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Risk of depression, suicide and psychosis with hydroxychloroquine treatment for rheumatoid arthritis: a multi-national network cohort study

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Risk of depression, suicide and psychosis with hydroxychloroquine treatment for rheumatoid arthritis: a multi-national network cohort study

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KEY MESSAGES

- This is the largest study on the neuro-psychiatric safety of hydroxychloroquine, including >900,000 users internationally
- We found no association between hydroxychloroquine treatment for RA and depression, suicide or psychosis compared to sulfasalazine.
- These findings do not support stopping hydroxychloroquine for RA based on concerns raised in COVID-19 patients.

ABSTRACT

Objectives Concern has been raised in the rheumatological community regarding recent regulatory warnings that hydroxychloroquine used in the COVID-19 pandemic could cause acute psychiatric events. We aimed to study whether there is risk of incident depression, suicidal ideation, or psychosis associated with hydroxychloroquine as used for rheumatoid arthritis (RA).

Methods New user cohort study using claims and electronic medical records from 10 sources and 3 countries (Germany, UK and US). RA patients aged 18+ and initiating hydroxychloroquine were compared to those initiating sulfasalazine (active comparator) and followed up in the short (30-day) and long term (on treatment). Study outcomes included depression, suicide/suicidal ideation, and hospitalization for psychosis. Propensity score stratification and calibration using negative control outcomes were used to address confounding. Cox models were fitted to estimate database-specific calibrated hazard ratios (HR), with estimates pooled where I^2<40%.

Results 918,144 and 290,383 users of hydroxychloroquine and sulfasalazine, respectively, were included. No consistent risk of psychiatric events was observed with short-term hydroxychloroquine (compared to sulfasalazine) use, with meta-analytic HRs of 0.96 [0.79-1.16] for depression, 0.94 [0.49-1.77] for suicide/suicidal ideation, and 1.03 [0.66-1.60] for psychosis. No consistent long-term risk was seen, with meta-analytic HRs 0.94 [0.71-1.26] for depression, 0.77 [0.56-1.07] for suicide/suicidal ideation, and 0.99 [0.72-1.35] for psychosis.

Conclusion Hydroxychloroquine as used to treat RA does not appear to increase the risk of depression, suicide/suicidal ideation, or psychosis compared to sulfasalazine. No effects were seen in the short or long term. Use at higher dose or for different indications needs further investigation.

TRIAL REGISTRATION Registered with EU PAS; Reference number EUPAS34497 (http://www.encepp.eu/encepp/viewResource.htm?id=34498). The full study protocol and analysis source code can be found at https://github.com/ohdsi-studies/Covid19EstimationHydroxychloroquine.

INTRODUCTION

Hydroxychloroquine (HCQ) has received much scientific and public attention during the COVID-19 pandemic as a leading therapeutic and prophylactic target. [1, 2] Commonly used for autoimmune disorders (e.g., systemic lupus erythematosus) and inflammatory arthritis, HCQ was released for emergency use for COVID-19 due to its postulated antiviral efficacy in cellular studies.[3-9] HCQ is currently being used in over 217 registered ongoing clinical trials for the treatment of SARS-Cov-2 as of 12th June 2020.[10, 11] Results to date have been conflicting, with emerging data suggesting a lack of clinical efficacy against COVID-19.[12-18] Case report literature suggests that chloroquine, the compound from which HCQ was derived, is associated with neurological and psychiatric side effects when used as an anti-malarial treatment or prophylaxis.[19] Similar, potential side effects have been described in the use of HCQ include neuropsychiatric side effects such as psychosis, depression, and suicidal behaviour.[20-22] Regulatory authorities have received reports of new onset psychiatric symptoms associated with the increased use of high dose HCQ during the pandemic.[23] Whilst Chloroquine and HCQ have multiple mechanisms of action, a major action is the disruption of lysosomal functioning and autophagy.[24] These actions to some degree mimic lysosomal storage diseases, disorders that are characterised by neurodevelopmental delay and neurodegeneration when manifested in the more common form in childhood, but also associated with neuropsychiatric manifestation in adulthood.[25, 26]

New reports of serious side effects associated with HCQ used in COVID-19 are concerning to the rheumatology community, leading to confusion and anxiety for patients who are taking HCQ for autoimmune conditions. Given the previous reports of neuropsychiatric symptoms with HCQ, together with a plausible mechanism for such phenomena, we performed a review of the literature to determine what was already known about the potential risks of psychosis, depression, and suicide associated with HCQ use from literature database inception until 14/05/2020 (Supplementary Appendix Section 1). Interrogation of adverse event registers have identified potential associations between HCQ and psychiatric disorders.[11] Case reports and case series describing new onset psychosis, bipolar disorder, seizures and depression associated with HCQ and chloroquine use for rheumatological disorders and malaria prophylaxis can be found as early as 1964.[20, 27-35] No clinical trial or observational study was found that had investigated the incidence of new onset neuropsychiatric symptoms associated with HCQ use.

Considering the wide-scale use of HCQ in rheumatology, we therefore aimed to determine if there is an association between incident HCQ use for rheumatoid arthritis (RA) (the most common indication for the drug) and the onset of acute psychiatric events, including depression, suicide, and psychosis compared to sulfasalazine.

METHODS

Study design

A new user cohort, active-comparator design was used, as recommended by methodological guidelines for observational drug safety research.[36] The study protocol is registered in the EU PAS Register as EUPAS34497.[37] Sulfasalazine (SSZ) was used as the active comparator for HCQ,

Data sources

Electronic health records (EHR) and administrative claims data from the UK and US were used, previously mapped to the Observational Medical Outcomes Partnership (OMOP) common data model (CDM). The study period covered from September 2000 until the latest data available at the time of extraction in each database. Data from 10 data sources were analysed in a federated manner using a distributed network strategy in collaboration with the Observational Health Data Science and Informatics (OHDSI) and European Health Data and Evidence Network (EHDEN) communities. The data used included primary care electronic medical records from the UK (Clinical Practice Research Datalink, CPRD; and IQVIA Medical Research Data, IMRD); specialist ambulatory care electronic health records from Germany (IQVIA Database Analyzer Germany; DAGermany); electronic health records in a sample of US inpatient and outpatient facilities the Optum® de-identified Electronic Health Record dataset (Optum EHR, and IQVIA US Ambulatory EMR;AmbEMR); and US claims data from the IBM MarketScan® Commercial Claims Database (CCAE), Optum® de-identified Clinformatics® Data Mart Database-Date of Death (Clinformatics), IBM MarketScan® Medicare Supplemental Database (MDCR), IBM MarketScan® Multi-State Medicaid Database (MDCD), and IQVIA OpenClaims (OpenClaims). In addition, data were obtained and analysed from electronic primary care data from the Netherlands (IPCI database) and Spain (SIDIAP), and from Japanese claims (JMDC) but none of these analyses were deemed appropriate due to low/no event counts in at least one of the cohorts. A more detailed description of all these data sources is available in Appendix Section 2.

Follow-up

Participants were followed up from the date of initiation (first dispensing or prescription) of HCQ or sulfasalazine (SSZ) (index date) as described in detail in Appendix Section 3.1. Sulfasalazine was proposed as an active comparator as it shares a similar indication as a second-line conventional synthetic DMARD for RA. Two different follow-up periods were pre-specified to look at short- and long-term effects, respectively. First, a fixed 30-day time window from index date was used to study short-term effects, where follow-up included from day 1 post-index until the earliest of: loss to follow-up/death, outcome of interest, or 30 days from therapy initiation, regardless of compliance/persistence with the study drug/s. Second, in a long-term (on treatment) analysis, follow-up went from day 1 post-index until the earliest of: therapy discontinuation (with a 14-day additional washout), outcome of interest, or loss to follow-up/death. Continued treatment episodes were constructed based on dispensing/prescription records, with a 90-day refill gap allowed to account for stockpiling.

Participants

All subjects registered in any of the contributing data sources for at least 365 days prior to index date, aged 18 years or older, with a history of RA (as defined by a recorded diagnosis any time before or on the same day as therapy initiation), and starting either HCQ or SSZ during the study period, were included.

Potential participant counts and age-, sex- and calendar year-specific incidence per database were produced for transparency and reviewed to check for data inconsistencies and face validity, and are available for inspection at https://data.ohdsi.org/Covid19CohortEvaluationExposures/, labelled as “New users of hydroxychloroquine with previous rheumatoid arthritis” and “New users of sulfasalazine with previous rheumatoid arthritis”.

Outcomes and confounders

Code lists for the identification of the study population, for the study exposures and for the relevant outcomes were created by clinicians with experience in the management of RA and by clinical epidemiologists using ATLAS, an open science analytics platform that provides a unified interface for researchers to work within.[38] Exposures and outcomes were reviewed by experts in OMOP vocabulary and in the use of the proposed data sources. A total of three outcomes were analysed: depression, suicide or suicidal ideation, and hospital admission for psychosis. Detailed outcome definitions with links to code lists are fully detailed in Appendix Section 3.2.[39]
[40] Cohort counts for each of the outcomes in the entire source database, and age-sex and calendar-time specific incidence rates were explored for each of the contributing databases, and reviewed to check for data inconsistencies and face validity. These are available for inspection at https://data.ohdsi.org/Covid19CohortEvaluationSafetyOutcomes/

A list of negative control outcomes was generated for which there is no biologically plausible or known causal relationship with the use of HCQ or SSZ. These outcomes were identified based on previous literature, clinical knowledge (reviewed by two clinicians), product labels, and spontaneous reports, and confirmed by manual review by two clinicians.*[41]* The full list of codes used to identify negative control outcomes can be found in Appendix Section 4.

Statistical methods

All analytical source code is available for inspection and reproducibility at https://github.com/ohdsi-studies/Covid19EstimationHydroxychloroquine2. All study diagnostics and the steps described below are available for review at https://data.ohdsi.org/Covid19EstimationHydroxychloroquine2/.
The following steps were followed for each analysis:
1.Propensity score estimation
Propensity score (PS) stratification was used to minimise confounding. All baseline characteristics recorded in the participants' records/health claims were constructed for inclusion as potential confounders (including demographics, past medical history, procedures and medication prescription within 30 and within 365 days prior to drug initiation) [35]. Covariate construction details are available in Appendix Section 5. Lasso regression models were fitted to estimate propensity scores (PS) as the probability of hydroxychloroquine versus sulfasalazine use based on patient demographics and medical history including previous conditions, procedures, healthcare resource use, and treatments.
The full resulting PS models are available for inspection by clicking on 'Propensity model' after selecting a database in the results app.

2.Study diagnostics
Study diagnostics were explored for each database-specific analysis before progressing to outcome modelling, and included checks for power, observed confounding, and potential residual (unobserved) confounding. Only database-outcome analyses that passed all diagnostics below were then conducted and reported, with all others marked as 'NA' in the accompanying results app.
Positivity and power were assessed by looking at the number of participants in each treatment arm, and the number with the outcome (see the 'Power' tab after clicking on a database in the results app). Small cell counts less than five (and resulting estimates) are reported as "<5" to minimise risk of secondary disclosure of data with patient identification. PS overlap was also plotted to visualize positivity issues and can be seen by clicking on 'Propensity Scores'.
Observed confounding was explored by plotting standardized differences before (X axis) vs after (Y) PS stratification, with standardized differences > 0.1 in the Y axis indicating the presence of unresolved confounding [36]: see by clicking on 'Covariate balance' in the results app.
Finally, negative control outcome analyses were assessed to identify systematic error due to residual (unobserved) confounding. The results for these are available in the 'Systematic error' tab of the

results app. The resulting information was used to calibrate the outcome models using empirical calibration *[37, 38].*

3.Outcome modelling

Cox proportional hazards models conditioned on the PS strata were fitted to estimate Hazard Ratios (HR) for each psychological outcome in new users of HCQ (vs SSZ). Empirical calibration based on the previously described negative control outcomes was used to minimise any potential residual confounding with calibrated HRs and 95% confidence intervals (CI) estimated[42, 43]. All analyses were conducted for each database separately, with estimates combined in random-effects meta-analysis methods where I^2 ≤40%.[44] The standard errors of the database-specific estimates were adjusted to incorporate estimate variation across databases, where the across-database variance was estimated by comparing each database-specific result to that of an inverse-variance, fixed-effects meta-analysis. No meta-analysis was conducted where I^2 for a given drug-outcome pair was >40%.

All analyses were conducted using the CohortMethod package, available at https://ohdsi.github.io/CohortMethod/ and the Cyclops package for PS estimation (https://ohdsi.github.io/Cyclops) [45].

Data Sharing

Open Science is a guiding principle within OHDSI. As such, we provide unfettered access to all open-source analysis tools employed in this study via https://github.com/OHDSI/, as well as all data and results artefacts that do not include patient-level health information via http://data.ohdsi.org/Covid19EstimationHydroxychloroquine2.

Data partners contributing to this study remain custodians of their individual patient-level health information and hold either IRB exemption or approval for participation.

RESULTS

A total of 918,144 HCQ and 290,383 SSZ users were identified. Participant counts in each data source are provided in Appendix Section 6. Before PS stratification, users of HCQ were (compared to SSZ users) more likely female (for example, 82.0% vs 74.3% in CCAE database) and less likely to have certain comorbidities such as Crohn's disease (0.6% vs 1.8% in CCAE) or psoriasis (3.0% vs 8.9% in CCAE). Prevalence of systemic lupus erythematous was higher in HCQ users as expected (1.5% vs 0.5% in CCAE), whilst use of systemic glucocorticoids was similar (46.1% vs 47.2% in the previous month in CCAE). The prevalence of depressive disorder was similar in both groups (13.4% vs 13.5% in CCAE) and so was the history of use of antidepressants in the previous year (36.4% vs 36.4% in CCAE). Average baseline dose of HCQ was homogeneous, with >97% in CCAE using an average dose of 420mg daily, and only <3% taking an estimate dose >500 mg. All the observed differences between groups were minimised to an acceptable degree (<0.1 standardised mean differences) after propensity score stratification: in CCAE, the most imbalanced variable was use of glucocorticoids on index date, with prevalence 36.1% vs 35.8%. Detailed baseline characteristics for the two pairs of treatment groups after PS stratification in CCAE are shown in Table 1 as an example, with similar tables and a more extensive list of features provided in Appendix Section 7. Study diagnostics including plots of propensity score distribution, covariate balance, and negative control estimate distributions are provided in Appendix Section 8.

Table 1. Baseline characteristics of patients with RA who are new users of hydroxychloroquine (HCQ) vs sulfasalazine (SSZ), before and after PS stratification, in the CCAE database

	Before PS stratification			After PS stratification		
	HCQ	SSZ		HCQ	SSZ	
	%	%	Std. diff	%	%	Std. diff
Socio-demographics						
Age group						
15-19	0.6	0.6	0.00	0.6	0.6	0.00
20-24	1.9	1.9	0.00	1.8	2.0	-0.01
25-29	2.6	2.6	0.00	2.5	2.8	-0.01
30-34	4.5	4.6	0.00	4.5	4.3	0.01
35-39	7.2	7.3	0.00	7.1	7.1	0.00
40-44	9.8	9.5	0.01	9.7	9.5	0.00
45-49	13.7	12.9	0.02	13.6	13.5	0.00
50-54	18.2	18.2	0.00	18.2	18.1	0.00
55-59	20.6	21.0	-0.01	20.8	20.8	0.00
60-64	19.0	19.7	-0.02	19.4	19.8	-0.01
65-69	1.8	1.7	0.01	1.8	1.6	0.01
Gender: female	82.0	74.3	0.19	80.1	79.7	0.01
Medical history						
Acute respiratory disease	35.5	34.3	0.03	35.1	34.7	0.01
Chronic liver disease	3.2	3.2	0.00	3.2	3.4	-0.01
Chronic obstructive lung disease	4.2	4.5	-0.01	4.3	4.5	-0.01
Crohn's disease	0.6	1.8	-0.12	0.7	1.1	-0.04
Depressive disorder	13.4	13.5	0.00	13.2	13.4	-0.01
Diabetes mellitus	13.5	13.4	0.00	13.6	13.7	0.00
Hypertensive disorder	34.7	34.9	0.00	34.7	35.0	-0.01
Obesity	9.3	9.1	0.00	9.2	9.4	-0.01
Psoriasis	3.0	8.9	-0.25	3.8	5.2	-0.07
Renal impairment	3.1	2.8	0.02	3.0	2.8	0.01
Systemic Lupus Erythematosus	1.5	0.5	0.10	1.3	0.9	0.03

Schizophrenia	0.1	0.1	-0.01	0.1	0.1	-0.01
Ulcerative colitis	0.6	1.9	-0.12	0.7	1.0	-0.04
Medication use						
Agents acting on the renin-angiotensin system	24.3	24.9	-0.01	24.5	24.7	0.00
Antidepressants	36.4	36.4	0.00	36.3	36.5	0.00
Antiepileptics	20.3	21.0	-0.02	20.4	20.2	0.00
Antiinflammatory and antirheumatic products	55.3	57.3	-0.04	55.8	56.7	-0.02
Antipsoriatics	0.7	1.3	-0.06	0.7	1.0	-0.03
Antithrombotic agents	7.4	7.3	0.01	7.4	7.3	0.00
Immunosuppressants	39.6	53.1	-0.27	43.4	43.6	0.00
Opioids	38.5	40.8	-0.05	39.0	39.3	-0.01
Psycholeptics	33.6	33.7	0.00	33.4	33.3	0.00
HCQ=hydroxychloroquine; SSZ=sulfasalazine						

Database-specific and overall counts and rates of the three study outcomes in the short- (30-day) and long-term ('on treatment') analyses are reported in detail in Table 2. Depression was the most common of the three study outcomes, with rates in the 'on treatment' analysis ranging from 1.99/1,000 person-years amongst HCQ users in CPRD to 17.74/1,000 amongst HCQ users in AmbEMR. Suicide/suicidal ideation was the least common outcome, with rates ranging from 0.32/1,000 (HCQ users in AmbEMR and SSZ users in IMRD) to 14.08/1,000 in SSZ users in MDCD. Database-specific counts and incidence rates (IR) for all three outcomes stratified by drug use are detailed in full in Appendix Section 9.

30-day follow up								On-treatment follow up					
		Patients		Events		IR (/1,000 py		Patients		Events		IR (/1,000 py	
Outcome	Database	T	C	T	C	T	C	T	C	T	C	T	C
Depression	AmbEMR	55,793	15,092	155	29	33.91	23.44	55,793	15,092	320	80	17.74	14.34
	CCAE	66,440	22,449	79	28	14.64	15.36	66,440	22,449	557	137	8.54	9.40
	Clinformatics	51,676	16,812	84	41	20.05	30.09	51,676	16,812	657	178	12.43	15.00
	CPRD	9,160	11,348	<5	8	<6.67	8.60	9,160	11,348	36	94	1.99	3.60
	DAGermany	3,937	5,109	<5	12	<15.48	28.63	3,937	5,109	40	70	15.47	19.66
	IMRD	8,844	8,456	<5	6	<6.91	8.67	8,844	8,456	38	51	2.20	2.72
	MDCD	7,950	2,286	14	6	21.61	32.29	7,950	2,286	90	13	15.81	10.12
	MDCR	15,735	5,275	13	6	10.14	13.98	15,735	5,275	97	38	5.37	9.27
	OpenClaims	620,081	183,312	654	161	12.85	10.70	620,081	183,312	4,810	957	5.59	5.58
	OptumEHR	78,528	20,244	321	66	50.56	40.30	NA	NA	NA	NA	NA	NA
	Meta-analysis	918,144	290,383	<1,335	363	<17.77	15.28	839,616	270,139	6,645	1,618	6.28	6.29
Suicide and suicidal ideation	AmbEMR	NA	NA	NA	NA	NA	NA	57,660	15,357	6	<5	0.32	<0.88
	CCAE	66,533	22,471	12	<5	2.22	<2.74	66,533	22,471	81	28	1.23	1.91
	Clinformatics	51,807	16,843	12	<5	2.85	<3.66	51,807	16,843	97	30	1.80	2.50
	CPRD	9,167	11,358	<5	<5	<6.66	<5.37	9,167	11,358	7	9	0.39	0.34
	IMRD	8,852	8,460	<5	<5	<6.91	<7.22	8,852	8,460	8	6	0.46	0.32
	MDCD	7,980	2,296	<5	<5	<7.68	<26.78	7,980	2,296	56	18	9.71	14.08
	MDCR	NA	NA	NA	NA	NA	NA	15,752	5,278	15	6	0.83	1.45
	OpenClaims	621,067	183,550	34	8	0.67	0.53	621,067	183,550	321	89	0.37	0.52
	OptumEHR	79,903	20,480	18	8	2.78	4.82	NA	NA	NA	NA	NA	NA
	Meta-analysis	845,309	265,458	<91	<41	<1.31	<1.89	838,818	265,613	591	<191	0.55	<0.75
Hospitalization for psychosis	OpenClaims	620,964	183,527	95	27	1.86	1.79	620,964	183,527	1,108	221	1.28	1.28
	OptumEHR	79,994	20,508	<5	<5	<0.77	<3.01	NA	NA	NA	NA	NA	NA
	Meta-analysis	700,958	204,035	<100	<32	<1.74	<1.91	NA	NA	NA	NA	NA	NA

T=target therapy; C=comparator therapy; IR=incidence rate; py=person-years at risk; NA=non-applicable (not reported because of failed diagnostics or on-treatment follow-up unavailable); HCQ=hydroxychloroquine; SSZ=sulfasalazine; AmbEMR=IQVIA Ambulatory EMR; CCAE=IBM Commercial Database; Clinformatics=Optum de-identified Clinformatics Data Mart Database; CPRD=Clinical Practice Research Datalink; DAGermany=IQVIA Disease Analyzer Germany; IMRD=IQVIA UK Integrated Medical Record Data; MDCD=IBM IBM Multi-state Medicaid; MDCR=IBM Medicare Supplemental Database; OpenClaims=IQVIA Open Claims; OptumEHR=Optum de-identified Electronic Health Record dataset

Table 2. Patient counts, event counts and incidence rates (IR) (/1,000 person years) of key events according to drug use

9 datasets passed cohort diagnostics and contained sufficiently robust data for inclusion into the short term analyses for depression; 6 passed for suicide and 2 passed for psychosis. A small imbalance with the incidence of a past medical history of SLE was seen in MDCD and with cutaneous lupus in DAGermany. As a result, we excluded both from the psychosis outcome but not for depression as we did not consider this was a confounder. Short-term (30-day) analyses showed no consistent association between HCQ use and the risk of depression, with database-specific HRs ranging from 0.21 [95%CI 0.03-1.25] in CPRD to 1.28 [0.85-1.95] in AmbEMR, and a meta-analytic HR of 0.96 [0.79-1.16] (See Figure 1, top). On-treatment analyses showed similar findings, with database-specific HRs from 0.62 [0.40-0.97] in DAGermany to 1.29 [0.69-2.39] in MDCD, and a meta-analytic HR of 0.94 [0.71-1.26] (Figure 1, bottom plot). Note only databases passing diagnostics are included within the plot and meta-analysis.

Similarly, no association was seen between the use of HCQ and the risk of suicidal ideation or suicide. In the short-term, HRs ranged from 0.27 [0.06-1.29] in MDCD to 10.46 [0.51-216.29] in CPRD, with meta-analytic HR of 0.94 [0.49-1.77] (Figure 2, top). Long-term effects were similar, with HRs ranging between 0.55 [0.20-1.49] in MDCR and 2.36 [0.21-26.87] in AmbEMR, and meta-analytic HR of 0.77 [0.56- 1.07] (Figure 2, bottom).

Finally, no association was seen between the use of HCQ (compared to SSZ) and the risk of acute psychosis. Short-term analyses showed database-specific HRs of 0.44 [0.05-3.49] in OptumEHR and 1.01 [0.65-1.58] in OpenClaims, with a meta-analytic estimated HR of 1.03 [0.66-1.60]. Only OpenClaims contributed to the 'on treatment' analysis of this event, with an estimated HR of 0.98 [0.73-1.33].

DISCUSSION

Principal findings

This large observational study shows that in routine healthcare treatment of RA, there is no association with the use of HCQ with acute psychosis, depression, or suicide as compared to SSZ. These results are seen both in the short-term and long-term risk analyses. Whilst an excess of psychiatric events have been reported during the COVID pandemic in those prescribed HCQ, this risk does not appear to be associated with HCQ prescribed in RA compared to those prescribed SSZ. This study uses data from three countries, with a variety of healthcare systems and modes of routine healthcare data included, enabling the study to produce more generalisable results.

Comparison with other studies

The bulk of the evidence prior to this study consisted of isolated case reports and case series, making it difficult to draw demographic comparisons with previous work. Sato *et al.* reported that neuropsychiatric adverse events found in the FDA adverse event reporting system associated with chloroquine use were predominantly in females in the sixth decade of life.[21]Increase in reporting of acute psychiatric disease during the COVID-19 pandemic may be multifactorial, with an increase in external stressors such as social isolation, financial uncertainty, and increased misuse of drugs and alcohol.[46-48] Considering that we find no association for HCQ use compared to SSZ with acute psychiatric outcomes in the RA population, evidence points towards external stressors being more likely involved in the aetiology of psychiatric events seen during this pandemic.

Strengths and weaknesses of the study

This study is based on new users of HCQ for RA and therefore, the results of this study are most directly relevant to the risk of neuropsychiatric side effects seen in the rheumatological population. The

regulatory warnings of possibly increased acute psychiatric events associated with HCQ warrant investigation in all available datasets to prevent harm in both rheumatological patients and those taking for emergency use, especially as very few clinical trials include acute psychiatric outcomes. Whilst the general population presenting with COVID-19 may differ from those with RA, within the context of emergency authorisation or off label use of HCQ, all available evidence must be taken into account when considering the risks associated.

