**PROTOCOL v0.5:**

**Effect of metformin on the risk of severe COVID and Long COVID among people living with type 2 diabetes mellitus in England: study protocol for an observational study in OpenSAFELY following the target trial emulation framework**

**Short title:** *Is metformin protective against severe COVID and Long COVID?*

**Date: March 10th, 2025**

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| --- | --- |
| *Version* | *Notes* |
| *0.1* | *Background, objectives & table 1* |
| *0.2* | *Variable definition tables* |
| *0.3* | *Updated protocol regarding design specifications* |
| *0.4* | *Changed causal question after initial causal question seemed unfeasible* |
| *0.5* | *Clarified landmark design, structured protocol according to TTE framework, and clarified treatment strategies* |

# **Background**

Type 2 diabetes mellitus (T2DM) has emerged as one of the most important risk factors for COVID-19 mortality[ref], and, more recently, research suggests the same is true for Long COVID.[1,2](https://www.zotero.org/google-docs/?toI1J1)

Long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC), is a health condition representing signs and symptoms that continue or develop after acute COVID-19. It may include both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). Common symptoms include fatigue, shortness of breath, and cognitive dysfunction, but are highly variable and wide ranging.[3–7](https://www.zotero.org/google-docs/?4cNXYa) Long COVID poses a significant public health burden with lasting physical health, mental health, and societal impacts - and at present without any established treatments.[8–10](https://www.zotero.org/google-docs/?uJQys5)

Metformin is the most commonly prescribed first-line treatment for T2DM and is an inexpensive readily accessible medication with a well-known safety profile. Randomised trials have evaluated the use of metformin during the acute phase of COVID-19 among a broad at-risk population.[11,12](https://www.zotero.org/google-docs/?DJXEW5) These trials have produced inconclusive evidence on severe COVID-19, and some evidence on reducing the likelihood of developing Long COVID-19[13](https://www.zotero.org/google-docs/?SH2oFg), and reducing SARS-CoV-2 viral load[14](https://www.zotero.org/google-docs/?y75N6p). However, people living with T2DM were largely excluded from these trials since randomising such patients to metformin or placebo is unfeasible and unethical.

While there is a large body of evidence from observational studies using prevalent user designs to assess the association between metformin use and severe COVID, especially at time of hospitalization[15](https://www.zotero.org/google-docs/?x5pZfY), evaluations of a) pre-exposure prophylactic use of metformin for the prevention of severe COVID, b) newly starting metformin (new/incident user designs), and c) effectiveness on Long COVID[16](https://www.zotero.org/google-docs/?oZ3TfU) are scarce.

Overall, metformin seems to be a promising antiviral treatment option, also for future viral respiratory pandemics, as highlighted in a recent editorial.[17](https://www.zotero.org/google-docs/?C0yy6m)

Following the target trial emulation framework, we aim to estimate the effect of starting metformin versus not starting metformin, just before the COVID-19 pandemic, among adults living with T2DM in England, on COVID-related hospitalisation and death and Long COVID.

# **Objectives**

***Primary Objective***

1. To estimate the effect of starting metformin monotherapy just before the COVID-19 pandemic compared to not starting metformin nor any other antidiabetic on the risk of COVID-related hospitalisation or death, among adults with T2DM

***Secondary Objectives***

1. To estimate the effect of starting metformin monotherapy just before the COVID-19 pandemic compared to not starting metformin nor any other antidiabetic on the risk of Long COVID, among adults with T2DM
2. To estimate the effect of starting metformin monotherapy just before the COVID-19 pandemic compared to not starting metformin nor any other antidiabetic on the risk of SARS-CoV-2 infection, among adults with T2DM
3. To estimate whether the treatment effects varies by age, sex, ethnicity, Index of Multiple Deprivation ([IMD], derived from the patient’s postcode at lower super output area level) and body mass index (BMI) and HbA1c

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# **Methods**

## Data Source

We will use primary care records managed by the General Practitioner (GP) software provider The Phoenix Partnership (TPP), linked to Office of National Statistics (ONS) death registration data (containing information on all deaths including those due to con-COVID-19 and those occurring in the community), the national coronavirus testing records from the Second Generation Surveillance System (SGSS), the national vaccine register (National Immunisation Management System [NIMS]), and the NHS Secondary Use Service (SUS) data, through OpenSAFELY, a data analytics platform created by our team on behalf of NHS England to address urgent COVID-19 research questions (<https://opensafely.org>). OpenSAFELY entails pseudonymised data of approximately 40% of the English population, including coded diagnoses, medications and physiological parameters.

## Specification of the target trial

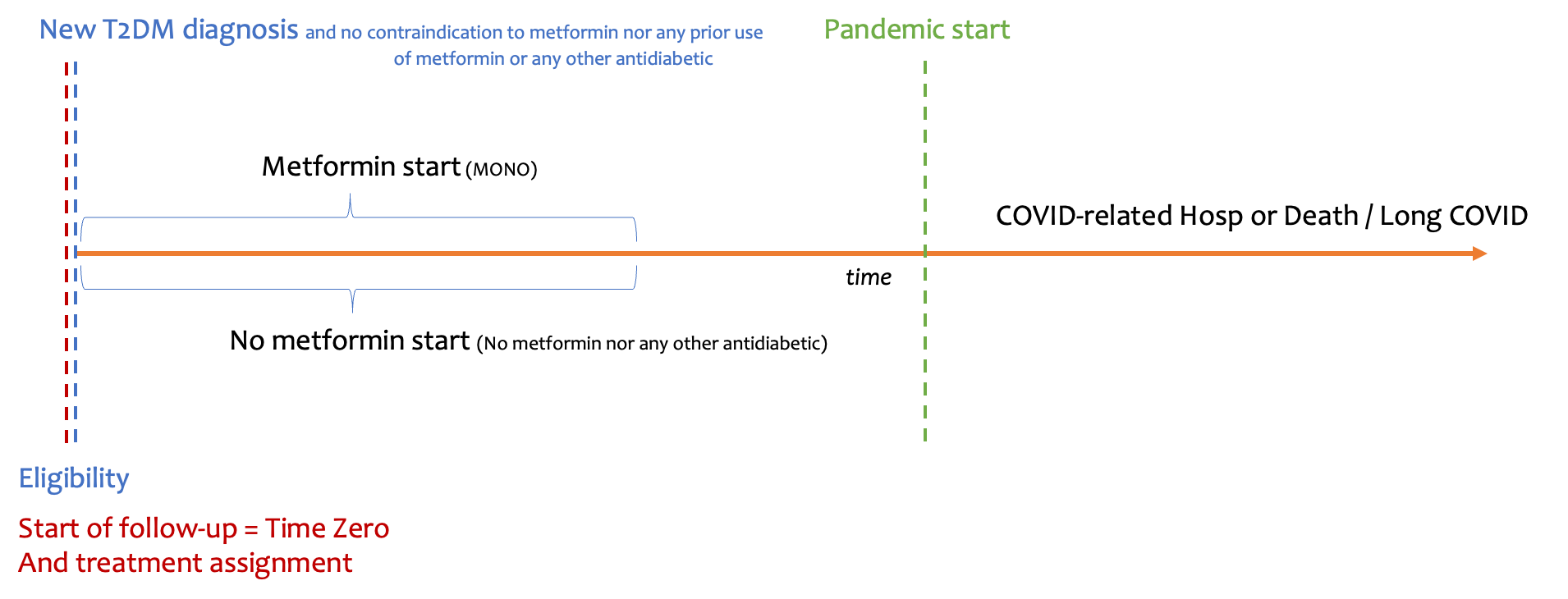
We designed this observational analysis from electronic health records to emulate a target trial (i.e., a hypothetical pragmatic trial that would have answered the causal question of interest). The key components of the target trial emulation are summarized in [table 1](#_1bit2gqjnde1), including the specification of the analysis. The study will be reported according to the REporting of studies Conducted using Observational Routinely collected health Data for PharmacoEpidemiological research (RECORD-PE) reporting guideline[18](https://www.zotero.org/google-docs/?ccMQAP) or the TrAnsparent ReportinG of observational studies Emulating a Target trial (TARGET) guideline[19](https://www.zotero.org/google-docs/?7QWZEb).

Due to technical limitations of OpenSAFELY to use a sequential trial approach ([Figure 1](#_l0amv78lewxm)), we will use a landmark approach ([Figure 2](#_wbuaplppx38b)). This impacts the exact causal question in this case only minimally. Once possible, we aim to use a sequential trial approach and will amend the protocol.

To assess the protective effect of starting metformin (instead of prevalent use of metformin), we ideally assign treatment at T2DM diagnosis and follow everyone from T2DM diagnosis date. However, this introduces the possibility of immortal time bias between T2DM diagnosis and knowing the treatment status. A landmark analysis can be used to avoid this type of bias.[20](https://www.zotero.org/google-docs/?7uJOGK) In a landmark analysis, a landmark time is selected and anyone lost to follow-up or died prior to this time is excluded from further analysis. For the remaining, those who initiated treatment by the landmark time are classified as the treated, those who do not initiated by the landmark time are classified as the untreated, even if they are treated later. This avoids immortal time bias. However, depending on their clinical vulnerability/susceptibility, participants may have a different risk of reaching the outcome of interest across the two groups, and therefore introduce selection bias at the landmark date. In our specific case, however, the outcome of interest is impossible to reach since the pandemic has not started yet.

