Air pollution, lung function and COPD: results from the population-based UK Biobank study

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In one of the largest analyses to date, ambient air pollution exposure was associated with lower lung function and increased COPD prevalence, with stronger associations seen in those with lower incomes http://bit.ly/2DLBPA6

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ABSTRACT Ambient air pollution increases the risk of respiratory mortality, but evidence for impacts on lung function and chronic obstructive pulmonary disease (COPD) is less well established. The aim was to evaluate whether ambient air pollution is associated with lung function and COPD, and explore potential vulnerability factors.

We used UK Biobank data on 303 887 individuals aged 40–69 years, with complete covariate data and valid lung function measures. Cross-sectional analyses examined associations of land use regression-based estimates of particulate matter (particles with a 50% cut-off aerodynamic diameter of 2.5 and 10 µm: $PM_{2.5}$ and PM_{10}, respectively; and coarse particles with diameter between 2.5 µm and 10 µm: PM_{coarse}) and nitrogen dioxide (NO_2) concentrations with forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), the FEV_1/FVC ratio and COPD (FEV_1/FVC <lower limit of normal). Effect modification was investigated for sex, age, obesity, smoking status, household income, asthma status and occupations previously linked to COPD.

Higher exposures to each pollutant were significantly associated with lower lung function. A 5 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ concentration was associated with lower FEV_1 (−83.13 mL, 95% CI −92.50– −73.75 mL) and FVC (−62.62 mL, 95% CI −73.91– −51.32 mL). COPD prevalence was associated with higher concentrations of $PM_{2.5}$ (OR 1.52, 95% CI 1.42–1.62, per 5 $\mu g \cdot m^{-3}$), PM_{10} (OR 1.08, 95% CI 1.00–1.16, per 5 $\mu g \cdot m^{-3}$) and NO_2 (OR 1.12, 95% CI 1.10–1.14, per 10 $\mu g \cdot m^{-3}$), but not with PM_{coarse}. Stronger lung function associations were seen for males, individuals from lower income households, and "at-risk" occupations, and higher COPD associations were seen for obese, lower income, and non-asthmatic participants.

Ambient air pollution was associated with lower lung function and increased COPD prevalence in this large study.

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Introduction

Ambient air pollution increases the risk of respiratory mortality, but evidence for impacts on lung function and obstructive lung disease is less well established. Recent studies and reviews have reported suggestive evidence linking outdoor air pollution and lung function and chronic obstructive pulmonary disease (COPD) [1–4]. Recently, the European Study of Cohorts for Air Pollution Effects (ESCAPE) project showed that higher ambient nitrogen dioxide (NO_2) and exposure to particulate matter with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10}), as well as higher traffic load on roads near residences were associated with impaired lung function in adults, using a meta-analysis across five European cohorts [5]. A separate meta-analysis of four of these same cohorts found positive but nonsignificant associations between chronic exposure to ambient air pollution and COPD [6]. Other large studies have not shown consistent evidence of long-term air pollution exposure on adult-onset COPD [7, 8]. Inconclusive findings have been, in part, attributable to lack of statistical power to detect small effects. Sample size limitations have also curtailed exploration of associations among population subgroups.

The objectives of this cross-sectional study were to examine whether air pollution was associated with lung function and COPD using a very large UK study. Secondly, potential vulnerability factors of the relationships between air pollution and lung function and COPD were explored.

Methods

Study participants

We used baseline questionnaire, anthropometric measures and spirometry data from the UK Biobank collected in 2006–2010. UK Biobank is a national cohort study of half a million participants aged 40–69 years, largely in urban areas of England, Wales and Scotland recruited from the UK National Health Services register [9]. Full study sampling methods are described elsewhere [9, 10]. A research protocol for our study obtained all necessary approvals from the UK Biobank's review committees.

Lung function and COPD

Trained healthcare technicians and nurses in UK Biobank assessment centres performed pre-bronchodilation lung function tests using the Vitalograph Pneumotrac 6800 spirometer (Maids Moreton, UK). Contraindications were chest infection in the past month; history of detached retina, heart attack or surgery to eyes, chest or abdomen in past 3 months; history of a collapsed lung; pregnancy (1st or 3rd trimester); or currently on medication for tuberculosis. Two blows were recorded for each participant and a third blow was administered if the differences between both forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) of the first two blows were >5%. Acceptability of spirometry data was assessed by quality appraisal of a sample of manoeuvres, as described previously [11]. The highest values for both FVC and FEV_1 from acceptable blows were used in analyses. Participants reporting having smoked or used an inhaler within an hour prior to spirometry testing were excluded.

To adjust for normative ageing effects as well as variations according to sex, height and ethnicity, we defined COPD outcomes using the Global Lung Function Initiative (GLI) 2012 reference values for lower limit of normal (LLN) [12], which were computed using the GLI R macro [13]. Individuals with a FEV_1/FVC ratio below the LLN were classified as having COPD [14].

Air pollution estimates

Land use regression (LUR)-based estimates of NO_2, PM_{10}, fine particles with diameter <2.5 µm ($PM_{2.5}$), and coarse particles with diameter between 2.5 µm and 10 µm (PM_{coarse}) for 2010 were generated as part of ESCAPE [15, 16] and linked to geocoded residential addresses of UK Biobank participants. Predictor variables used in final pollutant-specific LUR models and model R^2s are presented in supplementary table S1. Leave-one-out cross-validation, where each site is left out sequentially while the included variables of the models are left unchanged, showed good model performance for $PM_{2.5}$, PM_{10} and NO_2 (cross-validation R^2=77%, 88% and 87%, respectively) and a moderate performance for PM_{coarse} (cross-validation R^2=57%). Evaluation of ESCAPE LUR estimates was conducted by comparing model predictions to the UK's Automatic Urban and Rural Network monitoring data [17]. The LUR NO_2 model predicted measured concentrations reasonably well (R^2=0.67), while the LUR PM_{10} model predicted concentrations moderately well in central and southern areas of the UK (R^2=0.53), but R^2 values were <0.5 in northern England or Scotland, so these areas were dropped from PM analyses [18].

