**TITLE: The occupations at increased risk of chronic obstructive pulmonary disease (COPD): analysis of lifetime job-histories in the population-based UK Biobank Cohort**

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**‘Take home’ message:**

We identified jobs at increased COPD risk using the job-histories of a large population-based cohort. The results were confirmed in never-smokers and never-asthmatics. Focussed preventive strategies are warranted to avoid the occupational COPD burden.

**ABSTRACT**

Occupational exposures are important, preventable causes of chronic obstructive pulmonary disease (COPD). Identification of COPD high-risk jobs is key to focus preventive strategies, but a definitive job-list is unavailable.

We addressed this issue by evaluating the association of lifetime job-histories and lung function data in the population-based UK Biobank cohort, whose unprecedented sample size allowed analyses restricted to never-smokers to rule out the most important confounder, tobacco smoking. COPD was spirometrically-defined as forced expiratory volume in 1 s (FEV1)/ forced vital capacity (FVC) < lower limit of normal (LLN). Lifetime job-histories were collected via OSCAR, a new validated online-tool that automatically codes jobs into the UK Standard Occupational Classification v.2000.Prevalence ratios for COPD by employment duration in each job compared to lifetime office workers were estimated using robust Poisson regression adjusted for age, sex, centre and smoking. Only associations confirmed among never-smokers and never-asthmatics were considered reliable.

From the 116375 participants with complete job-histories, 94551 had acceptable/repeatable spirometry data and smoking information and were included in the analysis. Six occupations showed an increased COPD risk also among never-smokers and never-asthmatics; most of these also with positive exposure-response trends. Interesting new findings included sculptors, gardeners, and warehouse workers.

COPD patients, especially never-smokers, should be asked about their job-history for better disease management. Focussed preventive strategies in COPD high-risk jobs are warranted.

**Introduction**

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death globally [1]. It is estimated that about 15% of COPD cases are attributable to preventable occupational exposures overall [2], and up to 30% among never-smokers [3]. These percentages may increase in the near future due to the ageing workforce and the decrease in smoking habits in the general population. Defining a list of high-risk jobs for COPD is pivotal to focus preventive strategies and avoid the associated disability and mortality burdens. Several challenges have prevented this to date: workforce-based studies cannot explore the broad variety of jobs occurring in a general population; small studies have been underpowered to detect significant associations; there has been variable accuracy in the methods used to collect and code individual job-titles and when studies have been large and used lifetime job-histories there has often been inadequate adjustment for the main confounder, tobacco smoking [2] [4] [5] [6] [7] [8]. We previously overcame the above limitations in a cross-sectional analysis of the UK Biobank study, a large UK population-based cohort with good quality spirometry data and detailed lifetime information on tobacco smoking [9]. However, only current job at recruitment was available at the time; this is not only a potential limitation when assessing the risk for a chronic condition such as COPD but also increases the chance of a healthy worker survivor effect (HWSE) bias [10]. To advance our analyses, we developed an innovative web-based tool, OSCAR, to reliably collect and automatically code lifetime job-histories for all Biobank participants [11]. The aim of the present work was to analyse the lifetime job-histories collected and coded by OSCAR to study the association between COPD and type and duration of each job held over a lifetime of employment. The unprecedented large sample size allowed us to restrict the analyses to never-smokers to rule out confounding by smoking.

**Methods**

***Study base: the UK Biobank cohort***

The UK Biobank study is a large population-based prospective cohort of over half a million men and women recruited between 2006 and 2010 throughout the UK. Full details of the study protocol have been published elsewhere [9]. Briefly, a random sample of adults aged 40–69 years was identified from lists of those registered with the National Health Service in Britain, and who lived within specified distances of 22 health assessment centres. The reported response rate to the baseline UK Biobank survey was 5.5% (503325/9.2 million invited). Baseline assessment included collection of extensive personal and demographic data (including age, sex, lifetime smoking history, current employment and doctor-diagnosed asthma) through computer-assisted self-administered questionnaire and face-to-face interview, and physical health measurements (including height, weight and spirometry).

