Consequences of the COVID-19 pandemic on the mental health of patients with COVID-19 and patients with mental disorders as well as risk and protective factors for mental health – protocol for a living systematic review

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REVIEW QUESTION

Our objective is to identify and summarize the available literature on the impact of the COVID-19 pandemic on the mental health in COVID-19 patients and patients with pre-existing mental disorders as well as possible (demographic, psychosocial etc.) risk and protective factors for mental health.

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The living systematic review will be updated within the duration of the project **CEOsys** (https://www.ceosys.de; as part of the Network of University Medicine [Nationales Forschungsnetzwerk der Universitätsmedizin, NUM], Germany; https://www.netzwerk-universitaetsmedizin.de/projekte/ceo-sys) until June 30, 2021. The final update frequency will be determined as soon as the study selection process of the first search (in April 2021) has been completed and will be subsequently added to this protocol.

METHODS

PARTICIPANTS/POPULATION

- **Inclusion:**
  - ***Patients with COVID-19***, that is, patients with confirmed active or previous diagnosed (laboratory-confirmed) SARS-CoV-2 infection, aged 18 years or older
  - ***Patients with (pre-existing) mental disorders***, aged 18 years or older
  - If any of the above-mentioned groups is investigated, the study will be included irrespective of country, age, sex, health status (e.g., severity of COVID-19, type of mental disorder) and setting of study conduction (e.g., clinical setting, outpatient setting)
- **Exclusion:**
  - other target groups (e.g., general population, healthcare workers, other patient populations)

INTERVENTION(S), EXPOSURE(S)

- **Inclusion:**
  - Patients with COVID-19: exposure to COVID-19 pandemic and diagnosed (laboratory-confirmed) SARS-CoV-2 infection
  - Patients with mental disorders: exposure to COVID-19 pandemic (i.e., survey period after the first officially registered COVID-19 case in the respective country based on national infection dates published by the World Health Organization [WHO][1])
- **Exclusion:**
  - Patients with COVID-19: individuals with suspected, but not confirmed SARS-CoV-2 infection

COMPARATOR(S)/ CONTROL

- **Inclusion:**
  - Patients with COVID-19: n.a.
  - Patients with mental disorders: no exposure to COVID-19 pandemic (i.e., before first officially registered COVID-19 case in the respective country based on national infection dates published by the WHO[1])
- **Exclusion:**
  - Patients with COVID-19: n.a.
  - Patients with mental disorders: exposure to any other pandemics, epidemics or other macro-stressors (e.g., natural disasters)

TYPES OF STUDIES TO BE INCLUDED

- **Inclusion:**
  - *a) For the consequences on mental health – Patients with COVID-19*
    - quantitative **cross-sectional** survey studies measuring mental health after the diagnosis of COVID-19

- quantitative **longitudinal** survey studies measuring mental health after the diagnosis of COVID-19 in the same individuals
- quantitative **repeated cross-sectional** survey studies measuring mental health after the diagnosis of COVID-19 in different individuals, with data collected using the same methodology
- protocols for respective survey studies
- letters to the editor and commentaries (if they report the results of original research)

b) For the consequences on mental health – Patients with mental disorders

- quantitative **cross-sectional** survey studies measuring mental health after the pandemic outbreak (i.e., first COVID-19 case in respective country[1])
- quantitative **longitudinal** survey studies measuring mental health before and after the pandemic outbreak (i.e., first officially registered COVID-19 case in respective country[1]) in the same individuals
- quantitative **repeated cross-sectional** survey studies measuring mental health in different individuals with at least one assessment before the pandemic outbreak (i.e., first COVID-19 case in respective country[1]), with data collected using the same methodology
- protocols for respective survey studies
- letters to the editor and commentaries (if they report the results of original research)

c) For risk and protective factors for mental health – Patients with COVID-19 and patients with mental disorders

- (non-repeated, repeated) cross-sectional survey studies measuring risk/and or protective factors for mental health
- longitudinal survey studies measuring risk/and or protective factors for mental health
- protocols for respective survey studies
- letters to the editor and commentaries (if they report the results of original research)

- **Exclusion:**
  - intervention studies
  - qualitative survey studies
  - theoretical/discussion papers
  - editorials, letters to the editor, commentaries (if they do not report the results of original research)
  - reviews (for systematic reviews: although these will be excluded at the title/abstract screening stage, the reference lists of relevant reviews [i.e., reviews potentially including primary studies of interest] will be hand searched for further relevant studies)

PUBLICATION DATE

No restrictions

PUBLICATION LANGUAGE

No restrictions (translation of non-English articles)

PUBLICATION FORMAT

No restrictions (preprints will be included)

CONTEXT

Studies conducted among patients with COVID-19 and patients with mental disorders in the face of current COVID-19 pandemic, diverse settings

MAIN OUTCOMES

Mental health or mental burden or psychological distress, with a broad range of eligible outcomes

Primary outcomes

1. anxiety symptoms
2. depressive symptoms
3. (perceived) stress
4. posttraumatic stress symptoms

Secondary outcomes

1. sleep problems and/or sleep quality
2. general psychological distress
3. substance abuse, substance use disorder
4. self-harm, suicidal ideation, suicidality, suicide
5. loneliness
6. well-being, life satisfaction, quality of life
7. resilience

The missing reporting of the above described primary or secondary outcomes is not an exclusion criterion in this review.

