehensive national (Hel-

sinki and Stockholm) or regional (Barcelona) mortality registries or via municipal registries (Augsburg and Rome).

Air Pollution and Meteorology Data

Air pollution data from fixed monitors were collected for each city according to the APHEA (Air Pollution and Health, a European Approach) procedures[11] during the center-specific recruitment and follow-up periods.[12] Daily average concentrations of CO, NO_2, and PM_{10} and the maximum 8-hour average of ozone were calculated for each monitor, when at least 75% of the observations were available. For each pollutant, daily city means were calculated by averaging over all monitors with a modified APHEA procedure.[11]

In Augsburg, total suspended particles were measured until 1999. PM_{10} was assessed thereafter with the same device. PM_{10} was derived for 1995 to 1999 by scaling down total suspended particles by a factor of 0.83, a locally validated procedure,[13] which yielded 84% of PM_{10} data. For Barcelona, 20% of PM_{10} data (years 1996 and 1997) were estimated with a linear prediction model that used total suspended particles and black smoke, with adjustment for trend and season, based on periods for which all 3 pollutants were available. The R^2 of the model was 0.55, and the correlation (observed versus predicted values) was 0.77.

PNC was assessed retrospectively for the HEAPSS project as an indicator of the number concentration of ultrafine particles (diameter <100 nm). In each center, condensation particle counters (CPC 3022A, TSI) were set up in 2001 to measure PNC for at least 1 year.[12] On the basis of these data, PNC was fitted with other air pollutant and meteorological data in a regularized linear prediction model, and applied to the HEAPSS study period.[14]

Meteorological variables measured included daily mean temperature, dew point temperature, average barometric pressure at sea level, and relative humidity. Dates of temporary decreases in the local populations at risk due to vacations or holidays were recorded for each center.

Data Analysis

Poisson regression models were used to analyze the association of air pollution with hospital readmissions within the cohort. End points considered in the analyses were readmissions within the study area for (1) myocardial infarction, (2) angina pectoris, and (3) cardiac causes, a combined end point defined as the first readmission for acute myocardial infarction, angina pectoris, heart failure, or dysrhythmia. A person was considered to be at risk for each specific end point from the 29th day after the index event until the event of
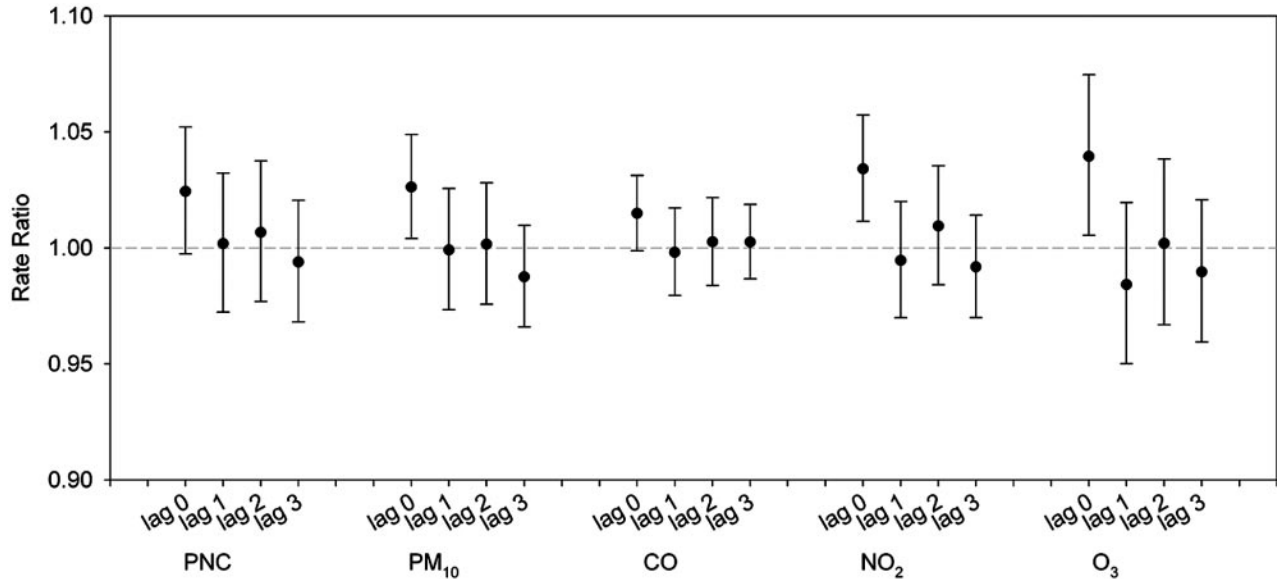
Figure 1. Pooled random effect estimates of the unconstrained distributed lag between air pollution and cardiac readmission. Associations were estimated simultaneously for the same day (lag 0) and previous 3 days (lag 1, 2, and 3), with air pollution concentrations for each pollutant separately. RRs and 95% CIs were calculated for an increase of 10 $\mu g/m^3$ in PM_{10}, 10 000/cm^3 in PNC, 0.2 mg/m^3 (0.172 ppm) in carbon monoxide, 8 $\mu g/m^3$ (4.16 ppb) in nitrogen dioxide, and 15 $\mu g/m^3$ (7.5 ppb) in ozone, respectively.

