

**Cause specific mortality in COPD sub-populations: a cohort study of 339,647 people in England**

## Supplementary material

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## Additional methodology

Currently, CPRD Aurum contains information on over 900 general practices including over 20 million individuals registered to these practices (both currently and historically) and is generalisable in terms of age and sex [1].

Specific cause of death was determined from death certificates through ONS mortality data using ICD10 codes that related to the patient's underlying cause of death. Every death in the UK must be reported by the General Register Office and information is recorded by the ONS. A medical certificate is required upon death which lists the underlying cause of death and up to 15 contributory causes of death. ONS derives underlying cause of death using standardised guidelines from information available on death certificates and coded using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [2].

Table S1: Baseline characteristics by exacerbation frequency

	<b>None</b>	<b>1</b>	<b>2+</b>
<b>Characteristic</b>	<b>n (%) or mean (SD)</b>	<b>n (%) or mean (SD)</b>	<b>n (%) or mean (SD)</b>
<b>Age</b>			
Mean (SD)	67.2 (11.7)	68.0 (11.6)	68.8 (11.8)
<50	20,200 (8.8)	5,088 (7.3)	2,684 (6.8)
50-59	41,845 (18.2)	12,355 (17.7)	6,623 (16.7)
60-69	70,082 (30.4)	20,732 (29.7)	11,452 (28.8)
70-79	64,764 (28.1)	20,185 (29.0)	11,612 (29.2)
80+	33,300 (14.5)	11,335 (16.3)	7,390 (18.6)
<b>Gender</b>			
Men	126,472 (54.9)	35,050 (50.3)	18,714 (47.1)
Women	103,719 (45.1)	34,645 (49.7)	21,047 (52.9)
<b>Smoking status</b>			
Ex-smoker	121,194 (52.7)	36,245 (52.0)	21,690 (54.6)
Current smoker	108,997 (47.4)	33,450 (48.0)	18,071 (45.4)
<b>MI</b>	15,966 (6.9)	5,590 (8.0)	3,650 (9.2)
<b>HF</b>	14,175 (6.2)	5,503 (7.9)	4,075 (10.3)
<b>Stroke</b>	55,394 (24.1)	17,843 (25.6)	10,738 (27.0)
<b>Depression</b>	58,089 (25.2)	20,155 (28.9)	12,749 (32.1)
<b>Anxiety</b>	48,539 (21.1)	17,001 (24.4)	11,133 (28.0)
<b>GORD</b>	34,584 (15.0)	12,026 (17.3)	7,835 (19.7)
<b>Lung cancer</b>	2,096 (0.9)	849 (1.2)	739 (1.9)
<b>BMI</b>			
Underweight	7,930 (3.4)	2,809 (4.0)	1,834 (4.6)
Normal	64,844 (28.2)	19,556 (28.1)	11,086 (27.9)
Overweight	68,041 (29.6)	19,672 (28.2)	10,991 (27.6)
Obese	59,505 (25.9)	18,628 (26.7)	10,990 (27.6)
Missing	29,871 (13.0)	9,030 (13.0)	4,860 (12.2)
<b>Hypertension</b>	98,490 (42.8)	30,654 (44.0)	17,887 (45.0)
<b>Diabetes</b>	33,747 (14.7)	11,551 (16.6)	7,306 (18.4)
<b>Asthma</b>	80,241 (34.9)	24,607 (35.3)	16,198 (40.7)
<b>GOLD</b>			
Mild	49,386 (21.5)	13,403 (19.2)	6,687 (16.8)
Moderate	90,819 (39.5)	27,989 (40.2)	14,816 (37.3)
Severe	29,369 (12.8)	10,502 (15.1)	6,685 (16.8)
Very severe	4,889 (2.1)	1,894 (2.7)	1,599 (4.0)
Missing	55,728 (24.2)	15,907 (22.8)	9,974 (25.1)

Legend: MI (myocardial infarction), HF (heart failure), GORD (gastro-oesophageal reflux disorder). SD (standard deviation). Numbers are proportions or means displayed as n (%) or mean (SD). Total population N=339,647.

