Environmental correlates of chronic obstructive pulmonary disease in 96 779 participants from the UK Biobank: a cross-sectional, observational study

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Summary

Background The role of environmental exposures in chronic obstructive pulmonary disease (COPD) remains inconclusive. We examined the association between environmental exposures (PM$_{2.5}$, greenness, and urbanicity) and COPD prevalence using the UK Biobank cohort data to identify key built environment correlates of COPD.

Methods In this cross-sectional, observational study we used baseline data for UK Biobank participants. Included participants were aged 39 years and older, white, had available spirometry data, and had complete data for phenotypes and exposures. COPD was defined by spirometry with the 2017 Global Initiative for Chronic Obstructive Lung Disease criteria. Environmental exposures were PM$_{2.5}$ derived from monitoring data and interpolated using land-use regression at the participants’ geocoded residential addresses. Built environment metrics of residential greenness were modelled in terms of normalised difference vegetation index from remotely sensed colour infrared data within a 500 m residential catchment, and an urbanicity index derived from spatial analyses and measured with a 1 km buffer around each participant’s residential address. Logistic regression models examined the associations between environmental exposures and COPD prevalence adjusting for a range of confounders. Subgroup analyses by urbanicity and effect modification by white blood cell count as an inflammatory marker were also done.

Findings We assessed 96 779 participants recruited between April 4, 2006, and Oct 1, 2010, of which 5391 participants had COPD with a prevalence of 5·6%. Each 10 µg/m$^3$ increment in ambient PM$_{2.5}$ exposure at a participant’s residential location was associated with higher odds of COPD (odds ratio 1·55, 95% CI 1·14–2·10). Among the built environment metrics, urbanicity was associated with higher odds of COPD (1·05, 1·01–1·08 per interquartile increment), whereas residential greenness was protective, being associated with lower odds of COPD (0·89, 0·84–0·93 for each interquartile increment). The results remained consistent in models of COPD prevalence adjusting for confounders, subgroup analyses by urbanicity and effect modification by white blood cell count as an inflammatory marker were also done.

Interpretation In this study of the built environment and COPD, to our knowledge the largest done in the UK, we found that exposure to ambient PM$_{2.5}$ and urbanicity were associated with a higher risk of COPD. Residing in greener areas, as measured by normalised difference vegetation index, was associated with lower odds of COPD, suggesting the potential value of urban planning and design in minimising or offsetting environmental risks for the prevention and management of COPD.

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Articles

Research in context

Evidence before this study
We searched PubMed, MEDLINE, Scopus, and Google or Google Scholar for research papers published in English from database inception until July 2, 2019, with search terms “particulate matter”, “PM₁₀”, “green space” OR “urbanicity”; AND “COPD” AND “chronic obstructive pulmonary disease”. Additionally, we manually searched the reference lists of related papers.

Several studies have established positive associations between exposure to PM₁₀ and risks of COPD prevalence, its exacerbation, and COPD-related mortality. There has been very little evidence linking COPD with greenness and urbanicity. The pathway from exposure to COPD development has been hypothesised to proceed via several mechanisms including inflammation, oxidative stress, immune dysfunction, altered airway epithelial structure, and the microbiome within the lung. Yet, the evidence regarding PM₁₀ exposure and COPD prevalence has been mostly suggestive and is far from conclusive. Most studies have examined PM₁₀ exposure in isolation without accounting for other potentially important built environment attributes. Many of the studies have used self-reported doctor-diagnosed COPD, whereas others used hospital visits for COPD or health insurance records of mortality due to COPD, which are methods that have reduced objectivity in capturing prevalent COPD cases. Large-scale evidence has thus far been scarce with most studies done on a homogeneous population with limited particulate exposure variability.

Added value of this study
To our knowledge, the present study is the first of its kind to use a UK-wide dataset of unprecedented size and heterogeneity (n=96,779) to examine the associations between COPD prevalence and multiple environmental exposures of PM₁₀.

SAGE cohort reported positive associations between odds of self-reported doctor diagnosed COPD and PM₁₀ exposure.¹⁹ Studies from China from 2018 and 2017 used spirometry to diagnose COPD and reported positive associations between exposure to PM₁₀ and COPD prevalence.²³²⁴ On the other hand, a Europe-wide study reported null associations between PM₁₀ exposure and both prevalent and incident COPD outcomes.²⁵ Several US studies used Medicare beneficiary data, which reported a positive association between long-term PM₁₀ exposure and COPD mortality.²⁶ Relatively, evidence exists for the detrimental effects of PM₁₀ on lung function²⁷²⁸ and COPD exacerbations.²⁹ Chronic bronchitis, a phenotype of COPD, has also been reported to be positively associated with PM₁₀ in a cohort of US women,³⁰ whereas two studies found null associations.³¹³² The links between short-term exposure to PM₁₀ and COPD-related emergency department visits, hospital admissions, and mortality have also been supported in time-series analyses.³³³⁴

The influence of built environment factors in respiratory health has been acknowledged.³⁵ Few studies indicate protective effects of residential greenness on respiratory health,³⁶ and COPD³⁷ in particular. Evidence for asthma, allergic rhinitis, and Aeroallergen sensitisation (thus far mostly among children) has been inconsistent³⁸ with some studies reporting protective effects,³⁹ as well as null,³⁸ or non-beneficial associations.³⁸³⁹

The evidence associating environmental exposures with COPD thus far has been inconclusive. Most studies have only examined PM₁₀ exposures without accounting for other potentially important built environment attributes such as residential greenness and urbanicity. Several studies have used self-reported doctor-diagnosed COPD, whereas others used hospital visits for COPD or health insurance records of mortality due to COPD, with very few studies using objectively defined COPD by spirometry, meaning a high likelihood of underestimation of the true burden. Many of the studies have been of small scale, insufficiently powered, and done on a homogeneous population with a narrow range of exposures.

With the aim of understanding environmental correlates of COPD prevalence, we used UK Biobank health datasets to examine the odds of COPD prevalence...
with respect to environmental correlates of PM₁₀, greenness, and urbanicity after adjusting for individual-level covariates and confounders. We also examined effects among non-smokers and across categories of urbanicity with white blood cell count used as an inflammatory marker.

Methods
Study design and participants
We did a cross-sectional, observational study using data from the UK Biobank, the largest European Biobank developed to study the environmental, social, and genetic causes of chronic diseases. The UK Biobank assessed 502,682 participants recruited from National Health Service patient registers and residing within approximately 25 miles of assessment centres located in 22 cities of England, Wales, and Scotland over the baseline period April 4, 2006, and Oct 10, 2010. More than 86·2% of the cohort participants resided in urban areas. Extensive data were collected through a set of questionnaires on sociodemographic, lifestyle, and psychosocial factors, and medical history. Data collection comprised touchscreen questionnaires involving direct participant responses into the data entry system at one of the assessment centres and verbal interviews done by a trained member of staff. Phenotypic characterisations comprised anthropometry, biosampling (blood, urine, and saliva), spirometry, imaging, and cognitive function assessments.