interest, death, migration out of the study area, loss to follow-up, or end of follow-up. Model specification was done for each city and outcome individually. All models included the natural logarithm of the number of persons at risk each day as an offset. The outcome was the daily number of readmissions. Generalized additive models were applied to allow for penalized spline functions of the continuous confounders with R software (the R Foundation for Statistical Computing, version 2.0.1) with the package "mgcv" (version 1.1-8).[15] To ensure model selection was independent of the results, potential confounders were selected before the addition of air pollution concentration as an independent variable. The covariates tested were penalized regression splines of trend (to control for long-term trends, seasonality, and changes in the baseline rate) and meteorology (daily temperature, relative humidity, air pressure, and the difference between current day temperature and the mean temperature of the previous 3 days), as well as indicators of weekdays, vacation periods, or holidays. Trend and 1 temperature term had to remain in the model. Criteria for the inclusion of other covariates were probability value ($P<0.1$), and minimization of generalized cross validation score and the absolute value of the sum of partial autocorrelation coefficients.

Next, the lag structure of the effect of each pollutant was assessed with unconstrained distributed lag models that considered air pollution concentrations for the same day and the 3 previous days.[16] City-specific results were pooled considering the variance covariance matrix of the estimates.[17] Given the results, same-day air pollution concentrations were considered subsequently. City-specific single pollutant estimates were pooled with random effect models if the χ^2 test suggested heterogeneous city-specific estimates ($P\leq0.1$).[17] Otherwise, variance-weighted averages of city-specific regression coefficients were calculated.

The association of readmissions with ozone was analyzed taking into account only the warm months (April to September), because levels and correlations with other pollutants depend on season, and health effects of ozone have generally been associated with summertime levels. Pollutants were first considered separately, in single-pollutant models, and then jointly, in 2-pollutant models, with subsequent pooling. Two-pollutant models were not performed for PNC, CO, and NO_2 because of high correlation between these pollutants. Sensitivity analyses were performed that compared the results of the final models with the estimates achieved when modifying the smooth functions (natural cubic splines or loess

instead of penalized splines), setting more stringent convergence criteria,[18] or changing confounders. For instance, temperature was replaced by apparent temperature[19] or dew point temperature. The results were robust to these changes. Analyses that used a time-stratified case-crossover design yielded comparable results.

Rate ratios (RRs) and 95% CIs for PM_{10} are expressed for an increase of 10 $\mu g/m^3$ to present results comparable to previous studies. Estimates for PNC, CO, NO_2, and O_3 are shown for an increase of 10 000/cm^3, 0.2 mg/m^3 (0.172 ppm), 8 $\mu g/m^3$ (4.16 ppb), and 15 $\mu g/m^3$ (7.5 ppb), respectively, equivalent to the mean of city-specific interquartile ranges multiplied by 0.5 (ratio of 10 $\mu g/m^3$ and the study mean of PM_{10} interquartile ranges: 20 $\mu g/m^3$).

