

Supplement Table A: Sensitivity analysis: self-controlled case-series analysis restricted to the first event of pneumonia during the observation period. (Age adjusted incidence rate ratio and 95% confidence intervals).

Period	Broad primary care definition of pneumonia (n=48,451)			Pneumonia definition Narrow primary care definition of pneumonia (n=4,461)			Hospital and mortality records based definition (in HES-ONS linked patients) (n=5,582)		
	No of events	Person years	IRR(95%CI)	No of events	Person years	IRR(95%CI)	No of events	Person years	IRR(95%CI)
Baseline unexposed period	40,236	550492	1.0	2880	46780.9	1.0	3840	43714.2	1.0
Pre-exposed (30 days before first PPI prescription)	1257	9550.72	1.70(1.60 to 1.80)	199	825.791	3.69(3.18 to 4.28)	323	886.324	3.71(3.30 to 4.17)
30 days exposer period (30 day after first PPI prescription)	722	9514.02	0.98(0.91 to 1.05)	132	822.658	2.46(2.06 to 2.94)	222	881.281	2.57(2.24 to 2.95)
The remaining exposure period	6236	88291.2	1.00(0.97 to 1.04)	1250	9467.21	2.98(2.73 to 3.26)	1197	9264.62	1.62(1.49 to 1.75)

Note: All comparisons to baseline pneumonia incidence rate in unexposed periods
HES=Hospital Episode Statistics; IRR=incidence rate ratio; ONS=Office for National Statistics

Supplement Table B: Sensitivity analysis: self-controlled case-series analysis after excluding cases with previous hospitalization.(Age adjusted incidence rate ratio and 95% confidence intervals).

Period	Pneumonia definition					
	Broad primary care definition of pneumonia			Narrow primary care definition of pneumonia		
	(n=34,122)			(n=2,682)		
	No of events	Person years	IRR(95%CI)	No of events	Person years	IRR(95%CI)
Baseline unexposed period	44,943	319090	1.0	1,734	23956.3	1.0
Pre-exposed (30 days before first PPI prescription)	1,722	6034.81	1.85(1.76 to 1.94)	73	470.322	1.96(1.54 to 2.49)
30 days exposer period (30 day after first PPI prescription)	1,066	5998.49	1.15(1.08 to 1.22)	73	467.762	1.98(1.56 to 2.52)
The remaining exposure period	9,101	45147.2	1.42(1.38 to 1.47)	641	4362.37	2.57(2.28 to 2.91)

Note: All comparisons to baseline pneumonia incidence rate in unexposed periods
IRR, incidence rate ratio ;CI, confidence interval

Supplement Table C: Sensitivity analysis: self-controlled case-series analysis excluding patients who died within 90 days of the date of pneumonia diagnosis. (Age adjusted incidence rate ratio and 95% confidence intervals) .

Period	Pneumonia definition								
	Broad primary care definition of pneumonia			Narrow primary care definition of pneumonia			hospital and mortality records based definition (in HES-ONS linked patients)		
	(n=46,496)			(n=3,554)			(n=3,870)		
	No of events	Person years	IRR(95%CI)	No of events	Person years	IRR(95%CI)	No of events	Person years	IRR(95%CI)
Baseline unexposed period	71,348	515040	1.0	2,633	38370.3	1.0	4,485	30278.6	1.0
Pre-exposed (30 days before first PPI prescription)	2,539	8827.25	1.86(1.79 to 1.94)	194	661.005	3.96(3.40 to 4.60)	350	612.526	3.57(3.19 to 4.00)
30 days exposer period (30 day after first PPI prescription)	1,490	8803.66	1.09(1.04 to 1.15)	102	656.287	2.11(1.72 to 2.58)	224	606.556	2.32(2.02 to 2.66)
The remaining exposure period	16,023	80970.8	1.39(1.35 to 1.42)	936	7809.01	2.05(1.86 to 2.26)	1,561	6735.69	1.71(1.59 to 1.84)

Note: All comparisons to baseline pneumonia incidence rate in unexposed periods
HES=Hospital Episode **Statistics**; IRR=incidence rate ratio; ONS=Office for National Statistics

Supplement Table D: Sensitivity analysis: PERR analysis after excluding cases with previous hospitalization, according to the 3 different definitions of community-acquired pneumonia