The present study was restricted to participants of white European ancestry with available spirometry data (forced expiratory volume in 1 s [FEV₁]; forced vital capacity [FVC] measurements meeting the American Thoracic Society or European Respiratory Society criteria), and complete data on phenotypes and exposures. The study’s analytical sample comprised 96,779 participants across 21 assessment centres. The UK Biobank received ethical approval from the National Health Service National Research Ethics Service (Ref:11/NW/0382) and all study procedures adhered to the World Medical Association Declaration of Helsinki ethical principles for medical research. We submitted a research proposal and data access application that was approved by the UK Biobank Scientific Committee (application number 26492). Participants provided electronically signed informed consent. The detailed study protocol including scientific rationale, sampling, and participant selection criteria has been described previously.

Procedures
Participants completed breath spirometry measurements using a Vitalograph Pneumotrac 6800 recording between two to three blows (each lasting for at least 6 s) within a period of about 6 min. The reproducibility of the first two blows was compared by the Spirometer software and if the difference between FVC and FEV₁ was 5% or less, it was deemed acceptable and a third blow was not required. Participants with previous contraindications including chest infection (eg, influenza, bronchitis, severe cold, pneumonia) in the past month; history of detached retina, heart attack, or surgery to eyes, chest, or abdomen in the past 3 months; history of a collapsed lung, pregnancy (first or third trimester), and those currently on medication for tuberculosis were excluded. Post-bronchodilator was not available for the study and participants were not instructed to withhold any drug treatment before spirometry. COPD was defined as per stage II plus classification of airflow limitation, as per the Global Initiative for Chronic Obstructive Lung Disease guidelines. Participants fulfilling the spirometric criteria of FEV₁/FVC ratio less than 0·7 and percentage predicted FEV₁, less than 80% were defined as COPD cases. Predicted percentage FEV₁ was calculated as per UK Biobank’s protocol. COPD cases with simultaneous doctor-diagnosed and self-reported asthma were excluded from the analyses.

The air pollution measures in the UK Biobank were provided by the Small Area Health Statistics Unit and were developed as a part of the BioSHaRE-EU Environmental Determinants of Health Project. Residential exposure to ambient PM₁₀ was obtained from UK Biobank’s linked air pollution exposure data obtained from the European Study of Cohorts for Air Pollution Effects (ESCAPE) project. Ambient PM₁₀ was measured between Jan 26, 2010, and Jan 18, 2011, across 20 sites each in the two study areas of Thames Valley London and Oxford and smaller towns using Harvard impactors. To consider the diverse factors responsible for pollution variability, one site was located outside the urban area and not influenced by traffic-related emissions, 12 sites were in urban areas but at least 50 m away from a major road, while seven were street sites located at building facades of residences adjacent to streets with traffic intensities of around 10 000 vehicles per day or more. Measurements were taken three times annually for 14 days in the cold, warm, and intermediate seasons of the year. To account for temporal variability, one centrally located site was deployed as the reference site where measurements were taken over the entire year. Mean annual PM₁₀ concentrations were generated for each site after correcting for temporal variability. The ESCAPE project was able to achieve a correlation (r²) between the measured annual mean PM₁₀ concentrations and other pollutant components for the London and Oxford areas; 0·84 (nitrogen dioxide), 0·86 (PM₁₀), and 0·79 (PM₂·5, absorbance). Individual-level PM₁₀ exposures were generated at each geocoded participant address with land-use regression models using land use, street network, and road traffic variables. The individual-level estimates have been validated to be reliable up to 400 km away from the Greater London area, and so all UK Biobank participant addresses outside this limit were assigned missing values. To consider the effects of reliable accumulated exposures, we restricted all analyses...
to participants who resided in their current address for 3 or more years.

Residential greenness and urbanicity, derived from the UK Biobank Urban Morphometric Platform (UKBUMP), were used as built environment exposures. UKBUMP was developed by some of the authors of this Article (CS, SK, JG, CW) based at the University of Hong Kong (Hong Kong) and University of Oxford (Oxford, UK). UKBUMP is a spatial database of objectively modelled built environment metrics of density, greenness, destination proximity, street-level accessibility, and physical environment around residential activity neighbourhoods of participants and developed to identify environmental predictors of chronic disease.43

Residential greenness was measured in terms of normalised difference vegetation index (NDVI), an objective index of relative overall green vegetation or biomass derived from the spectral reflectance values of image pixels in remotely sensed data. Chlorophyll in healthy vegetation absorbs radiation in the visible red region (630–690 nm) of the electromagnetic spectrum and reflects radiation in the near-infrared region (760–900 nm) and this differential in absorbance and reflectance wavelengths is used as a proxy for green quality and intensity. Index scores range between −1 to +1 with higher values indicating dense green vegetation. NDVI was modelled from a series of very high resolution (0·50 m by 0·50 m) Bluesky Colour Infrared imagery derived from specially developed sensors mounted underneath a survey aircraft (appendix pp 3–5). As per established protocols,42 data preparation involved mosaicking summer-time image tiles of the study areas around UK Biobank assessment centres collected over similar temporal scales (across the baseline phase of the UK Biobank study) to avoid potential temporal mismatch and effect of seasonal variability in greenness. We were able to exclude all large water bodies before the analyses of NDVI. We measured residential greenness as mean NDVI values within a 500-m catchment radius of geocoded UK Biobank participants’ dwellings as per previous studies.43 The NDVI greenness was measured for all the participants of 17 (77%) of 22 assessment centres (70% of the total number of individuals) based on colour infrared imagery data available for the study.

The land use and street-level physical accessibility metrics were developed from the Ordnance Survey GB spatial dataset. The density metrics were derived from the UK-wide AddressBase Premium dataset of Ordnance Survey consisting of approximately 36 million valid address point features with 550 different land-use classifications. The spatial analytics involved delineating street catchments around geocoded participant dwellings and measuring densities of more than 200 health promoting or inhibiting land-use destinations. We developed a composite index of urbanicity from the UKBUMP built environment database, which had been tested previously.44 It was derived from four key indicators: residential density, retail density, walkability (street movement density), and density of public transport measured within 1 km of a geocoded participant dwelling and expressed as:

\[
\text{Urbanicity} = Z \text{score}_{\text{resid}} + Z \text{score}_{\text{retail}} + Z \text{score}_{\text{PT}} + Z \text{score}_{\text{walkability}}
\]

where resid represents the density of residential housing units, retail represents the density of retail units per square km street catchment, and PT represents the density of public transport in units per square km street catchment, while walkability is expressed in terms of street movement potential. The former three metrics are expressed as number of units per km² within the 1 km buffer. Street movement potential was obtained by network modelling of the UK-wide street centreline data for the study area, derived from the Integrated Transport Network layer of the Ordnance Survey database comprising approximately 4 million street segments. The network data was transcribed into an access graph model and the street-level movement potential was modelled in the spatial Design Network Analysis network analysis algorithm.45 Movement potential is expressed as the simulated counts of movement passing through each link in the network, given its relative position and topological connectivity with other segments within the network. The measure also acts as a proxy for relative accessibility and centrality of a place.

