Atkinson, RW; Carey, IM; Kent, AJ; van Staa, TP; Anderson, HR; Cook, DG (2014) Long-term exposure to outdoor air pollution and the incidence of chronic obstructive pulmonary disease in a national English cohort. Occupational and environmental medicine. ISSN 1351-0711 DOI: https://doi.org/10.1136/oemed-2014-102266

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Long-term exposure to outdoor air pollution and the incidence of chronic obstructive pulmonary disease in a national English cohort

R W Atkinson,1 I M Carey,1 A J Kent,2 T P van Staa,3,4 H R Anderson,1,5 D G Cook1

ABSTRACT

Objectives The role of outdoor air pollution in the incidence of chronic obstructive pulmonary disease (COPD) remains unclear. We investigated this question using a large, nationally representative cohort based on primary care records linked to hospital admissions.

Methods A cohort of 812 063 patients aged 40–89 years registered with 205 English general practices in 2002 without a COPD diagnosis was followed from 2003 to 2007. First COPD diagnoses recorded either by a general practitioner (GP) or on admission to hospital were identified. Annual average concentrations in 2002 for particulate matter with an aerodynamic diameter <10 μm (PM10) and <2.5 μm (PM2.5), nitrogen dioxide (NO2), ozone and sulfur dioxide (SO2) at 1 km2 resolution were estimated from emission-based dispersion models. Hazard ratios (HRs) for interquartile range change were estimated from Cox models adjusting for age, sex, smoking, body mass index and area-level deprivation.

Results 16 034 participants (1.92%) received a COPD diagnosis from their GP and 2910 participants (0.35%) were admitted to hospital for COPD. After adjustment, HRs for GP recorded COPD and PM10, PM2.5 and NO2 were close to unity, positive for SO2 (HR=1.07 (95% CI 1.03 to 1.11) per 2.2 μg/m3) and negative for ozone (HR=0.94 (0.89 to 1.00) per 3 μg/m3). For admissions HRs for PM2.5 and NO2 remained positive (HRs=1.05 (0.98 to 1.13) and 1.06 (0.98 to 1.15) per 1.9 μg/m3 and 10.7 μg/m3, respectively).

Conclusions This large population-based cohort study found limited, inconclusive evidence for associations between air pollution and COPD incidence. Further work, utilising improved estimates of air pollution exposure for cohort participants, longer follow-up times and more precise disease definition, is required to clarify the role of air pollution in the initiation of COPD.

INTRODUCTION

Cohort studies have demonstrated associations between long-term exposure to outdoor air pollution and adverse health effects.1 Such studies, exemplified by the American Cancer Society cohort,2,3 have tended to focus on death as the health outcome with particular emphasis on fine particles and cardiovascular disease.4 Cohort studies of respiratory mortality have also tended to report positive associations but individually have lacked statistical power.5 Few studies have focused on chronic obstructive pulmonary disease (COPD).6 A recent report on the global impact of PM2.5 (mass of particulates with aerodynamic diameter <2.5 μm) on COPD was reliant on only three studies, all from the USA and all using mortality as the outcome.7

The possibility that air pollution is a risk factor for the initiation of COPD is important given the ubiquitous nature of the exposure and the substantial burden of COPD on individuals and healthcare services, further work, utilising improved estimates of air pollution exposure for cohort participants, longer follow-up times and more precise disease definition, is required to clarify the role of air pollution in the initiation of COPD.

What this paper adds

- Outdoor air pollution is a potential risk factor for the development of chronic obstructive pulmonary disease (COPD).
- Using a large, nationally representative cohort of patients registered with 205 English general practitioners (GP), we investigated the evidence linking exposure to particulate matter and gaseous pollutants to the first diagnosis of COPD recorded either by a GP or on admission to hospital.
- We found limited evidence for associations, although these were comparable with existing cohort evidence based on smaller and less nationally representative populations elsewhere. However, given the ubiquitous nature of the exposure and the substantial burden of COPD on individuals and healthcare services, further work, utilising improved estimates of air pollution exposure for cohort participants, longer follow-up times and more precise disease definition, is required to clarify the role of air pollution in the initiation of COPD.
METHODS
The Clinical Practice Research Datalink (CPRD) is a large, validated primary care database that has been collecting anonymous patient data from participating UK general practices since 1987. It includes a full longitudinal medical record for each registered patient containing coded information on diagnoses, prescriptions and tests carried out within the practice. The Hospital Episode Statistics (HES) database routinely records clinical, patient, administrative and geographical information on all National Health Service (NHS)-funded inpatient episodes in the UK. Subject to the practice’s approval, the CPRD patient data are routinely linked to HES by a ‘trusted third party’ via their NHS number, sex, date of birth and postcode and to the Index of Multiple Deprivation (IMD), a small area measure of deprivation used in England for allocation of resources.