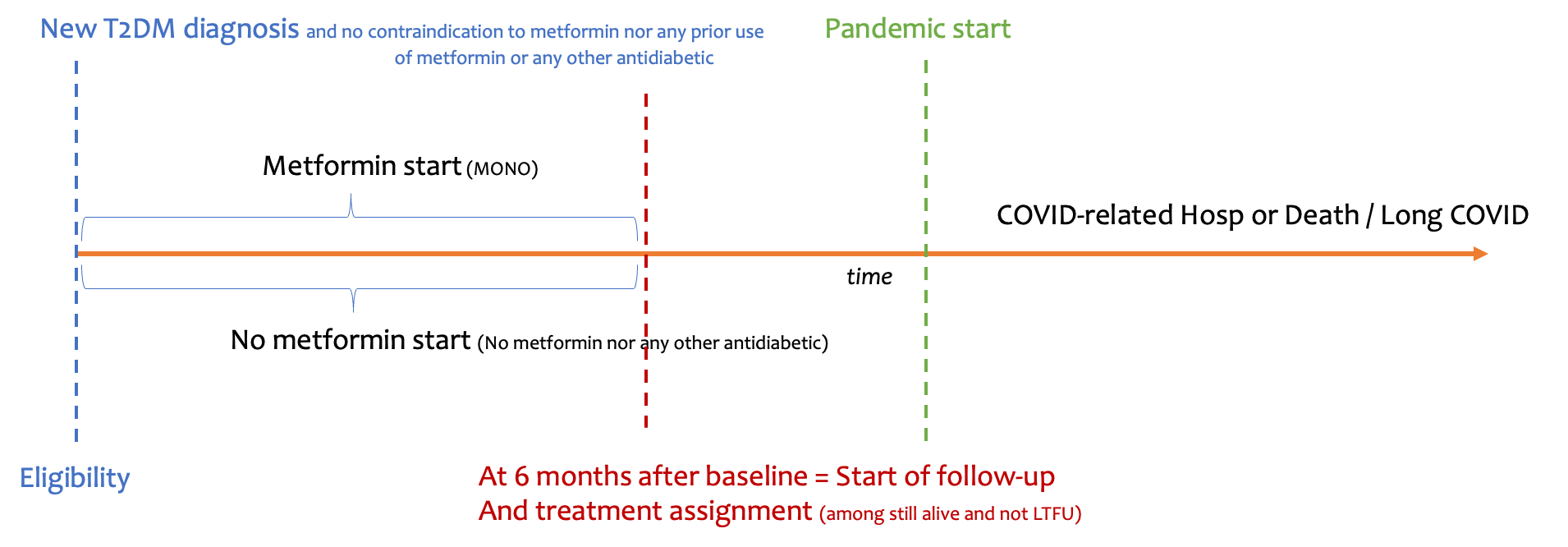
We set the end date of the eligibility window for new T2DM diagnosis to 01.08.2024 due to three- to six-monthly routine prescription of metformin in primary care. We set the start date of the eligibility windows for new T2DM diagnosis to 01.08.2024 to capture an effect of starting metformin (rather than prevalent users) and to ensure better comparability across the two groups. We set the study end date to 01.03.2022, the end of mass testing in the UK[21](https://www.zotero.org/google-docs/?aTYxFl). The dataset and analysis code are developed and shared in [this](https://github.com/opensafely/metformin_covid) public GitHub repository.

### **Figure 1:** Study design using the sequential trial approach (and moving the study start to pandemic start in a second step)



The pandemic start in the UK was recorded at/around 01/02/2020[22](https://www.zotero.org/google-docs/?t1P1uK)

### **Figure 2:** Study design using the landmark approach



### **Table 1:** Target trial specification and emulation

|  |  |  |  |
| --- | --- | --- | --- |
| **Protocol element** | **Hypothetical pragmatic target trial** | **Target trial emulation** (specifications in red) | **Notes** |
| **Eligibility criteria** | Inclusion criteria:   1. Aged ≥ 18 years 2. Recent diagnosis of type 2 diabetes mellitus, i.e,. in the past 6-18 months and no exposure to SARS-CoV-2   Exclusion criteria.   1. Use of metformin or another first-line antidiabetic\* prescription prior to T2DM for any reason 2. Known hypersensitivity / intolerance to metformin 3. Clinical history of moderate to severe renal impairment (eGFR of <30ml/min/1.73 m2) 4. Clinical history of advanced decompensated liver cirrhosis 5. Use of the following medications in the past 14 days: Cimetidine, hydroxychloroquine, tafenoquine, dolutegravir, patiromer, ranolazine, Monoamine Oxide Inhibitors (Phenelzine, Tranylcypromine, Selegiline, Isocarboxazide, moclobemide), Alpha-1 antagonists, Sotalol, Clonidine, Phosphodiesterase 5 inhibitors, Methyldopa, Prazosin, Terasozin, Doxazosin) | Inclusion criteria: *Same as the target trial, specifically:*   1. Aged ≥ 18 years 2. Recent diagnosis of type 2 diabetes mellitus,i.e., in the past 6-18 months *prior to pandemic start*   Exclusion criteria: *Same as the target trial, specifically:*   1. Use of metformin or another first-line antidiabetic\* prior to T2DM for any reason, defined as having any prescription in primary care prior to the T2DM diagnosis 2. Known hypersensitivity / intolerance to metformin, defined as any history of metformin allergy reported in primary or secondary care prior to the T2DM diagnosis 3. Clinical history of moderate to severe renal impairment (eGFR of <30ml/min/1.73 m2), defined as any history of moderate to severe renal impairment reported in primary or secondary care prior to the T2DM diagnosis 4. Clinical history of advanced decompensated liver cirrhosis, defined as any history of advanced decompensated liver cirrhosis reported in primary or secondary care prior to the T2DM diagnosis 5. Use of the medications listed in the past 14 days, defined as any prescription recorded in primary care up until 14 days prior to the T2DM diagnosis | In addition, we apply data quality assurance criteria to the entire database and data completeness criteria at baseline date  **Data quality assurance criteria:**  1. Remove individuals whose year of birth is missing  2. Remove individuals whose year of birth is after their year of death  3. Remove individuals whose year of birth is after the study end date or who were older than 110 years when the UK National Health Services (NHS) was established (1838, since NHS was established in 1948)  4. Remove individuals whose date of death is on or before 01/01/1900 or after current date (Sys.Date())  5. Remove men whose records contain pregnancy codes  6. Remove men whose records contain hormone replacement therapy or combined contraceptive pill medication codes  7. Remove women whose records contain prostate cancer codes  **Data completeness criteria:**  Patients will be included only if they meet all completeness criteria:  · Alive at landmark date  · Known age between 18 and 110 inclusive at baseline date  · Known sex (female/male)  · Known deprivation (Index of Multiple Deprivation [IMD]) at baseline date  · Known sustainability and transformation partnership (STP) region, an NHS administrative geographical area, at baseline date  · Registered in an English GP practice with TPP software for at least 12 months prior to the baseline date  Details regarding data quality assurance and data completeness criteria variables are presented in [table 2](#_p1f3vb2jjigu) and details regarding the eligibility criteria variables in [table 3](#_8xndjqjwl0r1). T2DM is defined based on a validated diabetes type adjudication algorithm, derived from diagnoses, treatment and measurement codes from primary and secondary care. The detailed adjudication algorithm is presented in [appendix figure S1](#_66b485waohz1) and the corresponding code [here](https://github.com/opensafely-actions/diabetes-algo/).  \* list of other antidiabetics specified in [table 3](#_8xndjqjwl0r1). |
| **Treatment strategies** | Eligible participants are randomized to either:   1. Initiate metformin monotherapy within 6 months 2. Not to initiate metformin nor any other antidiabetic within 6 months   Any titration regimen, any maintenance dosage, any metformin type and dosage allowed | *Same as the target trial,* *except:*  The date of medication initiation is the date of medication prescription. | We do not have data on whether the full course of treatment is completed nor dispensed.  Details regarding the exposure/treatment variable in [table 4](#_j5gdramnobzx).  Metformin monotherapy is the most common first-line T2DM treatment option across all cardiovascular risk groups, from literature and our own feasibility count assessment in OpenSAFELY.(ref) However, it may be combined with other antidiabetics, especially SGLT2 inhibitors, for high-risk groups - and if symptomatic hyperglycaemia is present, an insulin or a sulfonylurea might be prescribed[23](https://www.zotero.org/google-docs/?DmZ07v)  To keep confounding by indication to a minimum and have sufficient numbers in each group, we decided to compare these two treatment strategies. |
| **Treatment allocation** | Eligible participants are randomly assigned to one group, stratified by region, and are aware of which group they were assigned to (open-label). | *Same as for the target trial, except:*  We will assume randomization conditional on the following baseline covariates: age (restricted cubic splines), sex, calendar time (restricted cubic splines), ethnicity (grouped into five broad categories: White, Black or Black British, Asian or Asian British, Mixed, Other), Index of Multiple Deprivation ([IMD], as quintiles derived from the patient’s postcode at lower super output area level), STP region, rural/urban area, care home resident, health care worker, primary care consultation rate in previous year, smoking status, BMI (<18; 18-24; 25-29; 30+; missing), HbA1c in mmol/mol (<42; 42-58; 59-75; 75+; missing), Total Chol/HDL ratio, History of obesity, acute myocardial infarction, stroke, other arterial embolism, venous thromboembolism events, heart failure, angina, dementia, cancer, hypertension, depression, chronic obstructive pulmonary disease, liver disease, chronic kidney disease, prediabetes, PCOS, diabetes-related complications (diabetic foot/neuropathy/nephropathy/retinopathy) | Covariates were identified through literature review and discussions with domain experts and are presented in a directed acyclic graph ([figure 3a](#_kv153prt96gh)).  Details regarding all covariates are available in [table 5](#_pi9b0i6f4gmj).  Comorbidities were identified through SNOMED CT codes in primary care records and ICD-10 in secondary care records. Ethnicity was identified through SNOMED CT codes and supplemented with information from secondary care records.  Individuals with missing BMI, ethnicity, HbA1c, Total Chol/HDL ratio, rural/urban area, and smoking status were included with a missing indicator. Absence of recorded codes in terms of comorbidities, health care worker, and care home resident was assumed as not having such a diagnosis, not being part of such a group, respectively. |
| **Outcomes** | Primary:   * COVID-19-related hospitalisation or COVID-19-related death   Secondary:   * COVID-19 diagnosis * Long COVID diagnosis   Exploratory:   * Long COVID symptoms, including both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks after a COVID-19 event)[24](https://www.zotero.org/google-docs/?opFTe2) | *Same as for the target trial, specifically see notes* | Details regarding outcome variables are available in [table 6](#_73wvl4vaqzej).  Deaths were identified using linked ONS death registration data. COVID-19 related death was defined as a death where the underlying or contributory cause on the death certificate was COVID-19 (ICD-10 codes U07.1, U07.2, U10.9). COVID-19 related hospitalisations, obtained from secondary care SUS data, were defined as any hospitalisation listing a COVID-19 diagnosis in any position). For the primary outcome, if a person was hospitalised before death, the date of hospitalisation was used.  COVID diagnosis was defined using an established algorithm combining info from SGSS, HES-APC, SUS and ONS[25](https://www.zotero.org/google-docs/?1flSD3): Any event indicating a COVID diagnosis, i.e., a positive SARS-CoV-2 test, a COVID code in primary care, a COVID diagnostic code in secondary care (hospital episode and emergency care attendance), or a COVID-related death.  Long COVID diagnosis was defined using 15 established NHS Long COVID codes across diagnostic, referral and measurement domain. Despite coding guidance from NHS[26](https://www.zotero.org/google-docs/?TIxyog), using only codes from EHR to define Long COVID has major limitations[27](https://www.zotero.org/google-docs/?fNH9RM). Hence, in an exploratory analysis, we will operationalize this outcome with a sign-and-symptoms based approach to supplement these codes, see chapter xy below. |
| **Follow-up** | Primary:   * Each participant will be followed up from landmark date until COVID-19-related hospitalization, COVID-19-related death, non-COVID death, lost to follow-up, or end of study, whichever occurs first.   Secondary:   * Each participant will be followed up from landmark date until the diagnosis of Long COVID, all-cause death, lost to follow-up, or end of study, whichever occurs first. | *Same as for the target trial, except:*  We start follow-up 6 months after baseline date (T2DM diagnosis date) | Administrative study end: end of mass testing in UK (March 01, 2022)  Non-COVID deaths will be treated as a censoring event, to account for the competing risk |
| **Causal contrast** | Intention-to-treat effect  Once possible to incorporate time-updated covariates into the study design (sequential trial), we will try to estimate per-protocol effects, such as the effect if control participants adhered to their assigned strategy of not initiating any metformin, or the effect of still taking metformin at pandemic start in the intervention group, or to still continuously fulfill the eligibility criteria in the control group | Observational analogue of the intention-to-treat effect: “Effect of starting metformin monotherapy vs not starting any antidiabetic before the pandemic among adults diagnosed with T2DM between mid-2018 and mid-2019, irrespective what happens after the 6-months grace period in terms of metformin exposure” | Only information on treatment prescription is available and we therefore assume for our primary ITT analysis that everyone with a treatment prescription started and continued taking their medication.  Once possible to incorporate time-updated covariate, we will artificially censor individuals deviating from their assigned treatment strategy and use inverse probability of artificial censoring weights to account for this informative censoring. |
| **Statistical analysis** | Intention-to-treat analysis: Region-stratified adjusted hazard ratios, using a stratified Cox model and standard Wald 95% confidence intervals  Pooled logistic regression deriving cumulative incidence (risk) curves and estimates of 2-year risk, risk differences, and risk ratios comparing the two groups  Subgroup analyses by adding an interaction term in turn to test for a relative interaction: baseline age (below 60 vs 60 years and above), sex (female vs male), ethnicity (white versus non-white), IMD (most deprived vs other), BMI (below 30 versus 30 or above), and HbA1c (below 59 mmol/mol vs 59 mmol/mol and above)  Per-protocol analysis: Inverse probability weighting to control for treatment initiation (i.e. informative censoring) in the control group. | *Same as for the target trial intention-to-treat analysis, except:*  We use inverse probability weighting (IPW) to emulate randomization conditional on baseline covariates (see under ‘Treatment allocation’) and robust standard errors to derive 95% confidence intervals  *Same as for the target trial per-protocol analysis, except:*  We use IPW to emulate randomization conditional on baseline covariates (see under ‘Treatment allocation’) and robust standard errors to derive 95% confidence intervals | We plan to add sensitivity analyses such as exploring the impact of using only a minimal set of covariates to emulate the randomization (see [figure 3b](#_l7nwqplujsn)). |