Several considerations must be taken into account when interpreting these results.
Firstly, the doses used to treat RA are lower than those suggested in current clinical trials for the treatment of SARS-CoV2, and therefore adverse events seen in the treatment and prophylaxis of COVID-19 may be greater if dose dependent, as is the case with cardiac adverse effects.[49, 50] Secondly, this study could be affected by outcome misclassification. Only acute psychiatric events presenting to medical services will be captured, and this is especially important for the outcome of suicide. Suicide may not be fully recorded if patients do not reach medical care or cause-of-death information is not linked to the datasource, and therefore the true incidence of suicide may be under-recorded.[51] Similarly, this study only focused on acute psychosis and depression severe enough to be identified in medical consultation in patients with no history of either condition. Whilst we generated phenotypes that underwent full cohort diagnostics, and phenotypes were constructed using a multidisciplinary team of clinicians and bioinformaticians to ensure face validity, it should be noted that no formal validation was undertaken. We took all reasonable steps to ensure the validity of the phenotypes, whilst considering the risk-benefit tradeoff of what could be undertaken within the time frame used to respond to the serious questions raised by regulatory bodies following the HCQ use in COVID-19.
This study can highlight the association for patients without a prior history of psychosis or depression, but cannot inform of the risk of acute deterioration after beginning HCQ treatment for those already known to psychiatric services.

Thirdly, depression and hallucinations are listed as potential undesirable effects of sulfasalazine treatment, which may underestimate the true risk, if any, from HCQ.[52] However, the frequency of depression (described as changes in affect in the summary of product characteristics for HCQ) is reported to be common (≥1/100 to < 1/10) whilst for sulfasalazine depression is listed as being uncommon (≥1/1000 to < 1/100). Therefore, it is potentially reassuring for patients that we observed no difference compared to sulfasalazine for which there is a paucity of published evidence suggesting causailty.[53]

Propensity score stratification and matching, as well as a comprehensive examination of potential sources of systematic error, were undertaken prior to blinding of results to identify and reduce the risk of confounding. Baseline characteristics after PS stratification were adequately balanced; of note, the incidence of systemic lupus erythematosus (SLE) was balanced between treatment groups. Identifying the balance of SLE between treatment groups was undertaken prior to unblinding due to the potential neuropsychiatric sequelae of the condition aside from the potential side effects of pharmacological treatment. This study could also be limited by the fact that patients may overlap and exist in more than one dataset within the US. The meta-analysis assumes populations to be independent, and therefore the obtained estimates may slightly underestimate variance.

Future research

For rheumatological disorders, future work could expand into investigating the occurrence of acute psychiatric events in patients in SLE. This would enable greater understanding of whether

neuropsychiatric conditions are related to disease activity or due to pharmacological treatment. Similarly, in the emergency use of HCQ in COVID-19, there is already concern about the potential heightened risk of acute psychiatric disorder due to elevated number of psychosocial stressors present during a pandemic and high dose use.[54] Future work should consider including acute psychiatric outcomes in order to differentiate between psychiatric conditions generated by the impact of a global pandemic compared to iatrogenic events due to pharmaceutical therapies used.

Meaning of the Study

Exponential growth in research into the best treatment of SARS-CoV2 infection is generating rapidly evolving evidence for the relative efficacy of pharmaceutical agents. For the rheumatological community, media attention previously surrounded HCQ as a strong forerunner of COVID-19 prophylaxis and treatment. The results of the RECOVERY trial identifying dexamethasone reduced mortality in intensive care patients has now overtaken HCQ as the leading rheumatological drug for the pandemic, but the concerns regarding HCQ safety remain for those who take the drug for conventional indications.[17, 55] Cardiovascular safety, and reports that it might lack efficacy for both treatment and prophylaxis, have halted major HCQ clinical trials.[49, 56-59] The identification of acute psychiatric events associated with HCQ use has raised the need to clarify the risk within general rheumatological use. Our study identifies no increased risk in RA patients when compared with sulfasalazine, and provides evidence to users and clinicians alike that the reports presented during the pandemic are likely to be related to further causes aside from HCQ.

FIGURE LEGENDS

Figure 1. Forest plot of the association between short- (top) and long-term (bottom) use of HCQ (vs SSZ) and risk of depression, by database and in meta-analysis.

Figure 2. Forest plot of the association between short- (top) and long-term (bottom) use HCQ (vs SSZ) and risk of suicidal ideation or suicide, by database and in meta-analysis.

FOOTNOTES

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Public and patient involvement

No patients were directly involved in setting the research question, nor in design, conduct or interpretation of the study.

Competing interests

All authors have completed the ICJME uniform disclosure form from http://www.icjme.org/conflicts-of-interest/ uploaded with this study and report:
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Ethical Approval

All data partners received IRB approval or waiver in accordance to their institutional governance guidelines.

Database	Statement
AmbEMR	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI community studies.
CCAE	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
CPRD	Approval for CPRD was provided by the Independent Scientific Advisory Committee (ISAC). This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. The protocol for this study (20_059R) was approved by the Independent Scientific Advisory Committee (ISAC).
DA Germany	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI community studies.
IMRD	The present study is filed and under review for Scientific Review Committee for institutional adjudication. Due to the public health imperative of information related to these data, approval is provided for this publication.
IPCI	The present study was approved by the Scientific and Ethical Advisory Board of the IPCI project (project number: 4/2020).
JMDC	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
MDCD	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
MDCD	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Open Claims	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI community studies.

Clinformatics	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Optum EHR	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.

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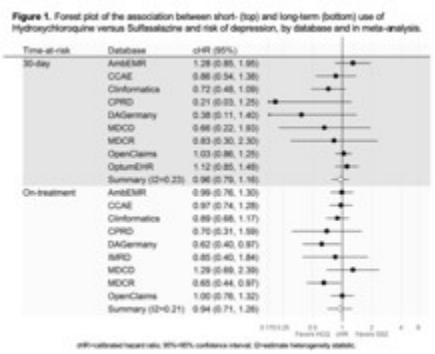
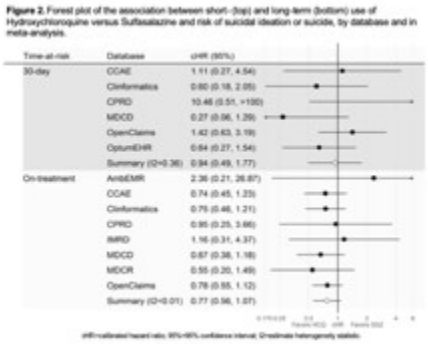


Forest plot of the association between short- (top) and long-term (bottom) use of HCQ (vs SSZ) and risk of depression, by database and in meta-analysis.

150x84mm (54 x 54 DPI)



Forest plot of the association between short- (top) and long-term (bottom) use HCQ (vs SSZ) and risk of suicidal ideation or suicide, by database and in meta-analysis.

150x84mm (54 x 54 DPI)

Supplemental Appendix to *Risk of depression, suicidal ideation, suicide and psychosis with hydroxychloroquine treatment for rheumatoid arthritis: a multi-national network cohort study*

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Contents

1. Literature review sources

1.1. PubMed search strategy

((((((((((("schizophrenia spectrum and other psychotic disorders"[mesh terms])) or (depressive disorder[mesh terms])) or (suicide, completed[mesh terms])) or (suicidal ideation[mesh terms])) or (suicide, attempted[mesh terms])) or (psychotic disorders[mesh terms])) or (psychos*[title/abstract])) or (psychot*[title/abstract])) or (depress*[title/abstract])) or (suicid*[title/abstract])) and (((((((("hydroxychloroquine"[mesh terms]) or (hydroxychloroquine[title/abstract])) or (chloro quinol[title/abstract])) or (ercoquin[title/abstract])) or (hydroxychloroquine[title/abstract])) or (hydroycloroquine[title/abstract])) or (oxychloroquine[title/abstract])) or (plaquenil[title/abstract])) or (quensyl[title/abstract]))

1.2. EMBASE search strategy (1974 to present)

1	schizophren* ti/ab	158752
2	depress* ti/ab	604149
3	psychos* ti/ab	213154
4	psychot* ti/ab	134304
5	suicid* ti/ab	95992
6	1 OR 2 OR 3 OR 4 OR 5	1016578
7	(Hydroxychloroquine).ti,ab	7869
8	(chloroquinol).ti,ab	2
9	(ercoquin).ti,ab	0
10	(hydrochloroquine).ti,ab	57
11	(hydrocloroquine).ti,ab	0
12	(oxychloroquine).ti,ab	6
13	(plaquenil).ti,ab	308
14	(quensyl).ti,ab	4
15	("sn 8137").ti,ab	1
16	HYDROXYCHLOROQUINE/	23778
17	7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16	24407
18	17 AND 6	451

2. Data Sources

Database name	Abbreviation	Population	Patients (millions)	Data History	Data capture process and short database description
IQVIA US Ambulatory EMR	AmbEMR	USA (General population)	49M	2006 –	General practice EHR, Outpatient specialist EHR - Dataset consists of longitudinal, de-identified ambulatory electronic health records data
IBM MarketScan Commercial Claims	CCAE	USA (Patients with commercial insurance aged <65 years)	142M	2000 –	Data from individuals enrolled in US employer-sponsored insurance health plans. The data includes adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy) as well as enrollment data from large employers and health plans who provide private healthcare coverage to employees, their spouses,and dependents. Additionally, it captures laboratory tests for a subset of the covered lives.
Optum de-identified Clinformatics® Data Mart Database	Clinformatics	USA (Patients with commercial insurance or commercial Medicare insurance)	85M	2000 -	Adjudicated administrative health claims database for members of private health insurance, who are fully insured in commercial plans or in administrative services only (ASOs) and commercial Medicare. Represents inpatient and outpatient medical services and prescriptions as dispensed, as well as results for outpatient lab tests processed by national lab vendors.
Clinical Practice Research Datalink	CPRD	UK (General population)	13M	1995 –	De-identified patient data from a network of general practitioners' practices across the UK. Primary care data are linked to a range of other health related data to provide a longitudinal, representative UK population health dataset.
IQVIA Disease Analyzer Germany	DAGermany	Germany (General population)	37M	1992 –	Anonymized patient records collected from Patient Management software used by general practitioners and selected specialists to document patients' medical records within their office-based practice during a visit.
IQVIA UK Integrated Medical Record Data	IMRD	UK (General population)	15M	1989 –	Pseudonymized Electronic Medical Records collected from patient management software used within UK Primary Care
IBM MarketScan Multi-State Medicaid Database	MDCD	USA	26M	2006 –	Adjudicated US health insurance claims for Medicaid enrollees from multiple states and includes hospital discharge diagnoses, outpatient diagnoses and procedures, and outpatient pharmacy claims as well as ethnicity and Medicare eligibility.
IBM MarketScan Medicare Supplemental Database	MDCR	USA (Patients with commercial insurance aged 65+ years)	10M	2000 –	Represents health services of retirees (aged 65 or older) in the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans. These data include adjudicated health insurance claims (e.g. inpatient, outpatient, and outpatient pharmacy). Additionally, it captures laboratory tests for a subset of the covered lives.
IQVIA US LRxDx Open Claims	OpenClaims	USA (General population)	654M	2010 –	Pre-adjudicated claims at the anonymized patient level collected from office-based physicians and specialists via office management software and clearinghouse switch sources for the purpose of reimbursement.
Optum® de-identified Electronic Health Record Dataset	OptumEHR	USA (General population)	93M	2006 –	Optum's de-identified electronic health record data medical records database. The medical record data includes clinical information, inclusive of prescriptions as prescribed and administered, lab results, vital signs, body measurements, diagnoses, procedures, and information derived from clinical notes using Natural Language Processing (NLP).

3. Cohort definitions

To view the concept sets and source code lists used in each cohort definition, navigate to the URL following the name of each cohort. Then, navigate to the Concept Sets tab. The concept sets used in defining the outcome are listed on this page. After selecting a concept set to view, a user can explore the standard concepts used in the definition or the source codes from which the standard concepts are mapped. The full specification of each cohort, including computer readable JSON and SQL representations, are publicly available at the URLs for each definition.

3.1. Exposures

The index event was defined as the first recorded dispensing or prescription of HCQ or SSZ in a patient's history.

Exposure commenced on the first day of dispensing or prescription recorded with at least 365 days of prior observation period to increase confidence that the exposure was incident. Exposure interval gaps of ≤90 days (HCQ and SSZ) between drug dispensing or prescription records were allowed and inferred as persistent exposure. Drug discontinuation was considered if a patient switched from exposure to the other. Patients who switched contributed follow-up time to the exposure cohort that they entered first and were censored at the time of switching in the 'on treatment' analysis.

3.1.1. New users of Hydroxychloroquine with prior rheumatoid arthritis

https://atlas.ohdsi.org/#/cohortdefinition/173

Initial Event Cohort

People having any of the following:

- a drug exposure of [OHDSI Cov19] Hydroxychloroquine[1]
    - for the first time in the person's history
    - with age >= 18

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Rules

Inclusion Criteria #1: has rheumatoid arthritis recorded any time on or prior to treatment

Having any of the following criteria:

- at least 1 occurrence of a condition occurrence of [OHDSI Cov19] Rheumatoid arthritis[2] where event starts between all days Before and 0 days After index start date
- or at least 1 occurrence of an observation of [OHDSI Cov19] Rheumatoid arthritis[2] where event starts between all days Before and 0 days After index start date

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of [OHDSI Cov19] Hydroxychloroquine[1]

- allowing 90 days between exposures
- adding 0 days after exposure end

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

3.1.2. New users of sulfasazine with prior rheumatoid arthritis

https://atlas.ohdsi.org/#/cohortdefinition/45

Initial Event Cohort

People having any of the following:

- a drug exposure of [OHDSI Cov19] sulfasalazine[2]
  - for the first time in the person's history

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Rules

Inclusion Criteria #1: has rheumatoid arthritis recorded any time on or prior to treatment

Having all of the following criteria:

- at least 1 occurrence of a condition occurrence of [OHDSI Cov19] Rheumatoid arthritis[1] where event starts between all days Before and 0 days After index start date

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

Custom Drug Era Exit Criteria

This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.

Use the era end date of [OHDSI Cov19] sulfasalazine[2]

- allowing 90 days between exposures
- adding 0 days after exposure end

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

3.2. Outcomes

3.2.1. Depression

https://atlas.ohdsi.org/#/cohortdefinition/237

Initial Event Cohort
People having any of the following:

- a condition occurrence of Depressive disorder[3]
  - for the first time in the person's history

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: **earliest event per person**.

Inclusion Rules
Inclusion Criteria #1: No treatment more than 30 days prior
Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of Antipsychotics[1]
  where event starts between all days Before and 30 days Before index start date
- and exactly 0 occurrences of a drug exposure of SSRI[9]
  where event starts between all days Before and 30 days Before index start date
- and exactly 0 occurrences of a drug exposure of SNRI[8]
  where event starts between all days Before and 30 days Before index start date
- and exactly 0 occurrences of a drug exposure of Tricyclic Anti-depressants[10]
  where event starts between all days Before and 30 days Before index start date
- and exactly 0 occurrences of a drug exposure of Monoamine oxidase inhibitors (MAOI), non-selective[5]
  where event starts between all days Before and 30 days Before index start date
- and exactly 0 occurrences of a drug exposure of Other antidepressants[6]
  where event starts between all days Before and 30 days Before index start date

Inclusion Criteria #2: No prior psychoses/mania
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of Dementia[2]
  where event starts between all days Before and 0 days After index start date
- and exactly 0 occurrences of a condition occurrence of Mania[4]
  where event starts between all days Before and 0 days After index start date
- and exactly 0 occurrences of a condition occurrence of Psychosis[7]
  where event starts between all days Before and 0 days After index start date

Limit qualifying cohort to: **earliest event per person**.

End Date Strategy
No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.
Cohort Collapse Strategy:
Collapse cohort by era with a gap size of 0 days.

3.2.2. Suicide and suicidal ideation

https://atlas.ohdsi.org/#/cohortdefinition/235

Initial Event Cohort
People having any of the following:

- a condition occurrence of Suicide and suicidal ideation1
- an observation of Suicide and suicidal ideation1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person**.

Limit qualifying cohort to: **earliest event per person**.

End Date Strategy
No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.
Cohort Collapse Strategy:
Collapse cohort by era with a gap size of 0 days.

3.2.3. Hospitalization for psychosis

https://atlas.ohdsi.org/#/cohortdefinition/236

Initial Event Cohort
People having any of the following:

- a visit occurrence of Inpatient visit1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person**.
For people matching the Primary Events, include:
Having all of the following criteria:

- at least 1 occurrences of a condition occurrence of Psychosis[2]
    - condition type is any of Inpatient detail - primary, Inpatient header - primary, Primary Condition, Inpatient detail - 1st position, Inpatient header - 1st position, Outpatient detail - 1st position, Outpatient header - 1st position, Carrier claim header - 1st position, Carrier claim detail - 1st position

  where event starts between all days Before and 0 days After index start date and event starts between 0 days Before and all days After index end date

Limit cohort of initial events to: **all events per person**.

Limit qualifying cohort to: **all events per person**.
End Date Strategy
Date Offset Exit Criteria
This cohort definition end date will be the index event's end date plus 0 days
Cohort Collapse Strategy:
Collapse cohort by era with a gap size of 0 days.

4. Negative control outcomes

Negative control outcomes are conditions believed to have no causal relationship with hydroxychloroquine, sulfasalazine, azithromycin, or amoxicillin exposure and therefore assumed *a priori* to return a hazard ratio (HR) of 1.0 when their risk is compared between exposure cohorts in a pairwise comparison. A HR of a negative control outcome that differs from 1.0 represents an estimate of the residual error of the analysis that was unaccounted for by the analytic specification such as propensity score adjustment. The distribution of residual error estimates from the negative control outcomes reflects a range of biases inherent to the analysis. The estimates on the negative control outcomes represents the empirical null distribution and we used it to compute hazard ratios and confidence intervals calibrated to reflect the observed residual error of the analysis. The negative controls were selected through a semi-automated process [2] and are listed below with the corresponding SNOMED concept ID.

Concept ID	Concept Name	Concept ID	Concept Name
378256	Abnormal reflex	374375	Impacted cerumen
4092879	Absent kidney	4344500	Impingement syndrome of shoulder region
433753	Alcohol abuse	440382	Learning difficulties
321689	Apnea	435516	Lipoprotein deficiency disorder
78200	Benign mammary dysplasia	438808	Mammary duct ectasia
4195873	Breath smells unpleasant	441553	Myoclonus
443792	Calculus of bile duct	4119307	Neurogenic claudication
197318	Cholesterolosis of gallbladder	4209423	Nicotine dependence
439125	Complete trisomy 21 syndrome	313601	Oxygen supply absent
433270	Cord entanglement without compression	4091513	Passing flatus
4311591	Cramp in limb	4022076	Patient dependence on care provider
441267	Cystic fibrosis	439971	Poisoning by anticoagulant
436233	Delayed milestone	46286594	Problem related to lifestyle
40486120	Delay in physiological development	199876	Prolapse of female genital organs
374801	Foreign body in ear	4049367	Psychologic conversion disorder
259995	Foreign body in orifice	73754	Restless legs
196456	Gallstone	138821	Seborrhea
4166231	Genetic predisposition	4198492	Shoulder joint unstable
434164	Glycosuria	25518	Sickle cell trait
4163735	Hemochromatosis	4176908	Snapping thumb syndrome
439871	Hemospermia	4248728	Snoring
4058388	Hypertrophic scar	138278	Sprains and strains of joints and adjacent muscles
435522	Hypervitaminosis D	4008710	Stenosis due to any device, implant AND/OR graft
443236	Hypnotic or anxiolytic dependence	440233	Strain of supraspinatus muscle AND/OR tendon
4098604	Hypomagnesemia	4194160	Thyroid function tests abnormal
435371	Hypothermia	4216708	Urgent desire for stool
443447	Iatrogenic hypotension		

5. Covariate construction

The following consistently extracted set of baseline patient characteristics will be constructed for input in the PS model. From this large set of typically tens of thousands of covariates, key predictors of exposure classification will be selected for inclusion in the PS model. Note that not all data sources necessarily include data for all covariates. Covariates to be included:

- Demographics (age in 5-year bands, sex, race, ethnicity, index year, index month)
- All conditions occurrence records aggregated to SNOMED clinical finding level during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
- All drug exposure records aggregated to RxNorm ingredient level and ATC classes during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
    - persistent exposure that overlaps index date
- All procedure occurrence records during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
- Measurements (including laboratories) within, above, and below normal range during the following lookback window:
    - in 365 days prior to and including index date
- Device exposure records during the following lookback windows:
    - in 365 days prior to and including index date
    - in 30 days prior to and including index date
- Comorbidity or risk scores including:
    - Charlson
    - DCSI
    - CHADS2
    - CHADS2VASc

6. Study population counts

The exposure cohort counts are calculated after the following study design criteria have been applied:

- Duplicate patients in the HCQ and SSZ with prior RA cohorts are removed from the cohort they qualified for second (i.e. retained in the cohort they qualified for first)
- Restricted to the calendar time when both exposures in the pairwise comparison (i.e. HCQ vs SSZ) are observed in the database.

After applying these design criteria to the original cohorts, the resulting patients are eligible to contribute data to study diagnostics and potentially to final population-level effect estimates.

Exposure	Database	Patients	Percent
Hydroxychloroquine with prior RA (n = 923,152)	AmbEMR	57,662	6.25
	CCAE	66,656	7.22
	Clinformatics	51,894	5.62
	CPRD	9,169	0.99
	DAGermany	3,966	0.43
	IMRD	8,855	0.96
	MDCD	7,994	0.87
	MDCR	15,765	1.71
	OpenClaims	621,124	67.28
	OptumEHR	80,067	8.67
Sulfasalazine with prior RA (n = 291,366)	AmbEMR	15,358	5.27
	CCAE	22,507	7.72
	Clinformatics	16,869	5.79
	CPRD	11,361	3.9
	DAGermany	5,136	1.76
	IMRD	8,463	2.9
	MDCD	2,301	0.79
	MDCR	5,281	1.81
	OpenClaims	183,566	63
	OptumEHR	20,524	7.04

7. Patient baseline characteristics before and after propensity score stratification

7.1. AmbEMR

	Before PS stratification			After PS stratification		
	HCQ	SSZ		HCQ	SSZ	
Characteristic	%	%	Std. diff	%	%	Std. diff
Age group						
15-19	0.1	0.1	0.00	0.1	0.1	0.00
20-24	0.7	0.6	0.01	0.7	0.6	0.01
25-29	1.3	1.4	-0.01	1.3	1.4	-0.01
30-34	2.4	2.2	0.02	2.3	2.2	0.01
35-39	3.5	3.7	-0.01	3.5	3.4	0.00
40-44	5.4	5.0	0.02	5.3	5.1	0.01
45-49	7.4	7.0	0.02	7.4	7.4	0.00
50-54	10.4	11.0	-0.02	10.5	10.4	0.00
55-59	13.1	13.4	-0.01	13.2	12.9	0.01
60-64	13.8	14.4	-0.02	13.9	14.1	-0.01
65-69	13.7	14.2	-0.01	13.8	13.7	0.00
70-74	13.1	13.3	-0.01	13.1	13.9	-0.02
75-79	11.2	9.8	0.05	10.9	10.9	0.00
80-84	3.9	3.9	0.00	3.9	3.7	0.01
Gender: female	79.7	74.1	0.13	78.3	78.4	0.00
Race						
race = Asian	1.4	1.5	-0.02	1.4	1.4	0.00
race = White	70.9	71.7	-0.02	71.1	71.3	0.00
race = African American	8.0	7.8	0.01	8.0	7.7	0.01
Ethnicity						
ethnicity = Hispanic or Latino	1.3	1.8	-0.04	1.4	1.5	-0.01
ethnicity = Not Hispanic or Latino	80.3	81.0	-0.02	80.5	80.4	0.00
Medical history: General						
Acute respiratory disease	13.5	14.2	-0.02	13.7	13.8	0.00
Attention deficit hyperactivity disorder	0.6	0.4	0.02	0.6	0.5	0.01
Chronic liver disease	1.5	1.5	0.00	1.5	1.4	0.01
Chronic obstructive lung disease	7.0	7.2	-0.01	7.1	6.9	0.01
Crohn's disease	0.4	1.1	-0.08	0.5	0.6	-0.02
Dementia	0.6	0.5	0.02	0.6	0.6	0.00
Depressive disorder	15.0	14.4	0.02	14.8	14.8	0.00
Diabetes mellitus	13.2	13.2	0.00	13.2	13.7	-0.01
Gastroesophageal reflux disease	15.9	14.6	0.04	15.6	15.7	0.00
Gastrointestinal hemorrhage	1.2	1.2	0.00	1.2	1.2	0.00
Human immunodeficiency virus infection	0.1	0.1	0.00	0.1	0.1	0.00
Hyperlipidemia	29.0	28.1	0.02	28.8	29.1	-0.01
Hypertensive disorder	38.0	37.1	0.02	37.8	38.1	-0.01
Lesion of liver	0.9	0.8	0.01	0.9	0.8	0.01
Lupus erythematosus	0.9	0.3	0.08	0.8	0.7	0.02
Obesity	8.9	8.9	0.00	8.9	9.0	0.00
Osteoarthritis	25.5	27.1	-0.04	25.8	25.1	0.02
Pneumonia	3.1	3.4	-0.01	3.2	3.2	0.00
Psoriasis	1.5	3.2	-0.11	1.7	2.0	-0.02
Renal impairment	5.3	4.8	0.02	5.2	5.4	-0.01
Rheumatoid arthritis	84.0	82.2	0.05	83.6	84.2	-0.02
Schizophrenia	0.1	0.1	0.00	0.1	0.1	0.00
Ulcerative colitis	0.3	1.2	-0.10	0.4	0.6	-0.03
Urinary tract infectious disease	6.0	5.2	0.04	5.8	5.5	0.02
Viral hepatitis C	1.0	1.0	0.00	1.0	0.9	0.01
Visual system disorder	8.6	8.8	0.00	8.6	8.5	0.00
Medical history: Cardiovascular disease						
Atrial fibrillation	3.3	3.1	0.01	3.2	3.2	0.00
Cerebrovascular disease	3.1	2.8	0.02	3.1	3.1	0.00
Coronary arteriosclerosis	5.7	5.6	0.00	5.7	5.6	0.00
Heart disease	15.9	14.6	0.04	15.6	15.6	0.00
Heart failure	2.6	2.3	0.02	2.6	2.4	0.01
Ischemic heart disease	1.7	1.6	0.01	1.7	1.5	0.02
Peripheral vascular disease	1.6	1.6	0.00	1.6	1.8	-0.02
Pulmonary embolism	0.8	0.7	0.01	0.8	0.8	0.00
Venous thrombosis	1.3	1.2	0.01	1.3	1.4	-0.01
Medical history: Neoplasms						
Hematologic neoplasm	0.4	0.3	0.02	0.4	0.4	0.01
Malignant lymphoma	0.4	0.5	-0.01	0.4	0.6	-0.03
Malignant neoplasm of anorectum	0.1	0.1	-0.01	0.1	0.1	-0.01
Malignant neoplastic disease	6.9	6.6	0.01	6.8	7.0	-0.01
Malignant tumor of breast	1.5	1.4	0.01	1.4	1.6	-0.01
Malignant tumor of colon	0.3	0.3	0.00	0.3	0.3	-0.01
Malignant tumor of lung	0.3	0.4	-0.02	0.3	0.3	-0.01
Malignant tumor of urinary bladder	0.2	0.3	-0.01	0.2	0.2	0.00
Primary malignant neoplasm of prostate	0.4	0.3	0.00	0.4	0.3	0.00
Medication use						
Agents acting on the renin-angiotensin system	33.2	33.6	-0.01	33.3	33.6	-0.01
Antibacterials for systemic use	24.7	25.3	-0.01	24.9	24.6	0.01
Antidepressants	36.1	34.9	0.02	35.8	35.7	0.00
Antiepileptics	24.0	24.1	0.00	24.0	24.0	0.00
Antiinflammatory and antirheumatic products	42.8	44.4	-0.03	43.1	43.5	-0.01
Antineoplastic agents	35.9	41.4	-0.11	37.3	37.6	-0.01
Antipsoriatics	0.6	0.7	0.00	0.6	0.7	0.00
Antithrombotic agents	25.2	23.5	0.04	24.9	25.2	-0.01
Beta blocking agents	25.2	25.1	0.00	25.2	25.8	-0.02

