Version history

V0.6	24/7/2020	Added details on models for sensitivity analyses after comments from KK, AW, RD and FZ. Definition of models, tables still needed
V0.7	20/8/2020	Discussion on TRE and adding details after discussion with Rachel Denholm and Farrington and updated comments
V0,8	26/8/2020	Updated all comments and changes from V0.7
V0.9	9/9/2020	Added Ben Bray comments, particularly firming analysis population, comments from meeting of WP 2.5 (7.9.20)
V0.10	11/9/2020	Comments from Abdel Douri, Khamlesh Khunti
V0.11	17/9/2020	Comments from C Smith and C Sudlow, added lay summary
V0.12	16/11/2020	Self-controlled case series analysis added, updated lay summary
V0.13	25/11/20	Further comments from Ashley Akbari, Craig Smith, Fatemeh Torabi, Frank Kee, Kamlesh Khunti, Anne Marie Docherty, Julian Halcox, MJ Macleod, Francesco Zaccardi
V0.14	5/1/21	Further comments from Kate Tilling, Tom Palmer, Jonathan Sterne
V0.15	2/1/21	Removed angina as an exclusion criterion

Lay summary

Coronavirus infection ('COVID') might increase the chance of having a stroke, heart attack or clots in the deep leg veins or lungs ('blood vessel diseases').

During the COVID pandemic, some doctors saw patients who had COVID who also had unusual strokes, clots or heart complaints. This suggested a link between COVID and blood vessel diseases. But no individual doctor saw enough patients to find out if COVID really did increase the risk of blood vessel diseases.

We will study every person alive in NHS England, Scotland and Wales at the beginning of the pandemic in 2020. We will find out how many people had a stroke, heart or other diseases of the blood vessels over the following year.

We will compare the number of people with COVID infection who had a blood vessel disease with the number of people without COVID infection who had a blood vessel disease. Different types of people might have different risks, so we will look in people of different ages, ethnicities and medical history as well. The result will be an estimate of how much COVID increases the risk of different blood vessel diseases.

This information is needed so that people with COVID know whether they need to worry about blood vessel diseases as they recover. If there is an increased risk, then preventative treatments might be needed.

AUTHORS

BHF Data Science Centre

TITLE

SARS-CoV-2 infection and risk of major vascular events

BACKGROUND

Better knowledge about the effect of SARS-CoV-2 infection on short- and longer-term risk of MI and stroke is important to estimate the magnitude of any effect, to identify those at greatest risk, and therefore whether preventative treatments (e.g. aspirin) for those with infection are needed. In the present study we plan a series of studies about the risk of stroke and myocardial infarction in patients with confirmed SARS-CoV-2.

Infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus - which causes the illness COVID-19 - induces a prothrombotic and pro-inflammatory state that may increase the risk of serious cardiovascular diseases. However, the absolute and relative risks of cardiovascular diseases after SARS-CoV-2 infection are uncertain at this stage of the pandemic. If the long-term risk of cardiovascular diseases is substantial in general or in particular populations, then an effective prevention strategy will be a public health priority for people in Scotland, UK and globally.

Any elevated risk of cardiovascular disease after SARS-CoV-2 infection needs to be put into context of risk after other acute viral infections, such as influenza. An estimation of the risk of vascular events of different types, such as myocardial infarction (MI), stroke, heart failure, cardiac arrhythmia, deep vein thrombosis (DVT) and pulmonary embolism (PE) will make an important contribution to our understanding of the clinical relevance of any long-standing endothelial or systematic inflammation.

Therefore, this project aims to estimate the risk of different cardiovascular diseases after SARS-CoV-2 infection, and if elevated identify the period and duration of risk**.**

There are plausible mechanisms by which SARS-CoV-2 infection could increase the risks of cardiovascular diseases: a direct effect on thrombosis, coagulation and fibrinolysis;[1] secondary antiphospholipid antibodies; systemic inflammation and its downstream effects on destabilization of atheroma and activation of thrombosis; endovascular inflammation ('endotheliopathy');[2,3] or cardiac dysfunction[4,5] leading to cerebral cardio-embolism;[6] or indeed a combination of these mechanisms.

