OX79 Coronavirus Record Linkage Project –

QResearch-ICNARC COVID-19 Collaboration

Investigating neuropsychological disease and treatments before and after severe COVID-19 disease

Collaboration between Intensive Care National Audit and Research Centre/University of Oxford Nuffield Department of Clinical Neurosciences Critical Care Research Group and QResearch, Department of Primary Health Sciences, University of Oxford

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RESEARCH PROGRAM PROTOCOL

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Acronyms

BMI	Body Mass Index
CMP	Case Mix Programme
COVID-19	Coronavirus Disease 2019
DAG	Directed Acrylic Graph
HES	Hospital Episode Statistics
ICD-10	International Classification of Diseases-10
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
NHS	National Health Service
RECORD	the REporting of studies Conducted using Observational Routinely-collected health Data
RNA	Ribose Nucleic Acid
RT-PCR	Real Time Reverse Transcription–Polymerase Chain Reaction
SARI	Severe Acute Respiratory Infection
SLE	Systemic Lupus Erythematosis
SSRI	Selective Serotonin Reuptake Inhibitor

Summary

Patients with neuropsychological diagnoses are reported to be more likely to develop severe COVID-19 disease. Previous work has shown an increased incidence of severe respiratory infection and worse critical care outcomes associated with pharmacological neuropsychological treatments. It remains unclear whether particular conditions or treatments predispose to severe COVID-19 disease (requiring hospital, critical care admission or death) more than to other acute respiratory infections. Patients with COVID-19 disease are reported to subsequently have a high incidence of neuropsychological disease. However, the incidence of neuropsychological sequelae is also high following other critical illness. It is unclear whether neuropsychological sequelae following severe COVID-19 disease are more serious or managed differently than following other severe acute respiratory infection (SARI) such as bacterial or viral pneumonia, particularly when accounting for risk factors associated with the disease.

Antecedent analysis

We will explore the associations between pharmacological treatments (hypnotics and anxiolytic, antidepressant, drugs used in psychoses and related disorders) of pre-existing neuropsychological diagnoses (anxiety, mood, psychotic disorders, or dementia), and severe clinical outcomes of COVID-19 infection (hospital admission, ICU admission and death) in comparison to those not receiving such treatments.

We will determine whether the associations between pre-existing neuropsychological treatments and severe clinical outcomes differ for patients with COVID-19 infection in comparison to patients with non-COVID-19 severe acute respiratory infections (SARI)

Sequelae analysis

We will determine the risks of receiving a new neuropsychological diagnosis or new neuropsychological medication within one year after discharge from hospital for patients admitted with COVID-19 infection in comparison to patients with non-COVID-19 severe acute respiratory infections (SARI) investigating the subgroups of hospitalised patients admitted to and not admitted to an ICU.

INTRODUCTION

Patients with underlying psychological illness have been reported to be at significantly greater risk of infection with and death from COVID-19 [1–3]. Previous work suggests specific drug classes, such as antipsychotics and antidepressants, are associated with an increased risk of respiratory infection, and death associated with that infection [4–6], though these findings may be associated with significant residual confounding [5]. Whether the associations of psychological illness with infection and death from SARS-COVID-19 are related to particular medication classes has not so far been determined.

Psychological illness prior to ICU admission has been poorly studied. However, use of Selective Serotonin Reuptake Inhibitors (SSRIs) prior to ICU admission has been associated with increased mortality, an effect related to the degree of re-uptake inhibition [7]. Whether prior psychological illness and use of particular classes of medication for these diseases is associated with ICU admission or outcome, either with COVID-19 or other severe acute respiratory infection has not been studied.

Previous SARS outbreaks have been associated with significant neuropsychological sequelae [8] In the United States, recent work has suggested that COVID-19 disease is associated with significant subsequent neuropsychological disease [3].

Prior to the COVID-19 outbreak, patients who have been admitted to an ICU had high incidences of subsequent neuropsychological sequelae [9] and ongoing cognitive impairment [10]. However, understanding the neuropsychological consequences of critical illness has been impaired by limited understanding of prior neuropsychological disease [11]. We will investigate whether neuropsychological sequelae of patients treated on an ICU with COVID-19 disease differ from those treated on ICU for different conditions, taking into account prior neuropsychological disease.