Calcium channel blockers	17.5	17.7	0.00	17.5	17.7	0.00
Diuretics	30.6	30.0	0.01	30.5	31.1	-0.01
Drugs for acid related disorders	41.6	41.6	0.00	41.6	42.1	-0.01
Drugs for obstructive airway diseases	30.9	30.0	0.02	30.8	31.0	0.00
Drugs used in diabetes	14.2	14.3	0.00	14.3	14.8	-0.01
Immunosuppressants	49.4	61.2	-0.24	52.2	52.0	0.00
Lipid modifying agents	33.2	33.7	-0.01	33.3	33.5	0.00
Opioids	28.4	30.7	-0.05	28.9	28.8	0.00
Psycholeptics	26.3	25.6	0.02	26.1	26.1	0.00
Psychostimulants, agents used for adhd and nootropics	4.0	3.8	0.01	4.0	4.0	0.00

7.2. CCAE

	Before PS stratification			After PS stratification		
	HCQ	SSZ		HCQ	SSZ	
Characteristic	%	%	Std. diff	%	%	Std. diff
Age group						
15-19	0.6	0.6	0.00	0.6	0.6	0.00
20-24	1.9	1.9	0.00	1.8	2.0	-0.01
25-29	2.6	2.6	0.00	2.5	2.7	-0.01
30-34	4.5	4.6	0.00	4.5	4.4	0.01
35-39	7.2	7.3	0.00	7.1	7.1	0.00
40-44	9.8	9.5	0.01	9.7	9.5	0.01
45-49	13.7	12.9	0.02	13.6	13.5	0.00
50-54	18.2	18.2	0.00	18.2	18.0	0.00
55-59	20.6	21.0	-0.01	20.8	20.8	0.00
60-64	19.0	19.7	-0.02	19.4	19.8	-0.01
65-69	1.8	1.7	0.01	1.8	1.6	0.01
Gender: female	82.0	74.3	0.19	80.1	79.7	0.01
Medical history: General						
Acute respiratory disease	35.5	34.3	0.02	35.1	34.8	0.01
Attention deficit hyperactivity disorder	1.5	1.5	0.00	1.5	1.5	0.00
Chronic liver disease	3.2	3.2	0.00	3.2	3.3	-0.01
Chronic obstructive lung disease	4.2	4.5	-0.01	4.3	4.5	-0.01
Crohn's disease	0.6	1.8	-0.12	0.7	1.1	-0.04
Dementia	0.2	0.2	0.01	0.2	0.2	0.00
Depressive disorder	13.4	13.5	0.00	13.3	13.5	-0.01
Diabetes mellitus	13.5	13.4	0.00	13.6	13.7	-0.01
Gastroesophageal reflux disease	13.7	13.5	0.01	13.6	13.6	0.00
Gastrointestinal hemorrhage	2.9	3.4	-0.03	3.0	3.2	-0.01
Human immunodeficiency virus infection	0.1	0.2	-0.01	0.1	0.1	0.00
Hyperlipidemia	31.5	30.6	0.02	31.2	31.4	0.00
Hypertensive disorder	34.7	34.9	0.00	34.7	35.1	-0.01
Lesion of liver	0.9	0.8	0.01	0.9	0.8	0.00
Lupus erythematosus	1.5	0.5	0.10	1.3	0.9	0.03
Obesity	9.3	9.1	0.00	9.2	9.4	-0.01
Osteoarthritis	43.4	44.3	-0.02	43.5	44.3	-0.01
Pneumonia	4.0	3.9	0.00	4.0	4.0	0.00
Psoriasis	3.0	8.9	-0.25	3.8	5.2	-0.07
Renal impairment	3.1	2.8	0.02	3.0	2.8	0.01
Rheumatoid arthritis	84.2	85.7	-0.04	84.9	85.3	-0.01
Schizophrenia	0.1	0.1	-0.01	0.1	0.1	-0.01
Ulcerative colitis	0.6	1.9	-0.12	0.7	1.0	-0.04
Urinary tract infectious disease	11.9	10.8	0.03	11.6	11.5	0.00
Viral hepatitis C	1.1	1.0	0.01	1.1	1.0	0.01
Visual system disorder	25.7	26.2	-0.01	25.7	25.8	0.00
Medical history: Cardiovascular disease						
Atrial fibrillation	1.4	1.3	0.02	1.4	1.3	0.01
Cerebrovascular disease	2.8	2.6	0.01	2.8	2.8	0.00
Coronary arteriosclerosis	4.4	4.6	-0.01	4.4	4.4	0.00
Heart disease	15.7	15.0	0.02	15.5	15.4	0.00
Heart failure	1.9	2.0	0.00	1.9	1.9	0.00
Ischemic heart disease	2.9	3.2	-0.01	3.0	3.1	-0.01
Peripheral vascular disease	1.6	1.5	0.01	1.5	1.6	0.00
Pulmonary embolism	0.8	0.6	0.03	0.8	0.6	0.02
Venous thrombosis	1.6	1.4	0.02	1.5	1.5	0.00
Medical history: Neoplasms						
Hematologic neoplasm	1.0	1.0	0.00	1.0	1.0	0.00
Malignant lymphoma	0.5	0.5	0.00	0.5	0.4	0.01
Malignant neoplasm of anorectum	0.1	0.1	0.00	0.1	0.1	0.00
Malignant neoplastic disease	6.5	6.5	0.00	6.5	6.5	0.00
Malignant tumor of breast	1.8	1.6	0.02	1.8	1.7	0.01
Malignant tumor of colon	0.2	0.2	0.00	0.2	0.2	0.00
Malignant tumor of lung	0.1	0.2	-0.01	0.2	0.1	0.00
Malignant tumor of urinary bladder	0.1	0.1	0.00	0.1	0.1	0.00
Primary malignant neoplasm of prostate	0.4	0.4	-0.01	0.4	0.4	0.00
Medication use						
Agents acting on the renin-angiotensin system	24.3	24.9	-0.01	24.5	24.7	0.00
Antibacterials for systemic use	43.8	44.3	-0.01	43.8	43.8	0.00
Antidepressants	36.4	36.4	0.00	36.3	36.5	0.00
Antiepileptics	20.3	21.0	-0.02	20.4	20.2	0.00
Antiinflammatory and antirheumatic products	55.3	57.3	-0.04	55.8	56.8	-0.02
Antineoplastic agents	30.7	37.9	-0.15	33.1	33.1	0.00
Antipsoriatics	0.7	1.3	-0.06	0.7	1.0	-0.03
Antithrombotic agents	7.4	7.3	0.01	7.4	7.3	0.00
Beta blocking agents	15.7	16.2	-0.01	15.9	16.2	-0.01
Calcium channel blockers	11.7	11.5	0.01	11.7	11.8	0.00
Diuretics	24.4	24.3	0.00	24.5	24.5	0.00
Drugs for acid related disorders	32.3	33.6	-0.03	32.6	32.6	0.00
Drugs for obstructive airway diseases	29.7	29.3	0.01	29.5	29.5	0.00
Drugs used in diabetes	10.4	10.5	0.00	10.5	10.8	-0.01
Immunosuppressants	39.6	53.1	-0.27	43.4	43.6	0.00
Lipid modifying agents	22.6	23.5	-0.02	22.8	23.2	-0.01
Opioids	38.5	40.8	-0.05	39.0	39.3	-0.01
Psycholeptics	33.6	33.7	0.00	33.4	33.3	0.00
Psychostimulants, agents used for adhd and nootropics	5.9	5.7	0.01	5.8	5.7	0.01

7.3. Clinformatics

	Before PS stratification			After PS stratification		
	HCQ	SSZ		HCQ	SSZ	
Characteristic	**%**	**%**	**Std. diff**	**%**	**%**	**Std. diff**
Age group						
15-19	0.3	0.4	-0.01	0.3	0.4	-0.02
20-24	1.1	1.2	-0.01	1.1	1.1	-0.01
25-29	1.8	2.0	-0.01	1.8	1.8	-0.01
30-34	3.4	3.2	0.01	3.3	3.3	0.00
35-39	4.9	5.2	-0.01	4.9	4.8	0.00
40-44	6.9	6.7	0.01	6.8	6.4	0.01
45-49	8.9	9.1	0.00	8.9	8.9	0.00
50-54	11.6	11.6	0.00	11.6	11.6	0.00
55-59	12.5	13.3	-0.02	12.7	12.9	-0.01
60-64	11.6	12.7	-0.03	11.9	12.0	0.00
65-69	11.3	12.2	-0.03	11.6	11.7	0.00
70-74	10.8	10.5	0.01	10.9	10.6	0.01
75-79	7.9	6.9	0.04	7.7	7.7	0.00
80-84	5.0	3.8	0.06	4.8	4.9	-0.01
85-89	1.9	1.3	0.05	1.8	1.7	0.01
90-94	0.0	0.0	0.03	0.0	0.0	0.03
Gender: female	79.5	72.1	0.17	77.6	77.6	0.00
Medical history: General						
Acute respiratory disease	34.6	33.4	0.02	34.2	34.2	0.00
Attention deficit hyperactivity disorder	1.2	1.1	0.00	1.2	1.1	0.00
Chronic liver disease	3.7	3.8	0.00	3.7	3.8	-0.01
Chronic obstructive lung disease	11.2	10.9	0.01	11.2	11.2	0.00
Crohn's disease	0.7	2.4	-0.14	0.9	1.4	-0.05
Dementia	1.3	1.2	0.01	1.2	1.5	-0.02
Depressive disorder	18.5	18.2	0.01	18.4	18.3	0.00
Diabetes mellitus	20.8	20.3	0.01	20.7	21.0	-0.01
Gastroesophageal reflux disease	21.6	21.2	0.01	21.5	21.7	-0.01
Gastrointestinal hemorrhage	4.0	4.5	-0.02	4.0	4.0	0.00
Human immunodeficiency virus infection	0.2	0.2	-0.01	0.2	0.2	-0.01
Hyperlipidemia	46.7	45.5	0.02	46.4	47.1	-0.01
Hypertensive disorder	51.3	51.1	0.00	51.3	51.7	-0.01
Lesion of liver	1.3	1.2	0.01	1.3	1.2	0.00
Lupus erythematosus	1.7	0.7	0.10	1.5	1.1	0.03
Obesity	12.1	12.6	-0.01	12.2	12.2	0.00
Osteoarthritis	56.3	55.5	0.02	56.1	56.7	-0.01
Pneumonia	6.5	5.8	0.03	6.3	6.4	0.00
Psoriasis	3.1	8.1	-0.22	3.8	4.9	-0.05
Renal impairment	9.9	9.3	0.02	9.7	9.9	-0.01
Rheumatoid arthritis	84.3	85.4	-0.03	84.8	85.1	-0.01
Schizophrenia	0.2	0.1	0.01	0.2	0.1	0.01
Ulcerative colitis	0.7	2.3	-0.13	0.8	1.3	-0.04
Urinary tract infectious disease	15.9	13.6	0.06	15.3	15.4	0.00
Viral hepatitis C	1.5	1.7	-0.02	1.5	1.7	-0.02
Visual system disorder	40.2	40.1	0.00	40.0	39.6	0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	5.0	4.2	0.04	4.8	4.7	0.00
Cerebrovascular disease	6.3	5.6	0.03	6.1	6.0	0.00
Coronary arteriosclerosis	10.8	10.5	0.01	10.7	10.9	-0.01
Heart disease	27.7	26.1	0.04	27.3	27.8	-0.01
Heart failure	6.3	5.8	0.02	6.1	6.4	-0.01
Ischemic heart disease	6.5	6.3	0.01	6.5	6.6	-0.01
Peripheral vascular disease	4.7	4.3	0.02	4.7	4.6	0.00
Pulmonary embolism	1.2	0.9	0.03	1.2	1.1	0.01
Venous thrombosis	2.3	2.1	0.02	2.2	2.4	-0.01
Medical history: Neoplasms						
Hematologic neoplasm	1.4	1.2	0.02	1.4	1.3	0.01
Malignant lymphoma	0.7	0.7	-0.01	0.7	0.8	-0.01
Malignant neoplasm of anorectum	0.2	0.3	-0.02	0.2	0.2	-0.01
Malignant neoplastic disease	10.4	10.4	0.00	10.4	10.6	-0.01
Malignant tumor of breast	2.5	2.0	0.03	2.4	2.4	0.00
Malignant tumor of colon	0.4	0.5	-0.01	0.4	0.5	-0.01
Malignant tumor of lung	0.4	0.4	0.01	0.4	0.4	0.01
Malignant tumor of urinary bladder	0.3	0.4	-0.01	0.3	0.3	0.00
Primary malignant neoplasm of prostate	1.0	1.2	-0.02	1.0	1.0	0.00
Medication use						
Agents acting on the renin-angiotensin system	32.3	32.7	-0.01	32.4	32.6	0.00
Antibacterials for systemic use	41.2	42.1	-0.02	41.3	41.2	0.00
Antidepressants	35.0	35.4	-0.01	35.0	35.0	0.00
Antiepileptics	22.1	22.8	-0.02	22.2	22.1	0.00
Antiinflammatory and antirheumatic products	48.0	50.0	-0.04	48.5	49.1	-0.01
Antineoplastic agents	30.1	37.9	-0.17	32.6	32.2	0.01
Antipsoriatics	0.8	1.1	-0.03	0.9	0.9	0.00
Antithrombotic agents	11.8	10.7	0.04	11.5	11.4	0.00
Beta blocking agents	23.2	22.5	0.02	23.1	23.1	0.00
Calcium channel blockers	17.8	16.7	0.03	17.6	17.7	0.00
Diuretics	30.3	29.0	0.03	30.0	30.5	-0.01
Drugs for acid related disorders	33.6	34.6	-0.02	33.8	34.4	-0.01
Drugs for obstructive airway diseases	29.3	29.2	0.00	29.2	29.5	-0.01
Drugs used in diabetes	14.1	14.2	0.00	14.1	14.5	-0.01
Immunosuppressants	39.0	52.6	-0.28	43.0	42.2	0.02
Lipid modifying agents	31.9	32.2	-0.01	32.0	32.7	-0.01
Opioids	38.4	40.2	-0.04	38.8	38.8	0.00

Psycholeptics	30.4	29.4	0.02	30.1	29.9	0.00
Psychostimulants, agents used for adhd and nootropics	4.0	3.7	0.02	4.0	3.7	0.02

7.4. CPRD

	Before PS stratification			After PS stratification		
	HCQ	SSZ		HCQ	SSZ	
Characteristic	%	%	Std. diff	%	%	Std. diff
Age group						
15-19	0.3	0.2	0.01	0.3	0.2	0.00
20-24	0.8	1.0	-0.02	0.8	0.9	-0.01
25-29	1.3	1.6	-0.03	1.4	1.6	-0.02
30-34	2.7	3.1	-0.02	2.9	3.0	0.00
35-39	4.5	4.6	0.00	4.7	4.5	0.01
40-44	5.6	6.6	-0.04	6.3	6.4	0.00
45-49	8.9	8.0	0.03	8.5	8.5	0.00
50-54	11.3	10.9	0.02	11.3	11.0	0.01
55-59	13.2	12.6	0.02	13.4	12.8	0.02
60-64	13.1	13.2	0.00	12.9	13.0	0.00
65-69	12.7	12.7	0.00	12.6	12.7	0.00
70-74	10.9	11.6	-0.02	11.1	11.2	0.00
75-79	8.3	8.1	0.01	8.0	8.0	0.00
80-84	4.5	4.3	0.01	4.2	4.4	-0.01
85-89	1.6	1.3	0.03	1.3	1.5	-0.01
90-94	0.3	0.2	0.03	0.3	0.2	0.01
Gender: female	72.8	67.9	0.11	70.0	70.2	0.00
Medical history: General						
Acute respiratory disease	9.2	9.1	0.00	9.4	9.3	0.01
Chronic liver disease	0.1	0.1	0.00	0.1	0.0	0.01
Chronic obstructive lung disease	2.3	2.0	0.02	2.2	2.0	0.01
Crohn's disease	<0.1	0.1	-0.03	0.1	0.1	-0.02
Dementia	0.2	0.0	0.06	0.2	0.0	0.05
Depressive disorder	2.7	3.2	-0.03	3.1	3.1	0.00
Diabetes mellitus	2.2	2.1	0.01	2.1	2.2	0.00
Gastroesophageal reflux disease	0.5	0.4	0.02	0.4	0.4	0.01
Gastrointestinal hemorrhage	1.0	1.4	-0.03	1.1	1.4	-0.02
Hyperlipidemia	1.2	1.0	0.02	1.2	1.0	0.01
Hypertensive disorder	3.0	4.0	-0.05	3.2	3.6	-0.02
Lesion of liver	0.1	0.1	0.01	0.1	0.1	0.01
Lupus erythematosus	0.2	0.0	0.05	0.2	0.0	0.07
Obesity	0.4	0.5	-0.01	0.4	0.5	-0.01
Osteoarthritis	7.7	10.4	-0.09	8.6	8.9	-0.01
Pneumonia	0.8	0.6	0.03	0.9	0.6	0.03
Psoriasis	0.8	1.9	-0.10	1.2	1.5	-0.02
Renal impairment	2.3	1.8	0.04	1.9	2.2	-0.02
Rheumatoid arthritis	61.5	72.2	-0.23	67.2	66.2	0.02
Schizophrenia	<0.1	0.0	0.00	0.0	0.0	0.00
Ulcerative colitis	<0.1	0.1	-0.03	0.0	0.1	-0.03
Urinary tract infectious disease	3.3	3.1	0.01	3.2	3.2	0.00
Viral hepatitis C	<0.1	0.0	0.00	0.0	0.0	0.00
Visual system disorder	6.9	6.9	0.00	6.7	7.0	-0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	0.7	0.7	0.00	0.8	0.7	0.02
Cerebrovascular disease	0.4	0.8	-0.05	0.5	0.7	-0.03
Coronary arteriosclerosis	0.1	0.1	0.00	0.1	0.1	0.00
Heart disease	3.0	3.3	-0.02	3.3	3.1	0.02
Heart failure	0.5	0.7	-0.02	0.7	0.6	0.01
Ischemic heart disease	1.0	1.5	-0.04	1.2	1.3	-0.01
Peripheral vascular disease	0.2	0.2	0.01	0.3	0.2	0.02
Pulmonary embolism	0.2	0.2	-0.01	0.2	0.3	-0.02
Venous thrombosis	0.8	1.0	-0.01	0.9	1.0	-0.01
Medical history: Neoplasms						
Hematologic neoplasm	0.1	0.0	0.01	0.1	0.0	0.01
Malignant lymphoma	<0.1	0.0	0.00	0.0	0.0	0.00
Malignant neoplastic disease	1.3	1.0	0.02	1.2	1.0	0.02
Malignant tumor of breast	0.1	0.1	0.00	0.1	0.1	-0.01
Malignant tumor of colon	0.1	0.0	0.01	0.0	0.0	0.00
Malignant tumor of lung	0.1	0.0	0.02	0.1	0.0	0.02
Medication use						
Agents acting on the renin-angiotensin system	22.1	16.7	0.14	19.3	19.3	0.00
Antibacterials for systemic use	37.3	35.0	0.05	35.9	36.3	-0.01
Antidepressants	26.6	22.6	0.09	24.9	24.9	0.00
Antiepileptics	6.5	4.3	0.10	5.5	5.2	0.01
Antiinflammatory and antirheumatic products	60.5	67.7	-0.15	64.3	64.0	0.01
Antineoplastic agents	51.5	28.5	0.48	39.3	40.8	-0.03
Antipsoriatics	0.7	1.3	-0.06	0.9	1.2	-0.02
Antithrombotic agents	17.9	16.6	0.03	17.2	17.1	0.00
Beta blocking agents	14.4	13.4	0.03	14.3	13.7	0.02
Calcium channel blockers	15.6	12.0	0.10	13.4	13.4	0.00
Diuretics	19.1	20.8	-0.04	20.0	20.0	0.00
Drugs for acid related disorders	58.3	51.0	0.15	54.1	54.6	-0.01
Drugs for obstructive airway diseases	22.5	18.9	0.09	20.1	20.1	0.00
Drugs used in diabetes	7.1	5.8	0.05	6.1	6.5	-0.02
Immunosuppressants	55.3	29.8	0.53	42.2	43.1	-0.02
Lipid modifying agents	23.0	17.1	0.15	19.4	19.7	-0.01
Opioids	36.3	41.1	-0.10	39.1	38.8	0.01
Psycholeptics	16.5	16.4	0.00	16.6	16.5	0.00
Psychostimulants, agents used for adhd and nootropics	0.1	0.1	0.01	0.1	0.1	0.01

