Ambient Air Pollution and Daily Mortality Among Survivors of Myocardial Infarction

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Background: Certain subgroups in the general population, such as persons with existing cardiovascular or respiratory disease, may be more likely to experience adverse health effects from air pollution.
Methods: In this European multicenter study, 25,006 myocardial infarction (MI) survivors in 5 cities were recruited from 1992 to 2002 via registers, and daily mortality was followed for 6 to 12 years in relation to ambient particulate and gaseous air pollution exposure. Daily air pollution levels were obtained from central monitor sites, and particle number concentrations were measured in 2001 and estimated retrospectively based on measured pollutants and meteorology. City-specific effect estimates from time-series analyses with Poisson regression were pooled over all 5 cities.
Results: Particle number concentrations and PM_{10} averaged over 2 days (lag 0–1) were associated with increased total nontrauma mortality for patients of age 35 to 74 (5.6% [95% confidence interval, 2.8%–8.5%] per 10,000/cm^3 and 5.1% [1.6%–9.3%] per 10 $\mu g/m^3$, respectively). For longer averaging times (5 and 15 days), carbon monoxide and nitrogen dioxide were also associated with mortality. There were no clear associations with ozone or sulfur dioxide.
Conclusion: Exposure to traffic-related air pollution was associated with daily mortality in MI survivors. Point estimates suggest a stronger effect of air pollution in MI survivors than among the general population.

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Ambient air pollution has been associated with increases in acute cardiorespiratory morbidity and mortality in many studies over the past 20 years.[1] Mortality effects have been confirmed in large multicenter studies at current ambient levels both in the United States[2] and in Europe.[3,4] Particulate matter seems to be the air pollutant most consistently associated with adverse health outcomes. In a recent meta-analysis of 74 single-city studies and 2 large multicity studies, the estimated increase in all-cause mortality was 0.6% (95% confidence interval [CI] = 0.5–0.7) per 10 $\mu g/m^3$ increase in particulate matter with aerodynamic diameter of <10 μm (PM_{10}).[5] Gaseous pollutants—in particular, nitrogen dioxide (NO_2) and carbon monoxide (CO)—have also repeatedly shown associations.[6–8] These may be indicators of vehicle emissions rather than single causative agents.[9]

Cardiovascular disorders, especially coronary heart disease, are the most prevalent chronic health conditions affecting both sexes in the western world and a leading cause of mortality. Patients hospitalized after a myocardial infarction (MI) are frail and at risk for subsequent death; an overall 30-day mortality rate of 14% to 15% and a 1-year mortality rate of 22% to 24% have been observed among these patients.[10] Cardiovascular mortality has repeatedly been linked to air pollution exposure. A recent meta-analysis of short-term studies estimated the increase in cardiovascular mortality as 0.5% (95% CI = 0.1–1.0) per 10 $\mu g/m^3$ increase in PM_{10},[11] and a large case-control study showed a positive association between life-long air pollution exposure and fatal MI.[12]

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The mechanisms behind cardiovascular effects of air pollution are not yet fully known. Small particles are able to penetrate into the pulmonary interstitium where they may cause inflammation.[13] Suggested mechanisms of the cardiovascular effects include changes in the viscosity or coagulability of blood,[14,15] increased local and systemic inflammation,[16] and changes in the autonomic regulation of the body, including increase in heart rate[17,18] and decreased heart rate variability,[17,19,20] either directly or via inflammation.[20] Increased levels of PM_{10} have also been associated with a decrease in peripheral hemoglobin and red cell count.[21]

Persons with preexisting disease may be more susceptible to the effects of air pollution. Few studies have investigated this aspect. The available studies indicate elevated risks of death associated with high concentrations of air pollution for patients with, for example, chronic obstructive pulmonary disease,[22] congestive heart failure,[23,24] diabetes, and previous MI.[25,26]

The Health Effects of Air Pollution on Susceptible Subpopulations Study (HEAPSS-Study) was initiated to answer questions about the effects of air pollution among MI survivors, who were followed with respect to reinfarction, hospitalization for related diseases and death. Earlier results from the project regarding the association between air pollution exposure and first time MI in the general population of the study areas supported an increased risk, especially for fatal MI.[27] Out-of-hospital MI mortality in the general population was also found to be associated with air pollution exposure in a study that included one of the centers included in the present study.[28] Among the MI survivors of primary interest in the project, an investigation of rehospitalization for MI and other cardiac conditions showed an increased MI risk in this subpopulation.[29] The present paper provides results from the analysis of associations between air pollution exposure and mortality among MI survivors.

