DAP_Cat
Grup de Recerca Epidemiològica en Diabetis des de l´Atenció Primària

STUDY PROTOCOL

Study information

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Title	All-cause and cardio-renal-metabolic mortality in people with type 2 diabetes: a comparative international trend study.
Ethical committee protocol number	
Internal code:	DAP-CRMM-2018-02
Protocol version identifier	2.0
Date of the last version of protocol	01/04/2019
Pathology of interest	Type 2 diabetes mellitus
Research question and objectives	To examine trends in the mortality rate over time in the Catalonian population with and without diabetes extracted from the SIDIAP and to compare them with those of other countries.
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Ethical Committee	CEIC IDIAP Jordi Gol Gran Via 587 àtic 08007 Barcelona

SIGNATURE OF THE PROTOCOL

For the study titled: "*All-cause and cardio-renal-metabolic mortality in people with type 2 diabetes: a comparative international trend study.*"

I confirm that I agree to carry out the study according to the protocol.

I acknowledge being responsible for the overall conduct of the study.

I agree to carry it out personally or supervise the conduct of the study described.

I agree to ensure that all researchers and associates involved in the study are informed of their obligations and that there are mechanisms in place to ensure that the staff at each participating center receives the appropriate information throughout the study.

_____

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Directior, Department of Endocrinology & Nutrition
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LIST OF ABBREVIATIONS

Abbreviation	Definition
T2DM	Type 2 Diabetes Mellitus
INE	Instituto Nacional de Estadística/ Spanish Statistical Office
CMBD-AH	Conjunt Mínim Bàsic de Dades de l'Alta Hospitalària / Basic minimum set of data for hospital discharge
HB1Ac	Glycated hemoglobin
CVD	Cardio Vascular Diseases
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
SBP/DBP	Systolic blood pressure/ diastolic blood pressure
GLP -1	Glucagon-like peptide-1
ICD-10	International Statistical Classification of Diseases and Related Health Problems
BMI	Body mass index
ICS	Institut Català de la Salut
ECAP	Estació clínica d'atenció primària
SAP	Statistical analysis plan
MPR	Medication possession ratios
BP	Blood pressure

RESPONSIBLE PARTIES

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ABSTRACT

Main objective:

To examine trends in the mortality rate over time in the Catalonian population with and without diabetes extracted from the SIDIAP and to compare them with those of other countries.

Methodology:

Using data collected from the Information System for the development of Primary Care Research (SIDIAP) database with linkage to Hospital discharge data (CMBD), we will investigate trends in all-cause and cardio-renal-metabolic mortality in patients with type 2 diabetes in the period 2006 – 2018 and compare these with subjects without diabetes. The cohort will include incident subjects with diabetes identified within SIDIAP (exposed individuals) along with a five to one ratio matched participants without diabetes (non-exposed individuals). The outcomes are all-cause and cardio-renal-metabolic deaths. All-cause and cause-specific (cardio-renal-metabolic) mortality rates will be estimated by age, sex, and calendar time in patients with type 2 diabetes and participants without diabetes; then, the rate ratio and rate differences between people with and without diabetes will be quantified separately for each country.

Expected results:

The data obtained from this study will improve the knowledge about All-cause and cause-specific (cardio-renal-metabolic) mortality and events.

Relevance:

It will be the first study conducted under real clinical conditions of practice that analyzes the trends in the mortality rate over time in the Catalonian population with and without diabetes extracted from the SIDIAP and to compare them with those of other countries.

Keywords: Complications; glycemic control; type 2 diabetes mellitus; treatment.

AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	01/04/2019	Substantial	variables	antidiabetic treatment data and HbA1C	Inclusion of the antidiabetic treatment data (prescription and billing data) to validate the diagnosis of type 2 diabetes in SIDIAP data base. HbA1C is a important laboratory variable the outcome for validation of the registers of type 2 diabetes.
-	-	-	-	-	-

MILESTONES

Milestone	Planned date
Presentation of the study protocol to the scientific committee of SIDIAP	*07/02/2019*
Protocol approval from ethical committee	*07/03/2019*
Start of data collection, study variables operational definition	*15/04/2019*
End of data collection (data management and extraction)	*06/05/2019*
Statistical analysis	*15/05/2019*
Final study report	*30/09/2019*
Article submission for publication in open access international journal	*30/11/2019*

RATIONALE AND BACKGROUND

Rationale

In the last decades, research into diabetes has been conducted in an attempt to improve the use of medication, blood glucose monitoring and identification of risk factors. To assess the impact of these and other changes on diabetes treatment, it is important to examine trends in mortality rates over time. This research aims to use the SIDIAP data to provide a real-world view of the change in mortality rates over time in people with and without diabetes in Spain/ Catalonian area and other countries. Although a previous study [1] did analyze changes in mortality rates over time in people with and without diabetes in the UK using The Health Improvement (THIN) data until the end of 2009, there are no updated estimates, no specific investigations about cause-specific mortality, and no direct comparisons among different countries.

Background

Diabetes is associated with many health complications, including renal failure, cardiovascular diseases, etc., and these combined diseases are known as "cardio-renal-metabolic events"; diabetes is also known to increase the risk of death, and a review of prospective studies published in 2011 found that diabetes is associated with premature death from cardiovascular disease along with other diseases and is associated with an approximate 80% increase in mortality [2]. With a prevalence of diabetes of 5.4% in 2017 in the Spain/ Catalonian area, a substantial number of people face premature death. Data from recently published national study for period from 1998 to 2013 shows that mortality from diabetes mellitus in Spain decreased by 25.3% in men and by 41.4% in women. This data shows trends in terms of death by diabetes itself, but not by total or cardio vascular deaths in this population [3].

However, the treatment of diabetes has been improved significantly in the last few decades, which leads to improved survival in patients with diabetes along with longer expectancy in people without diabetes than 20 years ago. Therefore, it is unclear whether the survival improvement is the same for people with and without diabetes and whether it is different across countries.

Several observational studies have been published which examined trends in mortality rates over time in people with and without diabetes [4-11] in different populations. These all found a reduction in diabetes mortality rates over time, although with differences by study and country. One UK study used data from the THIN database from January 1996 to December 2009, evidencing a reduction in age and sex-adjusted mortality rate of 55%, and that adjusted mortality rate ratios fell from 2.14 (95% CI: 1.97, 2.32) in 1996 to 1.65 (1.57, 1.72) in 2009. However, there are no updated UK data for cause specific mortality (not available in THIN) and for more recent years; moreover, it is not clear whether differences among countries are related to dissimilar exposure/outcome definitions and assessments or, rather, due to true inherently differences in mortality rates.

Research question and objectives

Hypothesis

Previous observational cohort studies have shown declining mortality rates over time among people with diabetes mainly from the USA and Sweden. Our hypothesis is that this trend would be confirmed in several European databases.

Research objectives

Previous observational cohort studies have shown declining mortality rates over time among in people with diabetes, mainly from the USA and Sweden. Our objective is to examine trends in the mortality rate over time in the Catalonian population with and without diabetes extracted from the SIDIAP data base and to compare them with those of other countries. The exposure measure is a diagnosis of diabetes and the outcome measures are all-cause and cardio-renal-metabolic mortality. There are many baseline characteristics and lifestyle factors which could influence the risk of death, in both people with and without diabetes. Our aim is not to attempt to adjust for all these potential confounders (i.e., aetiological research), but to provide a contemporary real-world assessment of mortality rates in people with and without diabetes, and to compare them across countries (descriptive epidemiology/demography).

Primary objectives:

1. To assess trends over time in all-cause mortality between 01/01/2006 and latest capture of SIDIAP in people with type 2 diabetes and without diabetes.

2. To assess the differences and ratios in all-cause mortality rates in people with type 2 diabetes and without diabetes between 01/01/2006 and the latest capture of SIDIAP.

