Mortality Associations with Long-Term Exposure to Outdoor Air Pollution in a National English Cohort

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Rationale: Cohort evidence linking long-term exposure to outdoor particulate air pollution and mortality has come largely from the United States. There is relatively little evidence from nationally representative cohorts in other countries.

Objectives: To investigate the relationship between long-term exposure to a range of pollutants and causes of death in a national English cohort.

Methods: A total of 835,607 patients aged 40–89 years registered with 205 general practices were followed from 2003–2007. Annual average concentrations in 2002 for particulate matter with a median aerodynamic diameter less than 10 (PM₁₀) and less than 2.5 μm (PM_{2.5}), nitrogen dioxide (NO₂), ozone, and sulfur dioxide (SO₂) at 1 km² resolution, estimated from emission-based models, were linked to residential postcode. Deaths (n = 83,103) were ascertained from linkage to death certificates, and hazard ratios (HRs) for all- and cause-specific mortality for pollutants were estimated for interquartile pollutant changes from Cox models adjusting for age, sex, smoking, body mass index, and area-level socioeconomic status markers.

Measurements and Main Results: Residential concentrations of all pollutants except ozone were positively associated with all-cause mortality (HR, 1.02, 1.03, and 1.04 for PM_{2.5}, NO₂, and SO₂, respectively). Associations for PM_{2.5}, NO₂, and SO₂ were larger for respiratory deaths (HR, 1.09 each) and lung cancer (HR, 1.02, 1.06, and 1.05) but nearer unity for cardiovascular deaths (1.00, 1.00, and 1.04).

Conclusions: These results strengthen the evidence linking long-term ambient air pollution exposure to increased all-cause mortality. However, the stronger associations with respiratory mortality are not consistent with most US studies in which associations with cardiovascular causes of death tend to predominate.

Keywords: air pollution; mortality; cohort study; respiratory

Epidemiologic studies suggest that long-term exposure to ambient air pollution is associated with increased mortality (1, 2). Much of this evidence comes from cohort studies in the United States where the focus has been on associations with fine particles. In particular, the American Cancer Society (ACS) study

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Long-term exposure to ambient levels of fine particulate matter has been associated with increased mortality, particularly from cardiovascular disease, in several US population cohorts. There is less cohort evidence available outside the United States on gaseous pollutants and on respiratory outcomes.

What This Study Adds to the Field

Concentrations of particulate matter, nitrogen dioxide, and sulfur dioxide, but not ozone, were associated with increased all-cause mortality in a large national cohort in England. However, unlike US studies we found larger associations for respiratory rather than cardiovascular causes of death. These findings add to the evidence that from an international perspective there is important heterogeneity in the effects of air pollution on cause-specific mortality.

(3) and the Six-Cities study (4) have been extensively reanalyzed confirming their initial findings (5–9). Associations with the air pollution mixtures experienced by populations in Europe (10–16) and worldwide (17–20) have also been reported.

Where studies have investigated cause-specific mortality, the focus has been on cardiovascular disease (2). By contrast, the evidence for associations with respiratory mortality is less convincing (1) because many studies have lacked statistical power, or used a combined cardiorespiratory outcome because of the smaller number of respiratory deaths (4, 12). A recent report on the global impact of particulate matter with a median aerodynamic diameter less than 2.5 μm (PM_{2.5}) on chronic obstructive pulmonary disease (COPD) was reliant on only three studies, all from the United States (21). Few cohort studies have used large, population-based, nationally representative samples to investigate a range of respiratory and cardiovascular causes separately, or considered a range of criteria pollutants.

In this study, we investigate the associations between long-term exposure to a range of outdoor air pollutants and both all-cause and cause-specific mortality using a national cohort of adults registered with family practitioners in England, using linkage to a national mortality register to provide details on date and underlying cause of death.

METHODS

The Clinical Practice Research Datalink is a large, validated, and nationally representative database containing anonymized patient data from UK primary care (22). It includes a full longitudinal medical

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record for each patient consulting their family practitioner including information on diagnoses made within the practice. We selected 205 English practices, recording high-quality data according to Clinical Practice Research Datalink internal standards, which had available linked death registrations from the Office for National Statistics. From these, we identified 836,557 patients aged between 40 and 89 years, fully registered for at least 1 year on January 1, 2003 (23).

The following information was extracted from the electronic patient record and used to construct covariates: age; sex; smoking (non-, ex-, and current smoker, with further categories of 1–19, 20–30, and 40+ cigarettes per day); and body mass index (BMI) (<20, ≥20 and <25, ≥25 and <30, ≥30). The last recorded status before January 1, 2003 was used to code the variables, except for nonsmokers, who were reclassified as ex-smokers if they had older historical codes indicating smoking. A “missing” category was assigned for subjects with no recorded value before 2003. Socioeconomic status (SES) was classified using three separate census measures of deprivation (income, employment, and education), measured on a geographic area of approximately 1,500 people (24). A total of 950 patients had no census information and were dropped from the analyses. Deaths were classified according to the underlying cause on the death certificate (ICD-10): circulatory, I00–I99; coronary heart disease (CHD), I20–I25; myocardial infarction, I21–I23; stroke, I61, I63–I64; heart failure, I50; respiratory, J00–J99; pneumonia, J12–J18; COPD, J40–J44, J47; and lung cancer, C33–C34. We performed sensitivity analyses defining circulatory deaths as any mention on the certificate, and respiratory deaths restricted to where there was no mention of circulatory disease on the certificate.

