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Long-term exposure to air pollution is associated with survival following acute coronary syndrome

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Aims The aim of this study was to determine (i) whether long-term exposure to air pollution was associated with all-cause mortality using the Myocardial Ischaemia National Audit Project (MINAP) data for England and Wales, and (ii) the extent to which exposure to air pollution contributed to socioeconomic inequalities in prognosis.

Methods and results Records of patients admitted to hospital with acute coronary syndrome (ACS) in MINAP collected under the National Institute for Cardiovascular Outcomes Research were linked to modelled annual average air pollution concentrations for 2004–10. Hazard ratios for mortality starting 28 days after admission were estimated using Cox proportional hazards models. Among the 154 204 patients included in the cohort, the average follow-up was 3.7 years and there were 39 863 deaths. Mortality rates were higher for individuals exposed to higher levels of particles with a diameter of $\leq$2.5 μm ($PM_{2.5}$; PM, particulate matter): the fully adjusted hazard ratio for a 10 μg/m^3 increase in $PM_{2.5}$ was 1.20 (95% CI 1.04–1.38). No associations were observed for larger particles or oxides of nitrogen. Air pollution explained socioeconomic inequalities in survival to only a small extent.

Conclusion Mortality from all causes was higher among individuals with greater exposure to $PM_{2.5}$ in survivors of hospital admission for ACS in England and Wales. Despite higher exposure to $PM_{2.5}$ among those from more deprived areas, such exposure was a minor contribution to the socioeconomic inequalities in prognosis following ACS. Our findings add to the evidence of mortality associated with long-term exposure to fine particles.

Keywords Air pollution • Myocardial infarction • Acute coronary syndrome • Mortality • Socioeconomic inequalities • Cohort

Introduction

Persuasive evidence continues to develop that exposure to air pollution, especially particulate matter (PM), is associated with heart disease, even at the relatively low concentrations currently found in the UK.[1,2] However, few studies have investigated the influence of long-term exposure to air pollution on survival and subsequent cardiac events among survivors of myocardial infarction (MI) and the findings have been inconsistent.[3–5] Individuals with pre-existing diseases such as ischaemic heart disease may be more susceptible to the adverse health effects of PM exposure.[6] Survivors of ischaemic cardiovascular events therefore may serve as a useful model of vulnerability, potentially allowing for the detection of the effects of PM on prognosis with relatively few years of follow-up.

Outcome after MI has repeatedly been found to show a strong socioeconomic gradient,[7–15] although the underlying pathways are not well understood.[16,17] Higher levels of air pollution frequently occur in more deprived areas across different populations.[18–20] This observation raises the possibility that exposure to air pollution may explain, in part, socioeconomic gradients in prognosis among MI patients.[21]

We therefore investigated (i) whether long-term exposure to air pollution was associated with all-cause mortality using the

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Myocardial Ischaemia National Audit Project (MINAP) data base for England and Wales, and (ii) the extent to which exposure to air pollution contributed to socioeconomic inequalities in prognosis.

Methods

Study population

The cohort consisted of patients admitted to hospital for acute coronary syndrome (ACS) identified through MINAP[22–24] who resided in England and Wales at the time of admission. We included patients with a final diagnosis (at discharge) of ST elevation MI (STEMI) and non-ST elevation MI (non-STEMI) between 1 January 2004 and 31 March 2007. Diagnosis of STEMI required the presence of electrocardiographic changes of ST elevation consistent with infarction (ST elevation $\geq$2 mm in contiguous chest leads and/or ST elevation $\geq$1 mm in two or more standard leads), and the presence of enzyme (twice the upper limit of reference range) or troponin elevation (above locally accepted cut-off value). Diagnosis of non-STEMI required electrocardiographic changes consistent with the diagnosis (new ST or T-wave changes except ST elevation), and the presence of enzyme or troponin elevation. Consistent with other researchers,[3,25] we excluded from the follow-up the 28 days immediately following admission. We restricted our analysis to patients with complete data on date of admission, age, sex, and vital status who were older than 25 and who lived inside the geographic range of modelled air pollution for England and Wales ($n = 154\,204$) (Supplementary material online, *Table S1*). Vital status was obtained from the Office of National Statistics. The follow-up continued until the date of death or the end of the study (1 April 2010). Our study was approved by the London School of Hygiene and Tropical Medicine research ethics committee (No. 5412).