We identified 205 English practices, recording high-quality data according to CPRD internal standards (eg, non-contiguous follow-up, incomplete data recording), which had been linked to HES data. From these, we identified 836 557 subjects aged 40–89 years fully registered for at least 1 year on 1/1/2003. Subjects with COPD Read codes on their GP record prior to 2003 (n=24 494) were excluded leaving 812 063 for analysis.

First diagnoses of COPD between 2003 and 2007 were identified from: (1) GP records by Read codes indicating a diagnosis of COPD and (2) hospital admissions records by International Classification of Disease codes (ICD-10 Version:2010) (J41–44) indicating a primary diagnosis of COPD. As a sensitivity analysis, we extended the exclusion criteria to include other markers of chronic respiratory disease recorded by the GP including asthma and regular inhaler prescribing (all Read codes available from authors on request). Figure 1 illustrates the cohort selection and exclusions.

Annual mean concentrations in 2002 of particles with a median aerodynamic diameter of <10 μm (PM<10), <2.5 μm (PM2.5), sulfur dioxide (SO2), nitrogen dioxide (NO2) and ozone (O3) for 1 km grid squares covering England were linked anonymously by the ‘trusted third party’ from a grid centroid to the nearest residential postcode centroid for each patient. Details of the dispersion models and the model validation including other years are provided in the online supplementary material. Briefly, the models for PM10, PM2.5, NO2 and SO2 were constructed by estimating emissions from a number of sources (eg, road transport or power generation) before calculating pollution concentrations using a dispersion model. O3 maps were constructed by interpolating data from rural monitoring stations and adjusting for effects of altitude and NOx emissions in urban areas.

Model validation was assessed using data from monitoring sites in the national network and from verification sites operated by NETCEN (part of AEA Technology Environment) in conjunction with local authorities and not part of the national network. Model validation was good for NO2 (R²=0.80 using the national network and 0.57 using verification sites), good for O3 (R²=0.48 and 0.71), moderate for PM10 (R²=0.29 and 0.46) and PM2.5 (R²=0.23 and 0.71), but poor for SO2 (R²=0 and 0.39).

Potential confounders extracted from the GP records included age, sex, smoking status (characterised as non/ex/current, with further categories of 1–19/20–39/40+ cigarettes per day) and body mass index (BMI) (<20, ≥20 and <25, ≥25 and <30, ≥30). The last recorded status before 1/1/2003 was used to code the variables, except for non-smokers, who were reclassified as ex-smokers if they had older historical codes indicating smoking. The amount of current smoking or ex-smoking was estimated by using the maximum cigarettes per day value and grouped accordingly. A ‘missing’ category was assigned for participants with no recorded smoking status prior to 2003. Individual measures of socioeconomic status (SES) were not available to us and we therefore assessed SES using 2007 IMD deciles, which are available for a small area comprising approximately 1500 people, modified to remove the air quality subdomain. Incidence rates of COPD, calculated from GP and hospital records separately, were compared across all confounders adjusted for age and sex (Stata V.12; StataCorp LP, College Station, Texas, USA).

We used Cox proportional hazards models (SAS V.9.1.3; SAS Institute, Inc, Cary, North Carolina, USA) to investigate associations between pollution concentrations in 2002 and incidence of COPD during 2003–2007. We adjusted cumulatively for (1) age and sex; (2) smoking and BMI and (3) IMD. In a sensitivity analysis, we assessed the impact on hazard ratios (HRs) after adjustment, in turn, for selected individual components of deprivation (income, employment and education). To account for clustering by practice, the modified sandwich estimate of variance was used to produce robust SEs. We further assessed the effect of clustering by fitting a random effect for practice using a shared frailty model in Stata. Two-pollutant models were considered only when the correlation coefficient between pollutants was below 0.5. We also carried out stratified analyses to assess effect modification by the covariates. To allow comparison across pollutants, HRs were quantified for an interquartile range (IQR) change in each pollutant. We also present the main estimates per 10 μg/m³ to enable comparison with results of other studies.