Annual mean concentrations in 2002 of PM₁₀ and PM_{2.5}, sulfur dioxide (SO₂), nitrogen dioxide (NO₂), and ozone (O₃) for 1-km grid squares covering England were linked anonymously from grid centroid to the nearest residential postcode centroid for each patient (23). The pollutant concentrations were estimated using air dispersion models, developed by AEA Technology (Didcot, Oxfordshire, UK) over the past 10 years (25), for reporting to the UK Government and the European Commission for policy formulation (26). The models for PM₁₀, PM_{2.5}, NO₂, and SO₂ were constructed by estimating quantities of emissions by sector (e.g., power generation, domestic combustion, road traffic) with subsequent pollution concentrations calculated by summing estimates for pollutant-specific components, such as point and local area sources. O₃ maps were constructed by interpolating data

from rural monitoring stations and adjusting for effects of altitude and nitrogen oxide emissions. Model validation using national air quality monitors and networks (*see* Tables E1 and E2 in the online supplement) was good for NO₂ ($R^2 = 0.57$ – 0.80) and O₃ ($R^2 = 0.48$ – 0.71); moderate for PM₁₀ ($R^2 = 0.29$ – 0.46) and PM_{2.5} ($R^2 = 0.23$ – 0.71); but less successful for SO₂ ($R^2 = 0$ – 0.39). Further details on the methodology and validation are provided in the online supplement.

We used Cox proportional hazards models (SAS version 9.1.3; SAS Institute, Inc., Cary, NC) to investigate associations between pollution concentrations in 2002 and subsequent mortality in 2003–2007. We adjusted cumulatively for (1) age and sex; (2) smoking and BMI; and (3) in turn, income, employment, and education. Two-pollutant models were considered only when the correlation coefficient between pollutants was below 0.5. We performed stratified analyses to assess effect modification by the covariates. To account for clustering, the modified sandwich estimate of variance was used to produce robust standard errors. As a sensitivity analysis, we investigated the impact of fitting a random effect for practice in a shared frailty model (Stata version 10.1; StataCorp LP, College Station, TX). To allow comparison across pollutants, hazard ratios (HRs) were quantified for an interquartile range change in each pollutant (Table 1).

RESULTS

Of the 835,607 patients with linked census data, successful post-code linkage to all pollutants was made for approximately 99% of patients (Table 1). There was significant variation in modeled pollution concentrations by practice region ($P < 0.001$). Practices in southern England (excluding Greater London) had the lowest annual concentrations of all pollutants except O₃. By contrast, practices within Greater London had the highest concentrations for PM₁₀, PM_{2.5}, and NO₂, the latter over 70% higher than other southern practices (33.3 vs. 19.4 μg/m³). Areas with a lower SES (higher census deprivation scores of income, employment, and education) were associated with higher concentrations for all pollutants except O₃. Within our cohort, annual concentrations of PM₁₀ and PM_{2.5} were both strongly correlated with NO₂ ($r = 0.9$); moderately correlated with SO₂ ($r = 0.5$); and negatively correlated with O₃ ($r = -0.5$).

TABLE 1. SUMMARY OF ASSIGNED POLLUTANT CONCENTRATIONS FOR STUDY COHORT (N = 835,607)

	Assigned Annual Average Concentration in 2002 (μg/m ³)				
	PM ₁₀	PM _{2.5}	SO ₂	NO ₂	O ₃
No. of patients with pollution linkage (%)	830,842 (99%)	830,842 (99%)	823,442 (99%)	830,429 (99%)	824,654 (99%)
Mean pollution (SD)	19.7 (2.3)	12.9 (1.4)	3.9 (2.1)	22.5 (7.4)	51.7 (2.4)
Minimum–maximum range	12.6–29.8	8.5–20.2	0.1–24.2	4.5–60.8	44.5–63.0
Interquartile range	3.0	1.9	2.2	10.7	3.0
Practice region means (SD)					
North (81 practices)	19.8 (2.3)	13.0 (1.5)	4.8 (2.1)	23.4 (6.3)	50.9 (2.4)
South (excluding London) (96 practices)	19.1 (2.0)	12.5 (1.2)	3.3 (1.9)	19.4 (6.1)	52.6 (2.2)
London (28 practices)	22.5 (1.2)	14.6 (0.8)	3.8 (1.2)	33.3 (4.5)	50.2 (0.8)
Test for heterogeneity	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
Correlation with census socioeconomic scores*					
Income deprivation	0.25	0.26	0.11	0.24	–0.11
Employment deprivation	0.15	0.17	0.17	0.16	–0.12
Education deprivation	0.14	0.15	0.20	0.05	–0.08
Correlation with other pollutants					
PM _{2.5}	0.99	—	—	—	—
SO ₂	0.45	0.46	—	—	—
NO ₂	0.84	0.85	0.37	—	—
O ₃	–0.40	–0.39	–0.41	–0.46	—
Intraclass correlation by practice†	0.87	0.85	0.77	0.90	0.94

Definition of abbreviations: NO₂ = nitrogen dioxide; O₃ = ozone; PM_{2.5} = particulate matter with a median aerodynamic diameter less than 2.5 μm; PM₁₀ = particulate matter with a median aerodynamic diameter less than 10 μm; SO₂ = sulfur dioxide.

