Dynamics of prescription drug use, diagnoses and health care utilization after community managed SARS-CoV-2 infection

Lars Christian Lund[1]
Jesper Hallas[1, 2]
Henrik Nielsen[3,4]
Anders Koch[5]
Stine Hasling Mogensen[6]
Nikolai Constantin Brun[6]
Christian Fynbo Christiansen[7]
Reimar Wernich Thomsen[7]
Anton Pottegård[1,8]

[1]Clinical Pharmacology, Pharmacy and Environmental Medicine, Department of Public Health, University of Southern Denmark, Odense, Denmark
[2]Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark
[3]Department of Infectious Diseases, Aalborg University Hospital, Aalborg, Denmark
[4]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[5]Infectious Disease Epidemiology & Prevention, Statens Serum Institut, Copenhagen, Denmark
[6]Department of Medical Evaluation and Biostatistics, Danish Medicines Agency, Copenhagen, Denmark.
[7]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[8]Hospital Pharmacy Funen, Odense University Hospital, Odense, Denmark

1. Introduction

The novel corona virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is currently the most urgent threat to public health. Many European countries have reported increasing infection rates in the end of summer 2020 (1) and case counts are expected to rise further during fall and winter. In Denmark, much of the increasing incidence of SARS-CoV-2 infection is due to younger individuals being infected (2). SARS-CoV-2 infection is mostly asymptomatic or mild in younger individuals (3,4), but little is known about delayed complications of SARS-CoV-2 infection. An increasing body of literature suggests that individuals who have been hospitalized with COVID-19 can experience long term persisting symptoms (5,6) such as dyspnea, cough and fatigue (7), but also may be at an increased risk of serious delayed complications such as myocarditis (8), pulmonary fibrosis (9), sensory disturbances and encephalitis (10), thromboembolic events (11), and pediatric inflammatory multisystem syndrome (PIMS) (12). Whether these complications also occur to any great extent in individuals with mild or asymptomatic SARS-CoV-2 infection is unknown, as the available literature mainly consists of case series and uncontrolled studies.

Therefore, we aim to examine drug use, hospital diagnoses and health care utilization after SARS-CoV-2 infection, mainly focusing on individuals with presumably mild infections, i.e. community-managed infections without any hospital contact. We compared the longer-term outcomes of these individuals with outcomes among SARS-CoV-2 negative individuals and individuals hospitalized for SARS-CoV-2 infection.

2. Methods

Using the Danish national health registries, we examine drug use, hospital diagnoses and health care utilization prior to and after SARS-CoV-2 infection among individuals with community managed SARS-CoV-2 infection, defined as individuals who have not been hospitalized during the 14 days after diagnosis. Analyses are repeated for an age and sex matched cohort of individuals tested negative for SARS-CoV-2 and individuals hospitalized with SARS-CoV-2 infection. An increase in utilization of prescription drugs, diagnoses and health care services may be due to individuals not returning to their usual state of health after having cleared the primary infection.

2.1 Study population

Any individual with a positive or negative reverse-transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2 in Denmark during the period 27-02-2020 to 31-05-2020 was eligible for inclusion in the study. During this period, 520,483 individuals tested negative and 11,673 individuals tested positive for SARS-CoV-2.

2.2 Data sources

Data on individuals tested for SARS-CoV-2 were obtained from the Danish COVID-19 cohort (13). In this cohort, individuals were identified using the Danish Microbiology Database (14), which contains information on SARS-CoV-2 test results and date. Using the Danish residents' unique personal identifier, test results were linked to the Civil Registration System (15) to obtain information on age, sex, migrations, ethnicity, marital- and vital status. Further, we obtained information on redeemed prescriptions (type of drug, amount redeemed, date of prescription fill) from the Danish Register of Medicinal Product Statistics (16). Healthcare seeking behavior was quantified using data on admissions (admission and discharge date and time, discharge diagnoses) and outpatient visits (visit date, duration and diagnoses) obtained from the Danish National Patient Register (17) and information on general practitioner visits (week of visit) from the Danish national Health Insurance Register (18). Finally, information on serum creatinine measurements (date of measurement, creatinine level) from the Danish register of laboratory results will be used to identify individuals with acute kidney injury (19).

2.3 Cohorts

Drug use, hospital diagnoses and healthcare utilization will be examined for the following three distinct cohorts:

1) 9080 individuals with community managed SARS-CoV-2 infection, defined as individuals who were not hospitalized on the day of the positive SARS-CoV-2 test or during the following 14 days (2). A hospitalization is defined as any physical hospital contact with a duration greater than 12 hours.

2) A SARS-CoV-2 test negative cohort. For each individual in cohort 1, we will randomly sample four of the 520,483 individuals with negative test results. Test-negative individuals will be matched to community managed individuals with SARS-CoV-2 infection on birth year, sex and week of test. Any individual can only be sampled once. To ensure comparability with the cohort of community managed SARS-CoV-2 infection, individuals hospitalized on the day of the negative test or during

the following 14 days were excluded, leaving 441,263 eligible individuals after exclusion.
3) A cohort of 1696 individuals hospitalized on the day of the positive test for SARS-CoV-2 or during the 14 days after the positive test.

Across all three cohorts, individuals who were hospitalized during the 14 days prior to their positive test were excluded, as these individuals may have been hospitalized due to SARS-CoV-2. Likewise, individuals with less than 380 days of residency in Denmark prior to their SARS-CoV-2 test were excluded, due to incomplete lookback. Individuals who experienced the outcome of interest prior to or during the SARS-CoV-2 infection will be excluded from respective analyses.