RESULTS
Postcode linkage to all pollutants was successful in 99% of patients (table 1). IQR values were lowest for PM2.5 (1.9 μg/m³) and highest for NO2 (10.7 μg/m³). There was significant variation in modelled pollution concentrations by practice region and IMD (p<0.001). The highest concentrations of particles and NO2 were observed in London, whereas the highest concentrations of SO2 and O3 occurred in the north and south, respectively. Areas with a lower SES were associated with higher concentrations for all pollutants except O3. Annual concentrations of PM10 and PM2.5 were strongly correlated with NO2 (r=0.8), moderately correlated with SO2 (r=0.5) and negatively correlated with O3 (r=−0.4).

Figure 1  Cohort and case identification.
Of the 812 063 cohort participants, 16 034 (1.92%) received a COPD diagnosis on their GP record and 2910 (0.35%) were admitted to hospital for COPD during the follow-up period 2003–2007 (figure 1). Of the 2910 patients admitted to hospital with a diagnosis of COPD, 1860 (64%) received a diagnosis of COPD on their GP record by the end of 2007. Extending the exclusion criteria for GP diagnosed COPD to patients with other previously recorded chronic respiratory diseases, such as asthma, reduced the cohort to 694 189 patients, with 8893 (1.28%) patients subsequently receiving an incident diagnosis of COPD. Table 2 shows the incidence of GP and HES recorded COPD stratified by sex, age, smoking status, BMI, practice region and IMD. Incidence of GP diagnosed COPD was higher in men than in women (2.2% vs 1.8%), but the sex ratio was similar for hospital admissions. Incident cases of COPD increased with age, with only a small reduction in the oldest group (80–89 years) for GP diagnosed COPD. Increasing smoking intensity at baseline, both current and historical, strongly predicted COPD incidence. There was also a strong gradient with IMD, both for GP recorded COPD and for hospital recorded COPD when adjusted for age and sex alone. Adjustment for smoking and BMI attenuated all associations, with further adjustment for IMD reducing nearly all associations to the null. The main exception was for SO2 where a 2.2 μg/m3 increment was associated with an HR=1.07 (95% CI: 1.03 to 1.11). Alternative adjustments for IMD based on individual components (income, education and employment) produced similar reductions in HRs (data not shown). Extending the exclusion criteria to also exclude patients with other previously recorded respiratory disease such as asthma strengthened associations for PM10 and PM2.5; however, CIs still included unity. In two-pollutant models, the SO2 association remained robust to adjustment for other pollutants (see online supplementary material table S3). Finally, alternative frailty models using a random effect to account for practice clustering did not materially alter our conclusions (data not shown).

Analyses using incident based on an admission to hospital for COPD generally produced associations with air pollution greater in magnitude than those seen with GP diagnosis alone (table 3). Again, adjustment for covariates and IMD in particular markedly reduced associations, with all 95% CIs including unity. For example, IQR increments in PM2.5 (1.9 μg/m³), SO2 (2.2 μg/m³) and NO2 (10.7 μg/m³) were associated with HRs of.

### Table 1 Summary of assigned pollutant concentrations in 2002 for participants with no diagnosis of COPD by end of 2002 (n=812 063)

<table>
<thead>
<tr>
<th>Modified IMD quintile means (SD)</th>
<th>PM10 (μg/m³)</th>
<th>PM2.5 (μg/m³)</th>
<th>SO2 (μg/m3)</th>
<th>NO2 (μg/m³)</th>
<th>O3 (μg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Most deprived) 21.0 (2.2)</td>
<td>13.7 (1.5)</td>
<td>4.7 (2.2)</td>
<td>26.9 (6.3)</td>
<td>50.9 (2.1)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21.1 (2.6)</td>
<td>13.8 (1.7)</td>
<td>4.2 (2.3)</td>
<td>26.5 (7.9)</td>
<td>51.3 (2.2)</td>
</tr>
<tr>
<td>3</td>
<td>20.4 (2.6)</td>
<td>13.3 (1.7)</td>
<td>4.5 (2.5)</td>
<td>24.2 (8.1)</td>
<td>51.2 (2.2)</td>
</tr>
<tr>
<td>4</td>
<td>20.0 (2.3)</td>
<td>13.1 (1.5)</td>
<td>4.4 (2.5)</td>
<td>23.2 (7.5)</td>
<td>51.3 (2.2)</td>
</tr>
<tr>
<td>5</td>
<td>19.5 (2.6)</td>
<td>12.7 (1.6)</td>
<td>3.9 (2.4)</td>
<td>21.6 (8.2)</td>
<td>51.2 (2.6)</td>
</tr>
<tr>
<td>6</td>
<td>19.3 (2.4)</td>
<td>12.6 (1.5)</td>
<td>3.7 (1.9)</td>
<td>21.1 (7.6)</td>
<td>51.6 (2.6)</td>
</tr>
<tr>
<td>7</td>
<td>19.3 (2.3)</td>
<td>12.6 (1.4)</td>
<td>3.9 (2.1)</td>
<td>21.3 (7.5)</td>
<td>51.6 (2.6)</td>
</tr>
<tr>
<td>8</td>
<td>19.3 (2.0)</td>
<td>12.6 (1.3)</td>
<td>3.6 (1.8)</td>
<td>20.9 (6.7)</td>
<td>51.8 (2.4)</td>
</tr>
<tr>
<td>9</td>
<td>19.4 (1.9)</td>
<td>12.6 (1.2)</td>
<td>3.6 (1.7)</td>
<td>21.8 (6.6)</td>
<td>51.9 (2.3)</td>
</tr>
<tr>
<td>10 (Least deprived) 19.6 (1.5)</td>
<td>12.8 (0.9)</td>
<td>3.6 (1.3)</td>
<td>22.1 (5.6)</td>
<td>52.2 (1.9)</td>
<td></td>
</tr>
</tbody>
</table>