* Income deprivation measures the proportion of the population experiencing income deprivation in an area. Employment deprivation measures deprivation conceptualized as involuntary exclusion of the working-age population from the labor market. Education deprivation measures the extent of deprivation in terms of education, skills, and training in a local area.

† Proportion of total variation explained by between-practice differences.

A total of 83,103 deaths (9.9% of all patients) were recorded between January 1, 2003 and December 31, 2007 with an underlying cause of death recorded in 80,505 (97%). There were 28,976 (35%) deaths from circulatory; 10,583 (13%) from respiratory; and 5,273 (6%) from lung cancer causes. A total of 37,443 (45%) had some mention of cardiovascular disease on the death certificate. Of all respiratory deaths, 7,740 (73%) had no mention of cardiovascular disease on the death certificate. Higher, age- and sex-adjusted, mortality rates were associated with greater deprivation, living in the North, abnormal BMI, and recorded smoking intensity at baseline (Table 2).

The relationships between residential air pollution concentrations in 2002 and all-cause mortality during 2003–2007 are shown in Table 3. Associations were positive for all pollutants, except for O₃, which were negative. After adjustment for smoking and BMI these ranged from 6–7% for interquartile range increases in PM₁₀, PM_{2.5}, SO₂, and NO₂, mostly reducing to 2–4% after adjustment for one of the area deprivation markers, with income having the biggest influence. For example, in a model adjusted for area income level, a 1.9 µg/m³ increase in PM_{2.5} was associated with an HR of 1.02 (95% confidence interval [CI], 1.00–1.05). In two-pollutant models all associations were attenuated, with associations with SO₂ proving the most robust (*see* Table E3).

Analyses for specific causes of death (Table 4) revealed that the strongest associations were for respiratory deaths where all pollutants, except O₃, were positively associated with increases in mortality. For example, in a model adjusted for area income, a 1.9 µg/m³ increase in PM_{2.5} was associated with an HR of 1.09 (95% CI, 1.05–1.13), whereas a 3.0 µg/m³ increase in O₃ was associated with an HR of 0.94 (95% CI, 0.90–0.97). Comparable HRs were also observed for deaths from COPD and pneumonia (*see* Table E4). By contrast, there was less evidence of associations with cardiovascular causes of death (Table 4), where only SO₂ showed a relationship (HR, 1.04; 95% CI, 1.03–1.06). The pattern was similar with deaths from CHD, myocardial infarction, or stroke, although associations were observed between PM₁₀ and PM_{2.5} and deaths from heart failure as underlying cause (*see* Table E4). For lung cancer (Table 4), the strongest associations were seen with NO₂ (HR, 1.06; 95% CI, 1.00–1.12). Extending the definition of cardiovascular deaths to any mention on the death certificate, combining them with respiratory deaths, or restricting the definition of respiratory deaths to those without mention of cardiovascular disease, did not materially alter the above findings (*see* Table E5).

Further analyses of the association with respiratory deaths by selected covariates showed that for PM_{2.5}, PM₁₀, and NO₂ there was still evidence of a relationship with respiratory mortality in younger ages (40–64 yr), nonsmokers, and those without any COPD or asthma at baseline (*see* Table E6). For example, for PM_{2.5} a 1.9 µg/m³ increase produced an HR of 1.14 (95% CI, 1.08–1.20) for patients classed as nonsmokers at baseline. The association was strongest in more income-deprived areas for PM₁₀, PM_{2.5}, and NO₂, but highest for SO₂ in least-deprived areas.

Adjustment for within-practice clustering using frailty models attenuated the associations for all pollutants, especially for PM₁₀ and PM_{2.5} when also adjusted for area income (*see* Table E7). However, the associations between the pollutants and respiratory mortality remained robust (e.g., for PM_{2.5} a 1.9 µg/m³ increase produced an HR of 1.07; 95% CI, 1.03–1.11).

DISCUSSION

This study of a national cohort has observed associations between annual concentrations of ambient air pollution and risk

TABLE 2. AGE-SEX ADJUSTED PERCENTAGES OF PATIENTS WHO DIE DURING FOLLOW-UP BY BASELINE FACTORS (N = 835,607)