Hypothesis

We hypothesise that prior neuropsychological disease increases the risk of severe COVID-19 outcomes as with other acute respiratory disease and that this increase is associated with treatment with particular medication classes.

We hypothesise that infection with COVID-19 results in severe neuropsychological outcomes following treatment in hospital or on an ICU and that these outcomes differ in type and severity from neuropsychological outcomes seen following admission for SARI.

Aims

This study will investigate neuropsychological disease and treatments before and after severe COVID-19 disease. The two main aims are:

1. to evaluate the associations of pre-existing neuropsychological diseases and treatments with severe COVID-19 outcomes in comparison to patients without pre-existing neuropsychological pathology;

2. to evaluate the associations between hospital or ICU admission due to COVID-19 and neuropsychological sequelae following discharge home in comparison to patients with ICU admission due to non-COVID-19 severe acute respiratory infections (SARI).

Objectives

1. To assess whether pre-existing neuropsychological diseases (by separate diseases and overall) are associated with severe COVID-19 outcomes (hospital and ICU admission and death) in comparison to the general population.
2. To assess whether pre-existing neuropsychological treatments (as a class and individually where possible) are associated with severe COVID-19 outcomes (hospital and ICU admission and death) and whether these explain disease associations in comparison to those not receiving such treatments.
3. To assess whether the risk of severe COVID-19 outcomes with prior neuropsychological disease differs from the risk of severe outcomes with SARI.

After discharge following a hospital admission for COVID -19 infection:

4. To assess the incidence of new neuropsychological diseases up to one year after hospital and ICU discharge following treatment for COVID-19 disease.
5. To compare the incidence of new neuropsychological diseases up to one year after hospital and ICU discharge with COVID-19 disease to the incidence following discharge after treatment for SARI.

Summary of the potential impact

This study will provide a better understanding of how pre-existing psychopathology and concomitant medication affect the risk of hospital and ICU admission and death due to COVID-19 and how any differences between those with and without pre-existing psychopathology and COVID-19 infection compare to other severe acute respiratory infections. We will discover the neuropsychological sequelae of admission to a hospital or ICU with COVID -19 disease, taking into account prior neuropsychological disease and whether these differ from patients discharged from an ICU following SARI. These findings will be key to prevention and management of ongoing problems for these patients.

METHODS

A retrospective cohort data linkage study of patients aged 18 years and above registered in English general practices. This protocol is written following RECORD guidance [12].

Settings *Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.*

1205 general practices in England contributing to the QResearch database, which is nationally representative. We defined cohorts during the COVID pandemic as between 24th January 2020 (the date of the first confirmed COVID-19 case in England) and study end (30th June 2021). We defined retrospective comparison cohorts as the 5 years prior to this date (24th January 2015- 23rd January 2020).

Data linkage

The study will include adult patients registered with the QResearch database. Practices must have been contributing to the QResearch database for at least 12 months. For the investigation of associations of pre-existing neuropsychological diseases and treatments (cohort 1) patients must be registered for at least a 12-month period before 24th January 2020 . For the investigation of incidence of new neuropsychological diseases (cohort 2) patients must be registered for at least a 12-month period between January 2015 to 2020. The date of study entry is separately defined below for each study cohort.

Patients in QResearch will be linked to: (1) the ICNARC Case Mix Programme (CMP) database, the national clinical database from adult critical care; (2) the Hospital Episode Statistics (HES) data warehouse containing records of all patients admitted to NHS hospitals and Emergency departments in England; (3) the national registry of COVID-19 RT-PCR positive test results from Public Health England (PHE); and (4) Office of National Statistics COVID-19 mortality data, which includes all deaths due to COVID-19 in England. Data linkage will be based primarily on NHS number. For a description of the datasets see Supplemental material S1.

Participants

Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. The methods of study population selection (such as codes or
algorithms used to identify subjects) should be listed in detail.

Aim 1.