*p* Spearman’s rank correlation coefficient.

COPD, chronic obstructive pulmonary disease; IMD, Index of Multiple Deprivation; IQR, interquartile range.
1.05 (95% CI 0.98 to 1.13), 1.01 (95% CI 0.97 to 1.07) and 1.06 (95% CI 0.98 to 1.15), respectively. The HR for ozone was 0.96 (95% CI 0.90 to 1.02). Restricting the analysis to admissions in participants with COPD confirmed by their GP did not materially alter our findings.

We stratified the adjusted HRs in table 3 by IMD deciles (figure 2). For PM$_{2.5}$ and NO$_2$, there was no consistent evidence of a positive association across different deprivation groups using either GP diagnoses or hospital admission as the outcome. For SO$_2$, the association consistently produced an HR > 1 for GP diagnoses, but was less uniform for hospital admissions. The reverse was true for O$_3$ where the HR was generally < 1 across the IMD deciles. Stratifying the analyses by other covariates such as age and smoking did not reveal any other patterns (data not shown).

**DISCUSSION**

In this cohort study of general practice patients, we investigated the relationship between estimates of long-term exposure to outdoor air pollution and the incidence of COPD recorded by GPs and by admission to hospital. While all pollutants except ozone were positively associated with increased risk for incident GP recorded COPD, adjustment for smoking, BMI and IMD in particular reduced associations towards the null except for SO$_2$. Associations with COPD hospital admissions were larger and remained positive for PM$_{2.5}$, PM$_{10}$ and NO$_2$ and negative for O$_3$ after full adjustment, although all CIs included unity. Sensitivity analyses based on excluding asthmatic patients from the analysis, or only counting hospital admissions with a diagnosis confirmed on the GP record, did not alter our findings materially.

Early longitudinal studies of air pollution and the development of COPD used respiratory symptoms to identify participants with COPD while others used forced lung function measurements, such as forced expiratory volume in the first second (FEV$_1$)/forced vital capacity (FVC) ratio or the GOLD criterion. A very recent reanalysis and meta-analysis of four European cohorts (in total 6550 participants and including a UK cohort) used FEV$_1$/FVC and the GOLD criterion to define

