Is SARS-CoV-2 infection and post-acute sequelae associated with suicide, admission to psychiatric hospital and higher use of psychoactive medication?

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## Background

Some patients experience symptoms at a late point in time, after the primary SARS-CoV-2 infection referred to in literature as post-acute sequelae of SARS-CoV-2 infection (PASC), Long-COVID or Long-haul COVID. Symptoms reported vary from chest pain, fatigue, dyspnea, coughing, cognitive impairment, psychological distress and several others [1, 2]. In most studies, the most frequently reported symptoms were physiological [3]. Outcomes of COVID-19/PASC on mental health are poorly investigated; more studies are needed to evaluate the direct and indirect implications of COVID-19 on mental health [4-6]. An American retrospective cohort study did find a link between COVID-19 and an increased risk of first psychiatric diagnosis (of which anxiety was the most prevalent) within 14 to 90 days post infection compared to the risk of psychiatric diagnoses after other infections such as influenza [7]. Other studies also find an increased occurrence of psychiatric disorders or altered mental state, where most psychiatric diagnoses were new/first diagnoses [8, 9]. For all the beforementioned studies, the follow-up time range from 2 to 24 weeks, which is a major weakness. Future studies on outcomes of COVID-19 on mental health with longer follow-up time hves been suggested [7]. To our knowledge, this study will be the first with a maximum follow-up time of up to 14 months.

Part of the elevated prevalence of the negative influence of SARS-CoV-2 infection on mental outcomes could plausibly have a biological etiology: A first case of suspected SARS-CoV-2 meningitis was seen back in February 2020 [10]. Since then, it has been established that SARS-CoV-2 infection indeed is associated with several neurobiological impacts, which may result from hyperinflammatory and hypercoagulable states, direct infection of the central nervous system (CNS) and postinfectious immune mediated processes [11-14], which are also known phenomena associated with infection with other coronaviruses [15, 16]. It is suggested, that these impacts on the CNS could be linked to the observed more prevalent psychiatric consequences [11].

It is particularly interesting whether a PASC-diagnosis itself is associated with worse mental health outcomes, as this may have implications for clinical practice after such a diagnosis. As there’s not yet an international standard definition of PASC, this study will not solely be dealing with diagnoses PASC cases, but all PCR-confirmed cases of SARS-CoV-2 compared to all adult citizens of Denmark. The big study population is a major strength of this important and much needed study on the current pandemic.

## Aim

The purpose of this study is to investigate if a first positive SARS-CoV-2 PCR-test is associated with an increased risk of suicide, admission to a psychiatric hospital or an increased risk of prescription of psycho-active medication. Furthermore, to investigate the beforementioned outcomes in patients with a PASC-diagnosis compared to patients with a positive SARS-CoV-2 PCR test without a PASC-diagnosis.

**Hypotheses**
1. SARS-CoV-2 infection leads to increased risk of suicide as compared to no SARS-CoV-2 infection.

2. SARS-CoV-2 infection leads to increased risk of psychiatric admission.

3. SARS-CoV-2 infection leads to increased risk of prescription of psychopharmacological medication as compared to no SARS-CoV-2 infection.

The above-mentioned hypotheses will also be tested in a sub-group analysis of patients with a PASC diagnosis compared to patients with a PCR confirmed SARS-CoV-2 infection not diagnosed with PASC.

## Data sources

1. The National Prescription Registry (Lægemiddelstatistikregistret, LSR): Holds information on all prescriptions dispensed in Danish pharmacies since 2004 (coded according to the Anatomical Therapeutic Chemical (ATC) classification system)
2. The Danish Central Personal Registry (CPR registret): Holds information on citizens of Denmark including whether the citizen is living or not.
3. The Danish National Patient Registry (Landspatientregistret, LPR): Holds information on all admissions to Danish hospitals since 1977 and hospital outpatient specialist clinic visits since 1995.
4. The Cause of death register (Dødsårsagsregistret, DAR): Holds information on all registered causes of deaths of Danish citizens since 1970.
5. The Danish Microbiology Database (MiBa). Holds information on infections.

## Method

**Study design**Nationwide epidemiological study utilizing the Danish registries.

**Study period**
January 1st 2020 – December 31th 2021.

**Study population**
Case population: The entire adult Danish population.

**Inclusion criteria**Over 18 years of age

**Primary Endpoints**Suicide within 6 months

**Secondary Endpoints**

1. Any prescription of psychoactive medication as defined in Table 1
2. Admissions to psychiatric hospitals
3. Psychiatric diagnoses defined as ICD-10 F20 to F50

**Table 1:** Psychopharmacological drugs

|  |  |  |
| --- | --- | --- |
| **Drug group** | **Code type** | **Codes** |
| Antidepressants | ATC Groups/codes | N06A |
| BZD and BZD-like drugs | ATC Groups/codes | N03AE, N05BA, N05CD, N05CF |
| Antipsychotics | ATC Groups/codes | N05A (N05AN01 excluded) |
| Lithium | ATC Groups/codes | N05AN01 |

Abbreviations: BZD, Benzodiazepines.

## Statistical analysis

Firstly, descriptive analysis, baseline tables and study flow charts will be made. Whenever possible, propensity score matching will be performed. When this is not possible, Cox multivariate regression analysis will be performed. The final sample size for the primary analysis should be no smaller than 3 mio. individuals (since suicide is a rare event).

Continuous data will be compared using either non-parametric statistics or parametric statistics depending on the distribution. Categorical data will be analyzed using chi-square and Fischer’s exact test.

The primary analysis will examine deaths due to suicide within 6 months after first confirmed positive SARS-CoV-2 PCR-test.

The secondary analysis is a COX-regression model that will be used to evaluate the risk of suicide, consumption of psychopharmacological drugs, admissions to psychiatric hospitals, and psychiatric diagnoses after a positive first SARS-CoV-2 PCR-test. Another COX-regression model for evaluation of the same parameters will be used for a subgroup analysis on the PASC-diagnosed.

Statistical analyses will be performed in SAS 9.4 and R.

## Social perspective

In a social context, it is useful to understand the impact of COVID-19 and PASC on mental health to figure whether this should be taken (more) seriously, or, on the other hand, if it should be considered an issue of limited importance to mental health. The results of this study could demonstrate if there’s a need for further studies investigating this phenomenon and indicate potential need for psychological support post infection or post-PASC diagnosis.

## Publication of results

The results of the study will be published whether they are positive, negative or inconclusive. Publication is planned in international peer-reviewed scientific journals. If publication in a scientific journal is not possible, the results of the study will be published in report format, which will be made available via the Internet.

## Ethical statement/approval

The study has been approved by the Danish Data Protection Agency. In Denmark, retrospective use of register data does not require ethical approval or patient consent.

## Name of institution responsible for data

Copenhagen Unit for Respiratory Epidemiology (CURE), Lungemedicinsk Afdeling.

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