From the linked dataset, we will extract two cohorts to explore the association between neuropsychological diseases and treatments and hospitalisation, ICU admission or death:

- Cohort one is adult patients aged 18 years of age or over on 24th January 2020 (the study entry date, when the first confirmed COVID-19 case occurred

in the UK) who were registered in a primary care practice within the QResearch programme on or before 24th January 2019.
Patients will be followed-up from study entry date until development of severe COVID-19 disease, defined as the first date of either hospitalisation, ICU admission, or death. Patients will be censored at the first occurrence of deregistration from the GP practise, death, or date of the final data extract from the linked datasets.

- Cohort two is an open cohort of patients aged 18 years of age or over (including those who become 18 within this period) who had been registered with a primary care practise within the QResearch database for at least one year, between 24th January 2015 and 23rd January 2020. For each patient, the earliest day on which all these conditions were met will be defined as their study entry date, and they will be followed-up until development of severe disease due to SARI, defined as hospitalization, ICU admission, or death. Patients will be censored at the earliest of first occurrence of deregistration from the GP practise, death from other causes, 24th January 2020 or date of the final data extract from the linked datasets.

Aim 2.

- Cohort three will include adult patients (aged 18+ on date of hospital admission) discharged alive following a hospital admission including an ICU admission resulting from COVID -19 infection (defined below) between 24 January 2020 and study end date, who were registered in a primary care practice within the QResearch programme before their ICU admission. It will be used to evaluate the risk of subsequent neuropsychological sequalae from the date of discharge. Patients will be censored at the earliest of first occurrence of deregistration from the GP practice, death from other causes, 12 months post discharge from hospital, or date of the final data extract from the linked datasets.

- Cohort four will include adult patients (aged 18+ on date of hospital admission) discharged alive following a hospital admission including an ICU admission resulting from SARI (defined below) admitted between 24 January 2015 and 23rd January 2020, who were registered in a primary care practice within the QResearch programme before their ICU admission. The cohort will allow comparisons to be made with cohort three. Follow-up will be from the date of discharge. Patients will be censored at the earliest of first occurrence of deregistration from the GP practise, death from other causes, 12 months post discharge from hospital or date of the final data extract from the linked datasets.

- Cohort 5 will include adult patients (aged 18+ on date of hospital admission) discharged alive following a hospital admission including an ICU admission resulting from SARI (defined below) between 24 January 2020 and study end date, who were registered in a primary care practice within the QResearch programme before their ICU admission. It will be used to allow comparison with cohort 3. Patients will be censored at the earliest of first occurrence of deregistration from the GP practice, death from other causes, 12

months post discharge from hospital, or date of the final data extract from the linked datasets.

Variables

Definition of outcomes

Aim 1

For cohort one, our primary outcome is the first occurrence of any one of the following:

1. Hospital admission resulting from COVID-19 infection defined as testing positive for SARS-CoV-2 (as recorded in the PHE database) in the 14 days prior to or during a hospital admission period in the HES dataset, or having an ICD10 code U07.01 for confirmed COVID-19 diagnosis in that HES admission record

2. Admission to an ICU resulting from COVID-19 infection which will be defined as patients admitted to an ICU within the ICNARC dataset of COVID-19 admissions.

3.All - cause mortality following COVID-19 infection.

Secondary outcomes are each of the three events defined above, considered separately (i.e. COVID-19 hospital admissions; ICU admission; death).

For cohort two, our primary outcome is the first occurrence of either hospital admission with SARI in the HES dataset (defined as a new ICD-10 code J09-J22 in the HES dataset) or ICU admission in the ICNARC CMP dataset with SARI (defined as any admission with unique diagnostic code any one of RE129 RE131 RE82 RE50 RE86 RE94 RE75 RE133 RE132 RE121 RE1 RE128 RE16 RE130 RE117 RE42 RE41) or death. Secondary outcomes will be each of these three events considered separately (I.e. SARI related hospital admission, ICU admission, death).

Aim 2.