Parameter	Pneumonia definition			
	Broad primary care definition of pneumonia 265,650		Narrow primary care definition of pneumonia 265,650	
	unexposed	Exposed	unexposed	exposed
Before prescription				
Pneumonia events	3,353(2.5)	7,300(5.5)	126(0.1)	321(0.2)
Incidence of pneumonia per 1,000 per person years (95%CI)	25.57 (24.72 to 26.45)	56.49 (55.21 to 57.80)	1.10 (0.79 to 1.13)	2.41 (2.16 to 2.69)
Hazard ratio(PPI/non-PP) (95%CI)	2.20 (2.11 to 2.29)		2.54 (2.07 to 3.13)	
After prescription				
Pneumonia events	3,518(2.6)	6,603(4.9)	222 (0.1)	428 (0.3)
Incidence of pneumonia per 1,000 per person years (95%CI)	26.86 (25.99 to 27.76)	51.09 (49.87 to 52.34)	1.78 (1.56 to 2.03)	3.50 (3.18 to 3.85)
Hazard ratio(PPI/non-PP) (95%CI)	1.91 (1.82 to 1.98)		2.15 (1.82 to 2.55)	
Prior event rate ratio(PERR)*	0.86 (0.74-0.97)		0.84 (0.65-1.16)	

*PERR= Hazard ratio for pneumonia between exposed and unexposed after proton pump inhibitor prescription divided by the hazard ratio for pneumonia before proton pump inhibitor prescription. CI, confidence interval

Supplement Table E: Sensitivity analysis: PERR analysis after excluding patients who died within 90 days of the date of pneumonia diagnosis, according to the 3 different definitions of community-acquired pneumonia

Parameter	Pneumonia definition					
	Broad primary care definition of pneumonia		Narrow primary care definition of pneumonia		Hospital and mortality records based definition (in HES-ONS linked patients)	
	249,816		249,860		195,770	
	unexposed	exposed	unexposed	exposed	Unexposed	exposed
Before prescription						
Pneumonia events	3,217(2.5)	7,190(5.7)	132(0.1)	396(0.3)	327(0.3)	1,070(1.09)
Incidence of pneumonia per 1,000 per person years (95%CI)	26.10 (25.21 to 27.02)	59.23 (57.88 to 60.62)	1.05 (0.89 to 1.25)	3.17 (2.87 to 3.50)	3.34 (3.00 to 3.72)	10.97 (10.33 to 11.65)
Hazard ratio(PPI/non-PP) (95%CI)	2.26 (2.17 to 2.36)		3.00 (2.46 to 3.65)		3.25 (2.87 to 3.68)	
After prescription						
Pneumonia events	3,461(2.7)	6,870(5.5)	141 (0.1)	343 (0.2)	362(0.3)	910(0.9)
Incidence of pneumonia per 1,000 per person years (95%CI)	28.11 (27.18 to 29.06)	56.63 (55.30 to 57.98)	1.12 (0.95 to 1.33)	2.74 (2.46 to 3.05)	3.70 (3.34 to 4.10)	9.34 (8.75 to 9.96)
Hazard ratio(PPI/non-PP) (95%CI)	2.01 (1.93 to 2.10)		2.45 (2.01 to 2.98)		2.54 (2.25 to 2.88)	
Prior event rate ratio(PERR)*	0.88 (0.79 to 0.97)		0.81 (0.62 to 1.00)		0.78 (0.60 to 1.01)	

*PERR= Hazard ratio for pneumonia between exposed and unexposed after proton pump inhibitor prescription divided by the hazard ratio for pneumonia before proton pump inhibitor prescription. HES, Hospital Episode Statistics data ; ONS, the Office for National Statistics mortality data; CI, confidence interval

Supplement Table F: Sensitivity analysis: PERR analysis restricted to those over the age of 65 years, according to the 3 different definitions of community-acquired pneumonia.