Baseline Variables	Level	No. Patients	No. Deaths	Adj %*
Sex	Male	404,716	41,207	10.2%
	Female	430,891	41,896	9.7%
Age	40–49	242,267	3,195	1.3%
	50–59	227,972	7,245	3.2%
	60–69	165,838	13,048	7.9%
	70–79	128,179	26,585	20.7%
	80–89	71,351	33,030	46.3%
Smoking	Non	386,591	31,404	8.0%
	Ex (unknown)	75,785	11,186	10.0%
	Ex (1–19 cigs/d)	54,344	6,572	10.7%
	Ex (20–39 cigs/d)	26,382	3,184	12.3%
	Ex (40+ cigs/d)	5,223	734	12.3%
	Current (unknown)	17,506	2,445	11.0%
	Current (1–19 cigs/d)	88,211	9,393	14.1%
	Current (20–39 cigs/d)	50,763	4,989	16.7%
	Current (40+ cigs/d)	4,552	602	19.7%
	Not recorded	126,250	12,594	10.0%
Body mass index	<20	33,078	4,189	14.5%
	≥20 and <25	269,925	23,218	9.2%
	≥25 and <30	243,289	23,950	9.1%
	≥30	108,966	11,636	11.4%
	Not recorded	180,349	20,110	10.9%
Practice region	North	319,455	33,633	10.7%
	South (excl. London)	424,165	41,477	9.5%
	London	91,987	7,993	9.5%
Income deprivation quintile†	1 (most deprived)	104,137	13,724	12.8%
	2	147,788	17,752	11.3%
	3	180,382	18,495	9.9%
	4	197,066	18,020	9.2%
	5 (least deprived)	206,234	15,112	8.2%
Employment deprivation quintile†	1 (most deprived)	114,006	15,711	12.8%
	2	149,663	17,264	10.9%
	3	170,764	17,156	9.8%
	4	190,694	17,295	9.2%
	5 (least deprived)	210,480	15,677	8.3%
Education deprivation quintile†	1 (most deprived)	120,795	15,959	12.8%
	2	158,955	17,761	10.9%
	3	168,465	16,504	9.7%
	4	178,578	16,279	9.3%
	5 (least deprived)	208,814	16,600	8.3%

* Percentages adjusted to age–sex structure of overall population.

† Census-based national rankings.

of subsequent death. These relationships were robust to adjustment for smoking and BMI, but attenuated when adjusting for small area SES markers. For cause-specific mortality, associations were larger for respiratory mortality and closer to unity for cardiovascular mortality. Associations with respiratory mortality were also found in nonsmokers and those without COPD or asthma at baseline.

Cohort studies of long-term exposure to air pollution and mortality are predominately based in the United States and have tended to focus on fine particulate matter (PM_{2.5}) (4, 6, 27–34). A 2010 review by the American Heart Association (2) reported HRs for PM_{2.5} and all-cause mortality ranging from 0.99–1.21 per 10 µg/m³, whereas a systematic review in 2008 calculated a pooled relative risk of 1.06 (1). Our estimate when scaled to a 10 µg/m³ increment, and adjusted for area income, produced an HR of 1.13 (95% CI, 1.00–1.27).

Previous cohort studies have tended to emphasize associations with cardiovascular disease, in part because respiratory deaths are far fewer (4, 12) and in part because cardiovascular

TABLE 3. HAZARD RATIOS FOR ALL-CAUSE MORTALITY IN 2003–2007 FOR AN INTERQUARTILE RANGE CHANGE IN 2002 POLLUTANT CONCENTRATIONS

Baseline Variables Adjusted For	PM ₁₀ (<i>n</i> = 830,842)		PM _{2.5} (<i>n</i> = 830,842)		SO ₂ (<i>n</i> = 823,442)		NO ₂ (<i>n</i> = 830,429)		O ₃ (<i>n</i> = 824,654)	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
+ age, sex	1.08	1.05–1.11	1.09	1.06–1.12	1.07	1.05–1.09	1.09	1.06–1.12	0.93	0.90–0.96
+ age, sex, smoking, BMI	1.06	1.04–1.09	1.07	1.05–1.10	1.06	1.04–1.08	1.07	1.04–1.11	0.94	0.91–0.96
+ age, sex, smoking, BMI, income*	1.02	1.00–1.04	1.02	1.00–1.05	1.04	1.03–1.05	1.03	1.00–1.05	0.93	0.90–0.96
+ age, sex, smoking, BMI, employment*	1.04	1.01–1.06	1.04	1.02–1.07	1.03	1.02–1.05	1.04	1.01–1.07	0.94	0.91–0.97
+ age, sex, smoking, BMI, education*	1.04	1.02–1.06	1.04	1.02–1.06	1.03	1.01–1.05	1.06	1.03–1.08	0.96	0.93–0.98
10 unit change (income model)	1.07	0.99–1.16	1.13	1.00–1.27	1.20	1.12–1.28	1.02	1.00–1.05	0.86	0.78–0.94

Definition of abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; NO₂ = nitrogen dioxide; O₃ = ozone; PM_{2.5} = particulate matter with a median aerodynamic diameter less than 2.5 µm; PM₁₀ = particulate matter with a median aerodynamic diameter less than 10 µm; SO₂ = sulfur dioxide.

Number of deaths for each pollutant analysis was as follows: PM₁₀/PM_{2.5} = 82,475; SO₂ = 81,636; NO₂ = 82,421; O₃ = 81,627. Interquartile ranges for each pollutant were as follows: PM₁₀ = 3.0 µg/m³; PM_{2.5} = 1.9 µg/m³; SO₂ = 2.2 µg/m³; NO₂ = 10.7 µg/m³; O₃ = 3.0 µg/m³.