METHODS

Cohort Definition and Follow-Up

The HEAPSS study has been described in detail elsewhere.[27,29] Briefly, the 5 centers included were Augsburg (Germany), Barcelona (Spain), Helsinki (Finland), Rome (Italy), and Stockholm (Sweden). For recruitment of the cohorts of first-time MI cases, local MONICA-style[30] MI registers were used in Augsburg (KORA-MI-Registry) and Barcelona, whereas Helsinki, Rome, and Stockholm relied on administrative hospital discharge registers. First-time MI patients who were 35 years of age or older were recruited, with

TABLE 1. Description of the 5 Cohorts of MI Survivors in the HEAPSS

	Augsburg	Barcelona	Helsinki	Rome	Stockholm
Register type	MI-specific	MI-specific	Administrative	Administrative	Administrative
Enrollment period	1995–1999	1992–1995	1993–1999	1998–2000	1994–2002
Last year of follow-up	2000	2000	2004	2004	2003
No. MI subjects followed	1,553	941	4,025	7,246	11,241
Age (yrs)					
35–64	977	547	1,329	3,118	2,845
65–74	576	295	1,083	2,081	2,841
75+	NA[a]	99[b]	1,613	2,047	5,555
Percent men					
All ages	75	80	54	70	59
Age 35–74 yr	75	83	68	77	72
No. nontrauma deaths					
Total no.	122	194	2,124	1,757	4,358
No. per day	0.056	0.061	0.485	0.687	1.193
Age (yrs)					
35–74	122	145	852	766	1,271
35–64	46	68	312	265	341
65–74	76	77	540	501	930
75+	NA[a]	49[b]	1,272	991	3,087
No. cardiovascular deaths	69	87	1,054	1,122	2,942
Deaths during 1st yr of follow-up					
All ages No. (%[c])	55[a] (3.5)	65[b] (6.9)	595 (14.8)	696 (9.6)	1,567 (13.9)
Age 35–74 yr No. (%[d])	55 (3.5)	43 (5.1)	206 (8.5)	257 (5.0)	388 (6.8)

[a]Upper age limit in Augsburg was 74 yr.
[b]Upper age limit in Barcelona was 79 yr.
[c]Percent of MI subjects followed.
[d]Percent of MI subjects age 35–74 followed.

upper age limits imposed by the registry coverage in Augsburg and Barcelona (Table 1). Because renewed myocardial ischemia within 1 month is generally considered to be a continuation of the initial MI event, the follow-up time with respect to mortality started on the 29th day after the incidence date, including only 28-day survivors in the cohorts.

MI cases in Augsburg and Barcelona were defined based on the MONICA recommendations[30] that distinguish between 3 categories of diagnosed coronary events: definite MI, possible MI, and cardiac arrest. All events were confirmed first-time MI. Cases in the centers using hospital discharge registers were defined by the first registered occurrence of an MI diagnosis (ICD-9 = 410 or ICD-10 = I21, I22) during the recruitment period as primary diagnosis for a patient admitted to an acute care hospital. First time MI was defined as no registered MI within 3 years before the index event. Any concurrent ICD code indicating a previous MI (ICD-9: 412 or ICD-10: I25.2) and discharge within 3 days of the index MI diagnosis (indicating likely miscoding) led to exclusion.

Mortality Outcome Data

Data on mortality were collected in Helsinki and Stockholm from national mortality registers and in Barcelona from regional mortality registers. In Augsburg and Rome, municipal registers were used to check vital status of persons, and death certificates were collected from local health authorities for further information on deaths. In the statistical analysis, the dependent variables were all-cause nontrauma mortality and cardiovascular mortality. Deaths with trauma as an underlying cause (ICD-9 codes 800-959, ICD-10 codes S00–T32.9, T79.0–T79.9, T90.0–T98.3) were considered censored on the death date. Cardiovascular mortality was defined as ICD-9 codes 390-495 or ICD-10 codes I00–I99. A person was considered to be at risk from the 29th day after the index MI event until the first of the following events: nontrauma death (the event studied here), migration out of study area, censored follow-up, or end of follow-up. If the location of nontrauma death was known to be outside the study area, the person was censored on that day. To achieve higher statistical power, the follow-up periods, and in the case of Stockholm also the recruitment period, were extended for the 3 cities with administrative registers (Helsinki, Rome, and Stockholm).