Confounder and effect modifier variables

Sociodemographic and behavioural confounders and potential effect modifiers were identified *a priori* through literature search. Age was derived from birth date and date of baseline assessment. Body mass index (BMI) was constructed from measured height and weight. The UK Biobank five-level before-tax household income variable was dichotomised to "less than" or "equal to or above" GBP 31 000 categories,

being closest to the UK median gross household income in 2009/2010 (GBP 27 789) [19]. Educational attainment was defined as "lower vocational qualification or less" *versus* "higher vocational qualification or more". The smoking status variable classified participants as never, previous or current tobacco smokers. Passive smoking exposure was defined as exposure ⩾1 h·week^{-1} to other people's tobacco smoke at home. Asthma status was based on a self-reported doctor diagnosis of asthma. Lastly, participants reporting current employment for one of 14 jobs associated with an increased risk (prevalence ratio ⩾1.30) for COPD identified by De Matteis *et al.* [11] (supplementary table S2) were classified as having an "at-risk" occupation.

Statistical analyses

We performed descriptive analyses followed by cross-sectional linear regression analyses for lung function and logistic regression analyses for COPD. The associations between baseline FEV_1, FVC and FEV_1/FVC ratio and annual average air pollutant concentrations at place of residence were adjusted for age, age-squared, sex, height, BMI (kg·m^{-2}), household income, education level, smoking status and passive smoking exposure. Associations for COPD (FEV_1/FVC <LLN) at baseline were adjusted for age, sex, BMI, household income, education level, smoking status and passive smoking exposure. In order to allow direct comparison with previous ESCAPE studies on air pollution and lung function impairment and COPD [5, 6, 20], all associations were reported per 5 μg·m^{-3} increase of $PM_{2.5}$ and PM_{coarse} and per 10 μg·m^{-3} increase of PM_{10} and NO_2. To allow interquartile range (IQR) comparison of pollutant effects in the UK Biobank population, results were also reported per IQR increase of air pollutant. Sensitivity analyses were conducted by restricting analyses to individuals living at the same address for ⩾10 years, to minimise exposure misclassification. In addition, we investigated whether pro-inflammatory characteristics modified the relationship between $PM_{2.5}$ and NO_2 air pollution and lung function and COPD. Stratified analyses were conducted for sex (male *versus* female), age (<65 *versus* ⩾65 years), obesity (non-obese *versus* obese), smoking status (never *versus* current or past smoker), household income (<GBP 31 000 *versus* ⩾GBP 31 000), asthma status (never *versus* ever diagnosed) and occupational status (at-risk *versus* not at-risk occupation) (supplementary table S2). Lastly, we calculated attributable fraction of COPD prevalence due to $PM_{2.5}$ exposure above World Health Organization (WHO) air quality guideline levels (>10 μg·m^{-3}), current/past smoking and passive smoking exposure at home.

All statistical analyses were limited to participants with complete exposure and model covariate data and were performed in R Statistical Software, version 3.4.4 [21].

Exclusions and missing data

Study population, exclusions, and missing data are outlined in figure 1. Of the 502 655 UK Biobank participants, 36 had withdrawn from the cohort prior to beginning analyses. 48 818 participants had not completed spirometry tests, and an additional 67 823 participants were excluded due to invalid spirometry measures (n=59 850) or having smoked or used an inhaler within an hour of lung function test (n=7973), resulting in 385 978 participants with valid FEV_1 and FVC measures. 82 091 participants had missing data for at least one covariate in fully adjusted models, leaving 303 887 participants with complete covariate data and valid lung function measures. The COPD outcome variable was available for 303 183 participants, as 704 individuals had no data for the ethnicity variable used to calculate the LLN threshold. After excluding participants with missing air pollution metrics, our final samples for lung function analyses were 299 537 (NO_2 population) and 278 228 (PM population). COPD analyses included 298 848 and 277 567 participants for NO_2 and PM populations, respectively.

Results

Characteristics for participants with complete data in fully adjusted lung function models and for excluded participants due to incomplete data are presented in table 1. The mean age of participants with complete data was 56 years and ∼53% of participants were female. The majority of participants were overweight (43%) or obese (24%), had higher education qualifications (48%) and came from households earning more than GPB 31 000 annually (55%). Three out of five participants were lifetime nonsmokers, only 3% were current smokers and 5% reported exposure to tobacco smoke at home. ∼11% of study subjects had been diagnosed with asthma and 2% were currently employed in an occupation associated with an increased COPD risk. Lastly, LLN-defined COPD prevalence was 7% in our final sample. Significant differences between individuals with complete data and those with incomplete data (n=203 082) were found for all variables, except asthma status. Notably, the incomplete data subset had a considerably lower percentage of individuals with higher educational qualifications (38% *versus* 48%) and from higher income households (42% *versus* 55%), and higher proportions of current smokers (22% *versus* 3%) and individuals in occupations at risk of COPD (4% *versus* 2%).