***COPD definition***

Details of the spirometry protocol in the UK Biobank have been previously reported [9]. Among the 502649 UK Biobank participants who completed the baseline questionnaire, 457282 subjects (91%) had lung function testing at recruitment. All spirometric measures were performed using a Vitalograph Pneumotrac 6800 in accordance with the ATS/ERS guidelines [12], but participants were allowed up to three attempts to provide two reproducible manoeuvres. The spirometer software compared the reproducibility of the first two blows and, if satisfactory (defined as a ≤5% difference in both FVC and FEV1), a third blow was not required. No post-bronchodilator measures were performed. For our work, we included acceptable spirometry data based on a quality appraisal of the flow curves from a random representative sample of these manoeuvres, as previously described [10]. We further excluded spirometry from participants who had smoked tobacco or used inhalers one hour prior to testing. We defined COPD as FEV1/FVC<LLN (i.e. the 5% lower tail of the normal distribution of the average predicted FEV1/FVC in a reference healthy never-smoking population) based on the age range of our study population. We used the Hankinson equation to calculate the predicted values for FEV1/FVC for each participant based on their individual age, sex, and height [13-15]. Of note, about 95% of the study participants reported a ‘White’ ethnic origin.

***Lifetime job-histories collection and coding: the online OSCAR tool***

To collect and code the lifetime job-histories for all the UK Biobank participants using traditional methods (e.g. personal interviews, or self-administered job questionnaires) was not feasible given the huge sample size; consequently we developed and validated a web-based system (OSCAR: Occupations Self-Coding Automatic Recording); the methodological details have been previously published [11]. Briefly, OSCAR is an online categorical decision tree, based on a simplified but faithful version of the hierarchical structure of the UK Standard Occupational Classification (SOC),v.2000 [16], that uses a three-level decision tree displayed as job-lists on three linked web-pages starting with 15 major job-groups (as a *proxy* for industry sectors), followed by job sub-groups and ending in specific job-titles (i.e. the original 353 4-digit SOC codes) to enable participants to quickly and easily find each job they have held in their life. On selection of a final job-title, a hidden 4-digit SOC code is automatically assigned to that job and retained in the database. By design, OSCAR records full time paid jobs held in life for at least six months. The year of start and end for each job are recorded and displayed together with any job gap in a timetable that can be edited anytime by the participants and helps to visualise and accurately build a ‘career timeline’.

***Statistical analysis***

To evaluate the association between lifetime occupational exposures and COPD risk, the job-histories were truncated, for each participant, to the time of spirometry used to define COPD; the same applies to exposures to the potential confounders.

We used a Poisson regression model with a robust error variance [17] to estimate prevalence ratios (PRs) and 95% confidence intervals (CIs) for ever employment and years of lifetime employment duration in each 4-digit SOC-coded job using lifetime office workers (i.e. subjects who had only ever held office-based jobs) as a fixed reference category.

The final statistical model included, as adjustment covariates, age (5-year categories), sex, recruitment centre (22 categories), and lifetime tobacco smoking (ever/never, pack-years and years since quitting).

Many SOC-coded occupations were tested (n=353), but we thought that the application of a formal statistical correction method (e.g. Bonferroni) might be too penalising, given that our approach was not completely agnostic (i.e. some occupations suspected *a priori* to be associated with an increased COPD risk). Therefore, to reduce the chance of false positive associations, we used the following approach. Firstly, we tested the COPD risk for ever employment in each of the 353 jobs. Secondly, the associations showing formal statistical significance (p<0.05), and moderate strength of association (PR≥1.30), and with at least five exposed persons in both cases and non-COPD participants, were tested for exposure-response trends by using lifetime job durations as categorical variables (<0.5 years; 0.5-10 years, and >10 years to ensure enough subjects per duration category). Finally, the associations showing significant/borderline exposure-response trends were assessed in analyses restricted to: 1) lifetime non-smokers (to rule out residual confounding by tobacco smoking) and 2) those who did not report a doctor’s diagnosis of asthma (to decrease the chance of disease misclassification given that only pre-bronchodilator spirometry measures were available). Only the associations confirmed in both sensitivity analyses were considered to be reliable and are reported for discussion.