Secondary objectives:

3. To assess trends over time in cardio-renal-metabolic mortality between 01/01/2006 and latest capture of SIDIAP in people with type 2 diabetes and without diabetes.

4.To assess the differences and ratios in cause-specific mortality rates in people with type 2 diabetes and without diabetes between 01/01/2006 and the latest capture of SIDIAP.

3. To compare mortality rates and rate ratios trends among different countries

4. To assess trends over time in cardiometabolic renal conditions

RESEARCH METHODS

Study design

This is a retrospective cohort study. All people diagnosed with diabetes between 01/01/2006 and the latest specific capture (31/12/2018) will constitute the exposed group. Non-exposed individuals are matched to exposed individuals at five to one ratio by year of birth (± 1 year), sex, and practice (or areas). The index date for the patients with type 2 diabetes is date of first ever code of type 2 diabetes diagnosis in SIDIAP; for the control group is same calendar time +/- 1 year. People will be followed-up until death (all-cause, cardio-renal-metabolic)latest linkage to Spanish statistical office, whichever came first. Also in case of patient transfer out of SIDIAP, the follow up will end.

Feasibility counts

For SIDIAP, a feasibility count performed in December 2017 indicated that there are 587,441 individuals with diagnostic history of type 2 diabetes (codes in the Appendix) aged 30 years or over between 2006 and December 2018. As such, the total number for the current study will be larger than 587 441.

Enrollment and follow-up period

The recruitment period is defined from January 1, 2006, to December 31, 2018.

Data Linkage

Linkage to INE death registration is required for death events and causes of death. The Catalan health institute (ICS) will be responsible for linkage of the study population with death records from Spanish statistical office and will pass the anonymized data to the investigators.

Study population

For all individuals' inclusion criteria:

- At least 12 months registration in the SIDIAP on the index date

For exposed individuals (diabetes)

- Subjects with a first ever diagnosis code of type 2 diabetes between 01/01/2007 and latest capture of SIDIAP
- Aged 35 years old or older on index date

Non-exposed individuals (non-diabetes)

A control group subjects randomly sampled from the SIDIAP, after removal of all patients with diabetes, and aged 35 years old or older at index date.

The process of selection of the non-exposed group includes:

1. Exclusion of subjects born after 1971 on 01/01/2006;
2. Exclusion of patients with diabetes codes (both type 1 and type 2 diabetes);
3. Matched to exposed individuals (type 2 diabetes) at five to one ratio by year of birth (± 1 year), gender and general practice in SIDIAP prior to the cases' index date

Index date

Exposed: Date of diagnosis of type 2 diabetes

Non-exposed: same as matched exposed individuals

Exclusion criteria

- Patients with cancer or cardio-renal-metabolic disease at index date or before.

Follow-up

End of follow-up is the latest linkage to Spanish statistics office or occurrence of the outcome of interest (all-cause and cause-specific mortality), whichever comes first.

The follow-up will end also in case of patient transfer out of SIDIAP.

Variables

Exposure

A diagnosis of diabetes type 2 in SIDIAP between 01/01/2006 and 31/12/2018

Outcomes

All-cause and cardio-renal-metabolic deaths defined by INE death records.

Cardiometabolic-renal conditions.

Characteristics at the index date:

Demographics close to index date will be derived from SIDIAP, for both exposed and non-exposed subjects:

- **Age**
- **Sex**
- **Social deprivation (MEDEA)**
- **Smoking status**

Table 1: Sociodemographic variables

Variable	Role	Source	Operational definition
Age	Baseline characteristics	SIDIAP	Birth date (month/year)
Gender	Baseline characteristics	SIDIAP	Male / female
Social deprivation (MEDEA)	Baseline characteristics	SIDIAP	R- rural U1-low deprivation U2-Medium-low deprivation U3-average deprivation U4-medium high deprivation U5-high deprivation

Outcomes

Variable	Role	Source	Operational definition
All-cause Mortality	Outcome	SIDIAP	All-cause
Specific Mortality	Outcome	Instituto nacional de estadística	cardio-renal-metabolic deaths