Table S2: Baseline characteristics by exacerbation severity

	None	Moderate	Severe
Characteristic	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)
<b>Age</b>			
Mean (SD)	67.2 (11.7)	67.9 (11.6)	71.1 (11.7)
<50	20,200 (8.8)	7,030 (7.4)	742 (5.1)
50-59	41,845 (18.2)	17,021 (17.9)	1,957 (13.4)
60-69	70,082 (30.4)	28,520 (30.1)	3,664 (25.1)
70-79	64,764 (28.1)	27,203 (28.7)	4,594 (31.5)
80+	33,300 (14.5)	15,079 (15.9)	3,646 (25.0)
<b>Gender</b>			
Men	126,472 (54.9)	46,194 (48.7)	7,570 (51.9)
Women	103,719 (45.1)	48,659 (51.3)	7,033 (48.2)
<b>Smoking status</b>			
Ex-smoker	121,194 (52.7)	49,803 (52.5)	8,132 (55.7)
Current smoker	108,997 (47.4)	45,050 (47.5)	6,471 (44.3)
<b>MI</b>	15,966 (6.9)	7,568 (8.0)	1,672 (11.4)
<b>HF</b>	14,175 (6.2)	7,587 (8.0)	1,991 (13.6)
<b>Stroke</b>	55,394 (24.1)	24,688 (26.0)	3,893 (26.7)
<b>Depression</b>	58,089 (25.2)	28,932 (30.5)	3,972 (27.2)
<b>Anxiety</b>	48,539 (21.1)	24,857 (26.2)	3,280 (22.5)
<b>GORD</b>	34,584 (15.0)	17,738 (18.7)	2,123 (14.5)
<b>Lung cancer</b>	2,096 (0.9)	1,291 (1.4)	296 (2.0)
<b>BMI</b>			
Underweight	7,930 (3.4)	3,685 (3.9)	958 (6.6)
Normal	64,844 (28.2)	26,590 (29.0)	4,052 (27.8)
Overweight	68,041 (29.6)	27,282 (28.8)	3,381 (23.1)
Obese	59,505 (25.9)	25,891 (27.3)	3,727 (25.5)
Missing	29,871 (13.0)	11,405 (12.0)	2,485 (17.0)
<b>Hypertension</b>	98,490 (42.8)	41,437 (43.7)	7,104 (48.7)
<b>Diabetes</b>	33,747 (14.7)	15,818 (16.7)	3,039 (20.8)
<b>Asthma</b>	80,241 (34.9)	35,936 (37.9)	4,869 (33.4)
<b>GOLD</b>			
Mild	49,386 (21.5)	18,591 (19.6)	1,499 (10.3)
Moderate	90,819 (39.5)	38,710 (40.8)	4,095 (28.0)
Severe	29,369 (12.8)	14,576 (15.4)	2,611 (17.9)
Very severe	4,889 (2.1)	2,662 (2.8)	831 (5.7)
Missing	55,728 (24.2)	20,314 (31.4)	5,567 (38.1)

Legend: MI (myocardial infarction), HF (heart failure), GORD (gastro-oesophageal reflux disorder). SD (standard deviation). Numbers are proportions or means displayed as n (%) or mean (SD). Total population N=339,647.

