Version history

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| --- | --- | --- |
| V1 | 15/12/21 | Developed by RD. |
| V2 | 07/03/22 | Code lists added and analyses commenced. |
| V3 | 07/10/22 | Additional analyses added. |

**Diabetes**

**PROTOCOL**

This document contains the outcome specific elements necessary to implement this protocol: [post-covid-events.docx](https://uob.sharepoint.com/:w:/r/teams/grp-ehr/Shared%20Documents/Protocols/post-covid-events/post-covid-events.docx?d=wf6024a40396c4b02a279e98cffb4ce62&csf=1&web=1&e=bfISrH)

**Diabetes study population**

CONVALESENCE study population

Additional exclusions

* Individuals with a recorded diagnosis of diabetes prior to index date.
* For gestational diabetes, men will be excluded from the analysis and the study population will be restricted to women.

**Outcomes**

We will use clinician-verified Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT) and International Classification of Disease Codes Version 10 (ICD-10) code lists for diabetes phenotypes and medications (see table below) and extract these from primary care and hospital admission data. We will subsequently apply a diabetes diagnostic adjudication algorithm, based on a previously published version to our study population defined in OpenSAFELY (see Appendix 1).

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| **Details** | **Link to primary care codelists** | **Link to secondary care codelists** |
| Type 1 diabetes | <https://www.opencodelists.org/codelist/user/hjforbes/type-1-diabetes/674fbd7a/> | [OpenCodelists: Type 1 diabetes (secondary care)](https://www.opencodelists.org/codelist/opensafely/type-1-diabetes-secondary-care/2020-09-27/) |
| Type 2 Diabetes | <https://www.opencodelists.org/codelist/user/hjforbes/type-2-diabetes/3530d710/> | [OpenCodelists: Type 2 diabetes secondary care Bristol](https://www.opencodelists.org/codelist/user/r_denholm/type-2-diabetes-secondary-care-bristol/0b7f6cd4/) |
| Non-diagnostic | <https://www.opencodelists.org/codelist/user/hjforbes/nondiagnostic-diabetes-codes/50f30a3b/> |  |
| Other or non-specific | <https://www.opencodelists.org/codelist/user/hjforbes/other-or-nonspecific-diabetes/0311f0a6/> |  |
| Gestational diabetes | <https://www.opencodelists.org/codelist/user/hjforbes/gestational-diabetes/1ed423d1/> |  |

# **POTENTIAL CONFOUNDERS**

**Core:**

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| **Confounder** | **Type** | **Definition** | **Data sources** |
| Sex | Categorical | Male, Female | Primary care |
| Age | Continuous | Modelled as age in years using a restricted cubic spline with 3 knots at the 10th, 50th and 90th percentiles | All |
| Ethnicity | Categorical | 1: White  2: Mixed  3: South Asian  4: Black  5: Other | All |
| Deprivation | Categorical | 10 categories from Index of Multiple Deprivation 2019 | Index of Multiple Deprivation |
| Region | Categorical | East of England  London  Midlands  North East and Yorkshire  North West  South East  South West  Scotland  Wales | Primary care |
| Consultation rate | Continuous | Number of primary care contacts in the year prior to index date | Primary care |
| Smoking status | Categorial | E: Ever smoker  M: Missing  N: Never smoker  S: Current smoker | Primary care |
| Obesity | Binary | 1 if BMI>=30 or coded diagnosis for obesity; 0 otherwise | Primary care, HES APC |
| Acute myocardial infarction | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| All stroke | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Other arterial embolism | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Venous thromboembolism events | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Heart failure | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Angina | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Dementia | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Liver disease | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Chronic kidney disease | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Cancer | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Hypertension | Binary | 1 if diagnosis or prescription present; 0 otherwise | Primary care, HES APC |
| Diabetes | Binary | 1 if diagnosis or prescription present; 0 otherwise | Primary care, HES APC |
| Depression | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Chronic obstructive pulmonary disease | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Healthcare worker | Binary | 1 if healthcare worker; 0 otherwise | NHS England COVID-19 data store (see: <https://docs.opensafely.org/study-def-variables/#cohortextractor.patients.with_healthcare_worker_flag_on_covid_vaccine_record>) |
| Care home resident | Binary | 1 if care home resident; 0 otherwise | Address matching CQC database (see: <https://docs.opensafely.org/study-def-variables/#cohortextractor.patients.care_home_status_as_of>)( |