Patients' demographic characteristics, postcode of residence, smoking and medical history, in-hospital treatment, and discharge drugs are recorded in the MINAP database, usually at the time of care.[22] Small-area deprivation data were based on the Index of Multiple Deprivation (IMD) 2007 for England and IMD 2008 for Wales calculated at the level of Lower Layer Super Output Area (LLSOA). We used the score from income, education, and employment domains of IMD, since the composite IMD measure includes data on air pollution levels.[26] Deciles of each score were generated using cut-points from the distribution across all LLSOAs in England, for residents of England, or the distribution from Welsh LLSOAs for residents of Wales.

Air pollution exposure

Annual average background concentrations of nitrogen dioxide (NO_2), oxides of nitrogen (NO_x), and two size fractions of particulate matter with diameter $\leq$10 μm (PM_{10}) and $\leq$2.5 μm ($PM_{2.5}$) in μg/m^3 for the years 2004–10 were obtained from the Department for Environment Food and Rural Affairs (http://uk-air.defra.gov.uk/data/pcm-data). Concentrations were modelled at a resolution of 1 km × 1 km, using an approach described elsewhere.[27,28] Briefly, point and area sources were modelled using ADMS, a second-generation Gaussian dispersion model.[29] Contributions from rural background were based on measurements at rural ambient monitors and a network of diffusion tubes. Sources contributing to background concentrations of PM included point and area sources of primary particles, regional primary particles, secondary organic and inorganic aerosols, sea salt, and a residual contribution. Each contribution was modelled separately or derived from measurements as described elsewhere.[27,28] Because PM concentrations prior to 2004 were modelled using other units, we restricted our analysis to admissions beginning in 2004 to ensure that exposures for each year were in comparable, gravimetric units.

For 2009, the background annual average NO_x model had an r^2 of 0.8 compared with 92 verification monitoring sites.[28] The PM_{10} model had an r^2 of 0.9 at 19 verification sites (tapered element oscillating microbalance sites corrected for volatile losses). The agreement between modelled $PM_{2.5}$ at background sites (20 FDMS sites) was fairly good: $r^2 = 0.7$.[28]

MINAP data were released with the coordinates of the residential postcode centroid rounded to 100 m to protect patient confidentiality. Individual level exposure was defined as the average concentration at model grid points within 1 km of each patient's postcode centroid for each year. Rather than considering oxides of nitrogen and PM as independent exposures (Spearman correlations in Supplementary material online, *Table S2*), we included NO_2 and NO_x because they can be considered surrogates for particles generated from specific sources such as traffic and had greater spatial variability compared with PM_{10} and $PM_{2.5}$.

Statistical analysis

Hazard ratios were estimated using a Cox proportional hazards model (coxph) in the R software package (2.13.2). Time was modelled as days of follow-up starting 28 days after hospital admission. Each admitting hospital was allowed to have its own baseline hazard rate. Air pollution concentrations were included as a time-varying exposure, where the annual average air pollution was assigned to the person-time falling within the corresponding calendar year. To adjust for longer term time trends in air pollution and risk of death, we adjusted for calendar time using a natural spline with 2 degrees of freedom (df).