Ambient Air Pollution and Meteorology

Air pollution data were collected from a varying number of fixed monitors in each city. Monitoring sites were chosen to represent inner-city urban background levels; these included some traffic-related sites but no curbside sites. We used an average of the available city monitors in the analyses.

Complete data apart from occasional missing days were available in all centers on CO, NO_2, and Ozone (O_3). PM_{10} data were unavailable for parts of the study periods in Augsburg and Barcelona. In Augsburg, total suspended particles were measured until 1999. PM_{10} was assessed, thereafter, with the same device. PM_{10} was derived from 1995 to 1999 (84% of the data) by scaling down total suspended particles by a factor of 0.83, a locally validated procedure.[31] 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 vs. predicted values) was 0.77.

Daily averages were calculated for CO, NO_2, sulfur dioxide (SO_2), and PM_{10} concentrations, and maximum 8-hour averages were used for ozone. As a primary hypothesis, analyses of ozone were restricted to the warm season (April–September) because levels and correlations with other pollutants depend on season, and health effects of ozone have generally been associated with summer-time levels. Before calculating the city average, we imputed missing values in single monitors. A missing value on day i from monitor j was replaced by the average for all nonmissing days for monitor j plus the average standardized value of day i over all monitors multiplied by the standard deviation of monitor j (Equation 1).

$$\hat{x}_{ij} = \bar{x}_{\cdot j} + \bar{z}_{i\cdot} s_{\cdot j} \quad (1)$$

where

$$\bar{z}_{i\cdot} = \frac{\sum_{j=1}^{n} \left(\frac{x_{ij} - \bar{x}_{\cdot j}}{s_{\cdot j}} \right)}{n}$$

This unbiased estimate considers not only differences in mean values among monitors, but also differences in variability. When data from all monitors were missing for a single day, we used the average of the day before and the day after. At least 75% of the hourly observations had to be available to calculate a daily mean.

Particle number concentrations were retrospectively assessed. At the beginning of the study (Spring of 2001) condensation particle counters were set up in each location to measure the total particle number concentration of ambient particles.[32] Ultra fine particles (diameter <100 nm) constitute most of all particles; thus, particle number concentration is an excellent indicator of the number concentration of ultra fine particles.[33] City-specific statistical models were developed using available data on other air pollutants and meteorologic variables during a period when particle number concentration was measured, to retrospectively estimate particle number concentration for the study follow-up periods.[34] Concurrent measurements of air pollutants and weather and selected

interactions between the two were used to fit a regularized linear model (also called ridge regression). The models fit the data relatively well, with R^2 of 0.77 (Augsburg), 0.80 (Barcelona), 0.58 (Helsinki), 0.84 (Rome), and 0.81 (Stockholm). The most important predictor variables in the models were the nitrogen oxides (NO and NO_2) in all cities.[34] For Augsburg, Helsinki, Rome, and Stockholm, the follow-up period also contained some periods when particle number concentrations were measured. For these days, measured, rather than estimated, particle number concentration was used.

Meteorologic variables collected included temperature, dew point temperature, relative humidity, solar radiation, barometric pressure, and wind speed and direction. Many of the meteorological variables were mainly used for modeling.

Statistical Analysis

A thorough comparison among various analytic strategies of this cohort has been carried out for the rehospitalization part of the project.[35] Drawing from the results of that investigation, we found that Poisson regression analysis was suitable for quantifying the relationship between air pollution exposure and daily mortality in the cohort of MI survivors.

