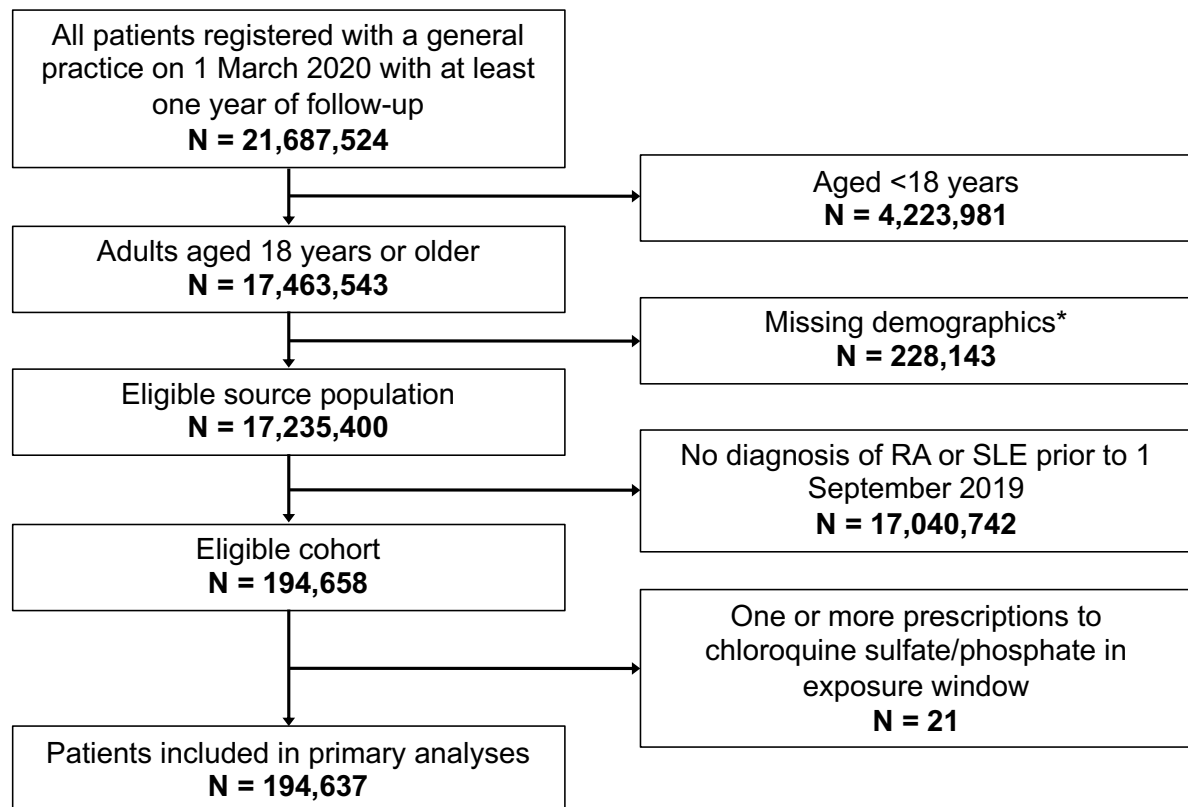


Figure 1. Flow chart



Abbreviations: RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

*Including sex and index of multiple deprivation

Table 1. Demographic and clinical characteristics of 194,637 patients with rheumatoid arthritis or systemic lupus erythematosus (SLE)

