EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 August 2020
EMA/456727/2020

Report on study results – Hydroxychloroquine – THIN Database
(final report for entry onto EU PAS register)

"Psychosis and psychotic disorders" and "Depression and suicide/self-injury" following exposure to Hydroxychloroquine and Chloroquine

Summary Information	
Title	"Psychosis and psychotic disorders" and "Depression and suicide/self-injury" following exposure to Hydroxychloroquine and chloroquine
Version identifier of the study report	3 (updated to include data on Chloroquine)
Date of report	27 August 2020
Version identifier of the study protocol	2.0
Date of last version of study protocol	04 August 2020
EU PAS register number	Will be completed once the study is registered on the EU PAS
Active substance	Hydroxychloroquine, chloroquine
Research question and objectives	1. To describe the pattern of use of HCQ and CQ. 2. To estimate the incidence rate of recorded psychiatric events as coded in primary care records whilst exposed and at any time following exposure to HCQ and CQ (psychiatric events: suicidality, self-endangering behaviour, psychosis and psychotic disorders and non-psychotic depression and other emotional disorders).
Country(-ies) of study	UK (IMRD UK)
Author	Name: Robert Flynn Tel: +31887818439 Email:robert.flynn@ema.europa.eu Name: Karin Hedenmalm

Summary Information	
	Tel: +31887818144 Email:karin.hedenmalm@ema.europa.eu Name: Jim Slattery Tel: +31887817161 Email:jim.slattery@ema.europa.eu Name: Gianmario Candore Tel: +31887817725 Email:gianmario.candore@ema.europa.eu Name: Valerie Strassmann Tel: +31887817194 Email: valerie.strassmann@ema.europa.eu
Contact mailbox	ICU@ema.europa.eu

Initial Analysis Request Contact	
Name	Anette Kirstine Stark
Affiliation	Danish Medicines Agency
Email Address	AKST@dkma.dk
Telephone Number	+45 44889595
Associated Procedure	PRAC Signal on HCQ/CQ and psychiatric disorders - EPITT no:19572

Acknowledgment

IQVIA Medical Research Data (IMRD) incorporates data from THIN, A Cegedim Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA.

Lay summary

The drug hydroxychloroquine is used to treat certain types of longstanding joint pain. In the early stages of the 2020 COVID-19 pandemic, hydroxychloroquine was widely used for the prevention and treatment of coronavirus, although it is now known not to be effective. Chloroquine is a similar drug which is used to stop travellers getting malaria or as a treatment for malaria. There were a very few reports of patients having mental health problems after starting hydroxychloroquine for the treatment of COVID. This report measures the occurrence of certain types of mental health problem after patients started taking hydroxychloroquine or chloroquine from before the COVID epidemic. It was prepared by EMA to support the evaluations of the European Union's Pharmacovigilance Risk Assessment Committee (PRAC) which is a regulatory body responsible for assessing and monitoring the safety of human medicines. It will be used by the PRAC to decide if regulatory action needs to be taken to protect patients taking hydroxychloroquine or chloroquine in the future.

Redaction of low cell counts

Acknowledgment

In order to prevent the unintentional identification of individual patients, cell counts where the number of patients is in the range 1 to 5 are suppressed and given as "< 5". Any numbers that allow the calculation of such low cell counts are also suppressed

Table of Contents

1.

1. Rationale and background

Hydroxychloroquine (HCQ) and chloroquine (CQ) are nationally authorised 4-aminoquinoline antimalarial agents originally developed as less toxic alternatives to quinine. Both have risen to prominence in the earlier months of 2020 as potential treatments in the current COVID-19 pandemic.

Hydroxychloroquine has a European Union reference date of 1955: although still used in the prevention and treatment of malaria, it is now more commonly used for rheumatoid arthritis, discoid and systemic lupus erythematosus, dermatological conditions caused or aggravated by sunlight, and Sjögren syndrome. In the paediatric population it can be used for juvenile idiopathic arthritis (in combination with other therapies), discoid and systemic lupus erythematosus, and prevention / treatment of malaria. Psychiatric Disorders are inconsistently recorded on SmPCs across member states, with suicidal behaviour and psychoses variously listed with frequency "rare" or "unknown", and with suicidality sometimes not listed. These side effects can occur at all ages, during acute or chronic use, and in patients with or without a history of mental illness (Gonzalez-Nieto et al, 2015; Pinho de Oliveira et al, 2013), (Juurlink et al, 2020). However, the labelling of such effects is inconsistent.

Chloroquine has a European Union reference date of 1947 and remains widely used in the prophylaxis and treatment of malaria. Other licenced indications are: amoebic hepatitis, lupus erythematosus and rheumatoid arthritis. Established psychiatric disorders are hallucinations (frequency "rare"), and psychotic disorder (including anxiety, personality change); insomnia; confusion and depression (frequency "unknown").

In May 2020, the Spanish regulatory Agency (AEMPS) warned about the occurrence of neuropsychiatric reactions associated with intake of HCQ and CQ in patients being treated for COVID-19. This new information let to initiation of a signal procedure at the European Union's Pharmacovigilance Risk Assessment Committee (PRAC) and led to further review of data pertaining to the association of neuropsychiatric reactions with chloroquine/hydroxychloroquine.

Suicide statistics from the UK show that since 2013 the annual suicide rate amongst males has been highest in the 45-59 years age group and stands at around 25 per 100,000. The suicide rate for males in the 45-49 years age group is 2.5 times high than in the 70-74 years age group (Office for National Statistics, 2017).

Analyses of primary healthcare records held at the EMA could support further analyses of data relating to this signal. Such analyses would allow estimation of incidence rates for events among patients initiating treatment and patients on chronic therapy (to evaluate whether risk might be highest at the beginning of treatment) and could determine whether there is an increased risk of events in patients with neuropsychiatric history. It would also allow the median time to first event to be ascertained allowing information on potential windows of increased risk.

To help contextualization of results, a comparison of the risk of events with treatments used for similar indications would be helpful. Selection of potential comparators requires careful consideration and needs to take into account changes in local prescribing practices with time. For HCQ, methotrexate and sulfasalazine are commonly used for the principal indication (rheumatoid arthritis) but are both associated with depression and have other indications that are different than for HCQ; leflunomide, gold injection and penicillamine have similar indications but are less commonly used. Cyclosporine and azathioprine are less commonly used and have multiple indications. Newer treatments (various-advanced therapies) are now used but could not be included as historic controls as their uptake (in the UK in particular) has been slow. An alternative would be exposure to NSAIDs where their use is associated with a diagnosis of rheumatoid arthritis. NSAIDs are not associated with depression; however, they are not Disease Modifying Antirheumatic Drugs (DMARDs) and their use in the rheumatoid arthritis population will follow a different (less chronic) pattern.

Potential comparators for CQ differs for the UK and Germany, as its pattern of use will be very different. In the UK, where CQ is mostly widely prescribed as an antimalarial, potential comparators would be mefloquine (although its widely-perceived association with neuropsychiatric side effects make it a poor choice), atovaquone with proguanil (for which depression is listed as a "common" side effect and hallucination and psychotic disorder are listed as less frequent effects), or doxycycline (which is seldom specified as being for prophylaxis of malaria). Given that CQ is most commonly used by relatively healthy travelers visiting countries where malaria is endemic, patients are out-of-range of their General Practitioners (GPs), so there will likely be delayed/underreporting of events of short latency, so careful consideration is needed as to whether an analysis in primary healthcare records would provide sound results to aid assessment. For the UK, such an analysis is considered futile. Such an analysis is more plausible in IMRD-DE where there is some CQ prescribing for rheumatoid arthritis. In view of the difficulties in selecting appropriate comparators and the imminent publication of findings from the OHDSI community also studying neuropsychiatric events following exposure to HCQ (Prieto-Alhambra et al, 2020, see also entry in EU PAS database: http://www.encepp.eu/encepp/viewResource.htm?id=36203) this study will not, at present, proceed with a comparator-based analysis.

This study has considered data recorded in two electronic primary electronic health records databases: IQVIA Medical Research Data-Germany (IMRD-Germany) and IQVIA Medical Research Data-United Kingdom incorporating data from THIN, a Cegedim Database (IMRD-UK). The two IMRD databases are contractually available to the EMA in-house.

2. Research Question and Objectives

The study has the following objectives for each database:

1. To describe the pattern of use of HCQ and CQ.
2. To estimate the incidence rate of recorded events as coded in primary care records whilst exposed and at any time following exposure to HCQ and CQ.
    a. Suicidality (composite)
        i. suicidal ideation
        ii. suicidal attempt
        iii. completed suicide
    b. Self-endangering behaviour (including self-harm)
    c. Affective, Psychosis and psychotic disorders
        i. Schizophrenia-like, including hallucinations
        ii. Affective related (mania, bipolar, psychotic depression)
    d. Non-psychotic depression and other emotional disorders, including violent behaviour and aggression.

3. Methods

3.1. Data Sources

In the United Kingdom, GPs play a gatekeeper role in the healthcare system, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests. IMRD-UK contains longitudinal electronic patient records

extracted from the VISION practice management software, which has been contributed to by > 790 general practices across the United Kingdom covering up to 6% of the UK population. Data are largely representative of the UK population in terms of age, sex, deprivation status, and geographic distribution. It contains GP prescriptions with medicinal products identified through a bespoke system of drug codes linked to generic drug names (substance names) or a substitute thereof in a drug and device dictionary.

3.2. Study design

This is a cohort study with cohorts defined based on patients' exposure to the medicines under investigation. Descriptive analyses are used to describe the pattern of use of HCQ and CQ. The occurrence of events in the exposed population are described as unadjusted event rates. Analyses require the use of a minimum one-year lookback period prior to the start of follow-up to establish any baseline characteristics and a new-user "inception" cohort of patients established through the one-year screening period to define incident use. In an "ever used" analysis (akin to "intention to treat"), Patients are followed from the date of first prescription until an event or censored (at the end of follow-up). In an "on treatment" analysis, patients are followed for the duration of their therapy.

3.3. Study population

The population eligible for the study consists of all patients registered with an IMRD-UK or IMRD-DE GP-practice for a duration of one-year or more. In IMRD-UK, patients are followed from the latest of date of registration, Acceptable Mortality Reporting (AMR) date or date of practice computerisation, and followed until the earliest of transfer out date, date of death or date of last data collection. The study subjects are followed from the first use of HCQ and QC on the database (1992 onwards) to most recent data available (for IMRD-UK January 2020. In any case data do not cover data collected from the ongoing COVID-19 pandemic.

3.4. Study variables

3.4.1. Drug Exposures

Patients included are those exposed to HCQ (ATC code P01BA02) or QC (P01BA01).

3.4.2. Outcomes

The following serious neuropsychiatric outcomes are defined as follows:

- **Suicidality**: This consists of the following: (i) completed suicide; (ii) attempted suicide; and (iii) suicidal ideation. In IMRD-UK it is known that suicide codes are often used for patients who are still alive after the event. Therefore, cases of suicide that weren't recorded as deaths within 14 days were re-classified at attempted suicides. Similarly, codes for attempted suicide were classified as completed suicides if death was recorded within 14 days. This approach has been used previously in drug safety studies using IMRD-UK data (Wijlaars et al, 2013). Relevant Read codes and their respective classifications will be listed in an attached appendix.
- **Self-endangering behaviour** (including self-harm)

- **Psychosis and psychotic disorders**: to include: (i) schizophrenia-like including hallucinations and (ii) associated affective disorders (mania, bipolar disease, psychotic depression).
- **Non-psychotic depression and other emotional disorders:** including violent behaviour and aggression

A composite of self-endangering behaviour and suicidality has been included as an additional endpoint.

3.5. Data Analysis

Analyses were conducted using SAS v9.4.

The analyses followed the objectives and were run in the databases indicated.

3.5.1. Pattern of use

Descriptive analyses were used to describe and summarise the study cohorts (HCQ and CQ) at baseline: this includes the number of patients exposed, age at first use, sex, year of first use and numbers of prescriptions and exposure windows per patient. This also describes indication, the proportion of patients with previous neuropsychiatric diagnoses, and dose of HCQ and CQ. The cumulative dose of HCQ or CQ at the time of event has been summarised.

3.5.2. Incidence rates

The initial analysis follows up from first use to event, end of treatment exposure or censoring. Incidence rates were calculated as the number of events occurring during follow-up divided by the person years of follow-up with 95% confidence intervals. As provided in the pilot analysis, these are broken down by type of treatment (HCQ or CQ), age & sex, dose (high dose vs low dose) and history of neuropsychiatric diagnoses, and (in addition) by indication. The time from exposure to onset of event is described using Kaplan-Meier survival curves: these were also broken down by age & sex, dose, history of neuropsychiatric diagnoses, and indication for the initial episode of exposure only.

4. Limitations

It is anticipated that there is incomplete recording of completed suicides in GP systems in IMRD-UK although the validity (Arana et al, 2010) and utility (Wijlaars et al, 2013) of using suicide and suicidality as an outcome in THIN has previously been shown. Although this could be enhanced by linkage to death certification data, this would still fall short of a true "gold standard", the deficiencies in coding of suicide on death certificates being well known (Carroll et al, 2012). It is not expected that any biases arising from incomplete ascertainment of outcomes would be differential and a comparative study between different treatments would be expected to generate valid results. IMS Germany has limited recording of suicidal events and self-harm events and is not expected to contribute significantly to the assessment of these events. Analysis of the other outcomes has been possible. Other approaches to the analysis were considered, for example using a self-controlled type design; however, such analysis relies on clear treatment windows with well-defined periods of "time on" and "time off" therapy: due to the excessively slow elimination of HCQ and QC from the body and the expected chronicity of treatment, and in IMRD-DE the possibility for incomplete data, such an approach was not considered feasible. In addition, for IMRD-UK, CQ exposure intended for prophylaxis of malaria would be suspectable to time-dependent bias with the exposures occurring at a time of increased susceptibility to neuropsychiatric events related to the stresses of travel. Again, this would make a self-controlled design inappropriate.

The data describing CQ exposure is flawed for both IMRD-UK (where non-specific dosage directions were common and where there was no clear standard dosage regimen) and IMRD-DE (where much exposure dated from before 2004 when there are concerns about data quality). This is described in further detail in section 8.2.

5. Ethical / data protection considerations

This work uses de-identified data provided by patients as a part of their routine primary care. Only aggregate data are presented. Cell counts of less than 5 will be suppressed in any output to be release into the public domain in order to prevent identification of individuals.

6. Publication of study results

This study will be registered in the EU PAS Register. After finalisation of analyses, the protocol as well as an abstract of the study results will be published in the EU PAS Register.

7. Results

7.1. Hydroxychloroquine

7.1.1. Pattern of use: HCQ

Descriptive analyses were performed to describe and summarise the study cohorts (HCQ) at baseline: this includes the number of patients exposed, age at first use, sex, year of first use and numbers of prescriptions and exposure windows per patient. This describes indication, the proportion of patients with previous neuropsychiatric diagnoses, and dose of HCQ. The cumulative dose of HCQ at the time of event has been summarised.