Parameter	Pneumonia definition					
	Broad primary care definition of pneumonia		Narrow primary care definition of pneumonia		hospital and mortality records based definition (in HES-ONS linked patients)	
	99,294		99,294		81,556	
	unexposed	exposed	unexposed	exposed	unexposed	exposed
Before prescription						
Pneumonia events	2,003 (4.03)	4,082 (8.22)	89(0.20)	358 (0.72)	116(0.28)	442(1.08)
Incidence of pneumonia per 1,000 per person years (95%CI)	41.22 (39.46-43.07)	85.57 (82.99-88.24)	1.97 (1.62-2.40)	7.22 (6.51-8.01)	2.84 (2.37-3.41)	10.87 (9.90-11.93)
Hazard ratio(PPI/non-PP) (95%CI)	2.07 (1.98-2.19)		3.66 (2.92-4.57)		3.82 (3.11-4.69)	
After prescription						
Pneumonia events	2,204 (4.44)	3,816 (7.69)	212 (0.43)	482 (0.97)	267 (0.65)	678 (1.66)
Incidence of pneumonia per 1,000 per person years (95%CI)	48.05 (46.09 to 50.10)	90.98 (88.14 to 93.9)	4.52 (3.95 to 5.17)	11.06 (10.12 to 12.10)	7.04 (6.24 to 7.93)	19.31 (17.91 to 20.82)
Hazard ratio(PPI/non-PP) (95%CI)	1.88 (1.78 to 1.98)		2.43 (2.07 to 2.86)		2.72 (2.36 to 3.14)	
Prior event rate ratio(PERR)*	0.90 (0.83 to 1.01)		0.66 (0.46 to 1.60)		0.71 (0.3 to 1.11)	

*PERR= Hazard ratio for pneumonia between exposed and unexposed after proton pump inhibitor prescription divided by the hazard ratio for pneumonia before proton pump inhibitor prescription. HES, Hospital Episode Statistics data ; ONS, the Office for National Statistics mortality data; CI, confidence interval

Supplement Table G: Sensitivity analysis: PERR analysis restricted to the time period prior to the availability of OTC PPIs, according to the 3 different definitions of community-acquired pneumonia.

Parameter	Pneumonia definition					
	Broad primary care definition of pneumonia		Narrow primary care definition of pneumonia		hospital and mortality records based definition (in HES-ONS linked patients)	
	45,146		45,146		27,704	
	unexposed	exposed	unexposed	exposed	unexposed	exposed
Before prescription						
Pneumonia events	721(3.1)	1,366(6.0)	33(0.1)	87(0.3)	70(0.5)	293(2.1)
Incidence of pneumonia per 1,000 per person years (95%CI)	28.32 (26.19 to 30.62)	66.17 (62.85 to 69.67)	1.46 (1.04 to 2.05)	3.86 (3.12 to 4.76)	5.06 (4.00 to 6.40)	21.31 (19.00 to 23.89)
Hazard ratio(PPI/non-PP) (95%CI)	2.34 (2.13-2.58)		2.63 (1.76-3.93)		4.12 (3.17 to 5.36)	
After prescription						
Pneumonia events	721 (3.19)	1,366 (6.05)	62 (0.27)	119 (0.53)	124 (0.9)	238 (1.7)
Incidence of pneumonia per 1,000 per person years (95%CI)	33.23 (30.89 to 35.75)	65.89 (62.49 to 69.48)	2.81 (2.19 to 3.60)	5.56 (4.65 to 6.66)	9.20 (7.72 to 10.97)	18.37 (16.18 to 20.86)
Hazard ratio(PPI/non-PP) (95%CI)	2.02 (1.84 to 2.22)		2.53 (1.80 to 3.54)		2.09 (1.66 to 2.62)	
Prior event rate ratio(PERR)*	0.86 (0.77 to 0.95)		0.96 (0.75 to 1.17)		0.50 (0.44 to 0.82)	

*PERR= Hazard ratio for pneumonia between exposed and unexposed after proton pump inhibitor prescription divided by the hazard ratio for pneumonia before proton pump inhibitor prescription. HES, Hospital Episode Statistics data ; ONS, the Office for National Statistics mortality data; CI, confidence interval

Supplement Table H: Sensitivity analysis: PERR analysis restricted to cases before the first large population-based study was published according to the 3 different definitions of community-acquired pneumonia.

