Supplement

Supplementary methods

Data sources

CPRD GOLD and Aurum are two databases of anonymized primary care records from the United Kingdom (UK). Collectively they contain records of more than 10 million currently registered patients covering more than 20% of the UK population.[1,2] They hold data from two separate primary care software systems, EMIS (Aurum) and Vision (GOLD). These datasets have been widely used for non-interventional research and found to be broadly representative of the general population in terms of both age and sex.[3,4]

Individuals from practices present in both databases were excluded from the GOLD cohort.

Covariates

Potential confounders were adjusted for in the cohort studies using stabilized inverse probability of treatment weights estimated using propensity scores fitted with logistic regression. The following potential confounders were includes as covariates:

- **Demographic and lifestyle variables:** age, sex, socioeconomic deprivation, body mass index (BMI), smoking status, alcohol consumption, ethnicity
- Indicators of frailty and comorbidity in 6 months prior to baseline: number of hospital admissions, number of GP appointments
- **Ever prior comorbidities:** coronary heart disease, hypertension, diabetes, uncontrolled diabetes, cerebrovascular disease, dementia, HIV, chronic liver disease, chronic kidney disease, peripheral vascular disease, myocardial infarction, carotid disease, multiple sclerosis
- **Additional risk factors for hospitalization with AA/AD:** statin use in 6 months prior, ever prior aortic aneurysm
- **Additional risk factors for tendon rupture:** corticosteroid use in 6 months prior, ever prior rheumatoid arthritis

Code lists for the exposure, outcome and covariates are available online at LSHTM Data Compass: https://doi.org/10.17037/DATA.00003243.

Individuals with no recorded smoking status were categorized as not current smokers and those with no recorded alcohol consumption as not heavy drinkers. BMI and age were modelled with a restricted cubic spline.

Median (IQR) look-back periods for covariate assessment at first treatment episode were: in the GOLD cohort 14.0 (6.4-23.0) years for fluoroquinolone users and 13.5 (6.8-23.5) years for cephalosporin users; and in the Aurum cohort 13.4 (6.12-23.7) years for fluoroquinolone users and 12.5 (5.7-22.3) years for cephalosporin users.

Multiple imputation

Multiple imputation with 10 imputed datasets was applied to impute missing values of body mass index (BMI) and ethnicity. In multiple imputation models, BMI was imputed using predictive mean matching and ethnicity using multinomial logistic regression. All covariates were included in imputation models alongside an estimate of the baseline hazard using the Nelson-Aalen estimator.[5]

Secondary analyses

As a secondary analysis, subsequent treatment episodes after the first within the eligibility window were included. Separate treatment episodes were defined by prescriptions more than 60 days apart.

Sensitivity analyses

In the cohort studies to assess the robustness of results to missing data assumptions, a sensitivity analysis was conducted using a complete case approach where individuals with missing ethnicity or BMI were excluded. In a post-hoc analysis the hazard ratio was estimated adjusting for sex only to explore the relative contribution to confounding of this variable.

The robustness of the case-crossover studies to time window chosen was assessed in sensitivity analyses by varying the length of exposure risk periods to 30 or 90 rather than 60 days and increasing the interval between case and control period from 30 to 60 days.

To assess the sensitivity of results to extreme weights, propensity score trimming was implemented by trimming individuals below the 5th percentile of propensity scores among fluoroquinolone users and above the 95th percentile among cephalosporin users.[6]

Some individuals may have received prior fluoroquinolone or cephalosporin within the 60 days prior to first treatment episode if treatment initiation was shortly after eligibility. To assess the sensitivity of analysis to this we excluded any individuals with a cephalosporin or fluoroquinolone prescription within the 60 days prior.

References

1. CPRD Aurum June 2021.
2. CPRD GOLD October 2021 (Version 2021.10.001)
3. Wolf A, Dedman D, Campbell J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol.* 2019;48(6):1740-1740g.
4. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research datalink (CPRD). 2015;44(3):827-836.
5. White IR, Royston P. Imputing missing covariate values for the Cox model. *Statistics in medicine.* 2009;28(15):1982-1998.
6. Stürmer T, Webster-Clark M, Lund JL, et al. Propensity score weighting and trimming strategies for reducing variance and bias of treatment effect estimates: a simulation study. *American journal of epidemiology.* 2021;190(8):1659-1670.