Cardiometabolic renal conditions **variables:** heart failure, peripheral vascular diseases, atrial fibrillation chronic kidney disease, ischemic heart disease, myocardial infarction, and stroke

Table 2: Cardiometabolic renal conditions variables

Variable	Role	Source	Operational definition ICD-10
Heart failure	after index date	SIDIAP	ICD-10:I50; I50.9; I11.0; I13.2 I13.0 ICD-9: 428; 428.0; 402.01; 402.11; 402.91; 404.03; 404.13; 404.93; 404.01; 404.11; 404.91
Peripheral vascular diseases	after index date	SIDIAP	ICD-10:I73.8, I73.9 ICD-9: 443, 443.9
Atrial fibrillation	after index date	SIDIAP	ICD-10: I48 ICD-9: **427.31**
Chronic kidney disease	after index date	SIDIAP	ICD-10: D63.1;E08.2 E11.2 ; E12.2; E14.2 I12-I13.9 N02-N08.8 N15.0 N18-N18.9 Q61-Q62.8 Z94.0 ICD-9: 285.21; 249.40; 581.81; 250.40; 403.01; 403.11; 403.91; 580-589; 583.89; 585; 753.1; V42.0
Ischemic heart disease	after index date	SIDIAP	ICD10:I20 , I25 ICD9: 411, 414
Myocardial infarction	after index date	SIDIAP	ICD10: I I21;I21.0; I21.1; I21.2 I21.3; I21.4; I21.9; I22 I22.0; I22.1; I22.8; I22.9; I23; I23.0; I23.1;

Stroke	after index date	I23.2; I23.3; I23.4; I23.5; I23.6; I23.8 ICD9: 410; 429.79; 429.7 ICD10: I61 - I69 G45 ICD9: 435; 430-438

Clinical variables related to T2DM: BMI closest to index date

Table 3: Clinical variables related to T2DM

Variable	Role	Source	Operational definition ICD-10
Smoking status	Baseline characteristics	SIDIAP	YES/NO
Date of diagnosis of type 2 diabetes	Baseline characteristics	SIDIAP	
Body mass index	Baseline characteristics and after index date	SIDIAP	
Glomerular filtration	Baseline characteristics and after index date	SIDIAP	Glomerular filtration estimated by CKD-epi (mL / min / 1.73m ^ 2)
HbA1C	Baseline characteristics and after index date	SIDIAP	%
albumin / creatinine ratio	Baseline characteristics and after index date	SIDIAP	albumin / creatinine (mg / g)
Total cholesterol: **LDL cholesterol :**	Baseline characteristics and after index date	SIDIAP	Mg/dl

***baseline determinations refer to the closest value before index date in a window period of 12 months**

Required for exclusion criteria

Prevalent cancer (SIDIAP/CMBD)

Prevalent cardio-renal-metabolic disease (SIDIAP/CMBD)

Variable	Role	Source	Operational definition
Heart failure	Before index date/ on index date	SIDIAP/CMBD	ICD-10:I50; I50.9; I11.0; I13.2 I13.0 ICD-9: 428; 428.0; 402.01; 402.11; 402.91; 404.03; 404.13; 404.93; 404.01; 404.11; 404.91
Peripheral vascular diseases	Before index date/ on index date	SIDIAP/CMBD	ICD-10:I73.8, I73.9 ICD-9: 443, 443.9
Atrial fibrillation	Before index date/ on index date	SIDIAP/CMBD	ICD-10: I48 ICD-9: **427.31**
Chronic kidney disease	Before index date/ on index date	SIDIAP/CMBD	ICD-10: D63.1;E08.2 E11.2 ; E12.2; E14.2 I12-I13.9 N02-N08.8 N15.0 N18-N18.9 Q61-Q62.8 Z94.0 ICD-9: 285.21; 249.40; 581.81; 250.40; 403.01; 403.11; 403.91; 580-589; 583.89; 585; 753.1; V42.0
Ischemic heart disease	Before index date/ on index date	SIDIAP/CMBD	ICD10:I20 , I25 ICD9: 411, 414
Myocardial infarction	Before index date/ on index date	SIDIAP/CMBD	ICD10: I I21;I21.0; I21.1; I21.2 I21.3; I21.4; I21.9; I22 I22.0; I22.1; I22.8;