Blood samples were drawn from each participant at baseline with standard procedures. Haematology analysis was done in 4 mL EDTA (edetic acid) vacutainers with four Beckman Coulter LH750 instruments. Haematology analysis comprised measuring a series of blood parameters including full red blood cell and white blood cell counts, proportion and counts of individual white blood cell populations, and proportion of reticulocytes of the red blood cell population. White blood cell count, neutrophil-to-lymphocyte ratio, and eosinophil-to-basophil ratio were used as inflammatory biomarkers, given their established role in the pathogenesis of COPD.46–48

Individual-level sociodemographic covariates comprised age, sex, highest qualification, and employment status. Highest qualification was a five-factor variable (coded as none; O levels, General Certificate of Secondary Education, or Certificate of Secondary Education; A levels or AS levels; National Vocational Qualification, Higher National Diploma, Higher National Certificate, or other professional qualification; college or university degree), while employment status was a three-factor variable (coded as employed; retired; and unemployed, home maker, others). Average total income before tax, measured at household-level was a four-factor variable (<£18000, £18000–30999, £31000–51999, ≥£52000). Among the individual lifestyle-level risk factors, smoking was expressed as a five-factor variable (never-smokers, current or past occasional smokers, pack years <10,
dose-response curves showing variation in lung function (defined as the ratio of FEV$_1$/FVC), and odds of COPD across the continuum of PM$_2.5$ and green exposures, using restricted cubic spline models with Harrell’s knots. To further examine potential pathways from PM$_2.5$ exposure to COPD through an inflammatory haematological biomarker, we introduced an interaction term between

### Statistical analysis

We used logistic regression models with robust variance estimates. Separate models were developed to examine the associations between the environmental risk factors of PM$_{2.5}$, urbanicity, residential greenness, and COPD after adjusting for a range of covariates and confounders (selection informed a priori by literature*) to include pertinent sociodemographics, lifestyle variables, neighbourhood socioeconomic status, anthropometrics, comorbidities, and haematological biomarkers. Models 1, 2, and 3 represent multiple adjusted models developed for PM$_{2.5}$, urbanicity, and residential greenness, respectively. The initial model building exercise consisted of assessing correlations between the exposure variables, doing bivariate analyses, and subsequently sequentially introducing blocks of risk factors to examine their confounding effects on point estimates, significance, collinearity (assessed with variance inflationary factor), and fit statistic to ensure a parsimonious fit. The final models selected comprised the selected blocks of sociodemographic, lifestyle, neighbourhood-level, biological, and haematological risk factors.

As sensitivity analysis, we tested our results using an alternative definition of COPD based on lower limit of normal criteria. Participants were assigned a COPD case if they fulfilled the spirometric criteria of FEV$_1$/FVC ratio less than the lower limit of normal, which is less than the lower fifth percentile tail of the normal distribution of mean predicted FEV$_1$/FVC in a reference healthy population. We used the Hankinson’s equation to estimate the predicted values of FEV$_1$/FVC.\textsuperscript{a} We further tested for non-linearity in the associations and developed
PM$_{2.5}$ and quartiles of white blood cell count in our restricted cubic spline model examining association of PM$_{2.5}$ exposure with lung function and COPD.

To study potential confounding effects of greenness on the association between COPD and PM$_{2.5}$, we introduced NDVI greenness in our primary analysis. We restricted analyses to non-smokers to understand the potential effects of PM$_{2.5}$, urbanicity, and greenness among non-smokers. We further ran subgroup analyses by quartiles of urbanicity scores to understand the potential impact of urbanicity on the effect estimates in our models of association of COPD with PM$_{2.5}$ and NDVI greenness.

We report odds ratios (ORs) and two-tailed 95% CIs estimated with robust variance estimator (Huber-White sandwich estimator) to account for potential clustering within data. All analyses were done in Stata version 15.1.

### Role of the funding source

UK Biobank was involved in data collection. The funders of the study had no role in developing the research questions, study design, data modelling and analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

The analytical sample comprised 96779 participants recruited between April 4, 2006, and Oct 1, 2010. Valid spirometry data as per American Thoracic Society or European Respiratory Society guidelines were available for 275897 participants. After restricting analyses to white European ancestry and excluding those with incomplete phenotypes and those not meeting the American Thoracic Society or European Respiratory Society criteria, as well as missing data for pack years of smoking, 208722 participants remained with valid data for prevalent COPD. After the further exclusion of participants who resided in their current residential address for less than 3 years (n=16996), and had missing data for PM$_{2.5}$ (n=15933), sociodemographic and lifestyle level variables (n=27777), comorbidities (n=15561), and haematological biomarkers (n=35676), the study included 96779 participants. Comparisons of the analytical sample with the full UK Biobank cohort are presented in the appendix (pp 1–2).

The sample had high residential stability, with 88.2% of the participants residing in their current address for 5 or more years; 69.3% had for 10 or more years, and mean duration of residence was 18.4 years. The mean age of the participants residing in their current address for 5 or more years; 69.3% had for 10 or more years, and mean duration of residence was 18.4 years. The mean age of the participants residing in their current address for 5 or more years; 69.3% had for 10 or more years, and mean duration of residence was 18.4 years.