Supplementary results

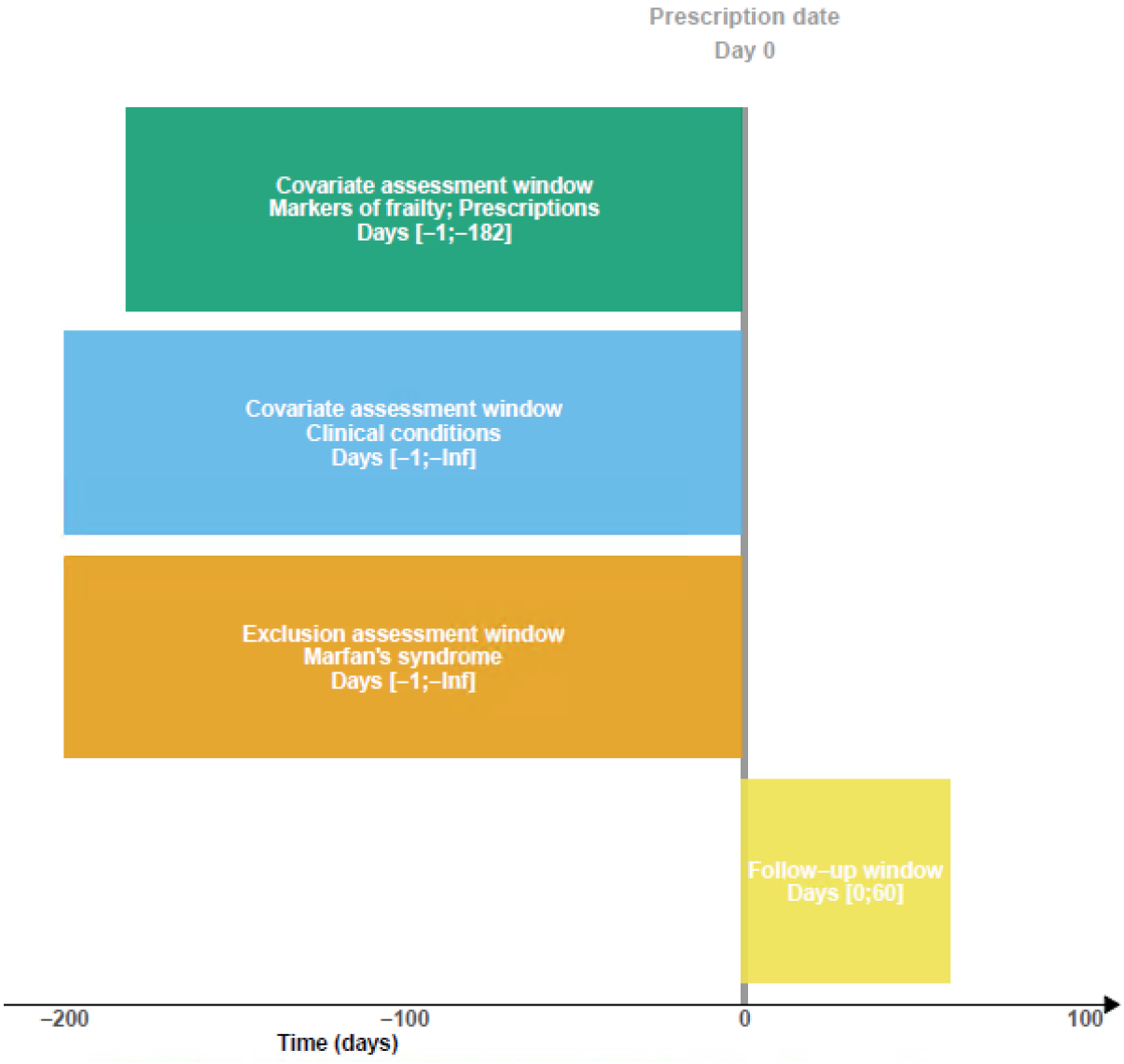
Secondary and sensitivity analyses

Similar effect estimates were observed when including all treatment episodes (eTable 4). In sensitivity analyses a complete case approach, excluding individuals with missing BMI or ethnicity, had minimal effect on estimates (eTables 5 and 6).

Varying the length of the periods under study and the time between periods in sensitivity analyses did not change findings (see eTables 11, 12, 13). Propensity score trimming did not change estimates substantially (eTable 14).