**Additional confounder for diabetes analysis:**

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| --- | --- | --- | --- |
| **Confounder** | **Type** | **Definition** | **Data sources** |
| Total cholesterol/high-density lipoprotein [HDL] cholesterol ratio [TC/HDL] | Continuous | Data from the five year prior to start date will be used to derive TV/HDL ratio. TC/HDL values are derived from the recorded total and HDL cholesterol values   * Remove Total Cholesterol values < 1.75 or > 20 * Remove HDL values < 0.4 or > 5 | Primary care  [Total Cholesterol](https://www.opencodelists.org/codelist/opensafely/cholesterol-tests-numerical-value/7e3a22f3/)  [HDL Cholesterol](https://www.opencodelists.org/codelist/bristol/hdl-cholesterol/64775990/) |
| BMI  N.B. This variable is to replace the cov\_bin\_obesity variable as a confounder in diabetes analyses. | Categorical | <18; 18-24; 25-29; 30+ | Primary care – patients most recent BMI value on or before index date. |
| History of prediabetes | Binary | Yes; no  Clinical diagnosis code | [Primary care](https://codelists.opensafely.org/codelist/opensafely/prediabetes-snomed/6bdbb7dd/) |
| History of gestational diabetes | Binary | Yes; no  Clinical diagnosis code | [Primary care](https://codelists.opensafely.org/codelist/user/hjforbes/gestational-diabetes/1ed423d1/) |

**Additional subgroup analysis:**

* Subgroups according to prior history of prediabetes subcategory (prior history of prediabetes subcategory / no prior history of prediabetes subcategory)
* Obesity yes/no

**Other additional analyses**

1. In the pre-vaccination cohort only: investigate COVID-19 infection and subsequent type 2 diabetes diagnosis up to 15th June 2020 (the day before the RECOVERY press release was published). For the pre-recovery analysis, we will censor at COVID on or after 16th June. For the post-recovery analysis, we would remove any people with COVID before 16th June from the study population. Outputs for this analysis to include:
   * Hazard ratios as for the main hospitalized COVID-19 analysis but splitting the date of hospitalization to before or on/after 16 June.
   * ~~Hazard ratios with follow-up restricted to 15~~~~th~~ ~~June using the following cox regression time points: normal (7, 14, 28, 56, 84, 166) and reduced (28, 166).~~
2. In all cohorts: Investigate how many of those diagnosed with type 2 diabetes following a covid-19 infection (any, non-hospitalized and hospitalized) were still being treated (defined as having received 2 or more separate prescriptions from: insulin, antidiabetic drugs and non-metformin drugs as used in the algorithm) OR had elevated HbA1c levels (>= 47.5 mmol), 4 months after initial diagnosis (i.e., the date of the “out\_date\_t2dm” variable defined using the diabetes diagnostic algorithm + 4 months). Outputs for this analysis to include:
   * A table showing: (i) N type 2 diabetes cases following a COVID-19 infection, (ii) N (% of (i)) that were included in the 4-month follow-up analysis and (iii) N (% of (ii)) of those that were followed up and still being prescribed medication or had elevated HbA1c.
3. In the pre-vaccination cohort only: repeat analysis in point 2 above but for 12 months instead of 4 months if numbers permit.
4. Repeat hospitalised cox regression analyses for type-2 diabetes with type-2 diabetes cases redefined to only those that were still being treated after 4 months. Outputs for this will be hazard ratios akin to the main analyses.

***Rationale for using 4 months for the analyses in points 2 and 3 above***

The rationale for using 4 months from COVID-19 diagnosis is that the onset of the hyperglycaemic trigger (i.e., systemic upset causing stress hyperglycaemia or steroid treatment causing steroid-induced diabetes) will be at diagnosis +/- a few days at most. The hyperglycaemic trigger is likely to last for a period of 1-2 weeks (most steroid courses are 10 days), and we would expect recovery within 1-2 weeks after the trigger is removed. Therefore, we are allowing 4 weeks for the duration and resolution of the triggering factor. In addition to this, we add on an extra 3 months to allow HbA1c to normalise, as it reflects blood glucose levels over the preceding 3 months.

Appendix 1 : Diabetes type & presence adjudication algorithm updated

