Alma Mater Studiorum – Università di Bologna

DOTTORATO DI RICERCA IN
SCIENZE MEDICHE GENERALI E SCIENZE DEI SERVIZI

Ciclo 35

Settore Concorsuale: 06/M1 - IGIENE GENERALE E APPLICATA, SCIENZE INFERMIERISTICHE E STATISTICA MEDICA

Settore Scientifico Disciplinare: MED/01 - STATISTICA MEDICA

THE BLUE SIDE OF DIABETES: ASSESSING THE IMPACT OF DEPRESSION IN PEOPLE WITH TYPE 2 DIABETES USING REAL-WORLD DATA

Presentata da: Marica Iommi

Coordinatore Dottorato
Fabio Piscaglia

Supervisore
Paola Rucci

Esame finale anno 2023

CONTENTS

ACKNOWLEDGMENTS

I would like to express my acknowledgement to Dr. Paolo Di Bartolo (*Diabetology Unit of Ravenna*), as Principal Investigator of the PSIGE-DIAB project on which my PhD thesis is based, to Dr. Mattia Altini and to Dr. Francesca Bravi (*Health Department of the Local Health Authority of Romagna*) for providing data, to Prof. Maria Pia Fantini (*Department of Biomedical and Neuromotor Sciences, University of Bologna*), as promoter of the study research.

I am extremely grateful to my supervisor Prof. Paola Rucci for her invaluable guidance, time, support and encouragement, allowing me to grow as a research scientist. This endeavour would not have been possible without her.

My sincere thanks go to my colleagues Ph.D. Rossella Messina and M.S. Simona Rosa, not only for the brilliant comments and suggestions about the research, but also for the cherished time spent together in and out of the office.

I would like to thank my friends Cristina and Monica: beside the continuous sharing of statistical knowledge, their friendship kept my motivation high during this journey.

Finally, I would be remiss in not mentioning my parents, Rosella and Demetrio, my siblings, Elisa and Gianluca, and my life partner, Leonardo. Their endless love and emotional support have always reassured me throughout my studies.

ABSTRACT

In the framework of PSIGE-DIAB project, this thesis aims to assess the impact of depression in people with type 2 diabetes.

Using Healthcare Utilization Databases, I estimated in a large population-based cohort with type 2 diabetes the incidence of depression over 10 year-period, identified the demographic and clinical predictors of depression, and sought to determine the extent to which depression is a risk factor for acute and long-term complications of diabetes and mortality. In the context of COVID-19 pandemic, I evaluated whether the presence of a history of depression in people with type 2 diabetes increased the Emergency Department access rate for diabetes-related complications, and I investigated changes in the incidence of depression during the first year of the pandemic in people with type 2 diabetes.

Findings from the first study indicated that developing depression was associated with being a woman, being over 65 years, living in rural areas, having insulin as initial diabetes medication and having comorbid conditions; the study also confirmed that depression was associated with an increased risk for acute and long-term diabetes complications and all-cause mortality.

The second observational study showed a higher rate of Emergency Department access for diabetes-related complications during the COVID-19 pandemic in people with type 2 diabetes and a history of depression than in those without a history of depression, similar to what was observed in a pre-pandemic period.

As shown in the third population-based study, the incidence of depression decreased in 2020 compared to 2019, mainly during the first and the second waves of the COVID-19 pandemic, when people with diabetes probably had difficulty reaching healthcare services.

This new real-world evidence will help healthcare professionals identify timely patients at high risk of developing depression and promote preventive strategies into diabetes care pathways. Lastly, health policy makers and physicians will benefit from new evidence of the effects of the COVID-19 pandemic on depression in people with type 2 diabetes to ensure a high level of care during crisis periods.

LIST OF TABLES, FIGURES AND SUPPLEMENTARY MATERIALS

Figure 5 - Comparison of the 2019 and 2020 incidence rate of depression in people with diabetes stratified by the four subperiods.

Supplementary material 1 - ICD-9-CM diagnosis and surgery procedure codes of acute and long-term diabetes complications.

Supplementary material 2 - ICD-9-CM diagnosis codes of depression.

Supplementary material 3 - ICD-9-CM diagnosis and ATC codes of comorbid conditions.

Supplementary material 4 - Initial antidepressant therapy of patients with diabetes and depression (n=5,146).

Supplementary material 5 – Additional analysis conducted to compare the incidence of different diseases or conditions in people with type 2 diabetes in four subperiods between 2020 and 2019.

ABBREVIATIONS

LHA: Local Health Authority

HUD: Healthcare Utilization Databases

COVID-19: Coronavirus disease 2019

ED: Emergency Department

RWD: Real-world data

NHS: National Health Service

HDR: Hospital Discharge Records

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

MHIS: Mental Health Information System

RMHC: Residential Mental Healthcare

ATC: Anatomical Therapeutic Chemical classification system

GLM: Glucose-Lowering Medication

IQR: Interquartile Range

SD: Standard Deviation

Dep: group of patients with type 2 diabetes and depression

Non-Dep: group of patients with type 2 diabetes without depression

95% CI: 95% Confidence Interval

HR: Hazard Ratio

SPSS: Statistical Package for the Social Sciences

SSRIs: Selective Serotonin Reuptake Inhibitors

TCAs: Tricyclic antidepressants

SNRIs: Serotonin–norepinephrine reuptake inhibitors

IR: Incidence Rate

PY: Person-years

IRR: Incidence Rate Ratio

1. INTRODUCTION

This thesis describes aims, the methods and results of PSIGE-DIAB project (original title "*Impatto dei disturbi PSIchici sulla GEstione del DIABete pre e post COVID-19 nell'AUSL Romagna: studio di coorte retrospettivo basato su flussi ammistrativi correnti*"[1],), a collaborative project between the Local Health Authority of Romagna, the Department of Biomedical and Neuromotor Sciences of the University of Bologna, and the Diabetology Unit of Ravenna.

The aims of the thesis project were 1) to estimate the incidence of depression over 10 years since the diagnosis of type 2 diabetes, 2) to identify the demographic and clinical predictors of depression, and 3) to determine the extent to which depression is a risk factor for acute and long-term complications of diabetes and mortality.

Two additional objectives were explored in the context of COVID-19 pandemic: 4) to evaluate whether a history of depression in people with type 2 diabetes increases the number of Emergency Department accesses for acute and long-term diabetes-related complications during the COVID-19 pandemic, and 5) to investigate changes in the incidence of depression in people with type 2 diabetes during the first year of the pandemic compared to a pre-pandemic period.

The data sources used to meet these objectives were the Healthcare Utilization Databases. The remainder of the thesis is structured as follows:

Paragraph 2 contains a description of the Healthcare Utilization Databases, providing an overview of their implementation and use in the Italian National Health Service.

[1] English translation: "Impact of mental disorders on the management of diabetes before and after COVID-19 in the Local Health Authority of Romagna: retrospective cohort study based on administrative databases"

Paragraph 3 illustrates the methods and results of the retrospective study on the incidence and on the short/ long-term effects of depression in patients with type 2 diabetes, published by Messina et al. [1].

Paragraph 4 describes the methods and results of the study on Emergency Department access patterns during COVID-19 pandemic in people with type 2 diabetes, according to the presence or absence of a history of depression, published by Messina et al. [2].

Paragraph 5 shows the study estimating the incidence of depression during COVID-19 in people with type 2 diabetes.

Lastly, the Conclusion paragraph summarizes the real-world evidence on the impact of depression in people with diabetes derived from the entire project.

