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Research Article

Particulate matter (PM10) and oxides of Nitrogen (NOx) each independently predict respiratory emergency outcomes

Abstract

Background: The impact of environmental air pollutants on the outcome of an emergency hospitalisation of respiratory patients has received limited study. We report on how levels of pollutants, particulate matter levels (PM_{10}) and oxides of Nitrogen (NOx) influence hospital outcomes (30-day in-hospital mortality).

Methods: All emergency respiratory admissions (35,523 episodes, in 15,037 patients) were tracked between (2002-2015). Daily levels of PM_{10} and NOx from the hospital catchment area were correlated with outcome; univariate and multivariate logistic regression examined relationships between air pollution and outcome following adjustment for complexity.

Results: There was a significant reduction between 2002 and 2015 in levels of both PM_{10} 20.4 to 12.9 ($\mu g/m^3$) and NOx levels 76.5 to 38.2 ($\mu g/m^3$). An increase in PM_{10} on the day of admission from lowest (Q1) to highest quintiles (Q5) increased the mortality risk- OR 1.31 (1.08−1.60) with absolute deaths rates increasing from 17.1% to 21.1%. Similarly, an increase in NOx at admission from lowest to highest quintiles increased mortality risk - OR 1.43 (1.17−1.74) and hospital mortality from 17.4% to 20.7%. Low Socio-Economic status (SES) conferred a greater mortality risk, if admitted on days with higher levels of pollution - PM_{10} (p<0.01) Odds Ratio 1.02 (95% CI: 1.01, 1.04) and NOx (p=0.04) − OR 1.02 (95% CI: 1.00, 1.04).

Conclusion: Levels of PM_{10} and NOx on the day of which respiratory patients had an emergency medical admission independently predicted the 30-day hospital mortality. Low SES status patients admitted on high pollution days had a worse outcome.

Introduction

In previous studies a clear association between particulate matter (PM) air pollution and daily mortality has been identified [1-3]. Chronic obstructive pulmonary disease (COPD) patients when exposed to increased PM concentrations experience a worsening of symptoms and higher morbidity as assessed by emergency room visits or hospital admissions [4-6]. Overall, epidemiological evidence also indicates an elevated mortality rate among individuals with COPD following exposure to PM [7,8]. A previous investigation at our institution, just over three decades ago, showed an association between increases in mortality and urban air pollution [9]. Thereafter, air quality in Dublin continued to deteriorate necessitating legislation in 1990, resulting in the banning of marketing, sale and distribution of bituminous coals. The air pollution control legislation brought about a decrease in the average black smoke concentration for Dublin approximating to a reduction of 35.6$\mu g/m^3$ [10] Death rates were also assessed with adjusted non-trauma death rates evidencing a decrease by 5.7%, respiratory deaths by 15.5% and cardiovascular deaths by 10.3%, providing solid evidence for the governmental intervention [10]. While the beneficial effects of this intervention in Ireland are clear, published evidence to date suggests that air pollution even when below the accepted international standards may still have detrimental effects on health [2,3,11,12]. We report on particulate matter and its relationship to hospital mortality outcomes at such lower levels.

The influence of Oxides of nitrogen (NOx) on mortality have been shown to be independently predictive for total, cardiovascular and respiratory mortality with stronger effects on cause-specific mortality; there was evidence of

confounding in respiratory mortality with particulate matter [13]. Our hospital St James's (SJH) has a catchment area which is predominantly inner city, combining over 50% of patients labelled as deprived and a largely ageing population [14], most ecologic studies of environmental equity show that groups with lower socioeconomic status (SES) are more likely to be exposed to higher air pollution levels than groups of higher SES [15]. Although each air pollutant can exert its own specific toxicity in the respiratory and cardiovascular systems, ozone, oxides of nitrogen, and suspended particulates all share a common property of being potent oxidants, either through direct effects on lipids and proteins or indirectly through the activation of intracellular oxidant pathways [16]. Oxidative stress may be particularly active during an emergency medical admission; there is interest in the role of oxidative stress in the progression and prognosis of acute disease [17]. Accordingly, in this work we investigated whether current levels of PM_{10} and NOx impact upon the mortality for acute medical admissions with respiratory disease, and whether the high deprivation population of our catchment area has increased susceptibility to the adverse effects of air pollution.