*Census deprivation score.

risks were found to be greater than respiratory (7, 35). US cohort studies of cardiovascular deaths and PM_{2.5} have reported HRs (per 10 µg/m³) in the range 1.12 (35) to 1.76 (30). Our finding of 1.01 for PM_{2.5} (when adjusted for income) is considerably lower and is more in line with the two European studies (13, 15) listed in the American Heart Association review (2), which reported associations closer to 1.00. The only cardiovascular subgroup in our study to show evidence of an association with PM_{2.5} was heart failure deaths. This corresponds to our analysis of disease incidence based on the same cohort (23). We have no firm explanation for the weaker associations between PM_{2.5} and CHD in our study as compared with the ACS (8). Both studies used standard ICD coding of death certificates as the outcome but there remains the possibility of differences in the certification practice of clinicians. Other relevant differences to consider include time period; population characteristics (including the likely greater use of statins among our patients with CHD); pollution sources; and the spatial scale of the pollution model.

In contrast to the results for cardiovascular mortality, we observed larger and more robust associations with respiratory mortality. Cohort studies that investigated respiratory mortality,

summarized in Table 5, have generally reported HR or risk ratios in excess of one, although many have lacked statistical power. The California Teachers Study focused results on cardiovascular rather than respiratory mortality, despite comparable HRs (36). The largest US study (the ACS) initially reported an HR of 0.92 (35); however, a more recent analysis based on almost twice as many respiratory deaths reported an HR of 1.03 (37). Elsewhere, population studies in Norway (13), Japan (18), New Zealand (17), and China (38) have all reported statistically significant, positive associations with respiratory mortality. In the United Kingdom, a national ecologic study (39) reported larger effects of black smoke (a reflectance measure of black carbon particles <4 µm in diameter) on respiratory mortality (HR, 1.19) in the most recent exposure periods (1990–1994), whereas a Scottish study (40) also found larger relationships with respiratory mortality (HR, 1.26). Our scaled findings for PM₁₀ and PM_{2.5} (HR, 1.30 and 1.54, respectively, per 10 µg/m³) adjusted for area income deprivation exceed all but one (38) of the reported estimates in Table 5; however, we note the smaller mean and standard deviation of our modeled concentrations compared with other studies.

TABLE 4. HAZARD RATIOS FOR SPECIFIC CAUSES OF MORTALITY IN 2003–2007 FOR AN INTERQUARTILE RANGE CHANGE IN 2002 POLLUTANT CONCENTRATIONS

Cause of Death and Baseline Variables Adjusted For	PM ₁₀ (<i>n</i> = 830,842)		PM _{2.5} (<i>n</i> = 830,842)		SO ₂ (<i>n</i> = 823,442)		NO ₂ (<i>n</i> = 830,429)		O ₃ (<i>n</i> = 824,654)	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Circulatory*										
+ age, sex	1.06	1.03–1.09	1.07	1.03–1.10	1.07	1.05–1.09	1.07	1.03–1.10	0.94	0.91–0.97
+ age, sex, smoking, BMI	1.05	1.02–1.08	1.05	1.02–1.09	1.06	1.04–1.08	1.05	1.02–1.09	0.95	0.92–0.97
+ age, sex, smoking, BMI, income†	1.00	0.97–1.03	1.00	0.97–1.03	1.04	1.03–1.06	1.00	0.97–1.03	0.96	0.94–0.99
+ age, sex, smoking, BMI, education†	1.02	0.99–1.04	1.02	1.00–1.05	1.03	1.01–1.05	1.03	1.00–1.07	0.96	0.94–0.98
Respiratory*										
+ age, sex	1.19	1.14–1.24	1.20	1.15–1.25	1.13	1.09–1.17	1.22	1.16–1.27	0.89	0.85–0.94
+ age, sex, smoking, BMI	1.16	1.12–1.21	1.17	1.12–1.22	1.12	1.09–1.15	1.17	1.12–1.23	0.91	0.87–0.95
+ age, sex, smoking, BMI, income†	1.08	1.04–1.12	1.09	1.05–1.13	1.09	1.06–1.12	1.09	1.04–1.14	0.94	0.90–0.97
+ age, sex, smoking, BMI, education†	1.11	1.08–1.15	1.12	1.08–1.16	1.07	1.04–1.10	1.15	1.10–1.20	0.93	0.90–0.96
Lung cancer*										
+ age, sex	1.12	1.05–1.20	1.14	1.07–1.22	1.10	1.05–1.15	1.20	1.12–1.27	0.89	0.84–0.95
+ age, sex, smoking, BMI	1.07	1.02–1.13	1.08	1.03–1.14	1.07	1.03–1.11	1.13	1.07–1.19	0.92	0.88–0.97
+ age, sex, smoking, BMI, income†	1.01	0.96–1.06	1.02	0.97–1.07	1.05	1.01–1.08	1.06	1.00–1.12	0.94	0.90–0.99
+ age, sex, smoking, BMI, education†	1.03	0.98–1.08	1.04	0.99–1.09	1.03	0.99–1.06	1.11	1.05–1.17	0.94	0.90–0.98

Definition of abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; NO₂ = nitrogen dioxide; O₃ = ozone; PM_{2.5} = particulate matter with a median aerodynamic diameter less than 2.5 µm; PM₁₀ = particulate matter with a median aerodynamic diameter less than 10 µm; SO₂ = sulfur dioxide.

Interquartile ranges for each pollutant were as follows: PM₁₀ = 3.0 µg/m³; PM_{2.5} = 1.9 µg/m³; SO₂ = 2.2 µg/m³; NO₂ = 10.7 µg/m³; O₃ = 3.0 µg/m³.