Results

Study Population and Follow-Up

Overall, during the follow-up periods, 2321 hospital readmissions for myocardial infarction, 3541 for angina pectoris, and 6655 for cardiac events were observed among the 22 006 cohort members (Table 1).

Air Pollution Levels

The highest levels of PNC were estimated for Barcelona and Rome, the 2 most polluted study centers (Table 2). PM_{10} and CO concentrations were on average also higher in Rome and Barcelona than in Helsinki and Stockholm, with Augsburg showing medium concentrations. NO_2 levels were comparably high in Augsburg, Barcelona, and Rome. Ozone in the warm months had a similar range in all 5 cities.

PNC was highly correlated with CO and NO_2 in Augsburg and Rome, with CO in Barcelona, and with NO_2 in Helsinki and Stockholm (Table 2). NO_2 and CO were moderately correlated in Augsburg, Rome, and Stockholm. Other correlations were below 0.5 in all centers other than Augsburg. Ozone concentrations in the summer were negatively correlated with all other pollutants.

Association of Air Pollution and Hospital Readmissions

Distributed lag models suggested immediate effects of all air pollutants on cardiac readmissions (Figure 1). No pattern of a delayed or cumulative effect was seen. Therefore, same-day air pollution levels were considered in the subsequent analyses. Whereas models in Figure 1 included lag day 0 to 3 of the analyzed pollutant, Figure 2 shows single lag 0 pollutant estimates. Same-day levels of air pollutants were significantly associated with cardiac readmissions. Although city-specific results differed, the effects were homogeneous from a statistical point of view. Combined effect estimates for myocardial infarction readmissions were higher for PNC, PM_{10}, and CO but had broader confidence intervals (Table 3). Associations of angina pectoris admissions with PM_{10} and CO were considerably lower than for cardiac or myocardial infarction admissions.

In 2-pollutant models, the effect of PNC, CO, and NO_2 on cardiac readmissions remained stable when controlling for PM10 or ozone (results available on request). The association with PM_{10} was only slightly attenuated by the traffic-related air pollutants. The effect of ozone remained, or was even stronger, when we adjusted for the other pollutants.

Discussion

In this multicenter cohort study of myocardial infarction survivors, an increased risk of cardiac readmissions during days with elevated concentrations of several markers of urban air pollution (PNC, PM_{10}, CO, NO_2, and ozone) was observed. The associations were similar overall for angina pectoris and reinfarction, but most had broader confidence intervals because of smaller numbers of cases in the follow-up.

Previous studies on air pollution health effects on cardiovascular morbidity primarily defined cardiac admissions more broadly (ICD-9 390 to 429) than the present study, and none