Myocardial inflammation may occur in some patients with COVID-19. Some studies have suggested that this is a myocarditis, although the pathological evidence to support this is not well established.[7] Instead, the pathophysiology may involve microvascular thrombosis.[8] A study in Denmark,[9] which examined infections from the beginning of the epidemic to July 2020 using a self-controlled case series design, suggested that the risk of stroke and MI was elevated, but between 3- and 15- fold. The development of new heart failure after infection is infrequent (reported to be ~2.5% in from hospital-based cohorts) but important.[10] Stroke occurs in about 1% of coronavirus admissions, and some studies suggest an increased risk of more severe stroke.[11,12]

Whether any of these factors lead to persistent risk of cardiovascular disorders is important. Some patient experience persistent symptoms after infection ('long-COVID'). The cause of this illness is unclear but is likely to be due to a combination of COVID-related inflammation and end organ damage, with an important psychosocial component. However, whether or not there is a more prolonged increase in risk of cardiovascular disease of different types after infection is uncertain but highly plausible based on descriptions of vascular inflammation.

A comparison of the magnitude and time-course of any risk after COVID-19 with the risk of cardiovascular diseases after other viral infections would help to put the risk after COVID-19 in perspective. Acute viral infections, such as influenza, are associated with an increase in the risk of stroke and MI. A number of studies have estimated this risk in the 2 to 4 weeks following infection: laboratory confirmed influenza was associated with 4–6 fold increase of the risk of MI in Ontario; a clinical diagnosis of influenza was associated with a 3–fold risk of stroke in

California;[13,14] and a respiratory tract infection with a 5-fold increase in MI risk and 3-fold increase in stroke-risk in the UK (although this study showed no association between influenza and either illness).[15] SARS Co-V2 appears to be vasculo-tropic;[16] and other vasculo-tropic viruses such as varicella zoster and HIV increase the risk of stroke.[17] A retrospective US hospital based cohort suggested that the risk of stroke after COVID-19 is approximately 7-fold greater than after influenza infection (OR, 7.6; 95% CI, 2.3-25.2).[12] A study in US Department of Veterans Affairs hospitals suggested that both cardiovascular and cerebrovascular disease risk is increased by COVID infection.[18] Therefore, it is plausible that SARS-CoV-2 increases the risk of vascular diseases, possibly to a greater degree than other respiratory infections.

The risk of arterial occlusive events, such MI or ischaemic stroke and venous events such as pulmonary thrombosis (whether this is in-situ or embolism is unclear) and of deep vein thrombosis appears to be increased after coronavirus infection. [4,11,19–21] An understanding of the absolute and relative risk of arterial and venous events is an essential pre-requisite to defining the need for and the nature of short and longer-term prevention strategies.

Existing studies have necessarily been hospital based and relatively small. Because the increased risk of any one of the vascular diseases after SARS-CoV-2 infection is likely to be small, a very large study that includes as many people as possible with SARS-CoV-2 infection is needed to provide reliable information on future risk, and risk estimates during subsequent waves of the pandemic, in a variety of people. A cohort study is the most appropriate research design, but a cohort that is large enough to detect an effect and that approaches and recruit participants to answer this question would be both very time-consuming and expensive, and prone to loss to follow up.

Here we propose a cohort study leveraging newly established, secure access to linked, nationally collated NHS electronic healthcare record (EHR) data sources covering the entire populations of England, Scotland and Wales (>65 million people). We will use all available prospectively collected SARS-CoV-2 infection data linked to hospitalisations, deaths and GP consultations to identify previous and new cardiovascular events. The project is supported by the BHF Data Science Centre and its CVD-COVID-UK consortium, with access to the relevant, linked data and secure analysis environments already in place.

The advantage of the proposed study design in comparison to the existing studies is that: it is very large with population-wide coverage (including almost all patients with a positive PCR for SARS-CoV2 in the Britain), so maximising the chance of detecting a modest effect on cardiovascular events of different types; since it draws on data covering the entire population, it is representative of all people in the UK who use healthcare services; it includes data from the beginning of the pandemic in the UK to the present day; and follow-up can be extended at low cost.

RESEARCH HYPOTHESES

There is a high-risk period for cardiovascular events after SARS CoV2 infection.