2.4 Observation periods

Prescription drug use, hospital diagnoses and healthcare utilization will be examined during the following periods (fig. S1):
1) Prior prescription drug use and hospital diagnoses received will be examined using all available lookback and until the date of recovery from a SARS-CoV-2 infection (day +14 in non-hospitalized cohorts, day +14 after discharge in the hospitalized cohort). Healthcare utilization prior to the SARS-CoV-2 test will be quantified during the subperiod -104 days to -15 days to ensure comparability with the follow up period.
2) Follow up is defined as the period +14 days to +104 days after a positive/negative test for non-hospitalized individuals or +14 to +104 days after discharge for the hospitalized cohort. Individuals will be censored on death or migration, but not excluded.

2.5 Outcomes

During follow up, we will examine the occurrence of initiation and reinitiation of prescription drugs representing possible complications (10,11,20,21) and persistent symptoms (7,22) of SARS-CoV-2 infection which may not lead to a hospital admission. Drugs of interest are:

- Bronchodilating agents
- Cough-suppressing medication
- Analgesics
- Glucose lowering drugs
- Antidepressants
- Anxiolytics

- Antipsychotics
- Platelet inhibitors
- Anticoagulants

We will determine the occurrence of receiving a first-ever diagnosis or being a readmitted for the following potential complications or sequelae to a SARS-CoV-2 infection during follow up:

- Pulmonary disease and related symptoms, representing persistent injury of lung tissue (23), and interstitial pulmonary fibrosis (9) specifically.
- Cardiovascular disease, specifically myocarditis (8), heart failure, venous thromboembolism (11) and peripheral vascular disease, representing arterial thromboses (24)
- Diabetes mellitus (25)
- Neurological disease overall (10) and specifically, anosmia, headaches (22), ischaemic stroke, cerebral haemorrhage, Guillian-Barré syndrome, peripheral neuropathie sand encephalitis.
- Acute kidney injury (26)
- Psychiatric illnesses, among these psychosis (21), depression and anxiety disorders (20) specifically.
- Kawasaki's disease and PIMS (27) among children.
- Persisting fatigue and nonspecific pain (7)

For the specific anatomical therapeutical classification (ATC) and international classification of disease, 10th revision (ICD-10) codes used to define these groups, please see appendix A and B.

For healthcare utilization, we will determine the rate of the following events during the prior comparator period and follow up, allowing for multiple occurrences:

- General practitioner visits
- Outpatient visits (acute and elective)
- Outpatient visits to a new department
- Hospitalization

Further, individual healthcare utilization will be visualized as a histogram over the number of visits per person during follow up. At the time of writing, data on general practitioner visits for the study

period is not available but access to the data has been granted. The reporting of this outcome will be dependent upon, whether data will be made available prior to the date of the final report for the study.

Finally, the number of deaths during follow up will be counted for each cohort.

2.6 Statistical analyses

Descriptive statistics will be used to describe drug utilization at baseline, the period prior to the SARS-CoV-2 test and during follow up. Categorical variables will be described as counts and percentages. Non-gaussian continuous variables will be described using medians and interquartile ranges, while variables following a gaussian distribution will be described using means and standard deviations.

The measure of occurrence for initiation of new medication, reinitiation of medication, first-ever diagnoses and readmissions will be the cumulative incidence proportion (IP) during follow up (duration: 90 days), as no new individuals can enter the cohort, the number of individuals leaving the cohort alive (i.e. being censored) during follow up is expected to be negligible and as the timing of the event within the 90 days of follow up is considered of minor clinical relevance. IPs for initiation of new medication and first-ever diagnoses will be determined among users who have never used the drug of interest or do not have a history of the diagnosis of interest before cohort entry. IPs for reinitiation of medication and readmission due to a given diagnosis will be calculated among former users of a drug, defined as not having filled a prescription for the drug during the last 12 months, or individuals with a history of the diagnosis of interest before cohort entry.
Further, IP differences (risk differences) comparing individuals with community managed SARS-CoV-2 infection to SARS-CoV-2 negative individuals and individuals hospitalized for SARS-CoV-2 infection, will be estimated using generalized linear models using a binomial distribution and an identity link. Confounding will be handled by including markers of frailty as covariates in the regression model (appendix A, B). For each outcome, covariates can be added to or removed from the regression model, based on causal knowledge about the association and the number of outcomes.
IPs and IP differences will be reported for pre-specified groups of drugs and diagnoses, and also hypothesis-free, i.e. for each drug and diagnosis according to the fifth level of the ATC

classification and second level of the ICD-10 classification, ranked in descending order according to the observed incidence proportion.

Healthcare utilization will be quantified during the prior comparator period and follow up (duration: 90 days each) for each cohort. The rate of general practitioner visits, outpatient visits, outpatient visits at a new department and hospitalizations per 1000 individuals during each period will be calculated and visualized as bar charts. Rates will be calculated for the whole population and stratified on age groups (0-17, 18-34, 35-44, 45-54, 55-64, 65-74, 75+). Rate ratios, rate differences and exact 95% confidence intervals comparing the prior comparator period to follow up will be calculated for each cohort. To identify the impact of temporal trends in healthcare seeking behavior (e.g. seasonality) on healthcare utilization, rate ratios for the SARS-CoV-2 positive cohorts will be compared to rate ratios for SARS-CoV-2 negative individuals.

For the outcome of death, we will calculate the 90-day mortality for each cohort. Survival will be compared between individuals with community managed SARS-CoV-2 infection and SARS-CoV-2 negative individuals using visual inspection of Kaplan-Meier curves.

Finally, the probability of the maximum level of health care received (general practitioner, outpatient, hospitalization) will be plotted as an area chart for each day, with death representing the final state.