2. Real-world data and Healthcare Utilization Databases

Real-world data (RWD) has been defined "an umbrella term for different types of data that are not collected in conventional randomised controlled trials. RWD in the healthcare sector comes from various sources and includes patient data, data from clinicians, hospital data, data from payers and social data"[3]. A consensus on the definition of RWD is still lacking, anyway most of the definitions agree in defining RWD as data collected in a non-randomized controlled trial setting [4].

Over the past decades, clinical and pharmaco-epidemiological studies have increasingly used RWD due to the digitalization of health information, especially administrative data related to the utilization of health services where financial and clinical information is routinely and continuously collected in large databases (Healthcare Utilization Databases, HUDs) [5]. There are several advantages of using HUDs: their immediacy to be analyzed at low cost, the wide geographical coverage, the long-term follow-up and the good detail of the clinical history of each individual, the good reliability in reflecting the state of clinical practice in the general population [6]. Therefore, HUDs can be used to estimate the incidence and prevalence of chronic and acute conditions [7], as well as rare diseases [8], to measure the comorbidity of the general population [9], [10], to conduct pharmaco-epidemiological investigations [11], to assess the healthcare pathway performance and costs [12]–[14].

Still, HUDs do not include information on the individual's lifestyle, social and economic status. Thus, observational studies based on HUDs may be affected by unmeasurable bias related to the lack of this kind of information. Nevertheless, these limitations can be minimized by a careful study design and adjustment in statistical analyses [15].

Italian residents have universal and equal access to the National Health Service (NHS), and all individual contacts and health service provisions are recorded in the computerized information systems of 21 Italian regions and autonomous provinces. Such information is then sent to the Ministry of Health and gathered into the "*Nuovo Sistema Informativo Sanitario*"[2], NSIS, to ensure uniformity in the collection and comparability of information [16].

The information assets currently available in the NSIS consists of a set of interconnectable HUDs which detect organizational and economic aspects of the NHS facilities, centered on the individual. In particular, to capture the complexity of care in citizens who need multiple levels of assistance, HUDs are designed to monitor the healthcare services provided in different care settings, to identify the care pathways and the healthcare resources utilization of the NHS, and to carry out integrated and cross-sectional analyses at the various "*Livelli Essenziali di Assistenza*"[3], LEA. To date, the HUDs of the NSIS cover 85% of the services included in the LEA [16].

Emilia-Romagna is one of the regions with the most advanced health information system which includes over 20 different individual level HUDs, such as hospital discharges, outpatient care, residential care and hospice, home healthcare, mental healthcare, emergency care, drug dispensing databases, childbirth assistance, mortality registries, and screening registries [17].

These HUDs collect each contact of the population residing in Emilia-Romagna with the NHS, even those services provided in health facilities outside the regional borders (passive interregional mobility). HUDs have been implemented in a SAS 9.3

[2] English translation: "New Health Information System"
[3] English translation: "Essential Levels of Assistance"

environment and reside on a regional server with the Windows operating system; access to the anonymized HUDs is possible via individual credentials to users enabled by the Regional Health Agency. The record-linkage of the HUDs is possible through the unique identifier code assigned by the Regional Health Agency to residents, which does not allow to trace the patient's identity, in conformity with the regulations on data management with the Italian law on privacy (Legislation Decree 196/2003 amended by Legislation Decree 101/2018).

3. Is it time to consider depression as a major complication of type 2 diabetes?

3.1 Introduction

Type 2 diabetes, like other chronic conditions requiring intensive self-care management, is associated with high levels of distress, affecting the physical and psychological well-being and possibly leading to depression [18]. Indeed, depression is a common comorbidity among people with type 2 diabetes [19], and its incidence seems higher in the first year after glucose-lowering treatment initiation [20]. However, the relationship between type 2 diabetes and depression might be bidirectional, even if the underlying mechanisms are still unclear. Type 2 diabetes could lead to the development of depression due to the sense of loss of health and effectiveness, to behavioral and social factors [21], to biological factors such as insulin resistance, systemic inflammation, alterations in the hypothalamic-pituitary-adrenal axis [22]. At the same time, there is little evidence of a shared genetic vulnerability between depression and diabetes [22]. Despite good evidence supporting the role of diabetes as a trigger of the onset or worsening of depressive symptoms [23], [24], there is less convincing evidence that depression is a risk factor for the onset of type 2 diabetes. Depression may impact self-care and lifestyle behaviors, particularly related to diet and physical activity [25], [26], even if there is uncertain evidence that antidepressants reduce the risk of developing diabetes in normoglycemic individuals [22].

Moreover, clinical data on depression treatment suggest that improvement in depressive symptoms correlates with improved glycemic control in people with type 2 diabetes [22].

A significantly higher risk of developing depression in people with diabetes than in the general population has been reported [19], although the prevalence of depression in type 2 diabetes varies according to the assessment method [27]. In a systematic review conducted in 2019, almost one in four adults with type 2 diabetes experience depressive symptoms [24]. In a comprehensive meta-analysis of studies [28] where the diagnosis of depression was made using standardized diagnostic instruments, the prevalence of major depressive disorder in type 2 diabetes was estimated to be 14.5%, with an odds ratio of 1.7 for people with type 2 diabetes compared to the general population.

In people with diabetes, depression may negatively impact self-care, diabetes management, self-efficacy, cognitive outcomes [29]–[31], and medication adherence [32], [33], increasing the risk of developing diabetes complications [34], [35] and activating an additional vicious cycle [21]. Depression can affect all the aspects of quality of life, included sexual activity [36]. To this proposal, it is important to take into account depression and sexual dysfunctions in people with diabetes, as these mutually influence each other [37]–[39].

Several studies reported that depression or depressive symptoms in people with type 2 diabetes are associated with increased healthcare expenditure, cardiovascular diseases, and mortality [35], [40], [41].

A meta-analysis found that depression is associated with a 1.5-fold increased mortality risk in patients with diabetes [42]. However, the impact of depression on mortality varies among studies [35], [41]–[45], and it is still unclear whether the increased occurrence of diabetes complications drives this association [46]. Depression seems unrelated to microvascular complications or higher glycemia levels [47], while it has been linked to an increased risk for cardiovascular complications

and all-cause mortality, but not with cardiovascular mortality or diabetes-related mortality [35]. On the other hand, a recent study from Quebec on individuals with type 2 diabetes newly treated with glucose-lowering drugs, showed that depression was consistently associated with a higher risk of all-cause and cardiovascular-related mortality, regardless of the level of adherence to medications and age [44]. The excess mortality may be partially explained by the association between depression and the increased risk of cardiac events and cardiovascular-related mortality [43]. No evidence from the literature is available on the effect of depression on acute complications in type 2 diabetes.

One of the drawbacks of the studies investigating the association between diabetes and depression and the impact of depression on diabetes complications is that the temporal sequence of events is not taken into account. To address this limitation, the association between diabetes and depression might be investigated using real-world data, in particular HUDs, in the attempt to determine the temporal sequence of depression and complications among new cases with type 2 diabetes.

Specifically, the aims of this study were to estimate the incidence and clinical predictors of depression over 10 years from the diagnosis of type 2 diabetes, and to determine the extent to which depression constitutes a risk factor for acute and long-term complications of diabetes and mortality.