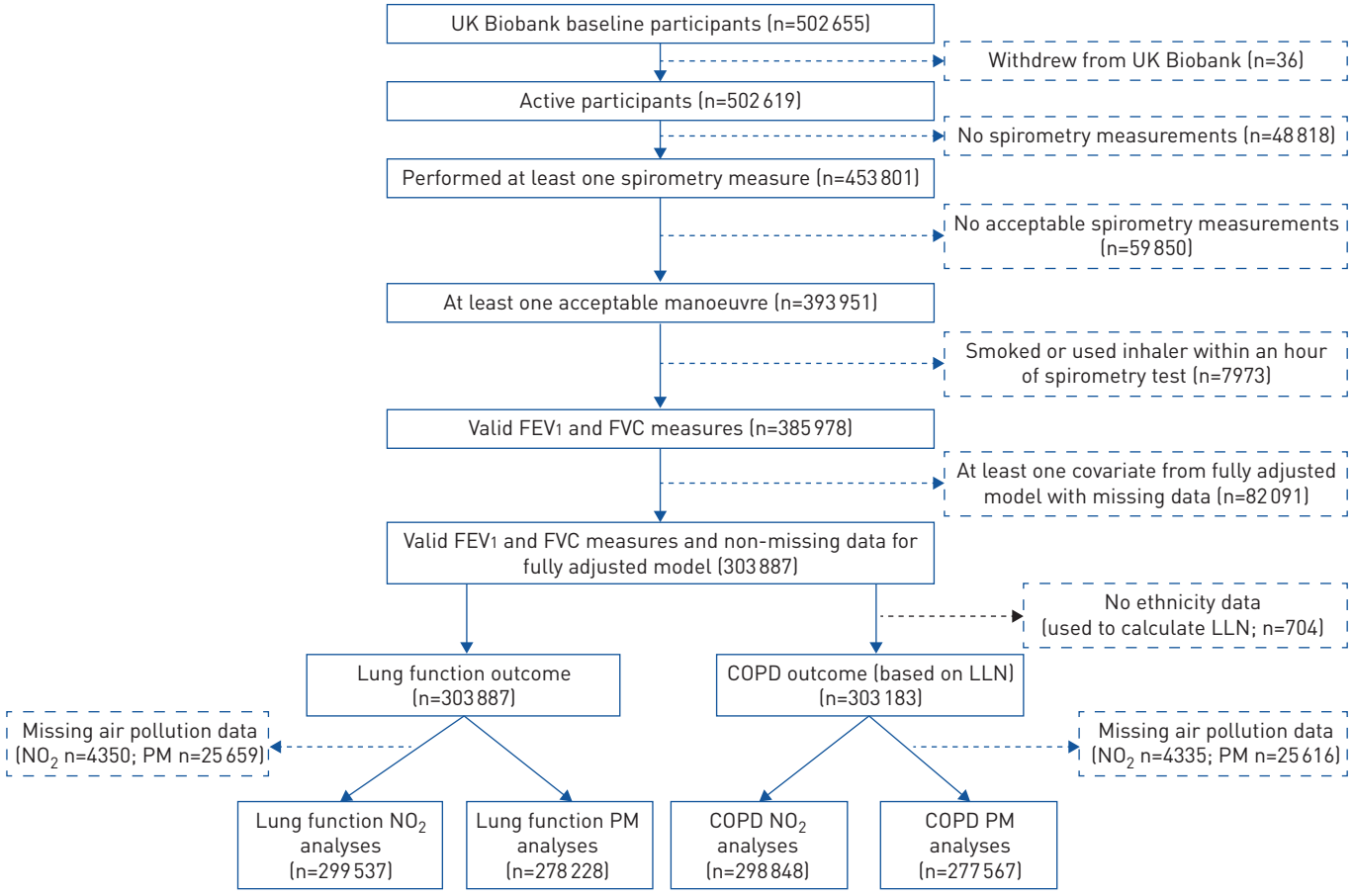

FIGURE 1 Study population, exclusions and missing data. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal; COPD: chronic obstructive pulmonary disease; NO_2: nitrogen dioxide; PM: particulate matter.

Table 2 shows the distribution of residential ambient air pollution concentrations. Mean±SD annual estimates of $PM_{2.5}$, PM_{10}, PM_{coarse} and NO_2 were 9.94±1.04 μg·m^{-3}, 16.18±1.90 μg·m^{-3}, 6.41±0.90 μg·m^{-3} and 26.31±7.49 μg·m^{-3}, respectively. NO_2 concentrations were highly correlated with $PM_{2.5}$ (r=0.87), but less so with other PM metrics. PM_{10} and PM_{coarse} were also highly correlated (r=0.81).

Higher exposure to all pollutants showed significant associations with lower lung function (table 3). In adjusted models, a 5 μg·m^{-3} increase in $PM_{2.5}$ exposure was associated with lower FEV_1 (−83.13 mL, 95% CI −92.50– −73.75 mL), FVC (−62.62 mL, 95% CI −73.91– −51.32 mL) and FEV_1/FVC ratio (−9.68, 95% CI −10.81– −8.56). For each 10 μg·m^{-3} increase in NO_2, lower FEV_1 (−33.85 mL, 95% CI −36.34– −31.36 mL), FVC (−33.47 mL, 95% CI −36.47– −30.46 mL) and FEV_1/FVC ratio (−2.27, 95% CI −2.57– −1.96) were observed. Furthermore, results showed negative associations between PM_{10} and PM_{coarse} concentrations and lung function, with stronger effects on FVC than FEV_1. The FEV_1/FVC ratio showed no association with ambient PM_{10} exposure and a small positive association with PM_{coarse} (1.34, 95% CI 0.04–2.63, per 10 μg·m^{-3}). In the main analyses for COPD prevalence, a significant association was observed for $PM_{2.5}$ (OR 1.52, 95% CI 1.42–1.62, per 5 μg·m^{-3}), PM_{10} (1.08, 95% CI 1.00–1.16, per 10 μg·m^{-3}) and NO_2 (1.12, 95% CI 1.10–1.14, per 10 μg·m^{-3}), but not for PM_{coarse} (table 4). Associations per IQR increase in exposure are presented in supplementary tables S3 (for lung function) and S4 (for COPD). When compared to associations with smoking status, lower levels of FEV_1 observed per 5 μg·m^{-3} increase in $PM_{2.5}$ represented 65% and 29% of FEV_1 loss associated with being a former and current smoker, respectively (supplementary table S5). Furthermore, the odds of COPD per 5 μg·m^{-3} increment of $PM_{2.5}$ was equivalent to more than half the odds of COPD associated with passive smoking exposure at home (supplementary table S5). Sensitivity analyses restricted to those who had lived in the same place for the past 10 years did not substantially change lung function or COPD associations (supplementary tables S6 and S7). Finally, attributable fraction of COPD prevalence for residential ambient $PM_{2.5}$ exposure above WHO guidelines was almost half (5.6%) that of current/past tobacco smoking (12.1%) in the cohort and over four times that of passive smoking exposure at home (1.2%).

