Table 1. Demographic and clinical characteristics of 194,326 patients with rheumatoid arthritis or systemic lupus erythematosus (SLE)
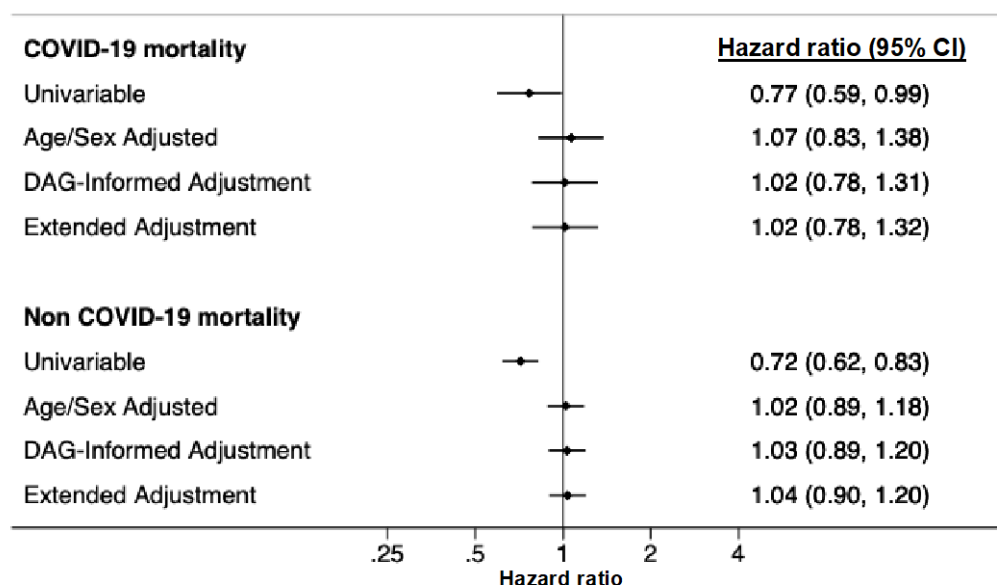
	Total	No HCQ	HCQ
Sample size, n	194,236 (100.0)	163,735 (100.0)	30,501 (100.0)
Population			
Rheumatoid arthritis	167,513 (86.2)	143,848 (87.9)	23,665 (77.6)
SLE	26,723 (13.8)	19,887 (12.1)	6,836 (22.4)
Demographics			
Age, years			
Median (IQR)	66 (54-75)	66 (55-76)	63 (53-72)
18-39	13,683 (7.0)	11,409 (7.0)	2,274 (7.5)
40-49	19,406 (10.0)	15,804 (9.7)	3,602 (11.8)
50-59	37,024 (19.1)	30,408 (18.6)	6,616 (21.7)
60-69	45,617 (23.5)	37,655 (23.0)	7,962 (26.1)
70-79	49,101 (25.3)	41,976 (25.6)	7,125 (23.4)
≥80	29,405 (15.1)	26,483 (16.2)	2,922 (9.6)
Sex			
Female	138,160 (71.1)	114,866 (70.2)	23,294 (76.4)
Male	56,076 (28.9)	48,869 (29.8)	7,207 (23.6)
Ethnicity			
White	132,408 (68.2)	112,126 (68.5)	20,282 (66.5)
South Asian	10,478 (5.4)	8,490 (5.2)	1,988 (6.5)
Black	2,995 (1.5)	2,424 (1.5)	571 (1.9)
Mixed	1,278 (0.7)	1,003 (0.6)	275 (0.9)
Other	1,837 (0.9)	1,504 (0.9)	333 (1.1)
Missing	45,240 (23.3)	38,188 (23.3)	7,052 (23.1)
Index of multiple deprivation			
1 (least deprived)	38,904 (20.0)	32,892 (20.1)	6,012 (19.7)
2	39,314 (20.2)	33,251 (20.3)	6,063 (19.9)
3	38,834 (20.0)	32,715 (20.0)	6,119 (20.1)
4	38,386 (19.8)	32,326 (19.7)	6,060 (19.9)
5 (most deprived)	38,798 (20.0)	32,551 (19.9)	6,247 (20.5)
Residence type			
Rural	45,364 (23.4)	38,051 (23.2)	7,313 (24.0)
Urban	148,872 (76.6)	125,684 (76.8)	23,188 (76.0)
Body mass index, kg/m^2			
<18.5	4,452 (2.3)	3,778 (2.3)	674 (2.2)
18.5-24.9	57,178 (29.4)	48,218 (29.4)	8,960 (29.4)
25-29.9	61,723 (31.8)	52,526 (32.1)	9,197 (30.2)
30-34.9	35,166 (18.1)	29,506 (18.0)	5,660 (18.6)
35-39.9	15,035 (7.7)	12,396 (7.6)	2,639 (8.7)
≥40	7,688 (4.0)	6,128 (3.7)	1,560 (5.1)
Missing	12,994 (6.7)	11,183 (6.8)	1,811 (5.9)
Smoking status			
Never	74,031 (38.1)	62,578 (38.2)	11,453 (37.5)
Former	92,235 (47.5)	77,578 (47.4)	14,657 (48.1)

