medway school of pharmacy

PROJECT PROTOCOL

INVESTIGATING THE LONG-TERM IMPACT OF COVID-19

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Background to the study

Despite the World Health Organization having announced in May 2023 that COVID-19 is no longer a public health emergency of international concern, many questions remain unanswered. It is still unclear why COVID-19 symptoms vary significantly between individuals, from mild or symptomless to very severe requiring hospitalisation and in some cases leading to death. Further to this, it is puzzling why some people recover within weeks whilst others experience pre-existing and/or new symptoms months after they have tested negative and develop long COVID.

Long COVID encompasses a wide range of symptoms (over 200 symptoms) with impact on multiple organ systems (1,2). Neurological complications (e.g. memory problems, brain fog, sleep problems, ageusia, anosmia, dizziness, anxiety, depression) are among the most common reported symptoms (1,3). There is a rising concern that long COVID may accelerate pre-existing conditions or trigger the onset of new ones such as Alzheimer's disease, Parkinson's disease, cardiovascular disease and cancer.

Long COVID is currently affecting at least 2 million people in the UK and 77 million worldwide (4,2). The number is likely much higher due to undocumented cases (2). Indeed, most of the ongoing research is focused on enrolling hospitalized patients ignoring that 10–30% of long COVID cases is due to non-hospitalized cases who had mild symptoms (5). This is an important gap as, beside COVID-19 symptoms severity, other key health, environmental and lifestyle factors may trigger long COVID. Thus, this research aims to investigate long COVID in the UK population, regardless of COVID-19 symptoms severity (including hospitalized and non-hospitalized people), to shed a light on risk factors which are still unknown. This is crucial for the development of effective diagnostic, preventive and therapeutic protocols.

Aim and objectives

<u>Aim</u>
To run a public survey for the investigation of long COVID in the UK population.
People with persistent symptoms following acute infection with SARS-CoV-2 will answer a web-based questionnaire and will be stratified - regardless of COVID-19 severity (from asymptomatic to severe) - according to neurological complications, demographics (e.g.

ethnicity), presence of pre-existing comorbidities and/or mental health issues, onset of new health related conditions/mental health issues, COVID-19 vaccine presence/absence, environmental (e.g. pollution) and lifestyle factors (e.g. diet). This is important to enable a robust comparable statistical analysis and better understand health, environmental and lifestyle factors that may trigger long COVID.

Objectives

1. To identify and group people according to COVID-19 symptoms severity (from asymptomatic to severe) and persistence (or long COVID), demographics, environmental and lifestyle factors;
2. To assess the impact of pre-existing conditions and other health conditions/mental health issues on COVID-19 symptoms severity and/or long COVID.
3. To assess the impact of long COVID and the development of neurological complications;
4. To assess the impact of long COVID on pre-existing diseases e.g. cancer, cardiovascular diseases, mental health issues;
5. To assess the impact of long COVID on newly diagnosed conditions within the last three years e.g. cancer, cardiovascular diseases, mental health issues;
6. To assess the impact of COVID-19 vaccination on long COVID.

Methodology

The project will involve the following phases and activities.

a. Design a web-based questionnaire (online survey) for data collection;

b. Pilot the draft questionnaire on a small group of people from UK Higher Education (i. e Medway School of Pharmacy, up to N=30) and obtain feedback and modify as required (July 2023). Laypersons will also check the questionnaire and provide feedback;

c. Distribute the final version of the survey (amended as appropriate and according to the feedback in b) via Qualtrics;

d. Promote the link/QR code to access the survey distributing a flyer via personal and professional networks (Medway School of Pharmacy, University of Kent, NHS Trusts, etc) including social media (i.e., LinkedIn, Twitter, WhatsApp, Facebook, Instagram, etc).

General method

The study is intended to be based on mixed (quantitative and qualitative) methodologies, using a questionnaire targeting the UK population, which will be distributed via personal and professional networks of the research team.

Participant inclusion and exclusion criteria

Inclusion criteria:

- Participants must live in the UK;
- Participants must be over 18 years old;
- Participants must be able to read and write in English as the survey will not be translated into any other language.

Exclusion criteria:

- Anyone not based in the UK;

- Anyone under 18 years of age;
- Anyone unable to read and write in English.

Participant recruitment

The research team will disseminate the link/QR code to the online survey via personal and professional networks (Medway School of Pharmacy, University of Kent, NHS Trusts, etc) including social media (i.e., LinkedIn, Twitter, WhatsApp, Facebook, Instagram, etc).