DATA SOURCES

NHS Scotland via trusted research environment (TRE)

- Hospitalisations (SMR01)
- Death registrations
- Scottish Stroke Care Audit
- SARS CoV2 infection
- Primary care for limited variables

NHS England (TRE)

- Subset of primary care (via General Practice Extraction Service, GPES)
- Secondary Uses Service hospital data
- Pillar 1 and Pillar 2 SARS CoV2 infection
- Admitted patient care
- Office of National Statistics death records
- Sentinel Stroke National Audit (SSNAP)
- Prescription data
- Myocardial Ischaemia National Audit Project (MINAP)

NHS Wales (via TRE)

- COVID C20 (all from 01/01/20) and C16 (counterfactual from 01/01/16 to end 2019) total population cohorts 3.2M. Censored by migration out of Wales and death.
- Patient Episode Database for Wales (PEDW).
- Consolidated mortality with 4 separate mortality data sources (Welsh Demographic Service – population spine weekly flows, ONS - monthly and daily flows, and records from the MPI (Master Patient Index) - daily flows).
- Pathology data COVID-19 test results (PATD) daily flows from NHS/PHW laboratories and Lighthouse laboratories, including antigen and antibody testing.
- SSNAP and MINAP.
- Primary care (available on 80% that provide data to SAIL on a monthly basis containing all diagnostic, referral, prescribed medication. Plus 100% GP daily flow since January 2020 for of COVID-19 specific coding and symptom respiratory codes).
- Community dispensing.

DISCUSSION OF METHODS

Cohort design

The simplest method to address this hypothesis is a comparison of the prognosis of patients with a positive coronavirus test with the population without a positive coronavirus test, before and after adjustment for confounders. This design is prone to unmeasured confounding by risk factors for vascular diseases and coronavirus infection.

If coronavirus exposure begins on the day of known infection (a necessary compromise, although most people have a pre-symptomatic infection period), then a matched population chosen at the date of infection would be needed. Matching can introduce selection and collider biases, reduce power, and the potential advantage – matching on date – can be mitigated by adjusting for calendar time.

Therefore, in order to utilise all the data, we will use a time-dependent exposure (SARS-CoV-2) in a Cox regression model to measure the association between SARS-CoV infection and cardiovascular disease. We will account for confounding by cardiovascular risk factors with time-independent covariates for cardiovascular risk factors. We will look for heterogeneity in the estimate of the association between SARS-CoV infection and cardiovascular disease across regions of the UK, and by calendar month.

Self-controlled design

A self-controlled case series can be used to estimate short term risks. The advantage of this methods is that each patient is their own control, avoiding confounding by non-time varying factors.This designs is prone to confounding by time varying factors such changing use of healthcare by patients during the pandemic and changing health status of individuals (mitigated by using relatively short periods of comparison).

A self-controlled case-series[23–25] uses a Poisson regression model, conditioning on exposure history. This conditioning assumes that cardiovascular events should not affect COVID exposure or period of estimation, which may not be true.[26] However, if MI or stroke do increase the risk of COVID-19, this would tend to reduce the strength of any association, hence this analysis would be conservative. In addition, fatal events influence time under observation, hence fatal events need to be excluded. Further assumptions are that time-varying covariates act multiplicatively on the baseline incidence, that outcomes arise according to a non-homogeneous Poisson process and are non-recurrent and rare.

RESEARCH QUESTIONS

Question 1. In patients with a positive coronavirus test compared with the general population without a positive coronavirus test, what is the hazard ratio of first fatal or non-fatal stroke or MI (‘arterial); PE or DVT (‘venous thromboembolism’); major arterial dissection; arrythmia; and heart failure incidence before and after adjustment for confounders (age, diabetes, poverty, ethnicity, sex)?

Question 2. From the start of the coronavirus pandemic, in patients who have a positive test for coronavirus and either arterial or venous thromboembolism, or heart failure, major vessel dissection or arrythmia and are alive at the date of linkage, is there a greater chance that the coronavirus infection was in a short risk period prior to the event than in another period?

STUDY POPULATION (Figure 1)

Cohort study:

Patients will be included if they meet ALL of the following criteria:

- An age of ≥ 18 can be calculated on 1st January 2020 and have known sex;
- Registered with a GP practice in England, Wales or Scotland included in the linked data extract on 31st January 2020;
- A minimum of 365 days continuous registration in at least one GP practice in England, Wales or Scotland included in the linked data extract prior to 31st January 2020;
- Alive on 31st January 2020.

Patients will be excluded if they meet ANY of the following criteria:

- A diagnosis of MI, stroke, TIA, arrythmia, heart failure, major vessel dissection, limb or mesenteric ischaemia, PE or DVT (as defined below) in any primary or secondary care record at any time before 1st January 2020
    - The aim of this exclusion is to reduce the chance that any events detected from 1st January 2020 are records of events prior to that date.
- Changed GP practice between 1st January 2019 and date of linkage;
- A positive COVID-19 PCR test prior to 1st January 2020.