Methods

Background

St James's Hospital, Dublin serves as a secondary care centre for emergency admissions in a catchment area with a population of 270,000 adults. All emergency medical admissions are admitted from the Emergency Department to an Acute Medical Admission Unit, the operation and outcome of which have been described elsewhere [18,19].

Data collection

An anonymous patient database was employed, assembling core information from each clinical episode including details from the patient administration system, national hospital in-patient enquiry (HIPE) scheme, the patient electronic record and laboratory data. HIPE is a national database of coded discharge summaries from acute public hospitals in Ireland [20,21]. All data was collected in the normal course of treatment, examined retrospectively, completely anonymised and, thus, ethics approval was not needed. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) has been used for both diagnosis and procedure coding from 1990 to 2005 and ICD-10-CM since then. Data included parameters such as the unique hospital number, admitting consultant, date of birth, gender, area of residence, principal and up to nine additional secondary diagnoses, principal and up to nine additional secondary procedures, and admission and discharge dates. Additional information cross-linked and automatically uploaded to the database includes physiological, haematological and biochemical parameters.

Deprivation Indices

Census returns reports are based on the Electoral Divisions (EDs), the smallest administrative areas for which population statistics are reported. Using principle components analysis (PCA), a weighted combination of four indicators, relating to unemployment, social class, type of housing tenure and car ownership was derived, as described by the SAHRU investigators [22]. The Deprivation Index Scores were ranked from low (least deprived) to high (most deprived) and divided into quintiles or deciles according to their ranked raw scores, as described previously [23]. We utilized the registered address on our Patient Administration System to allocate each address to a divisional area, with a corresponding matched SAHRU Deprivation raw score and decile rank. This attribute data were joined to the small area polygon geometries based upon their relative geographic positions, using the ArcGS Geographic Information System software implementation of the Point-in-Polygon algorithm [24].

Air quality

For the current study, data over the last fourteen years (2002-2015) from three stations within our hospital catchment area (Winetavern and Coleraine Street or Rathmines) were assessed and daily measures of Particulate Matter (PM_{10}) or hourly measures of oxides of nitrogen (NOx) were recorded according to methods described elsewhere [25]. A single average value for each day was calculated for the analyses. We divided the daily levels into equally spaced quintiles - PM_{10} quintile cutpoints were 9.9, 13.2, 16.9 and 23.3 µg/m³ respectively. The NOx quintile cutpoints were 26.8, 38.7, 53.0 and 80.9 µg/m³, respectively.

Risk predictors

Derangement of admission biochemical parameters may be utilised to predict clinical outcome. We derived and applied an Acute Illness Severity score [26], predicting in-hospital mortality from the following routine laboratory tests recorded in the Emergency Department - sodium (Na), potassium (K), urea, albumin, red cell distribution width (RDW) and white blood cell count (WCC). A weighted score, based on the relationship between these and 30-day mortality outcome was derived [27]. Then six risk groups (I – VI) were identified with cut-points for 30-day in hospital mortality rates set at 1, 2, 4, 8 and 16%. We adjusted for Co-Morbidity using the Charlson Index [28] and disabling disease [29] IDC9/ICD10 discharge codes of 1, 2, 3 or 4 separate systems (e.g. cardiovascular, respiratory, diabetes, renal). In addition sepsis categories of 1) No Culture requested 2) Culture Negative and 3) Culture Positive were examined. Each of these predictors estimated the outcome risk for each patient and these estimates were then used to adjust the estimate of the impact of PM_{10} and NOx on 30-day inpatient hospital mortality in the multiple variable logistic regression model.

Statistical methods

Descriptive statistics were calculated for demographic data, including means/standard deviations (SD), medians/interquartile ranges (IQR), or percentages. We examined 30-day in-hospital mortality as the primary outcome. We performed comparisons between categorical variables and 30-day in hospital mortality using chi-square tests; multiple comparisons were adjusted for multiplicity using Scheffe's comparison statistic. Logistic regression analysis was employed

to examine significant outcome predictors (p<0.10 from the univariate analysis) of 30-day in hospital mortality. Adjusted Odds ratios (OR) and 95% confidence intervals (CI) were calculated for those significant model predictors (p<0.10). A stepwise logistic regression analysis examined the association between 30-day mortality and the following predictor variables: Acute Illness Severity, Charlson Co-Morbidity Index [28], and Chronic Disabling Disease [29], sepsis status [30] and Deprivation index according to the Quintiles of the SAHRU deprivation number and the daily PM_{10} and NOx levels.