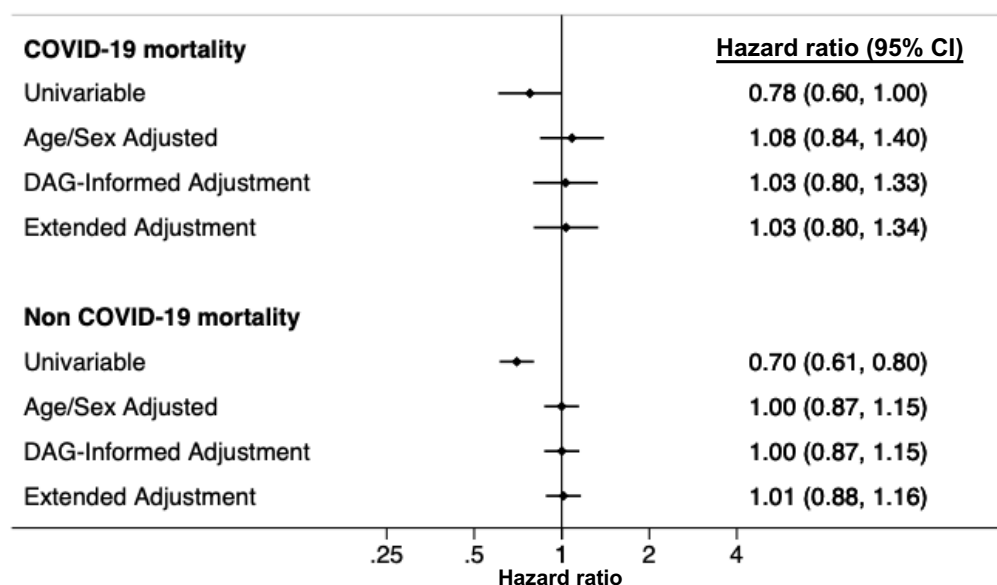
	Total	No HCQ	HCQ
Sample size, n	194,637 (100.0)	164,068 (100.0)	30,569 (100.0)
Population			
Rheumatoid arthritis	167,874 (86.2)	144,151 (87.9)	23,723 (77.6)
SLE	26,763 (13.8)	19,917 (12.1)	6,846 (22.4)
Demographics			
Age, years			
Median (IQR)	66 (54-75)	66 (55-76)	63 (53-72)
18-39	13,709 (7.0)	11,433 (7.0)	2,276 (7.4)
40-49	19,438 (10.0)	15,829 (9.6)	3,609 (11.8)
50-59	37,086 (19.1)	30,457 (18.6)	6,629 (21.7)
60-69	45,699 (23.5)	37,726 (23.0)	7,973 (26.1)
70-79	49,238 (25.3)	42,090 (25.7)	7,148 (23.4)

≥80	29,467 (15.1)	26,533 (16.2)	2,934 (9.6)
Sex			
Female	138,440 (71.1)	115,106 (70.2)	23,334 (76.3)
Male	56,197 (28.9)	48,962 (29.8)	7,235 (23.7)
Ethnicity			
White	132,697 (68.2)	112,367 (68.5)	20,330 (66.5)
South Asian	10,498 (5.4)	8,502 (5.2)	1,996 (6.5)
Black	2,997 (1.5)	2,425 (1.5)	572 (1.9)
Mixed	1,279 (0.7)	1,005 (0.6)	274 (0.9)
Other	1,838 (0.9)	1,508 (0.9)	330 (1.1)
Missing	45,328 (23.3)	38,261 (23.3)	7,067 (23.1)
Index of multiple deprivation			
1 (least deprived)	38,968 (20.0)	32,954 (20.1)	6,014 (19.7)
2	39,437 (20.3)	33,351 (20.3)	6,086 (19.9)
3	38,942 (20.0)	32,800 (20.0)	6,142 (20.1)
4	38,477 (19.8)	32,402 (19.7)	6,075 (19.9)
5 (most deprived)	38,813 (19.9)	32,561 (19.8)	6,252 (20.5)
Residence type			
Rural	45,656 (23.5)	38,305 (23.3)	7,351 (24.0)
Urban	148,981 (76.5)	125,763 (76.7)	23,218 (76.0)
Body mass index, kg/m ²			
<18.5	4,372 (2.2)	3,692 (2.3)	680 (2.2)
18.5-24.9	56,981 (29.3)	48,051 (29.3)	8,930 (29.2)
25-29.9	61,870 (31.8)	52,667 (32.1)	9,203 (30.1)
30-34.9	35,315 (18.1)	29,652 (18.1)	5,663 (18.5)
35-39.9	14,999 (7.7)	12,372 (7.5)	2,627 (8.6)
≥40	7,727 (4.0)	6,156 (3.8)	1,571 (5.1)
Missing	13,373 (6.9)	11,478 (7.0)	1,895 (6.2)
Smoking status			
Never	74,184 (38.1)	62,705 (38.2)	11,479 (37.6)
Former	92,432 (47.5)	77,740 (47.4)	14,692 (48.1)
Current	27,411 (14.1)	23,079 (14.1)	4,332 (14.2)
Missing	610 (0.3)	544 (0.3)	66 (0.2)
Clinical conditions			
Diabetes			
No diabetes	159,830 (82.1)	133,954 (81.6)	25,876 (84.6)