Table 1: Baseline characteristics

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|----------------------------------|
| Individuals without COPD (n=91388) | Individuals with COPD (n=5391) | Analytical sample (N=96779) | OR (95% CI)* |
| Townsend deprivation               |                                |                                |               |
| Quintile 1, low                    | 42 548 (46.6%)                 | 1984 (36.8%)                   | 44 532 (46.0%)| NA            |
| Quintile 2                         | 12 220 (14.5%)                 | 758 (14.3%)                    | 12 978 (14.4%)| 1.23 (1.13–1.34)|
| Quintile 3                         | 12 430 (12.6%)                 | 761 (14.1%)                    | 13 191 (12.6%)| 1.31 (1.20–1.43)|
| Quintile 4                         | 12 938 (14.2%)                 | 873 (16.2%)                    | 13 809 (14.3%)| 1.45 (1.33–1.57)|
| Quintile 5, high                   | 10 254 (11.2%)                 | 1035 (18.8%)                   | 11 269 (11.6%)| 2.12 (1.96–2.30)|

Cardiovascular problems

| None                              | 68 334 (74.8%)                 | 3282 (60.9%)                   | 71 616 (74.0%)| NA            |
| High blood pressure               | 19 655 (21.5%)                 | 1541 (28.6%)                   | 21 196 (21.9%)| 1.63 (1.53–1.74)|
| Heart attack, angina, stroke      | 1689 (1.8%)                    | 245 (4.5%)                     | 1934 (20.9%)  | 3.02 (2.63–3.47)|
| High blood pressure and heart attack, angina, stroke | 1710 (1.9%) | 323 (6.0%) | 2035 (21.4%) | 3.93 (3.47–4.45) |

Diabetes status

| No diabetes                       | 88 062 (94.4%)                 | 5033 (93.0%)                   | 93 075 (96.2%)| NA            |
| Diabetes                          | 3266 (3.6%)                    | 3787 (70.0%)                   | 3704 (3.8%)   | 2.00 (1.79–2.23)|

Parent’s COPD status

| No COPD                           | 78 543 (85.9%)                 | 4112 (76.3%)                   | 82 655 (85.4%)| NA            |
| One parent with COPD              | 12 199 (13.3%)                 | 1179 (21.9%)                   | 13 378 (13.8%)| 1.85 (1.73–1.97)|
| Both parents with COPD            | 646 (0.7%)                     | 100 (1.9%)                     | 746 (0.8%)    | 2.96 (2.39–3.66)|

White blood cell counts, 10$^9$ cells per L*

| White blood cell counts, 10$^9$ cells per L* | Quintile 1, low (<59) | 21 535 (23.6%) | 732 (13.6%) | 22 267 (23.0%) | NA |
| Quatril 2 (59–65) | 22 610 (24.7%) | 984 (14.3%) | 23 594 (24.4%) | 1.28 (1.16–1.41) |
| Quatril 3 (65–70) | 23 660 (25.9%) | 1337 (24.8%) | 24 907 (25.8%) | 1.66 (1.52–1.82) |
| Quatril 4, high (>70) | 23 583 (25.8%) | 2338 (43.4%) | 25 921 (26.8%) | 2.92 (2.68–3.18) |

Neutrophil-to-lymphocyte ratio

| Neutrophil-to-lymphocyte ratio | Quatril 1, low (+1.66) | 22 822 (25.0%) | 1142 (21.2%) | 23 964 (24.8%) | NA |
| Quatril 2 (1.66–2.11) | 23 098 (25.3%) | 1195 (22.2%) | 24 293 (25.1%) | 1.03 (0.95–1.12) |
| Quatril 3 (2.11–2.72) | 22 931 (25.1%) | 1367 (25.4%) | 24 298 (25.1%) | 1.10 (1.03–1.29) |
| Quatril 4, high (>2.72) | 23 537 (24.7%) | 1687 (31.3%) | 24 224 (25.0%) | 1.50 (1.38–1.62) |

Eosinophil-to-basophil ratio

| Eosinophil-to-basophil ratio | Quatril 1, low (+2.17) | 22 902 (25.1%) | 1299 (24.1%) | 24 208 (25.0%) | NA |
| Quatril 2 (2.17–4.00) | 23 495 (25.7%) | 1396 (25.9%) | 24 891 (25.7%) | 1.05 (0.97–1.13) |
| Quatril 3 (4.01–7.50) | 21 267 (25.5%) | 1321 (24.7%) | 24 595 (25.4%) | 1.01 (0.93–0.99) |
| Quatril 4, high (>7.50) | 21 712 (23.8%) | 1365 (25.5%) | 23 082 (23.9%) | 1.11 (1.03–1.20) |

Data are mean (SD) or n (%) unless specified. Physical activity (metabolic equivalent of task h per week) was available for 80 395 participants. COPD=chronic obstructive pulmonary disorder. OR=odds ratio. NA=not applicable. GCSE=General Certificate of Secondary Education. CSE=Certificate of Secondary Education. NVQ=National Vocational Qualification. HND=Higher National Diploma. HNC=Higher National Certificate. *Bivariate models of association between COPD defined as per Global Initiative for Chronic Obstructive Lung Disease stage II plus classification and each participant’s characteristics. 12 112299; 12 11238.
### Table 2: Environmental exposures

| Environmental exposures | Model 1 (n=96,779) | Model 2 (n=94,265) | Model 3 (n=77,679) |
|-------------------------|---------------------|---------------------|---------------------|
| **PM$_{2.5}$, per 10 µg/m$^3$** | 1.55 (1.14–2.10) | - | - |
| **Urbanicity, 1 km per IQR** | - | 1.05 (1.01–1.08) | - |
| **Mean NDVI greenness within 500 m, per IQR** | - | - | 0.89 (0.84–0.93) |
| **Demographics** | | | |
| **Age** | 1.06 (1.05–1.07) | 1.06 (1.05–1.07) | 1.06 (1.05–1.07) |
| **Sex** | | | |
| Female | 1 (ref) | 1 (ref) | 1 (ref) |
| Male | 1.11 (1.02–1.21) | 1.11 (1.02–1.22) | 1.07 (0.97–1.17) |
| **Household income** | | | |
| <£18,000 | 1 (ref) | 1 (ref) | 1 (ref) |
| £18,000–30,999 | 0.85 (0.78–0.92) | 0.85 (0.79–0.92) | 0.91 (0.83–1.00) |
| £31,000–51,999 | 0.75 (0.69–0.82) | 0.75 (0.69–0.83) | 0.78 (0.70–0.86) |
| ≥£52,000 | 0.71 (0.64–0.79) | 0.71 (0.64–0.79) | 0.78 (0.69–0.88) |
| **Highest qualification** | | | |
| None | 1 (ref) | 1 (ref) | 1 (ref) |
| O levels, General Certificate of Secondary Education, or Certificate of Secondary Education | 0.83 (0.75–0.91) | 0.82 (0.75–0.91) | 0.77 (0.69–0.86) |
| A levels or AS levels | 0.76 (0.66–0.88) | 0.74 (0.63–0.85) | 0.70 (0.59–0.82) |
| National Vocational Qualification, Higher National Diploma, Higher National Certificate, or other professional qualification | 0.84 (0.77–0.92) | 0.84 (0.77–0.92) | 0.80 (0.73–0.88) |
| College or university degree | 0.77 (0.70–0.84) | 0.76 (0.69–0.83) | 0.73 (0.66–0.81) |
| **Employment status** | | | |
| Employed | 1 (ref) | 1 (ref) | 1 (ref) |
| Retired | 0.96 (0.89–1.04) | 0.95 (0.88–1.03) | 0.95 (0.87–1.04) |
| Unemployed, home maker, others | 1.23 (1.10–1.38) | 1.22 (1.09–1.37) | 1.22 (1.07–1.38) |
| **Lifestyle** | | | |
| Alcohol intake frequency | | | |
| Never or occasional | 1 (ref) | 1 (ref) | 1 (ref) |
| 1–2 times per week | 0.95 (0.87–1.03) | 0.95 (0.88–1.03) | 0.95 (0.87–1.04) |
| 3–4 times per week | 0.89 (0.82–0.97) | 0.89 (0.82–0.98) | 0.90 (0.82–1.00) |
| Daily or almost daily | 0.98 (0.90–1.07) | 0.98 (0.91–1.08) | 1.04 (0.95–1.14) |
| Smoking status | | | |
| Never smokers | 1 (ref) | 1 (ref) | 1 (ref) |
| Current or past occasional smokers | 1.23 (1.10–1.36) | 1.22 (1.10–1.36) | 1.26 (1.13–1.41) |
| Pack years <10 | 1.24 (1.09–1.41) | 1.22 (1.08–1.39) | 1.23 (1.07–1.41) |
| Pack years 10–19 | 2.00 (1.80–2.21) | 1.94 (1.75–2.16) | 1.90 (1.69–2.13) |
| Pack years ≥20 | 5.57 (5.18–6.00) | 5.51 (5.12–5.94) | 5.51 (5.08–5.98) |