Our primary outcome is development of new neuropsychological disease up to 1 year following hospital discharge which we define as having received a diagnostic code as below:

- Anxiety and stress-related disorders [ICD F40-48 and corresponding Read codes]
- Mood disorders [ICD F30-39 and corresponding Read codes]
- Psychotic disorders [ICD F20-29 and corresponding Read codes]
- Dementia [ICD F00-F03, G30, G31.0 ? and corresponding Read codes]

Secondary outcomes are the diagnosis of new neuropsychological disorders (as defined above) with treatment, and where numbers are available the new diagnosis with or without treatment of each class of disorders, each considered as a separate endpoint.

Neuropsychological treatments are defined as:

- Hypnotics and anxiolytics: (hypnotics, anxiolytics, barbiturates and methyprylone, benzodiazepines)
- Antidepressant drugs (Tricyclic and related antidepressant drugs, Monoamine-oxidase inhibitors, Selective serotonin re-uptake inhibitors, Other antidepressant drugs)
- Drugs used in psychoses and related disorders (Antipsychotic drugs and depot injections, Lithium salts, Phenothiazine derivatives)

Definition of exposures

Aim 1

Neuropsychological disease will be defined as an ordinal variable with the following three categories: no relevant diagnosis or drugs; diagnosis ever recorded without recent drug treatment; diagnosis present with recent drug treatment (with at least two prescriptions for neuropsychological treatments as above within the six months preceding study entry).

Our primary exposure is active neuropsychological disease on the study entry date which we define as having received a diagnostic code as above (24th January 2020 for cohort 1 and 24th January 2015 for cohort 2).

Aim 2.

The primary exposure is a hospital or ICU admission resulting from COVID-19 infection. Comparator exposures are hospital or ICU admission resulting from SARI.

Covariates

The following variables of interest were chosen as either due to known association with risk of developing severe COVID-19 and/or known associations with neuropsychological disease. Distributions of each variable will be summarised by cohort using descriptive statistics.

Demographics (Aims 1 & 2)

- Age
- Gender
- Material deprivation by quintile of Townsend deprivation score

- Ethnicity (White, Indian, Pakistani, Bangladeshi, other Asian, Black African, Chinese, and other ethnic group),
- Geographical region
- Domicile (homeless, care home residence, neither)
- Household size

Lifestyle (Aims 1 & 2)

- Body mass index (BMI)
- Smoking status (non-smoker, ex-smoker, light smoker: 1–9 cigarettes/day, moderate smoker: 10–19 cigarettes/day, heavy smoker: ≥ 20 cigarettes/day, not recorded)
- Alcohol intake (none, trivial: < 1 unit/day, light: 1–2 units/day, medium: 3–6 units/day, heavy: 7–9 units/day, very heavy: > 9 units/day, not recorded).

Co-morbidities (Aims 1 & 2)

- Cardiovascular diseases - coronary heart disease, stroke/transient ischaemic attack, atrial fibrillation, congestive cardiac failure, thromboembolism, peripheral vascular disease, congenital heart disease, hypertension
- Respiratory diseases - asthma, chronic obstructive pulmonary disease, rare lung conditions (bronchiectasis, cystic fibrosis, alveolitis), pulmonary hypertension or pulmonary fibrosis
- Endocrine diseases - type 1 and 2 diabetes, hypothyroidism
- Chronic kidney disease
- Neurological conditions- epilepsy/seizures, Parkinson's disease, motor neurone disease, multiple sclerosis, myasthenia gravis, Huntington's disease
- Cancer - blood cancer, respiratory tract cancer, and other relevant cancer
- Bone and joint conditions- osteoarthritis, rheumatoid arthritis or Systemic Lupus Erythematosis (SLE), osteoporosis, osteoporotic fracture (hip, spine wrist, humerus)
- Gastrointestinal diseases - liver disease, liver cirrhosis
- Transplants - solid organ transplant (excluding kidney and bone marrow), bone marrow or stem cell transplant
- Sickle cell disease or severe immunodeficiency
- Traumatic brain injury
- Learning disability/Down's syndrome, cerebral palsy

Medications/treatments (Aims 1 & 2)