Poisson model specification was done separately for each city. In a hierarchical approach, we tested potential confounders and then selected a core model before adding air pollution concentration as an independent variable. Of the tested confounders, long-term trend was forced into all models, as was at least 1 of same day temperature and the difference between same day and the preceding 3 days. Same-day relative humidity, same-day barometric pressure, day of week, holidays, and days of population decrease (added to the model in that order) were included only if they improved the model. We used generalized additive models to allow the inclusion of smooth functions for covariates, using the package "mgcv" (version 1.3-17)[36] in the statistical program R (The R Foundation for Statistical Computing Version 2.3.1). Because the number of daily subjects at risk varied greatly over time as more subjects were enrolled into the cohort, all models included an offset-term to allow for the variable number of persons at risk.[35] To allow for possible over- or under-dispersion, the quasi-likelihood family was used to estimate the parameters without specifying the underlying distribution function. We initially used penalized regression splines for the continuous confounder variables. The choice of degrees of freedom for all splines was left to the algorithm "magic" in the mgcv package that minimized the generalized cross-validation criterion. If the smooth function was not significant at the 10% level or the estimated degrees of freedom were close to 1, a linear term was used instead. Decisions for keeping a covariate in a model were based on judgment using the P value (<0.10), the generalized cross-validation score (as small as possible), the autocorrelation function (the nearer to zero the better), visual inspection of the shape of the smooth function, and partial auto correlation function. Trend was included in the model as a penalized spline with 1 to 6 knots per year, to control for long-term trends, seasonality, and changes in the baseline risk. In the model-building process, all multiples of the number of years were evaluated; the choice was based on the generalized cross-validation score, the number of degrees of freedom for the smooth parameter, whether or not the model converged, visual inspection of the shape of the smooth function, and partial autocorrelation function.

To ensure that the results were not because of the analytic approach selected, we performed a sensitivity analysis using an extended Cox proportional hazards model described in detail when previously applied to data from this cohort.[34] The Cox models included the same covariates for each city as the Poisson regression, except that instead of penalized splines, quadratic terms were used.

To assess whether there was effect modification by time since enrollment or age at baseline, we conducted stratified Poisson regressions, separating the time series into the first year and later years of follow-up and into 3 age groups (35–64, 65–74, $\geq$75 years), respectively.

Following from previous studies, and to capture the immediate and possible cumulative effects, 2-day and 5-day moving averages were used in the final models calculated from the same day, and the 1 and 4 preceding days, respectively. In addition, a longer averaging time—15-day moving average—was also tested in all analyses based on recent data suggesting that more long-term effects are important for mortality.[37]

City-specific effect estimates were combined by meta-analytic pooling. If the city-specific estimates were not significantly heterogeneous, the pooled effect estimate was calculated as an inverse variance-weighted average of city-specific regression coefficients; if there was significant heterogeneity, random effects models were used.[38]

City-specific percent change in mortality ([RR-1] $\times$ 100) and 95% confidence intervals (CIs) were calculated for an increase of 1 city-specific interquartile range (IQR, indicates range 25th–75th percentile of study period daily values) and for a common metric for each pollutant, also used for the pooled estimates. The respective values were 10000/cm^3 for PNC, 10 $\mu g/m^3$ for PM_{10}, 0.2 mg/m^3 for CO, 8 $\mu g/m^3$ for NO_2, 2 $\mu g/m^3$ for SO_2, and 15 $\mu g/m^3$ for O_3.

RESULTS

Characteristics of the Study Population

The 5 cohorts of MI survivors are described in Table 1. The cohorts differed substantially in size, with larger cohorts recruited through administrative registers. The length of the follow-up ranged from 6 years in Augsburg to 12 years in Helsinki. All centers had the same lower age limit of 35 years. Helsinki, Rome, and Stockholm had no upper age limit, whereas Augsburg and Barcelona had upper limits of

TABLE 2. Median and IQR of Pollutant Levels for Each City, Calculated From Daily 24-h Means (Except Ozone: Maximum 8-h Average April–September)

