**Study protocol**: Exploring absolute risks of mortality and hospitalisation related to COVID-19 using the OpenSAFELY platform

**25th January 2021**

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Abstract

On March 11th 2020, the World Health Organization characterised COVID-19 as a pandemic. There are currently several promising vaccines to prevent COVID-19, and countries are planning how to prioritise vaccine allocation. WHO guidance in settings with widespread transmission (relevant to Europe) is that vaccination should aim to directly reduce mortality by prioritising individuals at highest risk of dying of COVID-19. Reducing COVID-19 related hospitalisation is also a priority for national healthcare systems. Age, underlying health conditions and ethnicity are all associated with increased relative risk of COVID-19 mortality and hospitalisation, but absolute risk is needed to understand how to target vaccines for the greatest reduction in mortality and hospitalisation.

The aim of this study is to use linked electronic health records within the OpenSAFELY platform to describe who is at highest absolute risk of hospitalisation and mortality from COVID-19 in England. We describe these absolute risks to support UK and other countries to prioritise vaccine allocation based on highest absolute risk of mortality and hospitalisation.

Keywords

COVID-19; absolute risk; mortality; hospitalisation.

# Background and aims

On March 11th 2020, the World Health Organization characterised COVID-19 as a pandemic after 118,000 cases and 4,291 deaths were reported in 114 countries. A range of demographic factors and health conditions have been shown to be associated with poor outcomes from COVID-19, including COVID-19 related death. In the UK, the report released by Public Health England in June 2020 identified age as the strongest disparity in COVID-19 death, additionally noting disparities between males and females, and higher risks among black and minority ethnic (BME) groups. Various pre-existing conditions correlate with increased risk of poor outcomes including diabetes, respiratory disease and cancer.

There are currently several promising vaccines to prevent COVID-19, and countries are planning how to prioritise vaccine allocation. WHO guidance in settings with widespread transmission (relevant to Europe) is that vaccination should aim to directly reduce mortality by prioritising individuals at highest risk of dying of COVID-19. Reducing COVID-19 related hospitalisation is also a priority for national healthcare systems. Age, underlying health conditions and ethnicity are all associated with increased relative risk of COVID-19 mortality and hospitalisation, but absolute risk is needed to understand how to target vaccines for the greatest reduction in mortality and hospitalisation.

Therefore, the aim of this study is to use linked electronic health records within the OpenSAFELY platform to describe who is at highest absolute risk of hospitalisation and mortality from COVID-19 in England. We describe these absolute risks to support UK and other countries to prioritise vaccine allocation based on highest absolute risk of mortality and hospitalisation.

# Methods

## Study Population, Outcome and Follow-up

### Study design

Data will be accessed using OpenSAFELY, a data analytics platform created on behalf of NHS England to address urgent COVID-19 research questions (https://opensafely.org). OpenSAFELY includes the electronic health record (EHR) data of 24 million people currently registered with primary care practices using TPP SystmOne software, representing approximately 40% of the English population (see supplementary materials for more details).

A population-based observational cohort study of adult patients in England will be used. Specifically, the cohort will comprise adult patients (males and females, aged between 18 and 105 years) registered as of 1st March 2020 in a general practice which employs the TPP system. Patients with missing age or a recorded age over 105 years, missing gender, or missing postcode (from which much of the household and geographic information is calculated) will be excluded. Patients with a record of HIV will be excluded, due to the partial suppression of outcomes for this group, leading to poor outcome ascertainment.

A smaller sub-cohort will be used in sensitivity analysis, restricting to households of at most 10 people, since risks experienced in institutions such as care homes are likely to be very different to those in smaller households.

### Outcomes

The three outcomes for this study are (i) COVID-19 related death and (ii) COVID-19 related hospitalisation, (iii) COVID-19 related death or hospitalisation.

Primary care data were linked to mortality data from the Office for National Statistics (ONS) mortality data and to Secondary Uses Services Admitted Patient Care data. COVID-19 related deaths were defined as deaths with an ICD-10 code of U071 or U072 anywhere on the death certificate. COVID-19 related hospital admissions were defined as admissions with any ICD-10 admission diagnosis (not restricted to primary diagnosis) of U071 or U072.