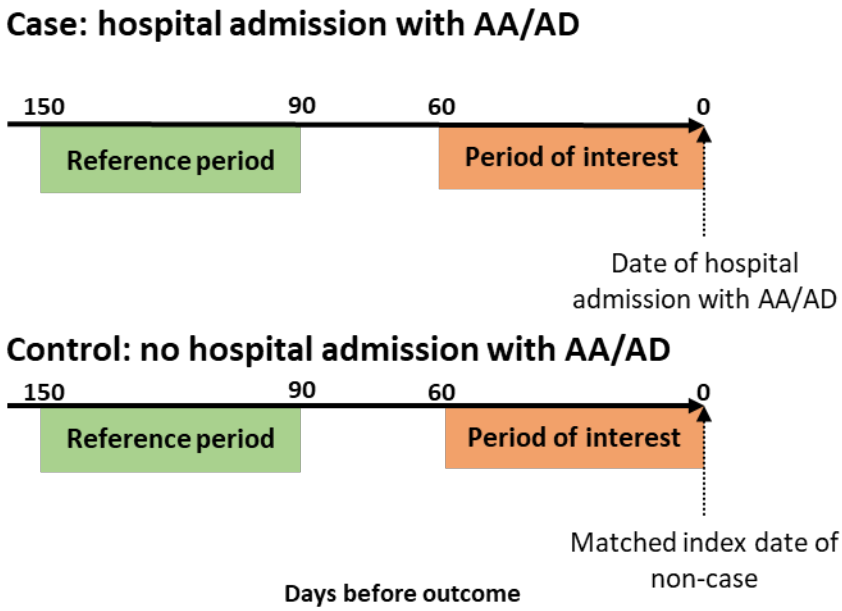
In GOLD 2,411 of 452,086 (0.5%) individuals and in Aurum 13,837 of 3,134,121 (0.4%) individuals at first treatment episode had received prior treatment with fluoroquinolones or cephalosporins within the 60 days prior. Exclusion of these individuals had minimal effect on the results (eTable 15).

Supplementary figures



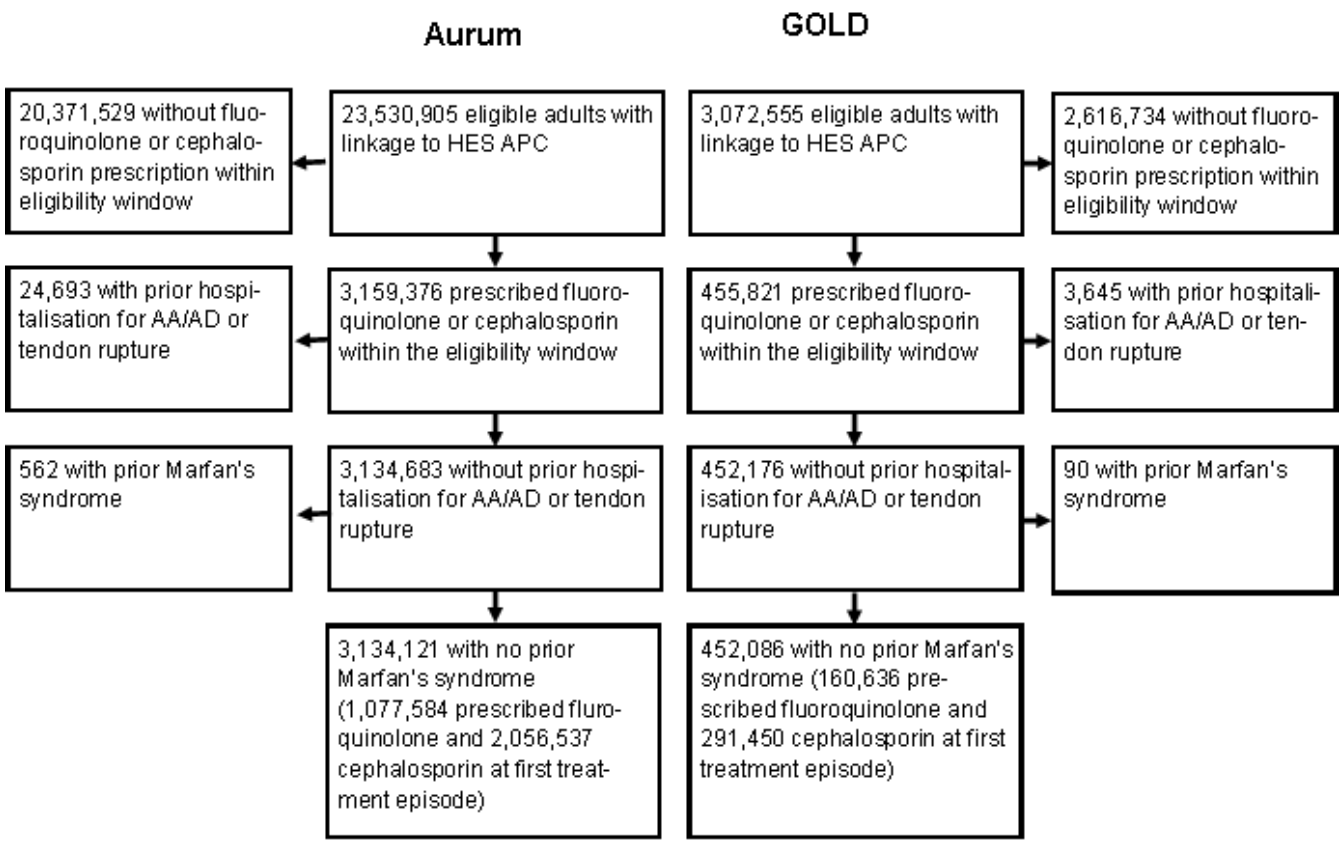
eFigure 1: Cohort studies: Graphical depiction of cohort design

Multiple treatment episodes were included per individual. Treatment episodes of fluroquinolone or cephalosporin among adults (aged 18+ years) without Marfan's syndrome eligible for HES APC linkage were included if occurring within the eligibility window.