7.5. DAGermany

	Before PS stratification			After PS stratification		
	HCQ	SSZ		HCQ	SSZ	
Characteristic	**%**	**%**	**Std. diff**	**%**	**%**	**Std. diff**
Age group						
15-19	0.3	0.5	-0.03	0.3	0.5	-0.04
20-24	1.1	1.3	-0.02	1.1	1.2	-0.01
25-29	1.9	2.4	-0.04	2.1	2.4	-0.02
30-34	2.3	3.6	-0.07	3.0	3.0	0.00
35-39	4.0	4.1	-0.01	3.9	4.1	-0.01
40-44	5.7	6.6	-0.04	6.0	6.2	-0.01
45-49	8.5	9.2	-0.03	8.9	9.1	-0.01
50-54	12.0	12.6	-0.02	12.7	12.4	0.01
55-59	14.2	14.8	-0.02	14.6	15.0	-0.01
60-64	13.3	12.1	0.04	12.3	12.4	0.00
65-69	11.5	10.7	0.02	11.3	10.7	0.02
70-74	10.3	9.5	0.03	9.8	9.7	0.00
75-79	9.0	7.4	0.06	8.2	8.0	0.00
80-84	4.5	3.9	0.03	4.3	4.0	0.02
85-89	1.4	1.0	0.04	1.3	1.0	0.03
90-94	0.2	0.2	0.00	0.2	0.2	0.00
Gender: female	81.4	72.7	0.21	76.2	77.2	-0.02
Medical history: General						
Acute respiratory disease	11.9	12.5	-0.02	12.2	11.8	0.01
Attention deficit hyperactivity disorder	<0.1	0.1	-0.01	0.1	<0.1	0.02
Chronic liver disease	0.6	0.3	0.05	0.6	0.3	0.05
Chronic obstructive lung disease	3.4	3.9	-0.03	3.3	3.7	-0.02
Crohn's disease	0.2	1.4	-0.14	0.4	1.0	-0.07
Dementia	0.6	0.5	0.01	0.6	0.5	0.01
Depressive disorder	7.5	7.7	-0.01	7.6	7.5	0.01
Diabetes mellitus	6.4	7.1	-0.03	6.9	6.6	0.01
Gastroesophageal reflux disease	1.9	2.0	0.00	1.8	1.9	-0.01
Gastrointestinal hemorrhage	0.5	0.6	-0.02	0.5	0.6	-0.02
Hyperlipidemia	7.1	8.3	-0.04	7.9	7.6	0.01
Hypertensive disorder	18.5	19.1	-0.02	18.9	18.2	0.02
Lesion of liver	0.5	0.3	0.03	0.4	0.3	0.03
Lupus erythematosus	0.3	<0.1	0.07	0.2	<0.1	0.06
Obesity	2.2	2.5	-0.02	2.2	2.4	-0.01
Osteoarthritis	11.5	13.3	-0.06	12.4	12.2	0.01
Pneumonia	1.9	1.4	0.04	2.0	1.5	0.03
Psoriasis	2.3	4.5	-0.12	3.6	3.5	0.00
Renal impairment	2.7	2.2	0.03	2.5	2.4	0.01
Rheumatoid arthritis	46.1	54.6	-0.17	52.1	49.9	0.04
Schizophrenia	<0.1	0.1	-0.03	<0.1	0.1	-0.01
Ulcerative colitis	0.2	1.6	-0.16	0.4	1.1	-0.09
Urinary tract infectious disease	4.0	4.0	0.00	4.0	3.9	0.00
Viral hepatitis C	0.3	0.1	0.04	0.3	0.1	0.04
Visual system disorder	5.7	5.5	0.01	5.4	5.4	0.00
Medical history: Cardiovascular disease						
Atrial fibrillation	0.8	0.8	0.00	0.8	0.8	0.00
Cerebrovascular disease	1.4	1.7	-0.03	1.4	1.6	-0.02
Coronary arteriosclerosis	1.0	1.1	-0.01	1.0	1.2	-0.02
Heart disease	10.5	11.4	-0.03	10.5	10.7	0.00
Heart failure	2.0	2.6	-0.04	2.0	2.4	-0.03
Ischemic heart disease	4.4	5.1	-0.04	4.6	4.5	0.00
Peripheral vascular disease	1.3	1.0	0.02	1.2	0.9	0.02
Pulmonary embolism	0.6	0.3	0.04	0.6	0.4	0.03
Venous thrombosis	1.2	1.4	-0.02	1.4	1.5	0.00
Medical history: Neoplasms						
Hematologic neoplasm	0.3	0.2	0.03	0.3	0.2	0.02
Malignant lymphoma	0.2	0.2	0.01	0.2	0.1	0.01
Malignant neoplasm of anorectum	0.2	0.2	0.02	0.2	0.2	0.00
Malignant neoplastic disease	3.3	3.2	0.00	3.2	3.2	0.00
Malignant tumor of breast	0.7	0.6	0.00	0.6	0.6	0.00
Malignant tumor of colon	0.3	0.1	0.03	0.3	0.1	0.04
Malignant tumor of lung	<0.1	<0.1	0.02	<0.1	<0.1	0.00
Malignant tumor of urinary bladder	<0.1	0.2	-0.05	<0.1	0.2	-0.05
Primary malignant neoplasm of prostate	0.2	0.3	-0.03	0.2	0.3	-0.02
Medication use						
Agents acting on the renin-angiotensin system	16.7	17.0	-0.01	16.9	16.5	0.01
Antibacterials for systemic use	12.7	14.6	-0.06	13.4	13.6	-0.01
Antidepressants	8.8	7.7	0.04	8.1	8.0	0.00
Antiepileptics	3.0	2.3	0.05	2.6	2.3	0.02
Antiinflammatory and antirheumatic products	33.1	35.9	-0.06	35.3	34.6	0.02
Antineoplastic agents	31.5	26.7	0.10	29.2	30.3	-0.02
Antipsoriatics	0.3	0.3	0.00	0.3	0.2	0.00
Antithrombotic agents	10.0	9.9	0.00	9.6	9.3	0.01
Beta blocking agents	13.7	13.2	0.02	12.8	13.0	0.00
Calcium channel blockers	7.5	7.7	-0.01	7.4	7.3	0.00
Diuretics	13.9	14.5	-0.02	14.3	13.6	0.02
Drugs for acid related disorders	32.0	32.5	-0.01	32.1	32.4	-0.01
Drugs for obstructive airway diseases	6.9	7.7	-0.03	7.2	7.2	0.00
Drugs used in diabetes	4.4	4.8	-0.02	4.7	4.6	0.01
Immunosuppressants	40.3	35.0	0.11	38.7	38.4	0.00
Lipid modifying agents	7.3	9.1	-0.06	8.0	8.1	0.00
Opioids	12.3	12.9	-0.02	12.2	12.2	0.00
Psycholeptics	4.8	5.9	-0.05	4.8	5.3	-0.02

Psychostimulants, agents used for adhd and nootropics	0.2	0.4	-0.03	0.2	0.3	-0.03

7.6. IMRD

	Before PS stratification			After PS stratification		
	HCQ	SSZ		HCQ	SSZ	
Characteristic	**%**	**%**	**Std. diff**	**%**	**%**	**Std. diff**
Age group						
15-19	0.2	0.2	0.02	0.2	0.2	0.01
20-24	0.8	1.0	-0.03	0.8	1.0	-0.02
25-29	1.2	1.6	-0.03	1.4	1.6	-0.02
30-34	2.8	3.2	-0.02	2.9	3.1	-0.01
35-39	4.8	5.0	-0.01	5.0	4.8	0.01
40-44	6.0	6.1	0.00	6.3	6.0	0.01
45-49	8.7	7.8	0.03	8.4	8.5	0.00
50-54	11.3	10.8	0.02	11.2	11.0	0.01
55-59	13.0	12.4	0.02	12.7	12.4	0.01
60-64	13.2	13.8	-0.02	13.4	13.5	0.00
65-69	13.0	12.8	0.01	12.9	13.0	0.00
70-74	11.0	11.4	-0.01	11.3	11.2	0.00
75-79	7.7	8.3	-0.02	7.8	7.9	0.00
80-84	4.4	4.1	0.02	4.1	4.2	0.00
85-89	1.5	1.3	0.02	1.3	1.4	-0.01
90-94	0.3	0.2	0.02	0.2	0.2	0.00
Gender: female	73.2	68.0	0.11	70.7	71.0	0.00
Race						
race = Asian	0.1	0.1	0.02	0.1	0.1	0.00
race = White	29.8	25.8	0.09	27.4	27.6	0.00
race = Asian Indian	0.7	0.4	0.04	0.6	0.5	0.02
race = Bangladeshi	0.1	<0.1	0.02	<0.1	<0.1	0.02
race = Chinese	0.1	<0.1	0.03	0.1	<0.1	0.03
race = Pakistani	0.3	0.2	0.03	0.3	0.2	0.03
race = Black	0.4	0.2	0.03	0.3	0.2	0.02
race = African	0.2	<0.1	0.05	0.2	<0.1	0.04
race = European	0.1	<0.1	0.02	0.1	<0.1	0.02
Medical history: General						
Acute respiratory disease	9.2	9.3	0.00	9.2	9.1	0.00
Chronic liver disease	0.1	0.1	0.00	<0.1	<0.1	0.00
Chronic obstructive lung disease	2.1	2.5	-0.02	2.2	2.3	-0.01
Crohn's disease	<0.1	0.2	-0.05	<0.1	0.1	-0.04
Dementia	0.2	0.1	0.03	0.1	0.1	0.02
Depressive disorder	2.6	2.9	-0.02	2.9	2.7	0.01
Diabetes mellitus	2.3	2.2	0.01	2.2	2.1	0.01
Gastroesophageal reflux disease	0.3	0.6	-0.03	0.4	0.6	-0.03
Gastrointestinal hemorrhage	0.9	1.3	-0.04	1.0	1.1	-0.01
Hyperlipidemia	1.1	1.3	-0.02	1.1	1.2	-0.01
Hypertensive disorder	3.1	3.7	-0.03	3.2	3.2	0.00
Lesion of liver	0.1	0.1	0.01	0.1	<0.1	0.01
Lupus erythematosus	0.1	0.0		0.1	0.0	
Obesity	0.3	0.5	-0.03	0.4	0.6	-0.03
Osteoarthritis	7.5	9.4	-0.07	8.1	8.1	0.00
Pneumonia	0.7	0.6	0.00	0.7	0.7	0.00
Psoriasis	0.8	2.2	-0.12	1.3	1.6	-0.02
Renal impairment	2.5	2.2	0.01	2.3	2.3	0.00
Rheumatoid arthritis	61.4	69.3	-0.17	65.7	63.7	0.04
Schizophrenia	<0.1	<0.1	0.01	<0.1	<0.1	0.02
Ulcerative colitis	<0.1	<0.1	-0.01	<0.1	<0.1	-0.01
Urinary tract infectious disease	3.1	2.9	0.01	3.1	3.0	0.01
Visual system disorder	6.6	7.0	-0.02	6.6	6.8	-0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	0.7	0.7	0.00	0.7	0.6	0.01
Cerebrovascular disease	0.5	0.7	-0.03	0.5	0.7	-0.02
Coronary arteriosclerosis	0.1	0.1	0.01	0.1	0.1	0.02
Heart disease	2.7	2.9	-0.01	2.8	2.6	0.02
Heart failure	0.4	0.4	-0.01	0.5	0.4	0.01
Ischemic heart disease	0.8	1.2	-0.04	1.0	1.0	0.00
Peripheral vascular disease	0.2	0.2	0.01	0.3	0.2	0.02
Pulmonary embolism	0.2	0.2	-0.01	0.2	0.3	-0.02
Venous thrombosis	0.8	1.1	-0.03	0.8	1.0	-0.02
Medical history: Neoplasms						
Hematologic neoplasm	0.1	0.1	0.01	0.1	<0.1	0.02
Malignant lymphoma	<0.1	<0.1	-0.01	<0.1	<0.1	0.00
Malignant neoplasm of anorectum	<0.1	<0.1	0.02	<0.1	<0.1	0.02
Malignant neoplastic disease	1.3	1.1	0.02	1.2	1.0	0.02
Malignant tumor of breast	0.2	0.2	0.02	0.2	0.2	0.01
Malignant tumor of colon	<0.1	<0.1	-0.01	<0.1	<0.1	0.00
Malignant tumor of lung	0.1	0.1	0.01	0.1	0.1	0.02
Medication use						
Agents acting on the renin-angiotensin system	0.6	0.6	0.00	0.6	0.8	-0.02
Antibacterials for systemic use	3.8	3.4	0.02	3.6	3.5	0.01
Antidepressants	1.1	1.1	-0.01	1.0	1.2	-0.02
Antiepileptics	0.1	0.2	-0.03	0.1	0.2	-0.03
Antiinflammatory and antirheumatic products	1.6	1.9	-0.03	1.7	1.7	-0.01
Antineoplastic agents	1.5	0.6	0.08	1.2	0.9	0.02
Antithrombotic agents	1.1	1.1	0.00	1.2	1.2	0.00
Beta blocking agents	0.4	0.6	-0.02	0.5	0.6	-0.01
Calcium channel blockers	0.6	0.5	0.00	0.6	0.5	0.02
Diuretics	0.8	1.0	-0.02	1.0	0.9	0.01
Drugs for acid related disorders	1.6	1.7	0.00	1.7	1.6	0.01
Drugs for obstructive airway diseases	0.4	0.4	0.00	0.5	0.4	0.00

Drugs used in diabetes	0.2	0.2	0.01	0.2	0.2	0.00
Immunosuppressants	1.6	0.7	0.08	1.3	1.0	0.02
Lipid modifying agents	0.9	0.9	0.00	0.9	1.0	-0.01
Opioids	0.6	0.6	-0.01	0.6	0.6	-0.01
Psycholeptics	0.4	0.5	-0.01	0.4	0.4	0.00

7.7. MDCD

	Before PS stratification			After PS stratification		
	HCQ	SSZ		HCQ	SSZ	
Characteristic	%	%	Std. diff	%	%	Std. diff
Age group						
15-19	1.2	1.3	-0.01	1.2	1.5	-0.02
20-24	2.2	2.7	-0.04	2.1	3.3	-0.07
25-29	4.3	4.2	0.01	4.2	4.6	-0.02
30-34	6.7	6.6	0.00	6.5	6.6	0.00
35-39	9.0	8.8	0.01	8.7	9.0	-0.01
40-44	10.2	9.1	0.04	10.1	9.0	0.04
45-49	13.3	12.8	0.02	13.3	13.7	-0.01
50-54	15.9	16.2	-0.01	16.2	15.8	0.01
55-59	15.7	16.3	-0.01	16.0	15.2	0.02
60-64	12.0	13.7	-0.05	12.2	12.9	-0.02
65-69	4.5	4.0	0.02	4.6	4.1	0.02
70-74	2.0	2.0	-0.01	2.0	1.8	0.01
75-79	1.6	1.0	0.05	1.6	1.1	0.05
80-84	1.0	0.9	0.01	1.0	0.9	0.01
85-89	0.4	0.2	0.03	0.4	0.3	0.00
Gender: female	86.0	79.1	0.18	84.4	84.3	0.00
Race						
race = Black or African American	28.7	25.2	0.08	28.0	26.3	0.04
race = White	54.4	57.1	-0.05	55.1	55.3	-0.01
Ethnicity						
ethnicity = Hispanic or Latino	2.4	1.9	0.03	2.4	2.1	0.02
Medical history: General						
Acute respiratory disease	41.9	40.2	0.03	41.6	41.4	0.00
Attention deficit hyperactivity disorder	2.6	2.0	0.04	2.6	2.5	0.00
Chronic liver disease	6.9	7.4	-0.02	6.9	7.1	-0.01
Chronic obstructive lung disease	21.1	21.5	-0.01	21.2	21.0	0.00
Crohn's disease	0.8	3.4	-0.18	1.0	1.8	-0.07
Dementia	1.2	0.9	0.03	1.1	1.1	0.00
Depressive disorder	36.0	35.3	0.02	35.4	36.2	-0.02
Diabetes mellitus	25.5	25.6	0.00	25.5	25.5	0.00
Gastroesophageal reflux disease	29.6	30.4	-0.02	29.5	30.4	-0.02
Gastrointestinal hemorrhage	5.0	6.3	-0.06	5.0	6.0	-0.04
Human immunodeficiency virus infection	0.5	0.8	-0.04	0.5	0.8	-0.04
Hyperlipidemia	36.4	36.9	-0.01	36.3	37.7	-0.03
Hypertensive disorder	55.6	53.3	0.05	55.2	54.3	0.02
Lesion of liver	2.0	2.0	0.00	2.0	2.0	0.00
Lupus erythematosus	3.0	1.2	0.13	2.8	1.8	0.07
Obesity	21.4	20.3	0.03	21.2	20.6	0.01
Osteoarthritis	57.2	56.7	0.01	57.3	57.4	0.00
Pneumonia	8.7	8.1	0.02	8.4	7.9	0.02
Psoriasis	2.0	6.4	-0.22	2.5	3.4	-0.05
Renal impairment	9.4	8.0	0.05	9.2	8.3	0.03
Rheumatoid arthritis	80.7	84.9	-0.11	81.9	83.2	-0.03
Schizophrenia	1.7	2.0	-0.02	1.6	2.1	-0.03
Ulcerative colitis	0.5	1.6	-0.11	0.6	1.3	-0.07
Urinary tract infectious disease	17.8	16.6	0.03	17.3	16.7	0.02
Viral hepatitis C	5.9	6.0	-0.01	5.9	6.2	-0.02
Visual system disorder	40.0	40.5	-0.01	40.0	39.5	0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	3.3	2.5	0.05	3.2	3.2	0.00
Cerebrovascular disease	5.3	5.3	0.00	5.1	5.6	-0.02
Coronary arteriosclerosis	9.8	8.6	0.04	9.6	9.4	0.01
Heart disease	29.6	27.2	0.05	29.0	27.9	0.02
Heart failure	8.7	7.5	0.04	8.4	8.0	0.01
Ischemic heart disease	7.3	7.0	0.01	7.1	7.4	-0.01
Peripheral vascular disease	4.8	4.2	0.03	4.6	4.2	0.02
Pulmonary embolism	2.0	1.1	0.08	1.9	1.6	0.02
Venous thrombosis	3.1	2.5	0.03	2.9	3.3	-0.02
Medical history: Neoplasms						
Hematologic neoplasm	1.5	1.2	0.03	1.4	1.2	0.02
Malignant lymphoma	0.4	0.5	-0.01	0.4	0.4	0.01
Malignant neoplasm of anorectum	0.2	0.2	-0.01	0.2	<0.2	0.00
Malignant neoplastic disease	7.2	7.5	-0.01	7.0	7.3	-0.01
Malignant tumor of breast	2.0	1.7	0.02	1.9	1.5	0.03
Malignant tumor of colon	0.4	0.3	0.01	0.4	0.3	0.02
Malignant tumor of lung	0.4	0.3	0.03	0.4	0.3	0.01
Malignant tumor of urinary bladder	0.2	<0.2	0.01	0.2	<0.2	0.02
Primary malignant neoplasm of prostate	0.2	0.2	-0.01	0.2	<0.2	0.01
Medication use						
Agents acting on the renin-angiotensin system	32.6	32.2	0.01	32.6	33.2	-0.01
Antibacterials for systemic use	50.4	48.6	0.04	50.1	48.0	0.04
Antidepressants	53.7	52.7	0.02	53.5	53.2	0.00
Antiepileptics	43.0	41.6	0.03	42.6	42.7	0.00
Antiinflammatory and antirheumatic products	58.3	59.8	-0.03	58.4	59.7	-0.03
Antineoplastic agents	30.3	42.0	-0.25	34.1	31.5	0.05
Antipsoriatics	0.8	0.7	0.02	0.8	0.6	0.03
Antithrombotic agents	18.8	17.0	0.04	18.5	17.7	0.02
Beta blocking agents	24.9	22.8	0.05	24.5	23.0	0.04
Calcium channel blockers	20.0	19.5	0.01	19.6	20.3	-0.02
Diuretics	33.7	32.3	0.03	33.3	32.0	0.03
Drugs for acid related disorders	50.1	50.7	-0.01	50.3	48.1	0.04
Drugs for obstructive airway diseases	46.3	46.5	0.00	46.1	46.7	-0.01

Drugs used in diabetes	18.4	19.8	-0.03	18.5	19.4	-0.02
Immunosuppressants	39.5	56.5	-0.35	44.5	40.8	0.07
Lipid modifying agents	29.1	30.1	-0.02	29.2	30.6	-0.03
Opioids	62.1	62.5	-0.01	62.0	62.7	-0.02
Psycholeptics	49.8	49.5	0.00	49.3	50.2	-0.02
Psychostimulants, agents used for adhd and nootropics	7.3	6.8	0.02	7.2	7.4	-0.01

7.8. MDCR

	Before PS stratification			After PS stratification		
	HCQ	SSZ		HCQ	SSZ	
Characteristic	**%**	**%**	**Std. diff**	**%**	**%**	**Std. diff**
Age group						
45-49	0.1	<0.1	0.01	0.1	<0.1	0.01
50-54	0.3	0.3	-0.01	0.3	0.3	0.00
55-59	0.7	1.0	-0.03	0.7	0.9	-0.01
60-64	1.7	2.0	-0.02	1.8	1.9	-0.01
65-69	23.7	26.4	-0.06	24.4	24.5	0.00
70-74	28.1	30.8	-0.06	28.6	28.7	0.00
75-79	22.6	20.5	0.05	22.2	21.9	0.01
80-84	14.6	13.3	0.04	14.3	14.2	0.00
85-89	6.8	4.3	0.11	6.2	6.2	0.00
90-94	1.3	1.2	0.01	1.3	1.3	0.00
95-99	0.1	0.1	0.01	0.1	0.1	0.01
00-04	0.0	<0.1	-0.01	0.0	<0.1	-0.02
Gender: female	73.0	68.5	0.10	71.7	71.6	0.00
Medical history: General						
Acute respiratory disease	27.5	26.5	0.02	27.3	27.3	0.00
Attention deficit hyperactivity disorder	0.2	0.2	0.00	0.2	0.2	0.00
Chronic liver disease	2.1	1.9	0.02	2.1	1.9	0.02
Chronic obstructive lung disease	15.7	16.2	-0.01	15.7	16.2	-0.01
Crohn's disease	0.5	1.3	-0.08	0.6	1.1	-0.05
Dementia	2.0	1.7	0.02	2.0	1.8	0.01
Depressive disorder	9.2	9.2	0.00	9.2	9.3	0.00
Diabetes mellitus	23.1	22.5	0.02	22.9	22.7	0.01
Gastroesophageal reflux disease	16.5	16.5	0.00	16.2	16.5	-0.01
Gastrointestinal hemorrhage	4.8	5.1	-0.01	4.8	4.9	0.00
Human immunodeficiency virus infection	0.1	<0.1	0.01	0.1	<0.1	0.01
Hyperlipidemia	41.3	39.3	0.04	40.7	41.3	-0.01
Hypertensive disorder	61.8	59.4	0.05	61.1	61.5	-0.01
Lesion of liver	1.0	1.0	-0.01	1.0	1.0	-0.01
Lupus erythematosus	0.9	0.2	0.09	0.8	0.2	0.09
Obesity	5.5	5.4	0.00	5.5	5.5	0.00
Osteoarthritis	62.0	59.6	0.05	61.2	61.9	-0.01
Pneumonia	9.1	9.3	0.00	9.1	9.2	0.00
Psoriasis	2.3	4.9	-0.14	2.7	3.3	-0.04
Renal impairment	11.3	10.5	0.03	11.1	11.2	0.00
Rheumatoid arthritis	88.4	89.7	-0.04	88.9	89.3	-0.01
Schizophrenia	0.1	<0.1	0.00	0.1	0.1	-0.01
Ulcerative colitis	0.6	2.0	-0.12	0.7	1.2	-0.05
Urinary tract infectious disease	13.6	12.7	0.03	13.5	12.7	0.02
Viral hepatitis C	0.5	0.5	-0.01	0.5	0.5	0.00
Visual system disorder	55.4	55.2	0.00	55.3	54.9	0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	10.6	9.5	0.04	10.4	10.2	0.00
Cerebrovascular disease	11.8	11.0	0.02	11.5	11.6	0.00
Coronary arteriosclerosis	19.7	19.8	0.00	19.6	19.3	0.01
Heart disease	44.3	44.4	0.00	44.0	44.7	-0.01
Heart failure	10.1	9.9	0.01	10.0	10.4	-0.01
Ischemic heart disease	10.1	10.1	0.00	10.1	10.3	-0.01
Peripheral vascular disease	6.4	5.5	0.04	6.3	6.0	0.01
Pulmonary embolism	1.5	1.3	0.02	1.5	1.3	0.02
Venous thrombosis	3.4	3.4	0.00	3.3	3.5	-0.01
Medical history: Neoplasms						
Hematologic neoplasm	2.2	2.3	0.00	2.2	2.4	-0.01
Malignant lymphoma	1.3	1.5	-0.02	1.3	1.4	-0.01
Malignant neoplasm of anorectum	0.4	0.4	0.00	0.4	0.4	0.01
Malignant neoplastic disease	18.5	19.8	-0.03	18.7	18.9	0.00
Malignant tumor of breast	3.8	4.0	-0.01	3.8	3.7	0.00
Malignant tumor of colon	0.8	0.7	0.02	0.9	0.6	0.03
Malignant tumor of lung	0.7	0.6	0.00	0.6	0.5	0.02
Malignant tumor of urinary bladder	1.0	1.2	-0.02	1.0	1.0	0.00
Primary malignant neoplasm of prostate	2.4	2.8	-0.03	2.5	2.4	0.00
Medication use						
Agents acting on the renin-angiotensin system	48.1	47.1	0.02	47.9	48.2	-0.01
Antibacterials for systemic use	46.3	49.0	-0.05	47.0	46.2	0.02
Antidepressants	31.5	31.4	0.00	31.6	31.5	0.00
Antiepileptics	20.1	21.8	-0.04	20.3	20.7	-0.01
Antiinflammatory and antirheumatic products	44.0	44.6	-0.01	44.1	44.9	-0.02
Antineoplastic agents	32.0	40.6	-0.18	34.8	33.0	0.04
Antipsoriatics	1.0	1.3	-0.03	1.0	1.3	-0.02
Antithrombotic agents	22.8	22.1	0.02	22.6	22.3	0.01
Beta blocking agents	39.4	39.4	0.00	39.3	39.1	0.00
Calcium channel blockers	30.1	28.5	0.04	29.6	30.4	-0.02
Diuretics	47.1	45.3	0.04	46.7	46.3	0.01
Drugs for acid related disorders	44.6	45.6	-0.02	44.6	45.1	-0.01
Drugs for obstructive airway diseases	33.2	32.5	0.02	33.1	32.9	0.00
Drugs used in diabetes	17.4	16.9	0.02	17.4	16.9	0.01
Immunosuppressants	41.1	55.1	-0.28	45.5	42.5	0.06
Lipid modifying agents	49.8	48.6	0.02	49.5	49.4	0.00
Opioids	43.6	44.0	-0.01	43.8	43.2	0.01
Psycholeptics	34.6	34.1	0.01	34.5	33.6	0.02
Psychostimulants, agents used for adhd and nootropics	2.0	2.0	0.00	2.0	1.9	0.01