We adjusted for several clinical- and individual-level demographic characteristics as well as area-level deprivation, which were predictors of prognosis and correlated with air pollution concentrations. Variables were included in the following form: age—natural spline with 3 df; reperfusion—categories of no reperfusion treatment (reference), lysis, or percutaneous coronary intervention; area-level income—deciles; smoking—categories of ex-smoker, current, non-current with unknown history, or never smoked (reference); binary indicators for STEMI, white ethnicity, history of diabetes, angina, and MI prior to the first admission recorded in MINAP. Whether a patient was discharged from hospital on ACE-inhibitors, aspirin, beta-blockers, or statins was also modelled using binary indicators. To adjust for large-scale spatial variation in mortality or re-admission due to factors other than air pollution, we included indicators for Wales and the nine Government Office Regions in England. Our analysis investigates the association of within region, within hospital catchment area variation in air pollution and mortality. It therefore takes into account clustering of individuals with similar attributes other than those included in our model within a fairly small area. We assessed violations of the proportional hazard assumption by including an interaction term with the follow-up for each covariate in the fully adjusted model (Model 5). Regression models were based on observations with complete data for all covariates included in the model.

Sensitivity analyses

We investigated whether our results for the association between air pollution and survival were sensitive to our adjustment for deprivation, modelling each hospital with its own baseline, and the degrees of freedom for the time trend. The fully adjusted model (Model 5) was fit using deciles of education and employment deprivation rather than income. To account for clustering of patients within hospital,

but allow some sharing of information across hospitals, we included hospital as a random effect rather than a stratification variable. We also fit the fully adjusted model with 3 rather than 2 degrees of freedom for time.

Attributable burden

We estimated the number of deaths brought forward due to exposure to $PM_{2.5}$ in this cohort by first estimating the attributable fraction and then applying it to the number of deaths observed during the follow-up. Similar to a previous study,[30] our calculation of attributable fraction compared the risk of exposure to $PM_{2.5}$ based on the distribution of exposure observed in the cohort relative to 4 $\mu g/m^3$, an estimate of $PM_{2.5}$ due to natural sources alone (details in Supplementary material online) and used the hazard ratio estimated from the fully adjusted proportional hazards model.

Results

Among the 154 204 patients who met our inclusion criteria, the average duration of the follow-up was 3.7 years (SD = 1.6). There were 39 863 deaths (26% of patients) during the follow-up. Deaths according to year of the follow-up are presented in Supplementary material online, *Table S3*. Patient's demographic characteristics, medical history, treatments received while in hospital, area-level deprivation are presented in *Table 1*. Patients were on average 68 years old and were predominantly white males. The average exposure during the follow-up for residents of England was 18.8 $\mu g/m^3$ for NO_2, 17.0 $\mu g/m^3$ for PM_{10}, and 11.0 $\mu g/m^3$ for $PM_{2.5}$. Patients living in London had the highest exposures compared with other regions (*Table 2*). The relationship between income deprivation and $PM_{2.5}$ according to admitting hospital is presented in Supplementary material online, *Figure S1*.

Exposure to a 10 $\mu g/m^3$ increase in $PM_{2.5}$ during the same calendar year as the follow-up was associated with a 20% (95% CI 4–38) increase in death from all causes after adjusting for area-level income deprivation and other confounders (*Table 3*). There were no associations with the other pollutants and mortality in the fully adjusted models. There was evidence of non-proportional hazards of death by lysis, current smoking, and discharge on ACE-inhibitors in the fully adjusted models. However, the estimated associations were very similar to those presented for Model 5 in *Table 3* after accounting for non-proportional hazards with an interaction term: confidence intervals around the HR for $PM_{2.5}$ ranged from 1.03 to 1.37. There was no evidence of effect modification of the fully adjusted $PM_{2.5}$ association with mortality by STEMI vs. non-STEMI ($P = 0.29$) or by reperfusion ($P = 0.25$ for interaction with primary PCI and $P = 0.26$ for lysis).

Adjusting for small-area income deprivation substantially attenuated the $PM_{2.5}$ association with mortality (Model 5, *Table 3*). The association between income deprivation and mortality was attenuated by smoking status and existing conditions like diabetes and previous MI (Model 3, *Table 3*). Further adjustment for $PM_{2.5}$ only slightly attenuated the income deprivation and mortality association (Model 5, *Table 3*).