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>Level</th>
<th>All eligible patients</th>
<th>COPD incidence (GP diagnosed)</th>
<th>COPD incidence (hospital admission)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Incidence (%)</td>
<td>Age–sex adjusted (%)</td>
<td>n</td>
</tr>
<tr>
<td>All</td>
<td>–</td>
<td>812 063</td>
<td>16 034 1.92</td>
<td>2910 0.35</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>392 574</td>
<td>8382 2.18</td>
<td>1435 0.38</td>
</tr>
<tr>
<td>Female</td>
<td>419 489</td>
<td>7652 1.84</td>
<td></td>
<td>1475 0.36</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40–49</td>
<td>241 580</td>
<td>1144 0.47</td>
<td>157 0.07</td>
</tr>
<tr>
<td></td>
<td>50–59</td>
<td>224 817</td>
<td>3472 1.55</td>
<td>400 0.18</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>159 628</td>
<td>4846 3.04</td>
<td>728 0.46</td>
</tr>
<tr>
<td></td>
<td>70–79</td>
<td>119 832</td>
<td>4728 3.95</td>
<td>965 0.81</td>
</tr>
<tr>
<td></td>
<td>80–89</td>
<td>66 206</td>
<td>1844 2.80</td>
<td>660 1.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>Non</td>
<td>381 579</td>
<td>2781 0.75</td>
<td>450 0.12</td>
</tr>
<tr>
<td></td>
<td>Ex (unknown)</td>
<td>72 646</td>
<td>1390 1.43</td>
<td>265 0.26</td>
</tr>
<tr>
<td></td>
<td>Ex (1–19 cigarettes/day)</td>
<td>50 670</td>
<td>1906 3.39</td>
<td>334 0.60</td>
</tr>
<tr>
<td></td>
<td>Ex (20–39 cigarettes/day)</td>
<td>23 896</td>
<td>1389 5.63</td>
<td>204 0.90</td>
</tr>
<tr>
<td></td>
<td>Ex (40+ cigarettes/day)</td>
<td>4616</td>
<td>330 6.32</td>
<td>48 0.82</td>
</tr>
<tr>
<td></td>
<td>Current (unknown)</td>
<td>17 048</td>
<td>268 1.28</td>
<td>60 0.26</td>
</tr>
<tr>
<td></td>
<td>Current (1–19 cigarettes/day)</td>
<td>84 386</td>
<td>3449 4.87</td>
<td>685 1.10</td>
</tr>
<tr>
<td></td>
<td>Current (20–39 cigarettes/day)</td>
<td>48 246</td>
<td>2572 7.07</td>
<td>471 1.69</td>
</tr>
<tr>
<td></td>
<td>Current (40+ cigarettes/day)</td>
<td>42 46</td>
<td>361 9.20</td>
<td>63 1.73</td>
</tr>
<tr>
<td></td>
<td>Not recorded</td>
<td>124 730</td>
<td>1588 1.27</td>
<td>330 0.29</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>&lt;20</td>
<td>31 134</td>
<td>935 4.04</td>
<td>232 0.99</td>
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<tr>
<td></td>
<td>≥20 and &lt;25</td>
<td>262 208</td>
<td>5263 2.16</td>
<td>830 0.35</td>
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<tr>
<td></td>
<td>≥25 and &lt;30</td>
<td>236 394</td>
<td>4715 1.85</td>
<td>783 0.31</td>
</tr>
<tr>
<td></td>
<td>≥30</td>
<td>105 469</td>
<td>2373 2.23</td>
<td>475 0.46</td>
</tr>
<tr>
<td></td>
<td>Not recorded</td>
<td>176 858</td>
<td>2748 1.72</td>
<td>590 0.36</td>
</tr>
<tr>
<td>Practice Region</td>
<td>North</td>
<td>307 826</td>
<td>7270 2.39</td>
<td>1305 0.44</td>
</tr>
<tr>
<td></td>
<td>South (excluding London)</td>
<td>414 539</td>
<td>7259 1.76</td>
<td>1313 0.32</td>
</tr>
<tr>
<td></td>
<td>London</td>
<td>89 698</td>
<td>1505 1.86</td>
<td>292 0.37</td>
</tr>
<tr>
<td>IMD Decile</td>
<td>1 (most deprived)</td>
<td>44 037</td>
<td>1785 4.18</td>
<td>380 0.88</td>
</tr>
<tr>
<td></td>
<td>=2</td>
<td>53 439</td>
<td>1640 3.19</td>
<td>323 0.62</td>
</tr>
<tr>
<td></td>
<td>=3</td>
<td>67 133</td>
<td>1906 2.89</td>
<td>371 0.56</td>
</tr>
<tr>
<td></td>
<td>=4</td>
<td>74 147</td>
<td>1726 2.36</td>
<td>354 0.48</td>
</tr>
<tr>
<td></td>
<td>=5</td>
<td>79 579</td>
<td>1586 1.97</td>
<td>287 0.35</td>
</tr>
<tr>
<td></td>
<td>=6</td>
<td>87 057</td>
<td>1648 1.92</td>
<td>293 0.35</td>
</tr>
<tr>
<td></td>
<td>=7</td>
<td>92 102</td>
<td>1517 1.65</td>
<td>289 0.32</td>
</tr>
<tr>
<td></td>
<td>=8</td>
<td>111 891</td>
<td>1737 1.57</td>
<td>251 0.23</td>
</tr>
<tr>
<td></td>
<td>=9</td>
<td>94 877</td>
<td>1361 1.48</td>
<td>195 0.22</td>
</tr>
<tr>
<td></td>
<td>=10 (least deprived)</td>
<td>106 870</td>
<td>1113 1.13</td>
<td>167 0.18</td>
</tr>
</tbody>
</table>