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## Exploratory: Long COVID outcome considerations

Despite clear Long COVID coding guidance from NHS[26](https://www.zotero.org/google-docs/?IHRnZe), using only diagnostic and referral codes from electronic health records has limitations[27](https://www.zotero.org/google-docs/?7ClNfU).

Hence, in an exploratory analysis, we will operationalize this outcome with a signs and symptoms based approach. We defined the most common Long COVID signs and symptoms based on the NICE guidelines[28](https://www.zotero.org/google-docs/?UJSBZw), as outlined below. We search for these individual signs and symptoms 30 to 365 days after a COVID-19 diagnosis, using an established algorithm combining info from SGSS, HES-APC, SUS.[25](https://www.zotero.org/google-docs/?T7y5uy) This window includes both, ongoing symptomatic COVID-19 (from 4 to 12 weeks), and post-COVID-19 syndrome (>12 weeks)[24](https://www.zotero.org/google-docs/?Pct4cr). We will estimate the association between metformin and the occurrence of individual signs and symptoms using the same approach as for the other outcomes.

The most common Long COVID signs and symptoms based on the NICE guidelines[28](https://www.zotero.org/google-docs/?k9qFrD) and the detailed variable definitions in [table 6](#_73wvl4vaqzej):

Respiratory symptoms

* Breathlessness
* Cough

Cardiovascular symptoms

* Chest tightness
* Chest pain
* Palpitations

Generalised symptoms

* Fatigue
* Fever
* Pain

Neurological symptoms

* Cognitive impairment ('brain fog', loss of concentration or memory issues)
* Headache
* Sleep disturbance
* Peripheral neuropathy symptoms (pins and needles and numbness)
* Dizziness
* Delirium
* Mobility impairment
* Visual disturbance

Gastrointestinal symptoms

* Abdominal pain
* Nausea and vomiting
* Diarrhoea
* Weight loss and reduced appetite

Musculoskeletal symptoms

* Joint pain
* Muscle pain

Ear, nose and throat symptoms

* Tinnitus
* Earache
* Sore throat
* Loss of taste and/or smell
* Nasal congestion

Dermatological symptoms

* Skin rashes
* Hair loss

Psychological/psychiatric symptoms

* Symptoms of depression
* Symptoms of anxiety
* Symptoms of post-traumatic stress disorder

The codelists for these symptoms in UK EHR, using OpenSAFELY, have been defined, coded and published separately (see [here](https://github.com/opensafely/long-covid-symptoms)).

This list also covers the 25 signs and symptoms defined by the World Health Organisation[29](https://www.zotero.org/google-docs/?oS0nmk), the most prevalent (>10%) signs and symptoms reported in the global meta-analysis[4](https://www.zotero.org/google-docs/?qNPBF5), the 23 most common symptoms among people with self-reported Long COVID in the UK COVID Infection Survey[30](https://www.zotero.org/google-docs/?JfXQCi), the 12 signs and symptoms used in the largest UK Long COVID trial[31](https://www.zotero.org/google-docs/?lA5dwJ).

## Limitations

Our study has limitations:

1. **Design:** In a landmark design, time zero (date of randomization and follow-up start) and date of eligibility are not completely aligned. An alternative design, such as a sequential trial approach, would need to be explored. However, the design bias is likely minor; a sequential trial approach will be explored if any non-null association is found.
2. **Misclassification:** Possible misclassifications of cause of death on death certificates. Possible misclassification of exposure since we only have metformin prescription but not dispensing nor intake.
3. **Confounding by indication:** Despite restricted study population with an indication for metformin (new T2DM diagnosis with no contraindication to metformin) and adjusting for potentially important confounders, we cannot completely rule out confounding by indication.
4. **Changes over time:** Interaction with lockdown/COVID measures that affect risk of SARS-CoV-2 infection, vaccinations, and changing risk behaviours among people living with T2DM, affecting the two groups differently.
5. **Underreporting of Long COVID codes in primary care**.

## Definition of all variables

Below we outline the details of all variables used in this study, including their codelists.

[Table 2](#_p1f3vb2jjigu): Data completeness and quality assurance variables

[Table 3](#_8xndjqjwl0r1):Eligibility variables

[Table 4](#_j5gdramnobzx): Treatment variables

[Table 5](#_pi9b0i6f4gmj): Demographic variables, covariates and potential confounders