Table 1.1 Patient demographic summary

	Hydroxychloroquine
Total no of patients	32,462
No. of female patients (%)	25,347 (78.1%)
Mean age in years (SD)	54.9 (15.1)
Median age (IQR)	55(44 - 66)
Min- max age	2 - 97
No. with missing age information	0
Start year before 2000	2,085 (6.4%)
Start year 2000-2004	4,142 (12.8%)
Start year 2005-2009	7,401 (22.8%)
Start year 2010-2014	11,740 (36.2%)
Start year 2015-2019	7,094 (21.9%)

Table 2.1. Prescriptions, doses (in mg) and treatment episodes

	Hydroxychloroquine
Total no. of patients	32,462
Total no. of episodes	52,681
Min-max episodes	1 - 27
Mean episodes (SD)	1.62 (1.39)
Median episodes (IQR)	1 (1 - 2)
Total no. of prescription dates	765,258
Min-max prescription dates	1 - 650
Mean prescription dates (SD)	23.6 (33.7)
Median prescription dates (IQR)	11 (3 - 31)
No. of patients with calculated start dose (calculated dose during first treatment episode)	32,447
Min-max calculated start dose in mg	3 - 992
Mean calculated start dose (SD) in mg	309.3 (93.2)
Median calculated start dose (IQR) in mg	317 (219 - 375)
No. of patients with a calculated start dose up to 100 mg	67 (0.2%)
No. of patients with a calculated start dose between 101-200 mg	3,760 (11.6%)
No. of patients with a calculated start dose between 201-300 mg	10,382 (32.0%)
No. of patients with a calculated start dose between 301-400 mg	14,304 (44.1%)
No. of patients with a calculated start dose between 401-500 mg	3,301 (10.2%)
No. of patients with a calculated start dose greater than 500 mg	633 (2.0%)

Table 3.1. Indications

	Hydroxychloroquine
Total no of patients with any diagnosis	19,172 (59.1%)
No of patients with no prior diagnosis	13,290 (40.9%)
No of patients with RA	15,636 (48.2%)
No of patients with juvenile RA	181 (0.6%)
No of patients with lupus	1,420 (4.4%)
No of patients with systemic lupus	2,128 (6.6%)
No of patients with other diagnoses	811 (2.5%)

Table 4.1. Prior neuropsychiatric diseases

	Hydroxychloroquine
All patients	32,462 (100%)
No of patients with any prior neuropsychiatric diagnosis	11,204 (34.5%)
No of patients with prior suicidal events	451 (1.4%)
No of patients with prior self-harm events	380 (1.2%)
No of patients with schizophrenia psychosis related events	124 (0.4%)
No of patients with affective psychosis related events	147 (0.5%)
No of patients with non-psychotic affective disorders	10,991 (33.9%)

Table 5.1. Cumulative dose of HCQ at the time of event

Drug	HCQ
	IMRD-UK
n patient with exposed event	2,285
n exposed patients with calculated cumulative dose	2,285
mean cumulative dose	193,866 mg
median cumulative dose	97,903
minimum, maximum	125 - 2,395,872 mg

7.1.2. Incidence rates: HCQ

The initial analysis follows up from first use to event, end of treatment exposure or censoring. Incidence rates are calculated as the number of events occurring during follow-up divided by the person years of follow-up with 95% confidence intervals. As provide in the pilot analysis, these are broken down by type of treatment (HCQ), age & sex, dose (high dose vs low dose), history of neuropsychiatric diagnoses, and by indication. The time from exposure to onset of event is described using Kaplan-Meier survival curves *for the initial episode of exposure only*: these are broken down by age & sex, dose, history of neuropsychiatric diagnoses, and indication. As the same patient may have more than one indication, for the purpose of stratifying Kaplan-Meier survival curves by indication, the following order of preference was applied: Juvenile rheumatoid arthritis>rheumatoid arthritis>systemic lupus erythematosis>lupus erythematosis.

Table 6.1. History of neuropsychiatric diagnoses: HCQ

Incident HCQ exposure [1]	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)					any follow-up time	*n* any time vents event rate (95% CI)				
			suicidality	self-endangering	suicidality or self-endangering	psychosis related	non-psychotic depression		suicidality	self-endangering	suicidality or self-endangering	psychosis related	non-psychotic depression
no neuropsychiatric history	21,217	63,909	9 1.41 (0.64-2.67)	9 1.41 (0.64-2.67)	18 2.82 (1.67-4.45)	9 1.41 (0.64-2.67)	1204 188 (178-199)	133,238	28 2.10 (1.4-3.04)	15 1.13 (0.63-1.86)	43 3.23 (2.34-4.35)	32 2.40 (1.64-3.39)	2436 183 (176-190)
suicidality	451	1,232	<5 - (-)	<5 - (-)	6 48.7 (17.9-106)	<5 - (-)	92 746 (602-916)	2,450	10 40.8 (19.6-75.1)	8 32.65 (14.1-64.3)	15 61.2 (34.3-101)	8 32.7 (14.1-64.3)	168 686 (586-798)
self-endangering behaviour	380	878	<5 - (-)	11 125.3 (62.5-224.2)	11 125.28 (62.5-224)	<5 - (-)	61 695 (531-892)	1,773	6 33.8 (12.4-73.7)	19 107 (64.5-167)	22 124 (77.8-188)	<5 - (-)	108 609 (500-735)
Psychosis and psychotic disorders	243	722	<5 - (-)	6 83.1 (30.5-180)	9 124.7 (57.0-237)	30 416 (280-593)	47 651 (478-866)	1,250	6 48 (17.6-104.5)	10 80 (38.4-147)	12 96 (49.6-168)	50 400 (297-527)	76 608 (479-761)
Non-psychotic depression and other emotional disorders	10,991	28,978	26 8.97 (5.86-13.2)	27 9.32 (6.14-13.6)	48 16.6 (12.2-22.0)	36 12.4 (8.70-17.2)	1796 620 (591-649)	59,710	73 12.2 (9.58-15.4)	52 8.71 (6.5-11.4)	112 18.8 (15.4-22.6)	77 12.9 (10.2-16.1)	3196 535 (517-554)

Table 7.1. Age & sex distribution in patients taking HCQ

Incident HCQ exposure [1]	sex	age (years)	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)				any follow-up time	*n* any time vents event rate (95% CI)			
					suicidality	self-harm	psychosis related	non-psychotic depression		suicidality	self-harm	psychosis related	non-psychotic depression
all	female	< 18	199	496	0 0 (0-74.4)	0 0 (0-74.4)	0 0 (0-74.4)	19 383 (231-599)	1,118	<5 - (-)	<5 - (-)	0 0 (0-33)	33 295 (203-415)
		18-50	9,391	29,076	15 5.16 (2.89-8.51)	24 8.25 (5.29-12.3)	17 5.85 (3.41-9.36)	1249 430 (406-454)	62,271	49 7.87 (5.82-10.4)	43 6.91 (5-9.3)	44 7.07 (5.13-9.49)	2327 374 (359-389)
		50-70	11,875	35,705	9 2.52 (1.15-4.79)	11 3.08 (1.54-5.51)	24 6.72 (4.31-10.0)	1058 296 (279-315)	73,580	26 3.53 (2.31-5.18)	19 2.58 (1.55-4.03)	48 6.52 (4.81-8.65)	2005 272 (261-285)
		>70	3,852	8,809	<5 - (-)	<5 - (-)	<5 - (-)	237 269 (236-306)	17,699	<5 - (-)	<5 - (-)	10 5.65 (2.71-10.4)	464 2626 (239-287)
	male	< 18	43	96	0 0 (0-384)	0 0 (0-384)	0 0 (0-384)	0 0 (0-384)	267	<5 - (-)	0 0 (0-138)	<5 - (-)	6 225 (82.5-489)
		18-50	1,869	4,872	5 10.26 (3.33-23.9)	<5 - (-)	<5 - (-)	164 337 (287-392)	12,162	13 10.7 (5.69-18.3)	7 5.76 (2.31-11.9)	7 5.76 (2.31-11.9)	320 263 (235-294)
		50-70	3,770	11,272	<5 - (-)	<5 - (-)	<5 - (-)	242 215 (188-244)	21,474	5 2.33 (0.76-5.43)	<5 - (-)	11 5.12 (2.56-9.17)	414 193 (175-212)
		>70	1,422	3,207	<5 - (-)	0 0 (0-11.5)	<5 - (-)	51 159 (118-209)	5,778	<5 - (-)	0 0 (0-6.38)	<5 - (-)	105 182 (149-220)
with neuropsychiatric history	female	< 18	18	33	0 0 (0-1123)	0 0 (0-1124)	0 0 (0-1124)	6 1828 (671-3979)	97	0 0 (0-380)	0 0 (0-380.3)	0 0 (0-380)	11 1134 (566-2029)
		18-50	3,766	10,658	12 11.26 (5.82-19.7)	18 16.9 (10.0-26.7)	15 14.1 (7.88-23.2)	764 717 (667-770)	22,446	35 15.59 (10.9-21.7)	35 15.6 (10.9-21.7)	38 16.9 (12.0-23.2)	1337 596 (564-628)
		50-70	4,718	12,522	8 6.39 (2.76-12.6)	10 7.99 (3.83-14.7)	21 16.8 (10.4-25.6)	695 555 (515-598)	25,800	23 8.91 (5.65-13.4)	16 6.2 (3.54-10.1)	36 13.9 (9.77-19.3)	1262 489 (463-517)
		>70	1,136	2,404	0 0 (0-15.35)	0 0 (0-15.4)	<5 - (-)	119 495 (410-592)	4,815	<5 - (-)	<5 - (-)	<5 - (-)	229 476 (416-541)
	male	< 18	<5	1.42	0 0 (0-25978)	0 0 (0-259782)	0 0 (0-259782)	0 0 (0-25978)	5	0 0 (0-7377)	0 0 (0-7378)	0 0 (0-7378)	<5 - (-)
		18-50	455	1,064	<5 - (-)	<5 - (-)	<5 - (-)	75 705 (554-883)	2,533	11 43.4 (21.7-77.7)	5 19.7 (6.41-46.1)	5 19.7 (6.41-46.1)	146 576.4 (487-678)
		50-70	871	2,444	<5 - (-)	<5 - (-)	<5 - (-)	132 540 (452-640)	4,548	<5 - (-)	<5 - (-)	7 15.4 (6.19-31.7)	213 468 (408-536)
		>70	239	496	<5 - (-)	0 0 (0-74.4)	<5 - (-)	25 504 (326-744)	867	<5 - (-)	0 0 (0-42.6)	<5 - (-)	39 450 (320-615)
no neuropsychiatric history	female	< 18	181	463	0 0 (0-79.7)	0 0 (0-79.7)	0 0 (0-79.7)	13 281 (150-480)	1,020	<5 - (-)	<5 - (-)	0 0 (0-36.2)	22 216 (135-327)
		18-50	5,625	18,418	<5 - (-)	6 3.26 (1.20-7.09)	<5 - (-)	485 263 (240-287.9)	39,825	14 3.52 (1.92-5.90)	8 2.01 (0.87-3.96)	6 1.51 (0.55-3.28)	990 249 (233-265)
		50-70	7,157	23,183	<5 - (-)	<5 - (-)	<5 - (-)	363 157 (141-174)	47,779	<5 - (-)	<5 - (-)	12 2.51 (1.3-4.39)	743 156 (145-167)
		>70	2,716	6,405	<5 - (-)	0 0 (0-5.76)	<5 - (-)	118 184 (152-221)	12,884	<5 - (-)	0 0 (0-2.86)	6 4.66 (1.71-10.1)	235 182 (160-207)
	male	< 18	42	94.6	0 0 (0-390)	0 0 (0-390)	0 0 (0-390.15)	0 0 (0-390)	262	<5 - (-)	0 0 (0-141)	<5 - (-)	5 191 (62.0-445)
		18-50	1,414	3,807	<5 - (-)	<5 - (-)	<5 - (-)	89 234 (188-288)	9,629	<5 - (-)	<5 - (-)	<5 - (-)	174 181 (155-210)
		50-70	2,899	8,828	<5 - (-)	<5 - (-)	<5 - (-)	110 125 (102-150)	16,926	<5 - (-)	<5 - (-)	<5 - (-)	201 119 (103-136)
		>70	1,183	2,711	0 0 (0-13.6)	0 0 (0-13.6)	<5 - (-)	26 95.9 (62.6-141)	4,911	0 0 (0-7.51)	0 0 (0-7.51)	<5 - (-)	66 134 (104-171)

Table 8.1. Dose (high dose vs low dose) in patients taking HCQ

Incident HCQ exposure [1]	daily dose (mg)	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)				any follow-up time	*n* any time vents event rate (95% CI)			
				suicidality	self-harm	psychosis related	non-psychotic depression		suicidality	self-harm	psychosis related	non-psychotic depression
all	≤300	14,196	43,141	13 3.01 (1.60-5.15)	18 4.17 (2.47-6.59)	22 5.1 (3.2-7.72)	1338 310 (294-327)	87,288	41 4.70 (3.37-6.37)	33 3.78 (2.6-5.31)	57 6.53 (4.95-8.46)	2489 285 (274-297)
	>300	18,210	50,329	22 4.37 (2.74-6.62)	21 4.17 (2.58-6.38)	32 6.36 (4.35-8.98)	1681 334 (318-350)	106,980	60 5.61 (4.28-7.22)	40 3.74 (2.67-5.09)	66 6.17 (4.77-7.85)	3184 298 (287-308)
with neuropsychiatric history	≤300	4,724	13,083	8 6.11 (2.64-12.1)	14 10.7 (5.85-18.0)	16 12.2 (6.99-19.9)	793 606 (565-650)	26,249	28 10.6 (7.09-15.4)	25 9.52 (6.16-14.1)	40 15.24 (10.9-20.8)	1379 525 (498-554)
	>300	6,478	16,538	18 10.9 (6.45-17.2)	16 9.67 (5.53-15.7)	29 17.5 (11.7-25.2)	1023 619 (581-658)	34,861	45 12.91 (9.42-17.3)	33 9.47 (6.52-13.3)	51 14.63 (10.9-19.2)	1859 533 (509-558)
no neuropsychiatric history	≤300	9,472	30,058	5 1.66 (0.54-3.88)	<5 - (-)	6 2 (0.73-4.34)	545 181 (166-197)	61,038	13 2.13 (1.13-3.64)	8 1.31 (0.57-2.58)	17 2.79 (1.62-4.46)	1110 182 (171-193)
	>300	11,732	33,790	<5 - (-)	5 1.48 (0.48-3.45)	<5 - (-)	658 194 (180-210)	72,118	15 2.08 (1.16-3.43)	7 0.97 (0.39-2.00)	15 2.08 (1.16-3.43)	1325 184 (174-194)