TABLE 1 Population characteristics

	Lung function (FEV_1 and FVC) and NO_2 population[#]	Lung function (FEV_1 and FVC) and PM population[¶]	Excluded from analyses due to incomplete data (for lung function and NO_2 population)	Difference p-value
Subjects	299 537	278 228	203 082	
Sex				
Male	47.1 (140 977)	47.2 (131 257)	43.4 (88 187)	<0.001
Female	52.9 (158 560)	52.8 (146 971)	56.6 (114 895)	
Age years	56±8.05	56±8.05	57.3±8.1	<0.001
Age				
<65 years	83.2 (249 067)	83.1 (231 221)	77.6 (157 526)	<0.001
⩾65 years	16.8 (50 470)	16.9 (47 007)	22.4 (45 556)	
BMI kg·m^{-2}	27.4±4.68	27.4±4.69	27.6±4.97	<0.001
Missing data			3105	
BMI				
Normal (<25 kg·m^{-2})	33.3 (99 832)	33.3 (92 673)	32.7 (65 350)	<0.001
Overweight (25–29.9 kg·m^{-2})	43.2 (129 271)	43.1 (120 024)	41.4 (82 872)	
Obese (⩾30 kg·m^{-2})	23.5 (70 434)	23.6 (65 531)	25.9 (51 755)	
Missing data			3105	
Education level				
A-level, O-level or CSEs	51.3 (153 657)	51.9 (144 504)	61.7 (119 076)	<0.001
College, university, NVQ or other professional qualifications	48.7 (145 880)	48.1 (133 724)	38.3 (73 864)	
Missing data			10 142	
Household income				
<GPB 31 000	44.2 (132 527)	44.6 (124 097)	57.9 (72 891)	<0.001
⩾GBP 31 000	55.8 (167 010)	55.4 (154 131)	42.1 (52 993)	
Missing data			77 198	
Smoking status				
Never-smoker	59.0 (176 817)	58.8 (163 686)	48.4 (96 773)	<0.001
Former smoker	38.1 (114 249)	38.3 (106 658)	29.4 (58 842)	
Current smoker	2.8 (8 471)	2.8 (7 884)	22.2 (44 515)	
Missing data			2952	
Passive smoking exposure at home				
None	94.7 (283 521)	94.8 (263 679)	93.6 (142 028)	<0.001
Any	5.3 (16 016)	5.2 (14 549)	6.4 (9 781)	
Missing data			51 273	
Asthma				
Never had asthma	89.4 (267 490)	89.3 (248 232)	89.3 (179 670)	0.53
Ever had asthma	10.6 (31 818)	10.7 (29 779)	10.7 (21 498)	
Missing data	229	217	1914	
Occupational status				
Non-"at-risk" occupation	98.2 (206 506)	98.2 (192 826)	96.4 (112 765)	<0.001
"At-risk" occupation	1.8 (3724)	1.8 (3552)	3.6 (4165)	
Missing data	89 307	81 850	86 152	
FEV_1 L	2.9±0.78	2.9±0.78	2.6±0.77	<0.001
Missing data			116 641	
FVC L	3.8±1.00	3.8±1.00	3.5±0.98	<0.001
Missing data			116 641	
FEV_1/FVC	0.8±0.07	0.8±0.07	0.8±0.08	<0.001
Missing data			116 641	
COPD				
No	92.7 (276 948)	92.6 (257 089)	87.9 (74 762)	<0.001
Yes	7.3 (21 900)	7.4 (20 478)	12.1 (10 267)	
Missing data	689	661	118 053	

Data are presented as n, % (n) or mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; NO_2: nitrogen dioxide; PM: particulate matter; BMI: body mass index; CSE: Certificate of Secondary Education; NVQ: National Vocational Qualification; COPD: chronic obstructive pulmonary disease. [#]: descriptive statistics shown are for participants with complete data for FEV_1 and FVC, age, sex, BMI, education level, household income, smoking status, passive smoking exposure at home and residential NO_2 exposure; [¶]: descriptive statistics shown are for participants with complete data for FEV_1 and FVC, age, sex, BMI, education level, household income, smoking status, passive smoking exposure at home and residential PM exposure.

TABLE 2 Pollutant descriptive statistics and correlation matrix#

	Subjects n	Mean±SD μg·m^{-3}	Minimum μg·m^{-3}	Maximum μg·m^{-3}	IQR μg·m^{-3}	Pearson correlation coefficients			
						$PM_{2.5}$	PM_{10}	PM_{coarse}	NO_2
$PM_{2.5}$	278 228	9.94±1.04	8.17	19.89	1.27	1	0.53	0.21	0.87
PM_{10}	278 228	16.18±1.90	11.78	31.39	1.77		1	0.81	0.50
PM_{coarse}	278 228	6.41±0.90	5.57	12.82	0.77			1	0.19
NO_2	299 537	26.31±7.49	12.93	108.49	9.70				1

IQR: interquartile range; $PM_{2.5}$: fine particulate matter with a 50% cut-off aerodynamic diameter <2.5 μm; PM_{10}: particulate matter with a 50% cut-off aerodynamic diameter <10 μm; PM_{coarse}: coarse particulate matter with diameter 2.5–10 μm; NO_2: nitrogen dioxide. #: descriptive statics shown are for participants with complete data for forced expiratory volume in 1 s, forced vital capacity, age, sex, body mass index, education level, household income, smoking status and passive smoking exposure at home.

Results of $PM_{2.5}$ and NO_2 subgroup analyses for lung function and COPD are shown in tables 5 and 6, respectively. FEV_1-stratified analyses showed stronger $PM_{2.5}$ and NO_2 associations among males, participants from lower income households and individuals with at-risk occupations. The same effect modification patterns were observed for FVC-stratified analyses, with never-smokers showing significantly lower FVC per $PM_{2.5}$ and NO_2 increase. Individuals from lower-income households had approximately twice as low FEV_1 and FVC levels compared to higher-income participants and individuals with at-risk for COPD occupations showed three-fold lower FEV_1 and FVC levels compared to individuals not in these occupations, per unit increase in $PM_{2.5}$ or NO_2 (table 5). Age, obesity, smoking status and household income, but not at-risk occupations modified the relationship between the FEV_1/FVC ratio and $PM_{2.5}$ and NO_2, with stronger adverse associations for older, obese, current/past smokers and lower-income individuals. In COPD subgroup analyses (table 6), $PM_{2.5}$ and NO_2 associations were stronger among obese, lower income and non-asthmatic participants. Again, household income especially influenced the exposure–outcome relationship, with over three times stronger associations between COPD and each pollutant among lower- compared to higher-income individuals.

Discussion

Ambient concentrations of particulate matter and NO_2 air pollution were associated with lower lung function and increased COPD prevalence in this very large UK cohort. Given the size of the study, we were able to investigate interactions, finding evidence for effect modification, with larger impacts of air pollution on 1) lung function in males, individuals from lower-income households and individuals with at-risk occupations; and 2) COPD in obese, lower-income and non-asthmatic participants.