3.2 Methods

3.2.1 Study Design and target population

In this population-based observational prospective study, the target population consisted of people with type 2 diabetes, aged 15 years or older, living in the Local Health Authority (LHA) of Romagna. The LHA of Romagna has a catchment area

of about 1.1 million people. The study period was between January 1, 2008, and October 31, 2020.

3.2.2 Data sources

The secondary data sources used for the present study were the HUDs of the LHA of Romagna, including:

- Hospital Discharge Records (HDR) database, which contains demographic characteristics, admissions and discharge dates, discharge status, the primary and up to five secondary diagnoses and up to six procedures/interventions, identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM coding system);
- Mental Health Information System (MHIS), which comprises demographic characteristics and the ICD-9-CM diagnoses of all the adults who have at least one contact with the community mental health centres;
- Residential Mental Healthcare (RMHC), which includes information on patients, discharged from no-profit or accredited private facilities, notably admission and discharge dates, principal diagnosis, and destination at discharge;
- Pharmaceutical databases, containing prescriptions and dispensation of drugs reimbursed by the healthcare system and prescribed by the general practitioner or a specialist, or directly delivered by the hospital pharmacies. These databases contain information on the patient's sex and age, prescriptions (substance name, Anatomical Therapeutic Chemical, ATC, classification system-V.2013, date of prescription filling, and number of packages), and prescribers;
- Regional mortality register, which was used to detect the patient's date of death.

These HUDs were linked through a deterministic record-linkage procedure using the unique anonymized identification code, generated by regional authorities and assigned to each NHS beneficiary.

The study was conducted according to the guidelines of the Declaration of Helsinki; the Ethics Committee of the Romagna Local Health Authority approved the study procedures (registration number: 9502/2020, 14/12/2020). This study was carried out in conformity with the regulations on data management with the Italian law on privacy (Legislation Decree 196/2003 amended by Legislation Decree 101/2018). The informed consent was not required because data were analysed anonymously.

3.2.3 Case definition of diabetes and of depression

Beneficiaries of the NHS aged 15 years or older and living in the LHA of Romagna were classified as patients with type 2 diabetes if they had at least one hospitalization with a primary or secondary diagnosis of diabetes (ICD-9-CM: 250.xx) and at least one prescription of Glucose-Lowering Medication (GLM) (ATC: A10), or at least three prescriptions of GLM in distinct periods during the period 01/01/2008 and 31/10/2017. The date of the first health service contact for type 2 diabetes was used as a proxy of disease diagnosis (date of cohort entry).

To identify incident cases, all patients with at least one hospitalization or a GLM prescription in the three years before the date of cohort entry were excluded (wash-out period 2005-2008). Uncertain cases of type 2 diabetes, such as patients with insulin as initial and unique treatment, and women diagnosed with gestational diabetes were excluded [48]. Patients with hospitalizations for the outcomes investigated (Supplementary material 1) and patients with hospitalizations for

depression or prescriptions of antidepressants in the three years before the diabetes diagnosis were further excluded.

The presence of depression was ascertained using the following criteria: at least 1 prescription of antidepressant drugs (ATC: N06A), or at least 1 hospitalization (sources HDR, RMHD), or at least 1 outpatient service (source RMHC) with ICD-9-CM diagnosis codes for depression (Supplementary material 2). The first date of health service contact for depression (inpatient, outpatient or drug prescription) was considered as the index depression date.

3.2.4 Comorbid conditions

The presence of comorbid conditions in the three years preceding the onset of diabetes, was determined for each patient.

The comorbid conditions considered were other mental disorders (psychosis, bipolar disorders, anxiety/obsessive-compulsive disorder, substance disorders), neurological disorders (epilepsy, dementia, Parkinson's disease), hypothyroidism, respiratory illness (chronic obstructive pulmonary disease, asthma), and cancer. The list of ICD-9-CM/ATC codes was determined using consolidated comorbidity indices, such as Elixhauser Comorbidity Index [49] and Modified-Chronic Disease Score [9], and combining multiple secondary data sources (Supplementary material 3).

3.2.5 Study outcomes

The new cases of depression in patients with type 2 diabetes were observed over the study period.

Acute complications of diabetes (Supplementary material 1) occurring within the first three years of follow-up, long-term complications of diabetes and all-cause deaths

occurring within ten years of diabetes onset (Supplementary material 1) were evaluated as outcomes. Complications were retrieved from the HDRs database; all-cause mortality was obtained by collecting the date of death from the regional mortality register.

3.2.6 Statistical analysis

Demographic and clinical characteristics of patients who developed depression (Dep) during 10 years of follow-up and those who did not develop depression (Non-Dep) were summarized using absolute frequencies and percentages, means and standard deviations (SD) or medians and interquartile range (IQR), as appropriate.

The ten-year cumulative probability of developing depression was estimated using Kaplan-Meier product limit estimator, with 95% Confidence Interval (95% CI); patients were followed-up from the date of cohort entry to index depression date, date of death, or to 10 years from date of cohort entry, whichever came first. Multiple Cox regression models were used to identify the predictors of depression, estimating the Hazard Ratio (HR) and its 95% CI. The possible predictors considered were sex, age (categorized as ≤35, 36-55, 56-65, 66-75, >75 years), urbanization level of the municipality of residence, presence of comorbid conditions, and initial diabetes medication in the first month (only 1 oral GLM, 2 or more oral GLM, only insulin, insulin plus oral GLM). Using the Eurostat's Degree of Urbanisation classification system (revised definition, 2014), the municipalities where the patients lived were subdivided into rural areas (alternative name: sparsely populated areas), medium-density area (towns or suburbs), and high-density area (cities).

Survival analysis was used to estimate the complications and mortality outcomes, using the Kaplan-Meier product limit estimator, with 95% CI.

When evaluating acute complications, patients were followed-up from the date of cohort entry to the earliest date between the outcome of interest, all-cause death, or after 3 years from date of cohort entry. In the analysis of the other two outcomes (long-term complication, all-cause mortality), patients' follow-up started at diabetes onset and ended at the occurrence of the outcome of interest, or after 10 years from date of cohort entry, whichever came first.

Unadjusted Cox proportional-hazard model was used to investigate whether depression was associated with complications and mortality; subsequently, adjusted analyses were performed using sex, age group, presence of comorbid conditions, and initial diabetes medication as covariates. The proportional-hazard assumption underlying these models was tested using Schoenfeld residuals. When adjusting covariates did not meet the proportional-hazard assumption, they were used as strata of the baseline hazard. Results are expressed as HR with 95% CI.

Patients were considered exposed to depression only if they developed depression before the outcomes or before the end of follow-up. In the Cox regression models, depression was included as a time-dependent covariate to take into account that its onset could take place at different times during the follow-up, avoiding immortal time bias.