7.9. OpenClaims

	Before PS stratification			After PS stratification		
	HCQ	SSZ		HCQ	SSZ	
Characteristic	**%**	**%**	**Std. diff**	**%**	**%**	**Std. diff**
Age group						
15-19	0.3	0.3	-0.01	0.3	0.3	0.00
20-24	1.2	1.2	-0.01	1.2	1.2	0.00
25-29	1.9	1.9	0.00	1.9	1.8	0.00
30-34	3.0	2.9	0.00	2.9	2.9	0.00
35-39	4.3	4.4	-0.01	4.3	4.3	0.00
40-44	5.8	5.9	0.00	5.8	5.7	0.00
45-49	8.3	8.3	0.00	8.2	8.1	0.00
50-54	11.5	11.9	-0.01	11.5	11.5	0.00
55-59	13.6	14.2	-0.02	13.7	13.8	0.00
60-64	13.4	13.8	-0.01	13.6	13.5	0.00
65-69	12.5	12.7	0.00	12.6	12.6	0.00
70-74	9.9	9.6	0.01	9.9	10.0	0.00
75-79	10.7	9.0	0.06	10.3	10.6	-0.01
80-84	3.7	3.5	0.01	3.6	3.6	0.00
85-89	0.2	0.2	0.00	0.2	0.2	0.00
Gender: female	81.0	73.5	0.18	79.3	79.1	0.00
Medical history: General						
Acute respiratory disease	20.1	19.2	0.02	19.9	19.9	0.00
Attention deficit hyperactivity disorder	0.7	0.7	0.00	0.7	0.7	0.00
Chronic liver disease	2.1	2.0	0.00	2.0	2.1	0.00
Chronic obstructive lung disease	7.6	7.7	0.00	7.6	7.8	0.00
Crohn's disease	0.4	1.6	-0.11	0.5	0.9	-0.04
Dementia	0.8	0.7	0.01	0.8	0.8	0.00
Depressive disorder	9.7	9.6	0.00	9.6	9.8	-0.01
Diabetes mellitus	15.6	16.1	-0.01	15.7	16.0	-0.01
Gastroesophageal reflux disease	4.3	5.0	-0.04	4.5	4.5	0.00
Gastrointestinal hemorrhage	2.4	2.5	-0.01	2.4	2.4	0.00
Human immunodeficiency virus infection	0.2	0.2	0.00	0.2	0.2	0.00
Hyperlipidemia	26.0	25.8	0.01	26.0	26.4	-0.01
Hypertensive disorder	35.0	34.5	0.01	34.9	35.2	-0.01
Lesion of liver	0.8	0.7	0.01	0.8	0.8	0.00
Lupus erythematosus	1.1	0.3	0.10	0.9	0.5	0.05
Obesity	6.3	6.6	-0.01	6.4	6.5	0.00
Osteoarthritis	36.0	37.0	-0.02	36.1	36.9	-0.02
Pneumonia	4.4	4.2	0.01	4.3	4.3	0.00
Psoriasis	1.9	5.4	-0.19	2.2	3.3	-0.06
Renal impairment	6.2	5.5	0.03	6.1	6.0	0.00
Rheumatoid arthritis	69.0	69.6	-0.01	69.3	69.7	-0.01
Schizophrenia	0.2	0.2	0.00	0.2	0.2	0.00
Ulcerative colitis	0.4	1.7	-0.12	0.5	1.0	-0.06
Urinary tract infectious disease	8.7	7.4	0.05	8.4	8.4	0.00
Viral hepatitis C	1.1	1.1	0.00	1.1	1.1	0.00
Visual system disorder	21.9	20.7	0.03	21.6	21.6	0.00
Medical history: Cardiovascular disease						
Atrial fibrillation	3.6	3.4	0.01	3.6	3.6	0.00
Cerebrovascular disease	3.4	2.8	0.03	3.2	3.3	0.00
Coronary arteriosclerosis	6.8	6.8	0.00	6.8	6.9	0.00
Heart disease	18.3	17.3	0.03	18.1	18.3	0.00
Heart failure	4.0	3.7	0.02	3.9	4.0	0.00
Ischemic heart disease	3.5	3.4	0.01	3.5	3.6	0.00
Peripheral vascular disease	9.7	9.1	0.02	9.6	9.6	0.00
Pulmonary embolism	0.8	0.7	0.01	0.8	0.8	0.00
Venous thrombosis	1.5	1.4	0.01	1.5	1.5	0.00
Medical history: Neoplasms						
Hematologic neoplasm	0.9	0.9	0.00	0.9	1.0	0.00
Malignant lymphoma	0.6	0.6	0.00	0.6	0.6	0.00
Malignant neoplasm of anorectum	0.1	0.1	0.00	0.1	0.1	0.00
Malignant neoplastic disease	7.2	7.2	0.00	7.2	7.4	0.00
Malignant tumor of breast	1.8	1.6	0.01	1.7	1.7	0.00
Malignant tumor of colon	0.3	0.3	0.00	0.3	0.3	0.00
Malignant tumor of lung	0.3	0.3	0.00	0.3	0.3	0.00
Malignant tumor of urinary bladder	0.2	0.3	-0.01	0.3	0.3	0.00
Primary malignant neoplasm of prostate	0.6	0.8	-0.02	0.7	0.7	0.00
Medication use						
Agents acting on the renin-angiotensin system	30.8	33.0	-0.05	31.4	31.4	0.00
Antibacterials for systemic use	36.1	38.8	-0.06	36.8	36.6	0.00
Antidepressants	34.5	35.7	-0.03	34.7	34.8	0.00
Antiepileptics	24.0	26.4	-0.05	24.5	24.6	0.00
Antiinflammatory and antirheumatic products	41.0	45.2	-0.08	42.0	41.9	0.00
Antineoplastic agents	31.6	38.0	-0.14	33.3	33.4	0.00
Antipsoriatics	0.7	1.0	-0.03	0.8	0.9	-0.01
Antithrombotic agents	12.9	12.8	0.00	12.9	12.9	0.00
Beta blocking agents	23.1	24.1	-0.02	23.3	23.5	0.00
Calcium channel blockers	17.1	17.1	0.00	17.1	17.1	0.00
Diuretics	28.1	28.8	-0.02	28.3	28.3	0.00
Drugs for acid related disorders	35.3	37.5	-0.04	35.8	35.8	0.00
Drugs for obstructive airway diseases	29.0	31.0	-0.04	29.5	29.5	0.00
Drugs used in diabetes	14.0	15.4	-0.04	14.3	14.6	-0.01
Immunosuppressants	41.9	53.4	-0.23	44.7	44.7	0.00
Lipid modifying agents	29.0	31.5	-0.05	29.6	29.8	-0.01
Opioids	34.8	37.8	-0.06	35.4	35.5	0.00
Psycholeptics	29.5	30.8	-0.03	29.7	29.9	0.00

Psychostimulants, agents used for adhd and nootropics	4.5	4.8	-0.01	4.5	4.6	0.00

7.10. OptumEHR

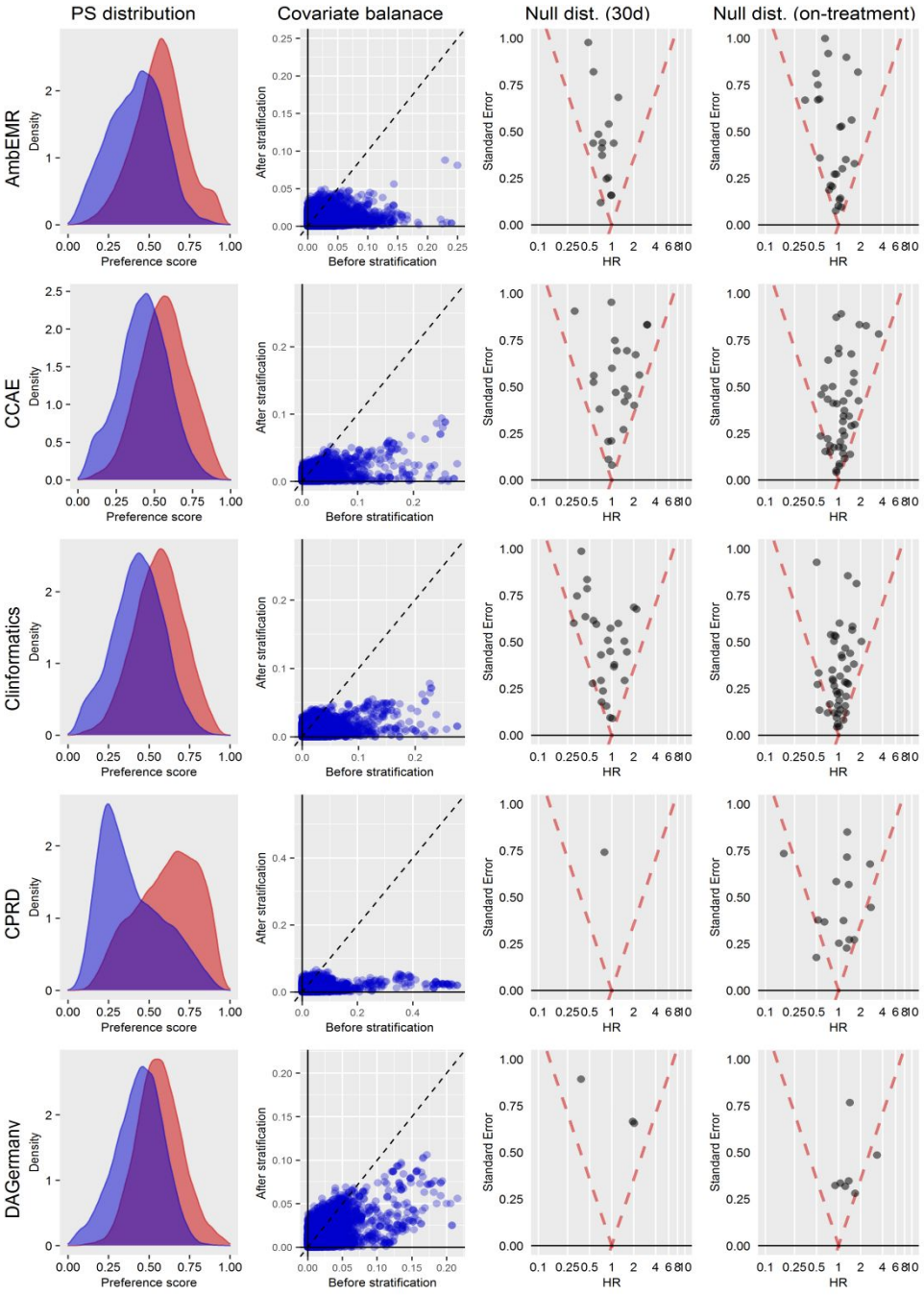
	Before PS stratification			After PS stratification		
	HCQ	SSZ		HCQ	SSZ	
Characteristic	**%**	**%**	**Std. diff**	**%**	**%**	**Std. diff**
Age group						
15-19	0.2	0.2	-0.01	0.2	0.2	-0.01
20-24	1.0	1.0	0.00	1.0	1.0	0.00
25-29	1.8	1.9	-0.01	1.8	1.9	-0.01
30-34	3.1	3.1	0.00	3.1	3.0	0.00
35-39	4.2	4.5	-0.02	4.2	4.2	0.00
40-44	5.9	5.7	0.01	5.9	5.5	0.02
45-49	7.9	8.3	-0.01	7.9	7.9	0.00
50-54	11.5	11.7	-0.01	11.6	11.4	0.00
55-59	13.8	14.8	-0.03	14.0	14.2	-0.01
60-64	13.3	13.9	-0.02	13.5	13.5	0.00
65-69	12.1	12.6	-0.02	12.2	12.6	-0.01
70-74	10.0	9.7	0.01	10.0	9.9	0.00
75-79	8.1	7.0	0.04	7.9	7.9	0.00
80-84	5.4	4.3	0.06	5.2	5.3	0.00
85-89	1.5	1.2	0.03	1.5	1.4	0.01
Gender: female	79.9	72.4	0.18	78.2	78.5	-0.01
Race						
race = Asian	1.5	1.1	0.04	1.5	1.4	0.01
race = Black or African American	10.0	8.6	0.05	9.8	9.5	0.01
race = White	81.4	83.3	-0.05	81.7	82.0	-0.01
Ethnicity						
ethnicity = Hispanic or Latino	5.3	6.0	-0.03	5.4	5.4	0.00
Medical history: General						
Acute respiratory disease	17.8	18.6	-0.02	17.9	17.8	0.00
Attention deficit hyperactivity disorder	0.9	0.8	0.01	0.9	0.8	0.01
Chronic liver disease	2.7	3.0	-0.02	2.8	2.9	0.00
Chronic obstructive lung disease	8.5	9.2	-0.03	8.7	8.9	-0.01
Crohn's disease	0.5	1.7	-0.12	0.6	1.0	-0.04
Dementia	1.1	1.0	0.01	1.0	1.1	-0.01
Depressive disorder	15.7	15.5	0.00	15.6	15.4	0.00
Diabetes mellitus	14.9	15.1	-0.01	15.0	15.2	0.00
Gastroesophageal reflux disease	18.3	18.3	0.00	18.3	18.0	0.01
Gastrointestinal hemorrhage	2.1	2.5	-0.02	2.1	2.2	0.00
Human immunodeficiency virus infection	0.1	0.2	-0.01	0.1	0.2	-0.01
Hyperlipidemia	30.3	31.5	-0.03	30.5	30.4	0.00
Hypertensive disorder	38.8	39.0	0.00	38.8	39.1	-0.01
Lesion of liver	1.1	0.9	0.02	1.0	1.0	0.01
Lupus erythematosus	1.0	0.3	0.09	0.9	0.5	0.04
Obesity	11.3	12.3	-0.03	11.4	11.7	-0.01
Osteoarthritis	35.0	36.8	-0.04	35.3	35.4	0.00
Pneumonia	4.9	5.1	-0.01	5.0	4.9	0.00
Psoriasis	1.7	4.6	-0.17	2.0	2.7	-0.04
Renal impairment	7.6	6.9	0.03	7.4	7.5	0.00
Rheumatoid arthritis	84.8	84.8	0.00	84.9	85.1	-0.01
Schizophrenia	0.2	0.1	0.01	0.2	0.2	0.00
Ulcerative colitis	0.4	1.5	-0.12	0.5	0.8	-0.04
Urinary tract infectious disease	7.5	6.4	0.04	7.3	7.0	0.01
Viral hepatitis C	1.2	1.5	-0.02	1.3	1.4	-0.01
Visual system disorder	13.7	13.9	0.00	13.7	13.3	0.01
Medical history: Cardiovascular disease						
Atrial fibrillation	4.5	4.0	0.03	4.5	4.5	0.00
Cerebrovascular disease	3.1	3.1	0.00	3.1	3.0	0.00
Coronary arteriosclerosis	8.3	8.5	-0.01	8.3	8.4	0.00
Heart disease	20.8	20.4	0.01	20.7	21.1	-0.01
Heart failure	4.7	4.4	0.01	4.7	4.8	-0.01
Ischemic heart disease	4.4	4.5	-0.01	4.4	4.4	0.00
Peripheral vascular disease	2.6	2.4	0.01	2.6	2.4	0.01
Pulmonary embolism	1.0	1.1	-0.01	1.0	1.0	-0.01
Venous thrombosis	1.9	2.0	-0.01	1.9	2.0	-0.01
Medical history: Neoplasms						
Hematologic neoplasm	1.1	1.2	-0.01	1.1	1.2	0.00
Malignant lymphoma	0.6	0.7	-0.01	0.6	0.7	-0.01
Malignant neoplasm of anorectum	0.2	0.2	0.01	0.2	0.2	0.01
Malignant neoplastic disease	8.5	8.8	-0.01	8.5	8.7	-0.01
Malignant tumor of breast	1.9	1.7	0.02	1.9	1.9	0.00
Malignant tumor of colon	0.4	0.4	0.00	0.4	0.4	0.00
Malignant tumor of lung	0.4	0.4	-0.01	0.4	0.4	-0.01
Malignant tumor of urinary bladder	0.2	0.4	-0.03	0.2	0.3	-0.02
Primary malignant neoplasm of prostate	0.6	0.9	-0.03	0.7	0.7	0.00
Medication use						
Agents acting on the renin-angiotensin system	30.5	31.8	-0.03	30.8	31.3	-0.01
Antibacterials for systemic use	28.0	30.2	-0.05	28.3	28.1	0.00
Antidepressants	35.9	35.9	0.00	35.9	36.1	-0.01
Antiepileptics	23.9	25.0	-0.03	24.2	24.4	-0.01
Antiinflammatory and antirheumatic products	43.8	47.3	-0.07	44.5	44.3	0.00
Antineoplastic agents	34.7	37.3	-0.05	35.4	36.6	-0.03
Antipsoriatics	0.6	0.7	-0.01	0.6	0.6	0.00
Antithrombotic agents	32.9	31.7	0.03	32.7	33.1	-0.01
Beta blocking agents	26.7	27.1	-0.01	26.8	27.3	-0.01
Calcium channel blockers	17.1	16.8	0.01	17.1	17.4	-0.01
Diuretics	29.2	28.5	0.02	29.1	29.2	0.00
Drugs for acid related disorders	45.1	45.7	-0.01	45.2	45.4	0.00

Drugs for obstructive airway diseases	34.5	35.5	-0.02	34.7	34.8	0.00
Drugs used in diabetes	15.1	15.9	-0.02	15.3	15.8	-0.02
Immunosuppressants	47.4	55.7	-0.17	49.2	50.3	-0.02
Lipid modifying agents	30.2	31.9	-0.04	30.6	30.9	-0.01
Opioids	39.3	41.5	-0.04	39.7	40.1	-0.01
Psycholeptics	35.1	35.4	-0.01	35.1	35.2	0.00
Psychostimulants, agents used for adhd and nootropics	4.3	4.1	0.01	4.2	4.0	0.01

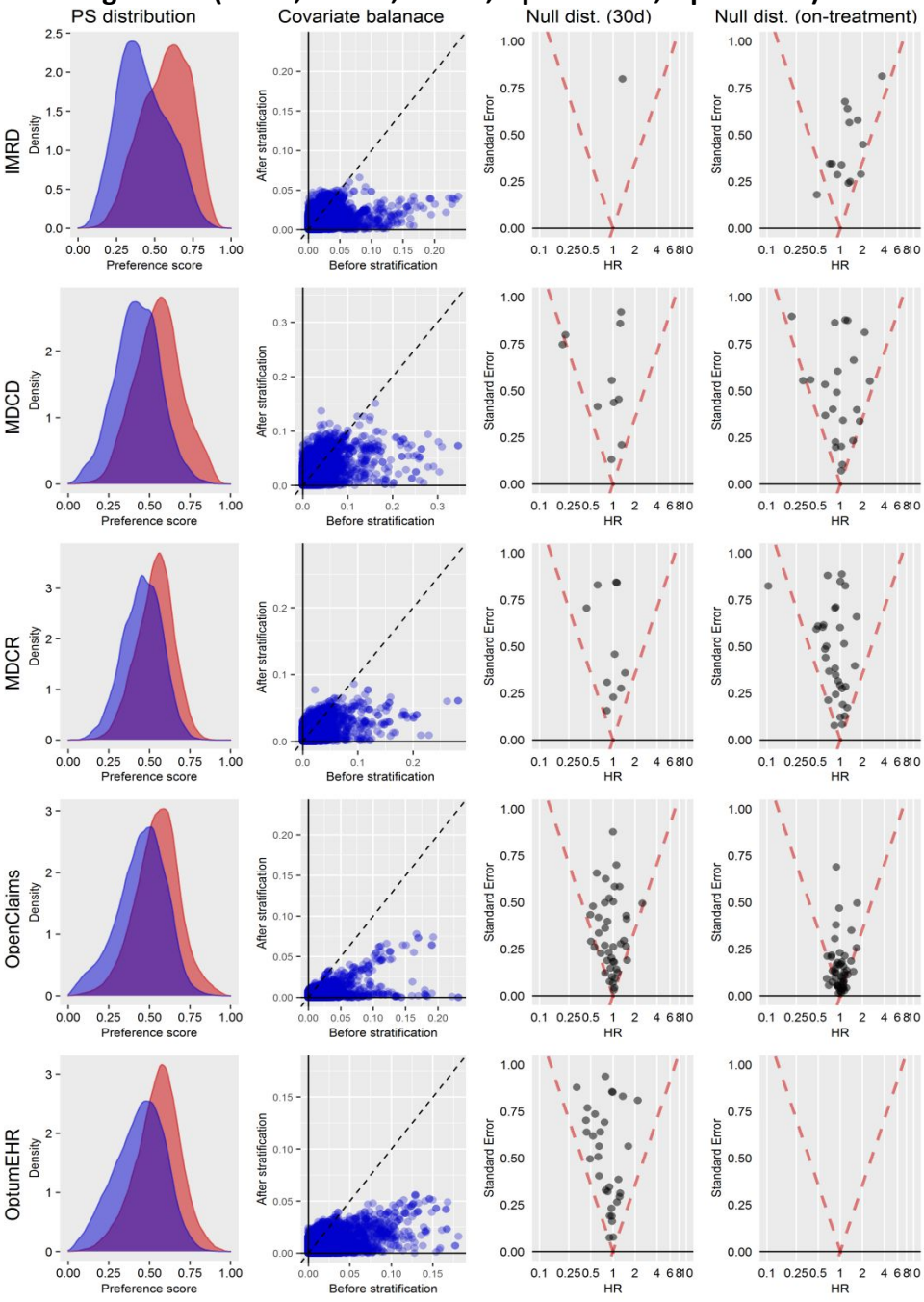
8. Study diagnostics

Preference score overlap, covariate balance, and empirical calibration plots are reported below. The preference score is a transformation of the propensity score that adjusts for differences in the sizes of the two exposure cohorts in a pairwise comparison. A higher overlap indicates patients in the two cohorts were more similar in terms of their predicted probability of receiving one exposure relative to the other. In the covariate balance plots, each dot represents the standardizes difference of means for a single covariate before and after propensity score stratification. The empirical calibration plots show effect estimates for the negative controls where the true hazard ratio is expected to equal 1. Estimates below the diagonal dashed lines are statistically significantly different (alpha = 0.05) from the true effect size. A well-calibrated estimator should produce the true effect sizes within the 95 percent confidence interval 95 percent of the time. Negative control estimates are not reported if fewer than 5 events are observed. *On-treatment* time-at-risk was unavailable in the OptumEHR databases so no negative control effects were estimated.

8.1. Diagnostics (AmbEMR, CCAE, Clinformatics, CPRD, DAGermany)



8.2. Diagnostics (IMRD, MDCD, MDCR, OpenClaims, OptumEHR)



9. Incidence rates

Patient counts, event counts, and incidence rates per 1,000 person-years are reported below for HCQ vs SSZ during the two follow-up periods. Note that the incidence rate does not account for stratification.

9.1. 30-day follow-up

		Patients		TAR		Events		IR		
Outcome	Database	T	C	T	C	T	C	T	C	MDRR
Depression	AmbEMR	55,793	15,092	4,571	1,237	155	29	33.91	23.44	1.66
	CCAE	66,440	22,449	5,395	1,822	79	28	14.64	15.36	1.87
	Clinformatics	51,676	16,812	4,190	1,362	84	41	20.05	30.09	1.79
	CPRD	9,160	11,348	749	930	<5	8	<6.67	8.60	>4.77
	DAGermany	3,937	5,109	322	419	<5	12	<15.48	28.63	>3.94
	IMRD	8,844	8,456	723	692	<5	6	<6.91	8.67	>5.42
	MDCD	7,950	2,286	647	185	14	6	21.61	32.29	4.50
	MDCR	15,735	5,275	1,282	429	13	6	10.14	13.98	4.40
	OpenClaims	620,081	183,312	50,893	15,046	654	161	12.85	10.70	1.26
	OptumEHR	78,528	20,244	6,348	1,637	321	66	50.56	40.30	1.42
	Meta-analysis	918,144	290,383	75,126	23,764	<1,335	363	<17.77	15.28	>1.17
Suicide and suicidal ideation	CCAE	66,533	22,471	5,405	1,825	12	<5	2.22	<2.74	>11.44
	Clinformatics	51,807	16,843	4,203	1,366	12	<5	2.85	<3.66	>11.72
	CPRD	9,167	11,358	750	931	<5	<5	<6.66	<5.37	>Inf
	IMRD	8,852	8,460	723	692	<5	<5	<6.91	<7.22	>Inf
	MDCD	7,980	2,296	650	186	<5	<5	<7.68	<26.78	>Inf
	OpenClaims	621,067	183,550	50,999	15,072	34	8	0.67	0.53	2.80
	OptumEHR	79,903	20,480	6,474	1,659	18	8	2.78	4.82	3.91
	Meta-analysis	845,309	265,458	69,208	21,734	<91	<41	<1.31	<1.89	>2.53
Hospitalization for psychosis	OpenClaims	620,964	183,527	50,988	15,069	95	27	1.86	1.79	1.83
	OptumEHR	79,994	20,508	6,482	1,661	<5	<5	<0.77	<3.01	>Inf
	Meta-analysis	700,958	204,035	57,470	16,731	<100	<32	<1.74	<1.91	>2.25

9.2. On-treatment follow-up

		Patients		TAR		Events		IR		
Outcome	Database	T	C	T	C	T	C	T	C	MDRR
Depression	AmbEMR	55,793	15,092	18,043	5,579	320	80	17.74	14.34	1.41
	CCAE	66,440	22,449	65,249	14,578	557	137	8.54	9.40	1.28
	Clinformatics	51,676	16,812	52,863	11,866	657	178	12.43	15.00	1.25
	CPRD	9,160	11,348	18,063	26,115	36	94	1.99	3.60	1.64
	DAGermany	3,937	5,109	2,585	3,561	40	70	15.47	19.66	1.71
	IMRD	8,844	8,456	17,274	18,765	38	51	2.20	2.72	1.81
	MDCD	7,950	2,286	5,691	1,284	90	13	15.81	10.12	1.94
	MDCR	15,735	5,275	18,059	4,098	97	38	5.37	9.27	1.74
	OpenClaims	620,081	183,312	859,978	171,406	4,810	957	5.59	5.58	1.09
	Meta-analysis	839,616	270,139	1,057,807	257,256	6,645	1,618	6.28	6.29	1.07
Suicide and suicidal ideation	AmbEMR	57,660	15,357	18,837	5,704	6	<5	0.32	<0.88	>967.23
	CCAE	66,533	22,471	65,931	14,687	81	28	1.23	1.91	1.85
	Clinformatics	51,807	16,843	53,786	11,999	97	30	1.80	2.50	1.78
	CPRD	9,167	11,358	18,127	26,379	7	9	0.39	0.34	4.09
	IMRD	8,852	8,460	17,362	18,928	8	6	0.46	0.32	4.47
	MDCD	7,980	2,296	5,764	1,278	56	18	9.71	14.08	2.19
	MDCR	15,752	5,278	18,168	4,125	15	6	0.83	1.45	4.10
	OpenClaims	621,067	183,550	869,744	172,782	321	89	0.37	0.52	1.39
	Meta-analysis	838,818	265,613	1,067,722	255,886	591	<191	0.55	<0.75	>1.39
Hospitalization for psychosis	OpenClaims	620,964	183,527	868,568	172,595	1,108	221	1.28	1.28	1.20

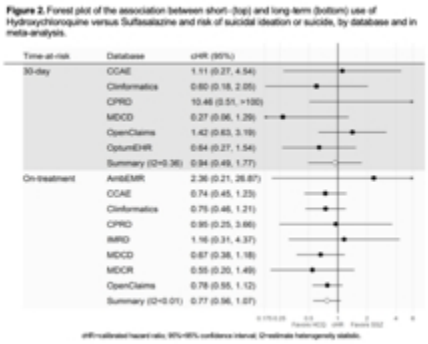
STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	supp
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	supplementary
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.