Lung function is a good indicator of respiratory morbidity and mortality, especially among COPD patients [22]. Given an average FEV_1 loss of 32–46 mL·year^{-1} after the age of 30 years [12], the associations per 5 μg·m^{-3} exposure of $PM_{2.5}$ found in our study are approximately equivalent to an additional 2 years of normal loss of lung function in healthy individuals if results in this cross-sectional study are confirmed in future longitudinal follow-up. We found significant reductions on lung function, even at a relatively low levels of ambient $PM_{2.5}$, thereby echoing the need for more actions to be taken to control air pollution [23].

TABLE 3 Associations of lung function and ambient air pollution exposure#

	Subjects n	FEV_1 (mL) β (95% CI)	FVC (mL) β (95% CI)	FEV_1/FVC β (95% CI)
$PM_{2.5}$ per 5 μg·m^{-3}	278 228	**−83.13 (−92.50– −73.75)**	**−62.62 (−73.91– −51.32)**	**−9.68 (−10.81– −8.56)**
PM_{10} per 10 μg·m^{-3}	278 228	**−94.41 (−104.59– −84.22)**	**−122.95 (−135.22– −110.68)**	−0.34 (−1.56–0.89)
PM_{coarse} per 5 μg·m^{-3}	278 228	**−68.61 (−79.37– −57.85)**	**−96.69 (−109.65– −83.73)**	**1.34 (0.04–2.63)**
NO_2 per 10 μg·m^{-3}	299 537	**−33.85 (−36.34– −31.36)**	**−33.47 (−36.47– −30.46)**	**−2.27 (−2.57– −1.96)**

Bold type represents statistical significance. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $PM_{2.5}$: fine particulate matter with a 50% cut-off aerodynamic diameter <2.5 μm; PM_{10}: particulate matter with a 50% cut-off aerodynamic diameter <10 μm; PM_{coarse}: coarse particulate matter with diameter 2.5–10 μm; NO_2: nitrogen dioxide. #: adjusted for age (continuous), age-squared, sex, height, body mass index (kg·m^{-2}), household income (<GBP 31 000/⩾GBP 31 000), education level (lower vocational or less/higher vocational or more), smoking status (never/former/current) and passive smoking exposure at home (none/any).

TABLE 4 Associations of chronic obstructive pulmonary disease and ambient air pollution exposure[#]

	Cases/non-cases n/n	OR (95% CI)
$PM_{2.5}$ per 5 μg·m^{-3}	20 478/257 089	**1.52 (1.42–1.62)**
PM_{10} per 10 μg·m^{-3}	20 478/257 089	**1.08 (1.00–1.16)**
PM_{coarse} per 5 μg·m^{-3}	20 478/257 089	0.99 (0.91–1.07)
NO_2 per 10 μg·m^{-3}	21 900/276 948	**1.12 (1.10–1.14)**

Bold type represents statistical significance. $PM_{2.5}$: fine particulate matter with a 50% cut-off aerodynamic diameter <2.5 μm; PM_{10}: particulate matter with a 50% cut-off aerodynamic diameter <10 μm; PM_{coarse}: coarse particulate matter with diameter 2.5–10 μm; NO_2: nitrogen dioxide. [#]: adjusted for age (continuous), sex, body mass index (kg·m^{-2}), household income (<GBP 31 000/⩾GBP 31 000), education level (lower vocational or less/higher vocational or more), smoking status (never/former/current) and passive smoking exposure at home (none/any).

Comparison with studies using the same air pollution estimates

The current study replicated cross-sectional analyses in ESCAPE, the previous largest European study to date, using a single cohort with >10-fold higher numbers and the same models to estimate air pollutant exposures [15, 16] and similar covariate adjustment. Findings from two ESCAPE meta-analyses [5, 6] and from a Dutch study using ESCAPE air pollution estimates [20] are presented in figure 2. Our large sample size resulted in much smaller confidence intervals, with more statistically significant results and stronger evidence of an adverse effect of air pollution (figure 2). We found stronger (more negative) effects on lung function than in the studies by ADAM *et al.* [5] or DE JONG *et al.* [20] for each of the four air pollutants studied ($PM_{2.5}$, PM_{10}, PM_{coarse}, NO_2). For COPD, our confidence intervals were much tighter than (but overlapped with) those in the study conducted by SCHIKOWSKI *et al.* [6], but unlike that study, we found significant associations with both $PM_{2.5}$ and NO_2.

The mean and range of estimated annual NO_2 concentrations in our study were similar to those of studies included in the original ESCAPE meta-analyses [5, 6], whereas mean PM concentrations were generally lower in our study, with the exception of the British National Survey of Health and Development, which were comparable (supplementary tables S8 and S9). The range of air pollutant concentrations used in DE JONG *et al.* [20] was smaller than in our own study (supplementary table S10). Using similar air pollution models to those used in past ESCAPE studies means that differences in lung function and COPD associations are less likely to be due to differences in exposure estimates [24]. However, given that the original ESCAPE meta-analyses by ADAM *et al.* [5] and SCHIKOWSKI *et al.* [6] back-extrapolated air pollution estimates to date of lung function measurement by up to two decades for some participating cohorts, the larger effect size seen in our study may in part relate to reduced air pollution exposure misclassification. Finally, the same spirometers and spirometry protocols were applied in UK Biobank, whereas this was not the case across original ESCAPE studies. This may have also contributed to more precise estimates in our study.

Comparison with studies using other air pollution estimates

Our results are consistent with the small number of studies investigating PM_{10}, $PM_{2.5}$ and NO_2 in relation to lung function, but few studies have investigated PM_{coarse}. In a study of UK residents, FORBES *et al.* [25] reported comparable results for FEV_1, showing a 92 mL and 22 mL decrease per 10 μg·m^{-3} increase in PM_{10} and NO_2, respectively. A study of 9651 healthy never-smokers in the Swiss Study of Air Pollution and Lung Disease in Adults (SAPALDIA) also found negative effects of both NO_2 and PM_{10} exposure on FEV_1 and FVC [26]. An analysis of Framingham Heart Study participants by RICE *et al.* [3] found significant negative associations of residential $PM_{2.5}$ exposure with both FEV_1 and FVC levels, and a faster decline in lung function levels.