Table S3: Baseline characteristics by chronic bronchitis and emphysema

Characteristic	Emphysema	Chronic bronchitis
	n (%) or mean (SD)	n (%) or mean (SD)
<b>Age</b>		
Mean (SD)	68.6 (11.8)	70.9 (11.3)
<50	1,709 (7.6)	226 (4.9)
50-59	3,602 (16.1)	557 (12.0)
60-69	6,279 (28.0)	1,301 (28.0)
70-79	6,754 (30.1)	1,498 (32.2)
80+	4,069 (18.2)	1,063 (22.9)
<b>Gender</b>		
Men	13,319 (59.4)	2,441 (52.6)
Women	9,094 (40.6)	2,204 (47.4)
<b>Smoking status</b>		
Ex-smoker	13,055 (58.3)	2,543 (54.7)
Current smoker	9,358 (41.8)	2,102 (45.3)
<b>MI</b>	1,851 (8.3)	386 (8.3)
<b>HF</b>	1,909(8.5)	428 (9.2)
<b>Stroke</b>	5,567 (24.9)	1,217 (26.2)
<b>Depression</b>	6,087 (27.2)	1,299 (28.0)
<b>Anxiety</b>	5,242 (23.4)	1,1665(25.1)
<b>GORD</b>	3,952 (17.6)	958 (20.6)
<b>Lung cancer</b>	447 (2.0)	57 (1.2)
<b>BMI</b>		
Underweight	1,715 (7.7)	195 (4.2)
Normal	8,135 (36.3)	1,346 (29.0)
Overweight	5,891 (26.3)	1,446 (31.2)
Obese	3,666 (16.4)	1,196 (25.7)
Missing	3,006 (13.4)	462 (10.0)
<b>Hypertension</b>	8,770 (39.1)	2,177 (46.9)
<b>Diabetes</b>	2,992(13.4)	824 (17.8)
<b>Asthma</b>	7,201 (32.1)	2,501 (53.9)
<b>GOLD</b>		
Mild	5,748 (25.6)	992 (21.4)
Moderate	6,752 (30.1)	1,735 (37.3)
Severe	3,302 (14.7)	773 (16.7)
Very severe	1,094 (4.9)	197 (4.2)
Missing	5,517 (24.6)	948 (20.4)
<b>AECOPD any</b>		
None	15,059 (67.2)	2,913 (62.7)
Any	7,354 (32.8)	1,731 (37.3)

Legend: MI (myocardial infarction), HF (heart failure), GORD (gastro-oesophageal reflux disorder). SD (standard deviation). Numbers are proportions or means displayed as n (%) or mean (SD). Total population N=27,058.

Table S4: Baseline characteristics by GOLD stage

	<b>GOLD A</b>	<b>GOLD B</b>	<b>GOLD C</b>	<b>GOLD D</b>
<b>Characteristic</b>	<b>n (%) or mean (SD)</b>	<b>n (%) or mean (SD)</b>	<b>n (%) or mean (SD)</b>	<b>n (%) or mean (SD)</b>
<b>Age</b>				
Mean (SD)	65.3 (11.1)	68.6 (11.2)	66.7 (11.2)	69.6 (11.4)
<50	4,038 (10.1)	7,653 (6.2)	351 (8.1)	1,310 (5.6)
50-59	8,206 (20.5)	19,635 (15.9)	810 (18.7)	3,544 (15.1)
60-69	13,578 (34.0)	37,633 (30.5)	1,481 (34.2)	6,639 (28.3)
70-79	10,585 (26.5)	38,001 (30.8)	1,167 (26.9)	7,338 (31.3)
80+	3,579 (9.0)	20,316 (16.5)	526 (12.1)	4,613 (19.7)
<b>Gender</b>				
Men	23,660 (59.2)	65,421 (53.1)	2,261 (52.2)	11,303 (48.2)
Women	16,326 (40.8)	57,817 (46.9)	2,074 (47.8)	12,141 (51.8)
<b>Smoking status</b>				
Ex-smoker	21,042 (52.6)	66,750 (54.2)	2,271 (52.4)	13,290 (56.7)
Current smoker	18,945 (47.4)	56,508 (45.9)	2,064 (47.6)	10,168 (43.4)
<b>MI</b>	2,091 (5.2)	9,612 (7.8)	322 (7.4)	2,314 (9.9)
<b>HF</b>	1,343 (3.4)	8,936 (7.3)	192 (4.4)	2,666 (11.4)
<b>Stroke</b>	9,050 (22.6)	30,599 (24.8)	1,039 (24.0)	6,313 (26.9)
<b>Depression</b>	8,844 (22.1)	32,838 (26.6)	1,169 (27.0)	7,355 (31.4)
<b>Anxiety</b>	7,867 (19.7)	27,108 (22.0)	1,050 (24.2)	6,286 (26.8)
<b>GORD</b>	5,687 (14.2)	20,024 (16.3)	716 (16.5)	4,591 (19.6)
<b>Lung cancer</b>	161 (0.4)	1,155 (0.9)	43 (1.0)	434 (1.9)
<b>BMI</b>				
Underweight	1,177 (2.9)	4,593 (3.7)	163 (3.8)	5,379 (3.6)
Normal	12,865 (32.2)	34,816 (28.3)	1,358 (31.3)	39,525 (26.6)
Overweight	13,262 (33.2)	36,817 (29.9)	1,349 (31.1)	40,792 (27.4)
Obese	8,271 (20.7)	35,161 (28.5)	942 (21.7)	38,076 (25.6)
Missing	4,411 (11.0)	11,851 (9.6)	523 (12.1)	24,872 (16.7)
<b>Hypertension</b>	15,024 (37.6)	56,267 (45.7)	1,693 (39.1)	10,909 (46.5)
<b>Diabetes</b>	4,702 (11.8)	19,389 (15.7)	592 (13.7)	4,329 (18.5)
<b>Asthma</b>	14,569 (36.4)	49,264 (40.0)	1,548 (35.7)	10,843 (46.2)