All analyses were performed using Stata version 14 (StataCorp. 2014. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

**Results**

OSCAR was administered by email to all UK Biobank participants with an available email address (n= 324653) between June 2015 and February 2016; reminder emails were sent to partial- and non-responders up until December 2015. Only the complete and validated job-histories collected by OSCAR were included in this study. Overall, 116375 Biobank participants completed OSCAR (response rate: 35.8%). Of these, 94551 had acceptable and repeatable spirometry data (according to the above reported criteria) and lifetime smoking information, and were consequently included in the final analyses. The detailed study flow diagram is reported in figure 1.

[figure 1 here]

**FIGURE 1*.*** **Study flow-diagram in the UK Biobank cohort: analysis of the lifetime job-histories.**

\*Absolute contraindications to spirometry included chest infection in the last month (i.e., influenza, bronchitis, severe cold, pneumonia); history of detached retina; heart attack or surgery to eyes, chest or abdomen in last 3 months; history of a collapsed lung; pregnancy (1st or 3rd trimester); and currently on medication for tuberculosis.

The main characteristics of our sample are shown in table 1. About 54% were women; the average age was 55.9 years (SD: 7.6), similar in both genders. The majority were lifetime non-smokers (n= 55596; 58.8%), both in men (n=21975; 52.6%) and women (n=33621; 63.7%); only a minority were current smokers (n=5302; 5.6%), both in men (n=2750; 6.6%) and women (n=2552; 4.8%). About 11% of participants reported that a diagnosis of asthma had been made at some point during their life.

The overall prevalence of spirometry-defined COPD in our sample was 8.0% corresponding to 7606 cases, similar in both genders. As expected the prevalence of COPD was higher among current smokers (16.8%) compared to ex- (8.6%) and never-smokers (6.9%).

**TABLE 1.** Selected characteristics of the study participants who collected their lifetime job-histories using OSCAR (n= 94551), overall and by sex, in the UK Biobank study, 2006-2010, UK.

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Women** | **Men** | **Total** |
|  | **n** | **%** | **n** | **%** | **n** | **%** |
| **Subjects** | 52756 | 54.3 | 41795 | 44.2 | 94551 | 100 |
| **Age category (years)** |  |  |  |  |  |  |
| 40-44 | 5384 | 10.2 | 3892 | 9.3 | 9276 | 9.8 |
| 45-49 | 7748 | 14.7 | 4956 | 11.9 | 12704 | 13.4 |
| 50-54 | 9783 | 18.5 | 6370 | 15.2 | 16153 | 17.1 |
| 55-59 | 11572 | 21.9 | 8643 | 20.7 | 20215 | 21.4 |
| 60-64 | 12093 | 22.9 | 11072 | 26.5 | 23165 | 24.5 |
| 65-69 | 6063 | 11.5 | 6714 | 16.1 | 12777 | 13.5 |
| 70-74 | 113 | 0.2 | 148 | 0.4 | 261 | 0.3 |
| **Age (years)** |  |  |  |  |  |  |
| Mean (SD) |  55.4 |  (7.5) |  56.6 | (7.7) | 55.9 | (7.6) |
| **Smoking status** |  |  |  |  |  |  |
| Never | 33621 | 63.7 | 21975 | 52.6 | 55596 | 58.8 |
| Former (quit >6 months ago) | 16583 | 31.4 | 17070 | 40.8 | 33653 | 35.6 |
| Current | 2552 |  4.8 | 2750 |  6.6 | 5302 |  5.6 |
| **Smoking pack-years\*** |  |  |  |  |  |  |
| median (IQR) | 14.0 | (7-24) | 17.6 | (9-30) | 15.7 | (8-27) |
| **Time since quitting smoking (years)†** |  |  |  |  |  |  |
| Mean (SD) | 19.4 | (11.4) | 20.6 | (11.9) | 20 | (11.7) |
| **Doctor’s diagnosis of asthma, n (%)** |  |  |  |  |  |  |
| Ever | 6182 | 11.7 | 4335 | 10.4 | 10517 | 11.1 |
| **COPD status, n (%)** |  |  |  |  |  |  |
| Current | 4224 | 8.0 | 3382 | 8.1 | 7606 | 8.0 |