The fully adjusted $PM_{2.5}$ results were not sensitive to the use of education or employment for adjustment of deprivation (*Table 4*)

Table 1 Characteristics of patients hospitalized with acute coronary syndrome in England and Wales between 2004 and 2007

	n (% missing[a])	
Mean (SD) age	154 204 (0)	68 (13) years
Male	154 204 (0)	66.6%
Ethnicity	141 236 (8)	
White		90.3%
Non-white		9.7%
Smoking	141 493 (8)	
Never		24.5%
Ex-smoker		33.9%
Current		32.1%
Non-current, unknown history		9.5%
Medical history prior to admission		
Hypertension	146 866 (5)	45.3%
Diabetes	146 129 (5)	16.6%
Angina	146 236 (5)	27.1%
Cerebrovascular disease	141 598 (8)	6.8%
Heart failure	141 812 (8)	4.4%
Previous AMI	148 698 (4)	19.9%
Final diagnosis		
ST elevation		47.1%
Non-ST elevation	154 204 (0)	52.9%
Reperfusion	151 641 (2)	
None		59.3%
Lysis		36.7%
Primary PCI[b]		4.0%
Discharge drugs		
ACE-inhibitor	128 946 (16)	83.4%
Beta-blocker	130 891 (15)	76.9%
Aspirin	132 951 (14)	93.2%
Statin	131 290 (15)	93.8%
Mean (SD) area level (LSOA) deprivation		
England	145 132 (0)	
% residents in income deprivation		16.4 (12.2)
% residents in employment deprivation		11.1 (7.1)
Wales	9072 (0)	
% residents in income deprivation		22.6 (20.0)
% residents in employment deprivation		22.7 (20.0)

AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme-inhibitor; LSOA, lower super output area.
[a]Percentage missing based on 154 204 sample size, whereas percentage distributions for a given covariate are based on number with complete information for that covariate.
[b]European Society of Cardiology guidelines published in 2005 state that primary PCI is the treatment of choice for patients with STEMI presenting in a hospital with PCI facility and an experienced team.[46] Among patients with STEMI, the percentage receiving primary PCI was 4% in 2004; 7% in 2005; 12% in 2006; 14% in 2007.

Table 2 Distribution of exposure to air pollution within person-time of the follow-up

Mean (SD) exposure by region ($\mu g/m^3$)	*n*	NO_2	NO_x	PM_{10}	$PM_{2.5}$
England	145 132	18.8 (6.8)	28.3 (12.7)	17.0 (2.7)	11.0 (1.9)
North East	12 045	17.7 (5.2)	25.6 (9.0)	13.7 (1.7)	8.4 (1.2)
North West	22 152	19.9 (6.0)	29.6 (10.9)	15.0 (2.3)	9.5 (1.6)
Yorkshire	16 998	18.4 (5.0)	27.5 (9.3)	16.1 (2.0)	10.2 (1.3)
East Midlands	14 185	17.0 (5.1)	25.4 (9.6)	17.6 (1.6)	11.4 (1.2)
West Midlands	13 609	20.8 (6.8)	32.8 (13.8)	17.6 (2.3)	11.4 (1.6)
East of England	18 462	16.6 (4.2)	24.8 (7.7)	18.2 (1.3)	12.0 (0.9)
London	12 949	30.5 (6.1)	50.2 (12.5)	21.7 (1.8)	14.1 (1.1)
South East	20 817	17.5 (4.7)	25.1 (8.5)	17.9 (1.5)	11.8 (1.0)
South West	13 915	12.8 (5.1)	17.4 (8.1)	15.7 (1.6)	9.8 (1.2)
Wales	9072	12.9 (5.5)	17.7 (8.7)	14.6 (1.9)	9.1 (1.3)

Table 3 Hazard ratios and 95% CI for air pollution and income deprivation associated with all-cause mortality