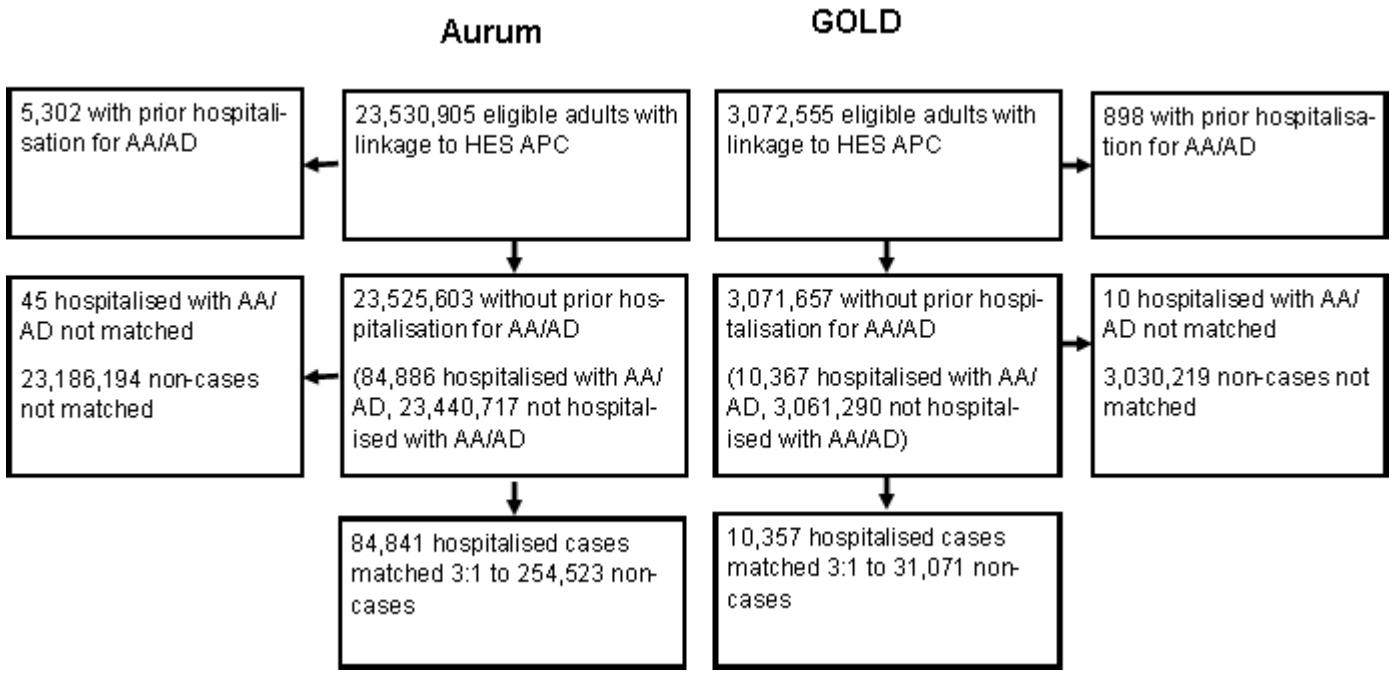


eFigure 2: Case-crossover study design

Definitions: AA/AD, aortic aneurysm or aortic dissection. Cases hospitalized with AA/AD were matched 1:1 to controls without AA/AD on calendar date, sex, year of birth and clinical practice. Odds of exposure prior to outcome occurrence relative to reference period were estimated using controls to adjust for trends in prescribing.



eFigure 3: Flow chart of cohort study subjects



eFigure 4: Flow chart of case-crossover study subjects

Supplementary tables

eTable 1: Cohort studies - Calendar year and ethnicity of individuals at first treatment episode

	Aurum		GOLD	
Characteristic	Cephalosporin, N = 2,056,537	Fluoroquinolone, N = 1,077,584	Cephalosporin, N = 291,450	Fluoroquinolone, N = 160,636
Calendar year				
1997-2001	658,943 (32%)	245,102 (23%)	77,171 (26%)	30,972 (19%)
2002-2006	694,271 (34%)	289,565 (27%)	117,356 (40%)	54,765 (34%)
2007-2011	462,329 (22%)	256,093 (24%)	75,987 (26%)	46,959 (29%)
2012-2016	185,097 (9.0%)	194,355 (18%)	18,053 (6.2%)	22,374 (14%)
2017-2019	55,897 (2.7%)	92,469 (8.6%)	2,883 (1.0%)	5,566 (3.5%)
Ethnicity				
White	1,746,817 (90%)	923,988 (91%)	255,187 (95%)	141,487 (95%)
South Asian	101,201 (5.2%)	45,262 (4.5%)	6,959 (2.6%)	3,283 (2.2%)
Black	52,470 (2.7%)	25,626 (2.5%)	2,951 (1.1%)	1,682 (1.1%)
Other	20,866 (1.1%)	10,269 (1.0%)	2,744 (1.0%)	1,350 (0.9%)
Mixed	14,034 (0.7%)	7,447 (0.7%)	1,080 (0.4%)	637 (0.4%)
Missing	121,149	64,992	22,529	12,197