We used the margins command in Stata 13.1 to estimate and interpret adjusted predictions for sub-groups, while controlling for other variables such as illness severity, using computations of average marginal effects. Margins are statistics calculated from predictions of a previously fitted model at fixed values of some covariates and averaging or otherwise over the remaining covariates. In the multi-variable model (logistic or Poisson), we adjusted univariate estimates of effect, using the previously described outcome predictor variables. The model parameters were stored; post-estimation intra-model and cross-model hypotheses could thereby be tested.

Adjusted odds ratios (OR) and 95% confidence intervals (CI) or IRRs were calculated for those predictors that significantly entered the model (p<0.10). Statistical significance at P<0.05 was assumed throughout. Stata v.13.1 (Stata Corporation, College Station, Texas) statistical software was used for analysis.

Results

Patient demographics

A total of 90,255 episodes, recorded in 47,947 unique patients admitted as acute medical emergencies between January 2002 and December 2015 (14-year peroid), were included for analysis, including those admitted directly into the Intensive Care or High Dependency Units. The proportion of males was 48.6%. The median (IQR) length of stay (LOS) was 6.0 (2.5, 13.1) days. The median (IQR) age was 64.9 (44.3, 78.7) years, with the upper 10% boundary at 85.6. The Charlson Comorbidity Score of 0, 1, or 2 was present in 44.2%, 27.5% and 28.2% respectively. The major disease categories (MDC) were respiratory (25.3%), cardiovascular (16.2%), neurological (16.8%) and gastrointestinal (10.0%).

A respiratory patient was defined as a patient who had been referred to the pulmonary function laboratory for formal testing (20.4% of total episodes) or with a discharge diagnosis of chronic obstructive pulmonary disease (26.0%) or of pneumonia (6.8%); this gave a total of all episodes labelled as respiratory of 39.4%. Patients with respiratory admissions had a significantly higher occurrence of Acute Illness Severity, Charlson Co-Morbidity and Chronic Disabling Disease.

Impact of air pollutants on 30-day in-hospital mortality

There was a considerable reduction in Air Pollution between 2002 and 2015. The PM_{10} level (μg/m³) median and IQR levels for example in 2002–2003 was 20.4 (15.6, 29.2), by 2004–

2007 these had fallen to 16.5 (12.8, 22.8) while 2008–2015 had medians of 12.9 (9.3, 18.2). Similarly the NOx level (μg/m³) median and IQR levels in 2002–2003 were 76.5 (54.6, 118.0), by 2004–2007 these had fallen to 48.9 (34.2, 74.3) while 2008–2015 had medians of 38.2 (25.6, 59.2) (Figure 1).

Overall the episode 30-day mortality for respiratory admission between 2002 and 2015 was 7.9% (95% CI 7.7%, 8.2%); considering unique patients only (last admission if >1 episode) the 30-day hospital mortality rate for respiratory patients was 18.7% (95% CI: 18.1, 19.4). Respiratory patients were frequently readmitted over time – only 21.7% of respiratory patients were admitted once, 18.5% twice, 11% thrice, 7.5% four and 4.2% five times.

We divided patients by quintile of particulate matter (PM_{10}). The data represented the average daily level across all three stations; where a value was missing, the average of the remaining stations was taken. We related the mortality to the PM_{10} level on the day of hospital admission i.e. from lowest Q1 (median, IQR) of 7.8 μg/m³ (6.4, 8.8) to highest Q5 level of 31.7 μg/m³ (26.9, 40.6). The 30-day hospital mortality was increased (Table 1) across these PM_{10} quintiles Q5 vs. Q1 (p<0.01) to 1.31 (1.08 – 1.60); after adjustment for the other mortality predictors of Acute Illness Severity, Charlson Co-Morbidity Index [28], and Chronic Disabling Disease [29], sepsis status [30] and Deprivation Index (SAHRU National Index) [31]. The model adjusted 30-day hospital mortality rate, related to the quintiles of PM_{10}, would be predicted to increase from Q1 17.1% to Q5 21.1% (Figure 2).