[Table 6](#_73wvl4vaqzej): Outcome variables

### **Table 2.** Data completeness and quality assurance variables

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Name** | **Type** | **Definition** | **Data sources ([tpp](https://docs.opensafely.org/ehrql/reference/schemas/tpp/" \l "tpp-schema)** [**schema**](https://docs.opensafely.org/ehrql/reference/schemas/tpp/#tpp-schema) **in brackets)** | **Notes** |
| Known sex | qa\_bin\_is\_female\_or\_male | Binary | T, F | Primary care (patients) | Based on entire dataset period, not elig\_date\_t2dm |
| Known age between 18 and 110 inclusive | qa\_bin\_was\_adult | Binary | T, F | Primary care (patients) | Based on elig\_date\_t2dm |
| Alive | qa\_bin\_was\_alive | Binary | T, F | Primary care (patients) | Based on elig\_date\_t2dm |
| Known deprivation (IMD) | qa\_bin\_known\_imd | Binary | T, F | Primary care (practice\_registration) | Based on elig\_date\_t2dm |
| Known region | *based on same variable as below* |  |  |  |  |
| Registered in an English GP with TPP for at least past 12 months | qa\_bin\_was\_registered | Binary | T, F | Primary care (practice\_registration) | 1 year = 365.25 days, taking into account leap years. => elig\_date\_t2dm - days(366) |
| Year of Birth | qa\_num\_birth\_year | Numeric | continuous (year only) | Primary care (patients) | Based on entire EHR, not elig\_date\_t2dm, |
| Date of Death | qa\_date\_of\_death | Date | Date | Death certificates (ons\_deaths) | Based on entire EHR, not elig\_date\_t2dm, |
| Pregnancy | qa\_bin\_pregnancy | Binary | T, F | Primary care (clinical\_events):  [pregnancy\_snomed\_clinical](https://www.opencodelists.org/codelist/user/RochelleKnight/pregnancy_and_birth_snomed/1d46bcb3/) | Based on entire EHR, not elig\_date\_t2dm, |
| Combined oral contraceptive pill | qa\_bin\_cocp | Binary | T, F | Primary care (medications):  [cocp\_dmd](https://www.opencodelists.org/codelist/user/elsie_horne/cocp_dmd/1666a7a3/) | Based on entire EHR, not elig\_date\_t2dm, |
| Hormone replacement therapy | qa\_bin\_hrt | Binary | T, F | Primary care (medications):  [hrt\_dmd](https://www.opencodelists.org/codelist/user/elsie_horne/hrt_dmd/19196799/) | Based on entire EHR, not elig\_date\_t2dm, |
| Prostata cancer diagnosis | qa\_bin\_prostate\_cancer | Binary | T, F | 1) Primary care (clinical\_events):  [prostate\_cancer\_snomed\_clinical](https://www.opencodelists.org/codelist/user/RochelleKnight/prostate_cancer_snomed/0437497e/)  3) HES APC (apcs):  [prostate\_cancer\_icd10](https://www.opencodelists.org/codelist/user/RochelleKnight/prostate_cancer_icd10/6b27d648/)  3) Death certificates (ons\_deaths):  [prostate\_cancer\_icd10](https://www.opencodelists.org/codelist/user/RochelleKnight/prostate_cancer_icd10/6b27d648/) | Based on entire EHR, not elig\_date\_t2dm,  Re [ons\_deaths](https://docs.opensafely.org/ehrql/reference/schemas/tpp/#ons_deaths): Search in underlying\_cause\_of\_death as well as in all other 15 cause\_of\_death fields |

### **Table 3.** Eligibility variables

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Name** | **Type** | **Definition** | **Data sources *([tpp](https://docs.opensafely.org/ehrql/reference/schemas/tpp/" \l "tpp-schema)*** [***schema***](https://docs.opensafely.org/ehrql/reference/schemas/tpp/#tpp-schema) ***in brackets)*** | **Notes** |
| New type 2 diabetes mellitus (T2DM) diagnosis in window 6-18 months before pandemic start | elig\_date\_t2dm | Date | Date | 1) Primary care: Diagnoses *(clinical\_events):*  - [diabetes\_type1\_ctv3\_clinical](https://www.opencodelists.org/codelist/user/hjforbes/type-1-diabetes/674fbd7a/)  - [diabetes\_type2\_ctv3\_clinical](https://www.opencodelists.org/codelist/user/hjforbes/type-2-diabetes/3530d710/)  - [diabetes\_other\_ctv3\_clinical](https://www.opencodelists.org/codelist/user/hjforbes/other-or-nonspecific-diabetes/0311f0a6/)  - [diabetes\_gestational\_ctv3\_clinical](https://www.opencodelists.org/codelist/user/hjforbes/gestational-diabetes/1ed423d1/)  - [diabetes\_diagnostic\_ctv3\_clinical](https://www.opencodelists.org/codelist/user/hjforbes/nondiagnostic-diabetes-codes/50f30a3b/)  - [hba1c\_new\_codes](https://www.opencodelists.org/codelist/user/alainamstutz/hba1c-bristol/7482c0c7/)  2) Primary care: Drugs *(medications):*  - [insulin\_dmd](https://www.opencodelists.org/codelist/opensafely/insulin-medication/2020-04-26/)  - [antidiabetic\_drugs\_snomed\_clinical](https://www.opencodelists.org/codelist/opensafely/antidiabetic-drugs/2020-07-16/)  - [non\_metformin\_dmd](https://www.opencodelists.org/codelist/user/r_denholm/non-metformin-antidiabetic-drugs_bristol/7207eb58/)  3) Secondary care: Diagnoses *(apcs):*  - [diabetes\_type1\_icd10](https://www.opencodelists.org/codelist/opensafely/type-1-diabetes-secondary-care/2020-09-27/)  - [diabetes\_type2\_icd10](https://www.opencodelists.org/codelist/user/r_denholm/type-2-diabetes-secondary-care-bristol/0b7f6cd4/)  - [diabetes\_gestational\_icd10](https://www.opencodelists.org/codelist/user/alainamstutz/gestational-diabetes-icd10-bristol/474e7a09/) | In ehrQL: search for **first code** before studyend\_date, apply 6-18m window later in R  See [Appendix 1](?tab=t.0#heading=h.2yudo3gkfjlx) regarding the algorithm to define Diabetes types.  **The final diabetes variables (elig\_date\_t2dm) are extracted from the algorithm outcome variable in R.** |
| Any metformin use, on or prior to the T2DM diagnosis | elig\_date\_metfin\_first (= exp\_date\_metfin\_first) | Date | Date | Primary care (medications):  - [metformin\_dmd](https://www.opencodelists.org/codelist/user/john-tazare/metformin-dmd/48e43356/) | In ehrQL: search for **first code** before elig\_date\_t2dm |
| Any other antidiabetic use, on or prior to the T2DM diagnosis | elig\_date\_\*\*\*\_first | Date | Date | Primary care (medications)\*\*\*:  - [sulfonylurea\_dmd](https://www.opencodelists.org/codelist/user/alex-walker/sulfonylureas-dmd/6e0ab9fd/)  - [dpp4\_dmd](https://www.opencodelists.org/codelist/user/alex-walker/dpp-4-inhibitors-dmd/57ae06be/)  - [tzd\_dmd](https://www.opencodelists.org/codelist/user/alainamstutz/thiazolidinedione-bristol-dmd/7de688dc/)  - [sglt2\_dmd](https://www.opencodelists.org/codelist/user/alex-walker/sglt-2-inhibitors-dmd/2029a068/)  - [glp1\_dmd](https://www.opencodelists.org/codelist/user/alainamstutz/glp1-bristol-dmd/7c628abb/)  - [meglitinides\_dmd](https://www.opencodelists.org/codelist/user/alainamstutz/meglitinides-bristol-dmd/79afcac5/)  - [agi\_dmd](https://www.opencodelists.org/codelist/user/alainamstutz/alpha-glucosidase-inhibitors-bristol-dmd/4790e45b/)  - [insulin\_dmd](https://www.opencodelists.org/codelist/opensafely/insulin-medication/2020-04-26/) | In ehrQL: search for **first code** before elig\_date\_t2dm |
| Known hypersensitivity and / or intolerance to metformin, on or prior to the T2DM diagnosis | elig\_date\_metfin\_allergy\_first | Date | Date | Primary care (clinical\_events):  - [metformin\_allergy\_snomed\_clinical](https://www.opencodelists.org/codelist/user/alainamstutz/metformin-intolerance-bristol/5af86d52/) | In ehrQL: search for **first code** before elig\_date\_t2dm |
| Clinical history of moderate to severe renal impairment (eGFR of <30ml/min/1.73 m2; chronic stage 4/5) on or prior to the T2DM diagnosis | elig\_date\_ckd\_45\_first | Date | Date | 1) Primary care (clinical\_events):  - [ckd\_snomed\_clinical\_45](https://www.opencodelists.org/codelist/nhsd-primary-care-domain-refsets/ckdatrisk1_cod/08a67d83/)  2) HES APC (apcs):   * ckd\_stage4\_icd10 -> ["N184"] * ckd\_stage5\_icd10 -> ["N185"] | In ehrQL: search for **first code** before elig\_date\_t2dm |
| Clinical history of advance decompensated liver cirrhosis, on or prior to the T2DM diagnosis | elig\_date\_liver\_cirrhosis\_first | Date | Date | 1) Primary care (clinical\_events):   * [advanced\_decompensated\_cirrhosis\_snomed\_clinical](https://www.opencodelists.org/codelist/opensafely/condition-advanced-decompensated-cirrhosis-of-the-liver/071038cf/) * [ascitic\_drainage\_snomed\_c](https://www.opencodelists.org/codelist/opensafely/procedure-ascitic-drainage/39388836/)linical   2) HES APC (apcs):   * [advanced\_decompensated\_cirrhosis\_icd10](https://www.opencodelists.org/codelist/opensafely/condition-advanced-decompensated-cirrhosis-of-the-liver-and-associated-conditions-icd-10/00e40554/) | In ehrQL: search for **first code** before elig\_date\_t2dm |
| Use of the following medications in the last 14 days: Cimetidine, hydroxychloroquine, dolutegravir, patiromer, ranolazine, Monoamine Oxide Inhibitors (Phenelzine, Tranylcypromine, Selegiline, moclobemide), Sotalol, Clonidine, Methyldopa, Prazosin, Doxazosin, on or prior to the T2DM diagnosis | elig\_date\_metfin\_interaction\_last | Date | Date | Primary care (medications):   * [metformin\_interaction\_](https://www.opencodelists.org/codelist/user/alainamstutz/metformin-drug-drug-interaction-bristol-dmd/76baa07d/)dmd | In ehrQL: search for **last code** before elig\_date\_t2dm |

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### **Table 4.** Treatment/Exposure variables