*(Table 3 continues on next page)*
(Continued from previous page)

| Residential tenureship                      | Model 1 (n=96 779) | Model 2 (n=92 256) | Model 3 (n=77 579) |
|---------------------------------------------|---------------------|---------------------|---------------------|
| Own outright                               | 1 (ref)             | 1 (ref)             | 1 (ref)             |
| Mortgage                                   | 0·99 (0·92–1·07)    | 0·99 (0·91–1·07)    | 0·96 (0·88–1·05)    |
| Rent                                       | 1·49 (1·33–1·65)    | 1·45 (1·30–1·62)    | 1·51 (1·34–1·71)    |

| Townsend deprivation                       |                     |                     |                     |
| Quintile 1, low                            | 1 (ref)             | 1 (ref)             | 1 (ref)             |
| Quintile 2                                 | 1·13 (1·03–1·23)    | 1·13 (1·03–1·24)    | 1·11 (1·01–1·23)    |
| Quintile 3                                 | 1·14 (1·04–1·25)    | 1·15 (1·05–1·26)    | 1·12 (1·01–1·23)    |
| Quintile 4                                 | 1·11 (1·02–1·22)    | 1·12 (1·01–1·22)    | 1·12 (1·01–1·23)    |
| Quintile 5, high                           | 1·22 (1·10–1·35)    | 1·22 (1·10–1·36)    | 1·22 (1·10–1·36)    |

| Anthropometrics and comorbidities          |                     |                     |                     |
| Standing height (cm)                       | 1·02 (1·02–1·03)    | 1·02 (1·02–1·03)    | 1·02 (1·02–1·03)    |
| Body-mass index status, kg/m²              |                     |                     |                     |
| <25                                        | 1 (ref)             | 1 (ref)             | 1 (ref)             |
| ≥25 to <30                                 | 0·71 (0·66–0·76)    | 0·71 (0·66–0·76)    | 0·72 (0·67–0·78)    |
| ≥30                                        | 0·64 (0·59–0·70)    | 0·65 (0·60–0·71)    | 0·65 (0·60–0·72)    |
| Cardiovascular problems                    |                     |                     |                     |
| None                                       | 1 (ref)             | 1 (ref)             | 1 (ref)             |
| High blood pressure                        | 1·14 (1·06–1·22)    | 1·13 (1·06–1·22)    | 1·12 (1·03–1·21)    |
| Heart attack, angina, or stroke            | 1·25 (1·07–1·45)    | 1·24 (1·07–1·45)    | 1·27 (1·08–1·50)    |
| High blood pressure and heart attack, angina, or stroke | 1·39 (1·21–1·60)    | 1·40 (1·21–1·62)    | 1·35 (1·15–1·58)    |

| Diabetes status                            |                     |                     |                     |
| No diabetes                                | 1 (ref)             | 1 (ref)             | 1 (ref)             |
| Diabetes                                   | 1·01 (0·89–1·14)    | 1·02 (0·89–1·15)    | 1·02 (0·89–1·17)    |

| Parent’s COPD status                       |                     |                     |                     |
| No COPD                                    | 1 (ref)             | 1 (ref)             | 1 (ref)             |
| One parent with COPD                       | 1·50 (1·40–1·61)    | 1·50 (1·39–1·61)    | 1·52 (1·40–1·64)    |
| Both parents with COPD                     | 2·29 (1·83–2·87)    | 2·31 (1·84–2·90)    | 2·38 (1·86–3·06)    |

| Haematological biomarkers                  |                     |                     |                     |
| White blood cell counts, 10⁹ cells per L*   |                     |                     |                     |
| Quartile 1 (<5·59)                         | 1 (ref)             | 1 (ref)             | 1 (ref)             |
| Quartile 2 (5·59–6·54)                     | 1·14 (1·03–1·26)    | 1·14 (1·03–1·27)    | 1·14 (1·02–1·27)    |
| Quartile 3 (6·55–7·70)                     | 1·35 (1·23–1·49)    | 1·35 (1·22–1·49)    | 1·33 (1·20–1·48)    |
| Quartile 4 (>7·70)                         | 1·93 (1·75–2·11)    | 1·91 (1·74–2·10)    | 1·92 (1·73–2·13)    |

| Neutrophil-to-lymphocyte ratio             |                     |                     |                     |
| Quartile 1 (<1·66)                         | 1 (ref)             | 1 (ref)             | 1 (ref)             |
| Quartile 2 (1·66–2·11*)                    | 0·98 (0·90–1·07)    | 0·97 (0·89–1·06)    | 0·95 (0·86–1·05)    |
| Quartile 3 (2·11–2·72)                     | 1·05 (0·96–1·14)    | 1·05 (0·96–1·15)    | 1·05 (0·95–1·15)    |
| Quartile 4 (>2·72)                         | 1·12 (1·03–1·22)    | 1·12 (1·03–1·22)    | 1·09 (0·99–1·20)    |

| Eosinophil-to-basophil ratio               |                     |                     |                     |
| Quartile 1 (<2·17)                         | 1 (ref)             | 1 (ref)             | 1 (ref)             |
| Quartile 2 (2·17–4·00)                     | 1·09 (1·00–1·18)    | 1·09 (1·00–1·18)    | 1·10 (1·00–1·20)    |
| Quartile 3 (4·01–7·50)                     | 1·02 (0·94–1·11)    | 1·03 (0·95–1·12)    | 1·03 (0·94–1·12)    |
| Quartile 4 (>7·50)                         | 1·13 (1·04–1·22)    | 1·12 (1·03–1·22)    | 1·14 (1·04–1·26)    |

Data are ORs (95% CI). Model 1, 2, and 3 represent multiple adjusted models developed for PM₂·₅, urbanicity, and residential greenness, respectively. ORs=odds ratios. COPD=chronic obstructive pulmonary disorder defined as per Global Initiative for Chronic Obstructive Lung Disease stage II plus classification. NDVI=normalised difference vegetation index.

