Supplemental material

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Frequency and severity of respiratory infections prior to COPD diagnosis and risk of future exacerbations and mortality: a UK routine health care data study

Supplementary material

Contents

Additional methodology

Analyses were performed in STATA17. Baseline characteristics were defined prior to COPD diagnosis. These included age, sex, smoking status (current or ex-smoker), BMI, history of depression, anxiety disorder, gastro-oesophageal reflux disease (GORD), lung cancer, myocardial infarction, heart failure and stroke, current asthma, socioeconomic deprivation, Medical Research Council (MRC) dyspnoea score, GOLD-defined airflow obstruction, and current elevated blood eosinophil level (using threshold of 300 cells/µl). These characteristics were described overall and by LRTI exposure sub-group using mean (SD) for continuous measures and numbers (%) for categorical measures. They included age at index date, sex, closest smoking status to index date (current or ex-smoker), current BMI within 5 years of index date (underweight <18.5kg/m2, normal 18.5-24.9kg/m2, overweight 25.0-29.9kg/m2, and obese ≤30.0kg/m2), history of depression, anxiety disorder, gastro-oesophageal reflux disease (GORD), lung cancer, myocardial infarction, heart failure and stroke ever recorded prior to index date, current asthma defined in a period of 3 years 2 years prior to index date, current socioeconomic deprivation using the Index of Multiple Deprivation (categorized into quintiles), current Medical Research Council (MRC) dyspnoea score identified within 2 years of index date (1-5, a higher score indicating more severe dyspnoea), current GOLD-defined airflow obstruction defined within 2 years of index date (GOLD 1: FEV1 % predicted ≥80%; GOLD 2: FEV1 % predicted 50-79%; GOLD 3: FEV1 % predicted 30-49%; GOLD 4: FEV1 % predicted <30%), and current elevated blood eosinophil level defined within 1 years of index date (using threshold of 300 cells/µl).

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Table S1: Incidence rates of at least one AECOPD (moderate or severe) following COPD diagnosis in different categories of baseline frequency and severity of LRTI

Baseline LRTI category	n (%) of events N=948,576	Rate 100py^{-1} (95% CI)	Crude IRR (95% CI)	Adjusted* IRR (95% CI)
No LRTI n=158,074	512,658	61.9 (61.7 – 62.1)	Reference	Reference
1 mild LRTI n=18,081	52,232	72.0 (71.3 – 72.6)	1.18 (1.15-1.20)	1.16 (1.14-1.18)
2+ mild LRTI n=6,133	21,717	95.7 (94.5 – 97.0)	1.56 (1.51-1.61)	1.51 (1.46-1.55)
1 moderate LRTI n=19,787	145,161	113.2 (112.6 – 113.8)	1.92 (1.88-1.95)	1.81 (1.78-1.85)
2+ moderate LRTI n=6,227	68,822	168.2 (167.0 – 169.5)	2.88 (2.80-2.97)	2.55 (2.48-2.63)
1+ severe LRTI n=6,932	22,280	96.1 (94.8 – 97.4)	2.05 (1.99-2.12)	1.75 (1.70-1.80)

Legend: AECOPD (Acute Exacerbations of Chronic Obstructive Pulmonary Disease), LRTI (Lower Respiratory Tract Infection), IRR (Incidence Rate Ratio). PY (Person years). *Adjusted for all baseline covariates listed in Table 1. Number of patients included crude and fully adjusted models N= 215,234.

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Table S2: Incidence rates of at least one moderate AECOPD following COPD diagnosis in different categories of baseline frequency and severity of LRTI

Baseline LRTI category	n (%) of events N=948,576	Rate 100py^{-1} (95% CI)	Crude IRR (95% CI)	Adjusted* IRR (95% CI)
No LRTI n=158,074	512,658	61.9 (61.7 – 62.1)	Ref	Ref
1 mild LRTI n=18,081	52,232	72.0 (71.3 – 72.6)	1.14 (1.12-1.16)	1.14 (1.12-1.16)
2+ mild LRTI n=6,133	21,717	95.7 (94.5 – 97.0)	1.54 (1.49-1.59)	1.50 (1.45-1.55)
1 moderate LRTI n=19,787	145,161	113.2 (112.6 – 113.8)	2.02 (1.98-2.06)	1.90 (1.87-1.94)
2+ moderate LRTI n=6,227	68,822	168.2 (167.0 – 169.5)	3.08 (2.98-3.17)	2.71 (2.64-2.79)
1+ severe LRTI n=6,932	22,280	96.1 (94.8 – 97.4)	1.60 (1.55-1.66)	1.44 (1.39-1.49)

Legend: AECOPD (Acute Exacerbations of Chronic Obstructive Pulmonary Disease), LRTI (Lower Respiratory Tract Infection), IRR (Incidence Rate Ratio). PY (Person years). *Adjusted for all baseline covariates listed in Table 1. Number of patients included crude and fully adjusted models N= 215,234.