Parameter	Pneumonia definition					
	Broad primary care definition of pneumonia		Narrow primary care definition of pneumonia		hospital and mortality records based definition (in HES-ONS linked patients)	
	77,972		77,972		57,982	
	unexposed	exposed	unexposed	exposed	unexposed	exposed
Before prescription						
Pneumonia events	1,034(2.6)	2,465(6.3)	57(0.1)	166(0.4)	171(0.5)	649(2.2)
Incidence of pneumonia per 1,000 per person years (95%CI)	26.88 (25.29 to 28.57)	65.27 (62.74 to 67.90)	1.46 (1.12 to 1.89)	4.26 (3.66 to 4.96)	5.91 (5.09 to 6.87)	22.57 (20.89 to 24.37)
Hazard ratio(PPI/non-PP) (95%CI)	2.43 (2.26 to 2.62)		2.91 (2.15-3.93)		3.78 (3.19 to 4.47)	
After prescription						
Pneumonia events	1,208(3.1)	2,383(6.1)	97(0.27)	211 (0.54)	253 (0.8)	503 (1.7)
Incidence of pneumonia per 1,000 per person years (95%CI)	32.28 (30.51 to 26.45)	66.84 (64.21 to 69.58)	2.55 (2.09 to 3.11)	5.74 (5.01 to 6.56)	8.99 (7.95 to 10.17)	18.59 (17.03 to 20.29)
Hazard ratio(PPI/non-PP) (95%CI)	2.13 (1.98 to 2.29)		2.68 (2.06 to 3.49)		2.25 (1.92 to 2.64)	
Prior event rate ratio(PERR)*	0.87 (0.86 to 0.98)		0.92 (0.59 to 1.13)		0.59 (0.48 to 0.95)	

*PERR= Hazard ratio for pneumonia between exposed and unexposed after proton pump inhibitor prescription divided by the hazard ratio for pneumonia before proton pump inhibitor prescription. HES, Hospital Episode Statistics data ; ONS, the Office for National Statistics mortality data; CI, confidence interval

Supplement Table I: Sensitivity analysis: adjusted and unadjusted hazard ratios and 95% confidence intervals (95% CI) for the association of community-acquired pneumonia with proton pump inhibitors (PPI) according to the 3 different definitions of community-acquired pneumonia; restricted to those over the age of 65 years.

Parameter	Pneumonia definition					
	Broad primary care definition of pneumonia		Narrow primary care definition of pneumonia		hospital and mortality records based definition (in HES-ONS linked patients)	
	99,294		99,294		80,974	
	unexposed	exposed	unexposed	exposed	unexposed	exposed
Number of pneumonia events	902(1.8)	2,047(4.1)	53(0.1)	281(0.5)	212(0.52)	885(2.1)
Rate of pneumonia per 1,000 person years(95%CI)	21.63 (39.05 to 44.49)	99.25 (95.04 to 103.64)	2.35 (1.79 to 3.08)	12.50 (11.12 to 14.05)	11.70 (10.23 to 13.39)	49.59 (46.43 to 52.97)
Unadjusted Hazard ratio (95%CI)	2.35 (2.16 to 2.54)		5.50 (4.08 to 7.42)		4.27 (3.67 to 4.97)	
Adjusted hazard ^a (95%CI)	1.61 (1.47 to 1.77)		4.02 (2.78 to 5.82)		3.27 (2.77 to 3.86)	

HES, Hospital Episode Statistics data ; ONS, the Office for National Statistics mortality data; CI, confidence interval

^a Adjusted model for the confounders that changed the multivariate Cox model by more than 10%: comorbidity index, number of GP visits, corticosteroid use, and immunosuppression

Supplement Table J: Sensitivity analysis: adjusted and unadjusted hazard ratios and 95% confidence intervals (95% CI) for the association of community-acquired pneumonia with proton pump inhibitors (PPI) according to the 3 different definitions of community-acquired pneumonia; restricted to the time period prior to the availability of OTC PPIs.

Parameter	Pneumonia definition					
	Broad primary care definition of pneumonia		Narrow primary care definition of pneumonia		hospital and mortality records based definition (in HES-ONS linked patients)	
	unexposed	exposed	unexposed	exposed	unexposed	exposed
Number of pneumonia events	280	640	12(0.1)	71(0.3)	39(0.2)	140(1.0)
Rate of pneumonia per 1,000 person years (95%CI)	31.06 (27.62 to 34.92)	75.23 (69.62 to 81.29)	1.28 (0.72 to 2.26)	7.61 (6.03 to 9.61)	6.68 (4.88 to 9.15)	24.22 (20.52 to 28.58)
Unadjusted Hazard ratio (95%CI)	2.41 (2.08 to 2.79)		5.91 (3.20 to 10.90)		3.63 (2.53 to 5.20)	
Adjusted hazard a (95%CI)	1.39 (1.16 to 1.67)		4.72 (1.66 to 13.39)		3.26 (2.13 to 5.01)	

CI, confidence interval

^a Adjusted model for the confounders that changed the multivariate Cox model by more than 10%: comorbidity index, number of GP visits, corticosteroid use, and immunosuppression.