			I22.9; I23; I23.0; I23.1; I23.2; I23.3; I23.4; I23.5; I23.6; I23.8 ICD9: 410; 429.79; 429.7
Stroke	Before index date/ on index date	SIDIAP/CMBD	ICD10: I61 - I69 G45 ICD9: 435; 430-438
Cancer	Before index date/ on index date	SIDIAP/CMBD	CIE10:C00-C96 CIE09: 190-199

Antidiabetic treatment

Variable	Function	Source	Definition
Biguanides	Baseline characteristics and after index date	SIDIAP	A10BA02
Sulfonylureas	Baseline characteristics and after index date	SIDIAP	A10BB
Glinides	Baseline characteristics and after index date	SIDIAP	A10BX02; A10BX03
Alpha glucosidase inhibitors	Baseline characteristics and after index date	SIDIAP	A10BF
Thiazolidinediones	Baseline characteristics and after index date	SIDIAP	A10BG
Dipeptidyl peptidase 4 (DPP-4) inhibitors	Baseline characteristics and after index date	SIDIAP	A10BH
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	Baseline characteristics and after index date	SIDIAP	A10BK
Combinations of oral blood glucose lowering drugs	Baseline characteristics and after index date	SIDIAP	A10BD
Glucagon-like peptide-1 (GLP-1) analogues	Baseline characteristics and after index date	SIDIAP	A10BJ
Insulins	Baseline characteristics and after index date	SIDIAP	A10A
Other blood glucose lowering drugs, excl. insulins	Baseline characteristics and after index date	SIDIAP	A10BX

Data sources

The Information System for the development of Primary Care Research (SIDIAP) will be used to obtain the data of the people attended in the 279 Primary Care Teams of the Institut Català de la Salut (ICS) with an assigned population of 5,835,000 patients (75% of the Catalan population). The SIDIAP contains anonymized clinical information that originates from different data sources: 1) eCAP™ (electronic medical records in Primary Care of the Institut Català de la Salut [ICS]); which includes information since 2006 on sociodemographic characteristics, health conditions registered as ICD10 codes, General Practitioners' prescriptions, clinical parameters and toxic habits. 2) Laboratory data. 3) Prescriptions and their corresponding pharmacy invoice data; available since 2005contain information on all pharmaceutical products dispensed by community pharmacies with Catalan Health System prescriptions, by ATC codes.

Study size

As this is primarily a descriptive study, a sample size calculation is not required.

Data management

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks. SIDIAP database will maintain any patient-identifying information securely on site according to internal standard operating procedures.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except authorized study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM or DVD), with a periodic backup of files to tape

Data analysis

A demographic approach to the cohort study will be used, whereby follow-up will be split by age and calendar time (i.e., Lexis diagram) and a generalized linear model with a log-link and a Poisson distribution will be used to model the effect of calendar time and age. Outcome-specific and population-specific (diabetes, non-diabetes) regression models will be used to predict mortality rates for combination of age, sex, and calendar time. The predicted rates will be then used to calculate rate differences and rate ratios between people with and without diabetes. All analyses will be stratified by country, which will contribute according the specific availability by calendar time and outcome.

Matching by calendar time, age and sex will be done, due to the data set characteristics. Data from the past had been more infra registered then the recent data in the SIDIAP data base. Matching by calendar time additionally to age and sex will be done to prevent or have less systematic bias, have better robustness, more comparability as well as less confounding factors non-registered or unknown.