Table 9.1. Recorded indications in patients with HCQ

Incident HCQ exposure [1]	indication	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)				any follow-up time	*n* any time vents event rate (95% CI)			
				suicidality	self-harm	psychosis related	non-psychotic depression		suicidality	self-harm	psychosis related	non-psychotic depression
all	RA	15617	46614	17 3.65 (2.12-5.84)	17 3.65 (2.12-5.84)	24 5.15 (3.3-7.66)	1334 286 (271-302)	92,386	43 4.65 (3.37-6.27)	30 3.25 (2.19-4.64)	24 2.6 (1.66-3.87)	1334 144 (137-152)
	juvenile RA	181	538	0 0 (0-68.57)	0 0 (0-68.6)	0 0 (0-68.6)	26 483 (316-708)	1,135	0 0 (0-32.5)	<5 - (-)	0 0 (0-32.5)	26 229 (150-336)
	lupus	1420	5127	<5 - (-)	<5 - (-)	<5 - (-)	173 337 (289-392)	10,821	7 6.47 (2.6-13.3)	<5 - (-)	<5 - (-)	173 160 (137-186)
	systemic lupus	2125	9607	5 5.2 (1.69-12.2)	<5 - (-)	9 9.37 (4.28-17.8)	349 363 (326-403)	15,280	11 7.2 (3.59-12.9)	5 3.27 (1.06-7.64)	9 5.89 (2.69-11.2)	349 228 (205-254)
	other	810	1836	0 0 (0-20.1)	0 0 (0-20.1)	<5 - (-)	61 332 (254-427)	4,271	<5 - (-)	0 0 (0-8.64)	<5 - (-)	61 143 (109-183)
	unknown	13271	33780	11 3.26 (1.63-5.83)	19 5.62 (3.39-8.78)	20 5.92 (3.62-9.14)	1214 359 (339-380)	77,548	42 5.42 (3.9-7.32)	36 4.64 (3.25-6.43)	20 2.58 (1.58-3.98)	1214 157 (148-166)
with neuropsychiatric history	RA	5009	13382	14 10.5 (5.72-17.6)	14 10.5 (5.72-17.6)	20 14.95 (9.13-23.1)	788 589 (548-631)	26,683	33 12.37 (8.51-17.4)	24 8.99 (5.76-13.4)	20 7.5 (4.58-11.6)	788 295 (275-317)
	juvenile RA	51	157	0 0 (0-234.96)	0 0 (0-235)	0 0 (0-235)	13 828 (441-1416)	299	0 0 (0-123)	0 0 (0-123)	0 0 (0-123)	13 435 (232-744)
	lupus	519	1742	<5 - (-)	0 0 (0-21.18)	<5 - (-)	103 591 (483-717)	3,575	<5 - (-)	<5 - (-)	<5 - (-)	103 288 (235-349)
	systemic lupus	750	3093	<5 - (-)	<5 - (-)	7 22.6 (9.1-46.6)	189 611 (527-705)	4,963	7 14.1 (5.67-29.1)	<5 - (-)	7 14.1 (5.67-29.1)	189 381 (328-439)
	other	322	702	0 0 (0-52.6)	0 0 (0-52.6)	<5 - (-)	42 598 (431-809)	1,514	<5 - (-)	0 0 (0-24.4)	<5 - (-)	42 277 (200-375)
	unknown	4919	11866	7 5.9 (2.37-12.2)	14 11.8 (6.45-19.8)	17 14.3 (8.35-22.9)	766 646 (601-693)	26,448	30 11.3 (7.65-16.2)	29 11.0 (7.34-15.8)	17 6.43 (3.74-10.3)	766 290 (269-311)
no neuropsychiatric history	RA	10608	33232	<5 - (-)	<5 - (-)	<5 - (-)	546 164 (151-179)	65,703	10 1.52 (0.73-2.8)	6 0.91 (0.34-1.99)	<5 - (-)	546 83.1 (76.3-90.4)
	juvenile RA	130	381	0 0 (0-96.8)	0 0 (0-96.8)	0 0 (0-96.8)	13 341 (182-583)	837	0 0 (0-44.1)	<5 - (-)	0 0 (0-44.1)	13 155 (82.7-266)
	lupus	901	3385	<5 - (-)	<5 - (-)	0 0 (0-10.9)	70 207 (161-261)	7,246	<5 - (-)	<5 - (-)	0 0 (0-5.09)	70 96.6 (75.3-122)
	systemic lupus	1375	6514	<5 - (-)	<5 - (-)	<5 - (-)	160 246 (209-287)	10,317	<5 - (-)	<5 - (-)	<5 - (-)	160 155 (132-181)
	other	488	1134	0 0 (0-32.5)	0 0 (0-32.5)	0 0 (0-32.5)	19 168 (101-262)	2,757	0 0 (0-13.4)	0 0 (0-13.4)	0 0 (0-13.4)	19 68.9 (41.5-107)
	unknown	8352	21914	<5 - (-)	5 2.28 (0.74-5.32)	<5 - (-)	448 204 (186-224)	51,100	12 2.35 (1.21-4.10)	7 1.37 (0.55-2.82)	<5 - (-)	448 87.7 (79.7-96.2)

Figure 1.1 Kaplan Meier survival curves showing time-to-event for neuropsychiatric events following first exposure: HCQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-720 days) than the 0-4200 days period of the large graph).

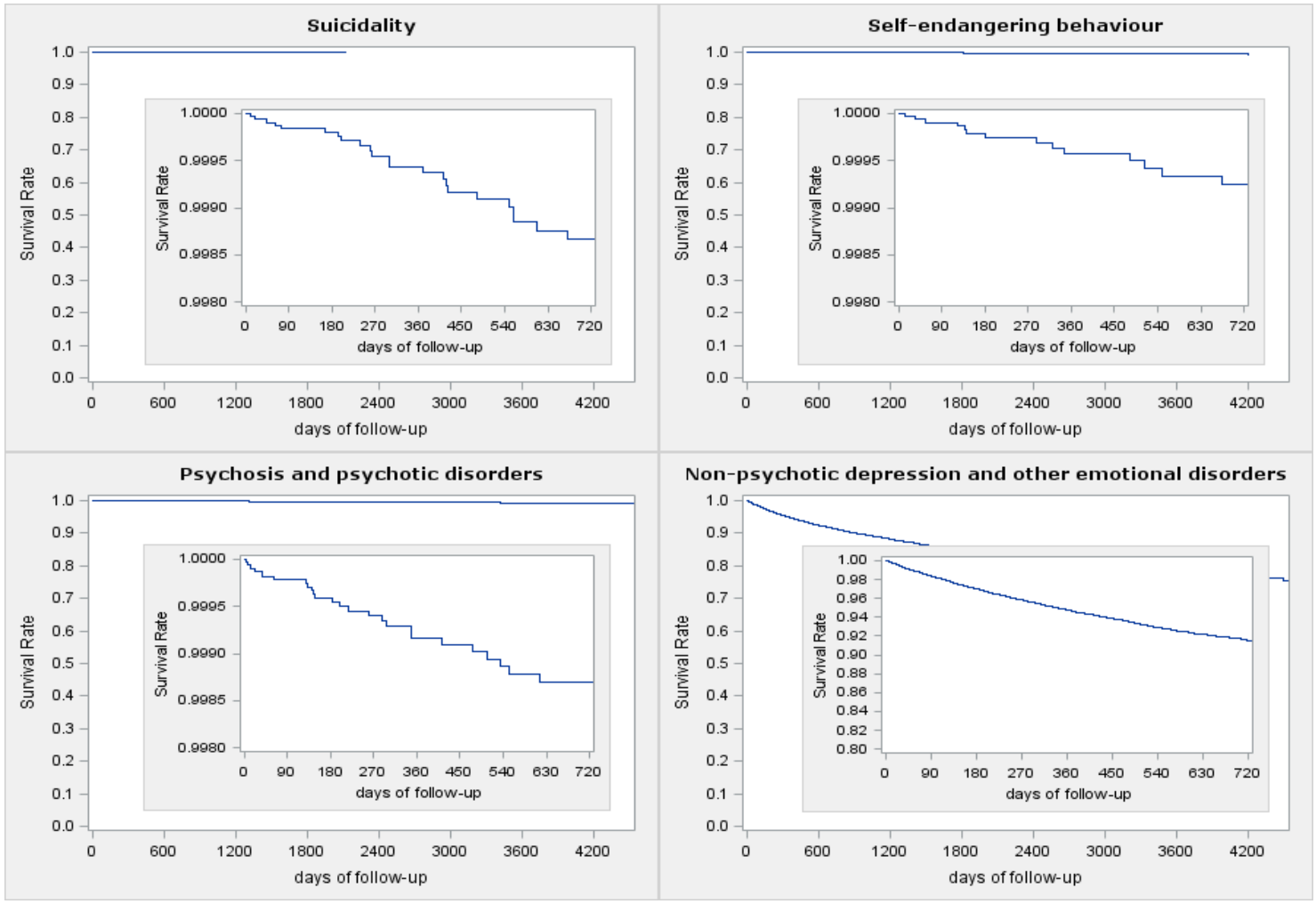


Figure 2.1 Kaplan Meier survival curves stratified by age: HCQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-720 days) than the 0-4200 days period of the large graph).

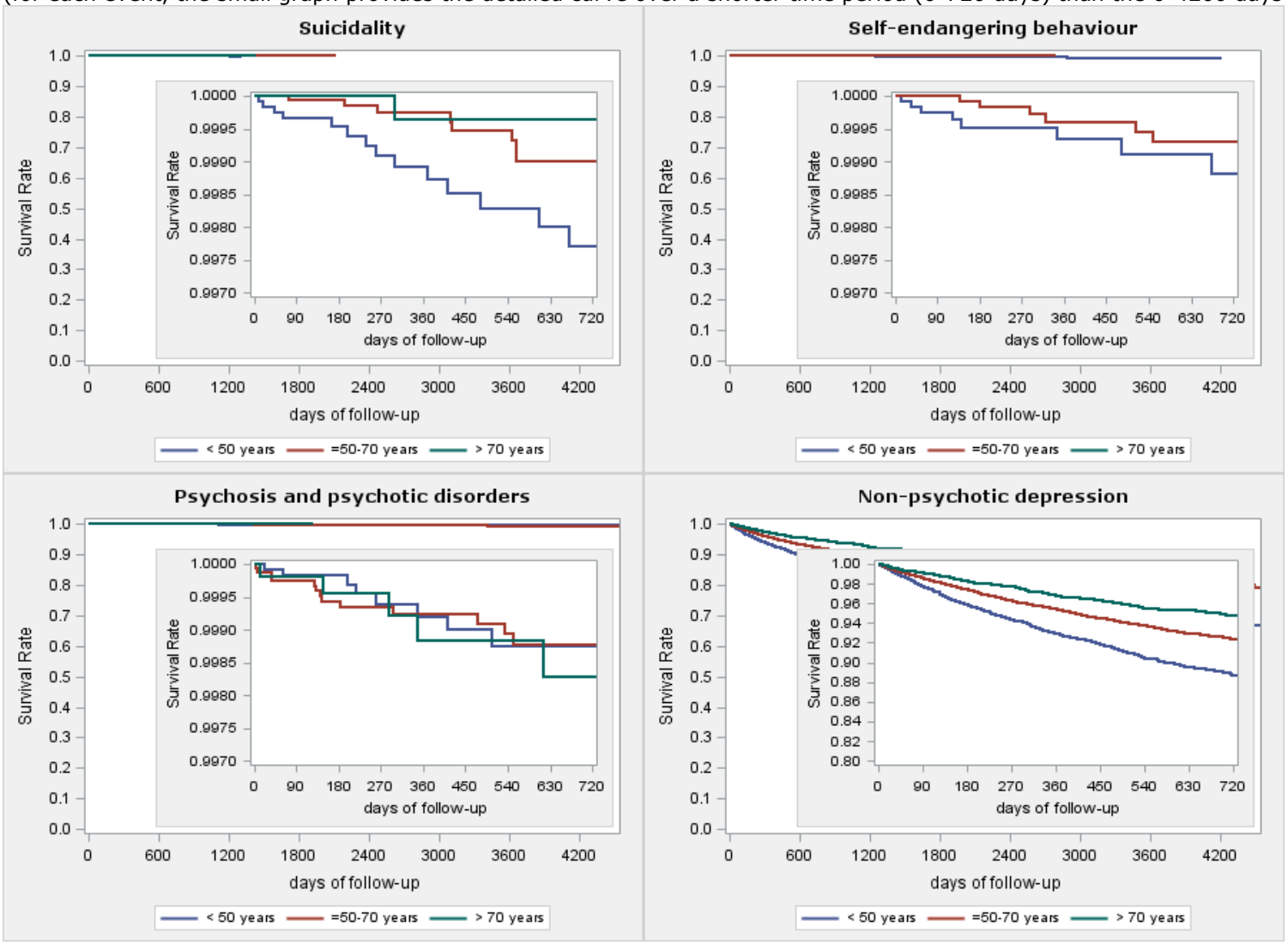


Figure 3.1 Kaplan Meier survival curves stratified by sex: HCQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-720 days) than the 0-4200 days period of the large graph).

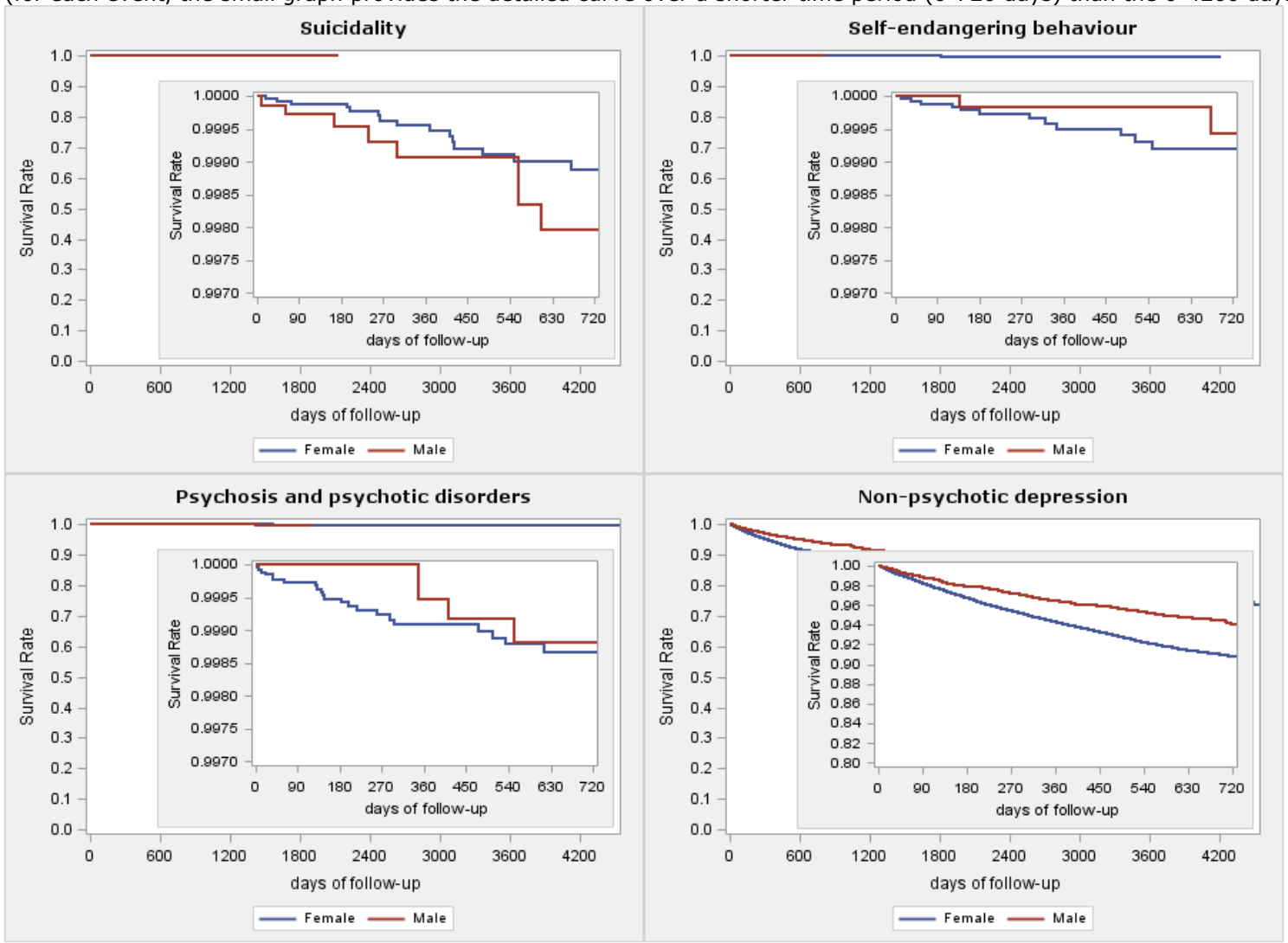


Figure 4.1 Kaplan Meier survival curves stratified by dose (≤300mg, >300mg): HCQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-720 days) than the 0-4200 days period of the large graph).