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Name** | **Type** | **Definition** | **Data sources ([tpp](https://docs.opensafely.org/ehrql/reference/schemas/tpp/" \l "tpp-schema)** [**schema**](https://docs.opensafely.org/ehrql/reference/schemas/tpp/#tpp-schema) **in brackets)** | **Notes** |
| Metformin prescription within 6m | exp\_bin\_metfin | Binary | T, F | Primary care (medications):  - [metformin\_mono\_dmd](https://www.opencodelists.org/codelist/user/alainamstutz/metformin-without-other-antidiabetic-bristol-dmd/40fca29a/#full-list) | First Metformin monotherapy prescription after elig\_date\_t2dm, within 6-months grace period |
| No antidiabetic prescription within 6m | exp\_bin\_treat\_nothing | Binary | T, F | Primary care (medications), none of these:  - [metformin\_dmd](https://www.opencodelists.org/codelist/user/alex-walker/metformin-dmd/258f2054/)  - [sulfonylurea\_dmd](https://www.opencodelists.org/codelist/user/alex-walker/sulfonylureas-dmd/6e0ab9fd/)  - [dpp4\_dmd](https://www.opencodelists.org/codelist/user/alex-walker/dpp-4-inhibitors-dmd/57ae06be/)  - [tzd\_dmd](https://www.opencodelists.org/codelist/user/alainamstutz/thiazolidinedione-bristol-dmd/7de688dc/)  - [sglt2\_dmd](https://www.opencodelists.org/codelist/user/alex-walker/sglt-2-inhibitors-dmd/2029a068/)  - [glp1\_dmd](https://www.opencodelists.org/codelist/user/alainamstutz/glp1-bristol-dmd/7c628abb/)  - [meglitinides\_dmd](https://www.opencodelists.org/codelist/user/alainamstutz/meglitinides-bristol-dmd/79afcac5/)  - [agi\_dmd](https://www.opencodelists.org/codelist/user/alainamstutz/alpha-glucosidase-inhibitors-bristol-dmd/4790e45b/)  - [insulin\_dmd](https://www.opencodelists.org/codelist/opensafely/insulin-medication/2020-04-26/) | No antidiabetic prescription after elig\_date\_t2dm, within 6-months grace period: No metformin (combo/mono), no SULFO, no DPP4, no TZD, no SGLT2, no GLP1, no AGI, no MEGLI, no INSULIN |

### **Table 5.** Demographic variables, covariates and potential confounders

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Name** | **Type** | **Definition** | **Data sources** | **Notes** |
| ***‘Same-day/most recent’ baseline covariates (recorded on elig\_date\_t2dm or most recent)*** | | | | | |
| Sex | cov\_cat\_sex | Categorical | Male, Female | Primary care (patients) | Any other code than M and F is excluded by design (see qa\_bin\_is\_female\_or\_male) |
| Age at elig\_date\_t2dm | cov\_num\_age  derived:  cov\_cat\_age | Continuous | "18-39", "40-59", "60-79", "80+" | Primary care (patients) | Will be modelled as |
| Ethnicity | cov\_cat\_ethnicity | Categorical | White  Black  Asian  Mixed  Other  Unknown | Primary care (clinical\_events) and SUS:  [ethnicity\_snomed](https://www.opencodelists.org/codelist/opensafely/ethnicity-snomed-0removed/2e641f61/) | Additionally included ethnicity\_from\_sus; codelist for primary care (snomed), based on recent publication: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11234682/> |
| Index of Multiple Deprivation (5 cat) at elig\_date\_t2dm | cov\_cat\_deprivation\_5 | Categorical | 5 categories: 1 (most deprived) - 5 (least deprived) | Primary care (addresses) | Based on the Index of Multiple Deprivation score: <https://docs.opensafely.org/legacy/study-def-variables/#cohortextractor.patients.address_as_of>  <https://data.cdrc.ac.uk/dataset/index-multiple-deprivation-imd>  The IMD combines multiple aspects of deprivation into an overall score. These aspects include:   * Household overcrowding * Homelessness * Housing affordability * Distance to key amenities like schools, supermarkets, and GP surgeries |
| Region at elig\_date\_t2dm | cov\_cat\_region | Categorical | East  London  Midlands  North East and Yorkshire  North West  South East  South West | Primary care (practice\_registrations) | Based on the Sustainable and Transformation Partnerships (STP) names and codes: <https://geoportal.statistics.gov.uk/documents/bec635f6c83e4582bcf76ce02c2be840/about>  <https://docs.opensafely.org/legacy/study-def-variables/#cohortextractor.patients.registered_practice_as_of> |
| Rural/urban classification at elig\_date\_t2dm | cov\_cat\_rural\_urban | Categorical | Urban conurbation  Urban city or town  Rural town or village | Primary care (addresses) |  |
| Practice registration at elig\_date\_t2dm | cov\_cat\_stp | Categorical | STP1 - STP10 | Primary care (practice\_registrations) |  |
| Smoking status on or before (most recent) elig\_date\_t2dm | cov\_cat\_smoking\_status | Categorial | Smoker  Ever  Never  Unknown/Missing | Primary care (clinical\_events):  A combination of [Smoking\_clear](https://www.opencodelists.org/codelist/opensafely/smoking-clear/2020-04-29/) &  [Ever\_smoking](https://www.opencodelists.org/codelist/user/alainamstutz/ever-smoking-bristol/00731978/) |  |
| Care home resident on or before (most recent) elig\_date\_t2dm | cov\_bin\_carehome\_status | Binary | T, F | 1) Primary care (clinical\_events):  - [carehome](https://www.opencodelists.org/codelist/primis-covid19-vacc-uptake/longres/v1/)  2) Primary care (addresses):  - care\_home\_is\_potential\_match  - care\_home\_requires\_nursing  - care\_home\_does\_not\_require\_nursing |  |
| Participant is a healthcare worker | cov\_bin\_healthcare\_worker | Binary | T, F | NHS England COVID-19 data store (see: <https://docs.opensafely.org/study-def-variables/#cohortextractor.patients.with_healthcare_worker_flag_on_covid_vaccine_record>) | Based on vaccination data, connected to the day of receiving a vaccination => at date in the future, but probably still a good proxy to use, since this status is long-term. |
| Consultation rate, in year prior to baseline, i.e. mid2017 to mid2018 | cov\_num\_consrate | Numeric | Number of primary care contacts | Primary care | # QC: restrict to max 365 (average of one per day) |
| BMI value, on or before elig\_date\_t2dm (max. 2 years back) | cov\_cat\_bmi\_groups;  cov\_num\_bmi | Categorical;  Numeric | <18; 18-24; 25-29; 30+; missing  continuous | Primary care (clinical\_events) | Cov\_cat\_bmi\_groups: NA coded as missing indicator (“missing”)  Cov\_num\_bmi: biologically implausible BMI < 12 and > 70 replace with NA |
| HbA1c value on or before elig\_date\_t2dm (max. 2 years back) | cov\_cat\_hba1c\_mmol\_mol  cov\_num\_hba1c\_mmol\_mol | Categorical  Numeric | <42; 42-52; 53-58; 59-75; 75+; missing  continuous | Primary care (clinical\_events):  [hba1c\_snomed](https://www.opencodelists.org/codelist/opensafely/glycated-haemoglobin-hba1c-tests-numerical-value/5134e926/) | Implausible values set to missing:  < 0 or > 120  Categories based on  <https://www.southtees.nhs.uk/resources/the-hba1c-test/> |
| Total cholesterol/high-density lipoprotein [HDL] cholesterol ratio [TC/HDL] on or before elig\_date\_t2dm (max. 2 years back) | cov\_cat\_tc\_hdl\_ratio  cov\_num\_tc\_hdl\_ratio | Categorical  Numeric | "below 3.5:1"; "3.5:1 to 5:1"; "above 5:1"; missing  continuous | Primary care (clinical\_events)  [cholesterol\_snomed](https://www.opencodelists.org/codelist/opensafely/cholesterol-tests-numerical-value/7e3a22f3/)  [hdl\_cholesterol\_snomed](https://www.opencodelists.org/codelist/bristol/hdl-cholesterol/64775990/) | TC/HDL values are derived from the recorded total and HDL cholesterol values.  Implausible values set to missing:   1. total Cholesterol values < 1.75 or > 20 2. HDL values < 0.4 or > 5 3. ratio values < 1 or > 50   Reference values/limits: <https://doi.org/10.1093/ije/dyz099>  <https://www.urmc.rochester.edu/encyclopedia/content?ContentTypeID=167&ContentID=lipid_panel_hdl_ratio#:~:text=Most%20healthcare%20providers%20want%20the,1%20is%20considered%20very%20good.> |
| ***‘Ever’ baseline covariates (any history of on/before elig\_date\_t2dm date)*** | | | | | |
| Obesity, on or before elig\_date\_t2dm | cov\_bin\_obesity | Binary | T if BMI>=30 (most recent in the past 2 years) or any obesity code/diagnosis; F otherwise | 1) Primary care (clinical\_events):  - [bmi\_obesity\_snomed\_clinical](https://www.opencodelists.org/codelist/user/elsie_horne/bmi_obesity_snomed/0764e9b4/)  2) HES APC (apcs):  - [bmi\_obesity\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/bmi_obesity_icd10/6e55767e/) |  |