\*Smoking pack-years = (n cigarettes/day ÷ 20 cigarettes) × n years; amongst ever smokers. †Time since quitting smoking = years since last smoked cigarette to time of interview; amongst former smokers. Abbreviations: IQR= Inter Quartile Range; SD=Standard Deviation. COPD: spirometry-defined as FEV1/FVC<LLN.

***Lifetime job-histories: descriptive statistics***

The job-histories reported by the 94551 OSCAR participants covered the period from 1949 to 2016. The maximum number of jobs reported by each participant was 40 with a median of three jobs (IQR: 2 - 4). Among them 18642 (19.7%) reported no job interruptions.

Within the 15 major job-group categories used by OSCAR as a *proxy* for industry sectors (figure 2), participants most commonly reported SOC-coded jobs in the office-based work sector (n=48570; 51.4%) and the least in the mining sector (n=1445; 1.5%). Gender-differences were present: for example, men dominated the mining sector, and women the cleaning sector (Supplementary table S1). Those who reported only ever working in office-based jobs numbered 19286 (20.4% of our sample; 12282 women and 7004 men), and were used as a reference category in all the analyses.

[figure 2 here]

**FIGURE 2. Distribution of SOC-coded jobs collected by OSCAR among the UK Biobank participants by industry sector\***

\*Industry sector = major job-grouping in OSCAR; emergency= jobs in emergency service, and armed forces

***Analysis of ever employment and lifetime job duration within each 4-digit SOC-coded occupation***

Among the evaluated 353 SOC-coded occupations, 24 showed a statistically/borderline significant increased risk of COPD (Supplementary table S2). We focused the analyses by lifetime employment duration on the 19 jobs with a significant (p<0.05) moderate COPD increased risk (PR≥1.30), and with at least five exposed persons in both COPD cases and ‘healthy’ (i.e. non-COPD) participants. Table 2 includes, in order of 4-digit SOC code, the 10 occupations that showed at least a moderate significant increased risk of COPD in one of the job duration categories, and significant/borderline positive exposure-response trends overall. When the analyses were restricted to never-asthmatics, the results remained substantially unchanged. However, the exclusion of ever-smokers from the analyses reduced the associations with COPD risk to seven occupations only (see occupations in bold in table 2). Prevalence ratios in each of the 353 SOC-coded occupations by lifetime duration of employment are available for reference in Supplementary Tables S3, S4, and S5, for all subjects, never-asthmatics, and never-smokers, respectively. Of note, among never-smokers only, a doubled COPD risk in ‘8121-Paper and wood machine operatives’ emerged with a positive exposure-response trend (Supplementary Table S5).