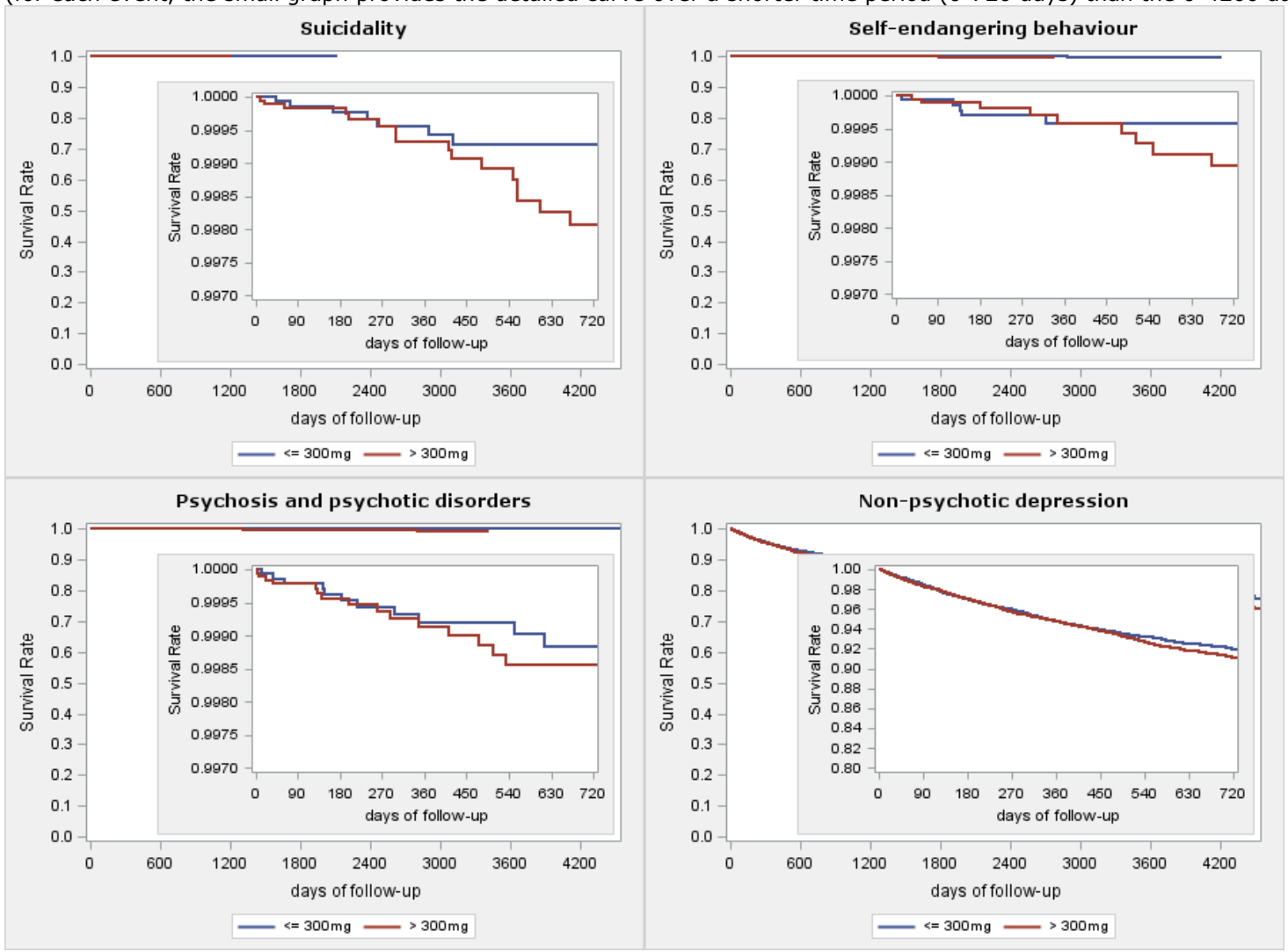


Figure 5.1 Kaplan Meier survival curves stratified by history of neuropsychiatric diagnoses: HCQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-720 days) than the 0-4200 days period of the large graph).

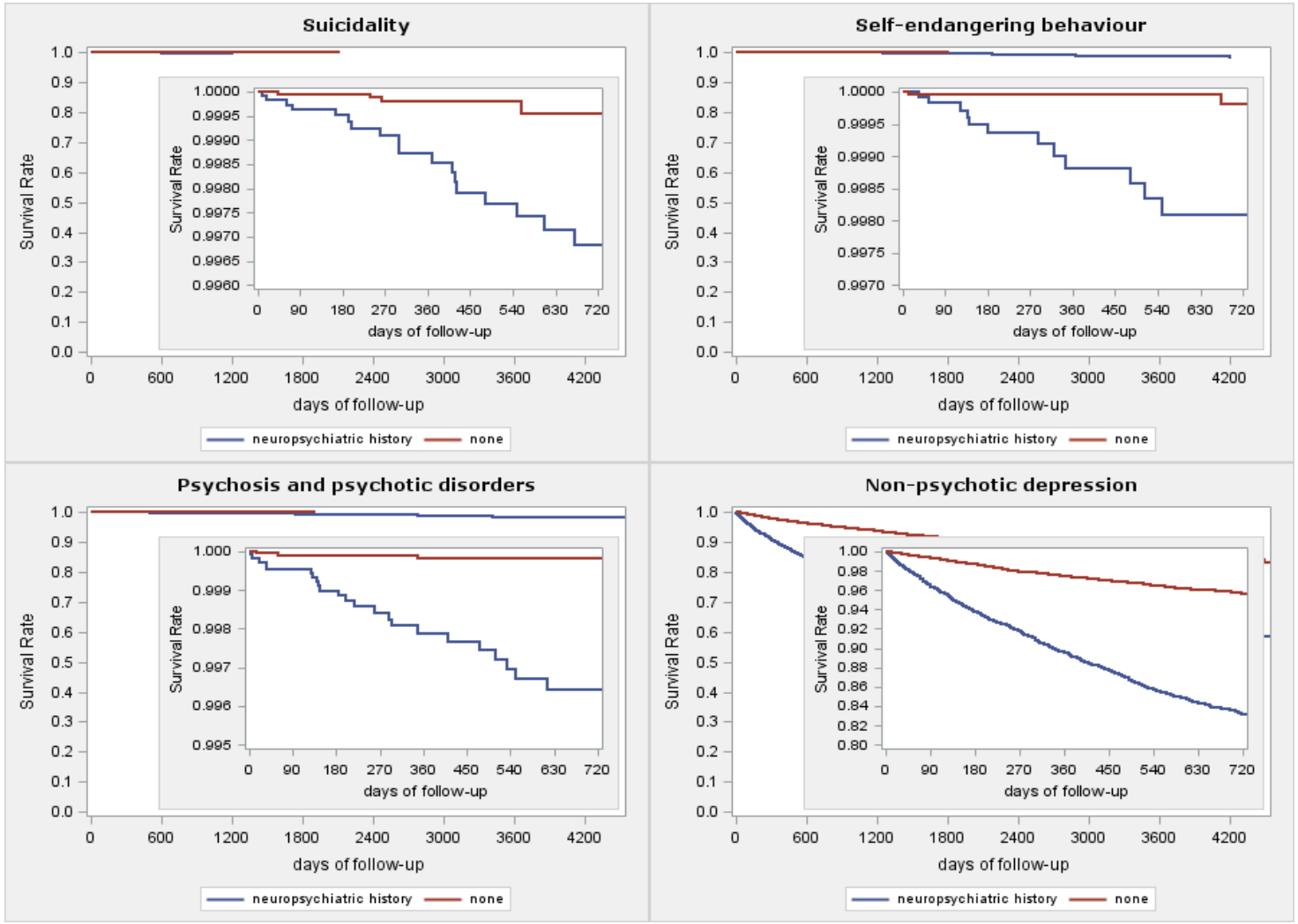
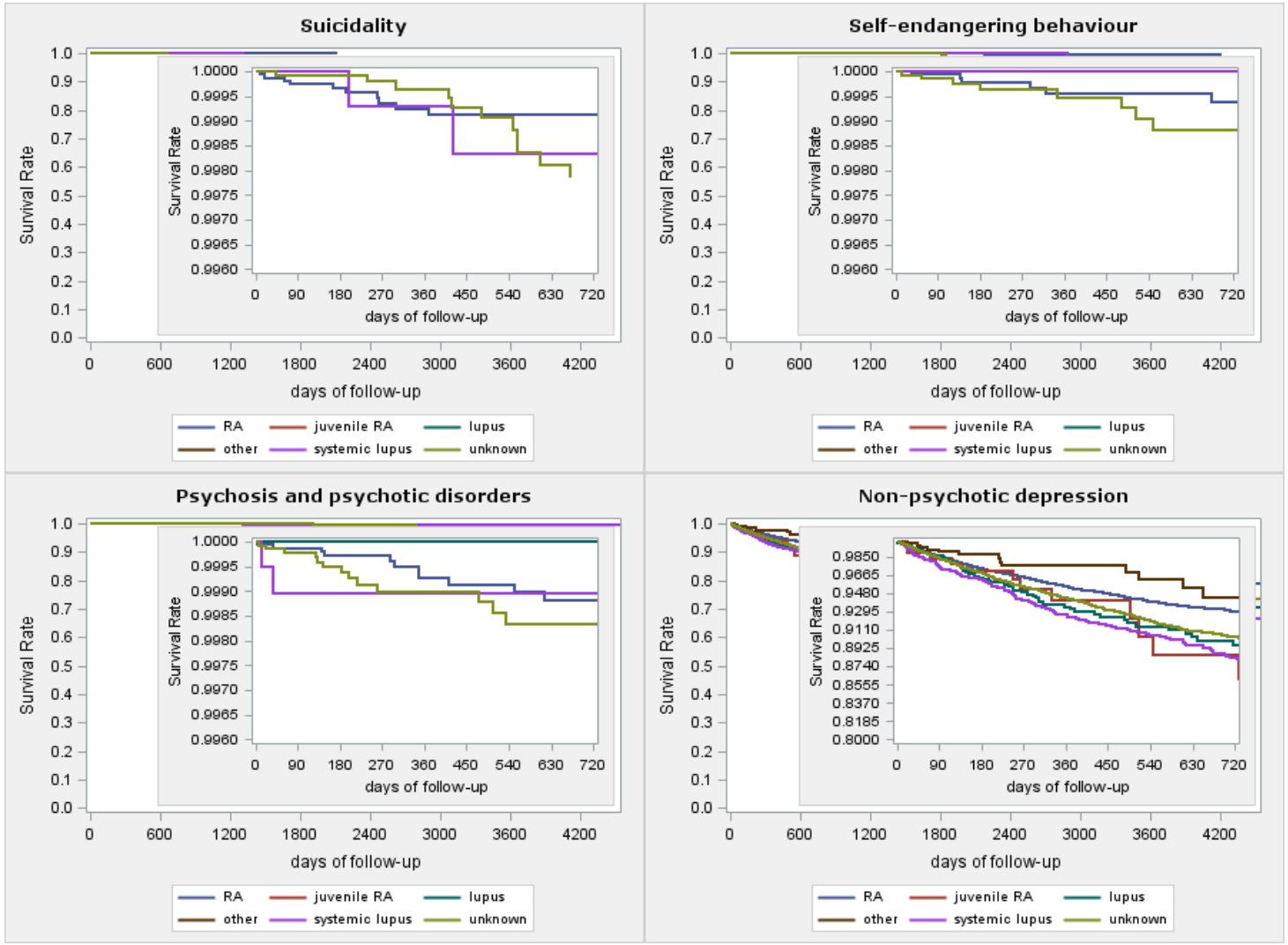


Figure 6.1 Kaplan Meier survival curves stratified by indication (RA, juvenile RA, lupus, other, unknown): HCQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-720 days) than the 0-4200 days period of the large graph).



7.2. Chloroquine

Prescribing data for CQ followed a very different pattern than for HCQ in IMRD-UK, with CQ having many more single prescription "spontaneous" episodes of use compared to the more typically chronic use HCQ. Dosage directions for such short-term use were frequently missing and the lack of a standard dosing regimen (which could be either based around daily-dosing for chronic autoimmune conditions or weekly-dosing for malarial prophylaxis) meant that only subjects with complete information on dosing were included. Similarly, calculation of cumulative dose was complicated by the lack of clear dosing instructions, the use of different dosage forms and the use of different salts of CQ (phosphate vs sulfate vs not stated) at different strengths: this meant that dose of CQ is simply classified as either daily- or weekly-base regimen.

7.2.1. Pattern of use: CQ

Descriptive analyses were performed to describe and summarise the study cohorts (CQ) at baseline: this includes the number of patients exposed, age at first use, sex, year of first use and numbers of prescriptions and exposure windows per patient. This describes indication, the proportion of patients with previous neuropsychiatric diagnoses, and dose of CQ. The cumulative dose of HCQ at the time of event has not been summarised.

Table 1.3. Patient demographic summary

	Chloroquine
Total no of patients	8,443
No. of female patients (%)	4,431 (52.5)
Mean age in years (SD)	41.4 (17.3)
Median age (IQR)	41(28 - 55)
Min- max age	1 - 89
No. with missing age information	0
Start year before 2000	6,619 (78.4%)
Start year 2000-2004	1,138 (13.5%)
Start year 2005-2009	522 (6.2%)
Start year 2010-2014	145 (1.7%)
Start year 2015-2019	19 (0.2%)

Table 2.3 Prescriptions and treatment episodes

	Chloroquine
Total no. of patients	8,443
Total no. of episodes	9,507
Min-max episodes	1 - 15
Mean episodes (SD)	1.13 (0.50)
Median episodes (IQR)	1 (1 - 1)
Total no. of prescription dates	11,671
Min-max prescription dates	1 - 154
Mean prescription dates (SD)	1.38 (3.19)
Median prescription dates (IQR)	1 (1 - 1)
No. of patients with calculated start dose (calculated dose during first treatment episode)	8,443
No. of patients with weekly dosed regimen	7,983 (94.6%)
No. of patients with daily dosed regimen	460 (5.5%)

Table 3.3 Indications

	Chloroquine
Total no of patients with any diagnosis	2,578 (30.5%)
No of patients with no prior diagnosis	5,865 (69.5%)
No of patients with RA	146 (1.7%)
No of patients with juvenile RA	<5 (<0.2%)
No of patients with lupus	22 (0.3%)
No of patients with systemic lupus	24 (0.3%)
No of patients with malaria diagnosis	97 (1.2%)
No of patients with malaria prophylaxis	2,284 (27.1%)

Table 4.3 Prior neuropsychiatric diseases

	Chloroquine
All patients	8,443 (100%)
No of patients with any prior neuropsychiatric diagnosis	905 (10.7%)
No of patients with prior suicidal events	58 (0.7%)
No of patients with prior self-harm events	9 (0.1%)
No of patients with schizophrenia psychosis related events	22 (0.3%)
No of patients with affective psychosis related events	12 (0.1%)
No of patients with non-psychotic affective disorders	862 (10.2%)

Table 5.3 Cumulative dose of HCQ at the time of event

Analysis not completed because of low numbers of events and inconsistencies in dosage used.