eTable 2: Cohort studies - Maximum across imputed datasets of absolute standardised mean differences before and after weighting at first treatment episode

	Aurum		GOLD	
Characteristic	Unweighted	Weighted	Unweighted	Weighted
Age	0.047	0.018	0.039	0.015
Female	0.494	0.001	0.456	<0.001
Below 10th percentile Carstairs Index	0.031	0.001	0.039	0.001
BMI[1]	0.014	0.005	0.05	0.002
Current smoker	0.027	0.001	0.047	0.001
Heavy drinker	0.066	<0.001	0.06	0.004
Statin in prior 6 months	0.079	0.004	0.08	0.004
Corticosteroid in prior 6 months	0.052	0.007	0.073	0.005
Coronary heart disease	0.005	0.010	<0.001	0.010
Hypertension	0.028	0.008	0.028	0.007
Diabetes	0.033	0.006	0.030	0.005
Uncontrolled diabetes	0.038	0.004	0.042	0.002
Cerebrovascular disease	0.015	0.007	0.024	0.009
Dementia	0.049	0.005	0.061	0.005
HIV	0.028	<0.001	0.014	<0.001
Chronic liver disease	0.033	<0.001	0.030	<0.001
Chronic kidney disease	0.013	0.008	0.007	0.007
Peripheral vascular disease	0.020	0.004	0.019	0.004
Myocardial infarction	0.011	0.006	0.010	0.006
Carotid artery disease	0.007	0.001	0.007	0.002
Aortic aneurysm	0.008	0.001	0.005	0.001
Multiple sclerosis	0.003	0.001	0.001	0.001
Rheumatoid arthritis	0.019	0.003	0.020	0.002

eTable 3: Characteristics of individuals included in cohort studies at all treatment episodes

	Aurum		GOLD	
Characteristic	Cephalosporin, N = 4,524,703	Fluoroquinolone, N = 2,279,956	Cephalosporin, N = 606,374	Fluoroquinolone, N = 327,831
Age[1]	58 (39, 74)	59 (43, 73)	59 (40, 74)	60 (44, 73)
Female	3,367,587 (74%)	1,214,994 (53%)	451,089 (74%)	180,332 (55%)
Calendar year				
1997-2001	1,043,936 (23%)	389,130 (17%)	118,034 (19%)	48,079 (15%)
2002-2006	1,545,696 (34%)	612,865 (27%)	238,022 (39%)	107,143 (33%)
2007-2011	1,248,274 (28%)	625,889 (27%)	193,793 (32%)	110,007 (34%)
2012-2016	528,571 (12%)	453,626 (20%)	48,868 (8.1%)	50,900 (16%)
2017-2019	158,226 (3.5%)	198,446 (8.7%)	7,657 (1.3%)	11,702 (3.6%)
Ethnicity				
White	3,968,937 (92%)	2,017,036 (92%)	545,693 (96%)	297,503 (96%)
South Asian	207,360 (4.8%)	91,163 (4.2%)	12,791 (2.2%)	6,016 (1.9%)
Black	90,341 (2.1%)	43,699 (2.0%)	4,750 (0.8%)	2,690 (0.9%)
Other	37,430 (0.9%)	17,562 (0.8%)	4,890 (0.9%)	2,288 (0.7%)
Mixed	25,276 (0.6%)	12,719 (0.6%)	1,895 (0.3%)	1,065 (0.3%)
Missing	195,359	97,777	36,355	18,269
Below 10th percentile Carstairs Index	221,928 (4.9%)	124,124 (5.4%)	22,084 (3.6%)	14,281 (4.4%)
BMI[1]	28 (25, 32)	28 (25, 32)	25.8 (22.8, 29.7)	26.1 (23.1, 29.8)
Missing	788,365	402,841	54,642	28,539
Current smoker	1,496,401 (33%)	723,603 (32%)	198,431 (33%)	100,893 (31%)
Heavy drinker	90,978 (2.0%)	64,940 (2.8%)	10,521 (1.7%)	8,200 (2.5%)
Number of GP appointments in prior 6m[1]	2.0 (0.0, 6.0)	2.0 (0.0, 7.0)	5 (2, 10)	6 (3, 12)
Hospitalised in prior 6m	961,020 (21%)	549,220 (24%)	128,172 (21%)	79,230 (24%)
Statin in prior 6 months	785,320 (17%)	450,769 (20%)	100,755 (17%)	64,374 (20%)
Corticosteroid in prior 6 months	435,657 (9.6%)	290,257 (13%)	68,715 (11%)	50,389 (15%)
Coronary heart disease	544,068 (12%)	280,867 (12%)	73,047 (12%)	41,103 (13%)