2.7 Sensitivity analyses

To explore the impact of varying test strategies, we will obtain IPs for drug initiation, IPs for new diagnoses and healthcare utilization rates, rate ratios and rate differences stratified on time (before or after 21-04-2020). Prior to the chosen cutoff, mainly symptomatic individuals were tested for SARS-CoV-2, while testing became more widespread afterwards.

3. Limitations

3.1 Selection and information bias

Due to all SARS-CoV-2 RT-PCR positive individuals in Denmark being included in the study, most selection bias will be eliminated. A minor selection bias may persist, due to selection regarding who is tested for SARS-CoV-2. This bias is assumed to be negligible as any Danish resident (with or without symptoms) can be tested for SARS-CoV-2 for free in Denmark.

Likewise, we expect no information bias as the Danish Health registries capture prescription drug use and hospital diagnoses for all residents of Denmark.

3.2 Exposure misclassification

The study uses an exposure assessment window of 14 days after a positive SARS-CoV-2 test to determine whether individuals are to be classified as community managed or hospitalized. This may result in exposure misclassification, as individuals who test positive for SARS-CoV-2 early during infection (e.g. due to contact tracing) may take a longer time to develop symptomatic disease and may be admitted due to the infection beyond day 14. We explored the implications of a longer assessment window (28 days) and found 66 individuals (0.7%) in the community managed cohort were hospitalized, and potentially misclassified, between 14 and 28 days after a positive test for SARS-CoV-2. We accept this small degree of misclassification to be consistent with epidemiological surveillance definitions used in Denmark.

3.3 Residual confounding

Frailty is expected to be an important confounder in all analyses. In analyses of drug initiation and new diagnoses after SARS-CoV-2 infection, frailty will be handled by including relevant comorbidities and current drug use as covariates in the regression model. This is an approximation of frailty, which does not include important unmeasured markers of frailty (e.g. activities of daily living or weight loss). Therefore, residual confounding may be present in these analyses.
In analyses of healthcare utilization, confounding will be handled by making within cohort comparisons, i.e. comparing rates prior to and after SARS-CoV-2 infection. This eliminates all confounders that are stable during the study period, such as frailty.

4. Ethical considerations

The institutional data protection board at the University of Southern Denmark and the Danish Health Data Authority approved the research project. According to Danish law, studies based entirely on registry data do not require approval from an ethics review board (18).

5. Timeline

Start of data collection: 27-02-2020

End of data collection: 31-08-2020

EU-PAS registration: 19-10-2020

Beginning of data analysis: 20-10-2020

Final report of study results: 15-11-2020

6. Data management

Data management and statistical programming will be performed remotely in the Danish Health Data Agency's protected computing environment. Data management will be performed by Lars Christian Lund. Programming will be validated by a second programmer employed by the University of Southern Denmark.

7. Dissemination

The study protocol will be registered in the EU-PAS registry. The Danish Medicines Agency will be informed prior to publication, as soon as the final results are available. Results will also be made available before peer-review on a preprint server, e.g. medrxiv.org and afterwards communicated in international peer-reviewed journals. Source code used for the analyses will be published on https://source.coderefinery.org/lcl

8. Amendments and deviations

Deviations from the protocol (25-11-2020):

1. Analyses regarding the healthcare utilization outcome of incident visits to a hospital outpatient clinic were not performed, due to difficulties in reliably identifying separate departments at the same hospital.

2. Stratified rates of healthcare utilization were obtained for slightly larger strata, corresponding to the following age groups 0-17, 18-34, 35-54, 55-74, 75+ years of age.

3. A sensitivity analysis stratified on the testing strategy employed (before and after 21-04-2020) was not performed, as potential confounding by varying test strategies was already handled by matching test positive and test negative individuals on age, sex and calendar time.

4. To increase statistical precision, up to ten test-negative individuals were matched to test-positive individuals.

5. The ICD-10 code F20 was added to the codes used to define psychiatric illness, as specified in the section outcomes, but not in the appendix.

Deviations from the protocol (30-11-2020):
6. The ICD-10 code for thiazides (a component of the ICD-10 codes used to define antihypertensive treatment) was corrected from C03CA to C03A.

Deviations from the protocol (21-01-2020):
7. Adjusted risk differences and risk ratios were obtained by weighting the generalized linear models using standardized mortality ratio weights derived from the propensity score, as this allowed the evaluation of covariate balance between cohorts using standardized mean differences (Austin. Statistics in Medicine. 2009, DOI: 10.1002/sim.3697).

8. Baseline and follow up periods were extended to 6 months to 2 weeks prior to a SARS-CoV-2 test (pre-baseline period) and 2 weeks to 6 months after a SARS-CoV-2 test (follow up) as more follow up became available in the registries. Analyses making use of 2 to 14 weeks of follow up are still reported as sensitivity analyses.

9. After the extension of follow up, individuals in the hospitalized cohort who were discharged after the end of the study inclusion period were excluded, to have complete follow up for all individuals.

10. Prior event rate ratio (PERR) adjusted rate ratios (Weiner et al. Pharmacoepidem Drug Safe. 2008, DOI: 10.1002/pds.1585) were calculated as measures of healthcare utilization instead of the previously described relative rate ratios, as the method is more well-described in the literature. Event rates for the outcomes of interest 6 months to 2 weeks prior to a SARS-CoV-2 test and 2

weeks to 6 months after a SARS-CoV-2 test were estimated using Possion regression. Rate ratios were calculated for both period and PERR-adjusted rate ratios were calculated by dividing the rate ratio during follow up with the rate ratio during the period prior to a SARS-CoV-2 test. Normal-approximation 95% confidence intervals were obtained using bootstrapping techniques with 200 replications per estimate.