*Number of deaths for each pollutant analysis was as follows. Circulatory: PM₁₀/PM_{2.5} = 28,743; SO₂ = 28,441; NO₂ = 28,726; O₃ = 28,427. Respiratory: PM₁₀/PM_{2.5} = 10,508; SO₂ = 10,408; NO₂ = 10,500; O₃ = 10,437. Lung cancer: PM₁₀/PM_{2.5} = 5,244; SO₂ = 5,192; NO₂ = 5,241; O₃ = 5,210.

†Census deprivation score. Results adjusting for employment were similar to those adjusting for education (data not shown).

TABLE 5. RESULTS FROM PUBLISHED COHORT STUDIES OF LONG-TERM EXPOSURE TO PARTICULATE MATTER AND RESPIRATORY MORTALITY

Study	Setting	N	Age (yr)	Definition of Respiratory Disease	No. of Respiratory Deaths	Exposure Years	Mean Exposure ($\mu\text{g}/\text{m}^3$) (SD)	Key Adjustments	HR per $10 \mu\text{g}/\text{m}^3$	95% CI per $10 \mu\text{g}/\text{m}^3$
PM₁₀										
Abbey <i>et al.</i> , 1999 (27)	California, United States	6,338 (nonsmokers)	27–95	ICD-9: 460–519	272	1973–1992	51.3 (16.6)	Past smoking, education, BMI, exercise	1.06	0.99–1.15
Naess <i>et al.</i> , 2007 (13)	Oslo, Norway	143,842	51–90	ICD-10: J40–J47	1,455	1992–1995	Range, 6.6–30.1	Occupation, education	1.06–1.28	n/a
Hales <i>et al.</i> , 2010 (17)	New Zealand	1,051,464	30–74	ICD-9: 162, 470–478, 490–519	3,213	1995–2001	8.3 (8.4)	Smoking, BMI, census SES	1.14	1.05–1.23
Lipsett <i>et al.</i> , 2011 (36)	California, United States	61,181 (female teachers)	20–80+	ICD-9: 460–519 & ICD-10: J00–J98	453	1996–2005	29.2 (9.7)	Smoking, BMI, exercise, census SES	1.08	0.98–1.19
Hart <i>et al.</i> , 2011 (34)	United States	53,814 (male truckers)	15–85	ICD-10: J10–18, J40–J98	317	1985–2000	26.8 (6.0)	Census region	1.04	0.85–1.27
Dong <i>et al.</i> , 2012 (38)	Shenyang, China	9,941	35–103	ICD-10: J00–J99	72	1998–2009	154 (41)	Smoking, education, income, BMI, exercise	1.67	1.60–1.74
Present study	United Kingdom	831,788	40–89	ICD-10: J00–J99	10,518	2002	19.8 (2.3)	Smoking, BMI, income	1.30	1.15–1.47
PM_{2.5}										
Naess <i>et al.</i> , 2007 (13)	Oslo, Norway	143,842	51–90	ICD-10: J40–J47 (COPD)	1,455	1992–1995	Range, 6.6–22.3	Occupation, education	1.07–1.41	n/a
Beelen <i>et al.</i> , 2008 (15)	Netherlands	117,528	58–67	ICD-10: J00–J99	904	1987–1996	28.3 (3.1)	Smoking, education, BMI, diet	1.07	0.75–1.52
Jerrett <i>et al.</i> , 2009 (37)	United States	448,850	30+	ICD-9: 460–519	9,891	1999–2000	13.8 (n/a)	Smoking, education, BMI, exercise	1.03	0.96–1.11
Katanoda <i>et al.</i> , 2011 (18)	Japan	63,520 (no baseline respiratory disease)	40–70+	ICD-9: 460–519	677	1974–1983	Area range, 16.8–41.9	Smoking, occupation	1.16	1.04–1.30
Lipsett <i>et al.</i> , 2011 (36)	California, United States	73,489 (female teachers)	20–80+	ICD-9: 460–519 and ICD-10: J00–J98	404	1996–2005	15.6 (4.5)	Smoking, BMI, exercise, census SES	1.21	0.97–1.52
Hart <i>et al.</i> , 2011 (34)	United States	53,814 (male truckers)	15–85	ICD-10: J10–18, J40–J98	317	1985–2000	26.8 (6.0)	Census region	1.18	0.91–1.54
Lepeule <i>et al.</i> , 2012 (9)	Six cities, United States	8,096	25–74	ICD-10: J40–J47 (COPD)	247	1974–2009	15.9 (n/a)	Smoking, education, BMI	1.17	0.85–1.62
Cesaroni <i>et al.</i> , 2013 (16)	Rome, Italy	1,265,058	30+	ICD-9: 460–519	8,825	2005	23.0 (4.4)	Education, occupation, census SES	1.03	0.97–1.08
Present study	United Kingdom	831,788	40–89	ICD-10: J00–J99	10,518	2002	12.9 (1.4)	Smoking, BMI, income	1.54	1.27–1.86
Black smoke										
Elliot <i>et al.</i> , 2007 (39)	United Kingdom	662,343	30+	ICD-9: 460–519	8,471	1990–1994	13.3 (5.3)	Area SES	1.19 [†]	1.05–1.36
Beelen <i>et al.</i> , 2008 (15)	Netherlands	117,528	58–67	ICD-10: J00–J99	904	1987–1996	13.9 (2.2)	Smoking, education, BMI, diet	1.22	0.99–1.50
Yap <i>et al.</i> , 2012 (40)	Scotland*	15,188/6,299	45–64/35–64	ICD-9: 480–487, 490–496, 786.0, 786.2	606/174	1970–1979	19.3 (3.9)/23.2 (7.5)	Smoking, BMI, social class, blood pressure	1.26/0.97	1.02–1.55/0.79–1.18
Total suspended particles										
Cao <i>et al.</i> , 2011 (19)	China	70,947	40+	ICD-9: “Respiratory”	921	1991–2000	289	Smoking, education, BMI, exercise	1.00	0.99–1.03