**TABLE 2.** Prevalence ratios (PRs) and 95% confidence intervals (CIs) of COPD risk spirometry-defined as FEV1/FVC<LLN for lifetime job duration in an occupation coded as 4-digit SOC code 2000 in the UK Biobank study: overall (n= 94551), never-asthmatics (n= 84034), and never-smokers (n=55596).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 4-digit SOC coded Occupations | Categories of job duration(years) | All subjects | Never-asthmatics | Never-smokers |
|  |  | **Healthy****Exposed** | **Cases****Exposed** | **PR** | **95%CI** | ***Ptrend*** | **PR** | **95%CI** | ***Ptrend*** | **PR** | **95%CI** | ***Ptrend*** |
| 3411-Sculptor, painter, engraver, art restorer |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0.5-10 | 86 | 11 | 1.12 | 0.55 | 2.28 | *0.05* | 1.14 | 0.50 | 2.62 | *0.08* | 0.96 | 0.32 | 2.90 | *0.004* |
| >10 | 88 | 12 | 1.77 | 1.01 | 3.11 | 1.84 | 0.94 | 3.60 | 2.99 | 1.59 | 5.61 |
| 3415-Musician, bandsman, instrumentalist |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0.5-10 | 54 | 10 | 2.20 | 1.28 | 3.78 | *0.01* | 1.70 | 0.78 | 3.70 | *0.001* | 1.29 | 0.33 | 4.97 | *0.29* |
| >10 | 93 | 15 | 1.83 | 1.14 | 2.93 | 2.12 | 1.28 | 3.53 | 1.52 | 0.70 | 3.30 |
| 3433-Public relations, press officer |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0.5-10 | 284 | 34 | 1.42 | 1.02 | 1.97 | *0.003* | 1.25 | 0.82 | 1.90 | *0.02* | 1.75 | 0.14 | 2.69 | *0.26* |
| >10 | 71 | 12 | 1.77 | 1.02 | 3.08 | 2.00 | 1.08 | 3.69 | 0.33 | 0.05 | 2.25 |
| 3442-Sports coach,athlete, instructor, scorer |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0.5-10 | 122 | 19 | 1.78 | 1.15 | 2.76 | *0.004* | 1.69 | 0.98 | 2.91 | *0.04* | 2.13 | 1.25 | 3.63 | *0.03* |
| >10 | 80 | 12 | 1.69 | 0.92 | 3.09 | 1.55 | 0.68 | 3.55 | 1.32 | 0.57 | 3.06 |
| 5113-Gardener, groundsman, park keeper |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0.5-10 | 329 | 37 | 1.24 | 0.89 | 1.73 | *0.007* | 1.19 | 0.79 | 1.79 | *0.07* | 1.08 | 0.64 | 1.84 | *0.03* |
| >10 | 138 | 19 | 1.72 | 1.13 | 2.63 | 1.55 | 0.91 | 2.64 | 2.07 | 1.19 | 3.63 |
| 8111-Food, drink and tobacco processor\* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0.5-10 | 129 | 23 | 1.70 | 1.17 | 2.48 | *0.16* | 1.75 | 1.12 | 2.72 | *0.08* | 2.12 | 1.18 | 3.84 | *0.13* |
| >10 | 81 | 9 | 0.97 | 0.51 | 1.85 | 1.18 | 0.59 | 2.35 | 1.07 | 0.37 | 3.14 |
| 8116-Plastics processor,moulder\*\* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0.5-10 | 122 | 12 | 0.90 | 0.52 | 1.56 | *0.11* | 1.01 | 0.55 | 1.87 | *0.04* | 1.28 | 0.65 | 2.98 | *0.03* |
| >10 | 44 | 11 | 1.86 | 1.09 | 3.17 | 2.16 | 1.19 | 3.90 | 2.74 | 1.15 | 6.48 |
| 9119- Agriculture, and fishing occupations n.e.c.\*\*\* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0.5-10 | 140 | 27 | 1.76 | 1.22 | 2.55 | *0.009* | 1.49 | 0.91 | 2.43 | *0.09* | 2.29 | 1.36 | 3.86 | *0.01* |
| >10 | 19 | 2 | 1.12 | 0.29 | 4.28 | 1.49 | 0.39 | 5.74 | 1.07 | 0.16 | 7.00 |
| 9229-Elementary personal services occupations n.e.c.\*\*\*\* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0.5-10 | 74 | 9 | 1.17 | 0.61 | 2.24 | *0.015* | 1.27 | 0.59 | 2.71 | *0.02* | 0.92 | 0.24 | 3.53 |  |
| >10 | 22 | 6 | 2.51 | 1.37 | 4.60 | 2.90 | 1.38 | 6.09 |  | - | - | - | - |
| 9251-Warehouse stock handler, stacker |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0.5-10 | 313 | 30 | 0.98 | 0.68 | 1.41 | *0.03* | 0.97 | 0.63 | 1.50 | *0.05* | 0.96 | 0.55 | 1.67 | *0.04* |
| >10 | 60 | 11 | 1.83 | 1.05 | 3.18 | 1.84 | 1.00 | 3.42 | 2.26 | 1.01 | 5.07 |