7.2.2. Incidence rates: CQ

The analysis follows up from first use to event, end of treatment exposure or censoring. Incidence rates are calculated as the number of events occurring during follow-up divided by the person years of follow-up with 95% confidence intervals. These are broken down by type of treatment (CQ), age & sex, dose (daily vs weekly dosing), history of neuropsychiatric diagnoses and indication. The time from exposure to onset of event is described using Kaplan-Meier survival curves for the first treatment episode only: these are also broken down by age & sex, dose, history of neuropsychiatric diagnoses and indication.

Table 6.3. History of neuropsychiatric diagnoses: CQ

Incident CQ exposure [1]	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)					any follow-up time	*n* any time events event rate (95% CI)				
			suicidality	self-endangering	suicidality or self-endangering	psychosis related	non-psychotic depression		suicidality	self-endangering	suicidality or self-endangering	psychosis related	non-psychotic depression
no neuropsychiatric history	7,538	3,636	0 0 (0-10.2)	0 0 (0-10.2)	0 0 (0-10.2)	0 0 (0-10.2)	45 124 (90.3-166)	94,901	39 4.11 (2.92-5.62)	9 0.95 (0.43-1.8)	45 4.74 (3.46-6.34)	24 2.53 (1.62-3.76)	1099 116 (109-123)
suicidality	58	42	<5 - (-)	0 0 (0-878)	<5 - (-)	0 0 (0-878)	6 1429 (524-3109)	686	<5 - (-)	<5 - (-)	<5 - (-)	0 0 (0-53.8)	34 496 (343-693)
self-endangering behaviour	9	4	0 0 (0-9222)	0 0 (0-9222)	0 0 (0-9222)	0 0 (0-9222)	<5 - (-)	95	<5 - (-)	<5 - (-)	<5 - (-)	0 0 (0-388)	<5 - (-)
Psychosis and psychotic disorders	30	15	0 0 (0-2459)	0 0 (0-2459)	0 0 (0-2459)	<5 - (-)	<5 - (-)	324	<5 - (-)	<5 - (-)	<5 - (-)	7 216 (86.9-445)	11 340 (169-607)
Non-psychotic depression and other emotional disorders	862	474	<5 - (-)	0 0 (0-77.8)	<5 - (-)	<5 - (-)	66 1392 (1076-1771)	10,295	14 13.6 (7.43-22.8)	6 5.83 (2.14-12.7)	18 17.5 (10.4-27.6)	18 17.5 (10.4-27.6)	406 394 (357-435)

Table 7.3. Age & sex distribution in patients taking CQ

Incident CQ exposure [1]	sex	age (years)	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)				any follow-up time	*n* any time vents event rate (95% CI)			
					suicidality	self-harm	psychosis related	non-psychotic depression		suicidality	self-harm	psychosis related	non-psychotic depression
all	female	< 18	309	141	0 0 (0-261)	0 0 (0-261)	0 0 (0-261)	0 0 (0-261)	3,756	<5 - (-)	<5 - (-)	0 0 (0-9.82)	63 168 (129-215)
		18-50	2,608	1244	<5 - (-)	0 0 (0-29.7)	0 0 (0-29.7)	63 506 (389-648)	31,279	19 6.07 (3.66-9.49)	5 1.6 (0.52-3.73)	17 5.43 (3.17-8.7)	633 202 (187-219)
		50-70	1327	737	0 0 (0-50.0)	0 0 (0-50.0)	0 0 (0-50.0)	22 298 (187-451)	18,399	8 4.35 (1.88-8.57)	<5 - (-)	6 3.26 (1.20-7.10)	290 158 (140-177)
		>70	187	108	0 0 (0-341)	0 0 (0-341)	0 0 (0-341)	<5 - (-)	2,004	0 0 (0-18.4)	0 0 (0-18.4)	0 0 (0-18.4)	43 215 (155-289)
	male	< 18	391	166	0 0 (0-223)	0 0 (0-223)	0 0 (0-223)	0 0 (0-223)	4,666	<5 - (-)	5 10.7 (3.48-25.0)	<5 - (-)	38 81.4 (57.6-112)
		18-50	2,254	1051	0 0 (0-35.1)	0 0 (0-35.1)	<5 - (-)	12 114 (59.0-199)	28,064	17 6.06 (3.53-9.70)	<5 - (-)	13 4.63 (2.47-7.92)	283 101 (89.4-113)
		50-70	1,199	601	0 0 (0-61.4)	0 0 (0-61.4)	0 0 (0-61.4)	9 150 (68.5-284)	15,913	<5 - (-)	0 0 (0-2.32)	5 3.14 (1.02-7.33)	146 91.8 (77.5-108)
		>70	168	82.1	0 0 (0-449)	0 0 (0-449)	0 0 (0-449)	<5 - (-)	1,595	<5 - (-)	0 0 (0-23.1)	<5 - (-)	22 138 (86.4-209)
with neuropsychiatric history	female	< 18	<5	0.4	0 0 (0-87830)	0 0 (0-87830)	0 0 (0-87830)	0 0 (0-87830)	12	0 0 (0-3074)	0 0 (0-3074)	0 0 (0-3074)	<5 - (-)
		18-50	367	182	<5 - (-)	0 0 (0-203)	0 0 (0-203)	36 1977 (1385-2737)	4,196	8 19.1 (8.23-37.6)	5 11.9 (3.90-27.8)	7 16.7 (6.71-34.4)	186 443 (382-512)
		50-70	239	158	0 0 (0-233)	0 0 (0-233)	0 0 (0-233)	14 885 (484-1485)	3,056	<5 - (-)	<5 - (-)	<5 - (-)	110 360 (296-434)
		>70	28	15.5	0 0 (0-2377)	0 0 (0-2377)	0 0 (0-2377)	<5 - (-)	297	0 0 (0-124)	0 0 (0-124)	0 0 (0-124)	12 4044 (209-706)
	male	< 18	<5	1.2	0 0 (0-29749)	0 0 (0-29749)	0 0 (0-29749)	0 0 (0-29749)	33	0 0 (0-1118)	0 0 (0-1118)	0 0 (0-1118)	<5 - (-)

Incident CQ exposure [1]	sex	age (years)	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)				any follow-up time	*n* any time vents event rate (95% CI)			
					suicidality	self-harm	psychosis related	non-psychotic depression		suicidality	self-harm	psychosis related	non-psychotic depression
					0	0	<5	8		<5	0	6	67
		18-50	148	79.7	0	0	-	1004	1,850	-	0	32.4	362
					(0-463)	(0-463)	(-)	(433-1978)		(-)	(0-19.9)	(11.9-70.6)	(281-460)
					0	0	0	5		0	0	<5	38
		50-70	107	52.2	0	0	0	958	1,218	0	0	-	312
					(0-707)	(0-707)	(0-707)	(311-2237)		(0-30.3)	(0-30.3)	(-)	(221-428)
					0	0	0	<5		0	0	0	<5
		>70	12	5.2	0	0	0	-	114	0	0	0	-
					(0-7053)	(0-7053)	(0-7053)	(-)		(0-324)	(0-324)	(0-324)	(-)
					0	0	0	0		<5	<5	0	62
		< 18	308	141	0	0	0	0	3,744	-	-	0	166
					(0-262)	(0-262)	(0-262)	(0-262)		(-)	(-)	(0-9.85)	(127-212)
					0	0	0	27		11	0	10	447
		18-50	2,241	1062	0	0	0	254	27,083	4.06	0	3.69	165
	female				(0-34.74)	(0-34.74)	(0-34.74)	(168-370)		(2.03-7.27)	(0-1.36)	(1.77-6.79)	(150-181)
					0	0	0	8		5	0	<5	180
		50-70	1,088	580	0	0	0	138	15,343	3.26	0	-	117
					(0-63.64)	(0-63.64)	(0-63.64)	(59.6-272)		(1.06-7.60)	(0-2.40)	(-)	(101-136)
					0	0	0	<5		0	0	0	31
		>70	159	92.7	0	0	0	-	17707	0	0	0	181.6
no neuropsychiatric history					(0-398.07)	(0-398.07)	(0-398.07)	(-)		(0-21.6)	(0-21.6)	(0-21.6)	(123-257.8)
					0	0	0	0		<5	5	<5	37
		< 18	388	164	0	0	0	0	4,633	-	10.8	-	79.9
					(0-225)	(0-225)	(0-225)	(0-225)		(-)	(3.5-25.2)	(-)	(56.2-110)
					0	0	0	<5		14	<5	7	216
		18-50	2,106	971	0	0	0	-	26,214	5.34	-	2.67	82.4
	male				(0-38.0)	(0-38.0)	(0-38.0)	(-)		(2.92-8.96)	(-)	(1.07-5.5)	(71.8-94.2)
					0	0	0	<5		<5	0	<5	108
		50-70	1,092	549	0	0	0	-	14,695	-	0	-	73.5
					(0-67.2)	(0-67.2)	(0-67.2)	(-)		(-)	(0-2.51)	(-)	(60.3-88.73)
					0	0	0	0		<5	0	<5	18
		>70	156	76.9	0	0	0	0	1,482	-	0	-	121.5
					(0-480)	(0-480)	(0-480)	(0-480)		(-)	(0-24.89)	(-)	(72.0-192)

Table 8.3. Dose (daily vs weekly based dosage regimens) in patients taking CQ

Incident CQ exposure	dosage regimen	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)				any follow-up time	*n* any time vents event rate (95% CI)			
				suicidality	self-harm	psychosis related	non-psychotic depression		suicidality	self-harm	psychosis related	non-psychotic depression
all	daily-based	7,983	3,692	0 0 (0-9.99)	0 0 (0-9.99)	<5 - (-)	90 244 (196-300)	100,254	49 4.89 (3.62-6.46)	15 1.5 (0.84-2.47)	42 4.19 (3.02-5.66)	1402 140 (133-147)
	weekly-based	460	439	<5 - (-)	0 0 (0-84.0)	0 0 (0-84.0)	21 478 (296-731)	5,422	<5 - (-)	<5 - (-)	<5 - (-)	116 214 (177-257)
with neuropsychiatric history	daily-based	820	374	0 0 (0-98.63)	0 0 (0-98.6)	<5 - (-)	58 1551 (1178-2005)	9,858	13 13.2 (7.02-22.6)	7 7.1 (2.85-14.6)	19 19.3 (11.6-30.1)	379 384 (347-425)
	weekly-based	85	121	<5 - (-)	0 0 (0-305)	0 0 (0-305)	8 661 (285-1303)	917	<5 - (-)	0 0 (0-40.2)	<5 - (-)	40 436 (312-594)
no neuropsychiatric history	daily-based	7,163	3,318	0 0 (0-11.1)	0 0 (0-11.1)	0 0 (0-11.12)	32 96.4 (66.0-136)	90,396	36 3.98 (2.79-5.51)	8 0.88 (0.38-1.74)	23 2.54 (1.61-3.82)	1023 113 (106-120)
	weekly-based	375	318	0 0 (0-116)	0 0 (0-116)	0 0 (0-116)	13 409 (218-699)	4505	<5 - (-)	<5 - (-)	<5 - (-)	76 169 (133-211)

Table 9.3. Recorded indications in patients with CQ

Incident CQ exposure	indication	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)				any follow-up time	*n* any time vents event rate (95% CI)			
				suicidality	self-harm	psychosis related	non-psychotic depression		suicidality	self-harm	psychosis related	non-psychotic depression
all	RA	146	181	0 0 (0-204)	0 0 (0-204)	0 0 (0-204)	7 387 (155-797)	1,795	0 0 (0-20.6)	0 0 (0-20.6)	0 0 (0-20.6)	7 39.0 (15.7-80.4)
	juvenile RA	3	6	0 0 (0-6148)	0 0 (0-6148)	0 0 (0-6148)	0 0 (0-6148)	40	0 0 (0-913)	0 0 (0-913)	0 0 (0-913)	0 0 (0-913)
	lupus	22	38	0 0 (0-971)	0 0 (0-971)	0 0 (0-9701)	<5 - (-)	254	0 0 (0-145)	0 0 (0-145)	0 0 (0-145)	<5 - (-)
	systemic lupus	24	50	0 0 (0-738)	0 0 (0-738)	0 0 (0-738)	0 0 (0-738)	260	0 0 (0-142)	0 0 (0-142)	0 0 (0-142)	0 0 (0-142)
	other	59	29	0 0 (0-1272)	0 0 (0-1272)	0 0 (0-1272)	<5 - (-)	659	0 0 (0-56.0)	<5 - (-)	0 0 (0-56.0)	<5 - (-)
	unknown	5,865	2,789	<5 - (-)	0 0 (0-13.23)	<5 - (-)	82 294 (234-365)	73,695	42 5.7 (4.11-7.70)	14 1.90 (1.04-3.19)	<5 - (-)	82 11.2 (8.85-13.8)
	malaria diagnosis	97	45	0 0 (0-820)	0 0 (0-820)	0 0 (0-820)	<5 - (-)	1,132	0 0 (0-32.6)	0 0 (0-32.6)	0 0 (0-32.6)	<5 - (-)
	malaria prophylaxis	2,284	1,046	0 0 (0-35.3)	0 0 (0-35.3)	0 0 (0-35.3)	19 182 (109-284)	28,427	11 3.87 (1.93-6.92)	<5 - (-)	0 0 (0-1.3)	19 6.68 (4.02-10.4)

Incident CQ exposure	indication	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)				any follow-up time	*n* any time vents event rate (95% CI)			
				suicidality	self-harm	psychosis related	non-psychotic depression		suicidality	self-harm	psychosis related	non-psychotic depression
with neuropsychiatric history	RA	36	59	0 0 (0-625)	0 0 (0-625)	0 0 (0-625)	<5 - (-)	459	0 0 (0-80.4)	0 0 (0-80.4)	0 0 (0-80.4)	<5 - (-)
	juvenile RA	0	0	-	-	-	-	0	-	-	-	-
	lupus	6	5	0 0 (0-7378)	0 0 (0-7378)	0 0 (0-7378)	0 0 (0-7378)	53	0 0 (0-693)	0 0 (0-693)	0 0 (0-693)	0 0 (0-693)
	systemic lupus	7	30	0 0 (0-1230)	0 0 (0-1230)	0 0 (0-1230)	0 0 (0-1230)	62	0 0 (0-599)	0 0 (0-599)	0 0 (0-599)	0 0 (0-599)
	other	15	7	0 0 (0-5270)	0 0 (0-5270)	0 0 (0-5270)	<5 - (-)	148	0 0 (0-250)	<5 - (-)	0 0 (0-250)	<5 - (-)
	unknown	612	305	<5 - (-)	0 0 (0-121)	<5 - (-)	50 1639 (1217-2161)	7,428	12 16.2 (8.35-28.2)	6 8.08 (2.96-17.6)	<5 - (-)	50 67.3 (50.0-88.8)
	malaria diagnosis	3	1	0 0 (0-36889)	0 0 (0-36889)	0 0 (0-36889)	0 0 (0-36889)	25	0 0 (0-1469)	0 0 (0-1469)	0 0 (0-1469)	0 0 (0-1469)
	malaria prophylaxis	237	109	0 0 (0-338)	0 0 (0-338)	0 0 (0-338)	13 1193 (635-2039)	2,708	<5 - (-)	0 0 (0-13.6)	0 0 (0-13.6)	13 48.0 (25.6-82.1)