Definition of abbreviations: BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; ICD = International Classification of Diseases; PM_{2.5} = particulate matter with a median aerodynamic diameter less than 2.5 μm ; PM₁₀ = particulate matter with a median aerodynamic diameter less than 10 μm ; SES = socioeconomic status.

Where a study has produced multiple estimates over time (e.g. American Cancer Society), we have only included the most recent estimate.

* Study included two separate cohorts, so both sets of results are included.

[†] This was not a cohort study, and so relative risk is given.

Our associations with respiratory mortality were similar if we further subcategorized into COPD and pneumonia, each representing about 40% of all respiratory deaths. A Norwegian study (13) found positive associations for PM_{2.5} and PM₁₀ across different age and sex groups for COPD death (Table 5), whereas the ACS (35) and a Japanese study (18) reported positive associations with pneumonia but not COPD. Our associations with respiratory mortality were found in patients classed as nonsmokers, and those without COPD or asthma at the study outset. Other studies have reported little variation of their association with respiratory mortality across their smoking groups (27, 36, 38), or have lacked power to test this (35). A Japanese study (18) demonstrated an effect of PM_{2.5} on respiratory mortality in female never-smokers (HR, 1.29). Only a Dutch study (15) reported stronger relationships for respiratory mortality and pollution exposure (in this case black smoke) in current smokers.

The evidence from cohort studies for an association between SO₂ and mortality is mixed (1). In the ACS reanalysis (8), SO₂ was associated with all-cause, cardiopulmonary, and ischemic heart disease mortality, and coefficients for fine particles and mortality were markedly reduced when SO₂ was included as a covariate (5). Our robust findings resonate with a UK study that found long-term associations between SO₂ and mortality (39), and found larger effects with respiratory deaths. Recent cohort studies from Japan (18) and China (19) have also reported associations with respiratory mortality, contrasting with earlier studies that found little evidence (15, 27). The causal nature of associations between SO₂ and mortality have been questioned in part because of the correlation between sulfur dioxide and particles and the lack of persuasive hypotheses linking exposure to low concentrations of sulfur dioxide and death (41).

NO₂ has been associated with increased all-cause mortality in some (11, 12, 15, 34, 38) but not all cohort studies (8, 36). Some studies have reported greater effects for respiratory deaths alone (15, 18, 34, 38). A large Dutch cohort found moderate associations with all-cause mortality (HR, 1.03 scaled to a 10 µg/m³ change), and larger associations with respiratory mortality (HR, 1.12) (15), which compares closely with 3% and 9% increases in our adjusted HRs for a similar incremental change. Similarly to the Dutch study (15), we also found no associations with cardiovascular mortality, unlike US studies, which reported positive associations for CHD (8, 34, 36), or a small German study that found elevated effects for cardiopulmonary, of which over 90% were cardiovascular deaths (12).

Evidence for long-term health effects of exposure to ozone has come exclusively from US cohorts (8, 27, 29, 36, 37, 42); however, the picture has not been consistent. A study of nonsmokers found raised HR between mean monthly O₃ concentrations and respiratory mortality but lacked precision (27). Extensive analyses of the ACS suggested small, long-term associations with mortality for summer, but not annual, ozone concentrations (8). A further analysis involving two-pollutant models including particles (PM_{2.5}) suggested associations with summer ozone persisted only for respiratory mortality (37), whereas another found relationships with cardiopulmonary mortality alone (42). Our data found negative associations with mortality irrespective of cause, which may be partly explained by negative correlations between ozone and the other pollutants; however, they were not completely explained away in two pollutant models. Because there was little variation within our practice clusters, the modeled O₃ concentrations may be largely representing regional levels, where ozone was higher in southern England, where mortality is lower. Because ozone is a highly seasonal pollutant and its production depends on the presence of precursors and sunlight, a metric based on summer ozone concentrations might have been more discriminatory and informative (8).

In our study, air pollution concentrations were derived from emission-based dispersion models, which potentially improve on other methods, such as geostatistical interpolation and land use regression (43) but depend on the quality of data used. A comparison of modeling methods using a large Dutch cohort concluded that dispersion models performed favorably compared with land use regression (44). We have previously applied these models in cross-sectional analyses of national English health survey data (45) and they have been used extensively by the UK Government for reporting to the European Commission (25) and for policy purposes including burden estimation (26).