| Acute myocardial infarction, on or before elig\_date\_t2dm | cov\_bin\_ami | Binary | T, F | 1) Primary care (clinical\_events):  - [ami\_snomed\_clinical](https://www.opencodelists.org/codelist/user/elsie_horne/ami_snomed/36d11028/)  2) HES APC (apcs):  - [ami\_prior\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/ami_prior_icd10/360a5c99/)  - [ami\_icd10](https://www.opencodelists.org/codelist/user/RochelleKnight/ami_icd10/3dea268d/) |  |
| All stroke, on or before elig\_date\_t2dm | cov\_bin\_all\_stroke | Binary | T, F | 1) Primary care (clinical\_events):   * [stroke\_isch\_snomed\_clinical](https://www.opencodelists.org/codelist/user/elsie_horne/stroke_isch_snomed/1cfae964/) * [stroke\_sah\_hs\_snomed\_clinical](https://www.opencodelists.org/codelist/user/elsie_horne/stroke_sah_hs_snomed/6adc02f9/)   2) HES APC (apcs):   * [stroke\_isch\_icd10](https://www.opencodelists.org/codelist/user/RochelleKnight/stroke_isch_icd10/278d734e/) * [stroke\_sah\_hs\_icd10](https://www.opencodelists.org/codelist/user/RochelleKnight/stroke_sah_hs_icd10/0e7e0019/) |  |
| Other arterial embolism, on or before elig\_date\_t2dm | cov\_bin\_other\_arterial\_embolism | Binary | T, F | 1) Primary care (clinical\_events):  - [other\_arterial\_embolism\_snomed\_clinical](https://www.opencodelists.org/codelist/user/tomsrenin/other_art_embol/3838d352/)  2) HES APC (apcs):  - [other\_arterial\_embolism\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/other_arterial_embolism_icd10/463adc5d/) |  |
| Venous thromboembolism events, on or before elig\_date\_t2dm | cov\_bin\_vte | Binary | T, F | 1) Primary care *(clinical\_events):*  - [portal\_vein\_thrombosis\_snomed\_clinical](https://www.opencodelists.org/codelist/user/tomsrenin/pvt/51484687/),  [dvt\_dvt\_snomed\_clinical](https://www.opencodelists.org/codelist/user/tomsrenin/dvt_main/1c76a027/),  [dvt\_icvt\_snomed\_clinical](https://www.opencodelists.org/codelist/user/tomsrenin/dvt_icvt/03672cf2/),  [dvt\_pregnancy\_snomed\_clinical](https://www.opencodelists.org/codelist/user/tomsrenin/dvt-preg/6a57b9bc/),  [other\_dvt\_snomed\_clinical](https://www.opencodelists.org/codelist/user/tomsrenin/dvt-other/1f29601d/),  [pe\_snomed\_clinical](https://www.opencodelists.org/codelist/user/elsie_horne/pe_snomed/6d8ec2ef/)  2) HES APC *(apcs):*  - [portal\_vein\_thrombosis\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/portal_vein_thrombosis_icd10/22606950/),  [dvt\_dvt\_icd10](https://www.opencodelists.org/codelist/user/RochelleKnight/dvt_dvt_icd10/24dab358/),  [dvt\_icvt\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/dvt_icvt_icd10/30a4dcad/),  [dvt\_pregnancy\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/dvt_pregnancy_icd10/6576830d/),  [other\_dvt\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/other_dvt_icd10/547f4fba/),  [icvt\_pregnancy\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/icvt_pregnancy_icd10/3b6fdc85/),  [pe\_icd10](https://www.opencodelists.org/codelist/user/RochelleKnight/pe_icd10/59ac59b8/) |  |
| Heart failure on or before elig\_date\_t2dm | cov\_bin\_hf | Binary | T, F | 1) Primary care (clinical\_events):  [hf\_snomed\_clinical](https://www.opencodelists.org/codelist/user/elsie_horne/hf_snomed/33579ca3/)  2) HES APC (apcs):  [hf\_icd10](https://www.opencodelists.org/codelist/user/RochelleKnight/hf_icd10/72bbcced/) |  |
| Angina on or before elig\_date\_t2dm | cov\_bin\_angina | Binary | T, F | 1) Primary care (clinical\_events):  [angina\_snomed\_clinical](https://www.opencodelists.org/codelist/user/hjforbes/angina_snomed/52df16a2/)  2) HES APC (apcs):  [angina\_icd10](https://www.opencodelists.org/codelist/user/RochelleKnight/angina_icd10/756e8ce3/) |  |
| Dementia on or before elig\_date\_t2dm | cov\_bin\_dementia | Binary | T, F | 1) Primary care (clinical\_events):  [dementia\_snomed\_clinical](https://www.opencodelists.org/codelist/user/elsie_horne/dementia_snomed/7bd3364c/)  [dementia\_vascular\_snomed\_clinical](https://www.opencodelists.org/codelist/user/elsie_horne/dementia_vascular_snomed/0eb67607/)  2) HES APC (apcs):  [dementia\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/dementia_icd10/2df21cb7/)  [dementia\_vascular\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/dementia_vascular_icd10/27c5e93c/) |  |
| Cancer on or before elig\_date\_t2dm | cov\_bin\_cancer | Binary | T, F | 1) Primary care (clinical\_events):  [cancer\_snomed\_clinical](https://www.opencodelists.org/codelist/user/elsie_horne/cancer_snomed/23271cdf/)  2) HES APC (apcs):  [cancer\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/cancer_icd10/55460349/) |  |
| Hypertension on or before elig\_date\_t2dm | cov\_bin\_hypertension | Binary | T, F | 1) Primary care (clinical\_events):  [hypertension\_snomed\_clinical](https://www.opencodelists.org/codelist/nhsd-primary-care-domain-refsets/hyp_cod/20210127/)  2) HES APC (apcs):  [hypertension\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/hypertension_icd10/1a48296e/) |  |
| Depression on or before elig\_date\_t2dm | cov\_bin\_depression | Binary | T, F | 1) Primary care (clinical\_events):  [depression\_snomed\_clinical](https://www.opencodelists.org/codelist/user/hjforbes/depression-symptoms-and-diagnoses/499814eb/)  2) HES APC (apcs):  [depression\_icd10](https://www.opencodelists.org/codelist/user/kurttaylor/depression_icd10/4dc56a05/) |  |
| Chronic obstructive pulmonary disease on or before elig\_date\_t2dm | cov\_bin\_copd | Binary | T, F | 1) Primary care (clinical\_events):  [copd\_snomed\_clinical](https://www.opencodelists.org/codelist/user/elsie_horne/copd_snomed/419c1000/)  2) HES APC (apcs):  [copd\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/copd_icd10/5aab8335/) |  |
| Liver disease on or before elig\_date\_t2dm | cov\_bin\_liver\_disease | Binary | T, F | 1) Primary care (clinical\_events):  [liver\_disease\_snomed\_clinical](https://www.opencodelists.org/codelist/user/elsie_horne/liver_disease_snomed/5c978f9c/)  2) HES APC (apcs):  [liver\_disease\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/liver_disease_icd10/75a702d1/) |  |
| Chronic kidney disease on or before elig\_date\_t2dm | cov\_bin\_chronic\_kidney\_disease | Binary | T, F | 1) Primary care (clinical\_events):  [ckd\_snomed\_clinical](https://www.opencodelists.org/codelist/user/elsie_horne/ckd_snomed/25d9dcd5/)  2) HES APC (apcs):  [ckd\_icd10](https://www.opencodelists.org/codelist/user/elsie_horne/ckd_icd10/0cca69a0/) |  |
| Polycystic Ovary Syndrome on or before elig\_date\_t2dm | cov\_bin\_pcos | Binary | T, F | 1) Primary care (clinical\_events):  [pcos\_snomed\_clinical](https://www.opencodelists.org/codelist/user/alainamstutz/pcos-bristol/796d6073/)  2) HES APC (apcs):  [pcos\_icd10](https://www.opencodelists.org/codelist/user/alainamstutz/pcos-icd10-bristol/605ded3e/) |  |
| Prediabetes  on or before elig\_date\_t2dm | cov\_bin\_prediabetes | Binary | T, F | Primary care (clinical\_events):  - [prediabetes\_snomed](https://www.opencodelists.org/codelist/opensafely/prediabetes-snomed/6bdbb7dd/) or  - [hba1c\_new\_codes](https://www.opencodelists.org/codelist/user/alainamstutz/hba1c-bristol/7482c0c7/), where((clinical\_events.numeric\_value>=42) & (clinical\_events.numeric\_value<=47.9)) | preDM HbA1c measure in period before index\_date in preDM range (mmol/mol): 42-47.9 |
| Diabetes-related complications (Diab. Foot/Neuro/Nephro/Ret) on or before elig\_date\_t2dm | cov\_bin\_diabetescomp | Binary | T, F | 1) Primary care (clinical\_events):  [diabetescomp\_snomed\_clinical](https://www.opencodelists.org/codelist/user/alainamstutz/diabetes-complications-bristol/33a486c0/)  2) HES APC (apcs):  [diabetescomp\_icd10](https://www.opencodelists.org/codelist/user/alainamstutz/diabetes-complications-icd10-bristol/1a95138b/) |  |