9. Conflicts of interest

Anton Pottegård and Jesper Hallas report participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the current proposal. Lars Christian Lund reports participation in research projects funded by Menarini Pharmaceuticals and LEO Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the current proposal. Henrik Nielsen reports participation in research projects funded by MSD and Novo Nordisk Foundation, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the current proposal. Christian Fynbo Christiansen and Reimar Wernich Thomsen have not received any personal fees, grants, travel grants, or teaching grants from companies, but the Department of Clinical Epidemiology is involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies are related to the current study. Anders Koch, Stine Hasling Mogensen and Nikolai Constantin Brun report no conflicts of interest.

10. References

1. European Centre for Desease Prevention and Control. Rapid Risk Assessment: Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK – eleventh update: resurgence of cases [Internet]. European Centre for Disease Prevention and Control. 2020 [cited 2020 Sep 22]. Available from: https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-coronavirus-disease-2019-covid-19-eueea-and-uk-eleventh

2. Statens Serum Institut. Overvågning af COVID-19 [Internet]. [cited 2020 Sep 22]. Available from: https://www.ssi.dk/sygdomme-beredskab-og-forskning/sygdomsovervaagning/c/covid19-overvaagning

3. Reilev M, Kristensen KB, Pottegård A, Lund LC, Hallas J, Ernst MT, et al. Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. Int J Epidemiol. 2020 Sep 5;

4. Petersen I, Phillips A. Three Quarters of People with SARS-CoV-2 Infection are Asymptomatic: Analysis of English Household Survey Data. CLEP. 2020 Oct;Volume 12:1039–43.

5. Williams FMK, Muirhead N, Pariante C. Covid-19 and chronic fatigue. BMJ [Internet]. 2020 Jul 30 [cited 2020 Oct 9];370. Available from: https://www.bmj.com/content/370/bmj.m2922

6. Rimmer A. Covid-19: Impact of long term symptoms will be profound, warns BMA. BMJ [Internet]. 2020 Aug 13 [cited 2020 Oct 9];370. Available from: https://www.bmj.com/content/370/bmj.m3218

7. Carfì A, Bernabei R, Landi F, Group for the GAC-19 P-ACS. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020 Aug 11;324(6):603–5.

8. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol [Internet]. 2020 Jul 27 [cited 2020 Sep 21]; Available from: https://jamanetwork.com/journals/jamacardiology/fullarticle/2768916

9. Ojo AS, Balogun SA, Williams OT, Ojo OS. Pulmonary Fibrosis in COVID-19 Survivors: Predictive Factors and Risk Reduction Strategies [Internet]. Vol. 2020, Pulmonary Medicine. Hindawi; 2020 [cited 2020 Oct 9]. p. e6175964. Available from: https://www.hindawi.com/journals/pm/2020/6175964/

10. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol. 2020 Sep;19(9):767–83.

11. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up. Journal of the American College of Cardiology. 2020 Jun;75(23):2950–73.

12. Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol. 2020;16(8):413–4.

13. Pottegård A, Kristensen KB, Reilev M, Lund LC, Ernst MT, Hallas J, et al. Existing Data Sources in Clinical Epidemiology: The Danish COVID-19 Cohort. Clinical Epidemiology. 2020.

14. Voldstedlund M, Haarh M, Mølbak K, Representatives the MB of. The Danish Microbiology Database (MiBa) 2010 to 2013. Eurosurveillance. 2014 Jan 9;19(1):20667.

15. Pedersen CB. The Danish Civil Registration System. Scand J Public Health. 2011 Jul;39(7 Suppl):22–5.

16. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol. 2017 Jun;46(3):798–798f.

17. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449–90.

18. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: Structure, access, legislation, and archiving. Scandinavian Journal of Public Health. 2011 Jul;39(7_suppl):12–6.

19. Arendt JFH, Hansen AT, Ladefoged SA, Sørensen HT, Pedersen L, Adelborg K. Existing Data Sources in Clinical Epidemiology: Laboratory Information System Databases in Denmark. Clin Epidemiol. 2020 May 18;12:469–75.

20. Tomasoni D, Bai F, Castoldi R, Barbanotti D, Falcinella C, Mulè G, et al. Anxiety and depression symptoms after virological clearance of COVID-19: a cross-sectional study in Milan, Italy. J Med Virol [Internet]. 2020 Aug 25 [cited 2020 Sep 22]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7461061/

21. Lim ST, Janaway B, Costello H, Trip A, Price G. Persistent psychotic symptoms following COVID-19 infection. BJPsych Open [Internet]. [cited 2020 Sep 22];6(5). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7477483/

22. Poncet-Megemont L, Paris P, Tronchere A, Salazard J, Pereira B, Dallel R, et al. High Prevalence of Headaches During Covid-19 Infection: A Retrospective Cohort Study. Headache [Internet]. 2020 Aug 5 [cited 2020 Sep 22]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7436456/

23. You J, Zhang L, Ni-jia-Ti M, Zhang J, Hu F, Chen L, et al. Anormal pulmonary function and residual CT abnormalities in rehabilitating COVID-19 patients after discharge. J Infect. 2020 Aug;81(2):e150–2.

24. Bellosta R, Luzzani L, Natalini G, Pegorer MA, Attisani L, Cossu LG, et al. Acute limb ischemia in patients with COVID-19 pneumonia. J Vasc Surg. 2020 Apr 29;

25. Hollstein T, Schulte DM, Schulz J, Glück A, Ziegler AG, Bonifacio E, et al. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. Nat Metab. 2020 Sep 2;

26. Vijayan A, Humphreys BD. SARS-CoV-2 in the kidney: bystander or culprit? Nat Rev Nephrol. 2020 Sep 14;1–2.

27. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking

Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dis. 2020 Aug;79(8):999–1006.