We also divided patients by quintile of oxides of nitrogen (NOx) and related 30-day hospital mortality to the admission NOx levels. The NOx levels increased (median and IQR) from lowest Q1 20.5 μg/m³ (16.8, 23.2) to highest Q5 114.7 μg/m³ (92.8, 160.1). The 30-day hospital mortality with the NOx quintile; for Q5 vs. Q1 of NOx the Odds Ratio's (OR) of an in-hospital
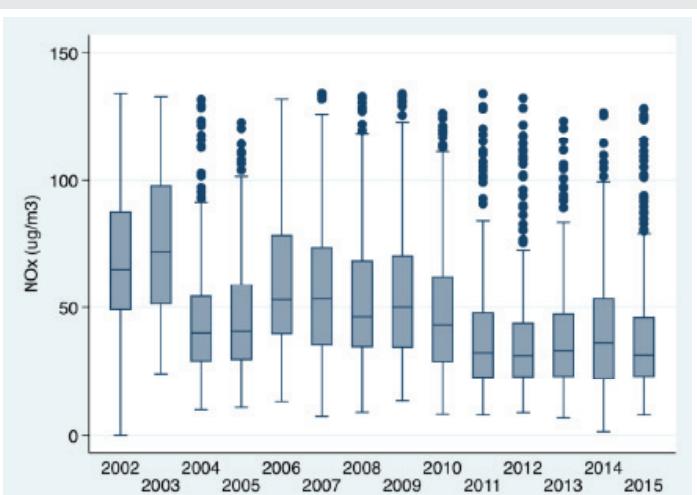

Figure 1: Trends of Air Pollution over time (NOx μg/m3) from 2002 to 2015 represented as boxplots. Boxes indicate the IQR; lines within boxes indicate medians; whiskers represent 5th and 95th percentile values; and circles represent outliers. The median and IQR are displayed for each year. The medians (IQR) for 2002–2003 were 76.5 (54.6, 118.0), for 2004–2007 48.9 (34.2, 74.3) while 2008–2015 had medians of 38.2 (25.6, 59.2), a significant fall over time.

death by day 30, adjusted for all other predictive variables was increased (p<0.001) to 1.43 (1.17 – 1.74). The model adjusted 30-day hospital mortality rate, related to the quintiles of NOx would be predicted to increase from Q1 17.4% to Q5 20.7%.

Daily PM_{10} and NOx levels and interaction on 30-day hospital mortality (Table 1, Figure 3)

In the full multivariate model, we incorporated both the daily level of PM_{10} and NOx at the time of the emergency medical admission and then adjusted these for Socio-Economic status (area of residence - National Deprivation Index (3440 Electoral Divisions ranked nationally by decile) and also adjusted also for Acute Illness Severity, Charlson Co-Morbidity Index, Chronic

Figure 3: The 30-day in hospital mortality related daily NOx levels by quintiles to the 30-day inhospital mortality and adjusted for Socio-Economic Status (SES) and other outcome predictors. We used margins to estimate the average marginal effect. As NOx Quintiles increased (level of pollution on day of admission), the rate of 30-day mortality increase was steeper for lower SES admissions.

Table 1: Logistic multivariable model of 30-day in Hospital mortality related to admission levels of PM10 and oxides of Nitrogen (NOx), with adjustment for other Risk Predictors.

Parameter	Group	OR	95% CI	p <
PM_{10} (µg/m³)	Q II	1.30	1.05, 1.62	0.02
	Q III	1.50	1.12, 2.02	0.008
	Q IV	1.51	0.96, 2.38	0.07
	Q V	2.04	1.04, 4.00	0.04
NOx (µg/m³)	Q II	0.90	0.73, 1.12	0.34
	Q III	1.32	0.99, 1.77	0.06
	Q IV	1.51	0.98, 2.34	0.07
	Q V	2.02	1.05, 3.92	0.04
Illness Severity		4.46	3.82, 5.21	0.001
Charlson Index		1.36	1.25, 1.49	0.001
Disabling Score		1.34	1.25, 1.43	0.001
Sepsis		1.51	1.91, 2.32	0.001
Deprivation - ED		1.07	1.01, 1.14	0.02