TABLE 2. Description of Air Pollution and Temperature by City

	Days, n	Sites, n	Mean	Percentile 5th	25th	75th	95th	Spearman Correlation Coefficient PNC	PM_{10}	CO	NO_2	O_3
Augsburg												
PNC, $1/cm^3$	2163	1	13 504	7330	9583	15 665	24 641	1				
PM_{10}, $\mu g/m^3$	2130	2	44.7	16.8	30.7	55.5	81.4	0.52	1			
CO, mg/m^3	1973	2	0.93	0.45	0.67	1.09	1.70	0.63	0.57	1		
NO_2, $\mu g/m^3$	2083	2	49.6	30.0	39.7	57.2	75.3	0.64	0.64	0.67	1	
O_3, $\mu g/m^3$	1061	1	37.6	3.6	20.0	53.6	72.9	−0.32	−0.26	−0.47	−0.14	1
Temperature, °C	2154	1	9.8	−2.8	3.7	16.2	21.6	−0.56	0.05	−0.27	0.03	0.29
Barcelona												
PNC, $1/cm^3$	3168	2	76 593	19 287	41 446	103 141	162 117	1				
PM_{10},* $\mu g/m^3$	3062	4	52.2	25.3	38.9	62.2	89.2	0.29	1			
CO, mg/m^3	3025	3	1.00	0.31	0.57	1.27	2.34	0.71	0.39	1		
NO_2, $\mu g/m^3$	2376	3	47.7	18.0	34.0	60.0	83.0	0.44	0.36	0.46	1	
O_3, $\mu g/m^3$	1504	3	32.8	9.2	19.7	42.3	65.4	−0.55	−0.14	−0.39	−0.14	1
Temperature, °C	3168	1	17.2	8.9	12.6	21.9	26.2	−0.68	0.09	−0.37	−0.20	0.18
Helsinki												
PNC, $1/cm^3$	2892	1	14 283	6821	10 217	17 214	24 908	1				
PM_{10}, $\mu g/m^3$	2682	1	25.3	9.5	15.0	30.3	57.6	0.46	1			
CO, mg/m^3	2852	1	0.42	0.20	0.31	0.50	0.70	0.47	0.21	1		
NO_2, $\mu g/m^3$	2883	1	30.1	13.0	21.2	36.7	52.9	0.83	0.40	0.44	1	
O_3, $\mu g/m^3$	1428	1	46.0	16.3	34.3	57.7	74.8	−0.16	0.02	−0.27	−0.13	1
Temperature, °C	2892	1	6.0	−7.7	0.0	13.1	18.8	−0.49	−0.02	−0.23	−0.11	−0.07
Rome												
PNC, $1/cm^3$	1432	2	49 195	21 150	34 066	60 010	93 558	1				
PM_{10}, $\mu g/m^3$	1426	2	51.1	23.3	36.1	63.1	89.4	0.33	1			
CO, mg/m^3	1432	5	2.21	1.07	1.54	2.62	4.00	0.80	0.31	1		
NO_2, $\mu g/m^3$	1432	5	70.0	46.8	60.5	79.1	94.3	0.71	0.48	0.64	1	
O_3, $\mu g/m^3$	697	2	49.2	10.1	25.9	69.2	100.8	−0.47	−0.22	−0.41	−0.02	1
Temperature, °C	1432	1	15.8	5.4	10.1	21.7	25.9	−0.72	0.06	−0.48	−0.25	0.38
Stockholm												
PNC, $1/cm^3$	2528	2	12 553	6157	8887	14 840	22 546	1				
PM_{10}, $\mu g/m^3$	2293	1	14.6	6.4	9.4	17.7	30.0	0.06	1			
CO, mg/m^3	2528	2	0.43	0.21	0.31	0.51	0.74	0.54	0.38	1		
NO_2, $\mu g/m^3$	2526	3	22.8	10.3	16.0	28.0	39.4	0.80	0.29	0.75	1	
O_3, $\mu g/m^3$	1247	3	56.0	29.4	44.9	66.6	82.4	−0.17	0.15	−0.30	−0.20	1
Temperature, °C	2528	1	7.4	−4.9	1.3	13.8	19.8	−0.65	0.11	−0.27	−0.33	−0.07

Values for PNC, PM_{10}, CO, NO_2, and temperature are 24-hour means. Values for ozone (O_3) are daily maximum 8-hour average, April through September.
*1996−1997: imputed values.
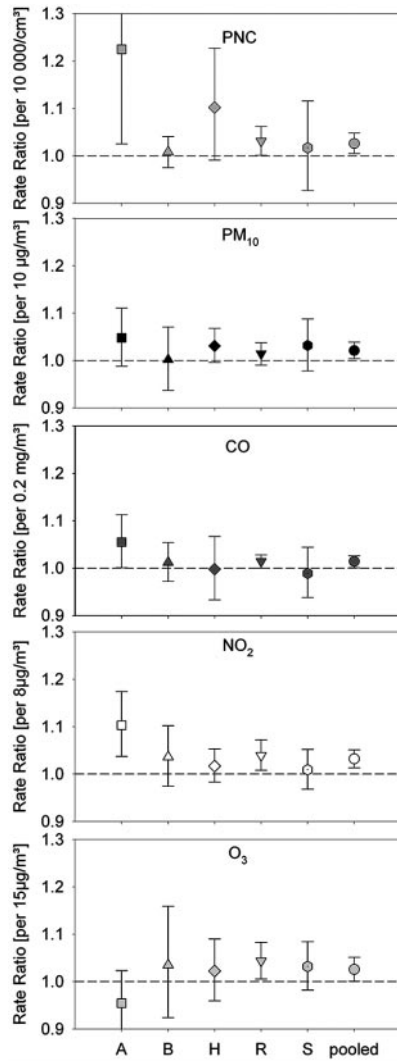
Figure 2. City-specific and pooled results of the association of same-day pollutant concentration and cardiac hospital readmissions estimated in single lag pollutant models. Cardiac readmissions include first hospital admission for acute myocardial infarction, angina pectoris, dysrhythmia, or heart failure. A indicates Augsburg; B, Barcelona; H, Helsinki; R, Rome; S, Stockholm; and pooled, fixed-effects summary estimate.