Prevalence Ratios (PRs) and 95% confidence intervals (95%CIs) for categories of lifetime job duration (years) in each 4-digit SOC coded occupation and COPD risk (defined as FEV1/FVC<LLN) were calculated by using a Poisson model with robust variance adjusted for sex, study centre (22 categories), age (5-years categories), and lifetime smoking exposure (ever, pack-years, and years since quitting). Reference category: ‘always office workers’. Healthy = non-COPD cases. Cases = COPD cases. n.e.c= not elsewhere classified. Ptrend: from test for categorical trend. Only jobs that overall showed significant (p<0.05) moderate COPD increased risk (PR≥1.30) in one of the job durations are displayed. NB. Occupations in bold are those with significant associations with COPD risk confirmed among all subjects, never-asthmatics, and never-smokers.

\*these jobs include: attendant, bakery assistant, blender, boiler, brewery worker, cook, crusher, cutter, dairy worker, dipper, dryer, filler, finisher, hand, machinist, maker, miller, mixer, preparer, pressman, vatman, washer. \*\*these jobs include: blender, cutter extruder, fabricator, filer, finisher, laminator, machinist, maker, moulder, operator, polisher, presser, trimmer, turner \*\*\*these jobs include: fishing boat (trawler) mate or bosun, fish farm assistant, fish breeder, aquarium assistant, fish hatcher, oyster bed worker, seaweed gatherer, shellfish digger, crabber, shrimper, fish breeder or shellfish cultivator, insect breeder, maggot breeder, mink farm assistant, sheep shearer, fruit and vegetable picker, hedger and ditcher, tree nursery worker/hand, horticultural worker, fruit picker, mushroom picker and other pickers. \*\*\*\*these jobs include: baths attendant, changing room attendant, stage hand, props hand, scenery hand.

***Further sensitivity analysis: the ‘super-normal lung’ effect* *bias***

Given the unexpected increased risk of COPD (confirmed in never-asthmatics) for ‘Sport-related occupations’, we examined whether this reflected ‘super-normal lung’, a condition sometimes referred to as ‘dysanaptic alveolar growth’ that is common in professional athletes. We excluded participants with both FEV1 and FVC higher than 100% predicted values as previously suggested [18]. The exclusion of 97 subjects with ‘super-normal lung’ from the 233 working in this job category (about 42%) reduced the magnitude and significance of the previous risk estimates (table 3) while making similar exclusions for the other six jobs associated with increased COPD risk made little change.

**TABLE 3.** Prevalence ratios (PRs) and 95% confidence intervals (CIs) of COPD risk spirometry-defined as FEV1/FVC<LLN for categories of lifetime job duration (years) in ‘Sport-related occupations’ before and after restriction for ‘super-normal’ lung bias in the UK Biobank study.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 4-digit SOC coded occupation | Categories of lifetime job duration (years) | HealthyExposed | CasesExposed | PR  |  95%CI  | P*trend* |
| 3442-Sports coach, athlete, instructor, scorer |  |  |  |  |  |  |  |
|  | 0.5-10 | 122 | 19 | 1.78 | 1.15 | 2.76 | *0.004* |
|  | >10 | 80 | 12 | 1.69 | 0.92 | 3.09 |
| After restriction for FEV1 and FVC>100%predicted |
|  |  |  |  |  |  |  |  |
|  | 0.5-10 | 77 | *8* | 1.43 | 0.55 | 2.73 | *0.288* |
|  | >10 | 47 | *4* | 1.28 | 0.51 | 3.20 |