Our findings of associations between $PM_{2.5}$ and airflow obstruction and COPD are consistent with a recent study of 285 000 Taiwan residents showing significant associations between ambient $PM_{2.5}$ and reduced FEV_1/FVC ratio and risk of COPD [4], and with findings from the German Study on the Influence of Air pollution on Lung, Inflammation and Aging (SALIA) cohort in relation to NO_2 and FEV_1/FVC ratio and spirometrically defined COPD [27]. A separate analysis of SALIA participants also showed a decline in COPD with reduced NO_2 concentrations [28]. However, in contrast to our findings, no associations of NO_2 or $PM_{2.5}$ exposure with FEV_1/FVC were reported by FORBES *et al.* [25] or RICE *et al.* [3].

TABLE 5 Lung function subgroup analyses for fine particulate matter with diameter <2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2)[#]

	FEV_1 mL				FVC mL				FEV_1/FVC			
	$PM_{2.5}$ per 5 μg·m^{-3}		NO_2 per 10 μg·m^{-3}		$PM_{2.5}$ per 5 μg·m^{-3}		NO_2 per 10 μg·m^{-3}		$PM_{2.5}$ per 5 μg·m^{-3}		NO_2 per 10 μg·m^{-3}	
	β (95% CI)	Interaction p-value	β (95% CI)	Interaction p-value	β (95% CI)	Interaction p-value	β (95% CI)	Interaction p-value	β (95% CI)	Interaction p-value	β (95% CI)	Interaction p-value
Sex		<0.001		<0.001		<0.001		<0.001		0.928		0.883
Male	−102.32 (−118.16– −86.48)		−41.22 (−45.44– −37.00)		−78.48 (−97.42– −59.54)		−40.85 (−45.89– −35.81)		−9.52 (−11.25– −7.80)		−2.27 (−2.73– −1.80)	
Female	−68.14 (−78.68– −57.59)		−28.01 (−30.82– −25.21)		−50.47 (−63.28– −37.67)		−27.66 (−31.06– −24.26)		−9.79 (−11.26– −8.32)		−2.25 (−2.65– −1.86)	
Age		0.574		0.113		0.187		0.014		<0.001		<0.001
<65 years	−83.63 (−93.85– −73.40)		−32.55 (−37.27– −31.83)		−65.06 (−77.40– −52.71)		−34.86 (−38.15– −31.58)		−8.92 (−10.11– −7.73)		−2.04 (−2.36– −1.72)	
⩾65 years	−85.32 (−108.62– −62.01)		−31.64 (−37.82– −25.47)		−54.05 (−81.85– −26.25)		−27.41 (−34.78– −20.05)		−13.73 (−16.91– −10.54)		−3.50 (−4.35– −2.65)	
Obesity		0.068		0.003		0.460		0.082		0.005		0.005
Non-obese	−78.68 (−89.31– −68.04)		−31.69 (−34.51– −28.87)		−58.93 (−71.78– −46.08)		−31.65 (−35.05– −28.24)		−9.07 (−10.36– −7.79)		−2.07 (−2.41– −1.73)	
Obese	−95.53 (−115.24– −75.82)		−40.36 (−45.68– −35.04)		−76.78 (−100.30– −53.27)		−40.78 (−47.12– −34.45)		−10.99 (−13.32– −8.67)		−2.61 (−3.24– −1.98)	
Smoking status		0.388		<0.001		<0.001		<0.001		<0.001		<0.001
Never-smoker	−84.49 (−96.74– −72.25)		−38.11 (−41.37– −34.85)		−76.56 (−91.51– −61.60)		−41.89 (−45.87– −37.91)		−6.91 (−8.35– −5.47)		−1.61 (−2.00– −1.23)	
Current or past smoker	−87.08 (−101.61– −72.55)		−30.42 (−34.28– −26.56)		−49.66 (−66.87– −32.46)		−24.42 (−28.99– −19.85)		−13.80 (−15.59– −12.00)		−3.31 (−3.79– −2.83)	
Household income	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
<GBP 31 000	−78.85 (−93.56– −64.13)		−35.76 (−39.79– −31.73)		−95.83 (−112.86– −78.79)		−46.92 (−51.58– −42.25)		−13.70 (−15.49– −11.91)		−3.46 (−3.96– −2.97)	
⩾GBP 31 000	−39.12 (−52.30– −25.94)		−21.81 (−25.24– −18.37)		−31.69 (−46.76– −16.62)		−22.15 (−26.08– −18.23)		−6.38 (−7.82– −4.95)		−1.41 (−1.78– −1.03)	
Asthma status		0.002		0.033		0.094		0.319		0.013		0.113
Never had asthma	−84.84 (−94.61– −75.08)		−33.93 (−36.53– −31.33)		−63.17 (−75.10– −51.24)		−33.21 (−36.38– −30.04)		−9.78 (−10.92– −8.64)		−2.27 (−2.57– −1.96)	
Ever had asthma	−70.01 (−99.76– −40.26)		−33.13 (−41.08– −25.17)		−54.57 (−89.32– −19.81)		−34.12 (−43.40– −24.85)		−9.25 (−13.30– −5.21)		−2.43 (−3.51– −1.34)	
Occupational status	0.001		<0.001		0.002		<0.001		0.431		0.594	
Non-"at-risk" occupation	−71.88 (−83.25– −60.51)		−30.88 (−33.87– −27.89)		−57.95 (−71.67– −44.24)		−32.20 (−35.81– −28.59)		−6.94 (−8.25– −5.62)		−1.57 (−1.92– −1.22)	
"At-risk" occupation	−183.85 (−271.13– −96.56)		−77.71 (−101.86– −53.57)		−192.19 (−296.36– −88.01)		−91.28 (−120.11– −62.46)		−9.18 (−19.57–1.20)		−1.81 (−4.71–1.09)	

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: adjusted for age (continuous), age-squared, sex, height, body mass index (kg·m^{-2}), household income (<GBP 31 000/⩾GBP 31 000), education level (lower vocational or less/higher vocational or more), smoking status (never/former/current) and passive smoking exposure at home (none/any).