	Aurum		GOLD	
Characteristic	Cephalosporin, N = 4,524,703	Fluoroquinolone, N = 2,279,956	Cephalosporin, N = 606,374	Fluoroquinolone, N = 327,831
Hypertension	1,282,770 (28%)	673,306 (30%)	167,496 (28%)	95,121 (29%)
Diabetes	466,141 (10%)	258,908 (11%)	72,824 (12%)	43,901 (13%)
Uncontrolled diabetes	317,315 (7.0%)	178,812 (7.8%)	38,710 (6.4%)	24,338 (7.4%)
Cerebrovascular disease	323,685 (7.2%)	157,459 (6.9%)	43,175 (7.1%)	21,733 (6.6%)
Dementia	104,643 (2.3%)	37,376 (1.6%)	13,374 (2.2%)	4,479 (1.4%)
HIV	3,239 (<0.1%)	3,503 (0.2%)	278 (<0.1%)	250 (<0.1%)
Chronic liver disease	21,521 (0.5%)	17,700 (0.8%)	2,295 (0.4%)	1,956 (0.6%)
Chronic kidney disease	886,816 (20%)	431,122 (19%)	126,181 (21%)	67,849 (21%)
Peripheral vascular disease	120,340 (2.7%)	70,277 (3.1%)	17,921 (3.0%)	10,919 (3.3%)
Myocardial infarction	178,732 (4.0%)	97,285 (4.3%)	24,509 (4.0%)	14,336 (4.4%)
Carotid artery disease	16,652 (0.4%)	9,312 (0.4%)	2,463 (0.4%)	1,522 (0.5%)
Aortic aneurysm	12,028 (0.3%)	7,471 (0.3%)	1,553 (0.3%)	924 (0.3%)
Multiple sclerosis	38,437 (0.8%)	22,145 (1.0%)	5,576 (0.9%)	3,219 (1.0%)
Rheumatoid arthritis	95,075 (2.1%)	43,209 (1.9%)	18,912 (3.1%)	9,199 (2.8%)

[1]Median (interquartile range)

eTable 4: Cohort studies - Hazard ratios between fluoroquinolone relative to cephalosporin use and AA/AD or tendon rupture at all treatment episodes

Outcome	Method	Aurum			GOLD			Pooled		
		Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Aortic aneurysm or dissection	Unadjusted	1.32	1.21-1.43	<0.001	0.98	0.78-1.24	0.875	1.27	1.18-1.37	<0.001
	IPTW weighted	1.04	0.96-1.14	0.310	0.86	0.67-1.09	0.219	1.02	0.94-1.11	0.582
Tendon rupture	Unadjusted	2.21	1.92-2.54	<0.001	2.97	1.91-4.62	<0.001	2.27	1.98-2.59	<0.001
	IPTW weighted	1.84	1.59-2.13	<0.001	2.45	1.55-3.88	<0.001	1.89	1.64-2.17	<0.001

eTable 5: Cohort studies - Complete case-analysis hazard ratios between fluoroquinolone relative to cephalosporin use and AA/AD or tendon rupture at first treatment episode

Outcome	Method	Aurum			GOLD			Pooled		
		Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Aortic aneurysm or dissection	Unadjusted	1.39	1.20-1.60	<0.001	1.15	0.80-1.63	0.448	1.35	1.19-1.54	<0.001
	IPTW Weighted	1.06	0.91-1.22	0.473	0.96	0.66-1.39	0.827	1.04	0.91-1.19	0.550
Tendon rupture	Unadjusted	2.36	1.84-3.04	<0.001	3.13	1.49-6.58	0.003	2.43	1.92-3.09	<0.001
	IPTW Weighted	1.89	1.45-2.46	<0.001	2.63	1.22-5.67	0.013	1.95	1.54-2.48	<0.001

eTable 6: Cohort studies - Complete case-analysis hazard ratios between fluoroquinolone relative to cephalosporin use and AA/AD or tendon rupture at all treatment episodes