11. Tables

Table 1. Baseline characteristics of individuals with mild or asymptomatic SARS-CoV-2 infection prior to infection.

A) Demographics and healthcare utilization
B) Prior diagnoses and prescription drug use during the previous year

A)

	Community managed SARS-CoV-2 infection (N=)	**SARS-CoV-2 negative individuals** (N=)	**SMD**
Demographics			
Age, median (IQR)			
<18			
18-45			
45-65			
65-75			
75+			
Sex			
Marital status			
Never married			
Married			
Divorced			
Healthcare utilization during the previous year			
GP visits			
0			
1			
2+			
Outpatient visits			
0			
1			
2+			
Hospitalization			
Intensive care unit admission			

B)

	Community managed SARS-CoV-2 infection (N=)	SARS-CoV-2 negative individuals (N=)	SMD
Prior diagnoses			
Charlson comorbidity index			
0			
1-2			
3+			
Pulmonary disease			
Cardiovascular disease			
Peripheral vascular disease			
Neurological disease			
Anosmia			
Headache			
Neuropathies			
Hospital diagnosis of chronic kidney disease			
Psychiatric illness			
Depression			
Anxiety disorders			
Psychosis			
Fatigue-relateed disorders			
Prescription drug use during the previous year			
Number of different medications redeemed			
0			
1			
2-4			
5+			
Bronchodilating agents			
SABA			
ICS			
Corticosteroids			
Analgesics			
Paracetamol			
NSAIDs			
Opioids and opiod-like drugs			
Triptans			
Antidepressants			
Benzodiazepines and Z-drugs			
Antipsychotics			
Platelet inhibitors			
VKA and DOACs			

Table 2. Number of initiators, cumulative incidence proportion and incidence proportion difference for drugs suspected to represent delayed complications of SARS-CoV-2 infection.
Initiation defined as the first ever prescription for a given drug

	Community managed SARS-CoV-2	SARS-CoV-2 negative	Comparison	
Drug group	**IP: n/N (‰)**	**IP: n/N (‰)**	**IPD: ‰ (95% CI)**	**Adj. IPD: ‰ (95% CI)**
Bronchodilating agents				
Cardiovascular medication				
Analgesics				
Triptans				
…				

IP = Cumulative incidence proportion, IPD = Cumulative incidence proportion difference, Adj. = adjusted

Table 3. Number of first-ever diagnoses, cumulative incidence proportion and cumulative incidence proportion difference for diagnoses suspected to represent delayed complications of SARS-CoV-2 infection.
Initiation defined as the first ever prescription for a given drug

	Community managed SARS-CoV-2	SARS-CoV-2 negative	Comparison	
Disease entity	**IP: n/N (‰)**	**IP: n/N (‰)**	**IPD: ‰ (95% CI)**	**Adj. IPD: ‰ (95% CI)**
Pulmonary disease				
Heart failure Peripheral vascular disease or VTE				
…				

IP = Cumulative incidence proportion, IPD = Cumulative incidence proportion difference, Adj. = adjusted

12. Figures

Figure 1. Rates of health care utilization prior to and after a SARS-CoV-2 test
Rate of general practitioner visits, outpatient visits, outpatient visits at a new department and hospitalizations after SARS-CoV-2 infection per 1000 individuals during follow up (90 days)

