## STATISTICAL ANALYSIS PLAN - CCU018_01

## Project title: COVID infection during pregnancy on cardiovascular disease and related risk factors


**SUMMARY**

The proposed study will compare the prognosis of pregnant women with a positive coronavirus test during pregnancy with those without a positive coronavirus test, before and after adjustment for confounders.

A time-dependent exposure (SARS-CoV-2) in a Cox regression model will be used to measure the association between SARS-CoV infection and pregnancy adverse outcomes /cardiovascular diseases during pregnancy and one year later. We will account for confounding considering time-independent covariates for cardiovascular risk factors. We will look for heterogeneity in the estimate of the association between SARS-CoV infection and pregnancy adverse outcomes/cardiovascular diseases across regions of the UK, and by calendar month.

Finally, we will examine the risk of foetus/child events at birth using logistic regression models and the one-year risk of adverse events after birth using Cox regression models comparing children from mothers with and without SARS-CoV infection during pregnancy.


| Period | Mother | Foetus/Child |
|---|---|---|
| **During pregnancy and at birth** | a time-dependent exposure (SARS-CoV-2) and time to event outcomes (hypertensive disorders, gestational diabetes, fatal and non-fatal cardiovascular events) | a time-independent exposure (SARS-CoV-2 during pregnancy) and outcomes at birth Preterm birth, low-birth weight, stillbirth, perinatal asphyxia, and neonatal morbidity |
| **Longer-term** | a time-dependent exposure (SARS-CoV-2) and time to event outcomes (cardiovascular disease, intermediate traits and associated factors) | a time-independent exposure (SARS-CoV-2 during pregnancy) and time to event outcomes (cardiovascular disease and associated factors) |

**STUDY DESIGN**
A population-based cohort study using linked electronic health records.

**RESEARCH QUESTIONS**
1. What is the risk of adverse pregnancy outcomes in pregnant women who test positive for SARS CoV2 during pregnancy compared to pregnant women without a positive test?
2. What is the one-year risk of cardiovascular outcomes and intermediate traits after the delivery in pregnant women and their babies who test positive for SARS CoV2 during pregnancy compared to pregnant women without a positive test?

**TARGET POPULATION**
Conclusions will be made about pregnant women population of the UK.

**INCLUSION CRITERIA**
Women will be included if they meet ALL of the following criteria:
- Pregnant women
- Alive on 1st June 2019.
- Mandatory fields completed: date of birth, NHS Number.
- Registered with a GP practice in England, Wales or Scotland included in the linked data extract on 31st January 2020;

**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.*

**MATERNAL OUTCOMES**
***During pregnancy***
- Gestational hypertension
- Preeclampsia
- Gestational diabetes

***During pregnancy and one-year follow-up****:*
- Cardiomyopathy (acute heart failure)

- Myocarditis.
- 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;

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)

**FETUS/CHILD OUTCOMES**

**At birth**

- Low birth weight for gestational age
- Preterm birth
- Asphyxia at birth using the Apgar score
- Birth-resuscitation
- Stillbirth
- Congenital malformation

**One-year follow-up**

- Death and neonatal death (defined as death during the first 4 weeks of life)
- Number of hospital admissions
- Hospitalization for infection
- Respiratory distress
- Cardiovascular event

**COVARIATES**

POTENTIAL CONFOUNDERS defined at the beginning of the pregnancy using primary and secondary care information for each woman

| Variable | Definition |
|---|---|
| Age | in years (continuous) |
| Ethnicity | categorical most recent recorded |
| Deprivation | continuous, most recent recorded |
| Obesity | yes/not recorded |
| BMI | where available |
| Smoking | current/ex-/never/unknown most recent |
| Previous pregnancy | number |
| Multiple foetuses | yes/not recorded |
| Previous adverse pregnancy outcomes | yes/not recorded |
| Polycystic ovary syndrome | yes/not recorded |
| Surgery | yes/not recorded |
| Hypertension | yes/not recorded |
| Cardiovascular disease | yes/not recorded |
| Diabetes | yes/not recorded |
| Depression | yes/not recorded |

| | |
|---|---|
| Cancer | yes/not recorded |
| COPD | yes/not recorded |
| Kidney diseases | yes/not recorded |
| Autoimmune diseases | yes/not recorded |
| Liver diseases | yes/not recorded |
| Medications | the total number of medications |
| Corticosteroids | yes/no/unknown. BNF chapter 8.2.2 at least one prescription. |
| Immunosuppressants (other than corticosteroids) | yes/no/unknown. BNF chapter 8.2 at least one prescription. |
| Antiplatelet | yes/no/unknown. BNF chapter 2.9 at least one prescription. |
| BP-lowering | yes/no/unknown BNF chapter 2.5 at least one prescription 1/10/19– 1/1/20. |
| Lipid-lowering | yes/no/unknown BNF chapter 2.12 at least one prescription 1/10/19– 1/1/20. |
| Anticoagulant | yes/no/unknown BNF chapter 2.8.2 at least one prescription 1/10/19– 1/1/20. |

**TIME VARYING COVARIATES**

- Gestational weight gain
- Calendar month of exposure
- Birth
- Change in testing policy 1st May 2020

**EFFECT MODIFIERS**

| **Variable** | **Definition** |
|---|---|
| Age | continuous variable (figured by fifths of age distribution); |
| Ethnicity | categorical most recent recorded prior to the index date, inpatient (IP) data I.e. APC, SMR01 or WAPC; |
| Medication | yes/no for each of antiplatelet, BP lowering, lipid-lowering, anticoagulant, as defined in 'confounders' |
| Previous pregnancy | yes/no as defined in 'confounders' |
| Previous pregnancy adverse outcomes | yes/no for each of the event as defined in 'confounders' |
| Pregnancy trimester | |
| Deprivation | continuous variable (figured by fifths of deprivation distribution), as defined in 'confounders' |
| Calendar Month | |
| Region | East of England, London, Midlands, NE and Yorkshire, North West, South East, South West, Scotland, Wales, most recent residence prior to beginning of the pregnancy as defined in 'confounders' |
| COVID+ and non-COVID+ severity groups | the severity of infection is defined as mild, moderate, and severe. |