Outcome	Method	Aurum			GOLD			Pooled		
		Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Aortic aneurysm or dissection	Unadjusted	1.39	1.27-1.51	<0.001	1.05	0.83-1.34	0.686	1.34	1.24-1.46	<0.001
	IPTW Weighted	1.07	0.98-1.18	0.119	0.87	0.68-1.13	0.297	1.05	0.97-1.14	0.259
Tendon rupture	Unadjusted	2.20	1.90-2.54	<0.001	3.06	1.95-4.81	<0.001	2.27	1.97-2.61	<0.001
	IPTW Weighted	1.81	1.56-2.11	<0.001	2.49	1.56-3.98	<0.001	1.87	1.62-2.15	<0.001

eTable 7: Cohort studies - Hazard ratios between fluoroquinolone relative to cephalosporin use and AA/AD or tendon rupture at all treatment episodes adjusting for sex only

Outcome	Method	Aurum			GOLD			Pooled		
		Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Aortic aneurysm or dissection	Unadjusted	1.39	1.20-1.60	<0.001	1.15	0.81-1.64	0.442	1.35	1.19-1.54	<0.001
	IPTW Weighted	0.99	0.86-1.15	0.891	0.90	0.63-1.30	0.584	0.98	0.85-1.12	0.736
Tendon rupture	Unadjusted	2.37	1.84-3.05	<0.001	3.14	1.49-6.59	0.003	2.44	1.92-3.10	<0.001
	IPTW Weighted	2.08	1.61-2.70	<0.001	3.00	1.40-6.40	0.005	2.16	1.70-2.75	<0.001

eTable 8: Case-crossover study - Characteristics of cases and non-cases in CPRD Aurum

Characteristic	Case, Reference period N = 84,841	Case, Risk period N = 84,841	Non-case, Reference period N = 254,523	Non-case, Risk period N = 254,523
Age[1]	76 (69, 83)	77 (70, 83)	76 (69, 83)	77 (70, 83)
Sex				
Female	23,551 (28%)		70,653 (28%)	
Male	61,290 (72%)		183,870 (72%)	
Calendar year				
1996-2000	9,068 (11%)	8,512 (10%)	27,204 (11%)	25,536 (10%)
2001-2005	14,365 (17%)	14,153 (17%)	43,095 (17%)	42,459 (17%)
2006-2010	20,012 (24%)	19,725 (23%)	60,036 (24%)	59,175 (23%)
2011-2015	23,926 (28%)	23,711 (28%)	71,778 (28%)	71,133 (28%)

2016-2019	17,470 (21%)	18,740 (22%)	52,410 (21%)	56,220 (22%)
Fluoroquinolone	813 (1.0%)	1,138 (1.3%)	695 (0.3%)	645 (0.3%)
Cephalosporin	1,273 (1.5%)	1,733 (2.0%)	1,063 (0.4%)	1,023 (0.4%)
Trimethoprim	1,783 (2.1%)	2,794 (3.3%)	1,670 (0.7%)	1,600 (0.6%)
Co-amoxiclav	1,143 (1.3%)	1,746 (2.1%)	938 (0.4%)	949 (0.4%)

[1]Median (interquartile range)

eTable 9: Case-crossover study - Characteristics of cases and non-cases in CPRD GOLD

Characteristic	Case, Reference period N = 10,357	Case, Risk period N = 10,357	Non-case, Reference period N = 31,071	Non-case, Risk period N = 31,071
Age[1]	76 (70, 82)	77 (70, 83)	76 (70, 82)	77 (70, 83)
Sex				
Female	2,809 (27%)		8,427 (27%)	
Male	7,548 (73%)		22,644 (73%)	
Calendar year				
1996-2000	937 (9.0%)	853 (8.2%)	2,811 (9.0%)	2,559 (8.2%)
2001-2005	2,424 (23%)	2,366 (23%)	7,272 (23%)	7,098 (23%)
2006-2010	3,369 (33%)	3,375 (33%)	10,107 (33%)	10,125 (33%)
2011-2015	2,756 (27%)	2,805 (27%)	8,268 (27%)	8,415 (27%)
2016-2019	871 (8.4%)	958 (9.2%)	2,613 (8.4%)	2,874 (9.2%)
Fluoroquinolone	92 (0.9%)	145 (1.4%)	100 (0.3%)	98 (0.3%)
Cephalosporin	169 (1.6%)	240 (2.3%)	152 (0.5%)	146 (0.5%)
Trimethoprim	255 (2.5%)	380 (3.7%)	212 (0.7%)	226 (0.7%)
Co-amoxiclav	129 (1.2%)	237 (2.3%)	136 (0.4%)	149 (0.5%)

[1]Median (interquartile range)

eTable 10: Case-crossover study – Odds ratios for AA/AD with fluoroquinolones and comparator antibiotics relative to non-use