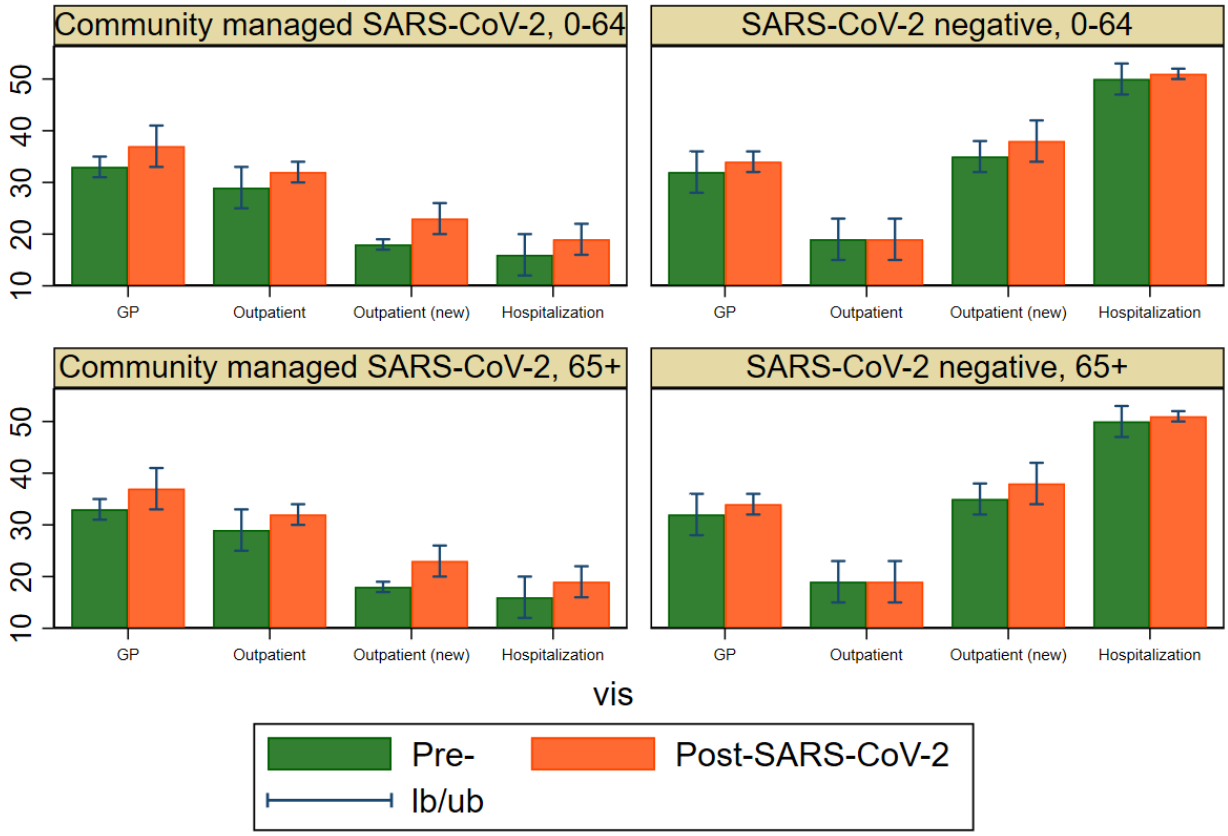
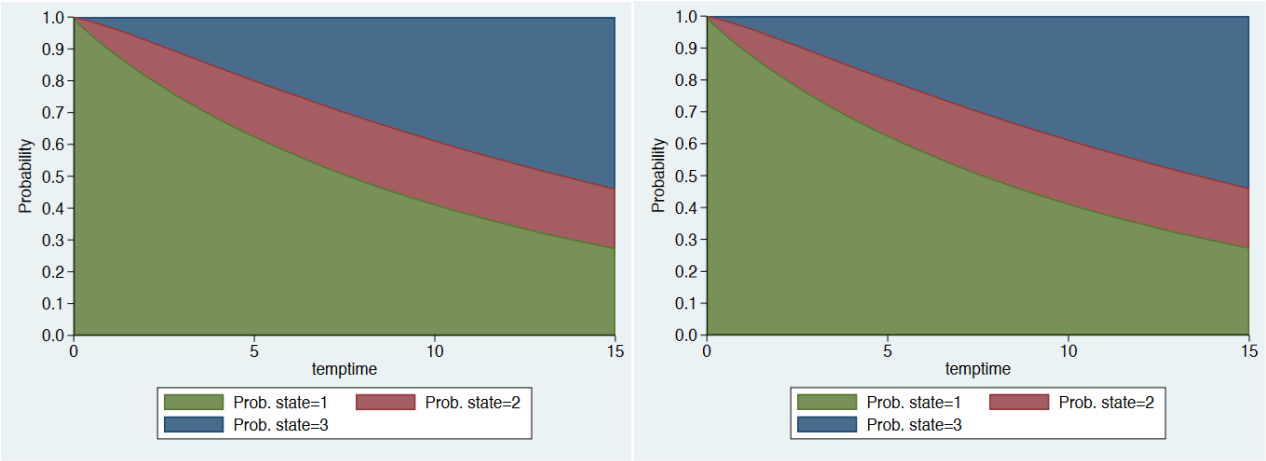


Figure 2. Area graph depicting the health care seeking state of individuals during follow up. States: 0 = No health care seeking behavior, 1 = Contacted GP, 2 = Outpatient visit, 3 = Hospitalized, 4 = Death.

A) Community managed SARS-CoV-2 infection
B) SARS-CoV-2 negative individuals



13. Supplementary material

Table S1. Baseline characteristics of individuals with mild or asymptomatic SARS-CoV-2 infection and individuals hospitalized with SARS-CoV-2 infection.

A) Demographics and healthcare utilization
B) Prior diagnoses and prescription drug use during the previous year

A)

	Community managed SARS-CoV-2 infection (N=)	**Hospitalized SARS-CoV-2** (N=)	**SMD**
Demographics			
Age, median (IQR)			
<18			
18-45			
45-65			
65-75			
75+			
Sex			
Marital status			
Never married			
Married			
Divorced			
Healthcare utilization during the previous year			
GP visits			
0			
1			
2+			
Outpatient visits			
0			
1			
2+			
Hospitalization			
Intensive care unit admission			

B)

	Community managed SARS-CoV-2 infection (N=)	Hospitalized SARS-CoV-2 (N=)	SMD
Prior diagnoses			
Charlson comorbidity index			
0			
1-2			
3+			
Pulmonary disease			
Cardiovascular disease			
Peripheral vascular disease			
Neurological disease			
Anosmia			
Headache			
Neuropathies			
Hospital diagnosis of chronic kidney disease			
Psychiatric illness			
Depression			
Anxiety disorders			
Psychosis			
Fatigue-relateed disorders			
Prescription drug use during the previous year			
Number of different medications redeemed			
0			
1			
2-4			
5+			
Bronchodilating agents			
SABA			
ICS			
Corticosteroids			
Analgesics			
Paracetamol			
NSAIDs			
Opioids and opiod-like drugs			
Triptans			
Antidepressants			
Benzodiazepines and Z-drugs			
Antipsychotics			
Platelet inhibitors			
VKA and DOACs			

Table S2. Top 30 drugs initiated after clearance of SARS-CoV-2 infection ranked according to cumulative incidence proportion difference.
Initiation defined as the first ever prescription for a given drug.