Model (M): covariates[a]	Events	NO_2 (per 10 $\mu g/m^3$)	NO_x (per 10 $\mu g/m^3$)	PM_{10} (per 10 $\mu g/m^3$)	$PM_{2.5}$ (per 10 $\mu g/m^3$)	Income (most vs. least deprived decile)
M1: age, sex, time	39 863	1.11 (1.08, 1.13)	1.05 (1.04, 1.07)	1.17 (1.10, 1.26)	1.44 (1.29, 1.60)	1.50 (1.43, 1.58)
M2: M1+reperfusion+region	38 917	1.10 (1.07, 1.13)	1.05 (1.04, 1.07)	1.18 (1.10, 1.27)	1.48 (1.33, 1.66)	1.50 (1.42, 1.58)
M3: M2+final diagnosis, smoking, ethnicity, diabetes, angina, previous MI	30 784	1.07 (1.04, 1.10)	1.04 (1.02, 1.05)	1.13 (1.05, 1.23)	1.42 (1.26, 1.62)	1.35 (1.27, 1.43)
M4: M3+discharge drugs	25 822	1.06 (1.03, 1.10)	1.03 (1.01, 1.05)	1.12 (1.03, 1.23)	1.40 (1.22, 1.60)	1.30 (1.22, 1.39)
M5: M4+pollutant and income (mutually adjusted)	25 822	1.01 (0.98, 1.04)	1.00 (0.99, 1.02)	1.01 (0.92, 1.10)	1.20 (1.04, 1.38)	1.28 (1.20, 1.37)[b]

[a]All models stratified by admitting hospital. Covariates modelled as time trend (natural spline with 2 df), age (natural spline with 3 df), reperfusion (none, lysis, PCI), STEMI (yes/no), smoking history (ex, current, non-smoker with unknown history, or never smoker), white ethnicity (yes/no), history of diabetes (yes/no), history of angina (yes/no), previous MI (yes/no), prescription for ACE-inhibitors (yes/no), beta-blockers (yes/no), aspirin (yes/no), or statins (yes/no) at discharge.
[b]Income hazard ratio adjusted for $PM_{2.5}$.

Table 4 Sensitivity of the $PM_{2.5}$ associations with mortality following admission for acute coronary syndrome

Hazard ratio (95% CI) per 10 $\mu g/m^3$ $PM_{2.5}$	
Fully adjusted model	
Education in place of income	1.22 (1.06, 1.40)
Employment in place of income	1.20 (1.04, 1.38)
Income with random effect for hospital	1.17 (1.04, 1.33)
Income with time trend using 3 df	1.20 (1.04, 1.38)

or an additional degree of freedom to model time. Less stringent control for differences across hospitals using a random intercept for hospital resulted in a slightly smaller HR compared with the main analysis.

We estimated that the mortality rate would be reduced by 12% if this cohort were exposed to naturally occurring $PM_{2.5}$ rather than their modelled exposure. This translates to 4783 deaths brought forward due to exposure to $PM_{2.5}$ from man-made sources.

Discussion

In this study of a large population of patients with advanced ischaemic heart disease, long-term exposure to air pollution was associated with all-cause mortality. The association was strongest for $PM_{2.5}$ concentrations; there was no evidence of an association for the other pollutants. Whereas small-area income deprivation explained a substantial amount of the association between $PM_{2.5}$ and mortality, exposure to $PM_{2.5}$ explained little of the large socioeconomic gradient in mortality rate. The association between $PM_{2.5}$ and mortality was not sensitive to adjustment for other measures of socioeconomic deprivation, including a random intercept for admitting hospital, or more flexibility in our model of time trends.