Self-controlled case series

- As for cohort study;
- And in addition, alive on the date of linkage.

EXPOSURE

PRIMARY

- A positive PCR test and date of test available in laboratory data

SECONDARY

- **Everyone with a positive PCR test or hospitalisation, or primary care record of COVID** taking first positive test or first hospital or primary care record coded as COVID from any source; this will allow us also to look at laboratory diagnosis only (test positive, no EHR diagnosis); clinically and laboratory diagnosis (test positive EHR diagnosis); and clinical diagnosis only (clinical diagnosis and no positive test – negative test data unavailable).
- **All COVID + severity assessable:**
    - *Mild – +ve test or diagnosis and no hospital admission with COVID in primary position within following 2 weeks and no death before 4 weeks with COVID in primary position;*
    - *Moderate – +ve test or diagnosis and hospital admission with COVID in primary position in APC within following 2 weeks but no critical care record within that hospital spell and no death before 4 weeks with COVID in primary position;*
    - *Severe - +ve test or diagnosis and hospital admission with COVID in primary position in APC within following 2 weeks and critical care record OR +ve test and death within 4 weeks with COVID in primary position.*

OUTCOMES

- **Arterial events:** first of ischaemic stroke or stroke or unknown type or myocardial infarction or retinal infarction;
- **Venous events:** first of pulmonary embolism or deep venous thrombosis or cerebral sinus thrombosis;
- Myocardial infarction
- Ischaemic stroke and stroke of unknown type;
- Intracerebral haemorrhage
- Subarachnoid haemorrhage;
- Pulmonary embolism;
- Deep vein thrombosis;
- Limb or mesenteric ischaemia;
- Dissection of major arteries;
- Life threatening cardiac arrhythmias + sudden cardiac death;
- Cardiomyopathy (acute heart failure) / myocarditis.

Date defined as: first recorded date in Scottish Stroke Care Audit or SSNAP or MINAP; OR first of date of start of spell with event; OR date of GP consultation with event; OR death with event (in cohort, not SCCS analysis)

CONFOUNDERS

Defined on 31st January 2020, with a look back in primary and secondary care for each patient:

- Sex categorical, GP, where >1 sex recorded, excluded;
- Age in years continuous, at 1st January 2020, GP, where age conflicts, exclude;
- Ethnicity categorical, most recent recorded prior to 1st January 2020, GP and if missing in inpatient (IP) I.e. APC, SMR01 or WAPC;
- Deprivation continuous, most recent recorded prior to 31st January 2020, in spine or GP data;
- Region: East of England, London, Midlands, NE and Yorkshire, North West, South East, South West, Scotland, Wales, most recent residence prior to 1st January 2020, GP;
- Consultation rate: number of primary care contacts from 1/1/19 to 1/1/20, GP;
- Medications: total number of medications by BHF chapters prescribed 1/10/19–1/1/20, GP;
- Diabetes: yes/not recorded from start of record to 1st January 2020, GP or IP;
- Depression: yes/not recorded from start of record to 1st January 2020, GP or IP;
- Obesity: yes/not recorded from start of record to 1st January 2020 or defined by ethnicity specific thresholds, GP;
- Cancer yes/not recorded from start of record to 1st January 2020, GP or IP;
- COPD yes/not recorded from start of record to 1st January 2020, GP or IP;
- CKD yes/not recorded from start of record to 1st January 2020, GP or IP;
- Liver disease: yes/not recorded from start of record to 1st January 2020, GP or IP;
- BMI where available from start of record to 1st January 2020, GP;
- Surgery yes/not recorded from start of record to 1st January 2020, GP or IP;
- Hypertension yes/not recorded from start of record to 1st January 2020, GP or IP;
- Dementia yes/not recorded from start of record to date of linkage, GP or IP;
- Smoking current/ex-/never/unknown most recent prior to 1st January 2020, GP;
- Antiplatelet yes/no/unknown (unknown if patient's GP practice not in prescription extract) BNF chapter 2.9 at least one prescription 1/10/19–1/1/20, GP;
- BP lowering yes/no/unknown BNF chapter 2.5 at least one prescription 1/10/19–1/1/20, GP;
- Lipid lowering yes/no/unknown BNF chapter 2.12 at least one prescription 1/10/19–1/1/20, GP;
- Anticoagulant yes/no/unknown BNF chapter 2.8.2 at least one prescription 1/10/19–1/1/20, GP;
- eFrailty index calculated on 1st January 2020 using all records, GP;
- Nursing home primary or secondary care yes/not recorded before 1st January 2020, latest GP or IP or Care Home Index.