Current	27,360 (14.1)	23,035 (14.1)	4,325 (14.2)
Missing	610 (0.3)	544 (0.3)	66 (0.2)
Clinical conditions			
Diabetes			
No diabetes	159,503 (82.1)	133,687 (81.6)	25,816 (84.6)
Diabetes, HbA1c <7.5%	24,809 (12.8)	21,330 (13.0)	3,479 (11.4)
Diabetes, HbA1c ≥7.5%	9,363 (4.8)	8,262 (5.0)	1,101 (3.6)
Diabetes, missing HbA1c	561 (0.3)	456 (0.3)	105 (0.3)
eGFR, ml/min/1.73m^2			
≥60	127,177 (65.5)	104,168 (63.6)	23,009 (75.4)
30-59	23,802 (12.3)	20,504 (12.5)	3,298 (10.8)
<30	1,885 (1.0)	1,646 (1.0)	239 (0.8)
Missing	41,372 (21.3)	37,417 (22.9)	3,955 (13.0)
Chronic cardiac disease	30,540 (15.7)	26,236 (16.0)	4,304 (14.1)
Chronic liver disease	2,709 (1.4)	2,220 (1.4)	489 (1.6)
Respiratory disease (excluding asthma)	26,617 (13.7)	22,101 (13.5)	4,516 (14.8)
Neurological condition	12,686 (6.5)	10,973 (6.7)	1,713 (5.6)
Hypertension	83,215 (42.8)	70,951 (43.3)	12,264 (40.2)
Cancer	19,962 (10.3)	17,092 (10.4)	2,870 (9.4)
Immunosuppression	2,964 (1.5)	2,395 (1.5)	569 (1.9)
Influenza vaccination 2019/20	122,005 (62.8)	100,869 (61.6)	21,136 (69.3)
Other medications			
Other DMARDs	71,342 (36.7)	55,638 (34.0)	15,704 (51.5)
Azithromycin	948 (0.5)	751 (0.5)	197 (0.6)
Oral corticosteroids	33,593 (17.3)	26,727 (16.3)	6,866 (22.5)
NSAIDs	33,256 (17.1)	26,614 (16.3)	6,642 (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
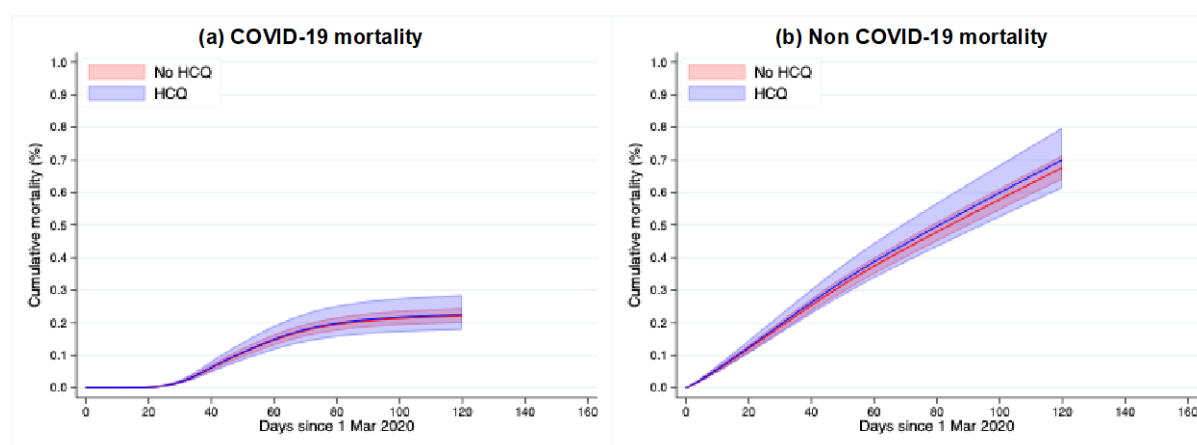
Figure 1. Flow diagram (coming soon)