BMI, body mass index; COPD, chronic obstructive pulmonary disease; GP, general practitioner; IMD, Index of Multiple Deprivation.
COPD and found positive, but not statistically significant, associations with NO2 and PM10. Epidemiological studies designed to identify the small associations between air pollution and health outcomes require disease recording in large populations, which precludes the use of individual lung function measurements. Only a small number of studies have used routine administrative databases such as hospital admissions records to identify COPD cases. Andersen et al\(^\text{10}\) studied 57 000 participants in a Danish cohort recording their first admission to hospital for COPD between 1993 and 2006. COPD incidence was associated with 35-year estimated residential mean NO2 concentrations (HR=1.08; 95% CI, 1.02 to 1.14, per IQR of 5.8 mg/m\(^3\))—an association larger for the same increment in our study (HR=1.03). Gan et al\(^\text{11}\) also studied hospitalisations for COPD in a cohort of almost 500 000 residents in metropolitan Vancouver aged 45–85 years and without a previous physician diagnosis of COPD at baseline. Residential exposures to NO2 estimated from land use regression models were not associated with COPD.

### Table 3: Hazard ratios for the incidence of COPD for an interquartile change in each pollutant

<table>
<thead>
<tr>
<th>Adjustment factors</th>
<th>PM(_{10}) (n=807 401)</th>
<th>PM(_{2.5}) (n=807 401)</th>
<th>SO(_2) (n=800 360)</th>
<th>NO(_2) (n=807 000)</th>
<th>O(_3) (n=801 380)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>1.10</td>
<td>1.06</td>
<td>0.99</td>
<td>1.09</td>
<td>0.88</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.02 to 1.19</td>
<td>1.07 to 1.15</td>
<td>1.00 to 1.05</td>
<td>1.09 to 1.19</td>
<td>0.82 to 0.94</td>
</tr>
<tr>
<td>Age and sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+Smoking and BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+IMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full model (10 unit increase)</td>
<td>0.97</td>
<td>0.97</td>
<td>0.97</td>
<td>0.97</td>
<td>0.82</td>
</tr>
</tbody>
</table>

| HR                 | 1.04                     | 1.03                     | 1.03                 | 1.03                 | 1.06                 |
| 95% CI             | 0.96 to 1.13             | 1.03 to 1.13             | 1.06 to 1.12         | 1.06 to 1.12         | 0.90 to 1.02         |
| Outcome=First diagnosis of COPD on GP record in 2003–2007, Exclusions=Any COPD recorded on GP record prior to 2003 |

| Age and sex        |                          |                          |                      |                      |                      |
| +Smoking and BMI   |                          |                          |                      |                      |                      |
| +IMD               |                          |                          |                      |                      |                      |
| Full model (10 unit increase) | 1.17 | 1.17 | 1.17 | 1.17 | 0.87 |

| Outcome=First Hospital Admission for COPD in 2003–2007, Exclusions=Any COPD recorded on GP record prior to 2003 |

| HR                 | 1.01                     | 1.05                     | 0.96                 | 1.04                 | 0.94                 |
| 95% CI             | 0.94 to 1.09             | 1.05 to 1.12             | 1.05 to 1.14         | 1.04 to 1.15         | 0.87 to 1.00         |
| +IMD               |                          |                          |                      |                      |                      |
| Full model (10 unit increase) | 1.05 | 1.05 | 1.05 | 1.05 | 0.90 |

| Outcome=First Hospital Admission for COPD in 2003–2007 with additional GP diagnosis, Exclusions=Any COPD recorded on GP record prior to 2003 |

| HR                 | 1.05                     | 1.05                     | 0.96                 | 1.04                 | 0.90                 |
| 95% CI             | 0.96 to 1.14             | 1.05 to 1.14             | 1.04 to 1.15         | 1.04 to 1.15         | 0.90 to 1.05         |
| +IMD               |                          |                          |                      |                      |                      |
| Full model (10 unit increase) | 1.05 | 1.05 | 1.05 | 1.05 | 0.90 |

Hazard ratios are for IQR change in pollutant level unless stated (PM\(_{10}\)=3.0 µg/m\(^3\), PM\(_{2.5}\)=1.9 µg/m\(^3\), SO\(_2\)=2.2 µg/m\(^3\), NO\(_2\)=10.7 µg/m\(^3\), O\(_3\)=3.0 µg/m\(^3\)). Practice is accounted for in the above models by the sandwich estimator to produce robust standard errors.