TIME VARYING COVARIATES

- Calendar month of exposure.
- Change in testing policy 1st May 2020

EFFECT MODIFIERS (see definitions in confounders)

- Age continuous variable (figured by fifths of age distribution);
- Sex: categorical;
- Ethnicity: categorical, most recent recorded in GP or IP if missing prior to 31st January 2020, or in Wales national ethnicity spine;
- Medication: yes/no for each of antiplatelet, BP lowering, lipid lowering, anticoagulant, as defined in 'confounders';
- Diabetes yes/not known, as defined in 'confounders';
- Deprivation continuous variable (figured by fifths of deprivation distribution) , as defined in 'confounders';

- Region East of England, London, Midlands, NE and Yorkshire, North West, South East, South West, Scotland, Wales, most recent residence prior to 31st January 2020, , as defined in 'confounders';
- Calendar month .

CENSORING FOR SURVIVAL METHODS

The cohort study will be censored at the first of:

- Death;
- Event of interest;
- Transfer to another nation or to a GP practice out of the linked data;

ANALYSES IN EACH NATION

Cohort

Risk of each event by region and time and COVID incidence

Distribution of baseline characteristics at index date in COVID+ and rest of population

Kaplan Meier plots for time to event in COVID+ and rest of population

Cox regression comparing patients with COVID exposure with rest of population, with and without confounders, for each of the fatal or non-fatal outcomes.

- For the primary COVID exposure to look at all of the defined outcomes, with estimates of effect modification for arterial and venous events (if important effect modification, to explode this outcome).
- For the secondary COVID exposures to look at 'venous events' and 'arterial events' with adjustment for confounders.
- Sensitivity analyses:
    - Exclude patients where outcome and test are during the same hospital admission because ordering or infection and event difficult to disentangle.
    - e-Value To assess the robustness to confounding as a measure of causality by calculating the E-value as proposed by VanderWeele, which has limitations.[27,28]
    - The following may be performed as exploratory analyses: Royston-Parmar models, which allow estimation of absolute incidence rates and competing risk models which may be useful when predicting absolute risks.

Self-controlled case series (SCCS)

Self-controlled case series models for patients with each of the following non-fatal outcomes: non-fatal stroke, ischaemic stroke, haemorrhagic stroke, arrythmia, limb ischaemia, heart failure, MI, PE, or DVT, from 31st January 2020 to date of linkage, giving an estimate for each outcome. The analysis will control for month.

We will examine first non-fatal events a risk period, starting 2 weeks before the positive test, ending 3 months later divided into 3 1-month periods, comparing with time outside the risk period. We will account for time varying confounders by adjusting for calendar month.

Sensitivity analyses:

- Exclude patients where outcome and test are during the same hospital admission because ordering or infection and event difficult to disentangle;
- Risk period of differing duration;
- Use secondary exposures as defined above;
- Include only post-test observation period;
- Perform SCCS for those with a negative test and no subsequent positive test, nor hospital admission with COVID, nor positive antibody test.

METAANALYSIS ACROSS NATIONS

To use a fixed inverse variance weighted meta-analysis to pool estimates of principal analysis across nations, testing for heterogeneity and reporting summary estimate and p-value.