Incident CQ exposure	indication	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)				any follow-up time	*n* any time vents event rate (95% CI)			
				suicidality	self-harm	psychosis related	non-psychotic depression		suicidality	self-harm	psychosis related	non-psychotic depression
no neuropsychiatric history	RA	110	122	0 0 (0-302)	0 0 (0-302)	0 0 (0-302)	5 410 (133-956)	1,335	0 0 (0-27.6)	0 0 (0-27.6)	0 0 (0-27.6)	5 37.4 (12.2-87.4)
	juvenile RA	<5	6	0 0 (0-6148)	0 0 (0-6148)	0 0 (0-6148)	0 0 (0-6148)	40	0 0 (0-913)	0 0 (0-913)	0 0 (0-913)	0 0 (0-913)
	lupus	16	32	0 0 (0-1153)	0 0 (0-1153)	0 0 (0-1153)	<5 - (-)	201	0 0 (0-184)	0 0 (0-184)	0 0 (0-184)	<5 - (-)
	systemic lupus	17	20	0 0 (0-1844)	0 0 (0-1844)	0 0 (0-1844)	0 0 (0-1844)	198	0 0 (0-186)	0 0 (0-186)	0 0 (0-186)	0 0 (0-186)
	other	44	21	0 0 (0-1757)	0 0 (0-1757)	0 0 (0-1757)	0 0 (0-1757)	511	0 0 (0-72.2)	0 0 (0-72.2)	0 0 (0-72.2)	0 0 (0-72.2)
	unknown	5,253	2484	0 0 (0-14.9)	0 0 (0-14.9)	0 0 (0-14.9)	32 129 (88.1-182)	66,268	30 4.53 (3.05-6.46)	8 1.21 (0.52-2.38)	0 0 (0-0.56)	32 4.83 (3.3-6.82)
	malaria diagnosis	94	44	0 0 (0-839)	0 0 (0-839)	0 0 (0-839)	<5 - (-)	1,107	0 0 (0-33.3)	0 0 (0-33.3)	0 0 (0-33.3)	<5 - (-)
	malaria prophylaxis	2,047	938	0 0 (0-39.3)	0 0 (0-39.3)	0 0 (0-39.3)	6 64.0 (23.4-139)	25,719	9 3.50 (1.60-6.64)	<5 - (-)	0 0 (0-1.43)	6 2.33 (0.86-5.08)

Figure 1.3 Kaplan Meier survival curves showing time-to-event for neuropsychiatric events following first exposure: CQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-720 days) than the 0-4200 days period of the large graph).

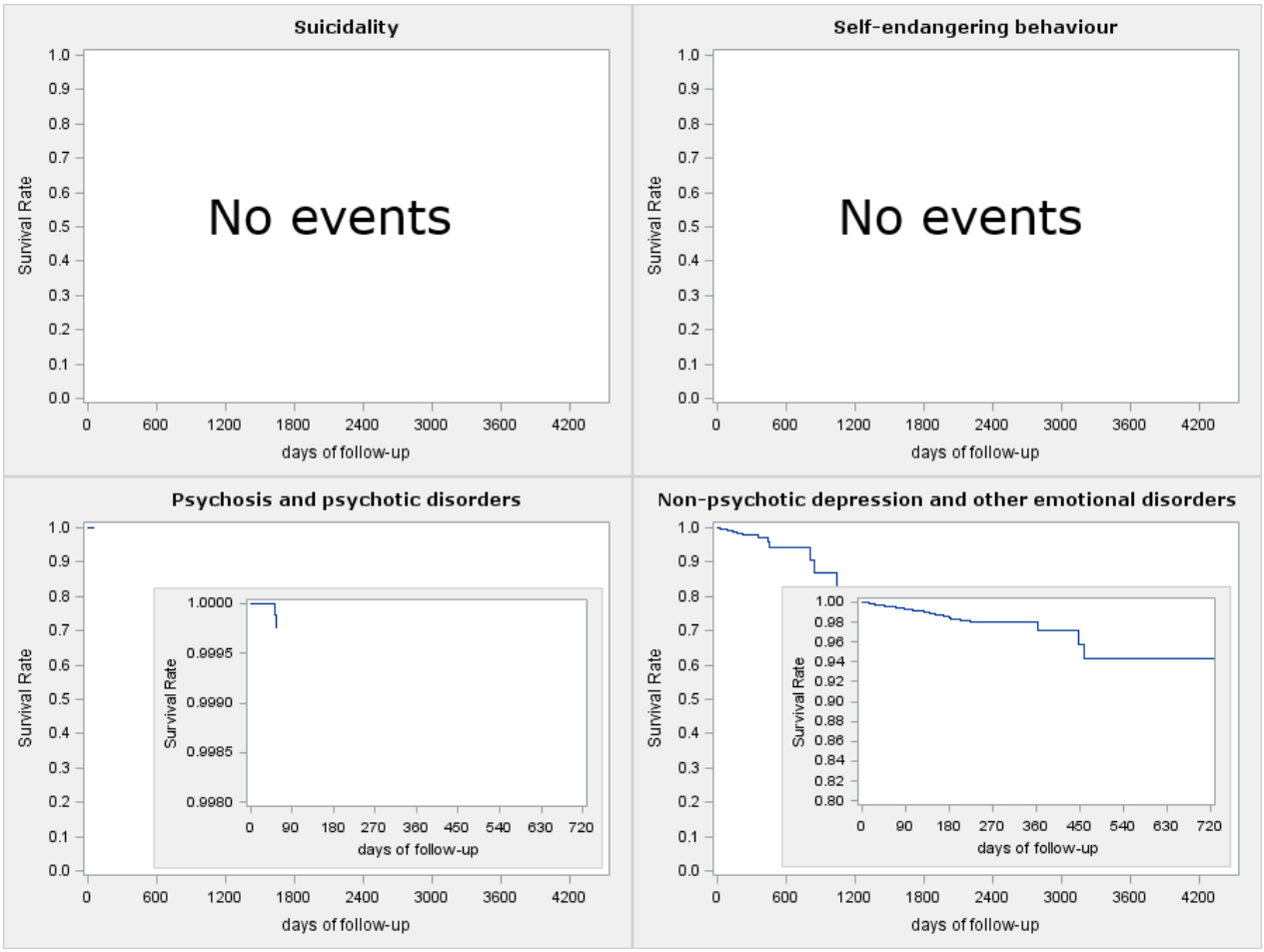


Figure 2.3 Kaplan Meier survival curves stratified by age: CQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-720 days) than the 0-4200 days period of the large graph).

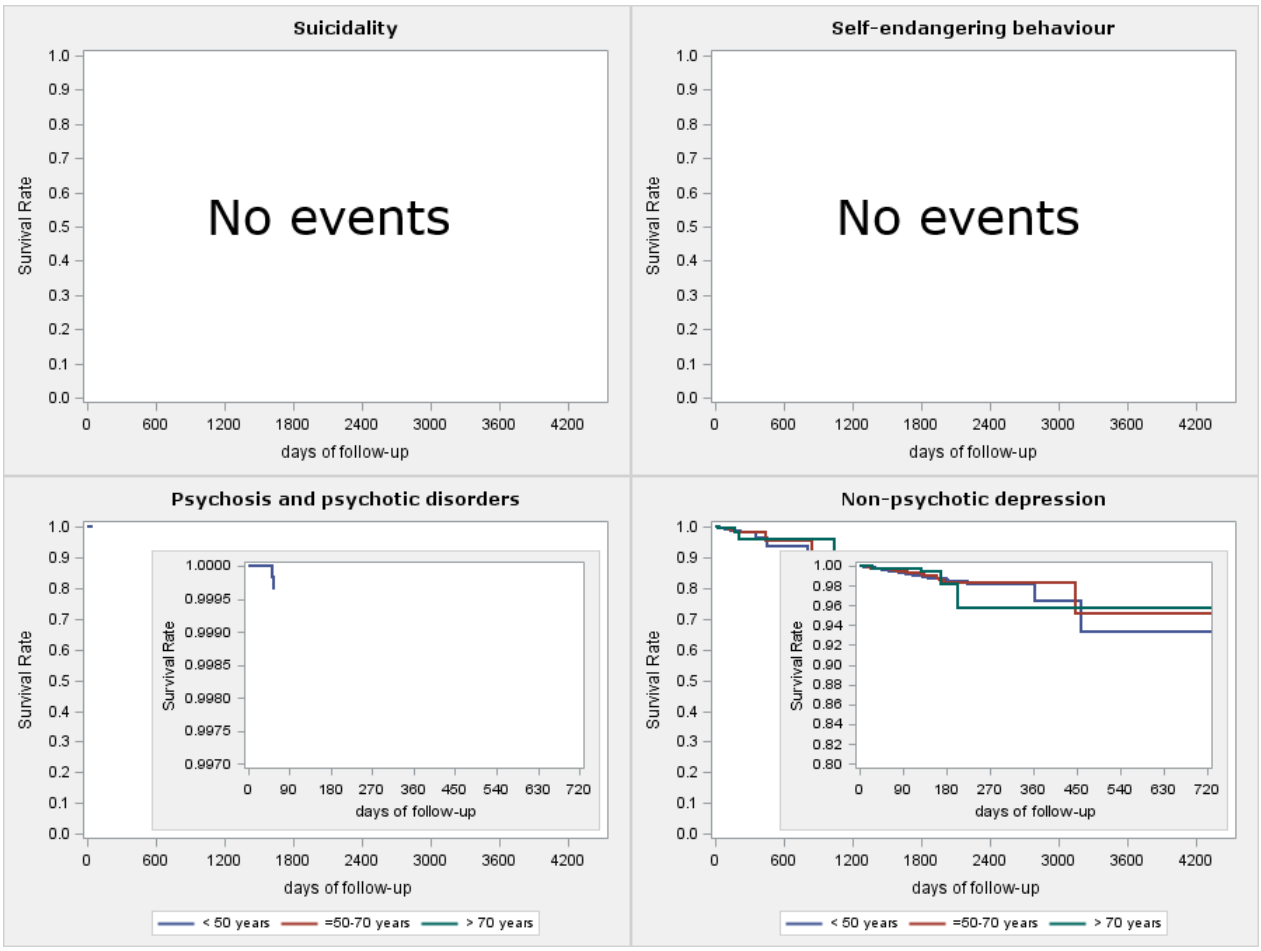


Figure 3.3 Kaplan Meier survival curves stratified by sex: CQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-720 days) than the 0-4200 days period of the large graph).

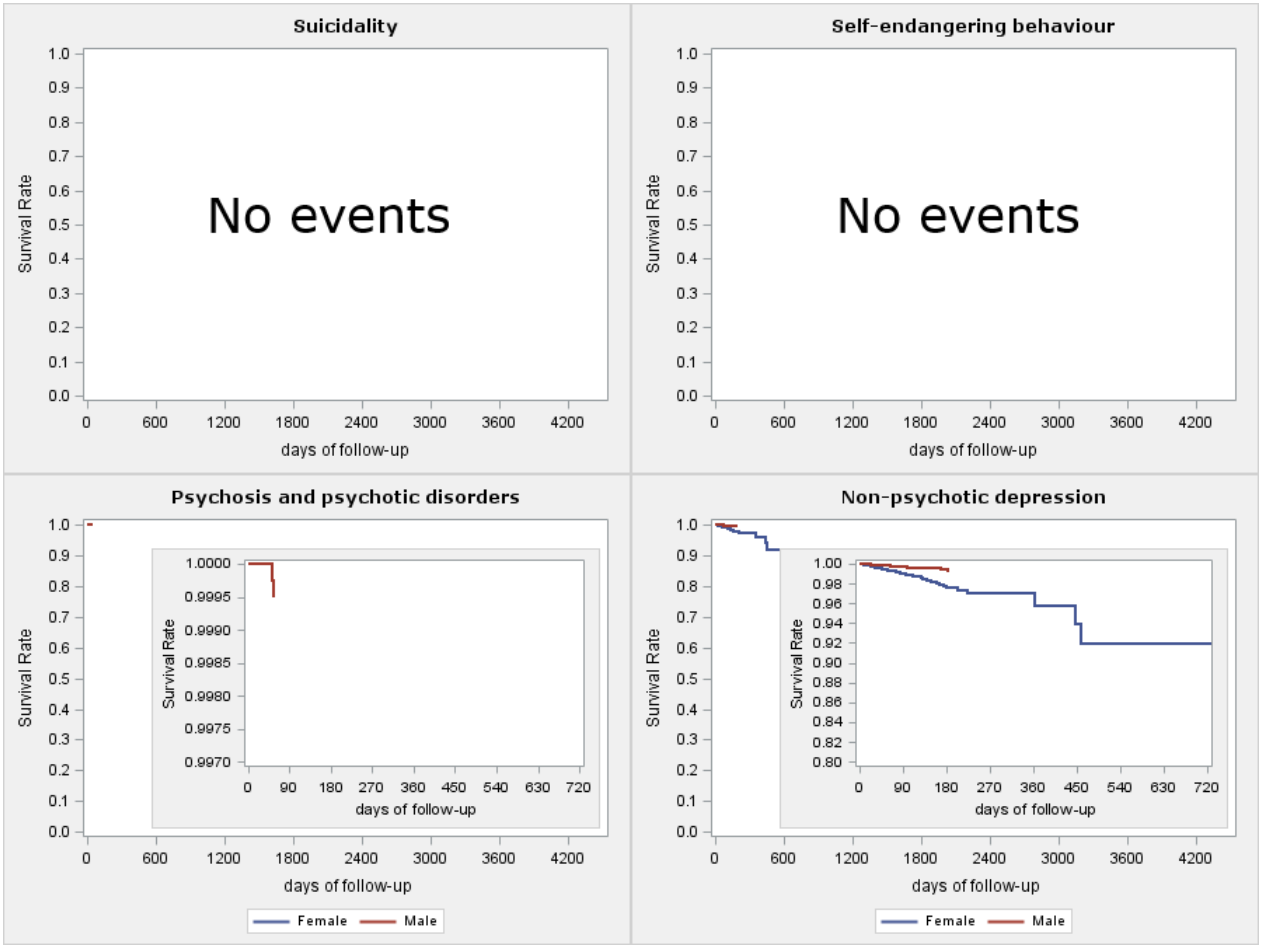


Figure 4.3 Kaplan Meier survival curves stratified by dose (≤300mg, >300mg): CQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-720 days) than the 0-4200 days period of the large graph).