TABLE 6 Chronic obstructive pulmonary disease subgroup analyses for fine particulate matter with diameter <2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2)#

	$PM_{2.5}$ per 5 μg·m^{-3}			NO_2 per 10 μg·m^{-3}		
	Cases/ non-cases	OR (95% CI)	Interaction p-value	Cases/ non-cases	OR (95% CI)	Interaction p-value
Sex			0.024			0.101
Male	10 615/120 233	1.40 (1.27–1.54)		11 279/129 269	1.10 (1.07–1.13)	
Female	9863/136 856	1.64 (1.49–1.81)		10 621/147 679	1.13 (1.10–1.16)	
Age			0.128			0.260
<65 years	16 685/214 004	1.49 (1.38–1.60)		17 854/230 661	1.11 (1.09–1.13)	
⩾65 years	3793/43 085	1.64 (1.40–1.92)		4046/46 287	1.13 (1.09–1.18)	
Obesity			0.002			0.002
Non-obese	16 508/195 722	1.44 (1.34–1.56)		17 646/210 967	1.10 (1.08–1.12)	
Obese	3970/61 367	1.80 (1.55–2.09)		4254/65 981	1.17 (1.12–1.22)	
Smoking status			0.009			0.181
Never-smoker	10 574/152 753	1.39 (1.26–1.53)		11 319/165 120	1.10 (1.07–1.13)	
Current or past smoker	9904/104 336	1.69 (1.53–1.85)		10 581/111 828	1.14 (1.11–1.17)	
Household income			<0.001			<0.001
<GBP 31 000	10 090/113 656	1.85 (1.69–2.04)		10 700/121 462	1.19 (1.15–1.22)	
⩾ GBP 31 000	10 388/143 433	1.25 (1.14–1.38)		11 200/155 486	1.06 (1.03–1.09)	
Asthma status			<0.001			<0.001
Never had asthma	14 484/233 176	1.66 (1.53–1.79)		15 510/251 382	1.14 (1.12–1.17)	
Ever had asthma	5967/23 729	1.24 (1.08–1.42)		6362/25 371	1.06 (1.02–1.10)	
Occupational status			0.742			0.725
Non-"at-risk" occupation	13 512/178 876	1.37 (1.26–1.49)		14 354/191 700	1.09 (1.06–1.11)	
"At-risk" occupation	381/3161	1.46 (0.89–2.39)		399/3314	1.11 (0.97–1.27)	

Data are presented as n/n, unless otherwise stated. #: adjusted for age (continuous), sex, body mass index (kg·m^{-2}), household income (<GBP 31 000/⩾GBP 31 000), education level (lower vocational or less/higher vocational or more), smoking status (never/former/current) and passive smoking exposure at home (none/any).

Effect modifiers of air pollution

We observed considerably stronger associations for lung function and COPD among individuals from lower-income households. The greater vulnerability of lower-income individuals to the respiratory health effects of air pollution exposure is in line with previous studies [18, 29, 30], and is probably due to numerous factors, including more childhood respiratory infections, poorer housing conditions and indoor air quality, poor nutrition and occupational exposures [31].

Our study found that occupational status in a job judged at risk of COPD to be an important effect modifier of associations between air pollution exposure and lung function, but not its associations with COPD. The latter may be due to the "healthy worker" effect, whereby those with COPD are less likely to be employed in an at-risk job; we did not have information on past occupation. Few studies are available for comparison, but the Harvard Six Cities Study found higher relative risks of death per unit of $PM_{2.5}$ among individuals reporting workplace exposure to dust or fumes [32].

We observed stronger $PM_{2.5}$ and NO_2 associations with FEV_1 and FVC among males and stronger associations between $PM_{2.5}$ exposure and COPD for females. Equivocal evidence has been found regarding effect modification of sex in associations between air pollution exposure and lung function and COPD in adults [33]. In studies reporting stronger effects in males, work-related exposures leading to greater predisposition to airway disease, and more time spent outdoors potentially resulting in higher exposures for a given concentration have been suggested as potential sources of differential effects [34, 35]. Hypotheses for a larger impact of air pollution on lung health among females include more time spent at home leading to better accuracy of residential air pollution exposure assignment, as well as biological factors such as greater airway reactivity [36, 37].

We also found significant effect modification by obesity, with higher air pollution associations with COPD risk and reduced lung function for obese individuals, which is consistent with other studies using ESCAPE air pollution estimates [5, 20]. Mechanistic studies have shown greater than additive effects of excess body