Figure 2. Comparisons between hydroxychloroquine (HCQ) use and no HCQ use among 194,326 patients with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE)

COVID-19 mortality	Hazard ratio (95% CI)
Univariable	0.77 (0.59, 0.99)
Age/Sex Adjusted	1.07 (0.83, 1.38)
DAG-Informed Adjustment	1.02 (0.78, 1.31)
Extended Adjustment	1.02 (0.78, 1.32)
Non COVID-19 mortality	
Univariable	0.72 (0.62, 0.83)
Age/Sex Adjusted	1.02 (0.89, 1.18)
DAG-Informed Adjustment	1.03 (0.89, 1.20)
Extended Adjustment	1.04 (0.90, 1.20)

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 non-steroidal anti-inflammatory drugs, chronic heart disease, lung disease, chronic respiratory disease excluding asthma, kidney disease, liver disease, body mass index, hypertension, influenza vaccination in 2019/20, cancer, stroke, and dementia

Figure 3. Cumulative mortality by hydroxychloroquine (HCQ) use among 194,326 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 parameterised as a 3-degrees-of-freedom cubic spline. Predictions standardised to the covariate distribution of the HCQ group.

NEED TO ADD RISK TABLE

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

SUPPLEMENTAL MATERIAL
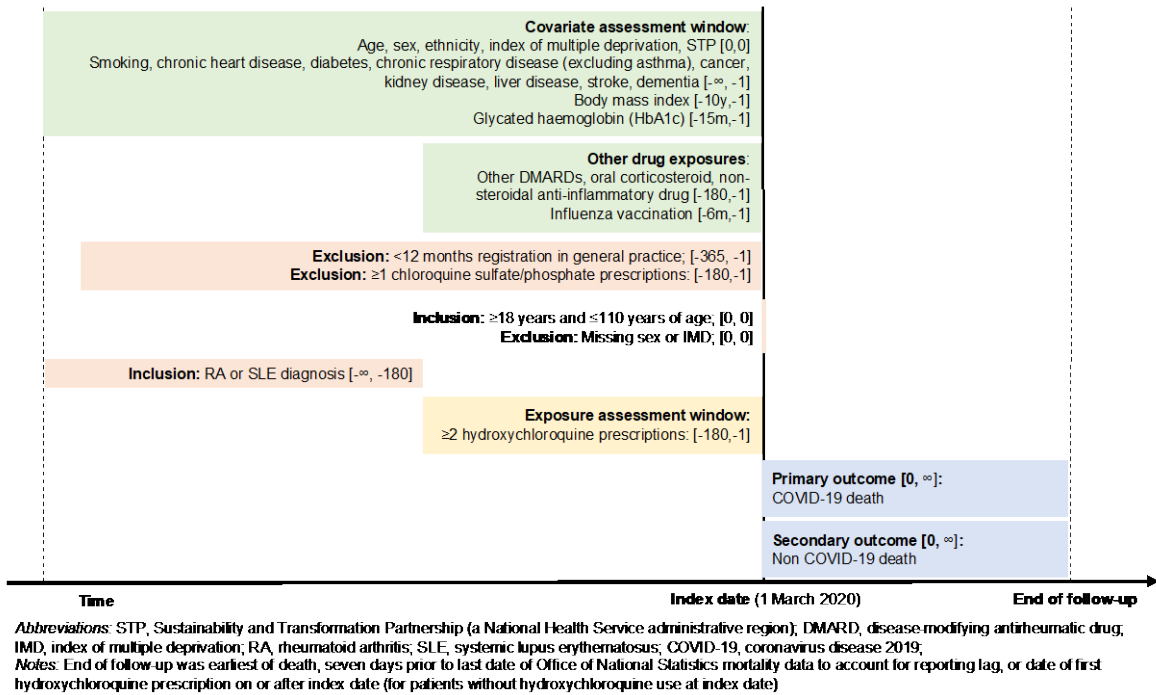
Supplementary Figure S1. Study diagram