Exposed and matched non-exposed by age, calendar time and sex will be extracted to be more homogeneous between datasets. For data harmonization, matched sample data will be given directly to the global dataset according:

1. Ratio Exposed/Non-exposed 1/5
2. Year of birth +/- 1 year
3. Practice
4. Sex

Plan for addressing confounding

Using the statistical approach defined above, age, sex, and calendar time are covariates in the regression models.

Plans for addressing missing data

We will initially carry out a complete-case analysis; however, as a sensitivity analysis we will repeat the models with database-specific missing values imputed.

Quality control

Standard operating procedures will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. All programming written by one study analyst will be reviewed independently by a different analyst, with oversight by a senior statistician. All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo quality control review, senior scientific review, and editorial review.

Limitations of the research methods

As in Spain there are no nationwide registries of diabetes, it is necessary to define a cohort using SIDIAP, which could not be completely representative of subjects with diabetes in Spain. Moreover, the comparison group is formed by patients without diabetes who are recorded in SIDIAP; in this circumstance, they might be not truly representative of the mortality of the general population. Lastly, detailed stratified analysis of mortality trends (for example, by BMI or smoking status), although possible, would suffer from the quality of covariates recording in the SIDIAP.

This is an observational study with data obtained from an electronic database. Therefore, it is subject to certain inherent limitations in all these studies, such as collecting non-random data, missing or incomplete information and potential confounders as well as coding errors, which may negatively influence in the validity of the results and the conclusions obtained by the study.

However, thanks to the availability of a population sample and the ability to apply the matching methodology, we can configure a higher quality standard in the selection of the final participant, eliminating potential selection biases, forming more homogeneous groups, also in the distribution of missing values and infra registers.

The strengths of our study are a large number of patients included, the representativeness of the general population (SIDIAP information comes from ICS, which manages more than 80% of the Catalan population), complete demographic and clinical data records and clinical practice.

Periodic evaluations carried out on the basis of SIDIAP data make it possible to verify that the quality of the data has progressively increased in recent years (http://www.sidiap.org/index.php/en). Despite these limitations, the study has strong points such as a large number of people included, the representativeness of the general population and the real clinical practice environment.

Other aspects

Relevance, Applicability

It will be the first study conducted under real clinical conditions of practice that analyzes the trends in the mortality rate over time in the Catalonian population with and without diabetes extracted from the SIDIAP and to compare them with those of other countries.

This may eventually influence the policy landscape for CVD prevention, potentially supporting targeted population-level prevention policies that could have a measurable impact even in the short time.

PROTECTION OF HUMAN SUBJECTS

Ethical Conduct of the Study

The study will be conducted in accordance with the indications of this protocol, the regulatory requirements applicable to observational studies and with the requirements expressed in international standards related to the realization of epidemiological studies, included in the International Guidelines for Ethical Review of Epidemiological Studies (Council for the International Organizations of Medical Sciences -CIOMS-, Geneva, 2009), as well as the Declaration of Helsinki (Fortaleza, Brasil, October 2013).

This defines the principles that must be scrupulously respected by all the members involved in this investigation.

The treatment, communication, and transfer of personal data of all participating subjects will be in accordance with the provisions of Ley Orgánica 3/2018, from 5 of December 2018, about the protection of personal data and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation-GDPR).

All the information registered in the SIDIAP database is anonymous and therefore does not include any information that allows knowing the identity of the patient.

This study will be classified by the Spanish Agency for Medicines and Sanitary Products (AEMPS) and reviewed and approved by an Ethics Committee before the study can begin.

Any change in the study protocol will be reflected in writing and communicated to the researchers involved and to the Clinical Research Ethics Committee that has evaluated the study, considering it as an amendment to the protocol.

Benefit-risk evaluation

The present study has no possibility of generating any risk, as it is a retrospective study without specific use of medication, which is limited to an anonymous data registry in a database that does not allow access to the patient's personal data.

Confidentiality of the data

All the information registered in the SIDIAP database is anonymous, so it does not include any data that allows knowing the identity of the patient.