Table 3: Multiple adjusted ORs for COPD associated with environmental risk factors among participants of the UK Biobank cohort.
status), lifestyle factors (alcohol intake, smoking, residential tenureship), neighbourhood socioeconomic status (Townsend index), anthropometrics (standing height, BMI status), and comorbidities (cardiovascular problems, diabetes, parental COPD), and haematological biomarkers (white blood cell counts, neutrophil-to-lymphocyte ratio, and eosinophil-to-basophil ratio). Exposure to PM$_{2.5}$ was associated with a higher risk of COPD (OR 1.55, 95% CI 1.14–2.10 per 10 µg/m$^3$ increment; $p=0.0047$; table 3). Each interquartile increment in urbanicity was associated with higher odds of COPD (1.05, 1.01–1.08 per IQR increment; $p=0.011$). Exposure to residential greenness had a protective effect, being associated with a lower risk of COPD (0.89, 0.84–0.93 per IQR increment; $p=0.0001$). Sensitivity analyses using an alternate definition of COPD based on the lower limit of normal criteria produced consistent results, reporting a higher risk of COPD per 10 µg/m$^3$ increments in PM$_{2.5}$ (OR 1.65, 95% CI 1.18–2.30; $p=0.0036$) as well as per interquartile increment in urbanicity (1.04, 1.00–1.08; $p=0.042$) and lower odds of COPD per interquartile increase in residential greenness (0.95, 0.90–1.00; $p=0.043$). In sensitivity analyses for testing the confounding effect of residential greenness on the association between COPD and PM$_{2.5}$ exposure (appendix pp 6–7), the introduction of residential greenness resulted in attenuation of the effect estimates and loss of significance of PM$_{2.5}$ (OR 1.17, 95% CI 0.83–1.66 per 10 µg/m$^3$ increment; $p=0.37$). The result was similar in the case of urbanicity subsequent to adjustment for residential greenness (1.02, 0.98–1.06 per interquartile increment in urbanicity; $p=0.29$).

The fitted restricted cubic spline models of the dose–response relationship between COPD prevalence and lung function and exposures are shown in figure 1. A consistent positive association between PM$_{2.5}$ exposure and both COPD prevalence and predicted lung function was observed (figures 1A, B). In the models for residential greenness (figure 1C), the beneficial effects of greenness on COPD prevalence were attenuated beyond the threshold of NDVI 0.21. Piece-wise regression identified significant beneficial associations below the identified point of inflection (OR 0.74, 95% CI 0.67–0.81; $p=0.0001$), while, above it, the results remained non-significant (0.89, 0.77–1.02; $p=0.092$). The trend remained consistent in our models of lung function with a non-beneficial effect in the high green areas (figure 1D). Tests for non-linearity of the effects of urbanicity on COPD ($p=0.73$) and lung function ($p=0.015$) were however not significant with Harrel’s knots. The results of our interaction effects model across quartiles of white blood cell counts indicated that the detrimental effects of PM$_{2.5}$ exposure on lung function were pronounced among participants in the highest white blood cell count quartile in reference to the lowest ($p_{interaction}=0.0003$).

The odds of COPD were also higher in white blood cell quartile 4 (>7.70); however, the interaction was not significant ($p_{interaction}=0.072$; figure 2A).

On rerunning the models by restricting analyses to non-smokers, the detrimental effects of PM$_{2.5}$ became slightly enhanced (OR 1.80, 95% CI 1.04–3.13 per 10 µg/m$^3$ increment; $p=0.037$) and so was the protective effect of residential greenness (0.82, 0.75–0.89 per IQR increment; $p<0.0001$; appendix pp 8–10). Stratifying analyses by urbanicity quartiles (table 4) indicated a more pronounced detrimental effect of PM$_{2.5}$ in the high urbanicity areas, being significant only in the highest quartile (OR 1.85, 95% CI 1.01–3.37 per 10 µg/m$^3$ increment; $p=0.046$). For residential greenness, the protective effects of greenness slightly attenuated towards the high urbanicity areas (OR 0.85, 95% CI 0.77–0.93; $p=0.0007$ in the second quartile; 0.87,

![Figure 1: Association of COPD prevalence and lung function with PM$_{2.5}$ and NDVI greenness, allowing for non-linear effects.](https://www.thelancet.com/planetary-health)

The continuous line represents the estimated odds of COPD and mean lung function and shaded areas represent 95% CIs. Separate models were fitted for odds of COPD and lung function, with restricted cubic splines with Harrel’s knots, adjusting for demographic characteristics (age, sex, household income, highest qualification, employment status), lifestyle factors (alcohol intake frequency, smoking, residential tenureship), neighbourhood socioeconomic status (Townsend index), anthropometrics (standing height, body-mass index status), comorbidities (cardiovascular problems, diabetes, parental COPD), and haematological biomarkers (white blood cell counts, neutrophil-to-lymphocyte ratio, and eosinophil-to-basophil ratio). Forced expiratory volume in 1 s to forced vital capacity ratio was used to indicate lung function. COPD=chronic obstructive pulmonary disorder, defined as per Global Initiative for Chronic Obstructive Lung Disease stage II plus classification. NDVI=normalised difference vegetation index.

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alternative definition of COPD based on biomarkers. The results remained consistent for an array of confounders including haematological inflammatory markers (neutrophil-to-lymphocyte ratio, and eosinophil-to-basophil ratio). Forced expiratory volume in 1 s to forced vital capacity ratio was used to indicate lung function. pinteraction in the lung function model=0·0718 (A). pinteraction in the COPD model=0·0718 (A). pinteraction in the lung function model=0·0003 (B). COPD=chronic obstructive pulmonary disorder defined as per Global Initiative for Chronic Obstructive Lung Disease stage II plus classification. NDVI=normalised difference vegetation index.