Interaction terms for PM_{10} and NOx were not statistically significant (OR 0.96 – p = 0.1).
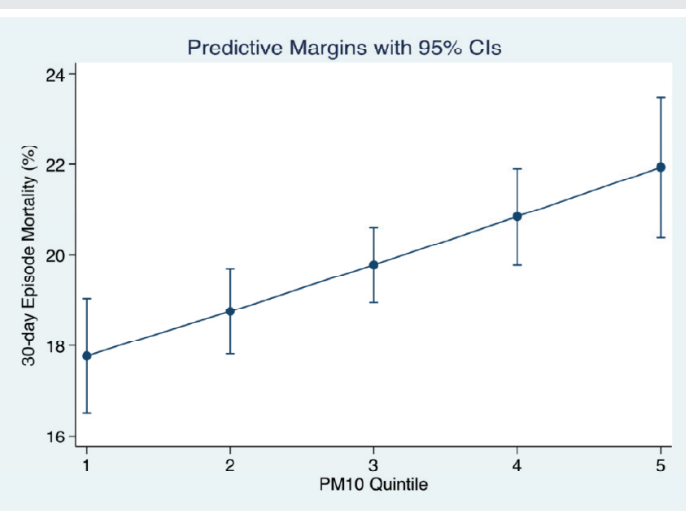

Figure 2: The 30-day in hospital mortality was related to the underlying level of admission Acute Illness Severity. We divided PM10 levels by quintiles; illustrate is the increase in 30-day mortality rates with the underlying level of the PM10 on the day of hospital admission. The risk estimate was derived from the logistic regression multivariable model and was adjusted for Charlson Co-Morbidity, Chronic Disabling Disease, Sepsis and Deprivation Status.
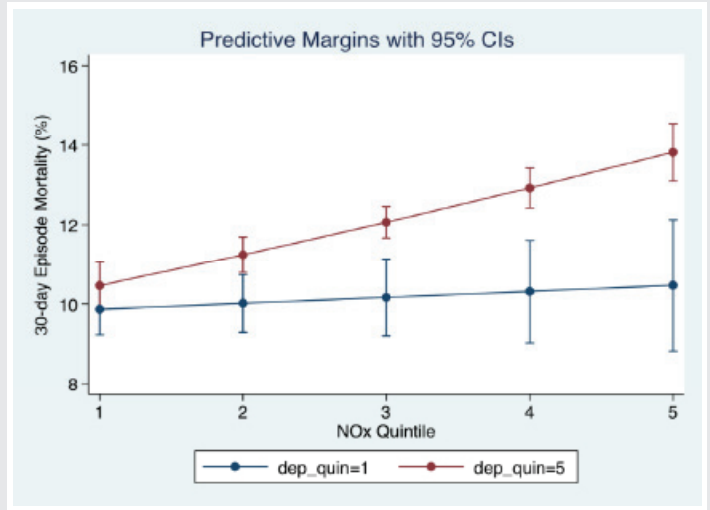
Disabling Disease Score and Sepsis Status. Both PM_{10} and NOx were independent predictors of 30-day inhospital mortality related to the quintiles of each of the day of admission levels. There was an approximate two fold risk increment increased comparing Q1 with Q5 for differences between highest and lowest pollutant states at time of admission – for PM_{10} Odds Ratio 2.04 (95% CI: 1.04, 4.00) and NOx 2.02 (95% CI: 1.05, 3.92). The interaction term between these pollutant parameters was not significant (p = 0.11) – OR 0.96 (95% CI: 0.91, 1.01). The interaction term for Deprivation status with the level of pollutant was significant – patients from high deprivation areas were more likely to die at high pollutant levels compared with patients from more affluent areas (Figure 3) - PM_{10} (p<0.01) Odds Ratio 1.02 (95% CI: 1.01, 1.04) and NOx (p=0.04) – OR 1.02 (95% CI: 1.00, 1.04).

Discussion

This study considered the impact on respiratory patients with an emergency medical admission when atmospheric air pollution was higher or lower; the data clearly demonstrated that both PM_{10} and NOx levels on the day on which respiratory patients had an emergency medical admission independently predicted the subsequent 30-day hospital mortality. Our hospital catchment area is predominantly inner city, combining over 50% of patients labeled as deprived [14], 47 of the 74 Electoral Divisions (small local areas) categorized in the top quintile of the National Deprivation Index [22]. Most ecologic studies of environmental equity show that groups with lower socioeconomic status (SES) are more likely to be exposed to higher air pollution levels than groups of higher SES [15]. We indeed confirmed that patients from small local areas (Electoral Division - Deprivation Index) of higher Deprivation status had a worse outcome compared with similar respiratory admissions from more affluent areas, despite adjustment for other clinical predictor parameters such as the Acute Illness Severity, Charlson Co-Morbidity Index [28] and Chronic Disabling Disease [29] and sepsis status [30]. We do

not know however, if this worse outcome was attributable to a higher level of background exposure or may be explained by the concentration in those areas of people with adverse personal or socio-economic factors and relate to community rather than personal disadvantage [32]. However, it illustrates the importance of area of residence influencing the healthcare outcomes.