Abbreviations: STP, Sustainability and Transformation Partnership (a National Health Service administrative region); DMARD, disease-modifying antirheumatic drug; IMD, index of multiple deprivation; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; COVID-19, coronavirus disease 2019;

Notes: End of follow-up was earliest of death, seven days prior to last date of Office of National Statistics mortality data to account for reporting lag, or date of first hydroxychloroquine prescription on or after index date (for patients without hydroxychloroquine use at index date)

Table S1. Demographic and clinical characteristics of 167,513 patients with rheumatoid arthritis

	Total	No HCQ	HCQ
Demographics			
Age, years			
Median (IQR)	67 (56-76)	67 (56-76)	65 (55-73)
18-39	10,065 (6.0)	8,936 (6.2)	1,129 (4.8)
40-49	15,086 (9.0)	12,802 (8.9)	2,284 (9.7)
50-59	30,868 (18.4)	25,984 (18.1)	4,884 (20.6)
60-69	39,962 (23.9)	33,400 (23.2)	6,562 (27.7)
70-79	44,359 (26.5)	38,167 (26.5)	6,192 (26.2)
≥80	27,173 (16.2)	24,559 (17.1)	2,614 (11.0)
Sex			
Female	116,161 (69.3)	99,023 (68.8)	17,138 (72.4)
Male	51,352 (30.7)	44,825 (31.2)	6,527 (27.6)
Ethnicity			
White	115,609 (69.0)	99,526 (69.2)	16,083 (68.0)
South Asian	8,492 (5.1)	7,070 (4.9)	1,422 (6.0)
Black	1,984 (1.2)	1,690 (1.2)	294 (1.2)
Mixed	878 (0.5)	721 (0.5)	157 (0.7)
Other	1,354 (0.8)	1,166 (0.8)	188 (0.8)
Missing	39,196 (23.4)	33,675 (23.4)	5,521 (23.3)