Diabetes, HbA1c <7.5%	22,713 (11.7)	19,560 (11.9)	3,153 (10.3)
Diabetes, HbA1c ≥7.5%	8,998 (4.6)	7,930 (4.8)	1,068 (3.5)
Diabetes, missing HbA1c	3,096 (1.6)	2,624 (1.6)	472 (1.5)
eGFR, ml/min/1.73m ²			
≥60	133,371 (68.5)	109,606 (66.8)	23,765 (77.7)
30-59	24,528 (12.6)	21,153 (12.9)	3,375 (11.0)
<30	1,944 (1.0)	1,698 (1.0)	246 (0.8)
Missing	34,794 (17.9)	31,611 (19.3)	3,183 (10.4)
Chronic cardiac disease	30,609 (15.7)	26,292 (16.0)	4,317 (14.1)
Chronic liver disease	2,718 (1.4)	2,227 (1.4)	491 (1.6)
Respiratory disease (excluding asthma)	26,680 (13.7)	22,159 (13.5)	4,521 (14.8)
Neurological condition	12,718 (6.5)	11,003 (6.7)	1,715 (5.6)
Hypertension	83,404 (42.9)	71,117 (43.3)	12,287 (40.2)
Cancer	20,028 (10.3)	17,144 (10.4)	2,884 (9.4)
Immunosuppression	2,969 (1.5)	2,399 (1.5)	570 (1.9)
Influenza vaccination 2019/20	122,295 (62.8)	101,112 (61.6)	21,183 (69.3)
Other medications			
Other DMARDs	71,523 (36.7)	55,780 (34.0)	15,743 (51.5)
Azithromycin	948 (0.5)	751 (0.5)	197 (0.6)
Oral corticosteroids	33,677 (17.3)	26,792 (16.3)	6,885 (22.5)
NSAIDs	33,356 (17.1)	26,686 (16.3)	6,670 (21.8)

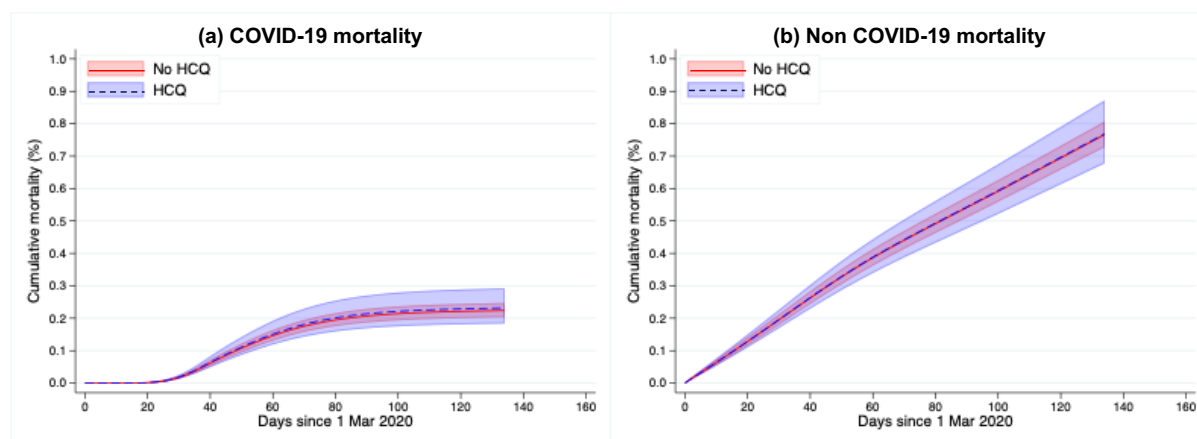
Abbreviations: IQR, interquartile range; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate; DMARD, disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug

Figure 2. Comparisons between hydroxychloroquine (HCQ) use and no HCQ use among 194,637 patients with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE)



Abbreviations: COVID-19, coronavirus disease 2019; DAG, directed acyclic graph; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; STP, Sustainability and Transformation Partnership (a National Health Service administrative region)
Notes: DAG-Informed models adjusted for age, sex, other immunosuppressives (other DMARDs, oral corticosteroids) and stratified by population (i.e., RA or SLE) and STP of the patient's general practice to allow for geographical differences in baseline hazards. Extended adjustment additionally included index of multiple deprivation, smoking status, non-steroidal anti-inflammatory drugs, body mass index, hypertension, diabetes severity, chronic heart disease, liver disease, respiratory disease excluding asthma, kidney disease, stroke, dementia, cancer, and influenza vaccination in 2019/20

Figure 3. Cumulative mortality by hydroxychloroquine (HCQ) use among 194,637 patients with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE)



Abbreviations: COVID-19, coronavirus disease 2019; DAG, directed acyclic graph; DMARD, disease-modifying antirheumatic drug; STP, Sustainability and Transformation Partnership (a National Health Service administrative region)
Notes: Cumulative mortality predicted using a Royston-Parmar model including all covariates from a DAG-Informed model, adjusted for age, sex, other immunosuppressives (other DMARDs, oral corticosteroids). Models further stratified by population (i.e., RA or SLE) and STP of the patient's general practice did not converge; however, comparisons between outputs of Cox models with and without such stratification demonstrated negligible differences. Baseline hazard parametrised as a 3-degrees-of-freedom cubic spline. Predictions standardised to the covariate distribution of the HCQ group.

Figure 4. QBA around missing biologics data (coming soon)

SUPPLEMENTAL MATERIAL

Supplementary Figure S1. Study diagram

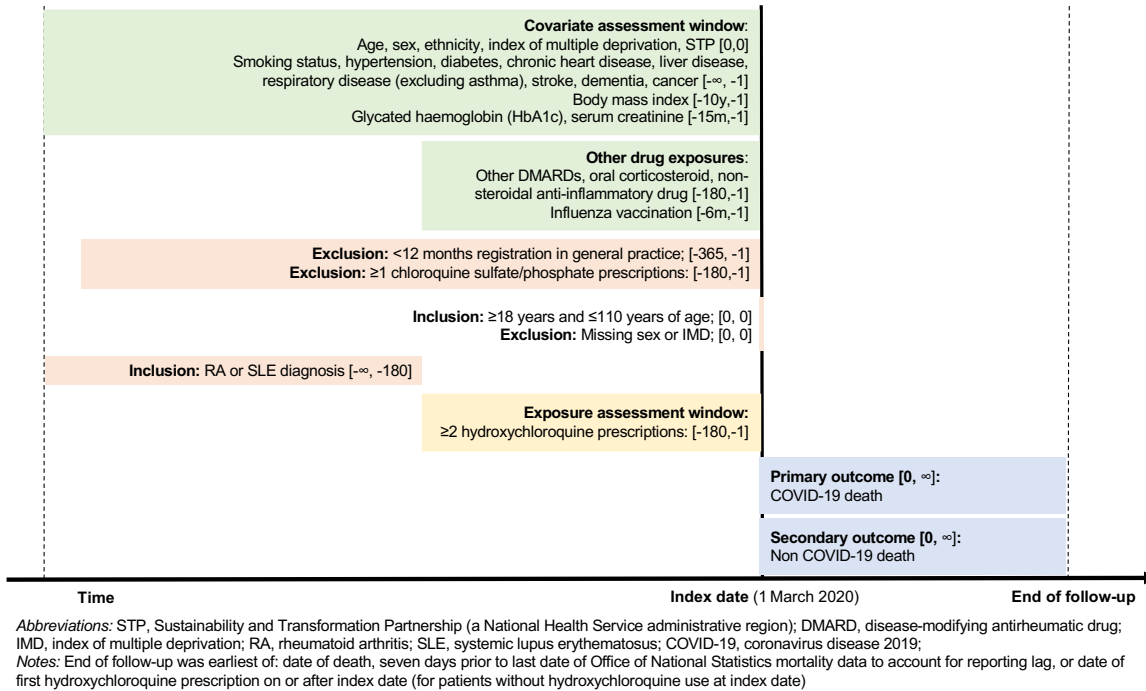


Table S1. Demographic and clinical characteristics of 167,874 patients with rheumatoid arthritis