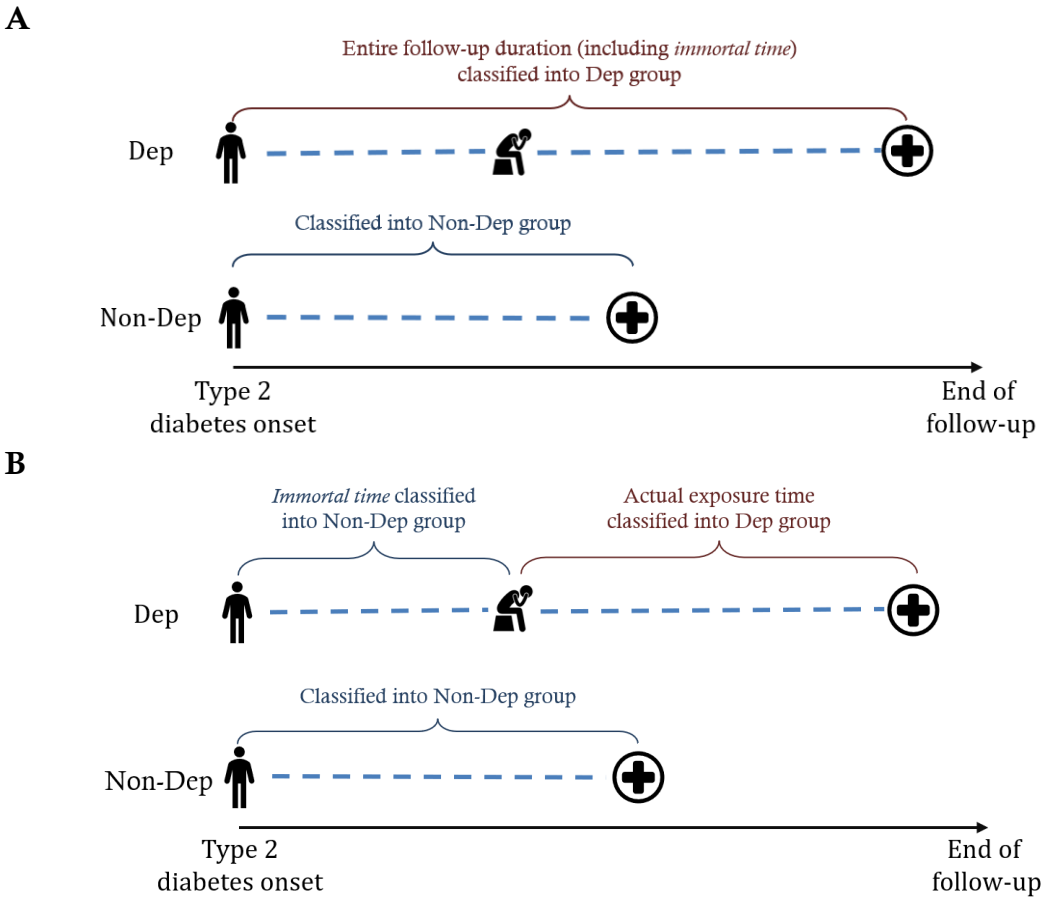
For all tests, significance was set as $p<0.05$; statistical analyses were performed using IBM Statistical Package for the Social Sciences-SPSS version 25.0 and Stata 15.

3.2.7 Immortal time bias

The immortal time bias occurs whenever the period between entry into the cohort and the exposure of interest is classified as a period at risk of experiencing the outcome even if, by study design, during this period the exposed individuals cannot

experience the outcome (the period is defined as "immortal", Figure 1A) [50]. This bias is typical of pharmacoepidemiology studies, where the apparent advantage of a therapy is artificially generated by the time lag between entry into the study and the assignment of a given therapy. Similarly, in this study, there is a time lag between cohort entry (type 2 diabetes onset) and the exposure (diagnosis of depression) during which the individual is effectively "immortal" and cannot experience the outcomes of interest.

Figure 1 – Immortal time bias misclassification (A) and correction using the time-dependent variable approach (B).



To handle immortal time bias, a valid and common statistical approach is to treat the exposure as a time-dependent variable [51], i.e. a variable whose value may change

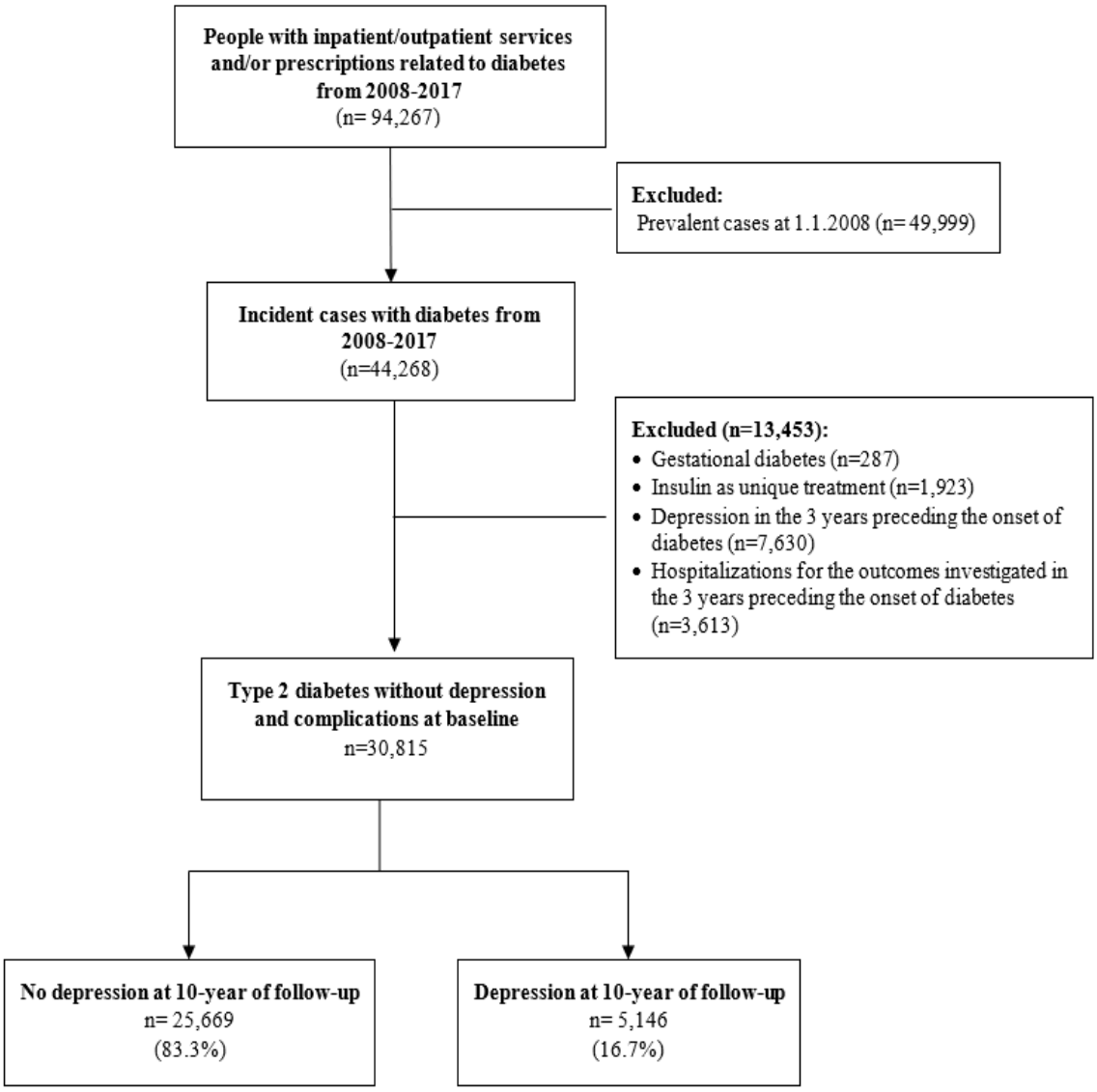
over time, when the individual actually experiences the exposure during the follow-up. Immortal time bias is managed by splitting the follow-up into time periods according to actual exposure status, so that all individuals contribute person-time to different exposure categories.