![Figure 2: Associations of COPD and lung function with PM2·5 exposure, allowing for effect modification by white blood cell counts](image)

Separate models were fitted for odds of COPD and lung function, with restricted cubic splines with Harrell’s knots, adjusting for demographic characteristics (age, sex, household income, highest qualification, employment status), lifestyle factors (alcohol intake frequency, smoking, residential tenureship), neighbourhood socioeconomic status (Townsend index), anthropometrics (standing height, body-mass index status), comorbidities (cardiovascular problems, diabetes, parental COPD), and haematological biomarkers (white blood cell counts, neutrophil-to-lymphocyte ratio, and eosinophil-to-basophil ratio). Forced expiratory volume in 1 s to forced vital capacity ratio was used to indicate lung function. pinteraction in the COPD model=0·0718 (A). pinteraction in the lung function model=0·0003 (B). COPD=chronic obstructive pulmonary disorder defined as per Global Initiative for Chronic Obstructive Lung Disease stage II plus classification.

Our study reports 54·8% higher odds of COPD per 10 µg/m³ increment in PM2·5 exposure. The results are consistent with other previous positive associations between COPD and PM2·5 exposure. A 2018 nationwide study of 50991 participants in China reported twice the odds of COPD (OR 2·00, 95% CI 1·36–2·92) among participants exposed to 75 µg/m³ or more as compared with those in the category of less than 50 µg/m³. A large-scale study reported 39% higher odds of COPD among participants in the highest PM2·5 exposure quartile. Reference to those in the lowest and associated reductions in lung function. A smaller-scale study of 1872 older adults reported higher odds of COPD (OR 1·21, 95% CI 1·13–1·30) corresponding to 10 µg/m³ increments in PM2·5 exposure. Our results remained consistent in the non-linear restricted cubic spline models for COPD prevalence and predicted lung function. Adjusting for the confounding by greenness produced null effects. This finding requires further investigation. As reported previously, it is possible that green spaces can reduce PM2·5 loads via absorption and deposition, or dispersion in urban street canyons, as well as provide ventilation corridors breaking air pollution flows.

Our study used objective and detailed building footprint-level spatial data to develop an index of urbanicity reporting 4·6% higher odds of COPD per interquartile increment in urbanicity. The detrimental effects of urban areas have been established in terms of rural–urban differences in self-reported COPD diagnosis and the effects of aggregated population density on COPD mortality.

Our study is the first, to our knowledge, to use a very high resolution (0·50 m) measure of residential green exposure and report an overall 11·4% lower odds of COPD per IQR increment in NDVI greenness. A Dutch study of 345143 participants had previously reported
beneficial effects of 10% increments in green cover within a 1 km residential buffer on COPD and asthma prevalence (OR 0·97, 95% CI 0·96–0·98); however, unlike the present study, prevalence data were derived from routine primary care electronic records and participants’ residences were geocoded at the postcode level with green cover expressed as the percentage within 1 km of the postcode centroid in which a participant resided.29 A UK study reported that green space and gardens were associated with reduced rates of asthma-related hospitalisations,30 while a Spanish study of children reported beneficial effects on wheezing and bronchitis.28 Our non-linear restricted cubic spline models, however, indicated that the beneficial effects of greenness on COPD levelled off after a threshold NDVI of 0·21 (figure 2A), while a slight negative effect on lung function was observed beyond this threshold, with a 1·15% net reduction in lung function (figure 2B). We were able to exclude large water bodies in our NDVI calculations and the remaining negative NDVI values correspond to characteristic urban features such as building rooftops and impervious spaces such as roads and parking spaces. High NDVI values are a proxy of low-density semi-urban or rural neighbourhoods with dense vegetation and agricultural land use (appendix pp 3–5). In other words, below the threshold, the observed beneficial effects accrue on account of increasing proportion of green in highly urban areas. Beyond the threshold, highly green areas might potentially increase susceptibility to allergic reactions to pollens34,54 and affect COPD. Further studies are needed to verify this theory and the potential confounding effects of small water bodies.

That our study detected a slightly pronounced effect of the PM2·5 and residential greenness among the non-smoking subgroup is noteworthy from a public health perspective. Approximately 20% of smokers develop COPD; as such, the roles of other factors (ie, environmental, occupational, socioeconomic, lung growth, and genetics) are of particular importance. Specific strategies to shield this susceptible subgroup from pollution levels to protect non-smokers from high pollution concentrations warrant further investigation.

With respect to pathophysiological mechanisms, several previous studies have hypothesised pathways via pulmonary or systemic inflammation, establishing direct links between COPD development, reduced lung function endpoints, and the presence of higher concentrations of systemic inflammatory markers.35 Direct evidence now suggests that exposure to air particulate matter enhances systemic inflammation, thereby causing airflow obstruction, and reducing lung function.56,57 Our analyses were able to adjust for haematological inflammatory markers, consistently finding higher odds of COPD in the higher quartiles of white blood cell counts, neutrophil-to-lymphocyte ratio, and eosinophil-to-basophil ratio.44 Consistent with previous studies, interaction effect models in our study indicated that the highest white blood cell quartile constituted a clinically susceptible subgroup, showing reduced lung function and higher odds of COPD with increasing PM2·5 exposure concentrations with significant interaction only in the model with lung function. Further longer-term measurements of exposure, lung function, and inflammatory biomarkers are needed to validate this mechanism with confidence.

The observed beneficial effects of residential green exposure on COPD could potentially point to a physical activity-related mechanism, although long-term longitudinal studies are needed to provide support for such hypotheses. We were able to rerun our models accounting for confounding effects of physical activity. Our results remained consistent and physical activity measured as metabolic equivalent of task h per week was beneficially associated with COPD (appendix pp 11–13).

Strengths of the study included the use of high-quality cohort data for the unprecedented size, population, and geographical variability; use of rigorous criteria for assessment of COPD by spirometry; objective and detailed assessment of built environment at a high resolution; and a range of sensitivity tests.