### Follow-up

The study will begin on 1st March 2020 and will end 9 months later on 30th November 2020 (inclusive). Follow-up for all eligible patients will begin 1st March 2020 and will end on the first of the outcome of interest or study end (30th November 2020). Note that censoring for competing outcomes (e.g. death due to other causes) will not be undertaken because the focus is on the sub-distribution hazard.

## Covariates

Primary care records were retrieved from the TPP SystmOne electronic health record system. These data include diagnoses (Read 3 CTV3), prescriptions (dm+d), basic sociodemographics and vital signs.

The outcome, COVID-19 related mortality, is the result of a number of processes: exposure, infection and then death following infection. Because of this, there are a range of mechanisms driving associations between patient characteristics and the outcome. We selected covariates based on known or plausible associations with exposure to COVID-19 infection, risk of respiratory tract infection or severity of illness, and factors associated with healthcare access or level of care, as shown in Table 1.

Covariates included are described below. These are derived from primary care records retrieved from the TPP SystmOne electronic health record system, including diagnoses (Read 3 CTV3), prescriptions (dm+d) and basic sociodemographics. The codelists used to define the included covariates are listed in the Appendix, Table A1.

Demographic measures: age (continuous); sex (male or female); e[thnicity](https://codelists.opensafely.org/codelist/opensafely/ethnicity/) (8 category: White, Indian, Pakistani, Bangladeshi/Other Asian, African/Other black, Caribbean, Chinese, Mixed/Other); deprivation (quintile of the index of multiple deprivation (IMD) derived from the patient’s postcode at lower super output area level). The region (seven regions of England: South West; South East; London; East; Midlands; North West; North East, Yorkshire and the Humber) and whether the individual lives in a rural or urban area will be included.

Lifestyle characteristics: obesity category and smoking status. Obesity will be grouped using categories derived from the World Health Organisation classification of Body Mass Index (BMI; kg/m2): underweight <18.5 kg/m2; obese I 30-34.9; obese II 35-39.9; obese III 40+; or no evidence of obesity or being underweight, with BMI ascertained from weight measurements within the last 10 years, restricted to those taken when the patient was over 16 years old. Smoking status will be grouped into evidence of current smoking in the last 18 months, former and never smokers.

Comorbidities will be defined through combinations of clinical measurements, prescriptions, and recorded diagnoses. Other comorbidities to be included: diagnosed hypertension; [chronic cardiac disease](https://codelists.opensafely.org/codelist/opensafely/chronic-cardiac-disease/) including chronic heart failure, ischaemic heart disease, and severe valve or congenital heart disease likely to require lifelong follow up; atrial fibrillation; surgery for peripheral arterial disease or lower limb amputation; prior deep vein thrombosis or pulmonary embolism; [diabetes](https://codelists.opensafely.org/codelist/opensafely/diabetes/) (additionally using HbA1c within last 15 months to determine level of HbA1c control, grouped into <58 mmol/mol (good control), >=58 mmol/mol (poor control) and no recent measure); stroke; [dementia](https://codelists.opensafely.org/codelist/opensafely/dementia/); and o[ther neurological conditions](https://codelists.opensafely.org/codelist/opensafely/other-neurological-conditions/) (motor neurone disease, myasthenia gravis, multiple sclerosis, Parkinson's disease, cerebral palsy, quadriplegia or hemiplegia, malignant primary brain tumour, and progressive cerebellar disease).