We have previously discussed the performance and validation of these models (23), and provide further details in the online supplement. Briefly, external validation of the model with monitoring sites in 2002 suggested better modeling of NO₂ compared with PM₁₀ and SO₂. Because of a limited number of monitoring sites, model validation statistics for PM_{2.5} were not available until 2009; however, the modeling for PM₁₀ and PM_{2.5} uses the same general methodology and model performance was similar between the two. The better relative performance of NO₂ is perhaps not surprising, because of the complexity of the PM mixture for which the sources are not well characterized. Although this suggests greater confidence in results for NO₂, we have emphasized our results with PM_{2.5} because it is the most important regulated pollutant, is regarded as more likely to be causal, and is commonly used for health impact assessments. The R² reported for NO₂ and PM₁₀ were comparable with those found in a study using land use regression models to estimate concentrations in the United Kingdom in 2001 (46).

Misclassification is also likely to have resulted from assigning pollution estimates at a 1 km² resolution. Although misclassification of exposure will likely bias effect estimates toward the

null (47), and may explain the lack of associations found with cardiovascular mortality, it seems unlikely to explain why stronger associations were found with respiratory mortality. The exposure estimates used for existing cohort studies vary from those that are at a larger community level spatial scale (4, 6, 48) to those where the estimate is at the residential address (13, 16). Our study therefore lies somewhere between the two, and it is possible that this may explain some of the differences between our results and those of other cohorts.

One of the strengths of our study was that it incorporated data from the clinical record, and linked in deaths from a national data collection system. Although we adjusted for individual confounders, such as smoking, misclassification may have arisen, either because of missing values or because of patients being incorrectly classed as nonsmokers on their medical record. Even if recorded correctly, our variable fails to quantify the lifetime burden of current or ex-smokers. Although this limits the precision of our smoking adjustment, it seems unlikely to completely explain away associations seen in nonsmokers.

Although we were unable to adjust for individual socioeconomic markers, neighborhood indicators of socioeconomic deprivation have been shown to be acceptable proxies (49). In our models, this adjustment attenuated all air pollution associations especially with cardiovascular mortality. Because the SES indices may be measured on a smaller geographic scale than our modeled pollution in urban areas, they could be representing concentration gradients not captured by the pollution models. However, given the modest correlations that exist nationally between SES and pollution concentrations, it seems unlikely that the SES indices are over adjusting and erroneously explaining all of the associations observed. Indeed, even if this was not the case for associations with cardiovascular mortality, it cannot explain the stronger associations we found with respiratory mortality before and after SES adjustment. Although we found patients in more socially deprived areas have higher pollution concentrations (except ozone), this contrasted with the ACS (8) where similar census variables were not strongly related, and subsequently had little impact on their effect estimates. In a national Canadian cohort (48), higher concentrations were found in more affluent areas, and HRs associated with exposure to PM_{2.5} increased after socioeconomic adjustment.

The potential limitations of using cause of death coding from death certificates to classify respiratory deaths has been identified by others (35). For example, a patient with their cause of death listed as pneumonia might have warranted a more appropriate underlying cause of death from long-term chronic conditions, such as CHD, stroke, or COPD (50). A recent report estimated that among all deaths in England and Wales, respiratory deaths are overrecorded by 7%, whereas circulatory deaths are underrecorded by 6% (51). However, for such misclassification to explain a spurious relationship with respiratory deaths and the absence of one with cardiovascular deaths, it requires that virtually all the excess deaths caused by air pollution were those being misclassified, and at a greater rate than the report suggested. Such a scenario seems unlikely. However, to account for potential misclassification we performed sensitivity analyses, which included any mention of circulatory death on the certificate, and restricted respiratory deaths to those with no mention of cardiovascular disease. These showed similar patterns to the underlying cause analyses, suggesting misclassification was unlikely to explain stronger associations with respiratory death. We also noted that associations with respiratory deaths remained when analyses were restricted to younger patients, who will have less comorbidity, and thus the issue of miscoding on their death certificate may be less relevant.

Because of the anonymous nature of the data, we were unable to investigate spatial autocorrelation beyond adjusting for clustering by practice. Patients from the same practice are likely to be

more similar to each other than patients from different practices, and this has implications for the precision of our estimates. We chose to conservatively account for this by using the modified sandwich estimate of variance to produce standard errors, which are robust to within practice correlation. As a sensitivity analysis we considered shared frailty models, which fit a random effect to explicitly model this correlation, and found an attenuation of all estimates. A similar attenuation was seen with other modeling approaches that estimated the within cluster effect by accounting for the mean practice concentration level or stratifying the model by practice (data not shown). The implication may be that differences in overall practice area concentrations are driving many of the associations, which is not surprising because this is where most of the variation in the pollution model arises. Although we advise caution when extrapolating our estimates to population impact calculations, we note that our associations with respiratory mortality remained whatever the approach.

This population-based, nationally representative English cohort extends the body of evidence linking air pollution to all-cause mortality but contrary to a number of studies from the United States and elsewhere found that the effects on respiratory mortality were greater than on cardiovascular mortality. When the evidence from existing published cohorts is considered as a whole it seems that there is important heterogeneity in the results for cause-specific mortality. The reasons may lie in differences in various aspects of the methods of investigation, population susceptibility, or toxicity of the air pollution mixture but remain to be elucidated.

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