Prevalence Ratios (PRs) and 95% confidence intervals (95%CIs) for categories of lifetime job duration (years) in each 4-digit SOC code and COPD risk (defined as FEV1/FVC<LLN) were calculated by using a Poisson model with robust variance adjusted for sex, study centre (22 categories), age (5-years categories), and lifetime smoking exposure (ever, pack-years, and years since quitting). Reference category: ‘always office workers’. Healthy = non-COPD cases. Cases = COPD cases.

**Discussion**

In a large UK population-based prospective cohort, we found that six SOC-coded occupations are associated with a significant increase in COPD risk: ‘Sculptor, painter, engraver, art restorer’; ‘Gardener, groundsman, park keeper’; ‘Food, drink and tobacco processor’; ‘Plastics processor, moulder’; ‘Agriculture, and fishing occupations n.e.c.’; and ‘Warehouse stock handler, stacker’. These associations were confirmed among never-smokers, and never-asthmatics and, for most, we found supporting positive exposure-response by categories of employment duration.

Compared to our previous cross-sectional analysis in the UK Biobank cohort [10], the largest previous population-based study on occupational exposures and COPD risk using a job-title approach, ‘Manufacturing’ emerged again as the sector at highest COPD risk. This industry has been previously reported at increased COPD risk because of the potential exposure to known respiratory occupational hazards [2]. In terms of job-titles, a few specific 4-digit SOC-codes identified at increased COPD risk in the cross-sectional analysis were confirmed (e.g. ‘8111-Food, drink, and tobacco processors’), and new ones emerged within the same job categories (e.g. ‘8116-Plastic process machine operator’ to add to the previous ‘8114-Chemical related process operative’). This supports the validity of our previous findings in terms of job categories and adds, likely due to the availability of lifetime job durations in this analysis, new specific occupations to the list of high-risk COPD jobs so far identified that deserve further attention. Also, in the present analysis we have found a significant increased COPD risk for ‘Agriculture’ occupations that did not emerge in the previous cross-sectional analyses. Agriculture is consistently reported as an important *a priori* high-risk COPD sector, probably because of potential exposure to organic and inorganic dusts, pesticides, herbicides, and diesel exhaust fumes [2] [4] [5] [6] [7] [8]. Using lifetime job history minimises the chance of HWSE bias that might have been present in our earlier cross-sectional study. This bias could also explain the attenuation of the exposure-response trend for Agriculture-related jobs at the highest exposure levels (over 10 years) found in the current analysis [19]. Of note, within the Agriculture sector, ‘Gardeners/groundsmen’ emerged at increased COPD risk; this has not been observed before but the finding is plausible given the potential exposure to hazardous airborne substances such as organic dusts, pesticides, bacteria and fungi spores potentially present in compost materials. Other new interesting jobs emerged in the Manufacturing sector: ‘Plastic processors’, ‘Paper/wood operatives’ (among never smokers only), ‘Sculptors/painters’, and ‘Warehouse stackers’, that deserve further attention due to potential exposure at work to a wide range of hazards including fumes (e.g. heating of plastics, diesel fumes), dusts (e.g. wood, paper, metals, paint pigments) and vapours (e.g. paint solvents and glues). Of note, for warehouse stackers who use diesel powered vehicles the exposure may occur in confined spaces or where ventilation is insufficient.

Interestingly, we found a ‘super-normal lung’ bias effect that led to an observed increased risk of COPD among sport occupations. This has been, previously reported in the occupational health setting [18]. From a qualitative review of the collected job-title descriptions within this cohort, about one-third were ex- or current professional swimmers, so potentially exposed to chloramines that are known respiratory irritants and sensitizers [20, 21]. It is still debated if this phenomenon is due to exercise-induced accelerated alveoli growth in those who start intense physical activity such as swimming in childhood or merely to the selection of children with genetically larger lungs into these highly physically demanding sports [22, 23]. Nevertheless, we would suggest that epidemiological studies should rule out this potential selection bias when evaluating spirometry-defined COPD risk among this category of workers.