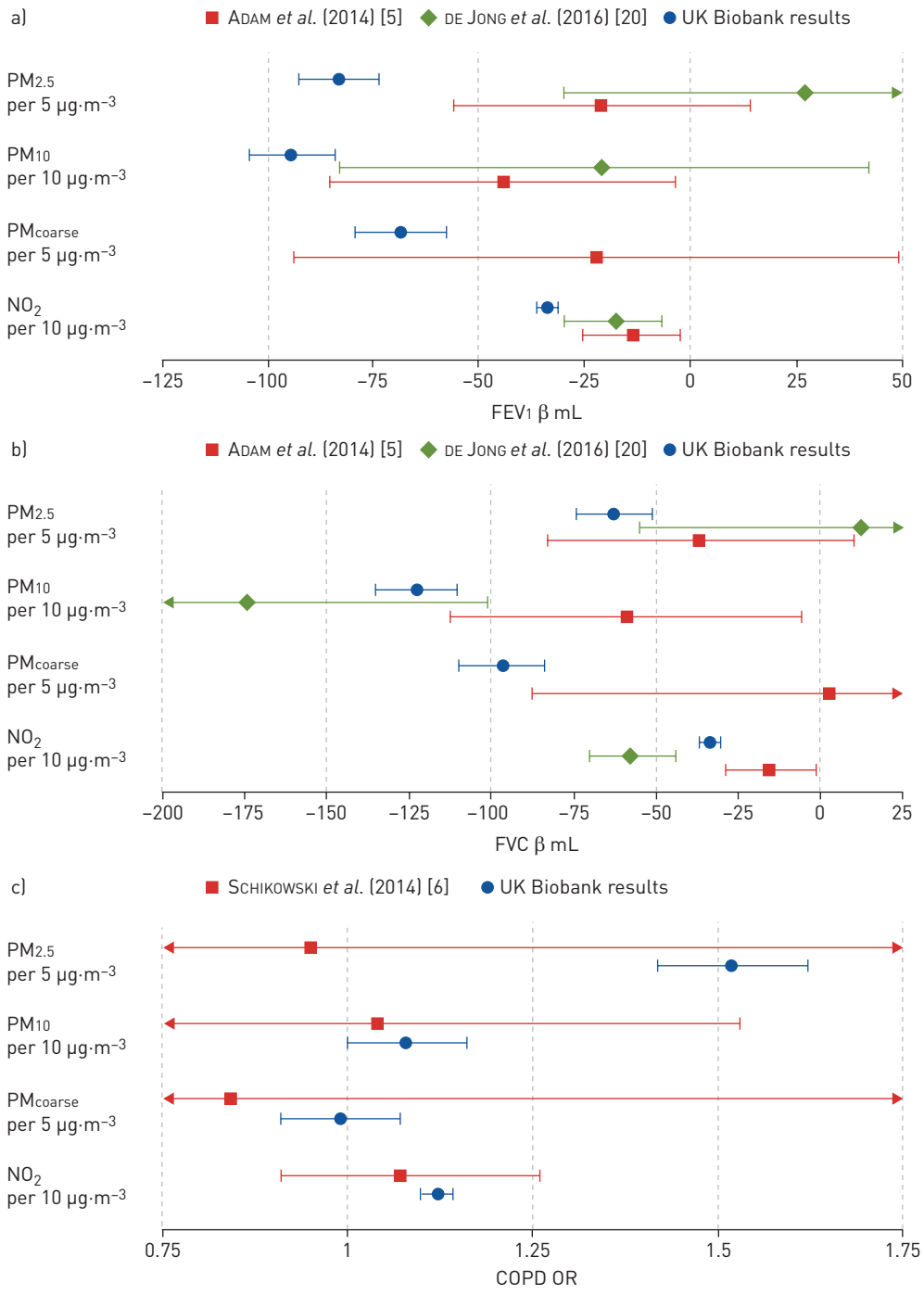

FIGURE 2 Air pollution exposure, a) forced expiratory volume in 1 s (FEV_1), b) forced vital capacity (FVC) and c) chronic obstructive pulmonary disease (COPD): comparison with other studies using European Study of Cohorts for Air Pollution Effects (ESCAPE) air pollution estimates. Cohorts included in each study: Adam *et al.* [5]: European Community Respiratory Health Survey (ECRHS), French Epidemiological Study on Genetics and Environment of Asthma (EGEA), National Survey of Health and Development (NSHD), Study on the Influence of Air Pollution on Lung Function, Inflammation and Aging (SALIA) and Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA); de Jong *et al.* [20]: Lifelines Cohort Study; Schikowski *et al.* [6]: ECRHS, NSHD, SALIA and SAPALDIA. $PM_{2.5}$: fine particulate matter with a 50% cut-off aerodynamic diameter <2.5 µm; PM_{10}: particulate matter with a 50% cut-off aerodynamic diameter <10 µm; PM_{coarse}: coarse particulate matter with diameter 2.5–10 µm; NO_2: nitrogen dioxide.

fat and air pollutant exposure on systemic inflammation and oxidative stress [38, 39], suggesting an enhanced response to inflammatory stimuli [39], resulting in airway damage and inflammation in obese individuals.

Stronger negative effects of air pollution on respiratory disease among never-smokers have been reported previously [6, 8, 40], which our analyses also found. As smoking might already reduce pulmonary function through inflammatory pathways, any additional impact of air pollution on respiratory abnormalities could be smaller or harder to detect in this subgroup.

In addition, we found that asthma status modified the associations between $PM_{2.5}$ and NO_2 and COPD prevalence, with significantly stronger associations in non-asthmatics. This may be related to treatment in asthmatics, modifying adverse impacts of air pollution or alternatively, avoidance in that asthmatics aware of impact of air pollution on symptoms may choose to live in less polluted areas.

Strengths and limitations

The large sample size of our study provided good statistical power to assess effects of air pollution, even in relatively small subgroups such as individuals in occupations with increased COPD risk. An additional strength of our study was the use of a single well-respected cohort with a rigorously defined protocol.

A potential major limitation of the study is the large number of participants with missing data for covariates included in our final regression models. This did not appear to be missing at random (therefore difficult to address using imputation), but gave us a wealthier and healthier cohort. This does not invalidate findings, but may affect generalisability. Given our findings of interactions with lower socioeconomic status individuals, we might expect this would underestimate associations of air pollution and lung function and COPD in a general population.

Another limitation is that while COPD should be classified using post-bronchodilator spirometry tests, only pre-bronchodilator measures were available, similar to the ESCAPE five-cohort analysis [5]. The extent that air pollution affects FEV_1 and FEV_1/FVC ratio could potentially have been mitigated if assessed post-bronchodilator.

Common to most other ambient air pollution studies, we used place of residence to estimate air pollution exposure, which will result in exposure misclassification. Furthermore, annual air pollution estimates at recruitment address were modelled to a single year (2010), which may differ by up to 4 years from when lung function was measured. We made a reasonable assumption that the spatial contrast in air pollution exposures will have been relatively stable in the UK over these years [41], but cannot exclude the possibility of exposure misclassification. Finally, the cross-sectional relationship between air pollution and lung function and COPD demonstrated in our study show associations, but are prone to the influence of confounders and do not allow us to examine temporal patterns between air pollution exposure and respiratory outcomes. Longitudinal analyses of future follow-up data in large cohorts such as UK Biobank are needed to strengthen inferences regarding causal relationships between air pollution and respiratory disease, particularly among vulnerable subpopulations.

In conclusion, this is one of the largest analyses to date to examine associations between ambient air pollution and lung function and COPD. Air pollutant concentrations were clearly associated with lower lung function and increased COPD prevalence with higher impacts in males, individuals from lower income households, those in occupations with adverse respiratory exposures and those who were obese.

Author contributions: D. Doiron, K. de Hoogh and A.L. Hansell proposed the study; all authors contributed to development of the study design; D. Doiron conducted the statistical analyses and wrote the first draft of the paper; all authors commented on results and contributed to the manuscript.

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