	Total	No HCQ	HCQ
Demographics			
Age, years			
Median (IQR)	67 (56-76)	67 (56-76)	65 (55-73)
18-39	10,088 (6.0)	8,957 (6.2)	1,131 (4.8)
40-49	15,111 (9.0)	12,822 (8.9)	2,289 (9.6)
50-59	30,917 (18.4)	26,023 (18.1)	4,894 (20.6)
60-69	40,035 (23.8)	33,464 (23.2)	6,571 (27.7)
70-79	44,491 (26.5)	38,279 (26.6)	6,212 (26.2)
≥80	27,232 (16.2)	24,606 (17.1)	2,626 (11.1)
Sex			
	116,406		17,168
Female	(69.3)	99,238 (68.8)	(72.4)
Male	51,468 (30.7)	44,913 (31.2)	6,555 (27.6)
Ethnicity			
	115,869		16,123
White	(69.0)	99,746 (69.2)	(68.0)
South Asian	8,511 (5.1)	7,081 (4.9)	1,430 (6.0)

Black	1,981 (1.2)	1,688 (1.2)	293 (1.2)
Mixed	881 (0.5)	724 (0.5)	157 (0.7)
Other	1,354 (0.8)	1,168 (0.8)	186 (0.8)
Missing	39,278 (23.4)	33,744 (23.4)	5,534 (23.3)
Index of multiple deprivation			
1 (least deprived)	33,439 (19.9)	28,787 (20.0)	4,652 (19.6)
2	33,922 (20.2)	29,199 (20.3)	4,723 (19.9)
3	33,702 (20.1)	28,860 (20.0)	4,842 (20.4)
4	33,311 (19.8)	28,614 (19.9)	4,697 (19.8)
5 (most deprived)	33,500 (20.0)	28,691 (19.9)	4,809 (20.3)
Residence type			
Rural	39,577 (23.6)	33,829 (23.5)	5,748 (24.2)
	128,297	110,322	17,975
Urban	(76.4)	(76.5)	(75.8)
Body mass index, kg/m ²			
<18.5	3,721 (2.2)	3,205 (2.2)	516 (2.2)
18.5-24.9	48,185 (28.7)	41,443 (28.7)	6,742 (28.4)
25-29.9	54,164 (32.3)	46,823 (32.5)	7,341 (30.9)
30-34.9	31,102 (18.5)	26,617 (18.5)	4,485 (18.9)
35-39.9	13,159 (7.8)	11,103 (7.7)	2,056 (8.7)
≥40	6,778 (4.0)	5,521 (3.8)	1,257 (5.3)
Missing	10,765 (6.4)	9,439 (6.5)	1,326 (5.6)
Smoking status			
Never	63,068 (37.6)	54,640 (37.9)	8,428 (35.5)
			11,928
Former	81,304 (48.4)	69,376 (48.1)	(50.3)
Current	23,023 (13.7)	19,696 (13.7)	3,327 (14.0)
Missing	479 (0.3)	439 (0.3)	40 (0.2)
Clinical conditions			
Diabetes			
	136,690	116,885	19,805
No diabetes	(81.4)	(81.1)	(83.5)
Diabetes, HbA1c <7.5%	20,294 (12.1)	17,659 (12.3)	2,635 (11.1)
Diabetes, HbA1c ≥7.5%	8,171 (4.9)	7,261 (5.0)	910 (3.8)
Diabetes, missing HbA1c	2,719 (1.6)	2,346 (1.6)	373 (1.6)

