Examining potential factors underlying the increased risk of severe COVID-19 experienced by people with intellectual or developmental disabilities: Research Protocol

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# Lay Summary

People with intellectual disabilities or developmental disabilities (autism) are more likely to be admitted to hospital and to die following infection with Covid-19. We will investigate whether pre-existing, complex health problems experienced by such people and/or vaccination patterns explain these poorer Covid-19 outcomes. We will analyse health data on 13 million people who had confirmed Covid-19. The findings will potentially help prevent some hospitalisations and deaths due to Covid-19 in people with intellectual or developmental disabilities.

# Background

People with intellectual or developmental disabilities (IDD) have higher rates of severe Covid infection (defined here as hospitalisation and/or death) [1–4]. People with more severe disabilities or Down syndrome are at particular risk of severe Covid-19 [3, 5]. However, not much is known about the clinical risk factors associated with severe Covid-19 infections experienced by people with IDD.

Pre-existing long-term conditions (LTCs) have been shown to have strong associations with severe Covid-19 in general population studies [6, 7]. People with IDD have high rates of many LTCs, including obesity, epilepsy, and lower respiratory tract infection [8], which may partly explain their increased risk of severe Covid-19. However, no studies to date have thoroughly examined the association between LTCs commonly experienced by people with IDD and severe Covid-19. One UK study found that the presence of LTCs does not account for all of the association between intellectual disabilities and severe Covid-19 infection [3], but it did not investigate some important LTCs such as epilepsy, and the study investigators did not report what proportion of excess severe Covid-19 cases among people with intellectual disabilities can be attributed to higher prevalence of LTCs, and which LTCs in particular. Another study attempted to investigate LTCs but most effect sizes were not statistically significant due to low sample size, and seizures were excluded from modelling [4].

No studies have examined the association between severe Covid-19 and multimorbidity (two or more LTCs), polypharmacy or psychotropic medication use by people with IDD. It is known that these three factors are independently associated with severe Covid-19 in the general population [9, 10], and that people with IDD experience higher rates of all three [8, 11–13]. It is therefore likely that these factors contribute to higher rates of severe Covid-19 among people with IDD simply because they are more common. However, it is not known whether the associations between these factors and severe Covid-19 are also stronger among people with IDD than among people without IDD. Therefore, it is currently not possible to determine what proportion of excess severe Covid-19 cases among people with IDD is due to multimorbidity, polypharmacy and psychotropic medication use.

Similarly, no studies have examined the associations between vaccination status, vaccine type, and severe Covid-19 in people with IDD. Data from the Covid-19 vaccination programme in England showed that adults with intellectual disability were significantly less likely to have received a Covid-19 vaccine in the first 3 months of the vaccine rollout [14]. A higher rate of severe Covid-19 infection would therefore be expected in this population. Research specific to people with IDD is however needed to find out if vaccination status and vaccine type have the same, or different association with severe Covid-19 among people with IDD than among people without IDD.

There is emerging evidence that disparities in hospital healthcare may have contributed to the excess Covid-19 mortality among people with intellectual disabilities in the early stages of the pandemic in the UK [4]. This might be related to the early NICE guidance that recommended use of the Clinical Frailty Score in decision-making about critical care for people with a Covid-19 infection [15]. Our study will attempt to validate this finding.

In this study, we will examine the LTCs that increase the risks of severe Covid-19 in people with IDD. We will also examine the extent to which multimorbidity, polypharmacy and the use of psychotropic medication explain the increased risk of severe Covid-19 experienced by people with IDD. Associations between vaccination status, vaccine type, and severe Covid-19 among people with IDD will also be examined. We will also explore the presence of potential interactions between factors: for example, whether the strength of the association between certain LTCs and severe Covid infection is affected by psychotropic medication use. Our analysis will also control for the variant of Covid-19 virus (conditional on data availability). The study has the potential to uncover evidence that could help prevent some hospitalisations and deaths due to Covid-19 among people with IDD.

# Research Aim

To identify clinical risk factors that are associated with increased risk of hospitalisation and death following infection with Covid-19 among people with IDD.

# Research Questions

1. How does Covid-19 mortality among people with IDD compare with that of the general population?

* How many people with IDD have died due to Covid-19?
* What number of IDD deaths would be expected if Covid-19 had not happened?
* What is the Covid-19 mortality rate among people with IDD, and how does it compare with that of the general population?
* What number of Covid-19 deaths in the IDD population would be expected if this population had the same (age-sex specific) Covid-19 mortality rate as the general population?
* What is the number of excess Covid-19 deaths among the IDD population, i.e. the difference between the expected and actual Covid-19 deaths?

2. What is the prevalence and incidence of Covid-19 hospitalisations among the IDD population, and how does it compare with the general population?

3. Are there significant differences in the associations between clinical risk factors (LTCs, multimorbidity, polypharmacy, psychotropic medication, vaccine status, and vaccine type) and risk of hospitalisation and death following Covid-19 infection in people with and without IDD?

* If there are significant differences, what proportion of excess Covid-19 deaths in the IDD population is accounted for by these factors, controlling for demographic variables?
* What proportion of excess Covid-19 deaths among people with IDD remains unaccounted for?
* Which exposure factors have, on balance, biggest influence on severe Covid-19 infection among people with IDD?

4. Which factors best predict a negative Covid outcome in the IDD population?

* How does the performance of the best predictive model compare with that of the Qcovid algorithm (designed for the general population)?

# Methods

## Study design and setting

This study will make use of the NHS Digital dataset that is administered by the BHF-Covid-UK Consortium. A retrospective cohort study will be constructed through linkage of individual-level primary care, hospital, death, dispensed pharmacy, vaccination and laboratory data and analysed in a Trusted Research Environment.