Legend: MI (myocardial infarction), HF (heart failure), GORD (gastro-oesophageal reflux disorder). SD (standard deviation). Numbers are proportions or means displayed as n (%) or mean (SD). Total population N=191,038.

Table S5: Baseline characteristics by airflow limitation (FEV1 % predicted)

	<b>≥80%</b>	<b>50-79%</b>	<b>30-49%</b>	<b>&lt;30%</b>
<b>Characteristic</b>	<b>n (%) or mean (SD)</b>	<b>n (%) or mean (SD)</b>	<b>n (%) or mean (SD)</b>	<b>n (%) or mean (SD)</b>
<b>Age</b>				
Mean (SD)	66.8 (11.7)	67.3 (11.1)	68.8 (10.6)	67.5 (10.4)
<50	6,415 (9.2)	9,939 (7.4)	2,243 (4.8)	472 (5.6)
50-59	13,125 (18.9)	24,626 (18.4)	7,184 (15.4)	1,431 (17.1)
60-69	21,058 (30.3)	42,416 (31.7)	15,115 (32.5)	2,967 (35.4)
70-79	19,329 (27.8)	38,809 (29.0)	14,868 (31.9)	2,544 (30.4)
80+	9,549 (13.8)	17,834 (13.4)	7,146 (15.4)	968 (11.6)
<b>Gender</b>				
Men	32,469 (46.7)	72,877 (54.5)	28,475 (61.2)	5,725 (68.3)
Women	37,007 (53.3)	60,747 (45.5)	18,081 (38.8)	2,657 (31.7)
<b>Smoking status</b>				
Ex-smoker	38,668 (55.7)	69,869 (52.3)	24,549 (52.7)	4,495 (53.6)
Current smoker	30,808 (44.3)	63,755 (47.7)	22,007 (47.3)	3,887 (46.4)
<b>MI</b>	4,299 (6.2)	10,121 (7.6)	3,733 (8.0)	556 (6.6)
<b>HF</b>	3,470 (5.0)	8,873 (6.6)	3,659 (7.9)	636 (7.6)
<b>Stroke</b>	17,927 (25.8)	32,810 (24.6)	10,661 (22.9)	1,730 (20.7)
<b>Depression</b>	20,501 (29.5)	35,453 (26.5)	10,414 (22.4)	1,885 (22.5)
<b>Anxiety</b>	17,257 (24.8)	29,257 (21.9)	8,766 (18.8)	1,624 (19.4)
<b>GORD</b>	13,483 (19.4)	21,510 (16.1)	5,728 (12.3)	844 (10.1)
<b>Lung cancer</b>	412 (0.6)	1,276 (1.0)	646 (1.4)	98 (1.2)
<b>BMI</b>				
Underweight	1,514 (2.2)	3,848 (2.9)	2,885 (6.2)	975 (11.7)
Normal	19,139 (27.6)	36,218 (27.1)	15,655 (33.6)	3,221 (38.4)
Overweight	22,769 (32.8)	40,451 (30.3)	12,486 (26.8)	1,877 (22.4)
Obese	18,911 (27.2)	38,729 (29.0)	10,010 (21.5)	1,240 (14.8)
Missing	7,143 (10.3)	14,378 (10.8)	5,520 (11.9)	1,069 (12.7)
<b>Hypertension</b>	28,615 (41.2)	59,076 (44.2)	20,380 (43.8)	3,176 (37.9)
<b>Diabetes</b>	9,247 (13.3)	21,286 (15.9)	6,988 (15.0)	1,015 (12.1)
<b>Asthma</b>	24,105 (34.7)	47,618 (35.6)	17,821 (38.3)	3,547 (42.3)
<b>AECOPD any</b>				
None	49,386 (71.1)	90,819 (68.0)	29,369 (63.1)	4,889 (58.3)
Any	20,090 (28.9)	42,802 (32.0)	17,187 (36.9)	3,493 (41.7)

Legend: MI (myocardial infarction), HF (heart failure), GORD (gastro-oesophageal reflux disorder). SD (standard deviation). Numbers are proportions or means displayed as n (%) or mean (SD). Total population N=258,083.