Forest plot of the association between short- (top) and long-term (bottom) use of HCQ (vs SSZ) and risk of depression, by database and in meta-analysis.

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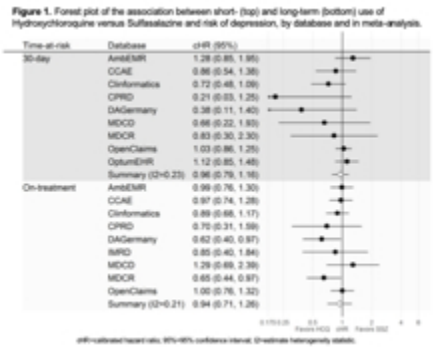

Forest plot of the association between short- (top) and long-term (bottom) use HCQ (vs SSZ) and risk of suicidal ideation or suicide, by database and in meta-analysis.

150x84mm (54 x 54 DPI)

Risk of depression, suicide and psychosis with hydroxychloroquine treatment for rheumatoid arthritis: a multi-national network cohort study

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Word count: max 3000

Keywords: hydroxychloroquine, safety, epidemiology, rheumatoid arthritis, psychosis, depression

KEY MESSAGES

- This is the largest study on the neuro-psychiatric safety of hydroxychloroquine, including >900,000 users internationally
- We found no association between hydroxychloroquine treatment for RA and depression, suicide or psychosis compared to sulfasalazine.
- These findings do not support stopping hydroxychloroquine for RA based on concerns raised in COVID-19 patients.

ABSTRACT

Objectives Concern has been raised in the rheumatological community regarding recent regulatory warnings that hydroxychloroquine used in the COVID-19 pandemic could cause acute psychiatric events. We aimed to study whether there is risk of incident depression, suicidal ideation, or psychosis associated with hydroxychloroquine as used for rheumatoid arthritis (RA).

Methods New user cohort study using claims and electronic medical records from 10 sources and 3 countries (Germany, UK and US). RA patients aged 18+ and initiating hydroxychloroquine were compared to those initiating sulfasalazine (active comparator) and followed up in the short (30-day) and long term (on treatment). Study outcomes included depression, suicide/suicidal ideation, and hospitalization for psychosis. Propensity score stratification and calibration using negative control outcomes were used to address confounding. Cox models were fitted to estimate database-specific calibrated hazard ratios (HR), with estimates pooled where I^2<40%.

Results 918,144 and 290,383 users of hydroxychloroquine and sulfasalazine, respectively, were included. No consistent risk of psychiatric events was observed with short-term hydroxychloroquine (compared to sulfasalazine) use, with meta-analytic HRs of 0.96 [0.79-1.16] for depression, 0.94 [0.49-1.77] for suicide/suicidal ideation, and 1.03 [0.66-1.60] for psychosis. No consistent long-term risk was seen, with meta-analytic HRs 0.94 [0.71-1.26] for depression, 0.77 [0.56-1.07] for suicide/suicidal ideation, and 0.99 [0.72-1.35] for psychosis.

Conclusion Hydroxychloroquine as used to treat RA does not appear to increase the risk of depression, suicide/suicidal ideation, or psychosis compared to sulfasalazine. No effects were seen in the short or long term. Use at higher dose or for different indications needs further investigation.

TRIAL REGISTRATION Registered with EU PAS; Reference number EUPAS34497 (http://www.encepp.eu/encepp/viewResource.htm?id=34498). The full study protocol and analysis source code can be found at https://github.com/ohdsi-studies/Covid19EstimationHydroxychloroquine.

INTRODUCTION

Hydroxychloroquine (HCQ) has received much scientific and public attention during the COVID-19 pandemic as a leading therapeutic and prophylactic target. [1, 2] Commonly used for autoimmune disorders (e.g., systemic lupus erythematosus) and inflammatory arthritis, HCQ was released for emergency use for COVID-19 due to its postulated antiviral efficacy in cellular studies.[3-9] HCQ is currently being used in over 217 registered ongoing clinical trials for the treatment of SARS-Cov-2 as of 12th June 2020.[10, 11] Results to date have been conflicting, with emerging data suggesting a lack of clinical efficacy against COVID-19.[12-18] Case report literature suggests that chloroquine, the compound from which HCQ was derived, is associated with neurological and psychiatric side effects when used as an anti-malarial treatment or prophylaxis.[19] Similar, potential side effects have been described in the use of HCQ include neuropsychiatric side effects such as psychosis, depression, and suicidal behaviour.[20-22] Regulatory authorities have received reports of new onset psychiatric symptoms associated with the increased use of high dose HCQ during the pandemic.[23] Whilst Chloroquine and HCQ have multiple mechanisms of action, a major action is the disruption of lysosomal functioning and autophagy.[24] These actions to some degree mimic lysosomal storage diseases, disorders that are characterised by neurodevelopmental delay and neurodegeneration when manifested in the more common form in childhood, but also associated with neuropsychiatric manifestation in adulthood.[25, 26]

New reports of serious side effects associated with HCQ used in COVID-19 are concerning to the rheumatology community, leading to confusion and anxiety for patients who are taking HCQ for autoimmune conditions. Given the previous reports of neuropsychiatric symptoms with HCQ, together with a plausible mechanism for such phenomena, we performed a review of the literature to determine what was already known about the potential risks of psychosis, depression, and suicide associated with HCQ use from literature database inception until 14/05/2020 (Supplementary Appendix Section 1). Interrogation of adverse event registers have identified potential associations between HCQ and psychiatric disorders.[11] Case reports and case series describing new onset psychosis, bipolar disorder, seizures and depression associated with HCQ and chloroquine use for rheumatological disorders and malaria prophylaxis can be found as early as 1964.[20, 27-35] No clinical trial or observational study was found that had investigated the incidence of new onset neuropsychiatric symptoms associated with HCQ use.

Considering the wide-scale use of HCQ in rheumatology, we therefore aimed to determine if there is an association between incident HCQ use for rheumatoid arthritis (RA) (the most common indication for the drug) and the onset of acute psychiatric events, including depression, suicide, and psychosis compared to sulfasalazine.

METHODS

Study design

A new user cohort, active-comparator design was used, as recommended by methodological guidelines for observational drug safety research.[36] The study protocol is registered in the EU PAS Register as EUPAS34497.[37]

Sulfasalazine (SSZ) was used as the active comparator for HCQ, as both SSZ and HCQ are second line csDMARDs used in addition to or instead of methotrexate. Whilst it is acknowledged that the drugs are not exactly equivalent, SSZ was felt to be the closest possible drug to HCQ in a RA cohort. Aware that there are other rheumatological indications for using HCQ such as systemic lupus erythematosus (SLE), we designed the study to include propensity score (PS) stratification and matching to prevent confounding. We used a set of diagnostic tools to check the propensity score adjustments in each data set for any imbalances that may have remained despite stratification, and also used negative control outcomes to identify if unobserved confounding had occurred. Analyses were not completed and are not reported if imbalance remained despite PS stratification, or there appeared to be a large proportion of negative control outcomes occurred outside our level of tolerance. All of these diagnostic tools were assessed whilst results were blinded, and can be freely reviewed online. Further details are given in the statistical analysis section.

Commented [JL1]: New paragraph added here to explain the use of SSZ as the active comparator to address reviewer 2 point 1

Data sources

Electronic health records (EHR) and administrative claims data from the UK and US were used, previously mapped to the Observational Medical Outcomes Partnership (OMOP) common data model (CDM). The study period covered from September 2000 until the latest data available at the time of extraction in each database. Data from 10 data sources were analysed in a federated manner using a distributed network strategy in collaboration with the Observational Health Data Science and Informatics (OHDSI) and European Health Data and Evidence Network (EHDEN) communities. The data used included primary care electronic medical records from the UK (Clinical Practice Research Datalink, CPRD; and IQVIA Medical Research Data, IMRD); specialist ambulatory care electronic health records from Germany (IQVIA Database Analyzer Germany; DAGermany); electronic health records in a sample of US inpatient and outpatient facilities the Optum® de-identified Electronic Health Record dataset (Optum EHR, and IQVIA US Ambulatory EMR;AmbEMR); and US claims data from the IBM MarketScan® Commercial Claims Database (CCAE), Optum® de-identified Clinformatics® Data Mart Database-Date of Death (Clinformatics), IBM MarketScan® Medicare Supplemental Database (MDCR), IBM MarketScan® Multi-State Medicaid Database (MDCD), and IQVIA OpenClaims (OpenClaims). In addition, data were obtained and analysed from electronic primary care data from the Netherlands (IPCI database) and Spain (SIDIAP), and from Japanese claims (JMDC) but none of these analyses were deemed appropriate due to low/no event counts in at least one of the cohorts. A more detailed description of all these data sources is available in Appendix Section 2.

Follow-up

Participants were followed up from the date of initiation (first dispensing or prescription) of HCQ or sulfasalazine (SSZ) (index date) as described in detail in Appendix Section 3.1. Sulfasalazine was proposed as an active comparator as it shares a similar indication as a second-line conventional synthetic DMARD for RA. Two different follow-up periods were pre-specified to look at short- and long-term effects, respectively. First, a fixed 30-day time window from index date was used to study short-term effects, where follow-up included from day 1 post-index until the earliest of: loss to follow-up/death, outcome of interest, or 30 days from therapy initiation, regardless of compliance/persistence with the study drug/s. Second, in a long-term (on treatment) analysis, follow-up went from day 1 post-index until the earliest of: therapy discontinuation (with a 14-day additional washout), outcome of interest, or loss to follow-up/death. Continued treatment episodes

were constructed based on dispensing/prescription records, with a 90-day refill gap allowed to account for stockpiling.

Participants

All subjects registered in any of the contributing data sources for at least 365 days prior to index date, aged 18 years or older, with a history of RA (as defined by a recorded diagnosis any time before or on the same day as therapy initiation), and starting either HCQ or SSZ during the study period, were included.

Potential participant counts and age-, sex- and calendar year-specific incidence per database were produced for transparency and reviewed to check for data inconsistencies and face validity, and are available for inspection at https://data.ohdsi.org/Covid19CohortEvaluationExposures/, labelled as "New users of hydroxychloroquine with previous rheumatoid arthritis" and "New users of sulfasalazine with previous rheumatoid arthritis".

Outcomes and confounders

Code lists for the identification of the study population, for the study exposures and for the relevant outcomes were created by clinicians with experience in the management of RA and by clinical epidemiologists using ATLAS, an open science analytics platform that provides a unified interface for researchers to work within.[38] Exposures and outcomes were reviewed by experts in OMOP vocabulary and in the use of the proposed data sources. A total of three outcomes were analysed: depression, suicide or suicidal ideation, and hospital admission for psychosis. Detailed outcome definitions with links to code lists are fully detailed in Appendix Section 3.2.[39]

[40] Cohort counts for each of the outcomes in the entire source database, and age-sex and calendar-time specific incidence rates were explored for each of the contributing databases, and reviewed to check for data inconsistencies and face validity. These are available for inspection at https://data.ohdsi.org/Covid19CohortEvaluationSafetyOutcomes/

A list of negative control outcomes was generated for which there is no biologically plausible or known causal relationship with the use of HCQ or SSZ. These outcomes were identified based on previous literature, clinical knowledge (reviewed by two clinicians), product labels, and spontaneous reports, and confirmed by manual review by two clinicians.[41] The full list of codes used to identify negative control outcomes can be found in Appendix Section 4.

Statistical methods

All analytical source code is available for inspection and reproducibility at https://github.com/ohdsi-studies/Covid19EstimationHydroxychloroquine2. All study diagnostics and the steps described below are available for review at https://data.ohdsi.org/Covid19EstimationHydroxychloroquine2/.

The following steps were followed for each analysis:

1.Propensity score estimation

Propensity score (PS) stratification was used to minimise confounding. All baseline characteristics recorded in the participants' records/health claims were constructed for inclusion as potential confounders (including demographics, past medical history, procedures and medication prescription within 30 and within 365 days prior to drug initiation). Covariate construction details are available in Appendix Section 5. Lasso regression models were fitted to estimate propensity scores (PS) as the probability of hydroxychloroquine versus sulfasalazine use based on patient demographics and medical history including previous conditions, procedures, healthcare resource use, and treatments. The balance of known characteristics that could cause of potential confounding were then reviewed whilst the results were blinded in order to determine if a dataset was able to contribute to the meta-analysis. This was undertaken in two ways. Firstly, using the PS scores themselves and the standardised difference between the scores prior to and after PS stratification to determine if the cohorts of SSZ and HCQ users are imbalanced. Secondly by looking at the propensity score model

pictorially in a graph to see if the populations appear to 'overlap' in their characteristics. The full resulting PS models are available for inspection by clicking on 'Propensity model' and 'Propensity scores' after selecting a database in the results app.

Commented [JL2]: Added explanation of PS stratification to address reviewer 1 point 2

2.Study diagnostics

Study diagnostics were explored for each database-specific analysis before progressing to outcome modelling, and included checks for power, observed confounding, and potential residual (unobserved) confounding. Only database-outcome analyses that passed all diagnostics below were then conducted and reported, with all others marked as 'NA' in the accompanying results app.

Positivity and power were assessed by looking at the number of participants in each treatment arm, and the number with the outcome (see the 'Power' tab after clicking on a database in the results app). Small cell counts less than five (and resulting estimates) are reported as "<5" to minimise risk of secondary disclosure of data with patient identification. PS overlap was also plotted to visualize positivity issues and can be seen by clicking on 'Propensity Scores'.

Observed confounding was explored by plotting standardized differences before (X axis) vs after (Y) PS stratification, with standardized differences > 0.1 in the Y axis indicating the presence of unresolved confounding see by clicking on 'Covariate balance' in the results app. [36]

Finally, negative control outcome analyses were assessed to identify systematic error due to residual (unobserved) confounding. The results for these are available in the 'Systematic error' tab of the results app. The resulting information was used to calibrate the outcome models using empirical calibration. [37, 38]

3.Outcome modelling

Cox proportional hazards models conditioned on the PS strata were fitted to estimate Hazard Ratios (HR) for each psychological outcome in new users of HCQ (vs SSZ). Empirical calibration based on the previously described negative control outcomes was used to minimise any potential residual confounding with calibrated HRs and 95% confidence intervals (CI) estimated.[42, 43] All analyses were conducted for each database separately, with estimates combined in random-effects meta-analysis methods where I^2 ≤40%.[44] The standard errors of the database-specific estimates were adjusted to incorporate estimate variation across databases, where the across-database variance was estimated by comparing each database-specific result to that of an inverse-variance, fixed-effects meta-analysis. No meta-analysis was conducted where I^2 for a given drug-outcome pair was >40%.

All analyses were conducted using the CohortMethod package, available at https://ohdsi.github.io/CohortMethod/ and the Cyclops package for PS estimation (https://ohdsi.github.io/Cyclops) [45].

Data Sharing

Open Science is a guiding principle within OHDSI. As such, we provide unfettered access to all open-source analysis tools employed in this study via https://github.com/OHDSI/, as well as all data and results artefacts that do not include patient-level health information via http://data.ohdsi.org/Covid19EstimationHydroxychloroquine2.

Data partners contributing to this study remain custodians of their individual patient-level health information and hold either IRB exemption or approval for participation.

RESULTS

A total of 918,144 HCQ and 290,383 SSZ users were identified. Participant counts in each data source are provided in Appendix Section 6. Before PS stratification, users of HCQ were (compared to SSZ users) more likely female (for example, 82.0% vs 74.3% in CCAE database) and less likely to have certain comorbidities such as Crohn's disease (0.6% vs 1.8% in CCAE) or psoriasis (3.0% vs 8.9% in CCAE). Prevalence of a past medical history of SLE was higher in HCQ users as expected (1.5% vs 0.5% in CCAE), whilst use of systemic glucocorticoids was similar (46.1% vs 47.2% in the previous month in CCAE). The prevalence of depressive disorder was similar in both groups (13.4% vs 13.5% in CCAE) and so was the history of use of antidepressants in the previous year (36.4% vs 36.4% in CCAE) which appears in keeping with the prevalence discussed in previous literature.[46] After PS stratification, prevalence of a past medical history of SLE, depressive disorder and the use of systemic glucocorticoids and antidepressants were balanced with a standard difference of less than 0.1 between HCQ and SSZ users. As these were balanced, these patients were not excluded from analyses.

Detailed baseline characteristics for the two pairs of treatment groups after PS stratification in CCAE are shown in Table 1 as an example, with balance of SLE, depression, and anti-depressant medication use included. Similar tables and a more extensive list of features provided in Appendix Section 7, and can also be searched for in the results app (click on a given dataset, then click on the population characteristics tab, raw and search for the condition or drug of interest). Study diagnostics including plots of propensity score distribution, covariate balance, and negative control estimate distributions are provided in Appendix Section 8.

Average baseline dose of HCQ was homogeneous, with >97% in CCAE using an average dose of 420mg daily, and only <3% taking an estimate dose >500 mg. All the observed differences between groups were minimised to an acceptable degree (<0.1 standardised mean differences) after propensity score stratification: in CCAE, the most imbalanced variable was use of glucocorticoids on index date, with prevalence 36.1% vs 35.8%.

Table 1. Baseline characteristics of patients with RA who are new users of hydroxychloroquine (HCQ) vs sulfasalazine (SSZ), before and after PS stratification, in the CCAE database

	Before PS stratification			After PS stratification		
	HCQ	SSZ		HCQ	SSZ	
	%	%	Std. diff	%	%	Std. diff
Socio-demographics						
Age group						
15-19	0.6	0.6	0.00	0.6	0.6	0.00
20-24	1.9	1.9	0.00	1.8	2.0	-0.01
25-29	2.6	2.6	0.00	2.5	2.8	-0.01
30-34	4.5	4.6	0.00	4.5	4.3	0.01
35-39	7.2	7.3	0.00	7.1	7.1	0.00
40-44	9.8	9.5	0.01	9.7	9.5	0.00
45-49	13.7	12.9	0.02	13.6	13.5	0.00
50-54	18.2	18.2	0.00	18.2	18.1	0.00
55-59	20.6	21.0	-0.01	20.8	20.8	0.00
60-64	19.0	19.7	-0.02	19.4	19.8	-0.01
65-69	1.8	1.7	0.01	1.8	1.6	0.01
Gender: female	82.0	74.3	0.19	80.1	79.7	0.01
Medical history						
Acute respiratory disease	35.5	34.3	0.03	35.1	34.7	0.01

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Chronic liver disease	3.2	3.2	0.00	3.2	3.4	-0.01
Chronic obstructive lung disease	4.2	4.5	-0.01	4.3	4.5	-0.01
Crohn's disease	0.6	1.8	-0.12	0.7	1.1	-0.04
Depressive disorder	13.4	13.5	0.00	13.2	13.4	-0.01
Diabetes mellitus	13.5	13.4	0.00	13.6	13.7	0.00
Hypertensive disorder	34.7	34.9	0.00	34.7	35.0	-0.01
Obesity	9.3	9.1	0.00	9.2	9.4	-0.01
Psoriasis	3.0	8.9	-0.25	3.8	5.2	-0.07
Renal impairment	3.1	2.8	0.02	3.0	2.8	0.01
Systemic Lupus Erythematosus	1.5	0.5	0.10	1.3	0.9	0.03
Schizophrenia	0.1	0.1	-0.01	0.1	0.1	-0.01
Ulcerative colitis	0.6	1.9	-0.12	0.7	1.0	-0.04
Medication use						
Agents acting on the renin-angiotensin system	24.3	24.9	-0.01	24.5	24.7	0.00
Antidepressants	36.4	36.4	0.00	36.3	36.5	0.00
Antiepileptics	20.3	21.0	-0.02	20.4	20.2	0.00
Antiinflammatory and antirheumatic products	55.3	57.3	-0.04	55.8	56.7	-0.02
Antipsoriatics	0.7	1.3	-0.06	0.7	1.0	-0.03
Antithrombotic agents	7.4	7.3	0.01	7.4	7.3	0.00
Immunosuppressants	39.6	53.1	-0.27	43.4	43.6	0.00
Opioids	38.5	40.8	-0.05	39.0	39.3	-0.01
Psycholeptics	33.6	33.7	0.00	33.4	33.3	0.00

HCQ=hydroxychloroquine; SSZ=sulfasalazine

Database-specific and overall counts and rates of the three study outcomes in the short- (30-day) and long-term ('on treatment') analyses are reported in detail in Table 2. Depression was the most common of the three study outcomes, with rates in the 'on treatment' analysis ranging from 1.99/1,000 person-years amongst HCQ users in CPRD to 17.74/1,000 amongst HCQ users in AmbEMR. Suicide/suicidal ideation was the least common outcome, with rates ranging from 0.32/1,000 (HCQ users in AmbEMR and SSZ users in IMRD) to 14.08/1,000 in SSZ users in MDCD. Database-specific counts and incidence rates (IR) for all three outcomes stratified by drug use are detailed in full in Appendix Section 9.

30-day follow up								On-treatment follow up					
		Patients		Events		IR (/1,000 py		Patients		Events		IR (/1,000 py	
Outcome	Database	T	C	T	C	T	C	T	C	T	C	T	C
Depression	AmbEMR	55,793	15,092	155	29	33.91	23.44	55,793	15,092	320	80	17.74	14.34
	CCAE	66,440	22,449	79	28	14.64	15.36	66,440	22,449	557	137	8.54	9.40
	Clinformatics	51,676	16,812	84	41	20.05	30.09	51,676	16,812	657	178	12.43	15.00
	CPRD	9,160	11,348	<5	8	<6.67	8.60	9,160	11,348	36	94	1.99	3.60
	DAGermany	3,937	5,109	<5	12	<15.48	28.63	3,937	5,109	40	70	15.47	19.66
	IMRD	8,844	8,456	<5	6	<6.91	8.67	8,844	8,456	38	51	2.20	2.72
	MDCD	7,950	2,286	14	6	21.61	32.29	7,950	2,286	90	13	15.81	10.12
	MDCR	15,735	5,275	13	6	10.14	13.98	15,735	5,275	97	38	5.37	9.27
	OpenClaims	620,081	183,312	654	161	12.85	10.70	620,081	183,312	4,810	957	5.59	5.58
	OptumEHR	78,528	20,244	321	66	50.56	40.30	NA	NA	NA	NA	NA	NA
	Meta-analysis	918,144	290,383	<1,335	363	<17.77	15.28	839,616	270,139	6,645	1,618	6.28	6.29
Suicide and suicidal ideation	AmbEMR	NA	NA	NA	NA	NA	NA	57,660	15,357	6	<5	0.32	<0.88
	CCAE	66,533	22,471	12	<5	2.22	<2.74	66,533	22,471	81	28	1.23	1.91
	Clinformatics	51,807	16,843	12	<5	2.85	<3.66	51,807	16,843	97	30	1.80	2.50
	CPRD	9,167	11,358	<5	<5	<6.66	<5.37	9,167	11,358	7	9	0.39	0.34
	IMRD	8,852	8,460	<5	<5	<6.91	<7.22	8,852	8,460	8	6	0.46	0.32
	MDCD	7,980	2,296	<5	<5	<7.68	<26.78	7,980	2,296	56	18	9.71	14.08
	MDCR	NA	NA	NA	NA	NA	NA	15,752	5,278	15	6	0.83	1.45
	OpenClaims	621,067	183,550	34	8	0.67	0.53	621,067	183,550	321	89	0.37	0.52
	OptumEHR	79,903	20,480	18	8	2.78	4.82	NA	NA	NA	NA	NA	NA
	Meta-analysis	845,309	265,458	<91	<41	<1.31	<1.89	838,818	265,613	591	<191	0.55	<0.75
Hospitalization for psychosis	OpenClaims	620,964	183,527	95	27	1.86	1.79	620,964	183,527	1,108	221	1.28	1.28
	OptumEHR	79,994	20,508	<5	<5	<0.77	<3.01	NA	NA	NA	NA	NA	NA
	Meta-analysis	700,958	204,035	<100	<32	<1.74	<1.91	NA	NA	NA	NA	NA	NA

T=target therapy; C=comparator therapy; IR=incidence rate; py=person-years at risk; NA=non-applicable (not reported because of failed diagnostics or on-treatment follow-up unavailable); HCQ=hydroxychloroquine; SSZ=sulfasalazine; AmbEMR=IQVIA Ambulatory EMR; CCAE=IBM Commercial Database; Clinformatics=Optum de-identified Clinformatics Data Mart Database; CPRD=Clinical Practice Research Datalink; DAGermany=IQVIA Disease Analyzer Germany; IMRD=IQVIA UK Integrated Medical Record Data; MDCD=IBM IBM Multi-state Medicaid; MDCR=IBM Medicare Supplemental Database; OpenClaims=IQVIA Open Claims; OptumEHR=Optum de-identified Electronic Health Record dataset

Table 2. Patient counts, event counts and incidence rates (IR) (/1,000 person years) of key events according to drug use

9 datasets passed cohort diagnostics and contained sufficiently robust data for inclusion into the short term analyses for depression; 6 passed for suicide and 2 passed for psychosis. A small imbalance with the incidence of a past medical history of SLE was seen in MDCD and with cutaneous lupus in DAGermany. As a result, we excluded both from the psychosis outcome but not for depression as we did not consider this was a confounder. Short-term (30-day) analyses showed no consistent association between HCQ use and the risk of depression, with database-specific HRs ranging from 0.21 [95%CI 0.03-1.25] in CPRD to 1.28 [0.85-1.95] in AmbEMR, and a meta-analytic HR of 0.96 [0.79-1.16] (See Figure 1, top). On-treatment analyses showed similar findings, with database-specific HRs from 0.62 [0.40-0.97] in DAGermany to 1.29 [0.69-2.39] in MDCD, and a meta-analytic HR of 0.94 [0.71-1.26] (Figure 1, bottom plot). Note only databases passing diagnostics are included within the plot and meta-analysis.