SEARCH STRATEGY

- **Electronic databases:**
  - MEDLINE Ovid
  - Cochrane Covid-19 Register (CC19R)
  - Cochrane Central Register of Controlled Trials (CENTRAL)
  - PsycINFO Ovid
  - Web Of Science (Core Collection)
- **Additional sources:** In addition to the electronic search, we will inspect the reference lists of all included studies and of relevant systematic reviews. If data are missing or unclear, we will contact the respective author.

The search strategy will be developed by an experienced information specialist (Maria-Inti Metzendorf) and will undergo a quality assessment by a second information specialist (Robin Featherstone). The strategy will comprise three blocks of search terms: 1) terms related to the COVID-19 pandemic (e.g., "COVID-19", "SARS coronavirus 2"), 2) terms associated with COVID-19 patients and patients with mental disorders as population of interest (e.g., "COVID-19 patient*", "psychiatric patient*", "patient* with mental disorder"), and 3) terms related to mental health (e.g., "mental health"). As appropriate for each database, different search terms and synonyms (e.g., MeSH terms, text words) are used. The timespan will be restricted from 2020 to current. Updates will be performed within the duration of the CEOsys project until June 30, 2021. The final search frequency will be determined as soon as the study selection process of the first search (in April 2021) has been completed. The search strategy is detailed for each database in Appendices 1–5.

DATA EXTRACTION (SELECTING AND CODING)

Two reviewers will independently screen the titles and abstracts of identified records to assess eligibility. Irrelevant papers will be excluded immediately. At full text level, the eligibility of relevant papers will also be checked in duplicate. Any disagreement will be resolved by discussion or by consulting a third reviewer. We will use EndNote to collect and de-duplicate studies. In order to accelerate the screening process and to guarantee an efficient workflow, we will use the systematic review software EPPI Reviewer[2]. Inter-rater reliability for both title/abstract and full text screening will be calculated, and the screening process will be reported in a preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram[3].

We will develop a customized data extraction sheet including the following information:

- full citation
- country
- participant characteristics (e.g., sociodemographic data, sample size)
- studied subpopulation (e.g., COVID-19 patients, patients with mental disorders)
- study design (e.g., longitudinal cohort study, repeated cross-sectional study)
- survey period and assessments
- outcomes and time points assessed, with outcome measures used
- results (e.g., means and standard deviations [SDs], prevalence rates, mean differences, results of t test, correlation coefficients, regression coefficients)
- miscellaneous aspects (e.g., cut-off values of the outcome measures used)

The data will be extracted by two reviewers, working independently. Any disagreements will be resolved by discussion or by consulting a third reviewer.
The process will adhere to the PRISMA standards[3].

DATA ANALYSIS

Quality (risk of bias) assessment

The quality of the included studies will be assessed independently and in duplicate with a tool based on the National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies[4], which assesses the following 14 domains:

1. research question
2. definition of the study population
3. participation rate
4. participant selection
5. sample size justification, power description, variance and effect estimates
6. measurement of the exposure prior to measurement of the outcome
7. timeframe
8. assessment of the exposure
9. definition, validity, reliability and consistence of exposure measures across the study
10. number of exposure assessments
11. definition, validity, reliability and consistence of outcome measures across the study
12. blinding of the outcome assessors regarding the exposure status
13. loss to follow-up
14. confounding variables

Due to the particular kind of exposure, some of the items of the original tool will be omitted or modified, other items will be added.

The following items will be omitted:

- Item 6. “For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?”: Since the exposure was not predictable, this question is not applicable.
- Item 7. “Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?”: This question is not applicable as the psychological burden probably varies over time (e.g., by increase or decrease of infection rates, aggravation or relaxation of containment measures et cetera). In any case, it is not known whether a longer exposure leads to greater psychological burden, which is the starting point of the question.
- Item 10. “Was the exposure(s) assessed more than once over time?”: The application of this question to the included studies would require a repeated assessment of the existence of the COVID-19 pandemic exists. Therefore, a reasonable use of this item is not possible.