		Community managed SARS-CoV-2	SARS-CoV-2 negative	Comparison	
Drug	**ATC**	**IP: n/N (‰)**	**IP: n/N (‰)**	**IPD: ‰ (95% CI)**	**Adj. IPD: ‰ (95% CI)**
Drug A					
Drug B					
…					

IP = Cumulative incidence proportion, IPD = Cumulative ncidence proportion difference, Adj. = adjusted

Table S3. Top 30 new discharge diagnoses after SARS-CoV-2 infection ranked according to cumulative incidence proportion difference.
New diagnosis is defined as a first-ever diagnosis.

		Community managed SARS-CoV-2	SARS-CoV-2 negative	Comparison	
Diagnosis	**ICD-10**	**IP: n/N (‰)**	**IP: n/N (‰)**	**IPD: ‰ (95% CI)**	**Adj. IPD: ‰ (95% CI)**
Diagnosis A					
Diagnosis B					
…					

IP = Cumulative incidence proportion, IPD = Cumulative ncidence proportion difference, Adj. = adjusted

Table S4. Number of reinitiators and cumulative incidence proportions for drugs suspected to represent delayed complications of SARS-CoV-2 infection.
Reinitiation is defined as a new prescription for the drug of interest during follow up among former users (individuals who have not redeemed a prescription for the drug of interest during the previous 12 months)

Drug group	**Community managed SARS-CoV-2** n/N (‰)	**SARS-CoV-2 negative** n/N (‰)
Bronchodilating agents		
Cardiovascular medication		
Analgesics		
Triptans		
…		

Table S5. Number of readmissions and cumulative incidence proportions for diagnoses suspected to represent delayed complications of SARS-CoV-2 infection.
Readmission is defined as a discharge diagnosis during follow up among individuals with a history of the diagnosis of interest

Disease entity	**Community managed SARS-CoV-2** n/N (‰)	**SARS-CoV-2 negative** n/N (‰)
Pulmonary disease		
Heart failure Peripheral vascular disease or VTE		
…		

Table S6. Number of initiators, cumulative incidence proportions and cumulative incidence proportion differences for drugs suspected to represent delayed complications of SARS-CoV-2 infection.
Community managed individuals compared to hospitalized individuals with SARS-CoV-2 infection.
Initiation defined as the first ever prescription for a given drug

	Community managed SARS-CoV-2	Hospitalized SARS-CoV-2	Comparison	
Drug group	**IP: n/N (‰)**	**IP: n/N (‰)**	**IPD: ‰ (95% CI)**	**Adj. IPD: ‰ (95% CI)**
Bronchodilating agents				
Cardiovascular medication				
Analgesics				
Triptans				
…				

IP = Cumulative incidence proportion, IPD = Cumulative incidence proportion difference, Adj. = adjusted

Table S7. Number of first-ever diagnoses, cumulative incidence proportions and cumulative incidence differences for diagnoses suspected to represent delayed complications of SARS-CoV-2 infection.
Community managed individuals compared to hospitalized individuals with SARS-CoV-2 infection.

	Community managed SARS-CoV-2	Hospitalized SARS-CoV-2	Comparison	
Disease entity	**IP: n/N (‰)**	**IP: n/N (‰)**	**IPD: ‰ (95% CI)**	**Adj. IPD: ‰ (95% CI)**
Pulmonary disease				
Heart failure Peripheral vascular disease or VTE				
…				

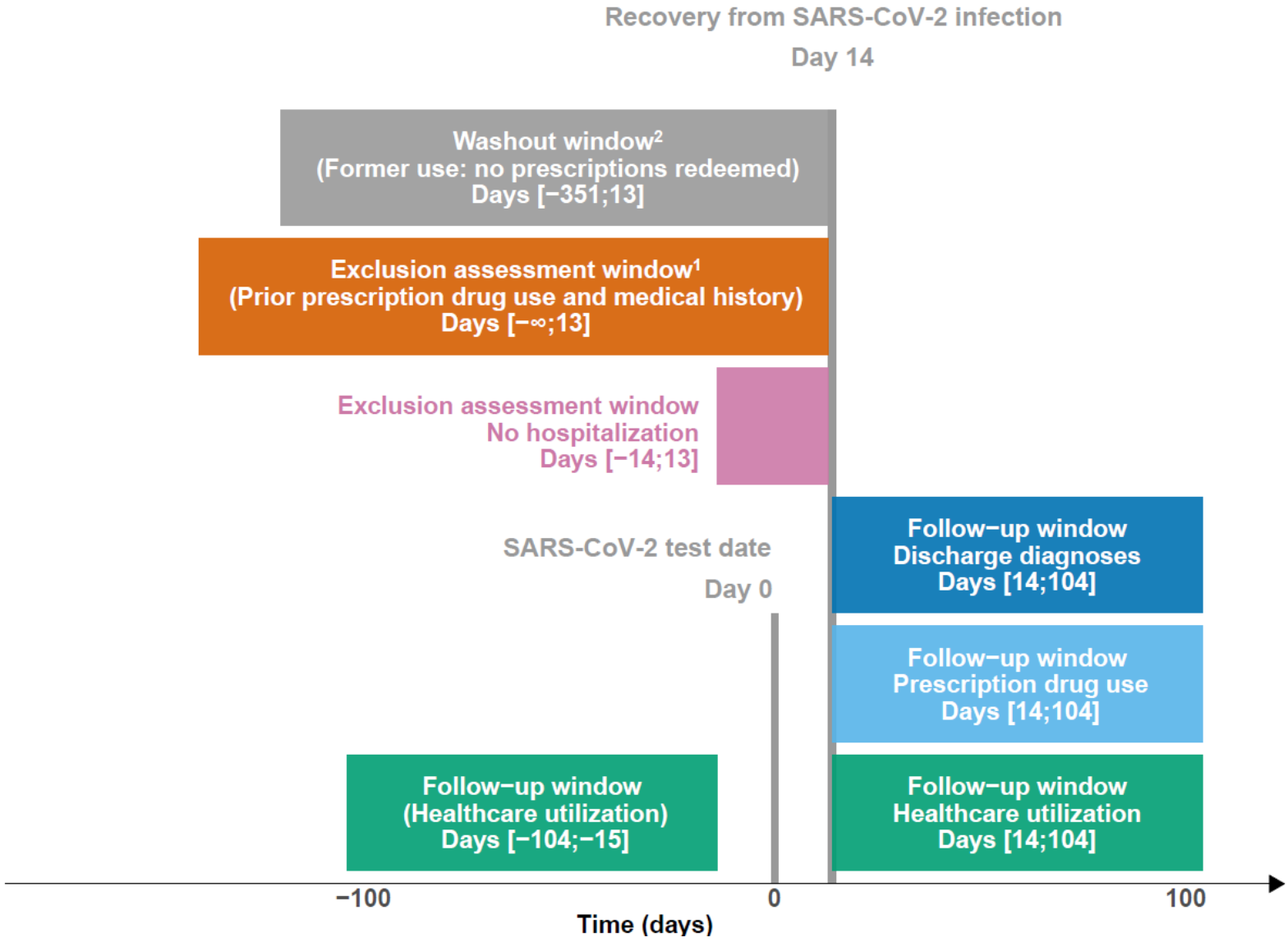
IP = Cumulative incidence proportion, IPD = Cumulative incidence proportion difference, Adj. = adjusted