### **Table 6.** Outcome and censoring variables

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Name** | **Type** | **Definition** | **Data sources *([tpp](https://docs.opensafely.org/ehrql/reference/schemas/tpp/" \l "tpp-schema)*** [***schema***](https://docs.opensafely.org/ehrql/reference/schemas/tpp/#tpp-schema) ***in brackets*)** | **Notes** |
| First COVID-19 related hospitalization or death after elig\_date\_t2dm | out\_date\_covid19\_severe | Date | First/any covid-19 (emergency) hospitalization or death after elig\_date\_t2dm | 1) HES APC (apcs): ["U071", "U072", "U109"]  2) Emergency care (emergency\_care\_attendances):  ["1240751000000100", "1325171000000109", "1325181000000106"]  3) Death registry from ONS (ons\_death):  ["U071", "U072", "U109"] | Including clinically diagnosed COVID-19.  Search in all 25 emergency diagnosis fields.  Search in underlying\_cause\_of\_death as well as in all other 15 cause\_of\_death fields |
| First COVID-19 event after elig\_date\_t2dm | out\_date\_covid19 | Date | First covid-19 event after elig\_date\_t2dm | 1) Primary care *(clinical\_events):*  -  [covid\_primary\_care\_code](https://www.opencodelists.org/codelist/opensafely/covid-identification-in-primary-care-probable-covid-clinical-code/2020-07-16/)  - [covid\_primary\_care\_positive\_test](https://www.opencodelists.org/codelist/opensafely/covid-identification-in-primary-care-probable-covid-positive-test/2020-07-16/)  - [covid\_primary\_care\_sequelae](https://www.opencodelists.org/codelist/opensafely/covid-identification-in-primary-care-probable-covid-sequelae/2020-07-16/)  2) SGSS *(sgss\_covid\_all\_tests)*  3) HES APC *(apcs):*  [Covid\_codes\_incl\_clin\_diag](https://codelists.opensafely.org/codelist/opensafely/covid-identification/2020-06-03/), but adapted to ["U071", "U072", "U109"] to add additionally: "Multisystem inflammatory syndrome associated with COVID-19, unspecified"  4) Emergency care (emergency\_care\_attendances):  covid\_emergency -> ["1240751000000100", "1325171000000109", "1325181000000106"] | SGSS: COVID-19 tests results from SGSS (the Second Generation Surveillance System)  HES APC: including clinically diagnosed covid-19.  Adaptation based on: <https://github.com/opensafely/comparative-booster-spring2023/blob/main/analysis/codelists.py> |
| Long Covid after elig\_date\_t2dm | out\_date\_long\_fatigue | Binary; Date | First/any diagnosis after elig\_date\_t2dm | Primary care (clinical\_events):  [long\_covid\_diagnostic\_codes](https://www.opencodelists.org/codelist/opensafely/nice-managing-the-long-term-effects-of-covid-19/64f1ae69/) [long\_covid\_referral\_codes](https://www.opencodelists.org/codelist/opensafely/referral-and-signposting-for-long-covid/12d06dc0/) [long\_covid\_assessment\_codes](https://www.opencodelists.org/codelist/opensafely/assessment-instruments-and-outcome-measures-for-long-covid/79c0fa8a/)  [post\_viral\_fatigue\_codes](https://www.opencodelists.org/codelist/user/alex-walker/post-viral-syndrome/70708fd6/) | Including post viral fatigue codes, see current long covid definition/repo [here](https://github.com/opensafely/long-covid) |
| De-registration date after elig\_date\_t2dm | cens\_date\_dereg | Date | Deregistration date after elig\_date\_t2dm | Primary care (practice\_registrations) |  |
| *Long COVID signs and symptoms:* In ehrQL: search for **first code** after elig\_date\_t2dm, apply outcome window afterwards in R | | | | | |
| Breathlessness, after elig\_date\_t2dm | out\_date\_breathlessness | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [breathlessness\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-breathlessness-new/5aee78ee/) |  |
| Cough, after elig\_date\_t2dm | out\_date\_cough | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [cough\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-cough/72d8934b/) |  |
| Unexplained chest pain, after elig\_date\_t2dm | out\_date\_chest\_pain | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [chest\_pain\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-chest-pain-unexplained/0d0d5f59/) |  |
| Unexplained chest tightness, after elig\_date\_t2dm | out\_date\_chest\_tightness | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [chest\_tightness\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-chest-tightness/40b9ace1/) |  |
| Palpitations, after elig\_date\_t2dm | out\_date\_palpitations | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [palpitations\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-palpitations/27aa39ac/) |  |
| Fatigue, after elig\_date\_t2dm | out\_date\_fatigue | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [fatigue\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-fatigue/0e9ac677/) | Includes post-exertional malaise, as well as chronic fatigue syndrome |
| Fever, after elig\_date\_t2dm | out\_date\_fever | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [fever\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-fever/758b5341/) |  |
| Pain, after elig\_date\_t2dm | out\_date\_pain | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [pain\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-pain/71385a33/#full-list) | Includes generalised, muscle and joint pain |
| Cognitive impairment, after elig\_date\_t2dm | out\_date\_cog\_impair | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [cog\_impair\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-cognitive-impairment/7af0d32d/) | Includes brain fog and loss of concentration and memory loss |
| Headache, after elig\_date\_t2dm | out\_date\_headache | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [headache\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-headache/4930920c/) |  |
| Sleep disturbances, after elig\_date\_t2dm | out\_date\_sleep | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [sleep\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-sleep-disturbance/59c92016/) |  |
| Peripheral neuropathy, after elig\_date\_t2dm | out\_date\_pnp | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [pnp\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-peripheral-neuropathy/09fbfa1a/) | Includes pins and needles and numbness |
| Dizziness, after elig\_date\_t2dm | out\_date\_dizziness | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [dizziness\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-dizzy/5c7be00c/) |  |
| Delirium, after elig\_date\_t2dm | out\_date\_delirium | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [delirium\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-delirium/73fdec23/) |  |
| Mobility impairment, after elig\_date\_t2dm | out\_date\_mob\_impair | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [mob\_impair\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-mobility-impairment/62a81387/) |  |
| Visual disturbance, after elig\_date\_t2dm | out\_date\_visual | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [visual\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-visual-disturbance/1711aba2/) |  |
| Abdominal pain, after elig\_date\_t2dm | out\_date\_abdo\_pain | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [abdo\_pain\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-abdominal-pain/344e73f1/) |  |
| Nausea/Vomiting, after elig\_date\_t2dm | out\_date\_nausea\_vomiting | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [nausea\_vomiting\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-nausea-and-vomiting/30211ed7/) |  |
| Diarrhoea, after elig\_date\_t2dm | out\_date\_diarrhoea | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [diarrhoea\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-diarrhoea/7b4f7876/) |  |
| Reduced weight and loss of appetite, after elig\_date\_t2dm | out\_date\_weight\_appetite | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [weight\_appetite\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-weight-loss-and-reduced-appetite/7e02386c/) |  |
| Tinnitus, after elig\_date\_t2dm | out\_date\_tinnitus | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [tinnitus\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-tinnitus/4be35202/) |  |
| Earache, after elig\_date\_t2dm | out\_date\_earache | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [earache\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-earache/32d3decd/) |  |
| Sore throat, after elig\_date\_t2dm | out\_date\_sore\_throat | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [sore\_throat\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-sore-throat/4e8ca8fb/) |  |
| Altered smell or/and taste, after elig\_date\_t2dm | out\_date\_smell\_taste | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [smell\_taste\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-loss-of-taste-or-smell/19c46b98/) |  |
| Nasal congestion, after elig\_date\_t2dm | out\_date\_nasal | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [nasal\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-nasal-congestion/357d35c6/) |  |
| Hair loss, after elig\_date\_t2dm | out\_date\_hair\_loss | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [hair\_loss\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-hair-loss/042e6be8/) |  |
| Skin rash, after elig\_date\_t2dm | out\_date\_skin\_rash | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [skin\_rash\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-rashes/6bd2da47/) |  |
| Anxiety, after elig\_date\_t2dm | out\_date\_anxiety | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [anxiety\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-anxiety/7519dbfe/) |  |
| Depression, after elig\_date\_t2dm | out\_date\_depression | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [depression\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-depression/0e294f34/) |  |
| Post traumatic anxiety disorder, after elig\_date\_t2dm | out\_date\_ptsd | Date | First/any diagnosis after elig\_date\_t2dm, 30-356 days after a COVID diagnosis | 1) Primary care (clinical\_events):  [ptsd\_snomed](https://www.opencodelists.org/codelist/opensafely/symptoms-ptsd/64f2c537/) |  |

# 

### **Figure 3a.** Directed Acyclic Graph, all relationships

CVD = Cardiovascular disease; DAG created using [dagify()](https://github.com/opensafely/metformin_covid/blob/main/analysis/dag.R)

\* CVDs other than T2DM: BMI, Total Chol/HDL ratio, obesity, preDM, PCOS, stroke, angina,

acute myocardial infarction, other arterial embolism, venous thromboembolism events, heart failure, hypertension

\*\* non-CVD comorbidities: dementia, cancer, chronic obstructive pulmonary disease, liver disease,

chronic kidney disease, depression

\*\*\* Health seeking behaviour: Is a healthcare worker, Primary care consultation rate in previous year, Care home resident

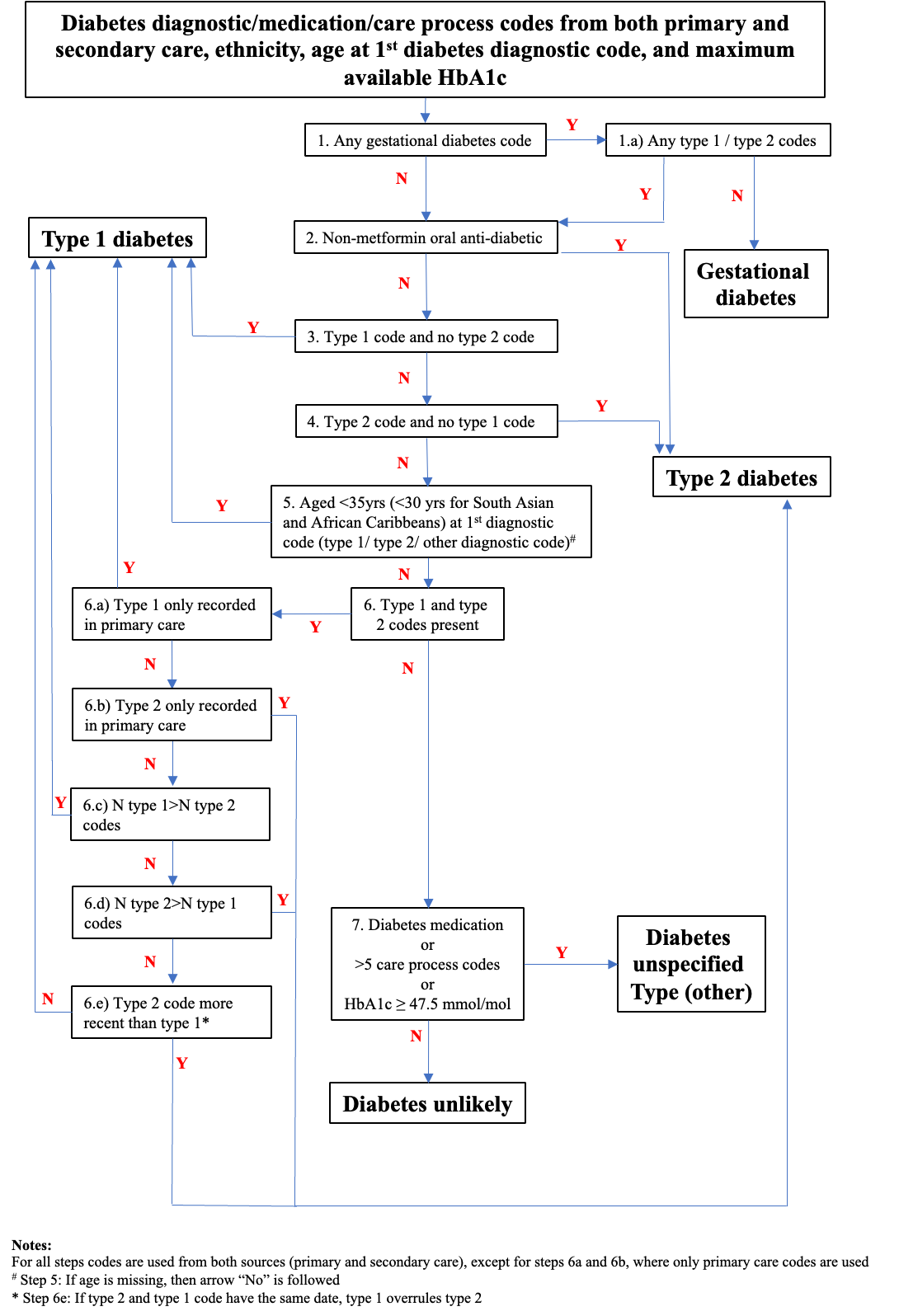
\*\*\*\* HbA1c levels and T2DM complications

### **Figure 3b.** Directed Acyclic Graph, minimal adjustment set (red)

### 

# **Appendix Figure S1:** Diabetes type adjudication algorithm

We 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 and extract these from primary care and hospital admission data. We subsequently apply a diabetes diagnostic adjudication algorithm developed for OpenSAFELY (see [here](https://github.com/opensafely-actions/diabetes-algo) and [here](https://actions.opensafely.org/actions/diabetes-algo/v0.0.5/)) and previously published.



