

## 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

<b>Additional methodology</b> .....	2
<b>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</b> .....	3
<b>Table S2: Incidence rates of at least one moderate AECOPD following COPD diagnosis in different categories of baseline frequency and severity of LRTI</b> .....	4
<b>Table S3: Incidence rates of at least one severe AECOPD following COPD diagnosis in different categories of baseline frequency and severity of LRTI</b> .....	5
<b>Table S4: Hazard ratios for all-cause mortality following COPD diagnosis in different categories of baseline frequency and severity of LRTI</b> .....	6
<b>Table S5: Hazard ratios for COPD-related mortality following COPD diagnosis in different categories of baseline frequency and severity of LRTI</b> .....	7
<b>Table S6: Hazard ratios for CVD-related mortality following COPD diagnosis in different categories of baseline frequency and severity of LRTI</b> .....	8
<b>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)</b> .....	9
<b>Figure S1: Inclusion of COPD patients</b> .....	10

### **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/ $\mu$ l). 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/m<sup>2</sup>, normal 18.5-24.9kg/m<sup>2</sup>, overweight 25.0-29.9kg/m<sup>2</sup>, and obese  $\leq$ 30.0kg/m<sup>2</sup>), 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  $\geq$ 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/ $\mu$ l).

**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 <sup>-1</sup> (95% CI)	Crude IRR (95% CI)	Adjusted* IRR (95% CI)
<b>No LRTI n=158,074</b>	512,658	61.9 (61.7 – 62.1)	Reference	Reference
<b>1 mild LRTI n=18,081</b>	52,232	72.0 (71.3 – 72.6)	1.18 (1.15-1.20)	1.16 (1.14-1.18)
<b>2+ mild LRTI n=6,133</b>	21,717	95.7 (94.5 – 97.0)	1.56 (1.51-1.61)	1.51 (1.46-1.55)
<b>1 moderate LRTI n=19,787</b>	145,161	113.2 (112.6 – 113.8)	1.92 (1.88-1.95)	1.81 (1.78-1.85)
<b>2+ moderate LRTI n=6,227</b>	68,822	168.2 (167.0 – 169.5)	2.88 (2.80-2.97)	2.55 (2.48-2.63)
<b>1+ severe LRTI n=6,932</b>	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.

**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 <sup>-1</sup> (95% CI)	Crude IRR (95% CI)	Adjusted* IRR (95% CI)
<b>No LRTI</b> n=158,074	512,658	61.9 (61.7 – 62.1)	Ref	Ref
<b>1 mild LRTI</b> n=18,081	52,232	72.0 (71.3 – 72.6)	1.14 (1.12-1.16)	1.14 (1.12-1.16)
<b>2+ mild LRTI</b> n=6,133	21,717	95.7 (94.5 – 97.0)	1.54 (1.49-1.59)	1.50 (1.45-1.55)
<b>1 moderate LRTI</b> n=19,787	145,161	113.2 (112.6 – 113.8)	2.02 (1.98-2.06)	1.90 (1.87-1.94)
<b>2+ moderate LRTI</b> n=6,227	68,822	168.2 (167.0 – 169.5)	3.08 (2.98-3.17)	2.71 (2.64-2.79)
<b>1+ severe LRTI</b> 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.

**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 <sup>-1</sup> (95% CI)	Crude IRR (95% CI)	Adjusted* IRR (95% CI)
<b>No LRTI</b> n=158,074	81,259	9.8 (9.7 – 9.9)	Ref	Ref
<b>1 mild LRTI</b> n=18,081	9,539	13.1 (12.9 – 13.4)	1.35 (1.29-1.40)	1.25 (1.20-1.29)
<b>2+ mild LRTI</b> n=6,133	3,629	16.0 (15.5 – 16.5)	1.65 (1.55-1.76)	1.48 (1.40-1.57)
<b>1 moderate LRTI</b> n=19,787	16,466	12.8 (12.6 – 13.0)	1.37 (1.32-1.42)	1.30 (1.26-1.34)
<b>2+ moderate LRTI</b> n=6,227	6,760	16.5 (16.1 – 16.9)	1.82 (1.72-1.93)	1.62 (1.54-1.70)
<b>1+ severe LRTI</b> 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.

**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)
<b>No LRTI</b> n=158,074	36,151 (22.9)	Ref	Ref
<b>1 mild LRTI</b> n=18,081	3,491 (19.3)	1.13 (1.09-1.17)	1.11 (1.07-1.15)
<b>2+ mild LRTI</b> n=6,133	1,096 (17.9)	1.15 (1.08-1.22)	1.14 (1.08-1.22)
<b>1 moderate LRTI</b> n=19,787	6,046 (30.6)	1.07 (1.04-1.09)	1.10 (1.07-1.13)
<b>2+ moderate LRTI</b> n=6,227	2,183 (35.1)	1.20 (1.15-1.26)	1.22 (1.17-1.27)
<b>1+ severe LRTI</b> 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.