Asthma will be grouped by use of oral corticosteroids as an indication of severity, with 2 or more prescriptions in the last year taken to indicate severe asthma); cystic fibrosis and associated diseases such as primary ciliary dyskinesia; and other r[espiratory disease](https://codelists.opensafely.org/codelist/opensafely/chronic-respiratory-disease/). Haematological malignancies and non-haematological malignancies were each grouped according to time since diagnosis (<1 year, 2-<5 years, 5+years). Haematological malignancies were considered separately from other cancers to reflect the immunosuppression associated with haematological malignancies and their treatment. Li[ver](https://codelists.opensafely.org/codelist/opensafely/chronic-liver-disease/) disease; solid organ transplant (any); dialysis, for patients who have not since had a kidney transplant; and kidney function (ascertained from the most recent serum creatinine measurement taken in the last 5 years excluding the most recent fortnight, where available, converted into estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation), with reduced kidney function grouped into no evidence of kidney impairment (no creatinine measurement or eGFR>=60 mL/min/1.73m2), stage 3 (eGFR in range 30-<60 mL/min/1.73m2) and stage 4-5 (<30 mL/min/1.73m2) will also be considered. Patients with a history of kidney dialysis or kidney transplant will be included in the category representing stage 4-5.

We will also include common autoimmune diseases including Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE) or psoriasis; inflammatory bowel disease, asplenia (splenectomy or a spleen dysfunction, including sickle cell disease); and other immunosuppressive conditions including a condition inducing permanent immunodeficiency ever diagnosed, or aplastic anaemia or temporary immunodeficiency recorded within the last year.

Finally, we will consider: learning disability, including Down’s syndrome; serious mental illness; and fragility fracture in the last two years for patients aged 65 or above.

## Statistical Analysis

For each outcome, a Royston-Parmar proportional hazards model will be fitted, including all of the covariates listed above. Age will be fitted as a cubic spline.

Absolute risks of the three outcomes will be estimated by age for females and males, for an average person, defined as: medium IMD, not obese, non-smoker, White ethnicity living in an urban area of the Midlands. Each individual comorbidity will be added one at a time to estimate the absolute risk for each individual comorbidity. with an individual comorbidity.

We will estimate the age at which the “age-65 risk” is attained for patients with an individual comorbidity, defining the age-65 risk as the risk of a patient of the same sex without any comorbidity, with the same demographic characteristics.

We will then count the number of major comorbidities and refit models adjusting only for the grouped comorbidity variable, allowing this to interact with age, sex and ethnicity. Comorbidities included will be: respiratory disease, severe asthma, chronic cardiac disease, diabetes, non-haematological cancer (diagnosed in last year), haematological cancer (diagnosed within 5 years), liver disease, stroke, dementia, poor kidney function, organ transplant, asplenia, other immunosuppression.

### Missing data

A large number of the candidate predictors will be fully observed, in the sense that an absence of a diagnosis is taken to indicate the absence of disease, as is typically assumed in electronic health record research. While this may lead to issues with misclassification and subsequent interpretation, this does not manifest itself in a missing data problem. Missing data will arise in some demographic variables and clinical measurements, with the later predominantly used to determine severity of certain conditions. The predictors that are expected to have missing data (with anticipated missing rates in brackets) are: ethnicity (~25%), BMI (~20%), Smoking (~5%), hba1c (~20% of patients with diabetes), and kidney function (missingness likely in serum creatinine measurement). Our previous analyses in these data suggested that the missingness mechanism for ethnicity may be somewhat missing not at random in one region, but little evidence against missing at random in the other regions.

A complete case approach will be used for ethnicity, restricting the analysis to the sub-population in which ethnicity is measured. Patients with missing BMI will be assumed non-obese and patients with no smoking information will be assumed non-smokers, on the assumption that smoking and obesity, if present, are likely to be recorded. Patients with no serum creatinine measurement will similarly be included in the “no evidence of poor kidney function”. Patients with diabetes but no Hba1c measurement will be included in a separate “diabetes, no Hba1c” category.

# Ethics and Information Governance

NHS England is the data controller; TPP is the data processor; and the key researchers on OpenSAFELY are acting on behalf of NHS England. This implementation of OpenSAFELY is hosted within the TPP environment which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant; patient data has been pseudonymised for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is via a virtual private network (VPN) connection, restricted to a small group of researchers, their specific machine and IP address; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell counts. The OpenSAFELY research platform adheres to the data protection principles of the UK Data Protection Act 2018 and the EU General Data Protection Regulation (GDPR) 2016. In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure. Taken together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. This study was approved by the Health Research Authority (REC reference 20/LO/0651) and by the LSHTM Ethics Board (reference 21863).