multicenter studies, the US NMMAPS (National Morbidity, Mortality, and Air Pollution Study)[18] and the European APHEA study,[21] reported 1% and 0.5% increases in cardiac hospital admission, respectively, in the general population per 10 $\mu g/m^3$ PM_{10} compared with an increase of 2.1% in the present study. For CO, increases in risk of 0.1% to 0.5% per 0.2 mg/m^3 were found,[22,23,28,29] which were lower than in the present work. For NO_2 and cardiac admissions, only 1 study reported a higher effect size than the present study,[22] whereas others reported similar or lower effects.[20,23,24,29] Associations with ozone in the warm months were inconsistent, with significant negative estimates,[20] nonsignificant estimates,[23,24] or, as here, significant positive[20,22,25] estimates.

Previously reported associations of air pollution (CO, NO_2, and ozone) with angina pectoris admissions[30] were weaker and statistically nonsignificant compared with the present study. Associations of myocardial infarction readmissions were positive but statistically nonsignificant for all air pollutants except ozone in the present study. The few previously conducted studies that examined associations of myocardial infarction with CO, NO_2, O_3, and particles have shown positive associations,[30–35] positive but not significant associations,[32,36–38] and occasionally negative[38] associations.

The present study, designed to examine health effects of air pollution in a cohort of subjects potentially vulnerable with respect to recurrent coronary events, showed positive and generally larger effects than studies conducted in the general population. Therefore, myocardial infarction survivors might indeed be a susceptible subpopulation.

Various biological mechanisms have been proposed that associate particulate air pollution with cardiac end points. We hypothesize that these mechanisms are most likely related to changes in plaque vulnerability and blood rheology. It has been observed that rapidly translocated particles or PM components might induce endothelial dysfunction that contributes to plaque instability.[2] Ambient particle inhalation may induce oxidative stress and inflammatory responses in the lung. Subsequent systemic inflammation may promote atherosclerosis progression, plaque instability, sudden arterial vasoconstriction, and a thrombosis-favoring blood rheology.[2] Furthermore, the cardiac autonomic balance might be disturbed via lung neural reflex arcs or via components of PM that directly pass the pulmonary epithelium. The present results suggest the immediacy of such effects, at least among myocardial infarction survivors.

The present data suggest an association of traffic-related air pollutants (NO_2, CO, and PNC) with cardiac readmissions. PNC,

investigated the association with PNC. There is consistent evidence of an association between PM_{10} and cardiac hospital admissions in the general population,[20–25] the elderly,[18,21,24,26,27] and subgroups with comorbidities.[26,27] Among these, 2 large

TABLE 3.   Pooled Results of Poisson Regressions of the Association of Hospital Readmissions and Same-Day Air Pollution Concentrations

Pollutant	Unit	Hospital Readmissions, RR (95% CI)		
		Myocardial Infarction	Angina Pectoris	Cardiac*
PNC	10 000/cm³	1.039 (0.998–1.082)†	1.020 (0.992–1.048)	1.026 (1.005–1.048)
PM_{10}	10 $\mu g/m^3$	1.026 (0.995–1.058)	1.008 (0.986–1.032)	1.021 (1.004–1.039)
CO	0.2 mg/m^3 (0.172 ppm)	1.022 (0.998–1.047)	1.009 (0.992–1.026)	1.014 (1.001–1.026)
NO_2	8 $\mu g/m^3$ (4.16 ppb)	1.028 (0.997–1.060)	1.032 (1.006–1.058)	1.032 (1.014–1.051)
O_3‡	15 $\mu g/m^3$ (7.5 ppb)	1.000 (0.954–1.048)	1.044 (1.012–1.077)	1.026 (1.001–1.051)