*The numbers of patients in the analyses with this additional exclusion were: PM\(_{10}\), n=690,102, PM\(_{2.5}\), n=684,261, SO\(_2\), n=689,767, NO\(_2\), n=684,261, O\(_3\), n=684,261.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; GP, general practitioner; HES, hospital episode statistics; IMD, Index of Multiple Deprivation.

**Figure 2** Hazard ratios and 95% confidence intervals for the incidence of Chronic Obstructive Pulmonary Disease for an interquartile change in each pollutant stratified by Index of Multiple Deprivation deciles.
with COPD hospitalisations (HR=1.00). They also found no
evidence of an association with PM_{2.5} (HR=1.02 (95% CI 0.98 to
1.06) per 1.58 μg/m³ increment, which compares to
HR=1.04 for the same increment in our study.

Our finding of an association between long-term exposure to
SO₂ and COPD is, to the best of our knowledge, new, although
we note that this finding is specific to GP recorded COPD and
hospital admission when confirmed by the GP. SO₂ has been
associated with respiratory mortality in some, but not all,
cohort studies.5 Short-term exposure time-series studies have
indicated associations between daily concentrations of SO₂ and
emergency hospital admissions for COPD22 but not GP consul-
tations for lower respiratory disease excluding asthma.24 Given
the lack of a plausible hypothesis linking current low levels of
SO₂ to health,26 it is possible that our finding reflects historical
exposure to higher concentrations of SO₂, or that our SO₂ model,
which showed an association with cardiovascular disease in a
previous analysis, is providing a geographical proxy of poor
overall health or acts as a marker for more toxic substances
produced by the combustion of sulfur-containing fossil fuel.

We also found that associations with ozone were consistently
negative, which we have seen previously with cardiovascular
disease and mortality.5 14 While this is in part explained by nega-
tive correlations between ozone and the other pollutants, the
smaller variation of ozone concentration by area probably results
in it better representing regional levels. An analysis confined to
the months in which ozone levels are highest might have been
informative, but we were unable to stratify by season.2

In our study, we used two distinct data sources to identify
COPD over time—GP diagnoses and hospital admissions. The
use of a nationally representative UK primary care database to
study COPD incidence has been established,25 but some import-
ant changes that might affect recording have taken place. One
of the most notable changes was the introduction of the Quality
and Outcomes Framework in 2004 which required GPs to
confirm their COPD diagnoses by spirometry from 2006 onwards.
This change may have temporarily introduced addi-
tional variability in the recording of diagnoses across practices.
However, the introduction of spirometry should improve diag-
nostic certainty and lead to improved and more specific
outcome measures for use in epidemiological studies of air pollu-
tion where large sample sizes are required to detect relatively
small effects.

We also used hospital admissions for COPD as an outcome.
Andersen et al10 noted the appeal of using an objective measure
such as first-ever hospital admission assessed objectively from a
nationwide register but recognised that such patients repre-
sented only those with severe or poorly controlled COPD.
Hence, admissions are unlikely to represent the real burden of
COPD in the population.10 In this respect, our study had the
benefit of two large, quality assured, independent sources of
data to identify incidence: hospital admissions records to iden-
tify participants at the severe end of the spectrum of disease and
primary care records incorporating participants with COPD
who had not yet required admission to hospital. However, the
consistency in recording of a COPD diagnosis between the two
was not complete—36% of incident hospital admissions for
COPD were not confirmed by a corresponding GP diagnosis
during the study. A sensitivity analysis restricting hospital admis-
sions to those corroborated by a subsequent GP diagnosis of
COPD did not alter substantively the associations observed with
hospital admissions. While the use of large-scale databases
allows us to detect small effects in large populations, the lack of
consistency between the two outcomes limits the conclusions
that can be drawn from each analysis.