The primary strengths of our study are its large size, including a patient population from all of England and Wales, and detailed data on in-hospital treatments, discharge drugs, and patient

characteristics which allowed for comprehensive confounder adjustment. One of the main limitations was the lack of cause-specific death, which limited our ability to analyse mortality outcomes in more detail. The majority of deaths among these ACS survivors is likely to be due to cardiovascular causes,[7,31] although we cannot rule out that deaths influenced by air pollution were due to non-cardiovascular causes. The spatial resolution of the exposure model was fairly modest and corresponded to background concentrations, limiting our ability to investigate the role of local sources such as traffic. Exposure was assigned to individuals based on their postcode of residence at time of first admission. Complete data on residential history were not available; however, we explored the stability of residential postcodes over time among individuals who were re-admitted to hospital. There was no change in postcode for 75% of patients who were re-admitted, and the postcode centroid changed by $\leq$300 m for 90%. Although individual-level deprivation data were unavailable, we adjusted for area-level deprivation as well as for individual-level smoking and clinical history, which are likely to be important mediators of the relationship between an individual's socioeconomic position and prognosis. Several studies have shown that area-level measures of deprivation are more correlated with air pollution exposure, and comprehensive adjustment using area-level measures can essentially remove the correlation between individual-level deprivation and air pollution exposure.[26,32] Although we adjusted for drugs prescribed at discharge, no data were available on drugs taken during the follow-up or for secondary prevention measures, which may have resulted in some residual confounding.

This study advances the field in several ways. First, our study provides the most comprehensive accounting for important differences in case management across hospitals through a combination of using detailed clinical data on treatments within the MINAP database and allowing each hospital to have its own baseline hazard. Differences across hospitals and potential clustering of patients within hospitals have not been accounted for in similar studies.[3,5] Second, the most comparable study in terms of size assigned exposure at the county level using ambient monitors and was consequently restricted to urban areas.[5] Third, the detailed data within MINAP allowed for comprehensive adjustment for confounding, particularly for smoking and discharge drugs which were not available for previous studies.[3] Finally, our study provides evidence that particulate air pollution exposure does not contribute substantially to socioeconomic inequalities in post-MI prognosis. This hypothesis has been discussed in the literature, but not tested.[33]

Our results for $PM_{2.5}$ are consistent with a broad body of evidence indicating that PM in this size range is especially relevant for cardiovascular mortality.[34–36] The biological plausibility of our findings is supported by accumulating evidence that pulmonary oxidative stress and inflammation in response to inhaled particles lead to systemic oxidative damage and inflammation[37] as well as consequent endothelial dysfunction,[38] increased thrombosis,[39] and plaque vulnerability. Brief exposure to combustion-related particles among MI survivors has been shown to promote myocardial ischaemia and inhibit fibrinolytic capacity.[40] Evidence from both human and animal studies suggests that long-term exposure to particulate air pollution enhances the progression and instability of underlying atherosclerosis via inflammatory processes, thereby promoting further ischaemic events.[41–43] This evidence is supported by epidemiological findings of an association with the occurrence of MI as well as cardiovascular mortality.[35,44] Our findings of a positive association between long-term exposure to air pollution and mortality were specific to $PM_{2.5}$, which was somewhat unexpected given that exposure to $PM_{2.5}$ was highly correlated with PM_{10}. The confidence intervals for the PM_{10} association were wider than those of NO_2 and NO_x, for which the evidence of a null association was clearer.

Studies with large numbers of events among the general population are required to answer the question of whether MI survivors are more susceptible to the effects of air pollution compared with the general population. We were not able to address this question in this study. If MI survivors are found to be more susceptible, this could have important public health implications. Thirty-day mortality for ACS has fallen year on year in England and Wales,[45] leading to a growing number of MI survivors for whom air pollution may pose an elevated risk that receives relatively little attention in clinical settings.

In conclusion, we observed an association between long-term exposure to $PM_{2.5}$ and all-cause mortality among patients with a previous ACS event. Exposure to air pollution explained relatively little of the large socioeconomic gradient in survival. The extent to which this population is at higher risk of death compared with the general population and implications for secondary prevention in this population requires further investigation.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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