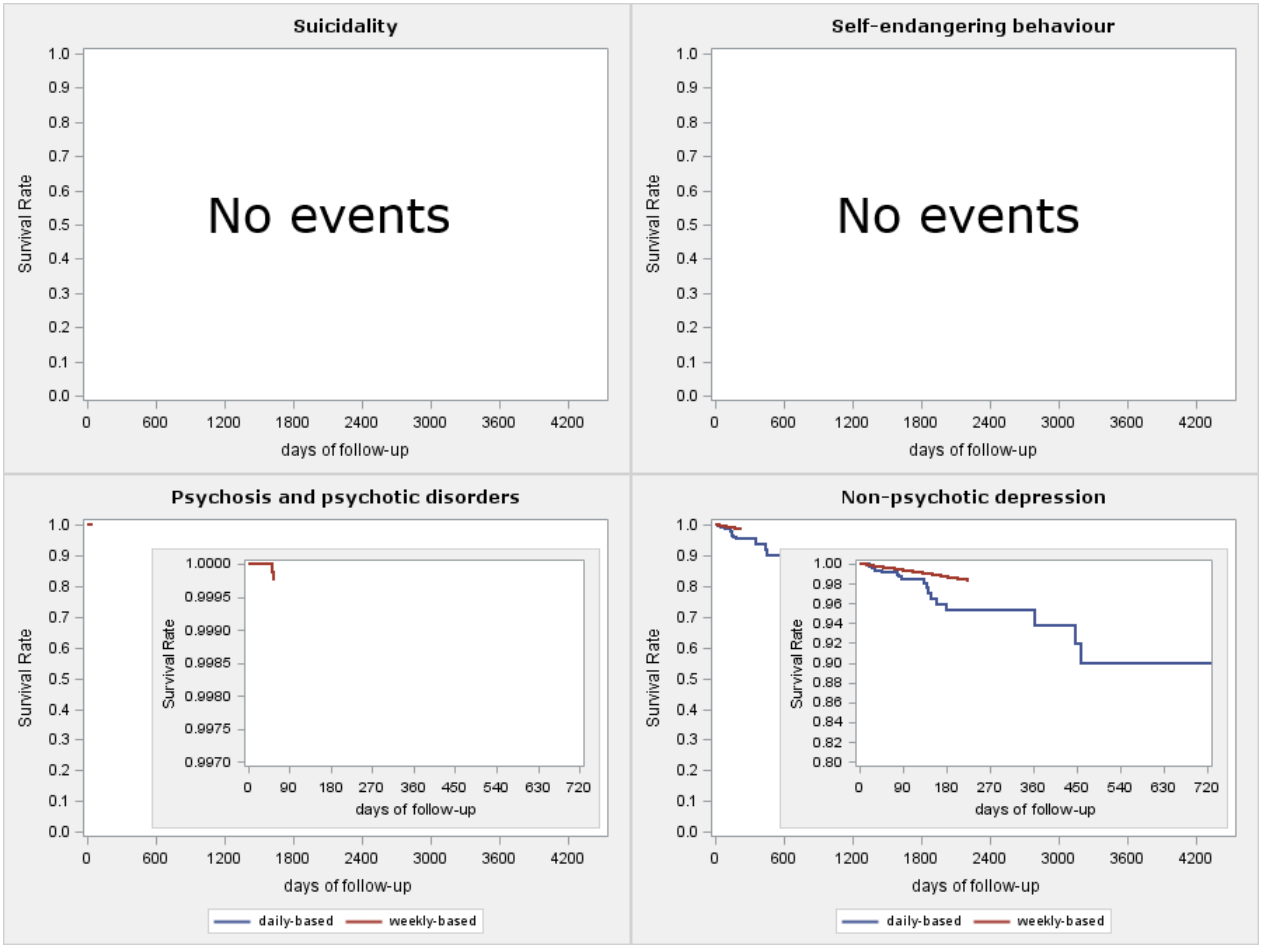


Figure 5.3 Kaplan Meier survival curves stratified by history of neuropsychiatric diagnoses: HCQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-720 days) than the 0-4200 days period of the large graph).

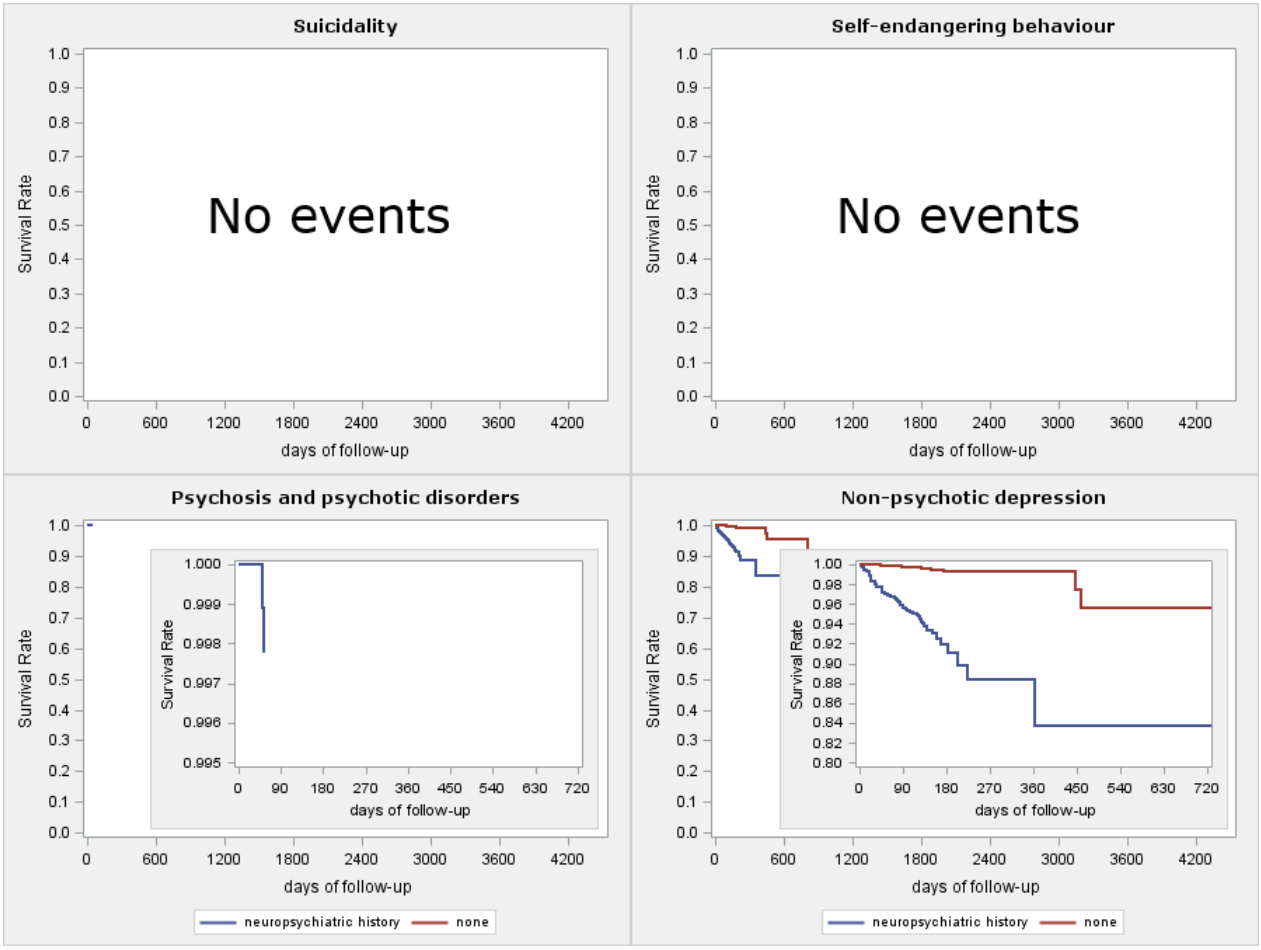
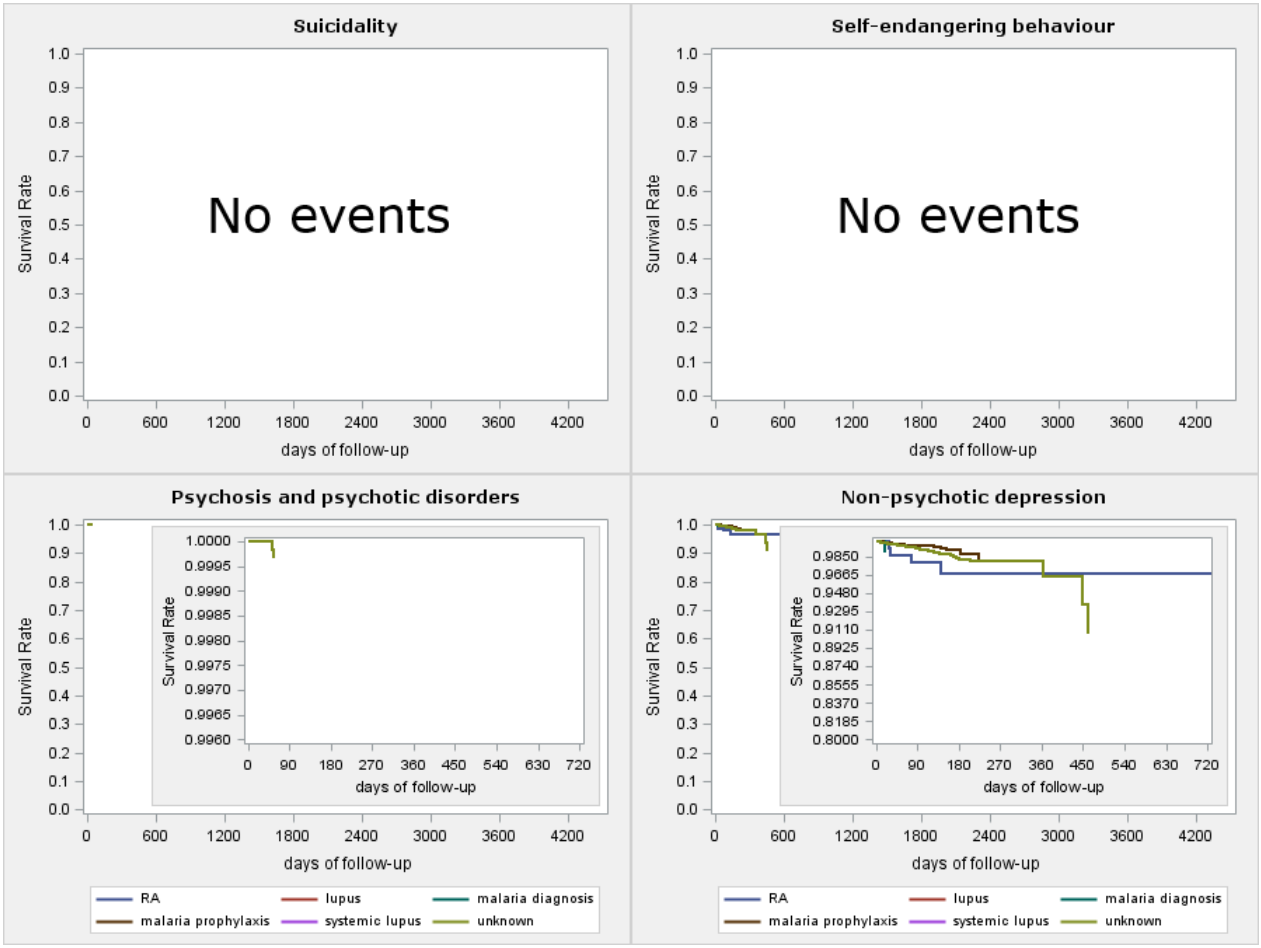


Figure 6.3 Kaplan Meier survival curves stratified by indication (RA, juvenile RA, lupus, other, unknown): CQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-720 days) than the 0-4200 days period of the large graph).



8. References

Arana A, Arellano F, Wentworth C, Price J. An Algorithm for the Diagnosis of Suicide in the THIN Database. Pharmacoepidemiol Drug Saf 2010;19:S309-10

Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424.

Carroll R, Hawton K, Kapur N, Bennewith O, Gunnell D. Impact of the Growing Use of Narrative Verdicts by Coroners on Geographic Variations in Suicide: Analysis of Coroners' Inquest Data. J Public Health (Oxf) 2012;34(3):447-53. doi: 10.1093/pubmed/fdr091.

Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. Am J Epidemiol 2006;163(12):1149-56.

Gonzalez-Nieto JA, Costa-Juan E. Psychiatric symptoms induced by hydroxychloroquine. Lupus. 2015;24(3):339-340. doi:10.1177/0961203314558863

Juurlink DN. Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. CMAJ. 2020;192(17):E450-E453. doi:10.1503/cmaj.200528

Lane JC, Weaver J, Kostka K, et al. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study. medRxiv; 2020. DOI: 10.1101/2020.04.08.20054551.

Office for National Statistics. Suicides in the UK: 2017 registrations. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/suicidesintheunitedkingdom/2017registrations (last accessed on 17/06/2020)

Prieto-Alhambra D, Lane J, Morales D, Schuemie M, Weaver J, Fišter K, Suchard M, Khosla S, Newby D, Wen H, Casajust P, Margulis A. Hydroxychloroquine safety and potential efficacy as an antiviral prophylaxis in light of potential wide-spread use in COVID-19: a multinational, large-scale network cohort and self-controlled case series study. Study protocol version. 1.6. http://www.encepp.eu/encepp/openAttachment/fullProtocolLatest/35592

Pinho de Oliveira Ribeiro N, Rafael de Mello Schier A, Ornelas AC, Pinho de Oliveira CM, Nardi AE, Silva AC. Anxiety, depression and suicidal ideation in patients with rheumatoid arthritis in use of methotrexate, hydroxychloroquine, leflunomide and biological drugs. Compr Psychiatry. 2013;54(8):1185-1189. doi:10.1016/j.comppsych.2013.05.010.

Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on hydroxychloroquine, 5 June 2020: No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19: https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19 (last accessed on 17/06/2020)

Tett SE, Cutler DJ, Day RO, Brown KF. A dose-ranging study of the pharmacokinetics of hydroxychloroquine following intravenous administration to healthy volunteers. Br J Clin Pharmacol. 1988;26(3):303-313. doi:10.1111/j.1365-2125.1988.tb05281.x

Wijlaars LP, Nazareth I, Whitaker HJ, Evans SJ, Petersen I. Suicide-related events in young people following prescription of SSRIs and other antidepressants: a self-controlled case series analysis. BMJ Open 2013;3(9):e003247

Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health 2010;13(2):273-7

9. Appendix

Classification of Read codes used to identify neuropsychiatric medical events in IMRD-UK.