Among limitations, the cross-sectional design constrains causal inference. Our analyses adjusted for several confounders; nonetheless, risk of residual confounding cannot be ruled out as in any observational study. Potential exposure misclassification might have arisen due to the use of ambient PM2·5 exposure, which disregards participants’ real diurnal activity space-time coordinates and personal exposures profiles could not be disaggregated by indoor or outdoor exposure or time spent commuting. The study did not have PM2·5 and built environment data to account for the specific effects of exposures in a participant’s work environment or related detrimental occupational exposures. Our assessment of COPD did not involve bronchodilator reversibility testing and hence bronchodilator lung function could not be measured. It has been suggested that reduced lung function on account of airflow obstruction can arise because of COPD or asthma, and so prevalence is likely to be overestimated.36 To compensate for this overestimation to some extent, we had excluded all COPD cases occurring in conjunction with doctor-diagnosed and self-reported asthma cases (n=709). Additionally, the use of rigorous inclusion criteria (Global Initiative for Chronic Obstructive Lung Disease stage 2+ spirometry) compensated for the absence of post-bronchodilator lung function, ensuring that most COPD cases are likely to have been captured. It has also been suggested that the bronchodilator reversibility test is often unreliable as the test performance can be affected by factors such as the day of testing, the severity of baseline lung-function impairment before testing, and the number of drugs given to test.37 The UK Biobank cohort had a low response rate of 5·5% and as such the prevalence of COPD and related comorbidities within the cohort are not representative of UK-wide prevalence and our analytical
sample was not representative of the full cohort. The study was also restricted to individuals of white European ancestry. Yet, given the very large sample size and diverse population-level characteristics and heterogeneous environmental exposures across a wide geographical scale, it is probable that the low response rate would have a minimal effect on the generalisability for the reported associations.43

In conclusion, in the largest cross-sectional study of COPD prevalence and the built environment thus far, PM<sub>2.5</sub> exposure and urbanicity were independently associated with higher odds of COPD, whereas green exposure had a net protective effect. Our results suggest the potential value of urban planning and design interventions such as green infrastructure and urban ventilation corridors in minimising or offsetting environmental risks associated with COPD.

Contributors
CS, BZ, and CW conceived the study. CS, BZ, MN, JG, and CW designed the study. CS, SK, and SB helped with the literature review. CS and SK developed the built environment metrics used in the study. CS and BZ did statistical analyses. CS developed the first draft. CW, JG, SB, MN, and SK commented on the draft and all the authors contributed to redrafting and interpretations. All the authors read and approved the final manuscript.

Declaration of interests
We declare no competing interests.

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References
1 Soriano JB, Abajobir AA, Alate KH, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 2017; 5: 691–706.
2 Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1659–544.
3 Vos T, Barber RM, Bell B, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 386: 743–800.
4 McLean S, Hoogendoorn M, Hoogenveen RT, et al. Projecting the COPD population and costs in England and Scotland: 2011 to 2030. Sci Rep 2016; 6: 31893.
5 Liu Y, Lee K, Perez-Padilla R, Hudson NL, Mannino DM. Outdoor and indoor air pollution and COPD-related diseases in high- and low-income countries. Int J Tuberc Lung Dis 2008; 12: 115–27.
6 Eiserer MD, Anthonisen N, Coutsou D, et al. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010; 182: 693–718.
7 Schikowski T, Mills IC, Anderson HR, et al. Ambient air pollution: a cause of COPD? Eur Respir J 2014; 43: 250–63.
8 Berend N. Contribution of air pollution to COPD and small airway dysfunction. Respir Res 2016; 21: 237–44.
9 Li J, Sun S, Tang R, et al. Major air pollutants and risk of COPD exacerbations: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis 2016; 11: 3079–91.
10 Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 2017; 389: 1907–18.
11 Ling SH, van Eeden SF. Particulate matter air pollution exposure: role in the development and exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2009; 4: 233–43.
12 Feng S, Gao D, Liao F, Zhou F, Wang X. The health effects of ambient PM<sub>2.5</sub> and potential mechanisms. Environ Sci 2016; 128: 67–74.
13 Lin H, Qian ZM, Guo Y, et al. The attributable risk of chronic obstructive pulmonary disease due to ambient fine particulate pollution among older adults. Environ Int 2018; 113: 141–48.
14 Wang C, Xu J, Yang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. Lancet 2018; 391: 1706–17.
15 Liu S, Zhou Y, Liu S, et al. Association between exposure to ambient particulate matter and chronic obstructive pulmonary disease: results from a cross-sectional study in China. Thorax 2017; 72: 788–95.
16 Schikowski T, Adam M, Marcon A, et al. Association of ambient air pollution with the prevalence and incidence of COPD. Eur Respir J 2014; 44: 614–26.
17 Wang Y, Shi I, Lee M, et al. Long-term exposure to PM2.5 and mortality among older adults in the southeastern US. Epidemiology 2017; 28: 207–14.
18 Pun VC, Kazemipourkhah F, Manson J, et al. PM<sub>2.5</sub> exposure and respiratory, cancer, and cardiovascular mortality in older US adults. Am J Epidemiol 2017; 186: 691–69.
19 Rice MB, Ljungman PL, Wilker EH, et al. Long-term exposure to traffic emissions and fine particulate matter and lung function decline in the Framingham Heart study. Am J Respir Crit Care Med 2015; 191: 656–64.
20 Guo C, Zhang Z, Lai AKH, et al. Effect of long-term exposure to fine particulate matter on lung function decline and risk of chronic obstructive pulmonary disease in Taiwan: a longitudinal, cohort study. Lancet Planet Health 2018; 2: e14–25.
21 Ni L, Chuan C-C, Zuo L. Fine particulate matter in acute exacerbation of COPD. Front Physiol 2015; 6: 294.
22 Hooper LG, Young MT, Keller JP, et al. Ambient air pollution and chronic bronchitis in a cohort of U.S. women. Environ Health Perspect 2018; 126: 027005.
23 Cai Y, Schikowski T, Adam M, et al. Cross-sectional associations between air pollution and chronic bronchitis: an ESCAPE meta-analysis across five cohorts. Thorax 2014; 69: 1005–14.
24 Nachman KE, Parker JD. Exposures to fine particulate air pollution and respiratory outcomes in adults using two national datasets: a cross-sectional study. Environ Health 2012; 11: 25.
25 DeVries R, Kriebel D, Sama S. Outdoor air pollution and COPD-related emergency department visits, hospital admissions, and mortality: a meta-analysis. COPD 2017; 14: 113–21.
26 Li M-H, Fan L-C, Mao B, et al. Short-term exposure to ambient fine particulate matter increases hospitalizations and mortality in COPD: a systematic review and meta-analysis. Chest 2016; 149: 447–58.
27 van Dorn A. Urban planning and respiratory health. Lancet Respir Med 2017; 5: 781–82.
28 Tischer C, Gasmon M, Fernández-Somoano A, et al. Urban green and grey space in relation to respiratory health in children. Eur Respir J 2017; 49: 1502112.
29 Maas J, Verheij RA, de Vries S, Spreeuwenberg P, Schellevis FG, Groenewegen PP. Morbidity is related to a green living environment. J Epidemiol Community Health 2009; 63: 967–73.
30 Lambert KA, Bowatte G, Thun M, et al. Residential greenness and allergic respiratory diseases in children and adolescents—a systematic review and meta-analysis. Environ Res 2017; 159: 212–21.
31 Alcock I, White M, Cherrie M, et al. Land cover and air pollution are associated with asthma hospitalisations: a cross-sectional study. Environ Int 2017; 109: 29–41.