eGFR, ml/min/1.73m²

	117,522		18,892
≥60	(70.0)	98,630 (68.4)	(79.6)
30-59	21,998 (13.1)	19,189 (13.3)	2,809 (11.8)
<30	1,622 (1.0)	1,445 (1.0)	177 (0.7)
Missing	26,732 (15.9)	24,887 (17.3)	1,845 (7.8)
Chronic cardiac disease	27,249 (16.2)	23,708 (16.4)	3,541 (14.9)
Chronic liver disease	2,111 (1.3)	1,787 (1.2)	324 (1.4)
Respiratory disease (excluding asthma)	23,925 (14.3)	20,083 (13.9)	3,842 (16.2)
Neurological condition	10,896 (6.5)	9,646 (6.7)	1,250 (5.3)
Hypertension	73,863 (44.0)	63,955 (44.4)	9,908 (41.8)
Cancer	17,603 (10.5)	15,238 (10.6)	2,365 (10.0)
Immunosuppression	2,200 (1.3)	1,851 (1.3)	349 (1.5)
	108,883		17,186
Influenza vaccination 2019/20	(64.9)	91,697 (63.6)	(72.4)
Other medications			
			14,089
Other DMARDs	68,490 (40.8)	54,401 (37.7)	(59.4)
Azithromycin	850 (0.5)	691 (0.5)	159 (0.7)
Oral corticosteroids	28,858 (17.2)	23,968 (16.6)	4,890 (20.6)
NSAIDs	30,606 (18.2)	25,042 (17.4)	5,564 (23.5)

Abbreviations: IQR, interquartile range; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate; DMARD, disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug

Table S2. Demographic and clinical characteristics of 26,763 patients with systemic lupus erythematosus (SLE)

	Total	No HCQ	HCQ
Demographics			
Age, years			
Median (IQR)	58 (47-70)	60 (48-71)	55 (44-66)
18-39	3,621 (13.5)	2,476 (12.4)	1,145 (16.7)
40-49	4,327 (16.2)	3,007 (15.1)	1,320 (19.3)
50-59	6,169 (23.1)	4,434 (22.3)	1,735 (25.3)
60-69	5,664 (21.2)	4,262 (21.4)	1,402 (20.5)
70-79	4,747 (17.7)	3,811 (19.1)	936 (13.7)
≥80	2,235 (8.4)	1,927 (9.7)	308 (4.5)
Sex			
Female	22,034 (82.3)	15,868 (79.7)	6,166 (90.1)
Male	4,729 (17.7)	4,049 (20.3)	680 (9.9)
Ethnicity			
White	16,828 (62.9)	12,621 (63.4)	4,207 (61.5)
South Asian	1,987 (7.4)	1,421 (7.1)	566 (8.3)
Black	1,016 (3.8)	737 (3.7)	279 (4.1)
Mixed	398 (1.5)	281 (1.4)	117 (1.7)
Other	484 (1.8)	340 (1.7)	144 (2.1)
Missing	6,050 (22.6)	4,517 (22.7)	1,533 (22.4)
Index of multiple deprivation			
1 (least deprived)	5,529 (20.7)	4,167 (20.9)	1,362 (19.9)
2	5,515 (20.6)	4,152 (20.8)	1,363 (19.9)
3	5,240 (19.6)	3,940 (19.8)	1,300 (19.0)
4	5,166 (19.3)	3,788 (19.0)	1,378 (20.1)
5 (most deprived)	5,313 (19.9)	3,870 (19.4)	1,443 (21.1)
Residence type			
Rural	6,079 (22.7)	4,476 (22.5)	1,603 (23.4)
Urban	20,684 (77.3)	15,441 (77.5)	5,243 (76.6)
Body mass index, kg/m ²			
<18.5	651 (2.4)	487 (2.4)	164 (2.4)
18.5-24.9	8,796 (32.9)	6,608 (33.2)	2,188 (32.0)
25-29.9	7,706 (28.8)	5,844 (29.3)	1,862 (27.2)
30-34.9	4,213 (15.7)	3,035 (15.2)	1,178 (17.2)
35-39.9	1,840 (6.9)	1,269 (6.4)	571 (8.3)
≥40	949 (3.5)	635 (3.2)	314 (4.6)