Similarly, no association was seen between the use of HCQ and the risk of suicidal ideation or suicide. In the short-term, HRs ranged from 0.27 [0.06-1.29] in MDCD to 10.46 [0.51-216.29] in CPRD, with meta-analytic HR of 0.94 [0.49-1.77] (Figure 2, top). Long-term effects were similar, with HRs ranging between 0.55 [0.20-1.49] in MDCR and 2.36 [0.21-26.87] in AmbEMR, and meta-analytic HR of 0.77 [0.56- 1.07] (Figure 2, bottom).

Finally, no association was seen between the use of HCQ (compared to SSZ) and the risk of acute psychosis. Short-term analyses showed database-specific HRs of 0.44 [0.05-3.49] in OptumEHR and 1.01 [0.65-1.58] in OpenClaims, with a meta-analytic estimated HR of 1.03 [0.66-1.60]. Only OpenClaims contributed to the 'on treatment' analysis of this event, with an estimated HR of 0.98 [0.73-1.33].

DISCUSSION

Principal findings

This large observational study shows that in routine healthcare treatment of RA, there is no association with the use of HCQ with acute psychosis, depression, or suicide as compared to SSZ. These results are seen both in the short-term and long-term risk analyses. Whilst an excess of psychiatric events have been reported during the COVID pandemic in those prescribed HCQ, this risk does not appear to be associated with HCQ prescribed in RA compared to those prescribed SSZ. This study uses data from three countries, with a variety of healthcare systems and modes of routine healthcare data included, enabling the study to produce more generalisable results.

Comparison with other studies

The bulk of the evidence prior to this study consisted of isolated case reports and case series, making it difficult to draw demographic comparisons with previous work. Sato *et al.* reported that neuropsychiatric adverse events found in the FDA adverse event reporting system associated with chloroquine use were predominantly in females in the sixth decade of life.[21] Increase in reporting of acute psychiatric disease during the COVID-19 pandemic may be multifactorial, with an increase in external stressors such as social isolation, financial uncertainty, and increased misuse of drugs and alcohol.[47-49] Considering that we find no association for HCQ use compared to SSZ with acute psychiatric outcomes in the RA population, evidence points towards external stressors being more likely involved in the aetiology of psychiatric events seen during this pandemic.

Strengths and weaknesses of the study

This study is based on new users of HCQ for RA and therefore, the results of this study are most directly relevant to the risk of neuropsychiatric side effects seen in the rheumatological population. The

regulatory warnings of possibly increased acute psychiatric events associated with HCQ warrant investigation in all available datasets to prevent harm in both rheumatological patients and those taking for emergency use, especially as very few clinical trials include acute psychiatric outcomes. Whilst the general population presenting with COVID-19 may differ from those with RA, within the context of emergency authorisation or off label use of HCQ, all available evidence must be taken into account when considering the risks associated.

Several considerations must be taken into account when interpreting these results.
Firstly, the doses used to treat RA are lower than those suggested in current clinical trials for the treatment of SARS-CoV2, and therefore adverse events seen in the treatment and prophylaxis of COVID-19 may be greater if dose dependent, as is the case with cardiac adverse effects.[50, 51] Secondly, this study could be affected by outcome misclassification. Only acute psychiatric events presenting to medical services will be captured, and this is especially important for the outcome of suicide. Suicide may not be fully recorded if patients do not reach medical care or cause-of-death information is not linked to the datasource, and therefore the true incidence of suicide may be under-recorded.[52] Similarly, this study only focused on acute psychosis and depression severe enough to be identified in medical consultation in patients with no history of either condition. Whilst we generated phenotypes that underwent full cohort diagnostics, and phenotypes were constructed using a multidisciplinary team of clinicians and bioinformaticians to ensure face validity, it should be noted that no formal validation was undertaken. We took all reasonable steps to ensure the validity of the phenotypes, whilst considering the risk-benefit tradeoff of what could be undertaken within the time frame used to respond to the serious questions raised by regulatory bodies following the HCQ use in COVID-19.
This study can highlight the association for patients without a prior history of psychosis or depression, but cannot inform of the risk of acute deterioration after beginning HCQ treatment for those already known to psychiatric services.

Thirdly, depression and hallucinations are listed as potential undesirable effects of sulfasalazine treatment, which may underestimate the true risk, if any, from HCQ.[53] However, the frequency of depression (described as changes in affect in the summary of product characteristics for HCQ) is reported to be common (≥1/100 to < 1/10) whilst for sulfasalazine depression is listed as being uncommon (≥1/1000 to < 1/100). Therefore, it is potentially reassuring for patients that we observed no difference compared to sulfasalazine for which there is a paucity of published evidence suggesting causailty.[54]

Propensity score stratification and matching, as well as a comprehensive examination of potential sources of systematic error, were undertaken prior to blinding of results to identify and reduce the risk of confounding. Baseline characteristics after PS stratification were adequately balanced; of note, the incidence of systemic lupus erythematosus (SLE) and a past medical history of depression and anti-depressant medication use was balanced between treatment groups. Identifying the balance of these conditions between treatment groups was undertaken prior to unblinding due to the potential neuropsychiatric sequelae of the SLE aside from the potential side effects of pharmacological treatment, and the increased likelihood of depression in those with prior history. This study could also be limited by the fact that patients may overlap and exist in more than one dataset within the US. The meta-analysis assumes populations to be independent, and therefore the obtained estimates may slightly underestimate variance.

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Future research

For rheumatological disorders, future work could expand into investigating the occurrence of acute psychiatric events in patients in SLE. This would enable greater understanding of whether neuropsychiatric conditions are related to disease activity or due to pharmacological treatment. Similarly, in the emergency use of HCQ in COVID-19, there is already concern about the potential heightened risk of acute psychiatric disorder due to elevated number of psychosocial stressors present during a pandemic and high dose use.[55] Future work should consider including acute psychiatric outcomes in order to differentiate between psychiatric conditions generated by the impact of a global pandemic compared to iatrogenic events due to pharmaceutical therapies used.

Meaning of the Study

Exponential growth in research into the best treatment of SARS-CoV2 infection is generating rapidly evolving evidence for the relative efficacy of pharmaceutical agents. For the rheumatological community, media attention previously surrounded HCQ as a strong forerunner of COVID-19 prophylaxis and treatment. The results of the RECOVERY trial identifying dexamethasone reduced mortality in intensive care patients has now overtaken HCQ as the leading rheumatological drug for the pandemic, but the concerns regarding HCQ safety remain for those who take the drug for conventional indications.[17, 56] Cardiovascular safety, and reports that it might lack efficacy for both treatment and prophylaxis, have halted major HCQ clinical trials.[50, 57-60] The identification of acute psychiatric events associated with HCQ use has raised the need to clarify the risk within general rheumatological use. Our study identifies no increased risk in RA patients when compared with sulfasalazine, and provides evidence to users and clinicians alike that the reports presented during the pandemic are likely to be related to further causes aside from HCQ.

FIGURE LEGENDS

Figure 1. Forest plot of the association between short- (top) and long-term (bottom) use of HCQ (vs SSZ) and risk of depression, by database and in meta-analysis.

Figure 2. Forest plot of the association between short- (top) and long-term (bottom) use HCQ (vs SSZ) and risk of suicidal ideation or suicide, by database and in meta-analysis.

FOOTNOTES

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Public and patient involvement

No patients were directly involved in setting the research question, nor in design, conduct or interpretation of the study.

Competing interests

All authors have completed the ICJME uniform disclosure form from http://www.icjme.org/conflicts-of-interest/ uploaded with this study and report:
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Ethical Approval

All data partners received IRB approval or waiver in accordance to their institutional governance guidelines.

Database	Statement
AmbEMR	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI community studies.
CCAE	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
CPRD	Approval for CPRD was provided by the Independent Scientific Advisory Committee (ISAC). This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. The protocol for this study (20_059R) was approved by the Independent Scientific Advisory Committee (ISAC).
DA Germany	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI community studies.
IMRD	The present study is filed and under review for Scientific Review Committee for institutional adjudication. Due to the public health imperative of information related to these data, approval is provided for this publication.
IPCI	The present study was approved by the Scientific and Ethical Advisory Board of the IPCI project (project number: 4/2020).
JMDC	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
MDCD	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
MDCD	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Open Claims	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI community studies.

Clinformatics	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Optum EHR	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.

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Rheumatology RHE-20-2034: Risk of depression, suicide and psychosis with hydroxychloroquine treatment for rheumatoid arthritis: a multi-national network cohort study

Dear Dr Bukhari

Thank you for your review of this study and your work to date. We have addressed the reviewer's comments in the revised manuscript, and have uploaded both a clean and marked up version for ease of review.
Please see below responses to the points raised by the reviewers:

Reviewer comments	Author response	Changes made	Page number in revised document
Reviewer 1			
This is an interesting paper presenting results on potential neuropsychiatric side effects of HCQ. The authors should be commended on making their documentation easily available and the results easier to explore using an online app	Thank you very much		
1.The resolution for the figures meant they were not readable (sufficient data are provided to understand the data presented)	Apologies for this. We have remade the figures in better resolution and uploaded them with the revised paper	New figures generated	NA
2.The propensity scoring approach appears to have balanced the data relatively well (they don't appear to unbalanced before stratification to be fair) but it would be useful to comment on this more explicitly in the methods/results	Understood- further explanation has been added	More discussion of how the propensity score model was used has been added to the study design section and results section	Pages 6-8
Reviewer 2			
This is a timely and well conducted study addressing the risk of depression, suicide and psychosis in patients with RA taking HCQ using a multi-national network cohort approach. This will be of interest (and reassuring) to both patients and clinicians, especially in view of the generalisability of the results given the large and well conducted nature of the study, for which the authors are to be commended.	Thank you very much		
1) Justification of choice of comparator- I am not sure why SSZ was selected as the active comparator-especially as this is considered an undesirable side effect of SSZ-I appreciate this would be likely to increase a null effect but the paper would benefit from a justification of this choice.	SSZ was used as an active comparator as both SSZ and HCQ are second line csDMARDs used in addition to or instead of methotrexate. They are not exactly equivalent, but SSZ is as close as we could use for an active comparator. We then used propensity score stratification and matching to minimise any confounding, and ensured that we looked through all of the diagnostics before including a dataset. Analyses were not completed (and are therefore not reported) where imbalance remained despite PS stratification, or if there appeared to be a large proportion of negative control outcomes outside of our level of tolerance for unobserved confounding. This was all undertaken whilst results were blinded, and before results were able to contribute to the meta-analysis they had to pass stringent diagnostic assessment by the core research team.	New paragraph added under heading 'study design'	Page 5
2)Patient inclusions- why were patients with SLE not excluded from analyses- especially given that the proportions were higher (as would be expected in people with SLE). Given the large populations included I cannot see a	Patients with a past medical history of SLE were not excluded as they were balanced in PS matching- apologies that this was not explicitly mentioned in the manuscript.	Further details given in results section to explain	Page 8

rationale for retaining these people in the study.	Diagnostics are available online in the shiny app for everyone to review to show the balance of patients with SLE between the cohorts. This can be seen by clicking on a given database, and then by clicking on Population Characteristics tab -> Raw, and then searching for a particular condition or drug. This shows the imbalance prior to and after propensity score (PS) stratification, and the Standard Difference is viewed there. For example if one searches 'lupus' in CPRD:		
3)People with a previous history of depression- surely these should be accounted for in analyses as a previous history of depression is likely to be associated with a future history of depression- I appreciate these were similar across the groups. Surely future work should include whether the risks of these outcomes are higher in patients with a history of depression or on anti-depressants.	Patients with a past medical history of depression were not excluded as they were balanced in PS matching- apologies that this was not explicitly discussed in the manuscript. Excluding patients with depression would have made a 'cleaner' cohort, but would have prevented us from being able to provide data on the safety of HCQ for patients with a previous depression history, which we felt was a significant proportion of the RA community. As above, the shiny app shows the balance of patients with a past medical history of depression. If one clicks on Population Characteristics tab -> Raw, and then searches 'depress' the standardised differences pre and post PS adjustment can be seen. Here are covariates with largest standardised differences out of the 64 covariates surrounding depression, all still below our threshold of 0.1 in this example in CPRD	Further details given in results section to explain	Page 8

Power | Attrition | Population characteristics | Propensity model | Propensity scores | Covariate balance | Systematic error | Kaplan-Meier

Table 2. Select characteristics before and after propensity score adjustment, showing the (weighted) percentage of subjects with the characteristics in the target (*Hydroxychloroquine with prior RA*) and comparator (*Sulfasalazine with prior RA*) group, as well as the standardized difference of the means.

○ Pretty ◉ Raw

Show 10 entries Search: lupus

Characteristic	Before PS adjustment			After PS adjustment		
	T %	C %	Std. diff.	T %	C %	Std. diff
condition_era group during day -365 through 0 days relative to index: Lupus erythematosus	0.2	0.0	0.05	0.2	0.0	0.07
condition_era group during day -30 through 0 days relative to index: Lupus erythematosus	0.1	0.0	0.03	0.1	0.0	0.04
observation during day -365 through 0 days relative to index: Lupus anticoagulant screening test	0.001	0	0.03	0.001	0	0.02
observation during day -30 through 0 days relative to index: Lupus inhibitor activity	0.001	0.001	-0.01	0	0.001	-0.01
observation during day -365 through 0 days relative to index: Lupus circulating anticoagulant index	-0.001	0	0.01	0	0	0.01
observation during day -365 through 0 days relative to index: Lupus inhibitor activity	0.004	0.003	0.02	0.003	0.003	0.00

Showing 1 to 6 of 6 entries (filtered from 18,093 total entries) Previous 1 Next

Power | Attrition | Population characteristics | Propensity model | Propensity scores | Covariate balance | Systematic error | Kaplan-Meier

Table 2. Select characteristics before and after propensity score adjustment, showing the (weighted) percentage of subjects with the characteristics in the target (*Hydroxychloroquine with prior RA*) and comparator (*Sulfasalazine with prior RA*) group, as well as the standardized difference of the means.

○ Pretty ◉ Raw

Show 25 entries Search: depress

Characteristic	Before PS adjustment			After PS adjustment		
	T %	C %	Std. diff.	T %	C %	Std. diff
condition_era group during day -365 through 0 days relative to index: O/E - depressed	0.1	0.1	0.02	0.2	0.1	0.04
condition_era group during day -365 through 0 days relative to index: Reactive depression	0.2	0.2	0.01	0.3	0.2	0.03
observation during day -365 through 0 days relative to index: H/O: depression	0.003	0.001	0.03	0.003	0.002	0.03
observation during day -365 through 0 days relative to index: FH: Depression	-0.001	0	-0.02	0	0.001	-0.03
observation during day -365 through 0 days relative to index: On depression register	-0.001	0	0.01	0.001	0	0.03
condition_era group during day -365 through 0 days relative to index: Endogenous depression - recurrent	0.1	0.0	0.03	0.1	0.0	0.03
condition_era group during day -365 through 0 days relative to index: Recurrent depression	0.2	0.1	0.02	0.2	0.1	0.03
condition_era group during day -30 through 0 days relative to index: Depression resolved	<0.1	0.0	0.00	0.0	0.0	0.03
condition_era group during day -365 through 0 days relative to index: Agitated depression	0.1	0.1	0.01	0.1	0.0	0.02
procedure_occurrence during day -365 through 0 days relative to index: Depression medication review	0.2	0.0	0.04	0.1	0.1	0.02
condition_era group during day -365 through 0 days relative to index: Major depression, single episode	<0.1	0.0	0.00	0.1	0.0	0.02
procedure_occurrence during day -365 through 0 days relative to index: Depression screen using quest	6.7	5.2	0.06	5.7	6.2	-0.02
condition_era group during day -365 through 0 days relative to index: Mild depression	<0.1	0.1	-0.02	0.0	0.0	-0.02
observation during day -30 through 0 days relative to index: Depression interim review	0.001	0.001	0.02	0.001	0.001	0.02
condition_era group during day -365 through 0 days relative to index: Symptoms of depression	0.3	0.2	0.03	0.3	0.2	0.02
observation during day -365 through 0 days relative to index: Depression - enhanced services administration	-0.001	0	0.00	0.001	0	0.02
observation during day -365 through 0 days relative to index: Depression management program	0.001	0.001	0.02	0.001	0.001	0.01
observation during day -365 through 0 days relative to index: Excepted from depression quality indicators - informed dissent	-0.001	0	0.00	0	0.001	-0.01

Here is a screen shot of the shiny app for the standardised differences after PS adjustment for anti-depressant use, where the standardised difference was below our threshold for imbalance.

Power | Attrition | Population characteristics | Propensity model | Propensity scores | Covariate balance | Systematic error | Kaplan-Meier

Table 2. Select characteristics before and after propensity score adjustment, showing the (weighted) percentage of subjects with the characteristics in the target (*Hydroxychloroquine with prior RA*) and comparator (*Sulfasalazine with prior RA*) group, as well as the standardized difference of the means.

○ Pretty ◉ Raw

Show 25 entries Search: depressant

Characteristic	Before PS adjustment			After PS adjustment		
	T %	C %	Std. diff.	T %	C %	Std. diff
drug_era group during day -30 through 0 days relative to index: Other antidepressants	2.6	2.0	0.04	2.3	2.4	-0.01
drug_era group during day -30 through 0 days relative to index: ANTIDEPRESSANTS	18.7	15.3	0.09	17.1	17.4	-0.01
drug_era group during day -365 through 0 days relative to index: Other antidepressants	3.7	3.0	0.04	3.3	3.5	-0.01
drug_era group during day 0 through 0 days relative to index: Other antidepressants	2.4	1.8	0.04	2.1	2.2	-0.01
drug_era group during day -365 through 0 days relative to index: ANTIDEPRESSANTS	26.6	22.6	0.09	24.8	24.9	0.00
drug_era group during day 0 through 0 days relative to index: ANTIDEPRESSANTS	17.2	13.6	0.10	15.6	15.6	0.00

Showing 1 to 6 of 6 entries (filtered from 18,093 total entries) Previous 1 Next

4)No comment is made about the prevalence of anti-depressant use but is reported as more than 1 in 3 which I find surprisingly higher and certainly higher than I observe in routine clinical practice.	Patients with a past medical history of anti-depressant were balanced in PS matching, and therefore felt not to be a cause of confounding. Our understanding from the literature and clinical practice is that a prevalence of 1 in 3 is consistent with other studies; a further reference has been added to substantiate this.	Further details given in results section to explain	Page 8

Risk of depression, suicide and psychosis with hydroxychloroquine treatment for rheumatoid arthritis: a multi-national network cohort study

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Word count: max 3000

Keywords: hydroxychloroquine, safety, epidemiology, rheumatoid arthritis, psychosis, depression

KEY MESSAGES

- This is the largest study on the neuro-psychiatric safety of hydroxychloroquine, including >900,000 users internationally
- We found no association between hydroxychloroquine treatment for RA and depression, suicide or psychosis compared to sulfasalazine.
- These findings do not support stopping hydroxychloroquine for RA based on concerns raised in COVID-19 patients.

ABSTRACT

Objectives Concern has been raised in the rheumatological community regarding recent regulatory warnings that hydroxychloroquine used in the COVID-19 pandemic could cause acute psychiatric events. We aimed to study whether there is risk of incident depression, suicidal ideation, or psychosis associated with hydroxychloroquine as used for rheumatoid arthritis (RA).

Methods New user cohort study using claims and electronic medical records from 10 sources and 3 countries (Germany, UK and US). RA patients aged 18+ and initiating hydroxychloroquine were compared to those initiating sulfasalazine (active comparator) and followed up in the short (30-day) and long term (on treatment). Study outcomes included depression, suicide/suicidal ideation, and hospitalization for psychosis. Propensity score stratification and calibration using negative control outcomes were used to address confounding. Cox models were fitted to estimate database-specific calibrated hazard ratios (HR), with estimates pooled where I^2<40%.

Results 918,144 and 290,383 users of hydroxychloroquine and sulfasalazine, respectively, were included. No consistent risk of psychiatric events was observed with short-term hydroxychloroquine (compared to sulfasalazine) use, with meta-analytic HRs of 0.96 [0.79-1.16] for depression, 0.94 [0.49-1.77] for suicide/suicidal ideation, and 1.03 [0.66-1.60] for psychosis. No consistent long-term risk was seen, with meta-analytic HRs 0.94 [0.71-1.26] for depression, 0.77 [0.56-1.07] for suicide/suicidal ideation, and 0.99 [0.72-1.35] for psychosis.

Conclusion Hydroxychloroquine as used to treat RA does not appear to increase the risk of depression, suicide/suicidal ideation, or psychosis compared to sulfasalazine. No effects were seen in the short or long term. Use at higher dose or for different indications needs further investigation.

TRIAL REGISTRATION Registered with EU PAS; Reference number EUPAS34497 (http://www.encepp.eu/encepp/viewResource.htm?id=34498). The full study protocol and analysis source code can be found at https://github.com/ohdsi-studies/Covid19EstimationHydroxychloroquine.

INTRODUCTION

Hydroxychloroquine (HCQ) has received much scientific and public attention during the COVID-19 pandemic as a leading therapeutic and prophylactic target. [1, 2] Commonly used for autoimmune disorders (e.g., systemic lupus erythematosus) and inflammatory arthritis, HCQ was released for emergency use for COVID-19 due to its postulated antiviral efficacy in cellular studies.[3-9] HCQ is currently being used in over 217 registered ongoing clinical trials for the treatment of SARS-Cov-2 as of 12th June 2020.[10, 11] Results to date have been conflicting, with emerging data suggesting a lack of clinical efficacy against COVID-19.[12-18] Case report literature suggests that chloroquine, the compound from which HCQ was derived, is associated with neurological and psychiatric side effects when used as an anti-malarial treatment or prophylaxis.[19] Similar, potential side effects have been described in the use of HCQ include neuropsychiatric side effects such as psychosis, depression, and suicidal behaviour.[20-22] Regulatory authorities have received reports of new onset psychiatric symptoms associated with the increased use of high dose HCQ during the pandemic.[23] Whilst Chloroquine and HCQ have multiple mechanisms of action, a major action is the disruption of lysosomal functioning and autophagy.[24] These actions to some degree mimic lysosomal storage diseases, disorders that are characterised by neurodevelopmental delay and neurodegeneration when manifested in the more common form in childhood, but also associated with neuropsychiatric manifestation in adulthood.[25, 26]

New reports of serious side effects associated with HCQ used in COVID-19 are concerning to the rheumatology community, leading to confusion and anxiety for patients who are taking HCQ for autoimmune conditions. Given the previous reports of neuropsychiatric symptoms with HCQ, together with a plausible mechanism for such phenomena, we performed a review of the literature to determine what was already known about the potential risks of psychosis, depression, and suicide associated with HCQ use from literature database inception until 14/05/2020 (Supplementary Appendix Section 1). Interrogation of adverse event registers have identified potential associations between HCQ and psychiatric disorders.[11] Case reports and case series describing new onset psychosis, bipolar disorder, seizures and depression associated with HCQ and chloroquine use for rheumatological disorders and malaria prophylaxis can be found as early as 1964.[20, 27-35] No clinical trial or observational study was found that had investigated the incidence of new onset neuropsychiatric symptoms associated with HCQ use.

Considering the wide-scale use of HCQ in rheumatology, we therefore aimed to determine if there is an association between incident HCQ use for rheumatoid arthritis (RA) (the most common indication for the drug) and the onset of acute psychiatric events, including depression, suicide, and psychosis compared to sulfasalazine.

METHODS

Study design

A new user cohort, active-comparator design was used, as recommended by methodological guidelines for observational drug safety research.[36] The study protocol is registered in the EU PAS Register as EUPAS34497.[37]

Sulfasalazine (SSZ) was used as the active comparator for HCQ, as both SSZ and HCQ are second line csDMARDs used in addition to or instead of methotrexate. Whilst it is acknowledged that the drugs are not exactly equivalent, SSZ was felt to be the closest possible drug to HCQ in a RA cohort. Aware that there are other rheumatological indications for using HCQ such as systemic lupus erythematosus (SLE), we designed the study to include propensity score (PS) stratification and matching to prevent confounding. We used a set of diagnostic tools to check the propensity score adjustments in each data set for any imbalances that may have remained despite stratification, and also used negative control outcomes to identify if unobserved confounding had occurred. Analyses were not completed and are not reported if imbalance remained despite PS stratification, or there appeared to be a large proportion of negative control outcomes occurred outside our level of tolerance. All of these diagnostic tools were assessed whilst results were blinded, and can be freely reviewed online. Further details are given in the statistical analysis section.

Data sources

Electronic health records (EHR) and administrative claims data from the UK and US were used, previously mapped to the Observational Medical Outcomes Partnership (OMOP) common data model (CDM). The study period covered from September 2000 until the latest data available at the time of extraction in each database. Data from 10 data sources were analysed in a federated manner using a distributed network strategy in collaboration with the Observational Health Data Science and Informatics (OHDSI) and European Health Data and Evidence Network (EHDEN) communities. The data used included primary care electronic medical records from the UK (Clinical Practice Research Datalink, CPRD; and IQVIA Medical Research Data, IMRD); specialist ambulatory care electronic health records from Germany (IQVIA Database Analyzer Germany; DAGermany); electronic health records in a sample of US inpatient and outpatient facilities the Optum® de-identified Electronic Health Record dataset (Optum EHR, and IQVIA US Ambulatory EMR;AmbEMR); and US claims data from the IBM MarketScan® Commercial Claims Database (CCAE), Optum® de-identified Clinformatics® Data Mart Database-Date of Death (Clinformatics), IBM MarketScan® Medicare Supplemental Database (MDCR), IBM MarketScan® Multi-State Medicaid Database (MDCD), and IQVIA OpenClaims (OpenClaims). In addition, data were obtained and analysed from electronic primary care data from the Netherlands (IPCI database) and Spain (SIDIAP), and from Japanese claims (JMDC) but none of these analyses were deemed appropriate due to low/no event counts in at least one of the cohorts. A more detailed description of all these data sources is available in Appendix Section 2.