*Only for foetus/child outcomes*

| | |
|---|---|
| Cephalic/non-cephalic presentation | |
| Induction of labour | yes/not recorded |
| Timing of labour | |
| Mode of delivery | categorized as vaginal delivery, assisted vaginal delivery using either obstetric forceps or vacuum (ventouse), caesarean section |
| Annual number of births per hospital | calculated on the number of births in 2019 |

**CENSORING FOR SURVIVAL METHODS**
The cohort study will be censored at the first of: death; or event of interest.

**PRINCIPAL ANALYSIS IN EACH NATION**

***Maternal outcomes***
We will examine the risk of each event by region, time and COVID incidence among pregnant women and the distribution of baseline characteristics at the beginning of the pregnancy. For the primary analysis, we will compare the incidence rate of fatal and non-fatal outcomes between women with and without COVID exposure during pregnancy and one-year follow-up using Cox regression, with and without confounders, and within subgroups to identify potential effect modification.

Sensitivity analyses:

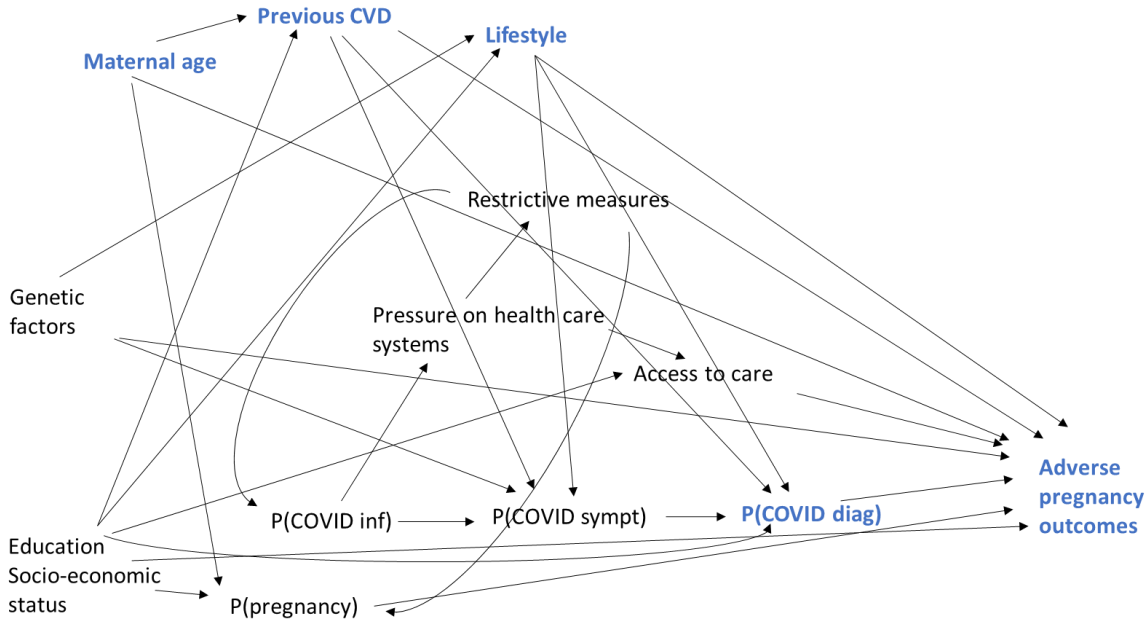
- Exclude patients where outcome and diagnosis are during the same hospitalization
- Assess the robustness of estimates quantifying unmeasured confounding
- Flexible parametric survival models, which allow estimation of absolute incidence rates and competing risk models which may be useful when predicting absolute risks.
- Including individuals with COVID before pregnancy

***Foetus/Child outcomes***
The risk of events at birth will be modelled by logistic regression comparing mother with and without COVID exposure during pregnancy, with and without confounders, for each of the fatal or non-fatal outcomes. Cox regression models will be used to examine the one-year risk of adverse outcomes in children comparing mother with and without COVID infection during pregnancy.

**META ANALYSIS 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.

**LIMITATIONS**
This design is prone to unmeasured confounding by risk factors for pregnancy adverse outcomes /cardiovascular diseases and coronavirus infection.

Figure. A framework of the associations between COVID infection and adverse pregnancy outcomes, ancestors and intermediate factors



**DATA SOURCES**

| *NHS England (TRE)* | *NHS Scotland* | *NHS Wales (via TRE)* |
|---|---|---|
| Subset of primary care (via General Practice Extraction Service, GPES)<br>Secondary Uses Service hospital data<br>Pillar 1 and Pillar 2 SARS CoV2 infection<br>Admitted patient care<br>Office of National Statistics death records<br>Sentinel Stroke National Audit (SSNAP)<br>Prescription data<br>Myocardial Ischaemia National Audit Project (MINAP) | Hospitalisations (SMR01)<br>Death registrations<br>Scottish Stroke Care Audit<br>SARS CoV2 infection<br>Primary care for limited variables | 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.<br>Patient Episode Database for Wales (PEDW).<br>Consolidated mortality methodology has been developed to use 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).<br>Pathology data COVID-19 test results (PATD) daily flows from NHS/PHW laboratories and Lighthouse laboratories, including antigen and antibody testing.<br>SSNAP and MINAP.<br>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).<br>Community dispensing.<br>Linked Census 2011 data for ethnicity |