Comparison	Aurum			GOLD			Pooled		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Fluoroquinolone vs. non-use	1.57	1.35-1.84	<0.001	1.65	1.09-2.50	0.017	1.58	1.37-1.83	<0.001
Cephalosporin vs. non-use	1.49	1.31-1.70	<0.001	1.57	1.11-2.22	0.010	1.50	1.33-1.70	<0.001
Trimethoprim vs. non-use	1.81	1.63-2.01	<0.001	1.52	1.15-2.01	0.003	1.77	1.61-1.95	<0.001
Co-amoxiclav vs. non-use	1.59	1.40-1.81	<0.001	1.78	1.26-2.51	0.001	1.61	1.43-1.82	<0.001

eTable 11: Case-crossover studies - Odds ratios for AA/AD with period length of 30 days and interval between periods of 30 days

Comparison	Aurum			GOLD			Pooled		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Fluoroquinolone vs. non-use	1.45	1.18-1.78	<0.001	1.49	0.85-2.61	0.159	1.46	1.20-1.77	<0.001
Fluoroquinolone vs. cephalosporin	0.87	0.67-1.13	0.304	1.04	0.51-2.11	0.924	0.89	0.70-1.14	0.351
Fluoroquinolone vs. trimethoprim	0.74	0.58-0.95	0.016	0.70	0.37-1.35	0.289	0.74	0.59-0.93	0.009
Fluoroquinolone vs. co-amoxiclav	0.82	0.63-1.07	0.146	0.70	0.34-1.42	0.323	0.81	0.63-1.03	0.088

eTable 12: Case-crossover studies - Odds ratios for AA/AD with period length of 60 days and interval between periods of 60 days

Comparison	Aurum			GOLD			Pooled		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Fluoroquinolone vs. non-use	1.62	1.39-1.89	<0.001	1.29	0.85-1.97	0.232	1.58	1.37-1.83	<0.001
Fluoroquinolone vs. cephalosporin	1.02	0.84-1.25	0.814	0.73	0.43-1.24	0.243	0.98	0.82-1.18	0.849
Fluoroquinolone vs. trimethoprim	0.85	0.71-1.02	0.080	0.78	0.48-1.28	0.331	0.84	0.71-1.00	0.048
Fluoroquinolone vs. co-amoxiclav	0.97	0.80-1.18	0.766	0.73	0.43-1.25	0.250	0.94	0.78-1.13	0.497

eTable 13: Case-crossover studies - Odds ratios for AA/AD with period length of 90 days and interval between periods of 30 days

Comparison	Aurum			GOLD			Pooled		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Fluoroquinolone vs. non-use	1.55	1.35-1.77	<0.001	1.27	0.89-1.83	0.188	1.51	1.33-1.71	<0.001
Fluoroquinolone vs. cephalosporin	1.07	0.90-1.28	0.420	0.77	0.49-1.21	0.254	1.03	0.88-1.21	0.725
Fluoroquinolone vs. trimethoprim	0.90	0.77-1.06	0.203	0.85	0.56-1.30	0.453	0.90	0.77-1.04	0.146
Fluoroquinolone vs. co-amoxiclav	0.92	0.78-1.09	0.350	0.79	0.50-1.25	0.315	0.90	0.77-1.06	0.220

eTable 14: Cohort studies - Hazard ratios between fluoroquinolone prescribing relative to cephalosporin prescribing and AA/AD at first treatment episode with propensity score trimming

Outcome	Method	Aurum			GOLD			Pooled		
		Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Aortic aneurysm or dissection	Unadjusted	1.34	1.17-1.54	<0.001	1.10	0.78-1.56	0.591	1.31	1.15-1.48	<0.001
	IPTW Weighted	1.05	0.91-1.20	0.518	1.10	0.78-1.56	0.591	1.04	0.91-1.18	0.577
Tendon rupture	Unadjusted	2.75	2.14-3.54	<0.001	3.63	1.64-8.04	0.003	2.83	2.23-3.59	<0.001
	IPTW Weighted	2.47	1.91-3.20	<0.001	3.38	1.50-7.64	0.005	2.55	1.99-3.26	<0.001

eTable 15: Cohort studies - Hazard ratios between fluoroquinolone prescribing relative to cephalosporin prescribing and AA/AD at first treatment episode excluding individuals with prior fluoroquinolone or cephalosporin treatment in 60 days prior

Outcome	Method	Aurum			GOLD			Pooled		
		Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Aortic aneurysm or dissection	Unadjusted	1.31	1.15-1.49	<0.001	1.07	0.77-1.50	0.676	1.28	1.13-1.44	<0.001
	IPTW Weighted	1.05	0.91-1.20	0.515	0.97	0.68-1.38	0.853	1.04	0.91-1.18	0.589
Tendon rupture	Unadjusted	2.33	1.83-2.96	<0.001	3.30	1.53-7.12	0.004	2.41	1.92-3.02	<0.001
	IPTW weighted	1.91	1.49-2.45	<0.001	2.90	1.31-6.42	0.010	1.99	1.57-2.52	<0.001