Missing	2,608 (9.7)	2,039 (10.2)	569 (8.3)
Smoking status			
Never	11,116 (41.5)	8,065 (40.5)	3,051 (44.6)
Former	11,128 (41.6)	8,364 (42.0)	2,764 (40.4)
Current	4,388 (16.4)	3,383 (17.0)	1,005 (14.7)
Missing	131 (0.5)	105 (0.5)	26 (0.4)
Clinical conditions			
Diabetes			
No diabetes	23,140 (86.5)	17,069 (85.7)	6,071 (88.7)
Diabetes, HbA1c <7.5%	2,419 (9.0)	1,901 (9.5)	518 (7.6)
Diabetes, HbA1c ≥7.5%	827 (3.1)	669 (3.4)	158 (2.3)
Diabetes, missing HbA1c	377 (1.4)	278 (1.4)	99 (1.4)
eGFR, ml/min/1.73m²			
≥60	15,849 (59.2)	10,976 (55.1)	4,873 (71.2)
30-59	2,530 (9.5)	1,964 (9.9)	566 (8.3)
<30	322 (1.2)	253 (1.3)	69 (1.0)
Missing	8,062 (30.1)	6,724 (33.8)	1,338 (19.5)
Chronic cardiac disease	3,360 (12.6)	2,584 (13.0)	776 (11.3)
Chronic liver disease	607 (2.3)	440 (2.2)	167 (2.4)
Respiratory disease (excluding asthma)	2,755 (10.3)	2,076 (10.4)	679 (9.9)
Neurological condition	1,822 (6.8)	1,357 (6.8)	465 (6.8)
Hypertension	9,541 (35.6)	7,162 (36.0)	2,379 (34.8)
Cancer	2,425 (9.1)	1,906 (9.6)	519 (7.6)
Immunosuppression	769 (2.9)	548 (2.8)	221 (3.2)
Influenza vaccination 2019/20	13,412 (50.1)	9,415 (47.3)	3,997 (58.4)
Other medications			
Other DMARDs	3,033 (11.3)	1,379 (6.9)	1,654 (24.2)
Azithromycin	98 (0.4)	60 (0.3)	38 (0.6)
Oral corticosteroids	4,819 (18.0)	2,824 (14.2)	1,995 (29.1)
NSAIDs	2,750 (10.3)	1,644 (8.3)	1,106 (16.2)

Abbreviations: IQR, interquartile range; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate; DMARD, disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug

Table S3. Interactions with HCQ use on the risk of COVID-19 mortality

	No. events	DAG-Informed Adjustment		
		HR	95% CI	p-value
Age				
18-59 years				
No HCQ	18 (0.0)	1	(ref)	0.78
HCQ	6 (0.0)	1.50	(0.59-3.79)	
60-69 years				
No HCQ	40 (0.1)	1	(ref)	
HCQ	10 (0.1)	1.17	(0.58-2.35)	
70-79 years				
No HCQ	148 (0.4)	1	(ref)	
HCQ	25 (0.3)	0.97	(0.63-1.48)	
≥80 years				
No HCQ	271 (1.0)	1	(ref)	
HCQ	29 (1.0)	0.92	(0.62-1.35)	
Other DMARDs				
No				
No HCQ	311 (0.3)	1	(ref)	0.22
HCQ	41 (0.3)	1.14	(0.82-1.59)	
Yes				
No HCQ	166 (0.3)	1	(ref)	
HCQ	29 (0.2)	0.83	(0.56-1.24)	
Oral corticosteroids				
No				
No HCQ	296 (0.2)	1	(ref)	0.97
HCQ	38 (0.2)	1.00	(0.71-1.41)	
Yes				
No HCQ	181 (0.7)	1	(ref)	
HCQ	32 (0.5)	0.99	(0.68-1.45)	
NSAIDs				
No				
No HCQ	443 (0.3)	1	(ref)	0.11
HCQ	62 (0.3)	0.98	(0.75-1.29)	
Yes				
No HCQ	34 (0.1)	1	(ref)	
HCQ	8 (0.1)	1.18	(0.55-2.56)	

Abbreviations: HCQ, hydroxychloroquine; COVID-19, coronavirus disease 2019; DAG, directed acyclic graph; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; STP, Sustainability and Transformation Partnership (a National Health Service administrative region)

Notes: DAG-Informed models adjusted for age, sex, other immunosuppressives (other DMARDs, oral corticosteroids) and stratified by population (i.e., RA or SLE) and STP of the patient's general practice to allow for geographical differences in baseline hazards.