- antihypertensive drugs,
- aspirin,
- statins,
- Anticoagulants,
- non-steroidal anti-inflammatory drugs,
- bisphosphonates,
- oral contraceptives,
- hormone replacement therapy,

- anticonvulsants
- chemotherapy
- radiotherapy
- immunosuppressant medication
- leukotriene or long-acting beta-agonist
- oral steroids

Intensive care stay (Aim 2)

- Length of stay
- Duration of advanced respiratory support (invasive ventilation)
- Use of sedation in the first 24 hours of admission

Effect Modifiers

For aim 1, we assessed these potential confounders by creating directed acyclic graphs (DAG) to determine which variables were likely to be to some extent caused by the presence of prior neuropsychological disorders (as the exposure of interest), and which were not likely to be caused by the presence of prior neuropsychological disorders, but were thought to be independently potential predictors of severe Covid outcomes.

Variables from the above list to be included in the model are all those grouped under: demographics; co-morbidities; lifestyle factors; plus prescription of any immunosuppressants and/or anticoagulants. Other medications (as these are not believed to affect the risk of severe Covid outcomes), and in-hospital factors (length of stay and use of sedation during intensive care admission, as these are outcomes potentially caused by Covid severity) will not be adjusted for.

For aim 2, our exposure of interest is admission to intensive care with SARI (compared to admission to intensive care with SARI. This exposure occurs at a fixed time which is used as the baseline for our time to event analysis in predicting the outcome of interest, and all other variables listed above are measured before this baseline. Therefore (depending on the available sample size and number of events), all the previously listed covariates of interest may be included in our adjusted models.

Data sources

Intensive Care Unit admission data will come from the ICNARC CMP dataset
Hospital admission and mortality will come from the HES dataset
All exposures and confounders and neuropsychological outcomes will come from the QResearch database.
COVID-19 infection test status will come from the national registry of COVID-19 RT-PCR positive test results from Public Health England (PHE).

Bias

To limit the possible impact of COVID-19 testing bias (collider bias) we will analyse the entire QResearch eligible population, rather than restricting analysis to only those with a positive COVID-19 test.

For aim 1, the various different neuropsychological conditions of patients in cohort 1 are likely to result in varying levels of exposure to covid-19, compared to the populations without these conditions, with some conditions likely to have a protective effect, but in other conditions the reverse is expected. We have added a secondary analysis to examine the effect of specific conditions in order to evaluate this.

For aim 2, the two cohorts have experienced their exposure of interest (ICU admission with either COVID or SARI) during different time frames. Patients with SARI (admitted to ICU between 2015 to 2020) will have longer follow-up, but patients with COVID (admitted to ICU during 2020/21) may have benefited from the recently increasing public awareness of mental health conditions. To combat this, we have capped all follow-up at a maximum of 1 year post ICU discharge, and we will include a time-dependent covariate to assess whether risk varies with time post discharge. We have also included a cohort of patients with SARI admitted during 2020/21 for comparison with the COVID cohort during the same time frame.

We will derive the E-value to estimate the extent unmeasured confounding.

Study Size

For aim 1 we will use the entire QResearch database of approx. 8.3 million adult patients to maximise precision and minimise selection bias. We chose to use the last 5 years of ICNARC data for SARI comparisons to use recent data whilst having sufficient numbers for comparison taking into account the numbers from previous studies and after linkage [13, 14].

For aim 2, we will use all known ICU admissions from the ICNARC database for SARI and/or COVID who can be linked to the QResearch database. In cohort 3 the expected sample size is in the region of 11,000 admissions in total, for cohort 4 it is likely to be in the region of 7,000 admissions per year, and for cohort 5 around 3,500 patients.

Quantitative variables

Quantitative variables will be treated as continuous variables without categorisation. Descriptive summary statistics (mean and standard deviation, median interquartile range or number (%) as appropriate) will be used to present sociodemographic and clinical characteristics of patients with and without COVID-19 infection for those with and without neuropsychiatric conditions or treatments.

Statistical Methods

Aim 1.

Royston Parmar flexible parametric survival models will be used to estimate the hazard ratio of severe COVID-19 outcome (hospital or critical care admission and death) in cohort 1 for patients with neuropsychological disease at study entry compared with those without disease, and for individual neuropsychological diseases and treatments.