In this study, individuals with type 2 diabetes who develop depression during the follow-up were assigned to the unexposed population (Non-Dep group) until the first diagnosis of depression, after which they were assigned to the exposed population (Dep group) (Figure 1B).

3.1 Results

From January 1, 2008, to October 31, 2017, people with hospitalizations or drug prescriptions related to diabetes identified were 94,267, of whom 44,268 were incident cases. After excluding 13,453 patients, the study cohort comprised 30,815 patients with type 2 diabetes (Figure 2). During 10 years of follow-up, 5,146 (16.7%) patients received a depression diagnosis or a prescription for an antidepressant drug after diabetes diagnosis (Dep group). Selective Serotonin Reuptake Inhibitors (SSRIs) was the initial antidepressant therapy in 56.8% of patients with diabetes and depression, while 1.3% of patients with diabetes and depression did not receive antidepressant drugs (see Supplementary Table 4).

Figure 2 - Flow-chart of the study cohort selection.



3.3.1 Incidence and clinical predictors of depression

The incidence of depression over 10 years from the diagnosis of type 2 diabetes was 7.1 cases per 100,000 person-days (26.1 cases per 1,000 person-years).

The ten-year cumulative probability of developing depression was 21.7% (95% CI 21.2%-22.3%); among patients in the Dep group, the onset of depression occurred on average 3.4 years after the diagnosis of diabetes (median=2.8 years; IQR=1.1-5.6). About 2.5% of the cohort developed depression within six months from diabetes onset.

Table 1 shows the baseline sociodemographic and clinical characteristics of the overall study population and of the Dep and Non-Dep groups; the results of the multiple Cox regression model used to estimate the risk of developing depression are also shown in Table 1.

Table 1 - Sociodemographic and clinical characteristics of the study cohort and their association with depression (multiple Cox regression model).

Sociodemographic and clinical characteristics	**Total (n=30,815)**		**Non-Dep (n=25,669)**		**Dep (n=5,146)**		**Multiple Cox regression model**	
	n	*%*	*N*	*%*	*n*	*%*	*HR*	*95% CI*
Sex								
Female	13,444	43.6%	10,615	41.4%	2,829	55.0%	1.49	(1.41; 1.58)
Male	17,371	56.4%	15,054	58.6%	2,317	45.0%	Ref.	
Age class								
≤35	1,049	3.4%	924	3.6%	125	2.4%	0.83	(0.69; 1.00)
36-55	7,782	25.3%	6,790	26.5%	992	19.3%	1.00	(0.92; 1.09)
56-65	8,332	27.0%	7,269	28.3%	1,063	20.7%	Ref.	
66-75	8,072	26.2%	6,614	25.8%	1,458	28.3%	1.45	(1.34; 1.57)
>75	5,580	18.1%	4,072	15.9%	1,508	29.3%	2.62	(2.42; 2.84)
Degree of urbanization								
High-density area	11,715	38.0%	9,816	38.2%	1,899	36.9%	Ref.	
Medium-density area	15,019	48.7%	12,525	48.8%	2,494	48.5%	1.04	(0.98; 1.10)
Rural area	4,081	13.2%	3,328	13.0%	753	14.6%	1.15	(1.06; 1.26)
Initial medications								
1 oral GLM	25,728	83.5%	21,379	83.3%	4,349	84.5%	Ref.	
2 or more oral GLM	2,462	8.0%	2,066	8.0%	396	7.7%	1.04	(0.93; 1.14)
Insulin	1,214	3.9%	1,026	4.0%	188	3.7%	1.15	(0.94; 1.27)
Insulin plus oral GLM	1,411	4.6%	1,198	4.7%	213	4.1%	1.17	(1.02; 1.34)
Comorbid conditions								
Other mental disorders	386	1.3%	283	1.1%	103	2.0%	1.78	(1.45; 2.19)
Neurological disorders	498	1.6%	343	1.3%	155	3.0%	1.90	(1.61; 2.26)
Hypothyroidism	2,332	7.6%	1,858	7.2%	474	9.2%	1.03	(0.93; 1.13)
Respiratory illness	2,789	9.1%	2,206	8.6%	583	11.3%	1.26	(1.16; 1.38)
Cancer	1,536	5.0%	1,233	4.8%	303	5.9%	1.33	(1.19; 1.50)

Non-Dep: people with type 2 diabetes without depression**; Dep:** people with type 2 diabetes with depression**;**
GLM: Glucose-Lowering Medications; **Ref**: reference category; **HR**: Hazard Ratio; **95%CI**: Confidence interval 95%

The risk of developing depression was significantly higher in females than males (HR=1.49, 95% CI 1.41-1.58). Compared to the age class 56-65, being in the age class 66-75 or in the age class >75 increased the risk of developing depression by 1.45 and

2.62-fold, respectively (66-75 age class: 95% CI 1.34-1.57; >75 age class: 95% CI 2.42-2.84). In patients living in rural areas the risk of developing depression increased by 15% compared to patients living in high-density areas (95% CI 1.06-1.26). Patients with an initial diabetes medication with insulin plus oral GLMs were at higher risk of developing of depression than patients with only one GLM as initial diabetes medication (HR=1.17, 95% CI 1.02-1.34).

Patients with comorbid conditions like other mental disorders (HR=1.78, 95% CI 1.45-2.19), neurological disorders (HR=1.90, 95% CI 1.61-2.26), respiratory illness (HR=1.26, 95% CI 1.16-1.38) and cancer (HR=1.33, 95% CI 1.19-1.50), had a higher risk of developing depression.

3.3.2 Depression and acute complications over three years

Over three years, 162 patients (0.5%) experienced acute complications, after a median of 15.2 months. Of these, 18 (11.1%) had depression.

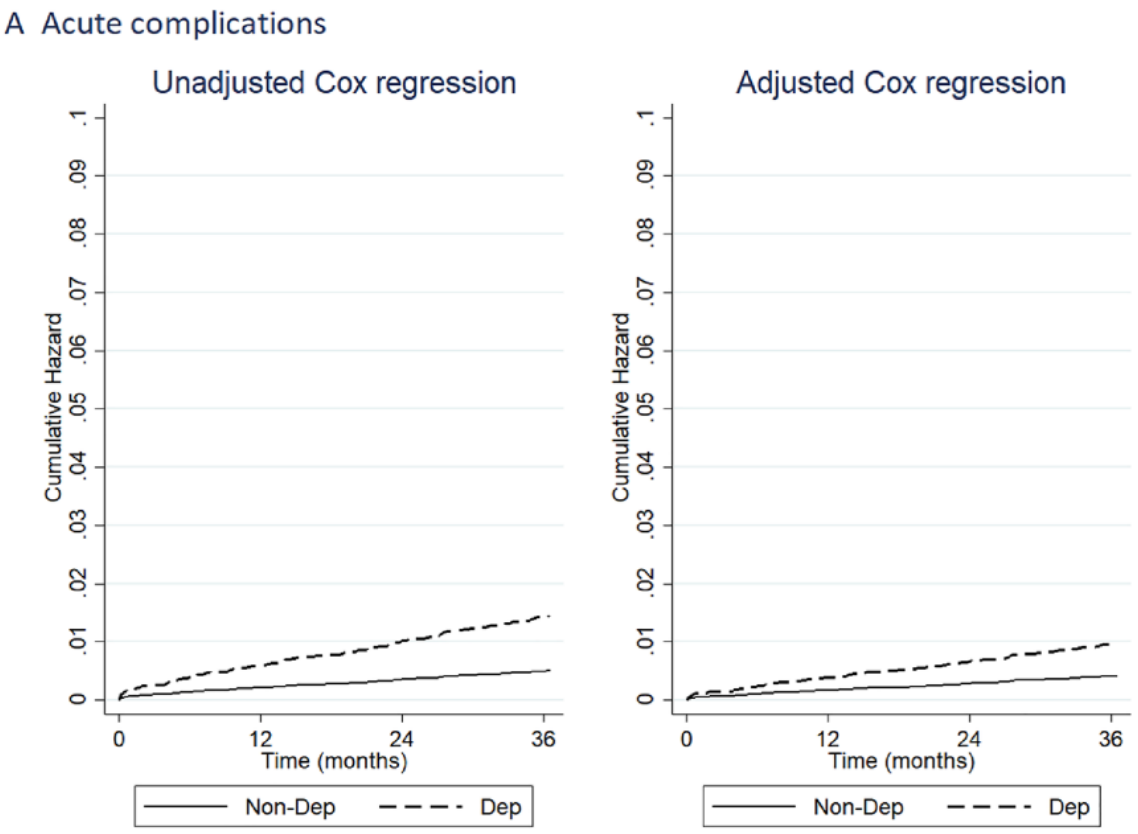
Results from univariate Cox-regression analysis indicate that depression was associated with an almost 3-fold risk of acute complications (HR=2.88, 95% CI 1.75-4.74), and after adjusting for covariates the risk was only slightly attenuated (HR=2.33, 95% CI 1.39-3.92). The cumulative hazard function by Dep and Non-Dep groups are shown in Figure 3 A.