# Discussion

Results from these analyses will provide a clear description of the absolute risks of COVID-19 hospitalisation and mortality across a range of comorbidities. These estimates will help inform vaccine prioritisation over the coming months, both in the UK and elsewhere.

### **Data and Software Availability**

All data were linked, stored and analysed securely within the OpenSAFELY platform (<https://opensafely.org/>). Detailed pseudonymized patient data are potentially reidentifiable and therefore not shared. We rapidly delivered the OpenSAFELY data analysis platform without

prior funding to deliver timely analyses on urgent research questions in the context of the global COVID-19 health emergency: now that the platform is established we are developing a formal process for external users to request access in collaboration with NHS England. Details of

this process will be published shortly on the OpenSAFELY website.

Data management was performed using Python 3.8 and SQL, with analysis carried out using Stata 16.1 and Python. All code is shared openly for review and reuse under an MIT open license. All code for data management and analysis is archived online at <https://github.com/opensafely/risk-prediction-research>. All clinical and medicines codelists are openly available for inspection and reuse at <https://codelists.opensafely.org/>.

### **Author Contributions**

B.G. conceived the platform and the approach; B.G. and L.S. led the project overall and are guarantors; S.B. led the software; E.J.W and K.B. led the statistical analysis with advice from HM; C.E.M. and A.J.W. led on codelists and implementation; and A.M. led on information governance. Contributions are as follows: data curation, C.B., J.P., J.C., S.H., S.B., D.E., P.I. and C.E.M.; analysis, E.J.W., K.B., A.J.W. and C.E.M.; funding acquisition, B.G. and L.S.; information governance, A.M., B.G., C.B. and J.P.; methodology, E.J.W., K.B., A.J.W., B.G., L.S., C.B., J.P., J.C., S.H., S.B., D.E., P.I., C.E.M., R.G., D.H., R.K. K. D-O, E.S. and R.P.; disease category conceptualization and codelists, C.E.M., A.J.W., P.I., S.B., D.E., C.B., J.C., J.P., S.H., H.J.C., K.B., S.B., A.M., B.M., L.T., I.J.D., H.I.M., R.M. and H.F.; ethics approval, H.J.C., E.J.W., L.S. and B.G.; project administration, C.E.M., H.J.C., C.B., S.B., A.M., L.S. and B.G.; resources, B.G., L.S. and F.H.; software, S.B., D.E., P.I., A.J.W., C.E.M., C.B., F.H., J.C. and S.H.; supervision, B.G., L.S. and S.B.; writing (original draft), E.J.W., J.T. All authors were involved in design and conceptual development and reviewed and approved the final manuscript.

### **Competing Interests**

All authors have completed the International Committee of Medical Journal Editors (ICMJE) uniform disclosure form at www.icmje.org/coi\_disclosure.pdf. C.B., J.P., F.H., J.C. and S.H. are employees of TPP. A.M. was interim Chief Medical Officer of NHS Digital April–Sept 2019 (left NHS Digital at the end of January 2020) and Digital Clinical Champion NHS England 2014–2015. All other authors have no competing interests.

### **Acknowledgements**

The OpenSAFELY Collaborative are grateful for all the support received from the TPP Technical Operations team throughout this work; for assistance from the information governance and database teams at NHS England and NHSX; and for additional discussions on disease characterization, codelists and methodology with H. Drysdale, B. Nicholson, N. DeVito, I. Lipska, J. Morley, J. Quint. TPP provided technical expertise and infrastructure within their data centre pro bono in the context of a national emergency.

