Medicines & Healthcare products Regulatory Agency

CPRD

PROTOCOL INFORMATION

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*' and justification provided
A. Study Title (Max. 255 characters) Prevalence, incidence, morbidity and mortality of early-onset type 2 diabetes.
B. Lay Summary (Max. 250 words) Type 2 diabetes is a serious condition that causes a person's blood sugar levels to become too high, often leading to various health complications including damage to the kidney, heart and blood vessels (cardio-renal complications). Traditionally, type 2 diabetes used to occur in older adults; however, in recent years it has increasingly been diagnosed in younger adults. This has been termed early-onset type 2 diabetes, and includes the diagnosis of type 2 diabetes in adults up to 40 or 50 years of age. These younger adults are likely to have other health conditions alongside diabetes, such as obesity, high blood pressure and depression. Studies have also found that when type 2 diabetes is diagnosed at a younger age, the risk of heart and kidney complications and death is higher compared to older adults diagnosed with type 2 diabetes. However, most of this research has been conducted outside the UK; therefore, we do not know how many younger adults have been diagnosed with early-onset type 2 diabetes, experienced co-occurring health conditions or diabetes-related complications or died with diabetes in the last two decades in this country. Therefore, we will do a study that investigates the following: 1. The change in number of younger adults diagnosed with early-onset type 2 diabetes between 2000 and the present day 2. The characteristics of young patients diagnosed with type 2 diabetes 3. The effect of age at type 2 diabetes diagnosis on the risk of experiencing co-occurring health conditions or death
C. Technical Summary (Max. 300 words) Data from the Clinical Practice Research Datalink (CPRD, GOLD and Aurum), linked to Hospital Episode Statistics (HES) and Office for National Statistics (ONS) data, will be used to investigate the following: 1. The characteristics of patients with early-onset type 2 diabetes at diagnosis and during disease trajectory - both cardiovascular risk factors (e.g. obesity, hypertension) and multimorbidity (cardio-renal outcomes, cancer, anxiety, depression) 2. The prevalence and incidence of early-onset type 2 diabetes between 2000 and the present day 3. The effect of age at type 2 diabetes diagnosis on the incidence of diabetes-associated complications (cardio-renal outcomes, cancer), all-cause and cause-specific mortality (cardiovascular, renal and cancer-related mortality) Poisson regression models and survival models will be used in the analysis. Analyses will adjust for key covariates including age, sex, ethnicity and socioeconomic status. Ethnicity data will be provided by linkage to HES data and socioeconomic status data will be provided by the linkage to patient level IMD data.
D. Outcomes to be measured • Prevalence and incidence of early-onset type 2 diabetes (Appendix 1 - medcodes, ICD-10 codes) (SNOMED codes will also be used in CPRD Aurum); • Characteristics of patients with early-onset type 2 diabetes at diagnosis and during disease trajectory - both cardiovascular risk factors (e.g. obesity, hypertension) and multimorbidity (cardio-renal outcomes, cancer, anxiety, depression); • Incidence of diabetes-related complications (cardio-renal outcomes, cancer) (Appendix 2-5 - medcodes and ICD-10 codes); • All-cause and cause-specific deaths (cardiovascular, renal and cancer-related deaths)

E. Objectives, Specific Aims and Rationale

Research objective

The objective of this research is to explore the effect of age at type 2 diabetes diagnosis on morbidity and mortality.

Specific aims

1. To describe patient's characteristics at diagnosis of early-onset type 2 diabetes, including clusters of comorbidities (cardio-renal outcomes, cancer, anxiety, depression) and trajectories of development of co-morbidities
2. To investigate trends in the prevalence and incidence of early-onset type 2 diabetes (aged 16-50 years at diagnosis) between 01/01/2000 and the last available dataset
3. To examine the effect of age at type 2 diabetes diagnosis on the incidence of diabetes-associated complications (cardio-renal outcomes, cancer), all-cause and cause-specific mortality (cardiovascular, renal and cancer-related mortality)

Rationale

Previous research has reported higher rates of multimorbidity, diabetes-related complications and mortality among adults with early-onset compared to later-onset type 2 diabetes. However, the epidemiology of early-onset type 2 diabetes in the UK remains largely unknown. An understanding of this is crucial in order for the development of interventions to manage and treat the needs of this growing patient group.