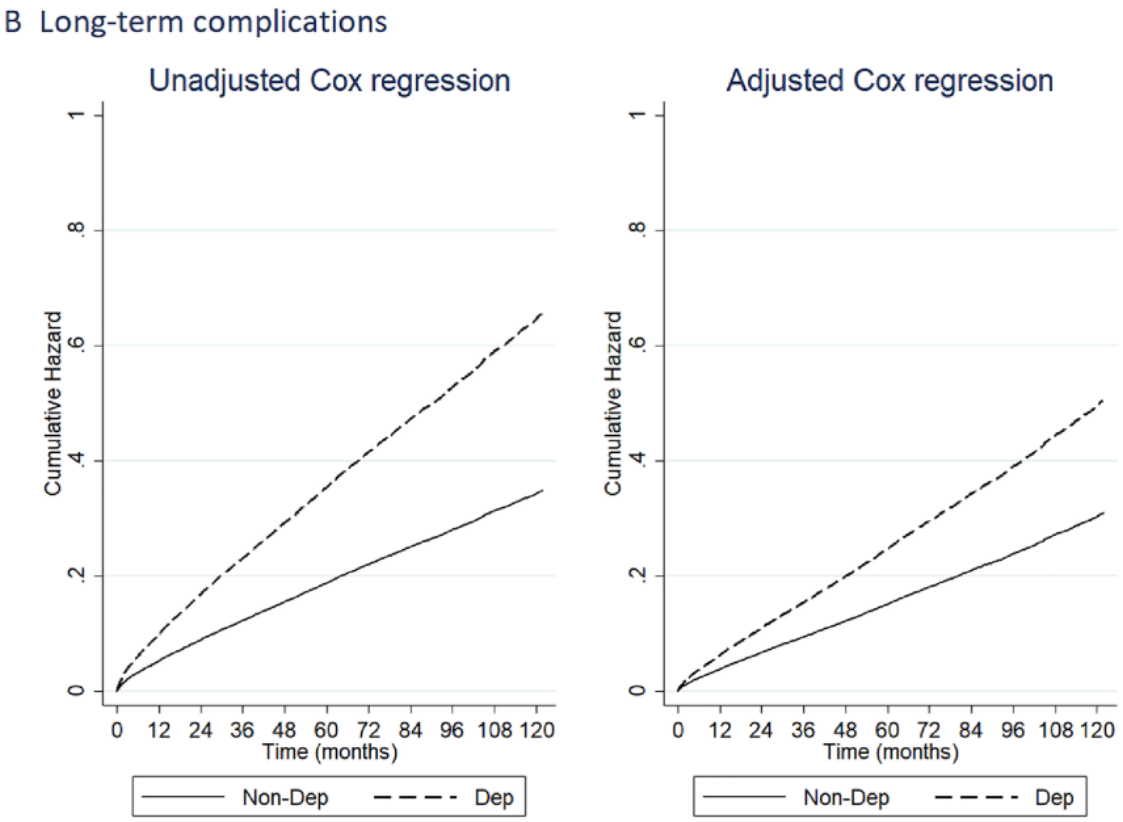
3.3.3 Depression and long-term complications over ten years

Over the ten years of follow-up, long-term complications occurred in 7,488 patients (24.3%), on average after 76.3 months. Of these, 980 (13.1%) were diagnosed with depression.

In a univariate Cox-regression model, patients with depression had a 1.9-time higher risk of long-term complications than patients without depression (HR=1.89, 95% CI 1.76-2.02). In multiple Cox regression analyses, adjusted for age group, sex, initial diabetes medication, and comorbidities, depression was confirmed as an independent predictor of complications (HR=1.64, 95% CI 1.52-1.76). The cumulative hazard functions for the Dep and Non-Dep groups are shown in Figure 3 B.

Figure 3 - Acute (follow-up at three years, panel A) and long-term (follow-up at ten years, panel B) complications: cumulative hazard function from unadjusted and adjusted Cox regression models according to the presence of depression.