Our study has several strengths. First, its large sample size which, to the best of our knowledge, is greater than that of any previous study conducted on lifetime occupations and COPD risk (spirometry-defined) in a general population. The large sample let us confirm our findings among never-smokers and never-asthmatics, so ruling out any potential residual confounding effect of tobacco smoking and disease misclassification with asthma, respectively. Of note, the important impact on our risk estimates of restricting the analyses to never smokers, confirms the strong causal relationship between COPD and smoking, and suggests that large studies among never smokers should be performed when assessing the effect of occupational risk factors. Second, our study is not limited to an industrial sector, but covers a broad variety of occupations and industry sectors in the general working population, increasing the chance of our analysis to detect all the potential COPD-high risk jobs. Third, the high quality of the spirometry definition of the COPD outcome, based on acceptable, and repeatable manoeuvres according to almost all ATS/ERS criteria [12]. Fourth, the reliable occupational exposure assessment, based on a new validated automatic online tool, OSCAR, which coded each job collected using standard occupational codes blind to COPD status, ruling out any differential misclassification. Finally, the collection of individual lifetime job-histories that allowed us to increase statistical power, to minimize the risk of a HWSE bias, and to explore exposure-response trends by using categories of job duration, so supporting the validity of our positive risk associations.

Nevertheless, we acknowledge some limitations: although all of the 353 4-digit SOC 2000 codes were present in UK Biobank population, there were only small numbers in some job categories (e.g. coal miners); this may have occurred because they were not prevalent in the populations recruited or because people in these job categories were less likely to respond to UK Biobank study overall and/or less likely to respond to the OSCAR tool. Also, for some jobs, the low number of subjects in the highest lifetime job duration categories may have prevented us detecting statistically significant exposure-response trends. This is expected in a low-exposed general population sample [24], and even more in a voluntary cohort that was designed to be internally valid, but not representative of the entire UK population [25]. Therefore, we cannot rule out a certain degree of selection bias due to the nature of the entire Biobank cohort (i.e. more women, educated, non-smokers, and mostly ‘White’) that might have affected our ability to detect increased COPD risk in some of the few expected at risk occupations.
Spirometry tests were conducted without bronchodilator, but we managed to overcome a potential COPD misclassification with asthma by restricting our analyses to those reporting never having had a diagnosis of, or treatment for, asthma. Of note, the COPD prevalence estimated in our sample was within the range of that expected in the UK based on our spirometry definition, and study population age range [13]. Finally, even if we used a standard job coding classification and a reliable occupational assessment tool, we cannot rule out a certain degree of job misclassification, but this is likely to be non-differential so resulting in a ‘bias towards the null’ that would underestimate the true associations [26].

In conclusion, analysing the lifetime job-histories of about 100,000 individuals from a general population, we found that six specific occupations are associated with an increased COPD risk. Given the unprecedented large sample, and the consistency of our results in sensitivity analyses, in particular in never-smokers, we are confident of the validity of these findings and that they deserve further investigation. Occupational risk factors for COPD are both important and preventable: the identification of the jobs at high-risk is pivotal to inform focussed workplace preventive strategies. This should be a public health policy priority, in particular in ageing working populations where the associated costs in terms of morbidity and disability are regrettably expected to increase.

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**Declaration of interests**

None to declare.

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**Authors’ contributions:**

Sara De Matteis conceived, and conducted the statistical analyses, interpreted the results, and wrote the article. Paul Cullinan, Lesley Rushton, and Deborah Jarvis, as PIs of the project, coordinated and supervised the analyses, and contributed to the interpretation of the results. All the Authors contributed to the project, and reviewed the final version of the manuscript.

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