# **References**

[1. Harding JL, Oviedo SA, Ali MK, Ofotokun I, Gander JC, Patel SA, et al. The bidirectional association between diabetes and long-COVID-19 - A systematic review. Diabetes Res Clin Pract. 2023 Jan;195:110202.](https://www.zotero.org/google-docs/?i6Wl3c)

[2. Su Y, Yuan D, Chen DG, Ng RH, Wang K, Choi J, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. Cell. 2022 Mar 3;185(5):881-895.e20.](https://www.zotero.org/google-docs/?i6Wl3c)

[3. Xie J, López-Güell K, Dedman D, Duarte-Salles T, Kolde R, López-Blasco R, et al. Incidence of post-acute COVID-19 symptoms across healthcare settings in seven countries: an international retrospective cohort study using routinely-collected data. eClinicalMedicine [Internet]. 2024 Nov 1 [cited 2025 Mar 21];77. Available from: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(24)00482-6/fulltext](https://www.zotero.org/google-docs/?i6Wl3c)

[4. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Sci Rep. 2021 Aug 9;11:16144.](https://www.zotero.org/google-docs/?i6Wl3c)

[5. Xie Y, Choi T, Al-Aly Z. Postacute Sequelae of SARS-CoV-2 Infection in the Pre-Delta, Delta, and Omicron Eras. New England Journal of Medicine. 2024 Aug 7;391(6):515–25.](https://www.zotero.org/google-docs/?i6Wl3c)

[6. Thaweethai T, Jolley SE, Karlson EW, Levitan EB, Levy B, McComsey GA, et al. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. JAMA. 2023 Jun 13;329(22):1934–46.](https://www.zotero.org/google-docs/?i6Wl3c)

[7. Gentilotti E, Górska A, Tami A, Gusinow R, Mirandola M, Rodríguez Baño J, et al. Clinical phenotypes and quality of life to define post-COVID-19 syndrome: a cluster analysis of the multinational, prospective ORCHESTRA cohort. EClinicalMedicine. 2023 Aug;62:102107.](https://www.zotero.org/google-docs/?i6Wl3c)

[8. Al-Aly Z, Agarwal A, Alwan N, Luyckx VA. Long COVID: long-term health outcomes and implications for policy and research. Nat Rev Nephrol. 2023;19(1):1–2.](https://www.zotero.org/google-docs/?i6Wl3c)

[9. Perlis RH, Trujillo KL, Safarpour A, Santillana M, Ognyanova K, Druckman J, et al. Research Letter: Association between long COVID symptoms and employment status. medRxiv. 2022 Nov 18;2022.11.17.22282452.](https://www.zotero.org/google-docs/?i6Wl3c)

[10. Cutler DM. The Costs of Long COVID. JAMA Health Forum. 2022 May 12;3(5):e221809.](https://www.zotero.org/google-docs/?i6Wl3c)

[11. Bramante CT, Huling JD, Tignanelli CJ, Buse JB, Liebovitz DM, Nicklas JM, et al. Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19. New England Journal of Medicine. 2022 Aug 17;387(7):599–610.](https://www.zotero.org/google-docs/?i6Wl3c)

[12. Reis G, Silva EA dos SM, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of early treatment with metformin on risk of emergency care and hospitalization among patients with COVID-19: The TOGETHER randomized platform clinical trial. The Lancet Regional Health – Americas [Internet]. 2022 Feb 1 [cited 2025 Mar 21];6. Available from: https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00138-1/fulltext](https://www.zotero.org/google-docs/?i6Wl3c)

[13. Bramante CT, Buse JB, Liebovitz DM, Nicklas JM, Puskarich MA, Cohen K, et al. Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial. The Lancet Infectious Diseases. 2023 Oct 1;23(10):1119–29.](https://www.zotero.org/google-docs/?i6Wl3c)

[14. Bramante CT, Beckman KB, Mehta T, Karger AB, Odde DJ, Tignanelli CJ, et al. Favorable Antiviral Effect of Metformin on SARS-CoV-2 Viral Load in a Randomized, Placebo-Controlled Clinical Trial of COVID-19. Clinical Infectious Diseases. 2024 Aug 15;79(2):354–63.](https://www.zotero.org/google-docs/?i6Wl3c)

[15. Zhan K, Weng L, Qi L, Wang L, Lin H, Fang X, et al. Effect of Antidiabetic Therapy on Clinical Outcomes of COVID-19 Patients With Type 2 Diabetes: A Systematic Review and Meta-Analysis. Ann Pharmacother. 2023 Jul;57(7):776–86.](https://www.zotero.org/google-docs/?i6Wl3c)

[16. Johnson SG, Abedian S, Stürmer T, Huling JD, Lewis V C, Buse JB, et al. Prevalent Metformin Use in Adults With Diabetes and the Incidence of Long COVID: An EHR-Based Cohort Study From the RECOVER Program. Diabetes Care. 2024 Sep 17;47(11):1930–40.](https://www.zotero.org/google-docs/?i6Wl3c)

[17. Siedner MJ, Sax PE. Repurposing Revisited: Exploring the Role of Metformin for Treatment of COVID-19. Clinical Infectious Diseases. 2024 Aug 15;79(2):292–4.](https://www.zotero.org/google-docs/?i6Wl3c)

[18. Langan SM, Schmidt SA, Wing K, Ehrenstein V, Nicholls SG, Filion KB, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). BMJ. 2018 Nov 14;363:k3532.](https://www.zotero.org/google-docs/?i6Wl3c)

[19. Hansford HJ, Cashin AG, Jones MD, Swanson SA, Islam N, Dahabreh IJ, et al. Development of the TrAnsparent ReportinG of observational studies Emulating a Target trial (TARGET) guideline. BMJ Open. 2023 Sep 12;13(9):e074626.](https://www.zotero.org/google-docs/?i6Wl3c)

[20. Hernán MA, Sterne JAC, Higgins JPT, Shrier I, Hernández-Díaz S. A Structural Description of Biases That Generate Immortal Time. Epidemiology. 2025 Jan 1;36(1):107–14.](https://www.zotero.org/google-docs/?i6Wl3c)

[21. Covid: England ending isolation laws and mass free testing. 2022 Feb 21 [cited 2025 Mar 21]; Available from: https://www.bbc.com/news/uk-60467183](https://www.zotero.org/google-docs/?i6Wl3c)

[22. du Plessis L, McCrone JT, Zarebski AE, Hill V, Ruis C, Gutierrez B, et al. Establishment and lineage dynamics of the SARS-CoV-2 epidemic in the UK. Science. 2021 Jan 8;eabf2946.](https://www.zotero.org/google-docs/?i6Wl3c)

[23. visual-summary-short-version-choosing-medicines-for-firstline-treatment-pdf-10956472094.pdf [Internet]. [cited 2025 Mar 21]. Available from: https://www.nice.org.uk/guidance/ng28/resources/visual-summary-short-version-choosing-medicines-for-firstline-treatment-pdf-10956472094](https://www.zotero.org/google-docs/?i6Wl3c)

[24. CKS is only available in the UK [Internet]. NICE. NICE; [cited 2025 Mar 21]. Available from: https://www.nice.org.uk/cks-uk-only](https://www.zotero.org/google-docs/?i6Wl3c)

[25. Thygesen JH, Tomlinson C, Hollings S, Mizani MA, Handy A, Akbari A, et al. COVID-19 trajectories among 57 million adults in England: a cohort study using electronic health records. The Lancet Digital Health. 2022 Jul 1;4(7):e542–57.](https://www.zotero.org/google-docs/?i6Wl3c)

[26. England NHS. NHS England » Commissioning guidance for post-COVID services for adults, children and young people [Internet]. [cited 2025 Mar 21]. Available from: https://www.england.nhs.uk/long-read/commissioning-guidance-for-post-covid-services-for-adults-children-and-young-people/](https://www.zotero.org/google-docs/?i6Wl3c)

[27. Henderson AD, Butler-Cole BF, Tazare J, Tomlinson LA, Marks M, Jit M, et al. Clinical coding of long COVID in primary care 2020-2023 in a cohort of 19 million adults: an OpenSAFELY analysis. EClinicalMedicine. 2024 Jun;72:102638.](https://www.zotero.org/google-docs/?i6Wl3c)

[28. COVID-19 rapid guideline: managing the long-term effects of COVID-19.](https://www.zotero.org/google-docs/?i6Wl3c)

[29. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. The Lancet Infectious Diseases. 2022 Apr;22(4):e102–7.](https://www.zotero.org/google-docs/?i6Wl3c)

[30. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK - Office for National Statistics [Internet]. [cited 2025 Mar 21]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/30march2023](https://www.zotero.org/google-docs/?i6Wl3c)

[31. Harris V, Holmes J, Gbinigie-Thompson O, Rahman NM, Richards DB, Hayward G, et al. Health outcomes 3 months and 6 months after molnupiravir treatment for COVID-19 for people at higher risk in the community (PANORAMIC): a randomised controlled trial. The Lancet Infectious Diseases. 2025 Jan 1;25(1):68–79.](https://www.zotero.org/google-docs/?i6Wl3c)