- Item 12. “Were the outcome assessors blinded to the exposure status of participants?”: Blinding the studies with the COVID-19 pandemic (exposure) is not possible, thus, the question is not applicable.

The following items of the NIH tool[4] will be modified:

- Item 8. “For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?”
  This item was modified as it is based on the assumption of a linear relationship between exposure and effect. Usually, a study receives a better evaluation if it is conducted at several points in time or exposure levels because the correlation becomes more visible. However, since in a linear relationship cannot be assumed for studies included in this review, the item will be modified to "Was the exposure (independent variable) clearly specified?".
- Item 9. “Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?”
  This question will be modified in the sense that the heterogeneity of exposure is assessed. In the case of the COVID-19 pandemic as exposure, significant differences over a longer period might occur, for example, through loosening or tightening of the initial restrictions or if the number of infections increases or decreases. Therefore, a smaller survey period in the
- sense of a more homogeneous sample is more desirable and the question was changed to: "Was the exposure consistent across all study participants?".

The following items will be added as optional comments:

a) Selection bias/possible selection bias because of insufficient information on the sample recruitment: A selection bias exists, for example, if the recruitment of study participants is carried out using snowball or other convenience sampling methods. In this case, it must be assumed that only particularly stressed persons may have responded.
b) No/insufficient details on survey period: If there are no details on the survey period, this comment will be added.
c) No scale range for the outcome assessment reported: If there are no details on the scale range for the relevant outcome measure, this comment will be added.
d) No validated assessment measure for the outcome/outcome measure not clearly defined: If the used assessment tool for the relevant outcome(s) is not a previously validated assessment tool (i.e., before the current COVID-19 pandemic), this comment will be added.
e) Insufficient description of the study sample: If there is no or not enough information on the study sample, i.e., on the in- and exclusion criteria or on demographic information (age, gender, region, occupation), this comment will be added.

For some studies, additional comments will be added.

The single items will provide the ranking categories “yes”, “no”, “not reported”, “not applicable”. The overall assessment will provide three ranking categories (high, fair or poor quality) and will be done by two independent reviewers. Disagreements will be resolved by discussion or by a third reviewer.

Overall Rating	**Criteria**
HIGH	- no selection bias + validated assessment tool AND - <2 of the original items rated as “not reported” or “no”
FAIR	- selection bias and/or no validated assessment tool AND - <2 of the original items rated as “not reported” AND - <3 of the original items rated as “no” AND - <3 of the original items rated as other than “yes” or “not available”
POOR	- selection bias and/or no validated assessment tool + ≥3 of the original items rated as “not reported”/”no” OR - >1 of the original items rated as “not reported” OR

	- ≥3 of the original items rated as “no” OR - ≥3 of the original items rated as other than “yes” or “not available”

Assessment of the certainty of evidence

The certainty of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[5] by one reviewer; the results will be discussed in the review team.

Data synthesis

Based on the extracted data, we will carry out a narrative synthesis of the included studies describing the study characteristics, measured outcomes and risk and protective factors for mental health in text and tabular form. We will summarize the reported outcomes for measures of mental health (e.g., prevalence rates, means and SDs, medians and interquartile ranges, mean differences before and after the COVID-19 pandemic) as well as risk and/or protective factors (e.g., results of t test, correlation coefficients, regression coefficients, etc.).

a) For consequences on mental health – Patients with COVID-19

If the included studies are sufficiently homogeneous (e.g., study design, outcome measures) and in case of available data (i.e., at least two studies assessing the same mental health outcome), we will perform meta-analyses (e.g., pooling prevalence rates of mental health symptoms at the first or further assessment after the diagnosis of COVID-19).

Pooled analyses will be performed for the primary outcomes. Further relevant outcomes for meta-analyses will be added during the review development process.

b) For consequences on mental health – Patients with mental disorders

If the included studies are sufficiently homogeneous (e.g., study design, outcome measures) and in case of available data (i.e., at least two studies assessing the same mental health outcome), we will perform pairwise meta-analyses comparing reported measures *during* the COVID-19 pandemic with data *before* the pandemic to quantify the mental burden attributable to the stressor COVID-19 pandemic. Pairwise meta-analyses will be performed for symptoms of anxiety, depression, and (perceived) stress and/or posttraumatic distress, which are anticipated to be the most frequently reported outcomes[5,6]. Further relevant outcomes for meta-analyses will be added during the review development process.

Primarily, the first assessment of any mental health outcome *after* the first officially registered COVID-19 case in the respective country (based on national infection dates published by the WHO[1]) will be compared to the last assessment *before* the first officially registered COVID-19 case. If possible, in a second step, we will compare the respective outcome at the first assessment after the first officially registered case with subsequent assessments, in order to depict the development of mental health status, respectively.