	Augsburg Median (IQR)	Barcelona Median (IQR)	Helsinki Median (IQR)	Rome Median (IQR)	Stockholm Median (IQR)
PNC (no. cm^3)	12,184 (6,464)	68,581 (61,628)	12,148 (7,557)	41,701 (29,408)	11,294 (5,939)
PM_{10} ($\mu g/m^3$)	42.3 (24.8)	49.3 (23.4)	19.9 (14.8)	46.7 (23.7)	12.6 (8.3)
CO (mg/m^3)	0.85 (0.43)	0.75 (0.55)	0.36 (0.19)	1.66 (1.11)	0.38 (0.20)
NO_2 ($\mu g/m^3$)	47.9 (17.8)	46.5 (26.0)	27.8 (15.1)	68.1 (19.5)	21.1 (11.5)
SO_2 ($\mu g/m^3$)	4.22 (3.70)	11.00 (5.00)	3.13 (3.51)	3.98 (3.93)	2.61 (2.60)
O_3 ($\mu g/m^3$)	82.8 (42.6)	62.3 (25.3)	71.1 (25.1)	107.7 (38.6)	77.5 (24.0)

PNC indicates particle member concentration.

74 and 79 years, respectively, and hence the age distribution differed between centers. In total, 25,006 MI cases were followed and of these 8555 (34%) died. In the common age range of 35 to 74 years, 15,692 MI cases were followed and 3156 (20%) died. The sex distribution was different among centers, even when restricting to the common age range of 35 to 74; the Nordic centers (Helsinki and Stockholm) had the highest proportion of women and Barcelona had the lowest.

Pollution and Meteorology Levels

The 2 southern cities, Barcelona and Rome, had the highest particle levels as measured by PM_{10} and particle number concentration (Table 2), with average estimated particle number concentration levels 3 to 5 times higher than the other cities. These 2 cities together with Augsburg also had the highest NO_2 levels. The mean CO level was highest in Rome and lowest in Helsinki and Stockholm.

Air Pollution and Daily Mortality

Figure 1 shows the city-specific percentage of change in daily mortality per IQR increase in the pollutants, for the available age range in each city. The comparison across IQRs is useful for comparing the different pollutants within centers because they reflect similar population exposure. The results are heterogeneous across centers, but some patterns can be clearly discerned. Short-term (2-day mean) effects on daily mortality for estimated particle number concentration and PM_{10} were observed for Augsburg and Barcelona. Other pollutants also showed mainly positive associations in these 2 centers, except ozone and SO_2 in Augsburg. In the other 3 centers, there was a clear trend toward positive associations for all pollutants except ozone.

In Table 3 the estimates for the separate cities are pooled and shown for the common age range of 35 to 74 years. Point estimates are presented for the same averaging times as in Figure 1, but per unit change as shown in the table. For the 2-day average, the strongest effect estimates were found for the particle measurements—both around 5%. For the 5-day average, NO_2 and CO were also associated with risk. The results for SO_2 and O_3 do not indicate an association with daily deaths except for the 15-day average of SO_2; a sensitivity analysis using full-year O_3 data similarly did not show any association. For all pollutants except NO_2 and O_3, the strongest association was observed for the 15-day average. The sensitivity analysis using the Cox-model generally yielded similar results as the Poisson regression, as shown in the supplementary eTable (available with the online version of this article).

Figure 2 shows the estimates by several subgroups for the 2-day average. Cause-specific cardiovascular mortality did not seem to be more strongly associated to daily mortality than all-cause mortality. There is no clear trend in terms of the effect estimates across the 3 age groups. Note that only Helsinki, Rome, and Stockholm are included in the age-specific results. Estimates for deaths occurring within 1 year after the first MI are few and imprecise, but there is a tendency toward stronger effects compared with deaths occurring after 1 year of follow-up.

DISCUSSION

Most researchers agree that not everyone is at equal risk of dying from air pollution exposure on days with high levels. Specifically, persons with an already high baseline risk of a cardiac event would be expected to be more likely to have a fatal event induced by an air pollution episode. To represent this group, we selected those who had an MI and survived for more than 28 days.

The overall pooled results in this multicenter study showed associations between short-term air pollution exposure and daily mortality in MI survivors, for the common study age range of 35 to 74 years. With longer averaging times of air pollution exposure, the mortality risk was more clearly elevated. Positive effects were seen primarily and most consistently for the particle measurements particle number concentration and PM_{10}, but NO_2 and CO also had a fairly consistent positive relationship with daily mortality. The point estimate for a 10-$\mu g/m^3$ increase of PM_{10} was 5.1% (95% CI = 1.1–9.3), compared with 0.6% (95% CI 0.4–0.8) from a recent meta-analysis of Air Pollution and Health: A European Approach 2 (APHEA2) data.[5] This estimate, however, includes different study populations.