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Table S3: Incidence rates of at least one severe AECOPD following COPD diagnosis in different categories of baseline frequency and severity of LRTI

Baseline LRTI category	n (%) of events N=948,576	Rate 100py^{-1} (95% CI)	Crude IRR (95% CI)	Adjusted* IRR (95% CI)
No LRTI n=158,074	81,259	9.8 (9.7 – 9.9)	Ref	Ref
1 mild LRTI n=18,081	9,539	13.1 (12.9 – 13.4)	1.35 (1.29-1.40)	1.25 (1.20-1.29)
2+ mild LRTI n=6,133	3,629	16.0 (15.5 – 16.5)	1.65 (1.55-1.76)	1.48 (1.40-1.57)
1 moderate LRTI n=19,787	16,466	12.8 (12.6 – 13.0)	1.37 (1.32-1.42)	1.30 (1.26-1.34)
2+ moderate LRTI n=6,227	6,760	16.5 (16.1 – 16.9)	1.82 (1.72-1.93)	1.62 (1.54-1.70)
1+ severe LRTI n=6,932	8,053	34.7 (34.0 – 35.5)	4.46 (4.22-4.72)	3.03 (2.87-3.18)

Legend: AECOPD (Acute Exacerbations of Chronic Obstructive Pulmonary Disease), LRTI (Lower Respiratory Tract Infection), IRR (Incidence Rate Ratio). PY (Person years). *Adjusted for all baseline covariates listed in Table 1. Number of patients included crude and fully adjusted models N= 215,234.

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Table S4: Hazard ratios for all-cause mortality following COPD diagnosis in different categories of baseline frequency and severity of LRTI.

Baseline LRTI category	n (%) of events N=51,669	Crude HR (95% CI)	Adjusted* HR (95% CI)
No LRTI n=158,074	36,151 (22.9)	Ref	Ref
1 mild LRTI n=18,081	3,491 (19.3)	1.13 (1.09-1.17)	1.11 (1.07-1.15)
2+ mild LRTI n=6,133	1,096 (17.9)	1.15 (1.08-1.22)	1.14 (1.08-1.22)
1 moderate LRTI n=19,787	6,046 (30.6)	1.07 (1.04-1.09)	1.10 (1.07-1.13)
2+ moderate LRTI n=6,227	2,183 (35.1)	1.20 (1.15-1.26)	1.22 (1.17-1.27)
1+ severe LRTI n=6,932	2,702 (39.0)	2.77 (2.66-2.88)	1.92 (1.84-1.99)

Legend: AECOPD (Acute Exacerbations of Chronic Obstructive Pulmonary Disease), LRTI (Lower Respiratory Tract Infection), HR (Hazard Ratio). *Adjusted for all

baseline covariates listed in Table 1. Number of patients included crude and fully adjusted models N= 215,234.

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Table S5: Hazard ratios for COPD-related mortality following COPD diagnosis in different categories of baseline frequency and severity of LRTI

Baseline LRTI category	n (%) of events N=11,770	Crude HR (95% CI)	Adjusted* HR (95% CI)
No LRTI n=158,074	7,886 (67.0)	Ref	Ref
1 mild LRTI n=18,081	823 (7.0)	1.27 (1.18-1.36)	1.19 (1.11-1.28)
2+ mild LRTI n=6,133	277 (2.4)	1.40 (1.24-1.58)	1.29 (1.14-1.45)
1 moderate LRTI n=19,787	1,425 (12.1)	1.13 (1.07-1.20)	1.13 (1.06-1.19)
2+ moderate LRTI n=6,227	546 (4.6)	1.35 (1.24-1.47)	1.27 (1.16-1.39)
1+ severe LRTI n=6,932	813 (6.9)	4.01 (3.73-4.31)	2.32 (2.15-2.50)

Legend: AECOPD (Acute Exacerbations of Chronic Obstructive Pulmonary Disease), LRTI (Lower Respiratory Tract Infection), HR (Hazard ratio). *Adjusted for all

baseline covariates listed in Table 1. Number of patients included crude and fully adjusted models N= 215,234.