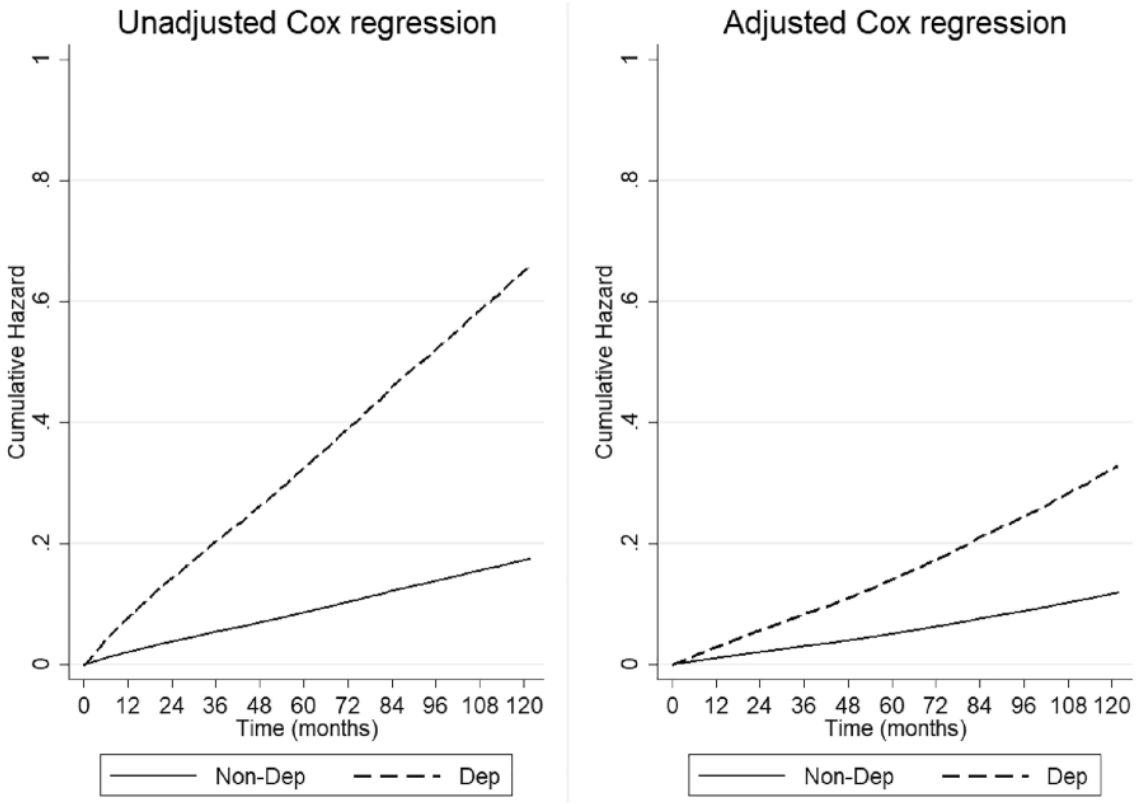




3.3.4 Depression and 10-year mortality risk

Among the 5,146 patients who developed depression, 1,348 (26.2%) died during the ten years of follow-up, while in the same period, there were 3,454 (13.5%) deaths in the Non-dep group. The median follow-up duration was 92.2 months (mean=86.1 months). Cox regression analyses showed that depression was associated with a 3.8 (95% CI 3.54-4.03) mortality risk, that decreased to 2.8 in the adjusted model (95% CI 2.58-2.96). Figure 4 shows the cumulative hazard function for the Dep and Non-Dep groups.

Figure 4 - Ten-year all-cause mortality: cumulative hazard function from unadjusted and adjusted Cox regression models according to the presence of depression



3.4 Discussion

The main results of this population-based observational cohort study are that a significant proportion of patients with type 2 diabetes and without a prior history of depression developed depression during follow-up and that depression negatively affects complications and mortality. The ten-year cumulative probability of developing depression was 21.7%, with a mean onset of 3.4 years after diabetes diagnosis; the incidence of depression was 26.1 cases per 1,000 person-years. This figure was extremely high compared with those reported in other studies using HUDs. In a study conducted in Quebec, using HUDs to assess the presence of depression, the authors reported a 12.6/1,000 person-years incidence rate of depression during the first year after initiating a GLM, and an incidence of 9.5/1,000

person-years in the eight-year study period [20]. Similar results were found in Saskatchewan, Canada [47] and Taiwan [52].

The results of the study indicate that female sex, age>65 years, living in rural areas, having insulin plus oral GLMs as initial diabetes medication and having comorbid conditions were independent predictors of the development of depression in type 2 diabetes.

A positive association between depression and female gender has been reported in other studies [20], [53]. Like a study carried out in Canada and based on claims data, in this study was also observed an increased risk of depression in people aged 65 years and more [20]. Nevertheless, another study found that lower age was associated with an increased risk for depression [54]. Consistent with [20], this study observed that the presence of specific comorbidities, and especially psychiatric comorbidities or cancer, increased the risk of depression. Conversely, this study found a higher risk of depression in patients living in rural versus urban areas.

The key findings of this study are that depression highly increased the risk of developing acute complications over three years (by 2.3 times) and the risk of developing long-term complications over ten years (by 1.6 times) above and beyond demographic characteristics, initial treatment and comorbid conditions.

Evidence from the literature suggests people with type 2 diabetes have a two-fold higher risk than the general population of fatal and non-fatal coronary heart disease, hemorrhagic or ischemic stroke [55]. Diabetes cardiovascular complications are considered major complications, that not only negatively affect the global health, but also the quality of life of people with diabetes [56], increasing the burden of the disease in terms of healthcare utilization [57], economic expenditure [58], and mortality.

Moreover, study results showed that 26.2% of people with depression vs. 13.5% without depression died during the ten-year follow-up. The findings of the study suggest that people with type 2 diabetes and subsequent depression should be protected from the increased risk of acute complications possibly caused by depression itself. Therefore, it is important to avoid, when possible, complex therapeutic regimens and the use of pharmacological treatments characterized by a high risk of hypoglycemia. Adherence to therapy and a regular glucose control assessment should be promoted for these patients by involving the family or by activating home care support systems (multidisciplinary taking and social network). The findings of the study highlight the significant impact of depression and suggest that it should be considered a major complication of type 2 diabetes and a mediator of poor outcomes. The presence of depression should be evaluated, especially in older people, as often as the presence of other major complications. In case of depression, a comprehensive medical evaluation and approach should be assured to these patients, given their high level of frailty. Furthermore, introducing new practices among healthcare professionals to take into account patients' emotional needs may enhance healthcare professionals' efforts to address psychological health in adults with diabetes [59].

3.4.1 Strengths and limitations

As for other studies based on HUDs, this study has some limitations. One intrinsic limitation is the lack of clinical information such as lab tests, that could allow a better characterization of patients and the identification of clinical predictors of poor outcomes. Moreover, the case definition for depression is a proxy of a clinical diagnosis, based on antidepressant prescriptions and information from

hospitalizations and outpatient services. The use of antidepressant prescriptions as a proxy may overestimate the incidence of depression because these drugs are also used as medications for other clinical conditions, such as anxiety disorders, eating disorders, sleep disorders, premature ejaculation and chronic pain. Vice versa, patients not seeking treatment for depression or those receiving psychological therapies in private practices may have been missed, leading to an underestimation of the actual risk of complications and mortality. Another limitation is that diabetes complications were collected from hospital discharge records; therefore, complications managed in outpatient settings were not identified.

This study also has several strengths. The main strength consists in its longitudinal design. Indeed, the temporal sequence of depression and complications in this large cohort of people newly diagnosed with type 2 diabetes was modeled. Using time-dependent Cox analyses, the immortal-time bias was avoided and the adjusted effect of depression on the onset time of complications and death was estimated. In this way, the hypothesis of a causal relationship between depression and diabetes outcomes was corroborated by empirical evidence. In addition, the use of a population-based cohort minimized the risk of selection bias. HUDs of Emilia-Romagna region proved to be high-quality and reliable data sources for epidemiological studies [12], [60].

4. Emergency Department accesses during COVID-19 pandemic in people with type 2 diabetes and depression

4.1 Introduction

Mental disorders are leading causes of the global health related burden [61]. In 2020, COVID -19 pandemic has created an environment where many determinants of poor mental health exacerbated [62]. Scientific literature has highlighted that people with diabetes are at higher risk of developing depression than the general population [19] and that depression interferes with the course of diabetes. In fact, depression in type 2 diabetes increases the risk of developing acute and long-term complications [1].

The aim of this study was to evaluate whether depression in people with type 2 diabetes increases the access rate to the Emergency Department (ED) for acute and long-term diabetes-related complications during COVID-19 pandemic.

4.2 Methods

4.2.1 Study design, population, and data sources

In this observational cohort study, data were retrospectively retrieved from the HUDs of the LHA of Romagna, in particular the following databases were used: HDR and Pharmaceutical Prescriptions databases to identify patients with type 2 diabetes; MHIS, RMHC, HDR and Pharmaceutical Prescriptions databases to identify patients with depression; ED database to detect access for acute and long-term diabetes-related complications.