Primary care data is needed to identify people with IDD and their health conditions. Prescribing data will be used to ascertain use of psychotropic medication and polypharmacy. Laboratory data will provide the dates and results of Covid-19 tests. Hospital admission and death certificate data will be used to classify infected individuals as severe or not. Vaccination data will be used to determine vaccination status and type at the time of Covid-19 infection.

## Population

The overall study population will be people in England with a confirmed Covid-19 infection. That is, they had a positive laboratory test for Covid-19 or died of Covid-19 (their death certificate mentions Covid-19). This study population will be divided into two cohorts: people with IDD and a comparison group of people without IDD. A comparison group is needed to examine whether the associations between long term conditions/ multimorbidity/ polypharmacy/vaccination and Covid-19 outcomes are different in people with IDD and to quantify and investigate the excess risk among people with IDD.

## Exposure

The exposures of interest are LTCs, multimorbidity, polypharmacy, psychotropic medication, vaccine status, vaccine type, and treatment type. Pre-existing LTCs will be described using a list of 36 commonly experienced LTCs [16], which includes the LTCs most commonly identified as risk factors for severe Covid-19 in general population studies. These LTCs will be considered individually but will also be used to construct an indicator of multimorbidity: at least three LTCs, of which at least one is physical [8]. A cut-off date of 15 days before the infection date (date of testing positive for Covid-19) will be set to examine prescribing data and all prescriptions dispensed in a 240-day interval before this cut-off date [10]. British National Formulary (BNF) drug codes for dispensed prescriptions issued in primary care will be extracted from the NHS BSA prescriptions dataset. Polypharmacy will be based on the number of participant medications used simultaneously and categorised into 0, 1-3, 4-6, 7-9 and ≥10 medications. Psychotropic medication use will be defined as yes/no and based on all prescriptions of antipsychotics, antidepressants, mood stabilisers and anxiolytics/ hypnotics (including benzodiazepines, antidementia drugs and drugs for attention deficit hyperactivity disorder. Vaccination status will be recorded as the number of vaccine doses (including zero, i.e. not vaccinated). Vaccine type will be the name of the vaccine. Treatment types will include: Non-Invasive Ventilation, Invasive Mechanical Ventilation, and admission to Intensive Care Unit.

## Outcomes

The outcomes will be:

* hospitalisation due to Covid-19 (defined as admissions with ICD-10 diagnosis of U07.1 or U07.2, not restricted to primary diagnosis; an additional analysis will look at hospitalisation with and without admission to ICU)
* death due to Covid-19 (defined as a ICD-10 code of U07.1 or U07.2 anywhere on the death certificate).

## Covariates

Demographic covariates will include age, sex, ethnicity and area deprivation (IMD).

## Data sources

The NHS Digital ‘Trusted Research Environment’ will be used to link the following datasets covering primary care, prescribing, Covid testing, hospital admissions, deaths and vaccinations:

1. GPES Data for Pandemic Planning and Research (GDPPR)
2. Hospital Episode Statistics (HES)
3. Covid-19 Second Generation Surveillance System (SGSS)
4. Vaccination events (VE)
5. Civil registration- Deaths from the ONS (ONS-D)
6. NHS BSA Dispensed Medicine (NHSBSA).

Overall, the analysis dataset will contain approximately 13 million cases.

## Data analysis

RQ1.

The GDPPR dataset will be primarily used to answer this question and sub-questions. Information in this dataset allows for identification of people with IDD. The number of deaths in GDPPR is slightly lower than the number of deaths in the ONS deaths dataset, and therefore we will proportionally upscale the former using the latter, to arrive at the correct number of Covid-19 deaths in the IDD population.

The number of deaths expected if Covid-19 had not happened will be calculated using GDPPR data from November 2019 – February 2020 (the deaths data in GDPPR is not reliable prior to November 2019), combined with ONS data about the monthly distribution of deaths in an average year.

RQ2.

We will use GDPPR as the base dataset (to identify people with IDD) and merge the HES dataset with it to answer this research question.

RQ3.

We will firstly compare the IDD and comparison groups in terms of demographic profile, prevalence of risk factors (LTCs, multimorbidity, polypharmacy, psychotropic medication use, vaccination status, and vaccination type) and crude rates of severe Covid-19.

Binary logistic regression models will be then fit to test for the associations between the clinical risk factors (LTCs, multimorbidity, polypharmacy, psychotropic medication, vaccination status and type) and severe Covid-19 outcome (hospitalisation and/or death) adjusting for demographic factors. The models will also test for theoretically informed interactions between exposure factors.

We will attempt to estimate what proportion of excess Covid-19 deaths among people with IDD is accounted for by exposure factors retained in the final logistic model. To this end, we will compute predicted values using regression coefficients from the model fit on general population and predicted values using regression coefficients from the model with on the IDD population. We will then calculate the difference between the two predicted numbers of excess deaths.

Our analysis will also explore which exposure factors have, on balance, more influence on severe Covid-19 infection than other factors, among people with IDD. We will use hierarchical Linear Probability Model analysis to determine predictors’ influence on the R squared.

RQ4.

We will use Machine Learning to find the model that best predicts severe Covid outcome on a validation dataset. Algorithms considered will include Support Vector Machine, Random Forests, and Gradient Boosting.

We will compare the performance of this model with Qcovid, an established algorithm that has been trained on whole population data.

# Research impact

This research will lead to public benefit by a) identifying health inequalities to target and prevent severe Covid-19 infections b) informing priorities for health improvement during the recovery from the pandemic and c) providing evidence on the potential need for further vaccinations for people with IDD. Our inclusive research approach that involves people with lived experience, third sector organisations and health and social care partners will maximise the public health benefit of our research.

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