F. Study Background

The prevalence of type 2 diabetes among younger adults, termed "early-onset adult type 2 diabetes" is increasing, now constituting over 15% of all adults with type 2 diabetes worldwide (1, 2). Early-onset type 2 diabetes is characterised by an extreme risk phenotype, with individuals, on average, displaying a higher BMI, worse glycaemic control and a more adverse lipid profile, along with less physical activity, compared to patients with later-onset type 2 diabetes (1-4). High rates of multimorbidity have also been found among adults with early-onset type 2 diabetes, including both concordant obesity-associated conditions (e.g. hypertension and non-alcoholic fatty liver disease) and psychological conditions, such as depression (1, 3, 5, 6). The impact of early-onset type 2 diabetes is severe, resulting in an increased risk of microvascular complications (2, 7, 8) and cardiovascular/renal (cardio-renal) events (9-11) compared to adults with later-onset type 2 diabetes. The risk of cardiovascular and non-cardiovascular mortality is also higher among individuals with early-onset type 2 diabetes compared to adults diagnosed later in life (9-12). However, the most recent study investigating the epidemiology of early-onset type 2 diabetes using CPRD was conducted in 2013; therefore analysis of current incidence, morbidity and mortality rates of early-onset type 2 diabetes in the UK is crucial (13).

G. Study Type

This is a descriptive and exploratory/hypothesis generating retrospective cohort study, which aims to explore trends in the prevalence and incidence of early-onset type 2 diabetes, its characteristics, and examine the effect of age at type 2 diabetes diagnosis on the incidence of diabetes-associated complications and mortality.

H. Study Design

This is a retrospective cohort study. The exposed group will consist of all individuals diagnosed with type 2 diabetes between 01/01/2000 and the last available dataset from CPRD. These individuals will be matched to non-exposed individuals who do not have a diagnosis of type 2 diabetes between 01/01/2000 and the last available dataset from CPRD. The index date for the diabetes cohort will be the date of diagnosis of type 2 diabetes. The index date for individuals in the control group will be the same as the index date of their matched exposed cases.

I. Feasibility counts

Using database release November 2020 (GOLD) and December 2020 (Aurum), since 01/01/2000 there are 67,282 subjects with type 2 diabetes aged 18-50 in GOLD and 173,032 in Aurum.

J. Sample size considerations

Sample size calculations were conducted based on 80% power and 0.05 significance level. The table below shows the total sample size required to detect hazard ratios of 1.05, 1.10 and 1.20 (previous studies have shown associations of this magnitude or larger (9, 14, 15)).

Hazard Ratio	Sample Size Required (1:1, exp/non-exp)	Sample Size Required (1:5)	Sample Size Required (1:10)
1.05	13198 (6599/6599)	24062 (4011/20051)	40553 (3687/36866)
1.10	3,464 (1732/1732)	6393 (1066/5327)	10802 (982/9820)
1.20	954 (477/477)	1797 (300/1497)	3050 (278/2772)

Therefore, approximately 13,000 participants are sufficient to estimate a hazard ratio of 1.05 or greater comparing subjects with vs without diabetes in the scenario of 1:1 matching (exposed/non-exposed) up to 40,000 if the ratio is 1:10 (see 'definition of the study population' section below).

K. Planned use of linked data (if applicable):

Linkage to HES APC data is required for data related to diabetes-related complications/multimorbidity. HES linkage will also allow ethnicity data to be gained, a key covariate in this analysis. Patient level IMD data is required for the analysis of the effects of socioeconomic status, another key covariate in this study. Linkage to ONS death registration is required for death events and causes of death.
The findings from this study will benefit patients in England and Wales by providing a better understanding of the epidemiology of early-onset type 2 diabetes in these countries, which will subsequently allow for the development of interventions to manage and treat the specific needs of this growing patient group.

L. Definition of the Study population

For all individuals:

- Patients with availability of linkage to HES admitted patient care and ONS death registration
- Patients belong to an “up to standard” practice
- At least 12 months registration at the practice on the index date
- Patients should be of acceptable research standards
- Patients ≥16 years of aged

For exposed individuals (diabetes):

- Patients with a diagnosis of type 2 diabetes between 01/01/2000 and the last available dataset

Non-exposed individuals (non-diabetes):

- Patients without a diagnosis of type 2 diabetes between 01/01/2000 and the last available dataset. This sample will be extracted from the denominator list of patients file (given the sample size of the exposed population, to account for the possibility of non-matching and the exclusion at baseline of subjects with prevalent cardio-renal diseases and cancer, the initial ratio of exposed/non-exposed will be 1/10).