This analysis will be adjusted for the listed covariates. The age variable will be included as a restricted cubic spline rather than a linear term. Before commencing analysis, we will assess the numbers of patients with each comorbidity, and may if necessary group the presence of certain less common comorbidities together. Any such grouping will be done on the basis of clinical similarities only and prior to examining any outcomes by comorbidity. We may also include a time-varying binary covariate to record any new diagnosis and/or treatment which occurs after study entry in patients originally free from both diagnosis and treatment, depending on the number of these events. Proportional hazards assumptions will be tested, and time dependent terms will be included if the hazard ratio changes over time (I.e. if the association between neuropsychological disease and risk of severe COVID-19 has changed during the course of the pandemic). A random frailty term will be included to account for similarities amongst patients registered in the same primary care practice. Possible interactions between exposure and age, sex and ethnicity will be considered and tested using a Wald test.

The same methods will be used for secondary analyses in which the main exposure variable will be defined as either the presence of a specific class of neuropsychological disorder or any other neuropyschological disorders or no disorder.

The primary analysis will be used to estimate the hazard ratio of severe SARI outcomes in cohort 2 using the same exposure variables.

If non-proportional hazards are observed in either cohorts 1 or 2, then maximum follow-up time will be capped at 1 year and a time-dependent covariate will be added to the analysis of both cohorts to maintain the comparability of results.

Aim 2.

Cause-specific Royston Parmar flexible parametric models will be used to estimate the hazard ratios of developing new neuropsychological diseases after having received intensive care, comparing patients who received intensive care for COVID-19 (cohort 3) vs those who received intensive care for SARI (cohort 4). This model will adjust for all previously listed covariates. The age variable will be included as a restricted cubic spline rather than a linear term. Follow-up will start on the date of discharge from hospital.

Proportional hazards assumption will be tested, and time dependent terms will be included if the hazard ratio changes over time. A random frailty term will be included to account for similarities amongst patients admitted in the same critical care unit

A limited number of two-way interactions which are considered to be clinically or biologically plausible will be identified prior to analysis, and tested using a Wald test.

Primary care data on some potential confounding variables is incomplete (e.g. smoking status, alcohol intake, ethnic group, BMI). Reason for admission is mandatory for all records in the ICNARC database (the core dataset for aim 2), so classification of these reasons as either SARI or COVID related will be non-missing for all patients. Only admission records for completed critical care stay (non-missing length of stay and survival status at end of critical care) will be included (n.b. outcomes are missing in <1% of COVID ICU admissions to date). Remaining variables from the critical care stay are use of sedation in the first 24 hours, and duration of advanced respiratory support, which are missing for a small number of patients (<1.5%).

Both aims.

To allow data analysis with all eligible patients, we will impute missing data in all cohorts. We will use multiple imputation with chained equations under the missing at random assumption to replace missing values and use these values in our main analyses [15]. We will include all exposure and confounding variables in the imputation model, along with the Nelson–Aalen estimator of the baseline cumulative hazard, and the outcome indicator. We will carry out five imputations. Analysis models will be fitted in each imputed dataset and Rubin's rules to will be used to combine the results across the imputed datasets.

As the analyses are on time to event data, patients will be censored at the date when they are lost to follow-up as defined in cohort definitions above.

Sensitivity analyses

We will undertake complete case analysis in those without missing data as a sensitivity analysis of our findings.

We will also restrict analysis to only include patients with confirmed COVID-19 diagnosis using RNA testing.

For Aim 2 we will carry out a sensitivity analysis in cohort four with additional censoring of follow-up on 24th January 2020, so that outcomes are assessed prior to the pandemic period. In comparing cohort 3 and 4 we will consider the competing risk of death by undertaking a competing risk analysis.

In order to compensate for the low expected event rates relative to our sample sizes for aim 2, we will combine cohorts 3 and 4 and use all available baseline characteristics (as listed previously) to calculate a propensity score to measure the likelihood of developing a new neuropsychological condition up to 1 year after ICU admission. We will then use these scores (with inverse probability weighting) to compare the adjusted hazard of developing a new neuropsychological condition in patients admitted to critical care for COVID compared to those admitted for SARI.