**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)
<b>No LRTI n=158,074</b>	7,886 (67.0)	Ref	Ref
<b>1 mild LRTI n=18,081</b>	823 (7.0)	1.27 (1.18-1.36)	1.19 (1.11-1.28)
<b>2+ mild LRTI n=6,133</b>	277 (2.4)	1.40 (1.24-1.58)	1.29 (1.14-1.45)
<b>1 moderate LRTI n=19,787</b>	1,425 (12.1)	1.13 (1.07-1.20)	1.13 (1.06-1.19)
<b>2+ moderate LRTI n=6,227</b>	546 (4.6)	1.35 (1.24-1.47)	1.27 (1.16-1.39)
<b>1+ severe LRTI n=6,932</b>	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.

**Table S6: Hazard ratios for CVD-related mortality following COPD diagnosis in different categories of baseline frequency and severity of LRTI**

<b>Baseline LRTI category</b>	<b>n (%) of events N=13,116</b>	<b>Crude HR (95% CI)</b>	<b>Adjusted* HR (95% CI)</b>
<b>No LRTI n=158,074</b>	9,325 (71.1)	Ref	Ref
<b>1 mild LRTI n=18,081</b>	875 (6.7)	1.08 (1.01-1.16)	1.06 (0.99-1.14)
<b>2+ mild LRTI n=6,133</b>	291 (2.2)	1.16 (1.03-1.30)	1.17 (1.04-1.31)
<b>1 moderate LRTI n=19,787</b>	1,432 (10.9)	0.99 (0.93-1.04)	1.03 (0.98-1.09)
<b>2+ moderate LRTI n=6,227</b>	544 (4.1)	1.17 (1.08-1.28)	1.20 (1.10-1.31)
<b>1+ severe LRTI n=6,932</b>	649 (4.9)	2.52 (2.33-2.73)	1.68 (1.55-1.82)

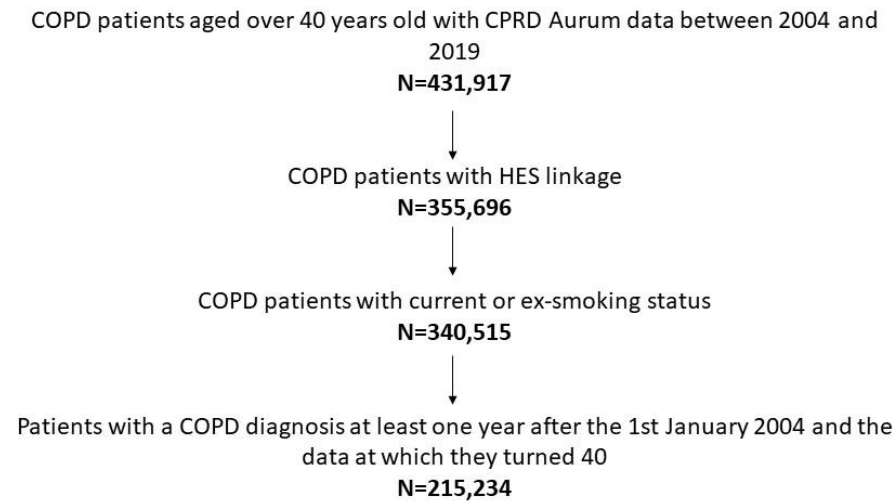
Legend: AECOPD (Acute Exacerbations of Chronic Obstructive Pulmonary Disease), LRTI (Lower Respiratory Tract Infection), HR (Hazard Ratio). \*Adjusted for all baseline covariates listed in Table 1. Number of patients included crude and fully adjusted models N= 215,234.



**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 <sup>-1</sup> (95% CI)	Crude IRR (95% CI)	Adjusted* IRR (95% CI)
<b>No LRTI</b> n=158,074	593,917	71.7 (71.5 – 71.9)	Ref	Ref
<b>1 GP LRTI</b> n=34,849	197,612	108.2 (107.7 – 108.7)	1.52 (1.20-1.55)	1.48 (1.46-1.50)
<b>2+ GP LRTI</b> n=10,315	75,068	136.7 (135.7 – 137.7)	1.95 (1.91-2.00)	1.83 (1.79-1.88)
<b>3+ GP LRTI</b> n=5,064	51,646	192.4 (190.7 – 194.1)	2.88 (2.78-2.97)	2.53 (2.45-2.61)
<b>1+ HES LRTI</b> 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.

**Figure S1: Inclusion of COPD patients**

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