In previous studies a clear association between particulate matter (PM) air pollution and daily mortality has been identified [1-3], epidemiological evidence also indicates an elevated mortality rate among individuals with COPD following exposure to PM [7,8]. The admission incidence rate was not related to the daily levels of PM_{10}; however, these levels have fallen in Dublin consistently over time. The PM_{10} level ($\mu g/m^3$) median and IQR levels for example in 2002–2003 was 20.4 (15.6, 29.2), by 2004–2007 these had fallen to 16.5 (12.8, 22.8) while 2008–2015 had medians of 12.9 (9.3, 18.2). Nonetheless the outcome (30-day in-hospital mortality) was worse for patients when admitted on days with PM_{10} higher levels. While the beneficial effects of this intervention in Ireland are clear, published evidence to date suggests that air pollution even when below the accepted international standards may still have detrimental effects on health [2,3,11,12].

Oxides of Nitrogen (NOx) are highly reactive gases; total NOx consists of Nitrogen Dioxide (NO_2) and nitric oxide (nitrogen monoxide). NOx is released into the atmosphere when fuels are burned (for example, petrol or diesel in a car engine, or natural gas in a domestic central- heating boiler or power station). The exposure to nitrogen dioxide is harmful to human health; a meta-analysis of 60 studies indicated that adverse health outcomes of short-term exposure to NO_2 were largely independent of particulate matter exposure [33]. There has been debate on the acute and long term impacts of exposure to nitrogen dioxide; ambient NO_2 in the UK may be associated with an increase in daily death rate and numbers of hospital admissions for cardiovascular or respiratory illness of less than 0.2% and probably less than 0.05%. However, this review concluded that the results of studies of the long term effects of exposure to NO_2 do not suggest an adverse effect [34]. However, more recent estimates of the health impacts of Air Pollution in London indicated substantial health consequences of particulate and oxides of nitrogen exposure; the total mortality burden of long-term exposure to NO_2 is estimated to be up to 88,113 life-years lost, equivalent to 5,879 deaths at typical ages (assuming the WHO value of up to a 30% overlap between the effects of $PM_{2.5}$ and NO_2) [35]. The APHEA project, relating air pollutant concentrations to health care outcomes on a multi-city basis, noted that most studies had indicated that NO_2 had been associated with a decrease in lung function, an increase in respiratory symptoms and an increase in asthma and COPD hospital admissions. The APHEA found that the cumulative effect over 6 days was larger by about 22% for total and cardiovascular mortality and by 45% for respiratory mortality compared with the average exposure over 2 days. This indicates that previous estimates of NO_2 effects may in fact represent an underestimation if they take into account only very short-term health effects [13]. Our data only considered the impact of the exposure to PM_{10} and NOx at the time of admission with a

medical emergency, we therefore cannot comment on possible longer term risk exposure. However, our data clearly shows that as both PM_{10} and NOx were independently predictive in the multi variable model and had no significant interaction, they should be viewed as separate and independent risk factors in terms of the impact on 30-day hospital mortality outcome. These results may implicate oxidative stress as a possible mechanism to explain the worsened outcome independent of clinical risk status [16].

This study, as with any, has its limitations. We have included a large emergency medical admission cohort, encompassing 14 years of episodes and reflecting real world clinical practice; however, the work has been conducted in one institution is local and, thus, its findings may not generalized to the population as a whole. In addition, there are groups of patients in more affluent areas who may present as emergencies outside the public health system unlike the more deprived, who have little other recourse when an emergency occurs. These patients will not be captured by our statistics and thus there may be an underrepresentation of the admission incidence rates of patients from the more affluent areas.

In conclusion, we have shown that the levels of PM_{10} and NOx on the day of which respiratory patients had are admitted to hospital independently predicted the 30-day hospital mortality. Further, those lower economic status respiratory patients when admitted on days of high pollution experienced worse outcomes.

Acknowledgments

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