Index of multiple deprivation			
1 (least deprived)	33,385 (19.9)	28,736 (20.0)	4,649 (19.6)
2	33,811 (20.2)	29,107 (20.2)	4,704 (19.9)
3	33,597 (20.1)	28,776 (20.0)	4,821 (20.4)
4	33,230 (19.8)	28,545 (19.8)	4,685 (19.8)
5 (most deprived)	33,490 (20.0)	28,684 (19.9)	4,806 (20.3)
Residence type			
Rural	39,321 (23.5)	33,604 (23.4)	5,717 (24.2)
Urban	128,192 (76.5)	110,244 (76.6)	17,948 (75.8)
Body mass index, kg/m^2			
<18.5	3,796 (2.3)	3,286 (2.3)	510 (2.2)
18.5-24.9	48,371 (28.9)	41,607 (28.9)	6,764 (28.6)
25-29.9	54,025 (32.3)	46,679 (32.5)	7,346 (31.0)
30-34.9	30,951 (18.5)	26,485 (18.4)	4,466 (18.9)
35-39.9	13,199 (7.9)	11,125 (7.7)	2,074 (8.8)
≥40	6,739 (4.0)	5,495 (3.8)	1,244 (5.3)
Missing	10,432 (6.2)	9,171 (6.4)	1,261 (5.3)
Smoking status			
Never	62,932 (37.6)	54,527 (37.9)	8,405 (35.5)
Former	81,125 (48.4)	69,225 (48.1)	11,900 (50.3)
Current	22,977 (13.7)	19,657 (13.7)	3,320 (14.0)
Missing	479 (0.3)	439 (0.3)	40 (0.2)
Clinical conditions			
Diabetes			
No diabetes	136,398 (81.4)	116,645 (81.1)	19,753 (83.5)
Diabetes, HbA1c <7.5%	22,134 (13.2)	19,236 (13.4)	2,898 (12.2)
Diabetes, HbA1c ≥7.5%	8,497 (5.1)	7,561 (5.3)	936 (4.0)
Diabetes, missing HbA1c	484 (0.3)	406 (0.3)	78 (0.3)
eGFR, ml/min/1.73m^2			
≥60	112,440 (67.1)	94,038 (65.4)	18,402 (77.8)
30-59	21,384 (12.8)	18,629 (13.0)	2,755 (11.6)
<30	1,583 (0.9)	1,409 (1.0)	174 (0.7)
Missing	32,106 (19.2)	29,772 (20.7)	2,334 (9.9)
Chronic cardiac disease	27,186 (16.2)	23,655 (16.4)	3,531 (14.9)
Chronic liver disease	2,104 (1.3)	1,782 (1.2)	322 (1.4)
Respiratory disease (excluding asthma)	23,864 (14.2)	20,027 (13.9)	3,837 (16.2)
Neurological condition	10,866 (6.5)	9,617 (6.7)	1,249 (5.3)
Hypertension	73,688 (44.0)	63,800 (44.4)	9,888 (41.8)
Cancer	17,542 (10.5)	15,190 (10.6)	2,352 (9.9)
Immunosuppression	2,195 (1.3)	1,847 (1.3)	348 (1.5)
Influenza vaccination 2019/20	108,614 (64.8)	91,472 (63.6)	17,142 (72.4)

Other medications

	Total	No HCQ	HCQ
Other DMARDs	68,315 (40.8)	54,262 (37.7)	14,053 (59.4)
Azithromycin	850 (0.5)	691 (0.5)	159 (0.7)
Oral corticosteroids	28,781 (17.2)	23,905 (16.6)	4,876 (20.6)
NSAIDs	30,516 (18.2)	24,974 (17.4)	5,542 (23.4)