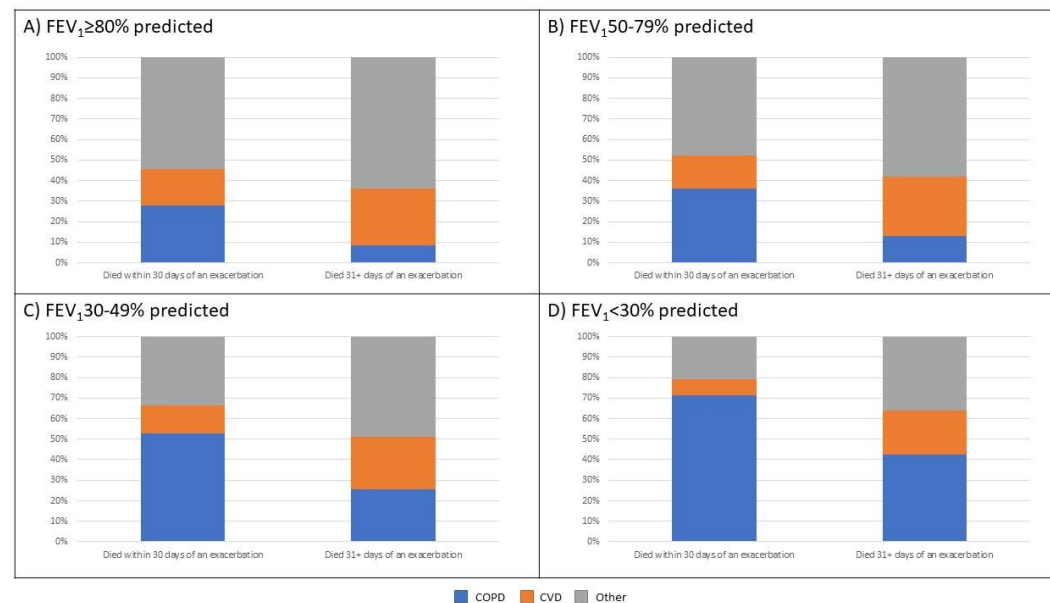
Table S6: Risk of all-cause, COPD, and CVD related mortality by baseline exposure groups.