Data access and cleaning methods

The authors will have full access to anonymised data from the Case Mix Programme, QResearch and Public Health England, and Hospital Episode statistics databases. We will remove duplicate records for the same individual, and set dates and values outside a pre-defined credible range as missing. For patients admitted with SARI between 2015-2020 the full set of standard data validation processes for unit level data intended for public reporting will have been carried out by ICNARC. Some of the more recent Covid admissions will have undergone a more restricted set of validations, but these do include confirming the total number of admission with Covid to each unit, checking that duration of organ support does not exceed duration of stay, and confirming with units that that aggregated units level summaries of length of stay and organ support (among other measures) are in line with expectations. All variables used in the analysis will be initially summarised in a table of baseline characteristics to include minimum, maximum, median and quartiles.

Data linkage

Person-level data linkage will be undertaken between QResearch, Hospital Episode Statistics, the Case Mix Programme and Public Health England. Cases will be matched on pseudonymised NHS number [15].

Discussion

This study will present analysis of the association between psychopathology and its treatments and the risks of severe COVID-19 disease. We will also report the risks of developing psychopathological outcomes following ICU admission with COVID-19 disease in comparison to admission with other severe respiratory disease.

An advantage of this work in comparison to previous database analyses is the detailed information available on therapies within the QResearch database. This will allow us to investigate whether previously reported associations between COVID-19 infection and neuropsychological conditions are related to specific treatments rather than the diagnoses alone [3, 8].

As far as we are aware analysis of the post-ICU neuropsychological consequences of COVID-19 disease has not been undertaken. We are not aware of previous work linking the primary care and ICU record. As a result, previous work on neuropsychological outcomes following ICU has been severely limited both by a lack of knowledge of whether patients had neuropsychological disease prior to their ICU admission [9, 16] and by limited understanding of the treatments applied following discharge in the community [9]. Our work will provide understanding of this pathway both for patients with COVID-19 disease and for the comparator group of patients admitted to an ICU with SARI.

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Figure 1: Data flow diagram for cohort 1 and cohort 2 for the antecedent study.

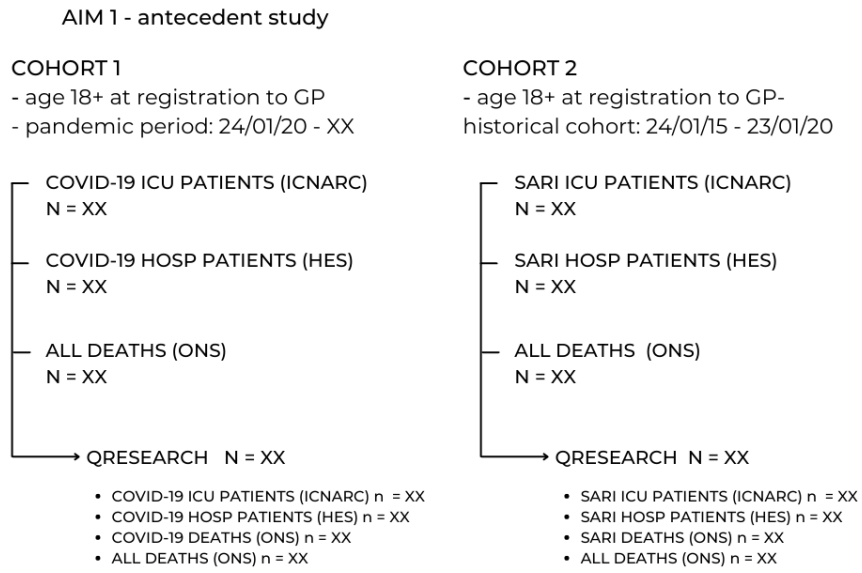


Figure 2: Data flow diagram for cohort 3 and cohort 4 for the antecedent study.