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 26,723 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	3,618 (13.5)	2,473 (12.4)	1,145 (16.7)
40-49	4,320 (16.2)	3,002 (15.1)	1,318 (19.3)
50-59	6,156 (23.0)	4,424 (22.2)	1,732 (25.3)
60-69	5,655 (21.2)	4,255 (21.4)	1,400 (20.5)
70-79	4,742 (17.7)	3,809 (19.2)	933 (13.6)
≥80	2,232 (8.4)	1,924 (9.7)	308 (4.5)
Sex			
Female	21,999 (82.3)	15,843 (79.7)	6,156 (90.1)
Male	4,724 (17.7)	4,044 (20.3)	680 (9.9)
Ethnicity			
White	16,799 (62.9)	12,600 (63.4)	4,199 (61.4)
South Asian	1,986 (7.4)	1,420 (7.1)	566 (8.3)
Black	1,011 (3.8)	734 (3.7)	277 (4.1)
Mixed	400 (1.5)	282 (1.4)	118 (1.7)
Other	483 (1.8)	338 (1.7)	145 (2.1)
Missing	6,044 (22.6)	4,513 (22.7)	1,531 (22.4)
Index of multiple deprivation			
1 (least deprived)	5,519 (20.7)	4,156 (20.9)	1,363 (19.9)
2	5,503 (20.6)	4,144 (20.8)	1,359 (19.9)
3	5,237 (19.6)	3,939 (19.8)	1,298 (19.0)
4	5,156 (19.3)	3,781 (19.0)	1,375 (20.1)
5 (most deprived)	5,308 (19.9)	3,867 (19.4)	1,441 (21.1)
Residence type			
Rural	6,043 (22.6)	4,447 (22.4)	1,596 (23.3)
Urban	20,680 (77.4)	15,440 (77.6)	5,240 (76.7)
Body mass index, kg/m^2			
<18.5	656 (2.5)	492 (2.5)	164 (2.4)
18.5-24.9	8,807 (33.0)	6,611 (33.2)	2,196 (32.1)
25-29.9	7,698 (28.8)	5,847 (29.4)	1,851 (27.1)

30-34.9	4,215 (15.8)	3,021 (15.2)	1,194 (17.5)
35-39.9	1,836 (6.9)	1,271 (6.4)	565 (8.3)
≥40	949 (3.6)	633 (3.2)	316 (4.6)
Missing	2,562 (9.6)	2,012 (10.1)	550 (8.0)
Smoking status			
Never	11,099 (41.5)	8,051 (40.5)	3,048 (44.6)
Former	11,110 (41.6)	8,353 (42.0)	2,757 (40.3)
Current	4,383 (16.4)	3,378 (17.0)	1,005 (14.7)
Missing	131 (0.5)	105 (0.5)	26 (0.4)
Clinical conditions			
Diabetes			
No diabetes	23,105 (86.5)	17,042 (85.7)	6,063 (88.7)
Diabetes, HbA1c <7.5%	2,675 (10.0)	2,094 (10.5)	581 (8.5)
Diabetes, HbA1c ≥7.5%	866 (3.2)	701 (3.5)	165 (2.4)
Diabetes, missing HbA1c	77 (0.3)	50 (0.3)	27 (0.4)
eGFR, ml/min/1.73m^2			
≥60	14,737 (55.1)	10,130 (50.9)	4,607 (67.4)
30-59	2,418 (9.0)	1,875 (9.4)	543 (7.9)
<30	302 (1.1)	237 (1.2)	65 (1.0)
Missing	9,266 (34.7)	7,645 (38.4)	1,621 (23.7)
Chronic cardiac disease	3,354 (12.6)	2,581 (13.0)	773 (11.3)
Chronic liver disease	605 (2.3)	438 (2.2)	167 (2.4)
Respiratory disease (excluding asthma)	2,753 (10.3)	2,074 (10.4)	679 (9.9)
Neurological condition	1,820 (6.8)	1,356 (6.8)	464 (6.8)
Hypertension	9,527 (35.7)	7,151 (36.0)	2,376 (34.8)
Cancer	2,420 (9.1)	1,902 (9.6)	518 (7.6)
Immunosuppression	769 (2.9)	548 (2.8)	221 (3.2)
Influenza vaccination 2019/20	13,391 (50.1)	9,397 (47.3)	3,994 (58.4)
Other medications			
Other DMARDs	3,027 (11.3)	1,376 (6.9)	1,651 (24.2)
Azithromycin	98 (0.4)	60 (0.3)	38 (0.6)
Oral corticosteroids	4,812 (18.0)	2,822 (14.2)	1,990 (29.1)
NSAIDs	2,740 (10.3)	1,640 (8.2)	1,100 (16.1)