Exposure group	All-cause mortality				COPD-related mortality				CVD-related mortality			
	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
<b>AECOPD any</b>												
None	Ref		Ref		Ref		Ref		Ref		Ref	
Any	1.36 (1.34-1.38)	<0.001	1.18 (1.16-1.20)	<0.001	1.75 (1.71-1.80)	<0.001	1.42 (1.37-1.46)	<0.001	1.15 (1.12-1.80)	<0.001	1.00 (0.97-1.04)	0.765
<b>AECOPD frequency</b>												
None	Ref		Ref		Ref		Ref		Ref		Ref	
<2	1.23 (1.21-1.25)	<0.001	1.11 (1.09-1.13)	<0.001	1.49 (1.45-1.54)	<0.001	1.28 (1.24-1.33)	<0.001	1.09 (1.05-1.12)	<0.001	0.97 (0.93-1.01)	0.187
2+	1.60 (1.57-1.63)	<0.001	1.32 (1.29-1.35)	<0.001	2.23 (2.15-2.30)	<0.001	1.64 (1.57-1.71)	<0.001	1.25 (1.20-1.30)	<0.001	1.06 (1.01-1.11)	0.019
<b>AECOPD mod/sev</b>												
None	Ref		Ref		Ref		Ref		Ref		Ref	
Moderate	1.22 (1.20-1.24)	<0.001	1.11 (1.09-1.13)	<0.001	1.51 (1.47-1.55)	<0.001	1.31 (1.26-1.35)	<0.001	1.07 (1.04-1.10)	<0.001	0.98 (0.95-1.02)	0.329
Severe	2.70 (2.64-2.77)	<0.001	1.81 (1.75-1.87)	<0.001	3.65 (3.50-3.81)	<0.001	2.17 (2.04-2.31)	<0.001	1.74 (1.65-1.84)	<0.001	1.16 (1.08-1.26)	<0.001
<b>COPD type</b>												
Chronic bronch	Ref		Ref		Ref		Ref		Ref		Ref	
Emphysema	1.09 (1.04-1.14)	0.001	1.17 (1.10-1.24)	<0.001	1.21 (1.11-1.32)	<0.001	1.24 (1.12-1.38)	<0.001	0.85 (0.77-0.94)	0.002	0.94 (0.83-1.06)	0.305
<b>GOLD ABCD</b>												
GOLD A	Ref		Ref		Ref		Ref		Ref		Ref	
GOLD B	1.96 (1.91-2.01)	<0.001	1.65 (1.60-1.69)	<0.001	3.00 (2.82-3.18)	<0.001	2.63 (2.48-2.80)	<0.001	1.73 (1.65-1.82)	<0.001	1.34 (1.27-1.41)	<0.001
GOLD C	1.41 (1.32-1.51)	<0.001	1.30 (1.21-1.39)	<0.001	2.05 (1.80-2.35)	<0.001	1.75 (1.51-2.02)	<0.001	1.36 (1.19-1.55)	<0.001	1.31 (1.14-1.51)	<0.001
GOLD D	3.08 (2.99-3.17)	<0.001	2.43 (2.34-2.52)	<0.001	6.20 (5.81-6.61)	<0.001	4.57 (4.23-4.93)	<0.001	2.07 (1.95-2.21)	<0.001	1.53 (1.41-1.65)	<0.001
<b>GOLD FEV1% pred</b>												
GOLD 1	Ref		Ref		Ref		Ref		Ref		Ref	
GOLD 2	1.51 (1.58-1.54)	<0.001	1.45 (1.42-1.48)	<0.001	2.10 (1.99-2.12)	<0.001	2.07 (1.96-2.19)	<0.001	1.43 (1.38-1.49)	<0.001	1.32 (1.27-1.38)	<0.001
GOLD 3	2.64 (2.58-2.70)	<0.001	2.33 (2.28-2.39)	<0.001	6.15 (5.81-6.45)	<0.001	5.30 (5.02-5.60)	<0.001	1.89 (1.79-1.97)	<0.001	1.61 (1.52-1.70)	<0.001
GOLD 4	4.26 (4.12-4.40)	<0.001	4.10 (3.95-4.25)	<0.001	14.62 (13.76-15.53)	<0.001	12.63 (11.82-13.51)	<0.001	1.83 (1.69-1.99)	<0.001	1.75 (1.60-1.91)	<0.001

Legend: COPD (chronic obstructive pulmonary disease), CVD (cardiovascular disease), AECOPD (acute exacerbation of COPD), HR (hazard ratio). Adjusted models are adjusted for all baseline characteristics. N unadjusted for exposure GOLD FEV1% predicted=258,038, N adjusted for exposure GOLD FEV1% predicted=229,928. N unadjusted for exposure GOLD ABCD=191,003, N adjusted for exposure GOLD ABCD=172,114. N unadjusted for exposure COPD type=27,058, N adjusted for exposure COPD type=18,528. N unadjusted for all other exposures=339,647, N adjusted for all other exposures=229,928.



Figure E1: Proportion of patients dying from all-cause, COPD-related, and CVD-related causes within 30 days of an exacerbation of COPD by baseline FEV<sub>1</sub> predicted.



Legend: A) FEV<sub>1</sub> ≥80% predicted; B) FEV<sub>1</sub> 50-79% predicted; C) FEV<sub>1</sub> 30-49% predicted; D) FEV<sub>1</sub> <30% predicted. COPD (Chronic Obstructive Pulmonary Disease), CVD (cardiovascular disease). Of those with at least 1 exacerbation during follow-up.

## References

1. Wolf, A., et al., *Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum*. International Journal of Epidemiology, 2019. **48**(6): p. 1740-1740g.
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