AIM 2 - sequelae study

COHORT 2
- age 18+ at hospital/ICU admission
- pandemic period: 24/01/20 - XX

- COVID-19 ICU DISCHARGED PATIENTS (ICNARC) N = XX
- COVID-19 HOSP DISCHARGED PATIENTS (HES) N = XX
- ALL DEATHS (ONS) N = XX

→ QRESEARCH N = XX

- COVID-19 ICU DISCHARGED PATIENTS (ICNARC) n = XX
- COVID-19 HOSP DISCHARGED PATIENTS (HES) n = XX
- ALL DEATHS (ONS) n = XX

COHORT 3
(to be used as compartor for COHORT 2)
- age 18+ at hospital/ICU admission
- historical cohort: 24/01/15 - 23/01/20

- SARI ICU DISCHARGED PATIENTS (ICNARC) N = XX
- SARI HOSP DISCHARGED PATIENTS (HES) N = XX
- ALL DEATHS (ONS) N = XX

→ QRESEARCH N = XX

- SARI ICU DISCHARGED PATIENTS (ICNARC) n = XX
- SARI HOSP DISCHARGED PATIENTS (HES) n = XX
- ALL DEATHS (ONS) n = XX

Figure 3. Directed Acyclic Graph for Aim 1.

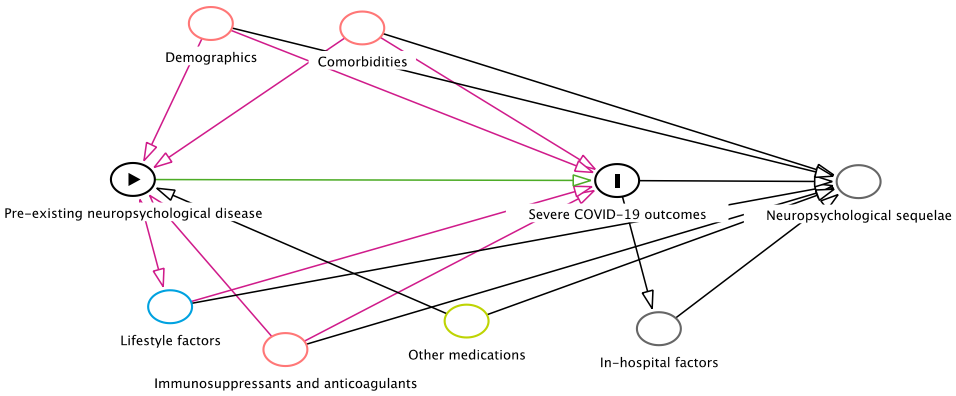
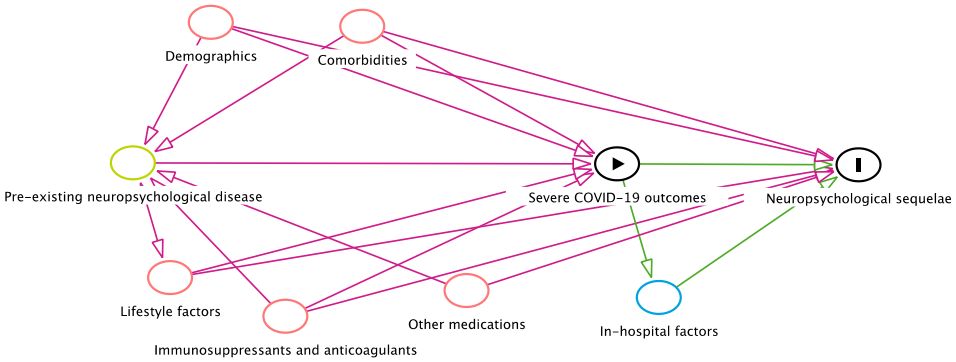


Figure 4. Directed Acyclic Graph for Aim 2.



Version history

Version	date	author	Notes
1.0	27.11.2020	PST, MP, RH, PW, CC	
1.2	12.12.2020	PST	Updated after teams meeting 11.12.20
1.3	22.03.2021	PW	
1.4	25.06.2021	PW,MP,CC,KT,DH	
1.5	23.07.2021	a/a	TR made final changes