Read code	Description
A. Suicidality: (i) complete suicide, (ii) attempted suicide, (iii) suicide ideation	
TK...00	Suicide and selfinflicted injury
TK...14	Suicide and self harm
TK0..00	Suicide + selfinflicted poisoning by solid/liquid substances
TK00.00	Suicide + selfinflicted poisoning by analgesic/antipyretic
TK01.00	Suicide + selfinflicted poisoning by barbiturates
TK01100	Suicide and self inflicted injury by Barbitone
TK01400	Suicide and self inflicted injury by Phenobarbitone
TK02.00	Suicide + selfinflicted poisoning by oth sedatives/hypnotics
TK03.00	Suicide + selfinflicted poisoning tranquilliser/psychotropic
TK04.00	Suicide + selfinflicted poisoning by other drugs/medicines
TK05.00	Suicide + selfinflicted poisoning by drug or medicine NOS
TK0z.00	Suicide + selfinflicted poisoning by solid/liquid subst NOS
TK2..00	Suicide + selfinflicted poisoning by other gases and vapours
TK3..00	Suicide + selfinflicted injury by hang/strangulate/suffocate
TK30.00	Suicide and selfinflicted injury by hanging
TK60.00	Suicide and selfinflicted injury by cutting
TKx..00	Suicide and selfinflicted injury by other means
TKz..00	Suicide and selfinflicted injury NOS
TK...15	Attempted suicide
U2...14	[X]Attempted suicide
1B19.00	Suicidal
1B19.11	Suicidal - symptom
1BD1.00	Suicidal ideation
1BD3.00	Suicidal plans
1BD4.00	Suicide risk
1BD5.00	High suicide risk
1BD6.00	Moderate suicide risk
B. Self-endangering behaviour: including intentional self-harm	
TK...11	Cause of overdose - deliberate
TK...12	Injury - self-inflicted
TK...13	Poisoning - self-inflicted
TK...17	Para-suicide
TK60100	Self inflicted lacerations to wrist
TK60111	Slashed wrists self inflicted
U2...00	[X]Intentional self-harm
U2...11	[X]Self inflicted injury
U2...12	[X]Injury - self-inflicted
U2...15	[X]Para-suicide
U20..00	[X]Intentional self poisoning/exposure to noxious substances
U20..11	[X]Deliberate drug overdose / other poisoning
U200.00	[X]Intent self poison/exposure to nonopioid analgesic
U200000	[X]Int self poison/exposure to nonopioid analgesic at home
U200z00	[X]Intent self poison nonopioid analgesic unspecif place
U202.00	[X]Intent self poison/exposure to sedative hypnotic
U204.00	[X]Intent self poison/exposure to psychotropic drug
U209.00	[X]Intent self poison/exposure to alcohol
U20B.00	[X]Intent self poison/exposure to other gas/vapour
U21..00	[X]Intent self harm by hanging strangulation / suffocation
U22..00	[X]Intentional self harm by drowning and submersion
U29..00	[X]Intentional self harm by sharp object

Read code	Description
U290.00	[X]Intentional self harm by sharp object occurrence at home
U29z.00	[X]Intentional self harm by sharp object occ unspecif place
U2E..00	[X]Self mutilation
U2y..00	[X]Intentional self harm by other specified means
ZX...00	Self-harm
ZX1..13	Deliberate self-harm
ZX13.00	Cutting self
ZX13.11	Cuts self
ZX13100	Cutting own wrists
ZX1I.00	Self-scalding
ZX1N.00	Stabbing self
C. Psychosis and psychotic disorders (i) schizophrenia type:	
285..11	Psychotic condition, insight present
286..11	Poor insight into psychotic condition
E1...00	Non-organic psychoses
E10..00	Schizophrenic disorders
E100.00	Simple schizophrenia
E100000	Unspecified schizophrenia
E100200	Chronic schizophrenic
E100500	Schizophrenia in remission
E102.00	Catatonic schizophrenia
E103.00	Paranoid schizophrenia
E103500	Paranoid schizophrenia in remission
E104.00	Acute schizophrenic episode
E106.00	Residual schizophrenia
E107.00	Schizo-affective schizophrenia
E107500	Schizo-affective schizophrenia in remission
E107z00	Schizo-affective schizophrenia NOS
E10z.00	Schizophrenia NOS
E121.00	Chronic paranoid psychosis
E12z.00	Paranoid psychosis NOS
E13..11	Reactive psychoses
E131.00	Acute hysterical psychosis
E13y.00	Other reactive psychoses
E13y100	Brief reactive psychosis
E13z.00	Nonorganic psychosis NOS
E13z.11	Psychotic episode NOS
E1z..00	Non-organic psychosis NOS
Eu2..00	[X]Schizophrenia, schizotypal and delusional disorders
Eu20.00	[X]Schizophrenia
Eu20000	[X]Paranoid schizophrenia
Eu20212	[X]Schizophrenic catalepsy
Eu20511	[X]Chronic undifferentiated schizophrenia
Eu20z00	[X]Schizophrenia, unspecified
Eu22.00	[X]Persistent delusional disorders
Eu22000	[X]Delusional disorder
Eu22011	[X]Paranoid psychosis
Eu23.00	[X]Acute and transient psychotic disorders
Eu23000	[X]Acute polymorphic psychot disord without symp of schizoph
Eu23100	[X]Acute polymorphic psychot disord with symp of schizophren
Eu23z00	[X]Acute and transient psychotic disorder, unspecified
Eu23z11	[X]Brief reactive psychosis NOS
Eu23z12	[X]Reactive psychosis
Eu25.00	[X]Schizoaffective disorders
Eu25000	[X]Schizoaffective disorder, manic type
Eu25112	[X]Schizophreniform psychosis, depressive type
Eu26.00	[X]Nonorganic psychosis in remission
Eu2z.00	[X]Unspecified nonorganic psychosis

Read code	Description
Eu2z.11	[X]Psychosis NOS

C. Psychosis and psychotic disorders (ii) affective related

E11..00	Affective psychoses
E11..11	Bipolar psychoses
E11..12	Depressive psychoses
E11..13	Manic psychoses
E110.00	Manic disorder, single episode
E110.11	Hypomanic psychoses
E110100	Single manic episode, mild
E110600	Single manic episode in full remission
E111000	Recurrent manic episodes, unspecified
E111600	Recurrent manic episodes, in full remission
E112400	Single major depressive episode, severe, with psychosis
E113400	Recurrent major depressive episodes, severe, with psychosis
E114.00	Bipolar affective disorder, currently manic
E114.11	Manic-depressive - now manic
E115.00	Bipolar affective disorder, currently depressed
E115.11	Manic-depressive - now depressed
E115100	Bipolar affective disorder, currently depressed, mild
E115200	Bipolar affective disorder, currently depressed, moderate
E115z00	Bipolar affective disorder, currently depressed, NOS
E116.00	Mixed bipolar affective disorder
E116000	Mixed bipolar affective disorder, unspecified
E116600	Mixed bipolar affective disorder, in full remission
E116z00	Mixed bipolar affective disorder, NOS
E117.00	Unspecified bipolar affective disorder
E11z.00	Other and unspecified affective psychoses
E11z000	Unspecified affective psychoses NOS
E11zz00	Other affective psychosis NOS
E130.00	Reactive depressive psychosis
E130.11	Psychotic reactive depression
Eu25100	[X]Schizoaffective disorder, depressive type
Eu30.00	[X]Manic episode
Eu30.11	[X]Bipolar disorder, single manic episode
Eu30100	[X]Mania without psychotic symptoms
Eu30200	[X]Mania with psychotic symptoms
Eu30z00	[X]Manic episode, unspecified
Eu30z11	[X]Mania NOS
Eu31.00	[X]Bipolar affective disorder
Eu31.11	[X]Manic-depressive illness
Eu31.12	[X]Manic-depressive psychosis
Eu31000	[X]Bipolar affective disorder, current episode hypomanic
Eu31200	[X]Bipolar affect disorder cur epi manic with psychotic symp
Eu31300	[X]Bipolar affect disorder cur epi mild or moderate depressn
Eu31500	[X]Bipolar affect dis cur epi severe depres with psyc symp
Eu31600	[X]Bipolar affective disorder, current episode mixed
Eu31700	[X]Bipolar affective disorder, currently in remission
Eu31900	[X]Bipolar affective disorder type II
Eu31y00	[X]Other bipolar affective disorders
Eu31y11	[X]Bipolar II disorder
Eu31z00	[X]Bipolar affective disorder, unspecified
Eu32300	[X]Severe depressive episode with psychotic symptoms
Eu32311	[X]Single episode of major depression and psychotic symptoms
Eu32312	[X]Single episode of psychogenic depressive psychosis
Eu32313	[X]Single episode of psychotic depression
Eu32800	[X]Major depression, severe with psychotic symptoms
Eu32900	[X]Single major depr ep, severe with psych, psych in remiss
Eu32A00	[X]Recurr major depr ep, severe with psych, psych in remiss

Read code	Description
Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms
Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp
Eu33311	[X]Endogenous depression with psychotic symptoms
Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis
Eu33315	[X]Recurrent severe episodes of psychotic depression
Eu3z.11	[X]Affective psychosis NOS
ZRby100	Profile of mood states, bipolar

D. Non-psychotic depression and other emotional disorders

1465.00	H/O: depression
2257.00	O/E - depressed
1B17.00	Depressed
1B17.11	C/O - feeling depressed
1B1J.11	Emotional upset
1B1U.00	Symptoms of depression
1B1U.11	Depressive symptoms
1BO..00	Mood swings
1BP0.00	Loss of interest in previously enjoyable activity
1BQ..00	Loss of capacity for enjoyment
1BT..00	Depressed mood
1BT..11	Low mood
1BT..12	Sad mood
1BU..00	Loss of hope for the future
1JJ..00	Suspected depression
1S40.00	Dysphoric mood
E112.00	Single major depressive episode
E112.11	Agitated depression
E112.12	Endogenous depression first episode
E112.13	Endogenous depression first episode
E112.14	Endogenous depression
E112000	Single major depressive episode, unspecified
E112100	Single major depressive episode, mild
E112200	Single major depressive episode, moderate
E112300	Single major depressive episode, severe, without psychosis
E112500	Single major depressive episode, partial or unspec remission
E112600	Single major depressive episode, in full remission
E112z00	Single major depressive episode NOS
E113.00	Recurrent major depressive episode
E113.11	Endogenous depression - recurrent
E113000	Recurrent major depressive episodes, unspecified
E113100	Recurrent major depressive episodes, mild
E113200	Recurrent major depressive episodes, moderate
E113300	Recurrent major depressive episodes, severe, no psychosis
E113500	Recurrent major depressive episodes,partial/unspec remission
E113600	Recurrent major depressive episodes, in full remission
E113700	Recurrent depression
E113z00	Recurrent major depressive episode NOS
E118.00	Seasonal affective disorder
E11y200	Atypical depressive disorder
E11z200	Masked depression
E135.00	Agitated depression
E200300	Anxiety with depression
E204.00	Neurotic depression reactive type
E204.11	Postnatal depression
E213.00	Explosive personality disorder
E21y200	Borderline personality disorder
E283z00	Other acute stress reaction NOS

Read code	Description
E284.00	Stress reaction causing mixed disturbance of emotion/conduct
E290.00	Brief depressive reaction
E290z00	Brief depressive reaction NOS
E291.00	Prolonged depressive reaction
E292.00	Adjustment reaction, predominant disturbance other emotions
E292400	Adjustment reaction with anxious mood
E292z00	Adjustment reaction with disturbance of other emotion NOS
E2B..00	Depressive disorder NEC
E2B1.00	Chronic depression
E2C4z00	Mixed disturbance of conduct and emotion NOS
Eu3..00	[X]Mood - affective disorders
Eu32.00	[X]Depressive episode
Eu32.11	[X]Single episode of depressive reaction
Eu32.12	[X]Single episode of psychogenic depression
Eu32.13	[X]Single episode of reactive depression
Eu32000	[X]Mild depressive episode
Eu32100	[X]Moderate depressive episode
Eu32200	[X]Severe depressive episode without psychotic symptoms
Eu32211	[X]Single episode agitated depressn w'out psychotic symptoms
Eu32212	[X]Single episode major depression w'out psychotic symptoms
Eu32213	[X]Single episode vital depression w'out psychotic symptoms
Eu32400	[X]Mild depression
Eu32500	[X]Major depression, mild
Eu32600	[X]Major depression, moderately severe
Eu32700	[X]Major depression, severe without psychotic symptoms
Eu32B00	[X]Antenatal depression
Eu32y00	[X]Other depressive episodes
Eu32y11	[X]Atypical depression
Eu32y12	[X]Single episode of masked depression NOS
Eu32z00	[X]Depressive episode, unspecified
Eu32z11	[X]Depression NOS
Eu32z12	[X]Depressive disorder NOS
Eu32z13	[X]Prolonged single episode of reactive depression
Eu32z14	[X] Reactive depression NOS
Eu33.00	[X]Recurrent depressive disorder
Eu33.11	[X]Recurrent episodes of depressive reaction
Eu33.12	[X]Recurrent episodes of psychogenic depression
Eu33.13	[X]Recurrent episodes of reactive depression
Eu33.15	[X]SAD - Seasonal affective disorder
Eu33000	[X]Recurrent depressive disorder, current episode mild
Eu33100	[X]Recurrent depressive disorder, current episode moderate
Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt
Eu33211	[X]Endogenous depression without psychotic symptoms
Eu33212	[X]Major depression, recurrent without psychotic symptoms
Eu33214	[X]Vital depression, recurrent without psychotic symptoms
Eu33400	[X]Recurrent depressive disorder, currently in remission
Eu33y00	[X]Other recurrent depressive disorders
Eu33z00	[X]Recurrent depressive disorder, unspecified
Eu33z11	[X]Monopolar depression NOS
Eu34.00	[X]Persistent mood affective disorders
Eu34100	[X]Dysthymia
Eu34111	[X]Depressive neurosis
Eu34112	[X]Depressive personality disorder
Eu34113	[X]Neurotic depression
Eu34114	[X]Persistant anxiety depression
Eu34y00	[X]Other persistent mood affective disorders
Eu34z00	[X]Persistent mood affective disorder, unspecified
Eu3y.00	[X]Other mood affective disorders
Eu3y000	[X]Other single mood affective disorders

Read code	Description
Eu3y100	[X]Other recurrent mood affective disorders
Eu3y111	[X]Recurrent brief depressive episodes
Eu3yy00	[X]Other specified mood affective disorders
Eu3z.00	[X]Unspecified mood affective disorder
Eu4..00	[X]Neurotic, stress - related and somoform disorders
Eu41200	[X]Mixed anxiety and depressive disorder
Eu41211	[X]Mild anxiety depression
Eu43012	[X]Acute reaction to stress
Eu43y00	[X]Other reactions to severe stress
Eu43z00	[X]Reaction to severe stress, unspecified
Eu53011	[X]Postnatal depression NOS
Eu53012	[X]Postpartum depression NOS
Eu60300	[X]Emotionally unstable personality disorder
Eu60311	[X]Aggressive personality disorder
Eu60312	[X]Borderline personality disorder
Eu60313	[X]Explosive personality disorder
Eu92.11	[X]Emotional behavioural problems
ZV11100	[V]Personal history of affective disorder

Related codes not used

1BD..00	Harmful thoughts
1BD2.00	Morbid thoughts
1BD7.00	Low suicide risk
1BD8.00	At risk of DSH - deliberate self harm
1BD9.00	No thoughts of deliberate self harm
1BDA.00	Thoughts of deliberate self harm
285..00	Neurotic condition, insight present
286..00	Poor insight into neurotic condition
E11z100	Rebound mood swings
E12..00	Paranoid states
E120.00	Simple paranoid state
E132.00	Reactive confusion
E13y000	Psychogenic stupor
E140.12	Autism
Eu22012	[X]Paranoid state
Eu22015	[X]Paranoia
Eu22300	[X]Paranoid state in remission
Eu30000	[X]Hypomania
Eu34000	[X]Cyclothymia
Eu3y200	[X]Premenstrual dysphoric disorder
U200.11	[X]Overdose - paracetamol
U200.13	[X]Overdose - aspirin
U202.11	[X]Overdose - sleeping tabs
U202.12	[X]Overdose - diazepam
U202.13	[X]Overdose - temazepam
U202.16	[X]Overdose - benzodiazepine
U204.11	[X]Overdose - antidepressant
ZRby.00	Profile of mood states
ZX11.11	Bites self
ZX11500	Biting own tongue
ZX14200	Pulling out sutures
ZX17100	Banging own head against object
ZX19300	Head-hitting
ZX1C.00	Nipping self
ZX1G.00	Scratches self
ZX1K.11	Setting fire to self
ZX1P.00	Swallowing substances