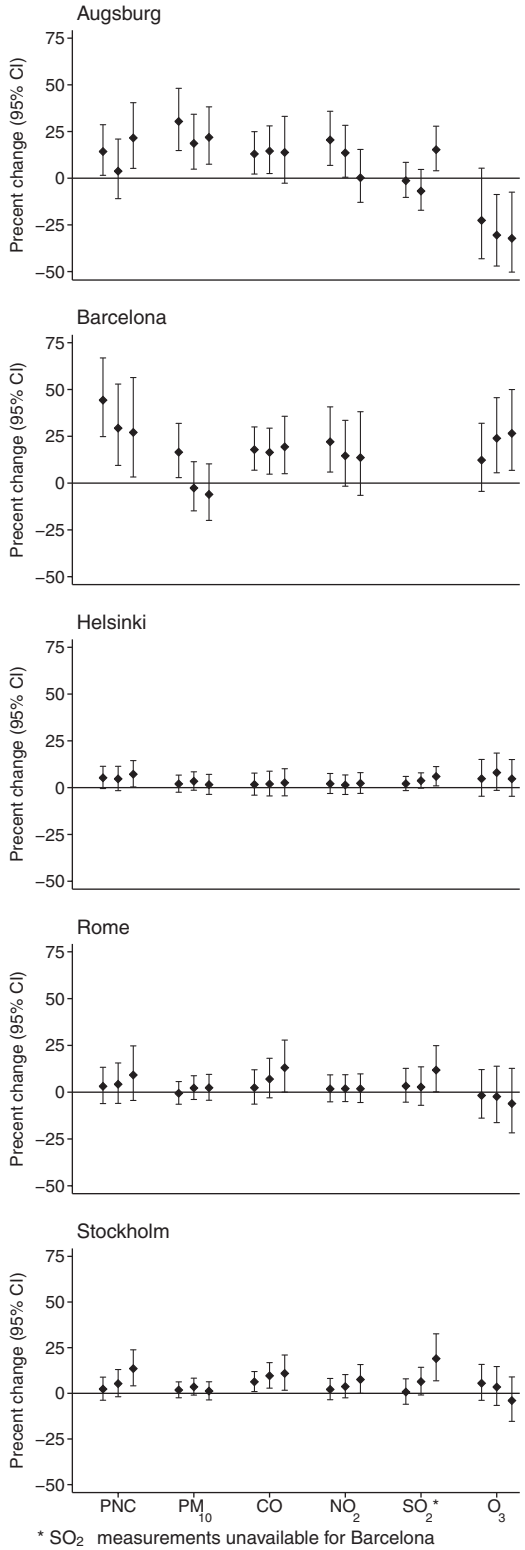

FIGURE 1. City-specific estimates of percent change in daily nontrauma deaths per city-specific interquartile range increase in air pollution levels. For each pollutant, means of lag 0–1, lag 0–4, and lag 0–14 are shown.

Therefore, we also used published data from APHEA2 (including city-specific effect estimates for PM_{10} on mortality for the average of lag 0 and 1 using a similar model) for all cities in our study except Augsburg.[39] Using the same technique for pooling as in the present study, we obtained a pooled effect estimate of 0.8% (95% CI = 0.5–1.1) for these data. In our MI cohort, excluding Augsburg that had the strongest effect for PM_{10}, the analysis gave an increase of 2.9% (95% CI 0.2–5.6), still substantially larger than what was observed for the general population in the same cities in the APHEA2 study. Although differences in data collection, age range, and modeling strategy may still potentially bias comparison with other studies, we feel that the results from this study provide definite support for the hypothesis that survivors of acute myocardial infarction constitute a sensitive subpopulation with respect to mortality from air pollution.