The data used in the DAP-CRMM-2018-02 study may involve special categories of personal data according to Art. 9 General Data Protection Regulation (Regulation (EU) 2016/679) (GDPR). The DAP-CRMM-2018-02 study will examine trends in the mortality rate over time in the Catalonian population with and without diabetes extracted from the SIDIAP and

their comparison with those of other countries. Accordingly, the processing of the data in the context of the DAP-CRMM-2018-02 study should be based on Art. 9(2)(i). Furthermore, the DAP-CRMM-2018-02 study is a research study that aims at answering scientific questions. The processing is necessary for scientific purposes; therefore this can also be justified based on Art. 9(2)(j) GDPR.

Use of electronic means

The extraction of data from the study will be done automatically from the database in electronic SIDIAP format.

Monitoring and final reports

A report will be made in which the descriptive data will be presented, which will be reviewed and approved by the group of researchers of the IDIAP Jordi Gol. Intermediate reports are not planned.

The report must be made on the dates provided in the calendar and a copy of it will be sent to the Clinical Research Ethics Committee that has authorized the realization of the same.

Plans for disseminating, communicating study results and publication conditions

The results will form the basis for an abstract to be submitted in scientific conferences and peer-reviewed publications. No cell containing < 5 events will be reported.

CEIC that evaluates the project

The study will be evaluated by IDIAP Jordi Gol Clinical Research Ethics Committee.

Conflict of interests

Investigators declare that they don’t have any conflict of interest.

Funding:

The University of Leicester will be responsible for funding of the project through a contract with the IDIAP Foundation - Jordi Gol.

Funding will always be independent of the results of the study.

EXPERIENCE OF THE RESEARCH TEAM

Epidemiologic Research Group in Diabetes from Primary Health Care DAP_CAT

The group is made up of family doctors from the Catalan Health Institute (ICS) with wide experience in the world of diabetes. All of them collaborate with other research groups or scientific societies such as the Spanish Diabetes Society, CAMFiC-SEMFyC, SEMERGEN, or CIBER-DM, and notably in coordination with the group GEDAPS Catalunya and the RedGEDAPS Espanya. It has also collaborated in drawing up the National Health System's diabetes strategy and the Diabetes mellitus type 2 Clinical Practice Guide for the Instituto de Salud Carlos III and the Ministry of Health. The Catalan Advisory Council on Diabetes systematically uses the group's data to prepare its recommendations. The group's main objective is the study of Diabetes mellitus type 2 in primary health care through epidemiological studies based on the exhaustive analysis of the data obtained from e-CAP (electronic clinical records), which will provide demographic and epidemiological information as well as better knowledge of metabolic control, the coexistence of other risk factors, the presence of complications, treatment compliance and therapeutic inertia.

Research Lines:

- Continuous improvement of the care quality
- Determination of cardiovascular risk in people with type 2 DM
- Evolution of prediabetes and factors influencing the onset of diabetes
- Association between cardiovascular risk factors and the presence of chronic kidney

In its research activity, the DAP_CAT group has had collaborations with different diabetes research centers at European level where joint projects have been established, among which the following stand out:

- University of York (Víctor Preckler) - costs of the DM
- Leicester Diabetes Center (Kamlesh Kunti) - glycemic control
- University of Oxford (Andrew Farmer) - adherence to treatment
- University of Oxford (Daniel Prieto) - fractures associated sl hypoglycemic treatment

According to the Impact Factors of the journals, the 5 most important publications of the group are:

- Vinegar, I; Mata, M; Hermosilla, E; Morros, R; Fine, F; Rosell, M; Castell, C; Franch, J; et al .: Control of Glycemia and Cardiovascular Risk Factors in Patients with Type 2 Diabetes in Primary Care in Catalonia (Spain). Diabetes Care. 2012; 35: 774-779. (doi: 10.2337 / dc11-1679 / - / DC1). IF 8,087