Index date:
Exposed: date of diagnosis of type 2 diabetes
Non-exposed: same as matched exposed individual

Exclusion criteria:
We will describe the characteristics at time of diagnosis of type 2 diabetes, including prevalent conditions. In the investigations of the associations between type 2 diabetes and cardio-renal outcomes and cancer, compared to subjects without diabetes, those with cardio-renal outcomes and cancer at or before the index date will be excluded.

Follow-up:
Patients followed up from index date until the earliest of the following:

- occurrence of the outcome of interest (cardio-renal outcome, cancer)
- transfer out of practice
- end of follow-up (last available dataset linkage)

M. Selection of comparison group(s) or controls

The group of non-exposed individuals will consist of individuals with no diagnosis of type 2 diabetes between 01/01/2000 and the last available dataset. Controls will be matched to exposed individuals by year of birth, sex and general practice, with an initial ratio of 1/10.

N. Exposures, Outcomes and Covariates

Exposure:
A diagnosis of type 2 diabetes at age 16-50 years old in CPRD between 01/01/2000 and the last available dataset.

Outcomes:
- Incidence of diabetes-related complications (cardio-renal outcomes, cancer)
- Cardiovascular, renal and cancer-related deaths, all-cause death

Covariates:
The following variables will be derived from CPRD and HES, for both exposed and non-exposed individuals:
- Age
- Sex
- Ethnicity (triangulated from HES database for CPRD)
- Socioeconomic status (linked patient-level Index of Multiple Deprivation data)
- Current medications
- Smoking
- BMI
- Systolic blood pressure
- Lipid levels
- Kidney function and CKD

Required for exclusion criteria:
- Prevalent cardio-renal disease (CPRD and HES)
- Prevalent cancer (CPRD and HES)

- **Data*l* Statistical Analysis**

Aim 1:* To describe patient's characteristics at diagnosis of early-onset type 2 diabetes, including cardiovascular risk factors (e.g. obesity, hypertension) and clusters of comorbidities (cardio-renal outcomes, cancer, anxiety, depression).
Cross-sectional analysis will be used to describe the characteristics of patients at diagnosis of early-onset type 2 diabetes (as outlined in the "outcomes to be measured" section); these characteristics will be compared across age at diagnosis and with the characteristics in matched subjects without type 2 diabetes. Further analysis will also be conducted to explore clusters of multimorbidity (cardio-renal outcomes, cancer, anxiety, depression) at diagnosis.

Aim 2:* To investigate trends in the prevalence and incidence of early-onset type 2 diabetes over time
The annual prevalence of early-onset type 2 diabetes (age 16-50 years) will be calculated. The incidence of early-onset type 2 diabetes will also be calculated overall and modelled by calendar year, age, sex, ethnicity and socioeconomic status. Poisson regressions, using a demographic approach whereby follow-up is split by age and calendar time (i.e. Lexis diagram), will be employed to generate crude and adjusted incidence rates for early-onset type 2 diabetes.

Aim 3:* To examine the effect of age at type 2 diabetes diagnosis on the incidence of diabetes-associated complications, all-cause and cause-specific mortality
A flexible Parmar-Royston model will be used to estimate the time to outcomes (non-fatal diabetes-related complications and cancer; cardiovascular, renal, cancer-related and all-cause deaths) comparing subjects with and without diabetes. This modelling approach allows the quantification of both the relative (i.e., hazard ratio) and absolute (i.e., rate difference) risk over time (16).

O. Plan for addressing confounding

The Poisson and Royston-Parmar models will be adjusted for all of the aforementioned covariates.

P. Plans for addressing missing data

A complete-case analysis will be used; however, the robustness of the results will be assessed using multiple imputation.

Q. Patient or user group involvement (if applicable)

As a database analysis study, no patient or user group will be involved in the current study. However, the current study will provide a comprehensive understanding of the epidemiology of early-onset type 2 diabetes in the UK, which will allow for the development of interventions to better manage and treat the needs of these patients.

R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The results will be disseminated via scientific conferences and peer-reviewed publications. No cell containing < 5 events will be reported. The data analysis is planned to be finished within 18 months of the data being extracted.

Conflict of interest statement:
No conflict of interests relevant to this application.

S. Limitations of the study design, data sources, and analytic methods

As there is no nationwide diabetes registry in the UK, the cohort will be defined using CPRD, which may not be entirely representative of subjects with diabetes in England. Additionally, some of the covariates which will be used in the analysis (e.g. BMI, smoking status, ethnicity) are likely to be incompletely recorded within CPRD.

T. References

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