### **Grant Information**

The OpenSAFELY collaborative has received funding from NIHR. The work of B.G. on better use of data in healthcare more broadly is currently funded in part by: the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, NIHR Applied Research Collaboration Oxford and Thames Valley, the Mohn-Westlake Foundation, NHS England and the Health Foundation; all DataLab staff are supported by the grants of B.G. for this work. L.S. reports grants from Wellcome, MRC, NIHR, UKRI, British Council, GSK, British Heart Foundation and Diabetes UK outside this work; K.B. holds a Sir Henry Dale fellowship jointly funded by Wellcome and the Royal Society; H.I.M. is funded by the NIHR Health Protection Research Unit in Immunisation (a partnership between Public Health England and LSHTM); A.Y.S.W. holds a fellowship from BHF; R.M. holds a Sir Henry Wellcome fellowship funded by the Wellcome Trust; E.J.W. holds grants from MRC; R.G. holds grants from NIHR and MRC; I.J.D. holds grants from NIHR and GSK; H.F. holds a UKRI fellowship; B.D.N. holds an NIHR fellowship. The views expressed are those of the authors and not necessarily those of the NIHR, NHS England, Public Health England or the Department of Health and Social Care. The funders had no role in the study design; the collection, analysis and interpretation of data; the writing of the report; and the decision to submit the article for publication.

# References

[to be added]

# Figures

# Tables

Table 1. Rationale for selection of candidate predictors

|  |  |  |
| --- | --- | --- |
| Category | Example predictors |  |
| Factors associated with exposure to infection | Age, sex, ethnicity, household size, deprivation, region |  |
| Risk factors for infection (given exposure) or severity of COVID-19 infection | Smoking, obesity, underlying health conditions known to be risk factors for severe respiratory tract infection, risk factors for thrombosis |  |
| Barriers to healthcare access or level of care | Markers of frailty, terminal illness, ethnicity, age, mental health status |  |

# Appendix 1

Table A1. Codelists used to define candidate predictors and suspected COVID-19 (as proxy for infection burden)