For continuous outcomes, we will calculate standardized mean differences (SMDs, Hedge’s g) and their respective 95% confidence intervals (CIs) as pooled effect estimates based on means, SDs and sample sizes (e.g., before and during the COVID-19 pandemic). If means and SDs are not available, we will contact the study authors to ask for the respective values or use alternative statistical information (e.g., t test, change score).

For studies reporting dichotomous outcomes (e.g., prevalence with number of participants below and above cut-off score for mental health outcome before and after the pandemic), we will contact the study authors to ask for the respective means, SDs and sample sizes in order to eventually calculate SMDs as well. If these values cannot be obtained by the authors, we plan to calculate the prevalence risk ratio (RR) as pooled effect estimate, with uncertainty being expressed using 95% CIs.

c) For risk and protective factors for mental health – Patients with COVID-19

The summary and analysis of possible risk and protective factors will be performed for factors that were measured *synchronously* with the outcome of mental health and may have occurred since the diagnosis of COVID-19 (e.g., disease severity).

If the included studies are sufficiently homogeneous (e.g., study design, outcome measures) and in case of available data, we will also perform meta-analyses for specific risk and protective factors (e.g., using correlation or regression coefficients as pooled effect estimate).

d) For risk and protective factors for mental health – Patients with mental disorders

The summary and analysis of possible risk and protective factors will be performed separately for:

1) factors that were assessed *prior* to the COVID-19 pandemic (i.e., exposure) or those assessed after the beginning of the exposure, but which were *already present* before (e.g., sociodemographic variables)
2) factors that were measured *synchronously* with the outcome of mental health and may have newly occurred since the exposure started (e.g., media consumption). In this case, the direction of a possible influence cannot be determined with certainty.

If the included studies are sufficiently homogeneous (e.g., study design, outcome measures) and in case of available data, we will also perform meta-analyses for specific risk and protective factors (e.g., using correlation or regression coefficients as pooled effect estimate).

In general:

Since we anticipate a considerable between-study heterogeneity in the reported assessment tools[5,6], meta-analyses will be performed based on random-effect models. In addition to the inspection of the clinical and methodological between-study diversity, we will investigate the statistical heterogeneity using different statistical indicators (e.g., I^2, Tau^2, Chi^2 test, 95% prediction intervals).

Sensitivity analyses will be performed based on the quality assessment, by excluding studies judged to be of "poor quality". Depending on the evidence found, further sensitivity analyses will be added during the review development process.

For a) – c), the statistical analyses will be performed using Review Manager 5.4 (RevMan 5.4)[7] or R 4.0.3 (e.g., libraries meta, metafor, metasens)[8-11], if appropriate.

If meta-analyses are not possible (e.g., lack of evidence, clinical and methodological diversity, statistical heterogeneity), we will use a combination of statistical synthesis (e.g., vote counting based on the direction of effect) and visual presentation (e.g., effect direction plot), following the SWiM reporting guidelines and the recommendations in the Cochrane Handbook.[12,13]

ANALYSIS OF SUBGROUPS OR SUBSETS

The publications will be clustered by the following characteristics:

- *population characteristics*
  - age
  - geographical location (e.g., country or region)
  - subpopulation of patients (e.g., patients with COVID-19, patients with pre-existing mental disorders)
  - severity of disease (e.g., hospitalization, intensive care, ventilation, severity score, number of mental disorders, if appropriate)
  - pre-existence of risk and protective factors in relation to the COVID-19 pandemic (i.e., first officially registered case[1])
- *study characteristics*
  - sample size
  - outcome measure used
  - survey period

Quantitative subgroup analyses and/or meta-regression regarding *population and study characteristics* will be conducted for the primary outcomes of symptoms if an adequate number of studies (at least 10 in the meta-analysis per outcome) is available.

Further potentially relevant subgroups will be added during the review development process.

TYPE AND METHOD OF REVIEW

Living systematic review; living synthesis; narrative and quantitative synthesis; meta-analysis

KEYWORDS

Mental health, risk factors, protective factors, pandemic, SARS-CoV-2, COVID-19, surveys, patients, COVID-19 patients, mental disorder, psychiatric

GENERAL INFORMATION

START DATE: April 2021

(ANTICIPATED) COMPLETION DATE: May 2021

LANGUAGE: English

COUNTRY: Germany

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CONFLICT OF INTEREST: The authors report grants from the German Federal Ministry of Education and Research (BMBF) during the conduct of the study. The funding source has no role in the design of the study, the collection, analysis and interpretation of data.

CURRENT REVIEW STATUS

Preliminary searches: not started
Piloting of the study selection process: not started
Screening of search results against eligibility criteria: not started
Data extraction: not started
Risk of bias assessment: not started
Data analysis: not started

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APPENDIX

Search strategy will be added