Table S4. Sensitivity analyses of the association between HCQ use and the risk of COVID-19 mortality

		DAG-Informed Adjustment	
	No. events	HR	95% CI
Ethnicity adjustments			
Exclude individuals with missing ethnicity			
No HCQ	358 (0.3)	1	(ref)
HCQ	48 (0.2)	0.94	(0.69-1.28)
Additional adjustment for ethnicity			
No HCQ	358 (0.3)	1	(ref)
HCQ	48 (0.2)	0.94	(0.69-1.27)
Shorten exposure ascertainment to 3 months			
No HCQ	477 (0.3)	1	(ref)
HCQ	70 (0.2)	1.03	(0.80-1.33)
Population adjustment			
Change from stratifying to indicator variable			
No HCQ	477 (0.3)	1	(ref)
HCQ	70 (0.2)	0.94	(0.69-1.27)
Model populations separately			
Rheumatoid arthritis (RA)			
No HCQ	449 (0.3)	1	(ref)
HCQ	60 (0.3)	0.98	(0.75-1.29)
Systemic lupus erythematosus (SLE)			
No HCQ	28 (0.1)	1	(ref)
HCQ	10 (0.1)	1.64	(0.68-3.97)

Abbreviations: HCQ, hydroxychloroquine; COVID-19, coronavirus disease 2019; DAG, directed acyclic graph; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; STP, Sustainability and Transformation Partnership (a National Health Service administrative region)

Notes: DAG-Informed models adjusted for age, sex, other immunosuppressives (other DMARDs, oral corticosteroids) and stratified by population (i.e., RA or SLE) and STP of the patient's general practice to allow for geographical differences in baseline hazards.

Table S5. Comparison of estimates between stratified Cox proportional hazards models (stcox) and flexible parametric models (stpm2)

	Stratified Cox (stcox)		Flexible parametric (stpm2)	
	HR	95% CI	HR	95% CI
COVID-19 mortality				
HCQ, yes vs. no	1.03	(0.80-1.33)	1.03	(0.80-1.33)
Sex, male vs. female	1.46	(1.23-1.74)	1.45	(1.22-1.72)
Age, spline 1	1.05	(0.98-1.13)	1.05	(0.98-1.13)
Age, spline 2	1.08	(0.97-1.19)	1.08	(0.97-1.19)
Age, spline 3	0.75	(0.50-1.11)	0.74	(0.50-1.10)
Other DMARD, yes vs. no	0.93	(0.78-1.12)	0.91	(0.76-1.09)
Oral corticosteroid, yes vs. no	2.47	(2.07-2.93)	2.45	(2.06-2.91)
Non COVID-19 mortality				
HCQ, yes vs. no	1.00	(0.87-1.15)	1.00	(0.87-1.15)
Sex, male vs. female	1.25	(1.14-1.37)	1.25	(1.14-1.37)
Age, spline 1	1.06	(1.03-1.10)	1.06	(1.03-1.10)
Age, spline 2	1.03	(0.98-1.09)	1.03	(0.98-1.09)
Age, spline 3	0.94	(0.77-1.14)	0.94	(0.77-1.14)
Other DMARD, yes vs. no	0.68	(0.61-0.75)	0.68	(0.62-0.75)
Oral corticosteroid, yes vs. no	2.03	(1.85-2.23)	2.03	(1.85-2.22)

Note: Cox models were stratified on STP and RA/SLE population. Flexible parametric models were stratified on STP and included a binary indicator for RA/SLE population as a fixed effect.