REFERENCES

1. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am. J. Emerg. Med. 2020;
2. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395:1417–1418.
3. Goshua G, Pine AB, Meizlish ML, Chang CH, Zhang H, Bahel P, Baluha A, Bar N, Bona RD, Burns AJ, Dela Cruz CS, Dumont A, Halene S, Hwa J, Koff J, Menninger H, Neparidze N, Price C, Siner JM, Tormey C, Rinder HM, Chun HJ, Lee AI. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. *Lancet Haematol*. 2020;7:e575–e582.
4. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of Coronavirus Disease 2019 (COVID-19) with Myocardial Injury and Mortality. JAMA Cardiol. 2020;
5. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. JAMA Cardiol. 2020;
6. South K, McCulloch L, McColl BW, Elkind MSV, Allan SM, Smith CJ. Preceding infection and risk of stroke: An old concept revived by the COVID-19 pandemic. Int. J. Stroke. 2020;174749302094381.
7. Halushka MK, Vander Heide RS. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmortem examinations. *Cardiovasc Pathol*. 2021;50:107300.
8. Siddiqi HK, Libby P, Ridker PM. COVID-19 – A vascular disease. *Trends Cardiovasc Med*. 2020;
9. Modin D, Claggett B, Sindet-Pedersen C, Lassen MCH, Skaarup KG, Jensen JUS, Fralick M, Schou M, Lamberts M, Gerds T, Fosbøl EL, Phelps M, Kragholm KH, Andersen MP, Køber L, Torp-Pedersen C, Solomon SD, Gislason G, Biering-Sørensen T. Acute COVID-19 and the Incidence of Ischemic Stroke and Acute Myocardial Infarction. Circulation. 2020;142:2080–2082.
10. Rey JR, Caro-Codón J, Rosillo SO, Iniesta ÁM, Castrejón-Castrejón S, Marco-Clement I, Martín-Polo L, Merino-Argos C, Rodríguez-Sotelo L, García-Veas JM, Martínez-Marín LA, Martínez-Cossiani M, Buño A, Gonzalez-Valle L, Herrero A, López-Sendón JL, Merino JL, Merino JL, Caro-Codon J, Castrejon-Castrejon S, Iniesta AM, Martinez-Cossiani M, Merino C, Martin-Polo L, Martinez LA, Marco I, Garcia-Veas JM, Rodriguez-Sotelo L, Rosillo SO, Lopez-Sendon JL, Rey JR, Rios JJ, Arribas JR, Arnalich F, Prados C, Alvarez-Sala R, Quintana M, García de Lorenzo A, Reinoso F, Rivera A, Torres RM, Garcia-Rodriguez J, Gonzalez-Valle L, Herrero A, Borobia A, Buño A. Heart failure in COVID-19 patients: prevalence, incidence and prognostic implications. *Eur J Heart Fail*. 2020;ejhf.1990.
11. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, Humphries F, Jäger HR, Losseff NA, Perry RJ, Shah S, Simister RJ, Turner D, Chandratheva A, Werring DJ. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry*. 2020;jnnp-2020-323586.
12. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, Lantos J, Schenck EJ, Goyal P, Bruce SS, Kahan J, Lansdale KN, Lemoss NM, Murthy SB, Stieg PE, Fink ME, Iadecola C, Segal AZ, Cusick M, Campion TR, Diaz I, Zhang C, Navi BB. Risk of Ischemic Stroke in Patients with Coronavirus Disease 2019 (COVID-19) vs Patients with Influenza. *JAMA Neurol*. 2020;
13. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, Katz K, Ko DT, McGeer AJ, McNally D, Richardson DC, Rosella LC, Simor A, Smieja M,

Zahariadis G, Gubbay JB. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. *N Engl J Med*. 2018;378:345–353.

14. Boehme AK, Luna J, Kulick ER, Kamel H, Elkind MS V. Influenza-like illness as a trigger for ischemic stroke. *Ann Clin Transl Neurol*. 2018;5:456–463.
15. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination. *N Engl J Med*. 2004;351:2611–2618.
16. Teuwen L-A, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nat Rev Immunol*. 2020;1–3.
17. Grau AJ, Urbanek C, Palm F. Common infections and the risk of stroke. Nat. Rev. Neurol. 2010;6:681–694.
18. Xie Y, Bowe B, Maddukuri G, Al-Aly Z. Comparative evaluation of clinical manifestations and risk of death in patients admitted to hospital with covid-19 and seasonal influenza: cohort study. *BMJ*. 2020;371:4677.
19. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, Shigematsu T, Ladner TR, Yaeger KA, Skliut M, Weinberger J, Dangayach NS, Bederson JB, Tuhrim S, Fifi JT. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med*. 2020;382:e60.
20. Morassi M, Bagatto D, Cobelli M, D'Agostini S, Gigli GL, Bnà C, Vogrig A. Stroke in patients with SARS-CoV-2 infection: case series. *J Neurol*. 2020;267:2185–2192.
21. D'Anna L, Kwan J, Brown Z, Halse O, Jamil S, Kalladka D, Venter M, Banerjee S. Characteristics and clinical course of Covid-19 patients admitted with acute stroke. J. Neurol. 2020;1:3.
22. Griffith G, Morris TT, Tudball M, Herbert A, Mancano G, Pike L, Sharp GC, Palmer TM, Smith GD, Tilling K, Zuccolo L, Davies NM, Hemani G. Collider bias undermines our understanding of COVID-19 disease risk and severity. *medRxiv*. 2020;2020.05.04.20090506.
23. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: The self-controlled case series method. *Stat Med*. 2006;25:1768–1797.
24. Maclure M. The case-crossover design: A method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133:144–153.
25. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ. 2016;354:i4515.
26. Collaborative TO, Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, Mcdonald HI, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong A, Grieve R, Harrison D, Forbes H, Schultze A, Croker RT, Parry J, Hester F, Harper S, Perera R, Evans S, Smeeth L, Goldacre B. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. *medRxiv*. 2020;2020.05.06.20092999.
27. Van Der Weele TJ, Ding P. Sensitivity analysis in observational research: Introducing the E-Value. *Ann Intern Med*. 2017;167:268–274.
28. Ioannidis JPA, Tan YJ, Blum MR. Limitations and misinterpretations of E-values for sensitivity analyses of observational studies. *Ann Intern Med*. 2019;170:108–111.