- Rodríguez-Poncelas A, Mundet-Tudurí X, Miravet-Jiménez S, Casellas A, Barrot-De la Puente JF, Franch-Nadal J, et al. Chronic Kidney Disease and Diabetic Retinopathy in Patients with Type 2 Diabetes. PLoS ONE 2016; 11 (2): e0149448. doi: 10.1371 / journal.pone.0149448 IF 3,234
- Barrot-de la Puente J, Mata-Cases M, Franch-Nadal J, Mundet-Tudurí X, Casellas A, Fernandez-Real JM, Mauricio D .: Older type 2 diabetic patients are more likely to achieve glycaemic and cardiovascular risk factors targets so younger patients: analysis of a primary care database. Int J Clin Pract. 2015; doi: 10.1111 / ijcp.12741 IF 2,566
- Mata, M; Casajuana, M; Franch, J; Hermosilla, E; Casellas, A; Castell, C; Vinegar, I; Mauricio, D; Bolibar, B .: Direct medical costs attributable to type 2 Diabetes Mellitus: a Population-Based Study in Catalonia, Spain. Eur J Health Econ. 2015; (doi: 10.1007 / s10198-015-0742-5 IF 1,774
- Baena-Diez, JM; Peñafiel, J; Subirana, I; Ramos, R; Elosua, R; Martinez-Ibañez, A; Franch-Nadal, J; Mata, M; et al. Risk of cause-specific death in individuals with diabetes mellitus: a competing risks analysis. Diabetes Care 2016 DOI: 10.2337 / dc16-0614 IF: 8,934disease in people with type 2 diabetes

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7. Gregg EW, Cheng YJ, Saydah S. Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006: findings from the National Health Interview Survey. Diabetes Care. 2012 Jun;35(6):1252-7

8. Norhammar A, Bodegard J, Nystrom T et al. Incidence, prevalence and mortality of type 2 diabetes requiring glucose-lowering treatment, and associated risks of cardiovascular complications; a nationwide study in Sweden, 2006-2013. Diabetologia. 2016 Aug;59(8):1692-701

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11. Harding JL Shaw Je Peeters et al. Mortality trends among people with type 1 and type 2 diabetes in Australia:1997-2010. Diabetes Care. 2014 Sep;37(9):2579-86

12. Rawshani A, Rawshani A, Franzén S et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2018; 379:633-644

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LIST OF TABLES

ANNEX 1. ICD-10 DIABETES CODES

Description	ICD-10
Insulin-dependent diabetes mellitus	E10.x
Non-insulin-dependent diabetes mellitus	E11.x

x:
0) Diabetic coma
1) Diabetic ketoacidosis
2) Diabetic nephropathy
3) Diabetic retinopathy
4) Diabetic neuropathy
5) Diabetic angiopathy
6) Diabetic arthropathy

Appendix 2. ICD-9 Diabetes codes

Description	ICD-9-CM
Diabetes mellitus without mention of complications	250.0x
Diabetes with ketoacidosis	250.1x
Diabetes with hyperosmolarity	250.2x
Diabetes with other coma	250.3x
Diabetes with renal manifestations	250.4x
Diabetes with ophthalmic manifestations	250.5x
Diabetes with neurological manifestation	250.6x
Diabetes with peripheral circulatory disorders	250.7x
Diabetes with other specified manifestations	250.8x
Diabetes with unspecified complications	250.9x
Diabetes – not stated as uncontrolled	250.x0 or 250.x1
Diabetes – uncontrolled	250.x2 or 250.x3

ANNEX 2. PROJECT BUDGET

ADMINISTRATIVE PROJECT MANAGEMENT SIDIAP	**COST ***
- Administrative support of the IDIAP and contract management - Evaluation of the project by the CEIC and Scientific Committee	1100 € 1000 €
Initial exploration. Extraction of data	14000 €
Data linkage with death registry of Spanish statistical office	2000 €
Subtotal Administrative Management	**18100 €**

SCIENTIFIC PROJECT MANAGEMENT – CRO	**COST***
Final report	1200€
Subtotal scientific Project management -CRO	**1200€**

Overheads (20% of the total project)	**3860 €**
TOTAL COST OF THE PROJECT *	**23160€**

* Does not include VAT