The analysis by age groups shown in Figure 2 does not provide a consistent picture. When PM_{10} was considered, we saw an effect mainly in the youngest age group (35–64 years), with no clear effect of air pollution in the older groups (although the CI indicates some uncertainty). A possible interpretation is that the older age group of MI survivors is depleted of persons susceptible to air pollution. Most short-term air pollution studies suggest a stronger effect on mortality in elderly, and we have previously extended this by showing, based on data from Rome, that out-of-hospital fatal cardiac events are particularly strongly associated with air pollution in the most elderly age groups. On the other hand, the age pattern is not consistent for other pollutants (in particular, particle number concentration), so that the above interpretation of the results maybe limited to PM_{10}. Furthermore, the result may be due to chance, or particle number concentration may be of more importance for reinfarctions as earlier suggested.[29]

We made every effort to ensure that the results from all centers would be as comparable as possible. For instance, we used a common study protocol for data collection in all centers, allowing for differences among centers only when no other option was available. Statistical model selection was also done based on a predefined protocol and identical for all centers. The core models were finalized before including the pollutants in the models, thus not allowing the models to be influenced in any way by the effect estimates for the pollutants. Despite these efforts, substantial differences that could not be compensated for in the study design and execution remain among the centers. Case identification was done differently in the centers using criteria from the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project, compared with centers relying on local clinical MI criteria as registered by treating physicians in hospital discharge registers. This may affect the composition and overall susceptibility of the selected cohorts. For example, the MONICA registers included cases of "pos-

TABLE 3. Percent Change in Daily Nontrauma Deaths per Unit Change in Air Pollutants. Overall Pooled Results of Poisson Regressions Over All 5 Centers for the Common Age Range 35–74

Pollutant[a]	Unit Change	Mean of Lag 0 and 1 % (95% CI)	Mean of Lag 0–4 % (95% CI)	Mean of Lag 0–14 % (95% CI)
PNC	10,000/cm^3	5.62[b] (2.83 to 8.47)	6.01 (3.41 to 8.68)	8.68[b] (5.35 to 12.1)
PM_{10}	10 μg/m^3	5.08[b] (1.06 to 9.27)	3.92[b] (1.19 to 6.72)	4.91[b] (1.30 to 8.65)
CO	0.2 mg/m^3	2.61[b] (−0.26 to 5.56)	3.82[b] (1.00 to 6.72)	4.92[b] (2.11 to 7.81)
NO_2	8 μg/m^3	2.31[b] (−1.26 to 6.01)	3.25[b] (0.19 to 6.39)	2.54 (−1.49 to 6.74)
SO_2[c]	2 μg/m^3	0.09 (−2.23 to 2.46)	1.60[b] (−1.28 to 4.57)	8.06[b] (4.38 to 11.9)
O_3	15 μg/m^3	1.04[b] (−6.32 to 8.96)	0.51[b] (−8.97 to 11.0)	–0.52[b] (−10.2 to 10.2)

[a]Daily 24-h mean, except ozone: maximum 8-h average (April–September).
[b]City-specific estimates were heterogeneous and a random effects pooling technique was used.
[c]SO_2 not available for Barcelona.

sible MI" that may include a proportion of unstable angina, and they permitted a more stringent identification of true first MI than administrative registers. Nonetheless, the use of ICD codes for identifying MI cases has been shown to have a reasonably high validity,[40–42] and cases with an MI diagnosis in the 3 years before the event defining cohort entry or an ICD