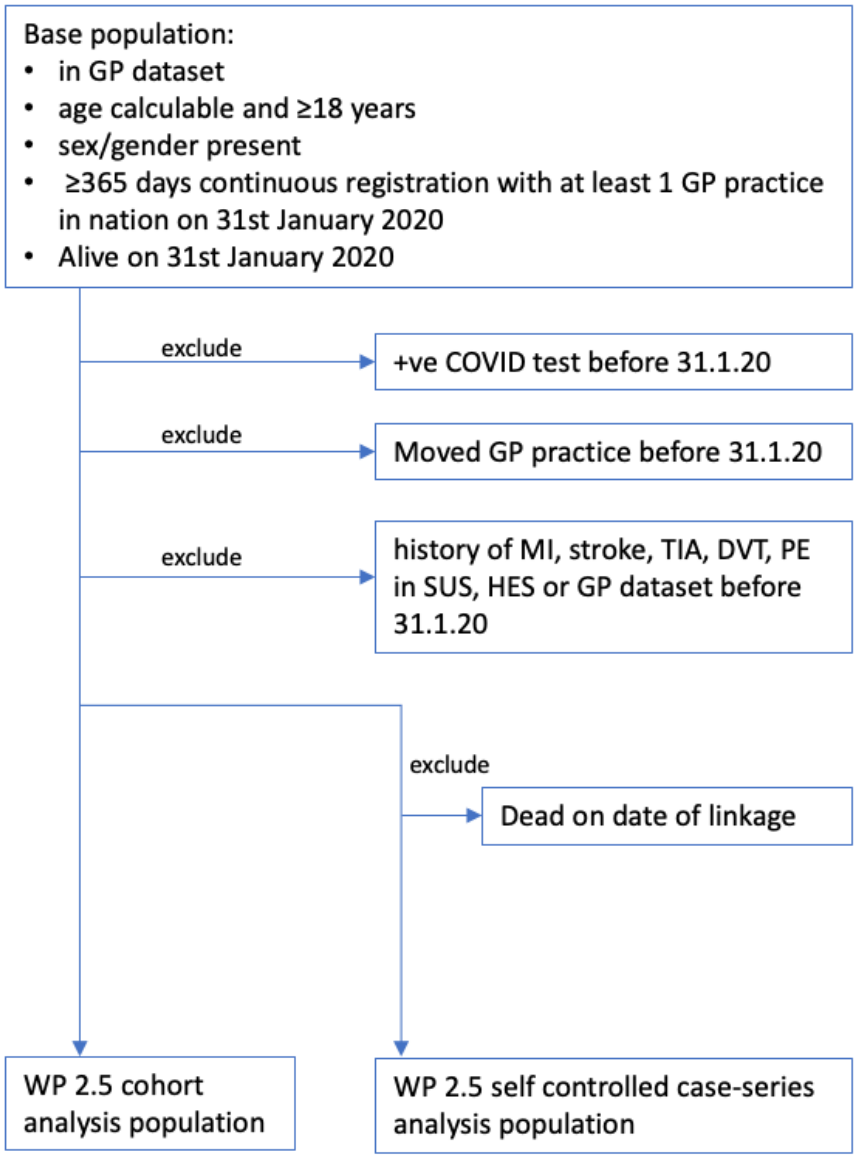

Figure 1 Patient flow