The research team will actively raise awareness of the project and promote the questionnaire link/QR code.

It is predicted that participants would spread the QR code for the survey, resulting in the use of a snowball sampling approach.

The survey will be accessible online for 6 months. The precise dates will be communicated with the ethics chair upon confirmation (September 2023 until March 2024). This will allow enough time for the questionnaire to be distributed online and for posting reminders.

Informed consent

Before entering the survey, participants will access the Participant Information Leaflet (PIL) to learn about the project and decide whether or not to take part.

Next, the participants, will be asked for their consent as follows: *by completing and submitting your responses to this questionnaire, you are giving your consent to be part of this study and for your data to be used as described in the Participant Information Leaflet. Please confirm your consent in taking part in this study*

- *Yes, I consent to take part*
- *No, I do not wish to take part (survey terminates)*

If participants decline to give their consent the survey will come to an end.

Finally, once participants are happy to take part, they will be asked to read a statement at the start of the questionnaire, "*If you have read the Participant Information Leaflet and consent to participate in this study, please select the 'Continue' option*". If participants wish to continue, they will select the continue option before starting the online survey.

Interventions

Participants will only be required to complete the questionnaire once.

At the end of the questionnaire, there will be an optional space to leave their contact details (i.e., name, email address) if they would like to take part in future research. The following statement will be added "*If you are interested to take part in our research, please leave your email and we will contact you with more information. Participation is optional."*

Participants will be reassured that their personal details will not be linked to their responses and the information will be stored securely in a password-protected file on University Computers and accessed only by the Research Lead (RV).

Instruments to be used

A questionnaire developed using a mixture of open and closed questions to get a range of responses for data analysis will be uploaded on Qualtrics, an online survey platform.

Outcome measures

The survey will allow us to stratify the UK population into specific clusters of people carrying similar phenotypic traits and understand whether there is any association between long COVID and pre-existing conditions or newly developed health conditions, presence/absence of COVID-19 vaccine, age, gender, ethnicity etc, environmental and lifestyle factors. As the survey will be open to hospitalised and not-hospitalised individuals (regardless of their COVID-19 symptoms severity) the data from this study will reflect the whole UK population and not part of it.
We anticipate that the data from this survey will lead to further research (genomic study) investigating genetic risk factors that may explain not only the heterogeneity of COVID-19 symptoms severity and recovery but also the susceptibility to diseases such as Alzheimer's disease. Altogether, this will provide a comprehensive picture which can help develop improved prognosis and tailored therapeutic strategies to halt post-infection mechanisms and prevent illnesses such as Alzheimer's disease.
Upon completion of the project, the study findings will be shared to the wider scientific community through publication in Open-Access pre-print server (bioRxiv), journal and presentation at conferences. The outcome of the study will be uploaded on the MSoP and University of Kent website/channels (i.e. KAR, Twitter) and disseminated through local research presentations. Following publication, reagents and raw data (where appropriate) will be available on Kent Data Repository (KDR) and from the PI on request.

Methods for data analysis

- The Statistical Package for the Social Sciences (SPSS) software, version 28, will be used to input the quantitative data from the questionnaires and analyse the results.
- Microsoft Excel and GraphPad prism will be used to create the graphical representations.
- The Qualtrics survey platforms has its own data analysis function which could also be used for the data.

Confidentiality and anonymity

In accordance with the General Data Protection Regulation (GDPR) and the Data Protection Act 2018, we will take the following steps to ensure data protection.

- The questionnaire does not require any identifiable personal data; thus, participants will remain anonymous at all times. Participants can withdraw at any time without giving any reason by simply closing the link. However, after a questionnaire is completed, we won't be able to withdraw the answers. There is no way of identifying participants or what they have written.
  There will be no chance that confidentiality will be breached at any point as no data will be personally identifiable throughout the survey and analysis of the results.
- Survey data will be anonymous and not identifiable; thus, if leaked, it will not have any implications for the participants.
- Only participants who wish to take part in research will be asked for their contact details (name and email address). They will be reassured that personal data will not be linked to the participant's responses (survey data).

- The contact details (name and email address) left by participants will only be accessible by the Research Lead (RV) and stored in a password-protected file on University computers; these will be deleted after the study has been completed and ceased.
- All completed questionnaires will be kept on the online survey software which will be password protected, such that only the Research Lead (RV) will be able to access. The other members of the research team will be provided with the anonymized data as a data file.
- All data will be deleted 12 months after the study has ceased.

References

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