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

		DAG-Informed Adjustment		
	No. events	**HR**	**95% CI**	**p-value**
Age				
18-59 years				
No HCQ	18 (0.0)	1	(ref)	0.83
HCQ	6 (0.0)	1.50	(0.59-3.80)	
60-69 years				
No HCQ	40 (0.1)	1	(ref)	
HCQ	9 (0.1)	1.06	(0.51-2.18)	
70-79 years				
No HCQ	146 (0.3)	1	(ref)	
HCQ	24 (0.3)	0.94	(0.61-1.45)	
≥80 years				
No HCQ	266 (1.0)	1	(ref)	
HCQ	29 (1.0)	0.93	(0.64-1.37)	
Other DMARDs				
No				
No HCQ	307 (0.3)	1	(ref)	0.22
HCQ	40 (0.3)	1.13	(0.81-1.57)	
Yes				
No HCQ	163 (0.3)	1	(ref)	
HCQ	28 (0.2)	0.82	(0.55-1.22)	
Oral corticosteroids				
No				
No HCQ	290 (0.2)	1	(ref)	0.91
HCQ	37 (0.2)	0.99	(0.70-1.40)	
Yes				
No HCQ	180 (0.7)	1	(ref)	
HCQ	31 (0.5)	0.97	(0.66-1.42)	
NSAIDs				
No				
No HCQ	436 (0.3)	1	(ref)	0.14
HCQ	60 (0.3)	0.97	(0.73-1.27)	
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

	No. events	DAG-Informed Adjustment	
		HR	95% CI
Ethnicity adjustments			
Exclude individuals with missing ethnicity			
No HCQ	352 (0.3)	1	(ref)
HCQ	47 (0.2)	0.93	(0.69-1.27)
Additional adjustment for ethnicity			
No HCQ	352 (0.3)	1	(ref)
HCQ	47 (0.2)	0.93	(0.68-1.27)
Shorten exposure ascertainment to 3 months			
No HCQ	470 (0.3)	1	(ref)
HCQ	68 (0.2)	1.02	(0.78-1.31)
Population adjustment			
Change from stratifying to indicator variable			
No HCQ	470 (0.3)	1	(ref)
HCQ	68 (0.2)	0.93	(0.68-1.27)
Model populations separately			
Rheumatoid arthritis (RA)			
No HCQ	442 (0.3)	1	(ref)
HCQ	59 (0.2)	0.98	(0.74-1.29)
Systemic lupus erythematosus (SLE)			
No HCQ	28 (0.1)	1	(ref)
HCQ	9 (0.1)	1.39	(0.55-3.56)

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 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	1.02	(0.78-1.31)	1.02	(0.79-1.32)
Sex, male vs. female	1.46	(1.22-1.74)	1.44	(1.21-1.71)
Age, spline 1	1.05	(0.98-1.13)	1.05	(0.98-1.13)
Age, spline 2	1.07	(0.97-1.19)	1.08	(0.97-1.19)
Age, spline 3	0.75	(0.51-1.11)	0.75	(0.50-1.11)
Other DMARD, yes vs. no	0.93	(0.77-1.11)	0.90	(0.75-1.08)
OCS	2.50	(2.10-2.97)	2.48	(2.09-2.95)
Non COVID-19 mortality				
HCQ, yes vs. no	1.03	(0.89-1.20)	1.04	(0.90-1.20)
Sex, male vs. female	1.28	(1.16-1.41)	1.28	(1.16-1.41)
Age, spline 1	1.06	(1.02-1.10)	1.06	(1.02-1.10)
Age, spline 2	1.03	(0.98-1.09)	1.03	(0.98-1.09)
Age, spline 3	0.95	(0.78-1.16)	0.95	(0.78-1.16)
Other DMARD, yes vs. no	0.65	(0.59-0.73)	0.66	(0.59-0.73)
OCS	2.01	(1.82-2.22)	2.01	(1.82-2.22)

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.