Table S8. Rates of health care utilization before and after the SARS-CoV-2 test.
Rate ratios and rate differences are obtained for each cohort, comparing follow up to the period before a SARS-CoV-2 test.
Rates are reported as the number of events per 1000 individuals during the 90 days of follow up.

	Community managed SARS-CoV-2				SARS-CoV-2 negative			
	Rate (pre-)	**Rate (post)**	**RR (95% CI)**	**RD (95% CI)**	**Rate (pre-)**	**Rate (post)**	**RR (95% CI)**	**RD (95% CI)**
GP visits								
Outpatient visits								
Outpatient visits at new department								
Hospitalizations								

RR = rate ratio, RD = rate difference, 95% CI = 95% confidence interval, GP = general practitioner

Figure S1. Graphical depiction of study design for non-hospitalized individual.
[1]Analyses regarding new use of prescription drugs and first-ever diagnoses.
[2]Analyses regarding reinitiation of prescription drugs.



14. Appendix

Appendix A. ICD-10 codes used to define disease entities

Disease entity	ICD-10 codes
Pulmonary disease*†	J40-J47, J80-J99
Dyspnoea*	R060
Cough*	R05
Interstitial pulmonary fibrosis*	J841
Cardiovascular disease*†	I20-I25, I26, I30-I32, I40-I43, I47-I50, I63, I64
Myocarditis*	I40, I41, I541
Heart failure*	I50
Venous thromboembolism*	I26, I801, I802, I803, I808, I809, I822, I823, I829
Peripheral vascular disease*	I739, I74, I779
Diabetes mellitus*	E10-E14
Neurological disease*	G04, G05, G40, G43, G44, G45, G50-G59, G60-G64
Anosmia*	R430
Headache*	R51, G43, G44
Ischaemic stroke/TIA*	I63, I64, G45
Cerebral haemorrhage*	I60-I62
Guillian-Barré syndrome*	G610
Neuropathies*	G50-G59, G60-G64
Encephalitis*	G04, G05
Acute kidney injury*	-**
Chronic kidney disease†	N00, N01, N03-N06, N08.8, N14.1, N14.2, N16.8, N17, N25.1, N26, N27
Psychiatric illness*	F30-F39, F40-F48
Depression*	F32
Anxiety disorders*	F41, F43
Psychosis*	F20-F29, F30 excl. F21
Autoimmune and inflammatory disorders	
Kawasakis disease*	M303
Pediatric inflammatory multisystemic syndrome*	M303, A483, I40, I41
Fatigue-related disorders*	R53, G933
Nonspecific pain*	R52
Markers of smoking†	J41-J44, F17, Z71.6, Z72.0
Alcohol related disorders†	F10, E24.4, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, Q86.0, Z50.2, Z71.4, Z72.1
Dementia†	F01-F04
Obesity†	E66
Cancer†	C00-C97, excluding C44

*Outcome, **Defined using biochemical measurements †Covariate

Appendix B. ATC codes used to define drug groups

Medication	ATC codes
Any drug*	-
Bronchodilating agents*	R03AC02-04, R03AC12-13, R03AC18-19, R03AK06-08, R03AK10-11, R03AL01-09, R03CC02, R03BB01, R03BB04-07
SABA*	R03AC02-04, R03AL01-02, R03CC02
ICS*	R03BA, R0AK, R03AL08, R03AL09
Cough preparations*	R05DA04, R05DA09
Analgesics*	
Paracetamol*	N02BE01
NSAIDs*	M01A excl. M01AX
Opioids and opiod-like drugs*†	N02A
Triptans*	N02CC
Glucose lowering drugs*†	A10
Antidepressants*	N06A
Benzodiazepines and Z-drugs*	N05BA, N05CF
Antipsychotics*†	N05A
Platelet inhibitors*†	B01AC06, B01AC07, B01AC22, B01AC24, B01AC30, N02BA01, B01AC04
VKA and DOACs*†	B01AA03, B01AA04, B01AF01-B01AF03, B01AE07
Antihypertensives†	C08, C03CA, C07, C09
Antidiabetic drugs†	A10
Loop diuretics†	C03CA, C03CB

* Outcome, †Covariate