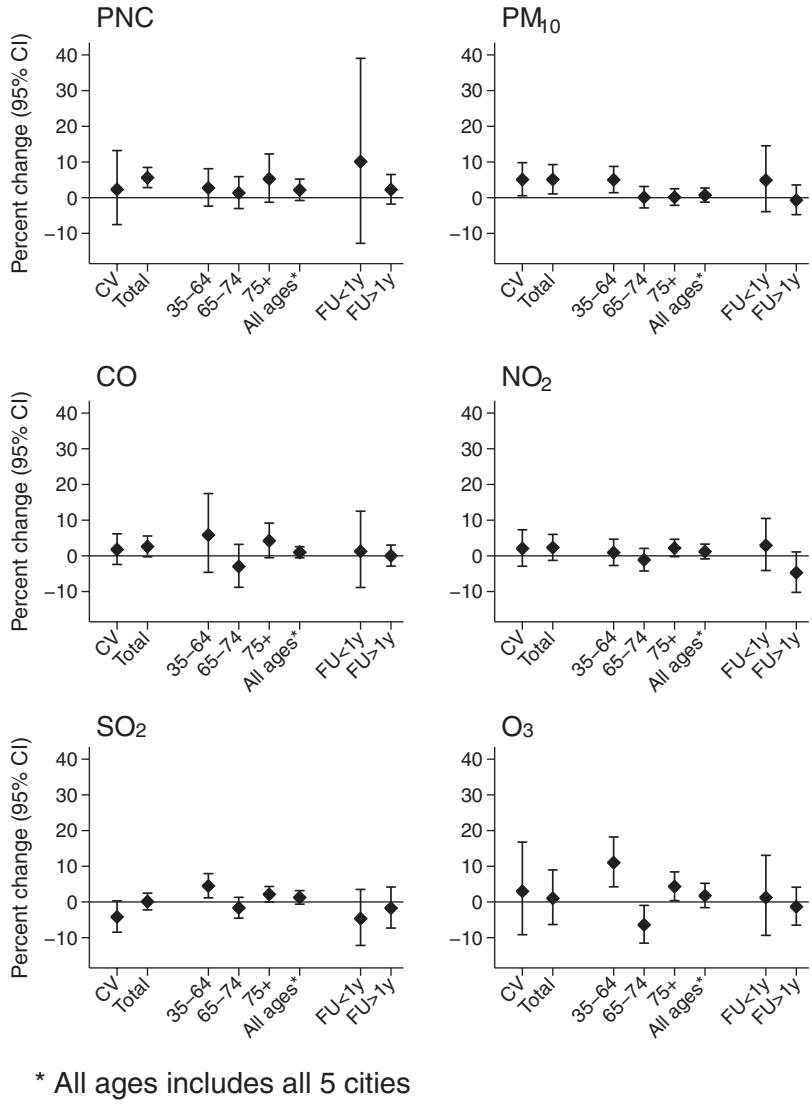

FIGURE 2. Percent change in daily deaths pooled over 5 cities for the 2-day mean of lag 0 and 1 for each pollutant in the 35–74 age group. Graphs show deaths from cardiovascular disease and all nontrauma causes (Total), total deaths by age groups (only Helsinki, Rome, and Stockholm), and total deaths occurring within and after the first year of follow-up from first MI. The number of MI cases followed and the number of deaths for each subgroup can be found in Table 1.

code indicating a previous MI were excluded in this study. There are other differences in medical practice between the cities with respect to treatment, medication, and the possibility of swift and adequate treatment at acute events. Age and sex distributions differ. Living conditions, including air quality and meteorological factors, are also different. All of these differences are likely to contribute to heterogeneity of results. Because of this, the pooled results will be quite different from the most extreme of the city-specific estimates that go into the pooling. The extreme results also have an impact on the overall results even though the pooling method makes sure that the estimates that have a large amount of imprecision have less impact on the pooled estimate, compared with the more precise estimates. Most of the main results were pooled using a random effects model, and they have confidence intervals for the point estimate that reflect this heterogeneity.

Selection of variables and choice of initial smooth parameter values were made before inclusion of air pollution variables, possibly resulting in a slightly suboptimal confounding model when those were included. Any slight decrease in precision (and power) is, however, counterbalanced by the advantage of not letting the main result influence the exact structure of the statistical model. The number of deaths was low in the cohort, which might be an issue for Poisson regression methods, but our sensitivity analysis using Cox regression showed that the results were not dependent on the analysis method.

Overall, we found that the associations were stronger when analyzing longer averaging times for exposure. For most pollutants the effect estimates slightly increased as averaging times increased, indicating a prolonged effect of the pollutants. It should be noted that longer averaging times reduce the variability of the concentration time series, and because we used a common unit change for all averaging times for the pooled estimates, the unit change represents a larger relative change for the longer averaging times. However, the same pattern of stronger effects for longer averaging times can be discerned in most city-specific results presented in Figure 1, where change is shown by interquartile range, which is insensitive to differences in variability. This finding, which was not what we had hypothesized when we started the study in 2000, is consistent with findings from other recent studies that have looked at prolonged effects of elevated air pollution levels.[24,37]

In summary, our results suggest that exposure to traffic-related air pollution is associated with all-cause daily mortality in MI survivors, with a stronger positive effects for longer averaging times. The effect estimates from this study are in general substantially higher than those for the general population.

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