*Hospital admissions for acute myocardial infarction, angina pectoris, dysrhythmia, or heart failure.
†Random-effects model.
‡Daily maximum 8-hour average.

dominated by fresh combustion particles that originate primarily from mobile sources but that possibly include some particles generated by photochemical processes from gaseous pollutants, might be the culprit from a pathological point of view. NO_2, which also originates mainly from motor vehicle emissions, has no known effect on the cardiovascular system. CO ambient concentrations, which are also mainly traffic-related, were low for causing acute poisoning, but associations have been shown at similar levels.[28] Because CO and PNC were highly correlated, which is due to the common source but additionally induced in the present study by the estimation process, future studies with measurements of both parameters might disentangle the effects of these traffic-related pollutants. The fact that NO_2, CO, and PNC were associated with the outcome in the present study and that the association was independent of PM_{10} and ozone, as shown in the 2-pollutant models, lends further support to evidence showing that traffic exposure might be linked to myocardial infarction onset 1 hour later.[39] The effect of PM_{10}, which is produced in combustion processes but which also comes from soil, tire fragmentation, and secondary particle formation, was only slightly attenuated in 2-pollutant models when the traffic markers were considered. The significant and independent association of ozone with hospital readmissions for angina pectoris and cardiac causes is a new finding that deserves consideration in future studies.

The retrospective PNC estimation is clearly a limitation of the present study. The first concern is the quality of the models. Models fitted PNC data relatively well, with R^2 of 0.77, 0.80, 0.58, 0.84, and 0.81 for Augsburg, Barcelona, Helsinki, Rome, and Stockholm, respectively.[14] The most important predictor variables were nitrogen oxides. Models were robust with respect to inclusion of irrelevant explanatory variables and were highly tolerant of missing data. The modeling process was fairly reliable, as seen when the estimated coefficients of half of the measurement period were applied to the other half. In these "split-halves" analyses, correlations of fitted and measured PNC were above 0.8 in all cities except Helsinki ($r=0.72$).

Second, we could not detect possible diverging time trends of PNC and the predictors used in the model, because the 1-year measurement period after April 2001 was used to estimate PNC levels as far back as 1992 (Barcelona). In Erfurt, Germany, time trends of PNC and other pollutants differed after the unification of East and West Germany. This was explained by changes in sources over time.[40] In Western European cities, similar changes might have occurred a decade earlier, before the HEAPSS study period.

Additionally, there are issues on exposure assessment of PNC in time series studies that should be considered.[41,42] Because ultrafine particles are mostly produced by local traffic, PNC is more heterogeneous spatially and depends more on distance from the roadway than other PM size fractions. The use of central monitors may limit the ability to detect a real PNC effect when data on average personal exposure for a population are lacking. Parallel measurements often showed a good overall correlation and suggested that background sites might well characterize average population exposure to ultrafine particles if the site is chosen carefully.[12,43]

For Barcelona, 2 years of PM_{10} data had been imputed with black smoke and total suspended particle data. Misclassification of PM_{10} might explain in part the finding of no association of cardiac readmissions with PM_{10} in this center. Sensitivity analyses that excluded the 2 years of imputed PM_{10} data showed higher but not statistically significant point estimates.

Although the centers differed with respect to myocardial infarction diagnosis in recruitment and in the follow-up, as described specifically in Methods, these diagnoses have been found to be highly comparable.[44–46] Differences in susceptibility due to sex, age, and risk factor prevalence and use of drug therapies in these coronary patients could not be evaluated systematically because of the lack of specific data and the limited power of the study. Despite these differences, pooled estimates suggested an association between urban air pollution and hospital readmissions for cardiac events in myocardial infarction survivors in this multicenter study that used a population-based prospective approach and applied a common protocol. These results might be generalized to Europe, because an overall effect was observed despite different inclusion criteria and pollution levels across centers.

Conclusions

The results suggest that ambient air pollution is associated with increased risk of hospital cardiac readmissions for myocardial infarction survivors in 5 European cities. The study highlights the potential health effects of pollutants that originate from mobile sources in Europe. Likewise, an association with secondary pollutants, including ozone, was indicated.

The HEAPSS Study Group

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Acknowledgments

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