We found that adjustment for deprivation had a substantial
effect on all HRs, moving all associations towards unity and statis-
tical non-significance. The direction of this adjustment is not
surprising as lower SES has been shown to be related to poorer
air quality and respiratory function in England previously.26
Adjustment for deprivation is important as it is associated with
air pollution as well as other factors that might be correlated
with COPD outcomes.27 We were limited by relying on census
measures of deprivation based on a geographical area of
approximately 1500 people;13 however, neighbourhood SES
indicators can be an acceptable proxy for individual measures.28
It is possible that in urban areas the IMD may represent
fine-scale variability in actual pollution levels not represented by
our modelled estimates. For example, within the modelled
1×1 km area, patients living closer to busy roads are assigned
identical exposure as those further away, but may have different
deprivation profiles.29 While this may raise the possibility that
we have overadjusted in our models, when we stratified our ana-
lysis by IMD deciles, we found little evidence of consistent
effects of air pollution within the separate groups and no evi-
dence of greater effects in areas of low socioeconomic character-
istics.30 It is also possible that some of the IMD adjustment may
be acting as a proxy for further smoking history, as our smoking
variable was unable to calculate lifetime pack years.

We have discussed previously the performance and validation
(see online supplementary material) of our air pollution disper-
sion models.5 We note that the validity of the modelled expo-
sure data (as measured by R² statistics in relation to monitored
data) varied among the pollutants and from year to year. In
2002, our chosen year for exposure assignment, model valid-
ization was good for NO₃ₓ, moderate for PM₁₀ and poor for SO₂,
although this varied substantially from year to year (R²=0.23–
0.45 at national network sites and 0–0.6 at the verification
sites). Models for ozone demonstrated good to reasonable
model performance. The difficulty in modelling PM and SO₂
has been well documented31 32 and we note also that alternative
pollution models have reported similar performance when
applied to the UK.31 32 Other sensitivity analysis using exposure
estimates averaged over a number of years, which include better
validation statistics, largely confirmed our findings based on the
2002 data only including associations with SO₂ (data not shown).
Nonetheless, we believe that the poorer model performance
for PM₁₀ and SO₂ relative to NO₂ should be taken into
consideration in the overall assessment of our results.

In comparison with other cohort studies of COPD, our pollu-
tion estimates differed in terms of spatial resolution (1×1 km
grids vs residential,10 postcode1) and historical exposure (3510
and 5 years11). The question of historical versus recent exposure
has been considered previously10 in relation to mortality in the
American Cancer Society cohort1 and no strong evidence was
found to support earlier over more recent pollution exposure
estimates. Annual estimates of pollution concentrations from
our model for other years around 2002 suggested strong corre-
lations over time, so a single exposure year provides an accept-
able proxy of longer exposure over time. However, we note that
our estimates of pollution exposure may not adequately repre-
sent cumulative exposure over prior decades, especially where
concentrations have generally been falling over time. A further
limitation of our study was the relatively short follow-up period
(up to 5 years), although this was mitigated to some extent by
the size of the study population and number of events (>16 000


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and >2900 incident COPD cases recorded by a GP and admission, respectively).

In a previous analysis of the same cohort, we found associations with COPD and respiratory mortality, which were comparable with those for hospitalisations reported in this case; however, owing to the relatively smaller number of mortality outcomes (less than 30%), the precision of our estimates was reduced. Hospital admissions may not represent a true incident point but may instead indicate the role of air pollution in exacerbating COPD. This hypothesis is supported by evidence from short-term exposure time-series studies which have found positive associations between daily concentrations of air pollution to increase in numbers of COPD hospital admissions and mortality in urban populations.

In conclusion, this large population-based cohort study found only limited, inconclusive evidence for associations between air pollution concentrations and COPD incidence and inconsistency between results for COPD identified from GP records and from hospital admissions. Given the ubiquitous nature of the exposure and the substantial social and economic burden of the disease, further work utilising improved estimates of air pollution exposure for cohort participants, individual markers of SES, longer follow-up times and a more precise disease definition is required to clarify the role of air pollution in the initiation of COPD.

Acknowledgements The views expressed in this paper are those of the authors and do not reflect the official policy or position of the MHRA. CPRD is owned by the Secretary of State of the UK Department of Health and operates within the MHRA. CPRD has received funding from the MHRA, Wellcome Trust, Medical Research Council, NIHR Health Technology Assessment programme, Innovative Medicine Initiative, UK Department of Health, Technology Strategy Board, Seventh Framework Programme EU, various universities, contract research organisations and pharmaceutical companies.

Contributors RWA, IMC, AJK, TPV5, DGC and HRA contributed in the conception and design of the study. IMC, RWA, DGC and HRA contributed in analysis, interpretation and drafting of the manuscript.


Competing interests None.

Ethics approval NIGB.

Provenance and peer review Not commissioned; externally peer reviewed.

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