|  |  |  |
| --- | --- | --- |
| Variable | Notes | Codelist |
| Suspected COVID-19 |  | <https://codelists.opensafely.org/codelist/opensafely/covid-identification-in-primary-care-suspected-covid-suspected-codes/2020-07-16/> |
| Ethnicity | 7 categories, obtained from 16 (White, Caribbean, Chinese, Indian/Pakistani, Mixed/Other, Bangladeshi/Other Asian, African/Other Black) | [https://codelists.opensafely.org/codelist/opensafely/ethnicity](https://codelists.opensafely.org/codelist/opensafely/ethnicity/) |
| Diagnosed hypertension |  | [https://codelists.opensafely.org/codelist/opensafely/hypertension](https://codelists.opensafely.org/codelist/opensafely/hypertension/) |
| C[hronic cardiac disease](https://codelists.opensafely.org/codelist/opensafely/chronic-cardiac-disease/) |  | <https://codelists.opensafely.org/codelist/opensafely/chronic-cardiac-disease/> |
| Atrial Fibrillation |  | <https://codelists.opensafely.org/codelist/opensafely/atrial-fibrillation-or-flutter/2020-07-30/> |
| Surgery for Peripheral Arterial Disease | Combined with lower limb amputation to form a peripheral arterial disease variable | <https://codelists.opensafely.org/codelist/opensafely/surgery-for-peripheral-artery-disease/2020-09-16/> |
| Lower limb amputation | Combined with surgery for peripheral arterial disease to form a peripheral arterial disease variable | <https://codelists.opensafely.org/codelist/opensafely/amputation/2020-09-21/> |
| Prior deep vein thrombosis / pulmonary embolism |  | <https://codelists.opensafely.org/codelist/opensafely/venous-thromboembolic-disease/2020-09-14/> |
| D[iabetes](https://codelists.opensafely.org/codelist/opensafely/diabetes/) | Combined with Hba1c measure within 18 months to determine level of control | <https://codelists.opensafely.org/codelist/opensafely/diabetes/> |
| S[troke](https://codelists.opensafely.org/codelist/opensafely/stroke-updated/) |  | <https://codelists.opensafely.org/codelist/opensafely/stroke/> |
| Dementia |  | <https://codelists.opensafely.org/codelist/opensafely/dementia/> |
| O[ther neurological conditions](https://codelists.opensafely.org/codelist/opensafely/other-neurological-conditions/) |  | <https://codelists.opensafely.org/codelist/opensafely/other-neurological-conditions/> |
| Asthma | Combined with ICS prescriptions in past year to determine severity | <https://codelists.opensafely.org/codelist/opensafely/asthma-diagnosis/> |
| Cystic Fibrosis and associated conditions |  | <https://codelists.opensafely.org/codelist/opensafely/cystic-fibrosis/2020-07-20/> |
| R[espiratory disease other than asthma](https://codelists.opensafely.org/codelist/opensafely/chronic-respiratory-disease/) or cystic fibrosis |  | <https://codelists.opensafely.org/codelist/opensafely/other-chronic-respiratory-disease/2020-07-20/> |
| Non-haematological cancer | Grouped by time since diagnosis (<1 year, 2-<5 years, 5+years) | <https://codelists.opensafely.org/codelist/opensafely/cancer-excluding-lung-and-haematological/> |
| Haematological cancer | Grouped by time since diagnosis (<1 year, 2-<5 years, 5+years) | <https://codelists.opensafely.org/codelist/opensafely/haematological-cancer/> |
| Lung cancer | Combined with other non-haematological cancer | <https://codelists.opensafely.org/codelist/opensafely/lung-cancer/> |
| L[iver disease](https://codelists.opensafely.org/codelist/opensafely/chronic-liver-disease/) |  | <https://codelists.opensafely.org/codelist/opensafely/chronic-liver-disease/> |
| Kidney dialysis | Used if no kidney transplant since most recent dialysis | <https://codelists.opensafely.org/codelist/opensafely/dialysis/2020-07-16/> |
| Kidney transplant | Combined with non-kidney transplant for transplant indicator. Also used to determine which of dialysis/transplant is most recent. | <https://codelists.opensafely.org/codelist/opensafely/kidney-transplant/2020-07-15/> |
| Organ transplant (other than kidney) | Combined with kidney transplant for transplant indicator. | <https://codelists.opensafely.org/codelist/opensafely/other-organ-transplant/2020-07-15/> |
| A[splenia](https://codelists.opensafely.org/codelist/opensafely/asplenia/) |  | <https://codelists.opensafely.org/codelist/opensafely/asplenia/> <https://codelists.opensafely.org/codelist/opensafely/sickle-cell-disease/> |
| Autoimmune diseases ([rheumatoid arthritis, lupus, psoriasis](https://codelists.opensafely.org/codelist/opensafely/ra-sle-psoriasis/)) |  | <https://codelists.opensafely.org/codelist/opensafely/ra-sle-psoriasis/> |
| HIV | (used to exclude) | [https://codelists.opensafely.org/codelist/opensafely/hiv/2020-07-13/](https://codelists.opensafely.org/codelist/opensafely/hiv/2020-07-13/#full-list) |
| Other immunosuppressive condition | Temporary and aplastic anaemia within last year; permanent ever. | <https://codelists.opensafely.org/codelist/opensafely/permanent-immunosuppresion/>  <https://codelists.opensafely.org/codelist/opensafely/aplastic-anaemia/>  <https://codelists.opensafely.org/codelist/opensafely/temporary-immunosuppresion/> |
| Inflammatory bowel disease |  | <https://codelists.opensafely.org/codelist/opensafely/inflammatory-bowel-disease/2020-04-07/> |
| Learning disability, including Down’s syndrome |  | <https://codelists.opensafely.org/codelist/opensafely/intellectual-disability-including-downs-syndrome/2020-08-27/> |
| Serious mental illness |  | <https://codelists.opensafely.org/codelist/opensafely/psychosis-schizophrenia-bipolar-affective-disease/2020-07-09/> |
| Fragility fracture |  | <https://codelists.opensafely.org/codelist/opensafely/fragility/2020-09-14/> |