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Table S6: Hazard ratios for CVD-related mortality following COPD diagnosis in different categories of baseline frequency and severity of LRTI
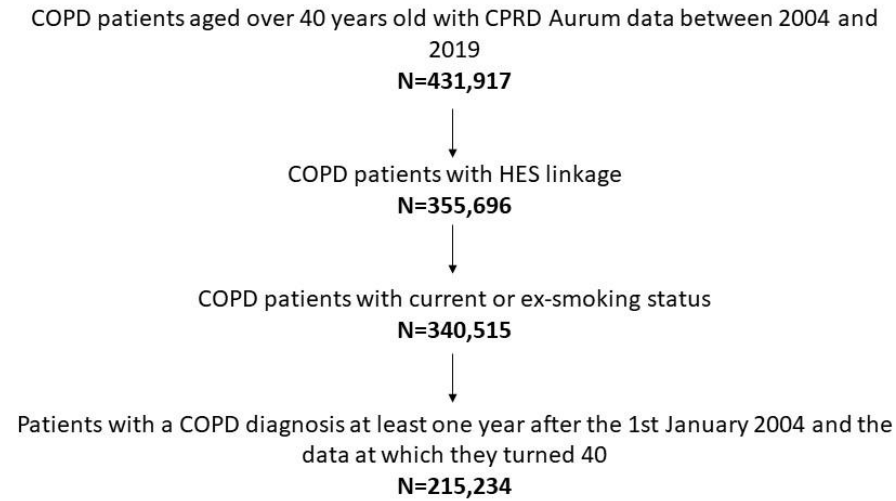
Baseline LRTI category	n (%) of events N=13,116	Crude HR (95% CI)	Adjusted* HR (95% CI)
No LRTI n=158,074	9,325 (71.1)	Ref	Ref
1 mild LRTI n=18,081	875 (6.7)	1.08 (1.01-1.16)	1.06 (0.99-1.14)
2+ mild LRTI n=6,133	291 (2.2)	1.16 (1.03-1.30)	1.17 (1.04-1.31)
1 moderate LRTI n=19,787	1,432 (10.9)	0.99 (0.93-1.04)	1.03 (0.98-1.09)
2+ moderate LRTI n=6,227	544 (4.1)	1.17 (1.08-1.28)	1.20 (1.10-1.31)
1+ severe LRTI n=6,932	649 (4.9)	2.52 (2.33-2.73)	1.68 (1.55-1.82)

Legend: AECOPD (Acute Exacerbations of Chronic Obstructive Pulmonary Disease), LRTI (Lower Respiratory Tract Infection), HR (Hazard Ratio). *Adjusted for all baseline covariates listed in Table 1. Number of patients included crude and fully adjusted models N= 215,234.

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Table S7: Incidence rates of at least one AECOPD (moderate or severe) following COPD diagnosis in different categories of baseline frequency and severity of LRTI (mild and moderate GP events combined)

Baseline LRTI category	n (%) of events N=948,576	Rate 100py^{-1} (95% CI)	Crude IRR (95% CI)	Adjusted* IRR (95% CI)
No LRTI n=158,074	593,917	71.7 (71.5 – 71.9)	Ref	Ref
1 GP LRTI n=34,849	197,612	108.2 (107.7 – 108.7)	1.52 (1.20-1.55)	1.48 (1.46-1.50)
2+ GP LRTI n=10,315	75,068	136.7 (135.7 – 137.7)	1.95 (1.91-2.00)	1.83 (1.79-1.88)
3+ GP LRTI n=5,064	51,646	192.4 (190.7 – 194.1)	2.88 (2.78-2.97)	2.53 (2.45-2.61)
1+ HES LRTI n=6,932	30,33	130.8 (129.4 – 132.3)	2.05 (1.99-2.12)	1.76 (1.70-1.81)

Legend: AECOPD (Acute Exacerbations of Chronic Obstructive Pulmonary Disease), LRTI (Lower Respiratory Tract Infection), IRR (Incidence Rate Ratio). PY (Person years). *Adjusted for all baseline covariates listed in Table 1. Number of patients included crude and fully adjusted models N= 215,234.

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Figure S1: Inclusion of COPD patients

COPD patients aged over 40 years old with CPRD Aurum data between 2004 and 2019
N=431,917

↓

COPD patients with HES linkage
N=355,696

↓

COPD patients with current or ex-smoking status
N=340,515

↓

Patients with a COPD diagnosis at least one year after the 1st January 2004 and the data at which they turned 40
N=215,234

Legend: CPRD (Clinical Practice Research Datalink); HES (Hospital Episode Statistics)