Follow-up

Participants were followed up from the date of initiation (first dispensing or prescription) of HCQ or sulfasalazine (SSZ) (index date) as described in detail in Appendix Section 3.1. Sulfasalazine was proposed as an active comparator as it shares a similar indication as a second-line conventional synthetic DMARD for RA. Two different follow-up periods were pre-specified to look at short- and long-term effects, respectively. First, a fixed 30-day time window from index date was used to study short-term effects, where follow-up included from day 1 post-index until the earliest of: loss to follow-up/death, outcome of interest, or 30 days from therapy initiation, regardless of compliance/persistence with the study drug/s. Second, in a long-term (on treatment) analysis, follow-up went from day 1 post-index until the earliest of: therapy discontinuation (with a 14-day additional washout), outcome of interest, or loss to follow-up/death. Continued treatment episodes

were constructed based on dispensing/prescription records, with a 90-day refill gap allowed to account for stockpiling.

Participants

All subjects registered in any of the contributing data sources for at least 365 days prior to index date, aged 18 years or older, with a history of RA (as defined by a recorded diagnosis any time before or on the same day as therapy initiation), and starting either HCQ or SSZ during the study period, were included.

Potential participant counts and age-, sex- and calendar year-specific incidence per database were produced for transparency and reviewed to check for data inconsistencies and face validity, and are available for inspection at https://data.ohdsi.org/Covid19CohortEvaluationExposures/, labelled as "New users of hydroxychloroquine with previous rheumatoid arthritis" and "New users of sulfasalazine with previous rheumatoid arthritis".

Outcomes and confounders

Code lists for the identification of the study population, for the study exposures and for the relevant outcomes were created by clinicians with experience in the management of RA and by clinical epidemiologists using ATLAS, an open science analytics platform that provides a unified interface for researchers to work within.[38] Exposures and outcomes were reviewed by experts in OMOP vocabulary and in the use of the proposed data sources. A total of three outcomes were analysed: depression, suicide or suicidal ideation, and hospital admission for psychosis. Detailed outcome definitions with links to code lists are fully detailed in Appendix Section 3.2.[39]

[40] Cohort counts for each of the outcomes in the entire source database, and age-sex and calendar-time specific incidence rates were explored for each of the contributing databases, and reviewed to check for data inconsistencies and face validity. These are available for inspection at https://data.ohdsi.org/Covid19CohortEvaluationSafetyOutcomes/

A list of negative control outcomes was generated for which there is no biologically plausible or known causal relationship with the use of HCQ or SSZ. These outcomes were identified based on previous literature, clinical knowledge (reviewed by two clinicians), product labels, and spontaneous reports, and confirmed by manual review by two clinicians.[41] The full list of codes used to identify negative control outcomes can be found in Appendix Section 4.

Statistical methods

All analytical source code is available for inspection and reproducibility at https://github.com/ohdsi-studies/Covid19EstimationHydroxychloroquine2. All study diagnostics and the steps described below are available for review at https://data.ohdsi.org/Covid19EstimationHydroxychloroquine2/.

The following steps were followed for each analysis:

1.Propensity score estimation

Propensity score (PS) stratification was used to minimise confounding. All baseline characteristics recorded in the participants' records/health claims were constructed for inclusion as potential confounders (including demographics, past medical history, procedures and medication prescription within 30 and within 365 days prior to drug initiation). Covariate construction details are available in Appendix Section 5. Lasso regression models were fitted to estimate propensity scores (PS) as the probability of hydroxychloroquine versus sulfasalazine use based on patient demographics and medical history including previous conditions, procedures, healthcare resource use, and treatments. The balance of known characteristics that could cause of potential confounding were then reviewed whilst the results were blinded in order to determine if a dataset was able to contribute to the meta-analysis. This was undertaken in two ways. Firstly, using the PS scores themselves and the standardised difference between the scores prior to and after PS stratification to determine if the cohorts of SSZ and HCQ users are imbalanced. Secondly by looking at the propensity score model

pictorially in a graph to see if the populations appear to 'overlap' in their characteristics. The full resulting PS models are available for inspection by clicking on 'Propensity model' and 'Propensity scores' after selecting a database in the results app.

2.Study diagnostics

Study diagnostics were explored for each database-specific analysis before progressing to outcome modelling, and included checks for power, observed confounding, and potential residual (unobserved) confounding. Only database-outcome analyses that passed all diagnostics below were then conducted and reported, with all others marked as 'NA' in the accompanying results app.

Positivity and power were assessed by looking at the number of participants in each treatment arm, and the number with the outcome (see the 'Power' tab after clicking on a database in the results app). Small cell counts less than five (and resulting estimates) are reported as "<5" to minimise risk of secondary disclosure of data with patient identification. PS overlap was also plotted to visualize positivity issues and can be seen by clicking on 'Propensity Scores'.

Observed confounding was explored by plotting standardized differences before (X axis) vs after (Y) PS stratification, with standardized differences > 0.1 in the Y axis indicating the presence of unresolved confounding see by clicking on 'Covariate balance' in the results app. [36]

Finally, negative control outcome analyses were assessed to identify systematic error due to residual (unobserved) confounding. The results for these are available in the 'Systematic error' tab of the results app. The resulting information was used to calibrate the outcome models using empirical calibration. [37, 38]

3.Outcome modelling

Cox proportional hazards models conditioned on the PS strata were fitted to estimate Hazard Ratios (HR) for each psychological outcome in new users of HCQ (vs SSZ). Empirical calibration based on the previously described negative control outcomes was used to minimise any potential residual confounding with calibrated HRs and 95% confidence intervals (CI) estimated.[42, 43] All analyses were conducted for each database separately, with estimates combined in random-effects meta-analysis methods where I^2 ≤40%.[44] The standard errors of the database-specific estimates were adjusted to incorporate estimate variation across databases, where the across-database variance was estimated by comparing each database-specific result to that of an inverse-variance, fixed-effects meta-analysis. No meta-analysis was conducted where I^2 for a given drug-outcome pair was >40%.

All analyses were conducted using the CohortMethod package, available at https://ohdsi.github.io/CohortMethod/ and the Cyclops package for PS estimation (https://ohdsi.github.io/Cyclops) [45].

Data Sharing

Open Science is a guiding principle within OHDSI. As such, we provide unfettered access to all open-source analysis tools employed in this study via https://github.com/OHDSI/, as well as all data and results artefacts that do not include patient-level health information via http://data.ohdsi.org/Covid19EstimationHydroxychloroquine2.

Data partners contributing to this study remain custodians of their individual patient-level health information and hold either IRB exemption or approval for participation.

RESULTS

A total of 918,144 HCQ and 290,383 SSZ users were identified. Participant counts in each data source are provided in Appendix Section 6. Before PS stratification, users of HCQ were (compared to SSZ users) more likely female (for example, 82.0% vs 74.3% in CCAE database) and less likely to have certain comorbidities such as Crohn's disease (0.6% vs 1.8% in CCAE) or psoriasis (3.0% vs 8.9% in CCAE). Prevalence of a past medical history of SLE was higher in HCQ users as expected (1.5% vs 0.5% in CCAE), whilst use of systemic glucocorticoids was similar (46.1% vs 47.2% in the previous month in CCAE). The prevalence of depressive disorder was similar in both groups (13.4% vs 13.5% in CCAE) and so was the history of use of antidepressants in the previous year (36.4% vs 36.4% in CCAE) which appears in keeping with the prevalence discussed in previous literature.[46] After PS stratification, prevalence of a past medical history of SLE, depressive disorder and the use of systemic glucocorticoids and antidepressants were balanced with a standard difference of less than 0.1 between HCQ and SSZ users. As these were balanced, these patients were not excluded from analyses.

Detailed baseline characteristics for the two pairs of treatment groups after PS stratification in CCAE are shown in Table 1 as an example, with balance of SLE, depression, and anti-depressant medication use included. Similar tables and a more extensive list of features provided in Appendix Section 7, and can also be searched for in the results app (click on a given dataset, then click on the population characteristics tab, raw and search for the condition or drug of interest). Study diagnostics including plots of propensity score distribution, covariate balance, and negative control estimate distributions are provided in Appendix Section 8.

Average baseline dose of HCQ was homogeneous, with >97% in CCAE using an average dose of 420mg daily, and only <3% taking an estimate dose >500 mg. All the observed differences between groups were minimised to an acceptable degree (<0.1 standardised mean differences) after propensity score stratification: in CCAE, the most imbalanced variable was use of glucocorticoids on index date, with prevalence 36.1% vs 35.8%.

Table 1. Baseline characteristics of patients with RA who are new users of hydroxychloroquine (HCQ) vs sulfasalazine (SSZ), before and after PS stratification, in the CCAE database

	Before PS stratification			After PS stratification		
	HCQ	SSZ		HCQ	SSZ	
	%	%	Std. diff	%	%	Std. diff
Socio-demographics						
Age group						
15-19	0.6	0.6	0.00	0.6	0.6	0.00
20-24	1.9	1.9	0.00	1.8	2.0	-0.01
25-29	2.6	2.6	0.00	2.5	2.8	-0.01
30-34	4.5	4.6	0.00	4.5	4.3	0.01
35-39	7.2	7.3	0.00	7.1	7.1	0.00
40-44	9.8	9.5	0.01	9.7	9.5	0.00
45-49	13.7	12.9	0.02	13.6	13.5	0.00
50-54	18.2	18.2	0.00	18.2	18.1	0.00
55-59	20.6	21.0	-0.01	20.8	20.8	0.00
60-64	19.0	19.7	-0.02	19.4	19.8	-0.01
65-69	1.8	1.7	0.01	1.8	1.6	0.01
Gender: female	82.0	74.3	0.19	80.1	79.7	0.01
Medical history						
Acute respiratory disease	35.5	34.3	0.03	35.1	34.7	0.01

Chronic liver disease	3.2	3.2	0.00	3.2	3.4	-0.01
Chronic obstructive lung disease	4.2	4.5	-0.01	4.3	4.5	-0.01
Crohn's disease	0.6	1.8	-0.12	0.7	1.1	-0.04
Depressive disorder	13.4	13.5	0.00	13.2	13.4	-0.01
Diabetes mellitus	13.5	13.4	0.00	13.6	13.7	0.00
Hypertensive disorder	34.7	34.9	0.00	34.7	35.0	-0.01
Obesity	9.3	9.1	0.00	9.2	9.4	-0.01
Psoriasis	3.0	8.9	-0.25	3.8	5.2	-0.07
Renal impairment	3.1	2.8	0.02	3.0	2.8	0.01
Systemic Lupus Erythematosus	1.5	0.5	0.10	1.3	0.9	0.03
Schizophrenia	0.1	0.1	-0.01	0.1	0.1	-0.01
Ulcerative colitis	0.6	1.9	-0.12	0.7	1.0	-0.04
Medication use						
Agents acting on the renin-angiotensin system	24.3	24.9	-0.01	24.5	24.7	0.00
Antidepressants	36.4	36.4	0.00	36.3	36.5	0.00
Antiepileptics	20.3	21.0	-0.02	20.4	20.2	0.00
Antiinflammatory and antirheumatic products	55.3	57.3	-0.04	55.8	56.7	-0.02
Antipsoriatics	0.7	1.3	-0.06	0.7	1.0	-0.03
Antithrombotic agents	7.4	7.3	0.01	7.4	7.3	0.00
Immunosuppressants	39.6	53.1	-0.27	43.4	43.6	0.00
Opioids	38.5	40.8	-0.05	39.0	39.3	-0.01
Psycholeptics	33.6	33.7	0.00	33.4	33.3	0.00
HCQ=hydroxychloroquine; SSZ=sulfasalazine						

Database-specific and overall counts and rates of the three study outcomes in the short- (30-day) and long-term ('on treatment') analyses are reported in detail in Table 2. Depression was the most common of the three study outcomes, with rates in the 'on treatment' analysis ranging from 1.99/1,000 person-years amongst HCQ users in CPRD to 17.74/1,000 amongst HCQ users in AmbEMR. Suicide/suicidal ideation was the least common outcome, with rates ranging from 0.32/1,000 (HCQ users in AmbEMR and SSZ users in IMRD) to 14.08/1,000 in SSZ users in MDCD. Database-specific counts and incidence rates (IR) for all three outcomes stratified by drug use are detailed in full in Appendix Section 9.

		30-day follow up						On-treatment follow up					
		Patients		Events		IR (/1,000 py		Patients		Events		IR (/1,000 py	
Outcome	Database	T	C	T	C	T	C	T	C	T	C	T	C
Depression	AmbEMR	55,793	15,092	155	29	33.91	23.44	55,793	15,092	320	80	17.74	14.34
	CCAE	66,440	22,449	79	28	14.64	15.36	66,440	22,449	557	137	8.54	9.40
	Clinformatics	51,676	16,812	84	41	20.05	30.09	51,676	16,812	657	178	12.43	15.00
	CPRD	9,160	11,348	<5	8	<6.67	8.60	9,160	11,348	36	94	1.99	3.60
	DAGermany	3,937	5,109	<5	12	<15.48	28.63	3,937	5,109	40	70	15.47	19.66
	IMRD	8,844	8,456	<5	6	<6.91	8.67	8,844	8,456	38	51	2.20	2.72
	MDCD	7,950	2,286	14	6	21.61	32.29	7,950	2,286	90	13	15.81	10.12
	MDCR	15,735	5,275	13	6	10.14	13.98	15,735	5,275	97	38	5.37	9.27
	OpenClaims	620,081	183,312	654	161	12.85	10.70	620,081	183,312	4,810	957	5.59	5.58
	OptumEHR	78,528	20,244	321	66	50.56	40.30	NA	NA	NA	NA	NA	NA
	Meta-analysis	918,144	290,383	<1,335	363	<17.77	15.28	839,616	270,139	6,645	1,618	6.28	6.29
Suicide and suicidal ideation	AmbEMR	NA	NA	NA	NA	NA	NA	57,660	15,357	6	<5	0.32	<0.88
	CCAE	66,533	22,471	12	<5	2.22	<2.74	66,533	22,471	81	28	1.23	1.91
	Clinformatics	51,807	16,843	12	<5	2.85	<3.66	51,807	16,843	97	30	1.80	2.50
	CPRD	9,167	11,358	<5	<5	<6.66	<5.37	9,167	11,358	7	9	0.39	0.34
	IMRD	8,852	8,460	<5	<5	<6.91	<7.22	8,852	8,460	8	6	0.46	0.32
	MDCD	7,980	2,296	<5	<5	<7.68	<26.78	7,980	2,296	56	18	9.71	14.08
	MDCR	NA	NA	NA	NA	NA	NA	15,752	5,278	15	6	0.83	1.45
	OpenClaims	621,067	183,550	34	8	0.67	0.53	621,067	183,550	321	89	0.37	0.52
	OptumEHR	79,903	20,480	18	8	2.78	4.82	NA	NA	NA	NA	NA	NA
	Meta-analysis	845,309	265,458	<91	<41	<1.31	<1.89	838,818	265,613	591	<191	0.55	<0.75
Hospitalization for psychosis	OpenClaims	620,964	183,527	95	27	1.86	1.79	620,964	183,527	1,108	221	1.28	1.28
	OptumEHR	79,994	20,508	<5	<5	<0.77	<3.01	NA	NA	NA	NA	NA	NA
	Meta-analysis	700,958	204,035	<100	<32	<1.74	<1.91	NA	NA	NA	NA	NA	NA

T=target therapy; C=comparator therapy; IR=incidence rate; py=person-years at risk; NA=non-applicable (not reported because of failed diagnostics or on-treatment follow-up unavailable); HCQ=hydroxychloroquine; SSZ=sulfasalazine; AmbEMR=IQVIA Ambulatory EMR; CCAE=IBM Commercial Database; Clinformatics=Optum de-identified Clinformatics Data Mart Database; CPRD=Clinical Practice Research Datalink; DAGermany=IQVIA Disease Analyzer Germany; IMRD=IQVIA UK Integrated Medical Record Data; MDCD=IBM IBM Multi-state Medicaid; MDCR=IBM Medicare Supplemental Database; OpenClaims=IQVIA Open Claims; OptumEHR=Optum de-identified Electronic Health Record dataset

Table 2. Patient counts, event counts and incidence rates (IR) (/1,000 person years) of key events according to drug use

9 datasets passed cohort diagnostics and contained sufficiently robust data for inclusion into the short term analyses for depression; 6 passed for suicide and 2 passed for psychosis. A small imbalance with the incidence of a past medical history of SLE was seen in MDCD and with cutaneous lupus in DAGermany. As a result, we excluded both from the psychosis outcome but not for depression as we did not consider this was a confounder. Short-term (30-day) analyses showed no consistent association between HCQ use and the risk of depression, with database-specific HRs ranging from 0.21 [95%CI 0.03-1.25] in CPRD to 1.28 [0.85-1.95] in AmbEMR, and a meta-analytic HR of 0.96 [0.79-1.16] (See Figure 1, top). On-treatment analyses showed similar findings, with database-specific HRs from 0.62 [0.40-0.97] in DAGermany to 1.29 [0.69-2.39] in MDCD, and a meta-analytic HR of 0.94 [0.71-1.26] (Figure 1, bottom plot). Note only databases passing diagnostics are included within the plot and meta-analysis.

Similarly, no association was seen between the use of HCQ and the risk of suicidal ideation or suicide. In the short-term, HRs ranged from 0.27 [0.06-1.29] in MDCD to 10.46 [0.51-216.29] in CPRD, with meta-analytic HR of 0.94 [0.49-1.77] (Figure 2, top). Long-term effects were similar, with HRs ranging between 0.55 [0.20-1.49] in MDCR and 2.36 [0.21-26.87] in AmbEMR, and meta-analytic HR of 0.77 [0.56- 1.07] (Figure 2, bottom).

Finally, no association was seen between the use of HCQ (compared to SSZ) and the risk of acute psychosis. Short-term analyses showed database-specific HRs of 0.44 [0.05-3.49] in OptumEHR and 1.01 [0.65-1.58] in OpenClaims, with a meta-analytic estimated HR of 1.03 [0.66-1.60]. Only OpenClaims contributed to the 'on treatment' analysis of this event, with an estimated HR of 0.98 [0.73-1.33].

DISCUSSION

Principal findings

This large observational study shows that in routine healthcare treatment of RA, there is no association with the use of HCQ with acute psychosis, depression, or suicide as compared to SSZ. These results are seen both in the short-term and long-term risk analyses. Whilst an excess of psychiatric events have been reported during the COVID pandemic in those prescribed HCQ, this risk does not appear to be associated with HCQ prescribed in RA compared to those prescribed SSZ. This study uses data from three countries, with a variety of healthcare systems and modes of routine healthcare data included, enabling the study to produce more generalisable results.

Comparison with other studies

The bulk of the evidence prior to this study consisted of isolated case reports and case series, making it difficult to draw demographic comparisons with previous work. Sato *et al.* reported that neuropsychiatric adverse events found in the FDA adverse event reporting system associated with chloroquine use were predominantly in females in the sixth decade of life.[21] Increase in reporting of acute psychiatric disease during the COVID-19 pandemic may be multifactorial, with an increase in external stressors such as social isolation, financial uncertainty, and increased misuse of drugs and alcohol.[47-49] Considering that we find no association for HCQ use compared to SSZ with acute psychiatric outcomes in the RA population, evidence points towards external stressors being more likely involved in the aetiology of psychiatric events seen during this pandemic.

Strengths and weaknesses of the study

This study is based on new users of HCQ for RA and therefore, the results of this study are most directly relevant to the risk of neuropsychiatric side effects seen in the rheumatological population. The

regulatory warnings of possibly increased acute psychiatric events associated with HCQ warrant investigation in all available datasets to prevent harm in both rheumatological patients and those taking for emergency use, especially as very few clinical trials include acute psychiatric outcomes. Whilst the general population presenting with COVID-19 may differ from those with RA, within the context of emergency authorisation or off label use of HCQ, all available evidence must be taken into account when considering the risks associated.

Several considerations must be taken into account when interpreting these results.
Firstly, the doses used to treat RA are lower than those suggested in current clinical trials for the treatment of SARS-CoV2, and therefore adverse events seen in the treatment and prophylaxis of COVID-19 may be greater if dose dependent, as is the case with cardiac adverse effects.[50, 51] Secondly, this study could be affected by outcome misclassification. Only acute psychiatric events presenting to medical services will be captured, and this is especially important for the outcome of suicide. Suicide may not be fully recorded if patients do not reach medical care or cause-of-death information is not linked to the datasource, and therefore the true incidence of suicide may be under-recorded.[52] Similarly, this study only focused on acute psychosis and depression severe enough to be identified in medical consultation in patients with no history of either condition. Whilst we generated phenotypes that underwent full cohort diagnostics, and phenotypes were constructed using a multidisciplinary team of clinicians and bioinformaticians to ensure face validity, it should be noted that no formal validation was undertaken. We took all reasonable steps to ensure the validity of the phenotypes, whilst considering the risk-benefit tradeoff of what could be undertaken within the time frame used to respond to the serious questions raised by regulatory bodies following the HCQ use in COVID-19.
This study can highlight the association for patients without a prior history of psychosis or depression, but cannot inform of the risk of acute deterioration after beginning HCQ treatment for those already known to psychiatric services.

Thirdly, depression and hallucinations are listed as potential undesirable effects of sulfasalazine treatment, which may underestimate the true risk, if any, from HCQ.[53] However, the frequency of depression (described as changes in affect in the summary of product characteristics for HCQ) is reported to be common (≥1/100 to < 1/10) whilst for sulfasalazine depression is listed as being uncommon (≥1/1000 to < 1/100). Therefore, it is potentially reassuring for patients that we observed no difference compared to sulfasalazine for which there is a paucity of published evidence suggesting causailty.[54]

Propensity score stratification and matching, as well as a comprehensive examination of potential sources of systematic error, were undertaken prior to blinding of results to identify and reduce the risk of confounding. Baseline characteristics after PS stratification were adequately balanced; of note, the incidence of systemic lupus erythematosus (SLE) and a past medical history of depression and anti-depressant medication use was balanced between treatment groups. Identifying the balance of these conditions between treatment groups was undertaken prior to unblinding due to the potential neuropsychiatric sequelae of the SLE aside from the potential side effects of pharmacological treatment, and the increased likelihood of depression in those with prior history. This study could also be limited by the fact that patients may overlap and exist in more than one dataset within the US. The meta-analysis assumes populations to be independent, and therefore the obtained estimates may slightly underestimate variance.

Future research

For rheumatological disorders, future work could expand into investigating the occurrence of acute psychiatric events in patients in SLE. This would enable greater understanding of whether neuropsychiatric conditions are related to disease activity or due to pharmacological treatment. Similarly, in the emergency use of HCQ in COVID-19, there is already concern about the potential heightened risk of acute psychiatric disorder due to elevated number of psychosocial stressors present during a pandemic and high dose use.[55] Future work should consider including acute psychiatric outcomes in order to differentiate between psychiatric conditions generated by the impact of a global pandemic compared to iatrogenic events due to pharmaceutical therapies used.

Meaning of the Study

Exponential growth in research into the best treatment of SARS-CoV2 infection is generating rapidly evolving evidence for the relative efficacy of pharmaceutical agents. For the rheumatological community, media attention previously surrounded HCQ as a strong forerunner of COVID-19 prophylaxis and treatment. The results of the RECOVERY trial identifying dexamethasone reduced mortality in intensive care patients has now overtaken HCQ as the leading rheumatological drug for the pandemic, but the concerns regarding HCQ safety remain for those who take the drug for conventional indications.[17, 56] Cardiovascular safety, and reports that it might lack efficacy for both treatment and prophylaxis, have halted major HCQ clinical trials.[50, 57-60] The identification of acute psychiatric events associated with HCQ use has raised the need to clarify the risk within general rheumatological use. Our study identifies no increased risk in RA patients when compared with sulfasalazine, and provides evidence to users and clinicians alike that the reports presented during the pandemic are likely to be related to further causes aside from HCQ.

FIGURE LEGENDS

Figure 1. Forest plot of the association between short- (top) and long-term (bottom) use of HCQ (vs SSZ) and risk of depression, by database and in meta-analysis.

Figure 2. Forest plot of the association between short- (top) and long-term (bottom) use HCQ (vs SSZ) and risk of suicidal ideation or suicide, by database and in meta-analysis.

FOOTNOTES

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Public and patient involvement

No patients were directly involved in setting the research question, nor in design, conduct or interpretation of the study.

Competing interests

All authors have completed the ICJME uniform disclosure form from http://www.icjme.org/conflicts-of-interest/ uploaded with this study and report:

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Ethical Approval

All data partners received IRB approval or waiver in accordance to their institutional governance guidelines.

Database	Statement
AmbEMR	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI community studies.
CCAE	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
CPRD	Approval for CPRD was provided by the Independent Scientific Advisory Committee (ISAC). This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. The protocol for this study (20_059R) was approved by the Independent Scientific Advisory Committee (ISAC).
DA Germany	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI community studies.
IMRD	The present study is filed and under review for Scientific Review Committee for institutional adjudication. Due to the public health imperative of information related to these data, approval is provided for this publication.
IPCI	The present study was approved by the Scientific and Ethical Advisory Board of the IPCI project (project number: 4/2020).
JMDC	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
MDCD	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
MDCD	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Open Claims	This is a retrospective database study on de-identified data and is deemed not human subject research. Approval is provided for OHDSI community studies.

Clinformatics	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.
Optum EHR	New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.

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