Prevalent cases of type 2 diabetes at February 15, 2020, were identified among individuals aged 18 years or older, residing in the LHA of Romagna, if they had in the two preceding years at least one HDR claim with a primary or secondary

diagnosis of diabetes (ICD-9-CM: 250.xx), or at least two distinct prescriptions of GLM (ATC: A10).

The presence of depression was defined as at least one prescription of antidepressant drugs (ATC: N06A), or at least one hospitalization/outpatients service with a primary or secondary diagnosis of depression (Supplementary material 2) in the 10 preceding years. Therefore, patients were distinguished between type 2 diabetes with depression (Dep) and without depression (Non-Dep).

The cohort was followed up over a 12 months period (until death or February 15, 2021, whichever came first) and the number of ED accesses for acute and long-term complications related to diabetes were investigated. With the same criteria, a prevalent cohort of type 2 diabetes at February 15, 2019, was identified to assess what was the impact of depression in a pre-pandemic period.

The study was conducted according to the guidelines of the Declaration of Helsinki; the Ethics Committee of the Romagna Local Health Authority approved the study procedures (registration number: 9502/2020, 14/12/2020), and the study was carried out in conformity with the regulations on data management with the Italian law on privacy (Legislation Decree 196/2003 amended by Legislation Decree 101/2018).

4.2.2 Statistical analysis

Demographic and clinical characteristics of Dep and Non-Dep groups of the 2020 prevalent cases were summarized using absolute frequencies and percentages.

The impact of depression on the access rate to the ED was evaluated with a multiple negative binomial regression model to estimate the Incidence Rate Ratio (IRR) and its 95% confidence interval. The multiple model was adjusted for gender, age groups (18–39, 40-59, 60-75,>75 years), drug therapy of the last 5 years (1 oral GLM, 2 or

more oral GLM, insulin, insulin and oral GLM), number of comorbidities detected in the two previous years from prevalence date (0, 1, 2 or more comorbidities) and duration of diabetes (<1, 1-4, 5-9, ≥10 years). The number of comorbid conditions was determined for each patient using the Elixhauser algorithm. The significance level was set at $p<0.05$. Statistical analyses were performed using IBM SPSS version 25.0 and Stata 15.

4.3 Results

At 15/02/2020, 61,887 prevalent cases of type 2 diabetes were found, 28.3% patients were in the Dep group and 71.7% in the Non-Dep group. During COVID-19 period 541 ED accesses were observed.

As shown in Table 2, Dep group had a higher rate of ED accesses for acute and long-term complications related to diabetes during COVID-19 pandemic compared to Non-Dep group (IRR=1.47, 95% CI 1.18-1.83), adjusted for gender, age groups, duration of type 2 diabetes, drug therapy of the last 5 years, and number of comorbidities.

This significantly different rate of ED accesses was also observed in the prevalent cases of non-pandemic period (n=60,618; total ED accesses=659), in which Dep group had an IRR of 1.43 (95% CI 1.18-1.73) compared to Non-Dep one, adjusted for clinical and demographic factors. The higher rate of ED accesses in Dep group compared to Non-Dep group was similar between COVID-19 period and the pre-pandemic period (group-period interaction term: IRR=1.01, 95% CI 0.76-1.34).

Table 2 – Characteristics of the prevalent cases of type 2 diabetes at 15/02/2020 (n=61,887) and results of the multiple negative binomial regression model to estimate the incidence rate ratio of ED accesses for acute and long-term complications.

	n (%)	IRR	95% CI		p-value
Group					
Non-Dep	44,380 (71.7%)	*Ref.*			
Dep	17,506 (28.3%)	1.47	1.18	1.83	<0.001
Gender					
Female	28,677 (46.3%)	*Ref.*			
Male	33,209 (53.7%)	1.06	0.86	1.32	0.576
Age groups (years)					
18-39	1,438 (2.3%)	2.38	1.32	4.27	0.004
40-59	10,150 (16.4%)	1.77	1.26	2.5	0.001
60-75	23,910 (38.6%)	*Ref.*			
>75	26,388 (42.6%)	1.66	1.29	2.15	<0.001
Duration of type 2 diabetes					
<1 year	4,416 (7.1%)	0.4	0.21	0.77	0.006
1-4 years	13,729 (22.2%)	0.66	0.48	0.91	0.011
5-9 years	14,491 (23.4%)	0.68	0.49	0.93	0.015
≥10 years	29,250 (47.3%)	*Ref.*			
Drug therapy					
1 oral GLM	24,261 (39.2%)	*Ref.*			
2 or more oral GLM	19,252 (31.1%)	2.38	1.66	3.42	<0.001
Insulin	3,992 (6.5%)	5.57	3.4	9.13	<0.001
Oral GLM plus insulin	14,381 (23.2%)	4.14	2.87	5.98	<0.001
N. of comorbidities					
None	47,164 (76.2%)	*Ref.*			
1	6,232 (10.1%)	1.31	0.93	1.82	0.119
2 or more	8,490 (13.7%)	2.66	2.04	3.48	<0.001

Non-Dep: people with type 2 diabetes without depression**; Dep:** people with type 2 diabetes with depression**;**
GLM: Glucose-Lowering Medications; **Ref**: reference category;
IRR: Incidence Rate Ratio; **95%CI**: Confidence interval 95%

4.4 Discussion

The diagnosis of depression in type 2 diabetes is associated with a higher rate of ED accesses for acute and long-term complications, both during the COVID-19 pandemic and in the pre-pandemic period.

Despite the overall decrease in ED access rate during the COVID-19 pandemic (−19.6% percentage variation compared to the preceding year) due to the restrictions, a clear difference in ED accesses was observed in patients with type 2 diabetes and depression compared to patients with type 2 diabetes without depression. This is consistent with evidence on the impact of depression on short-term complications [1] in people with type 2 diabetes and depression.

Since COVID-19 is associated with poor mental health [63], the special health needs of patients with diabetes and depression should be taken into account.

5. Incidence of depression in patients with diabetes during COVID-19 pandemic

5.1 Introduction

The outbreak of the COVID-19 pandemic in Italy in February 2020 was followed by containment restrictions starting from March 10, when confirmed cases of COVID-19 were 10,149 and deaths 631 [64]. Specifically, the Italian government enforced a national lockdown until May 2020 to limit the spread of the SARS-Cov-2 infection (first wave of COVID-19); on May 4, 2020, several important restrictions were eased and during the summer period there was a sharp reduction of daily confirmed new cases. A second wave of COVID-19 hit Italy at the beginning of October 2020, so the Government adopted progressive and differentiated restrictive measures, based on the spread of the pandemic and the burden on health services, for each region.

The lockdown measures, overload of healthcare services and the extended state of emergency, had a negatively impact on the access and use of healthcare service, consequently affecting the care of chronic conditions like diabetes [65], [66].

In addition to the direct effects of COVID-19, social restrictions, fear of contagion and uncertainty about the future had an impact on psychological wellbeing. A recent systematic review reported an increased prevalence of major depressive disorder associated with daily SARS-CoV-2 infection rates and reductions in human mobility [62].

Since people with type 2 diabetes have a significantly higher risk of developing depression than the general population [19], and depression represents a risk factor for diabetes complications and mortality [1], I focused on the impact of COVID-19 pandemic on mental health of people living with type 2 diabetes.

The aim of the study was to investigate the impact of COVID-19 pandemic on the incidence of depression in people with type 2 diabetes compared to a pre-pandemic period.

5.2 Methods

5.2.1 Study design, population, and data sources

In this prospective observational study, adult patients with type 2 diabetes residing in the LHA of Romagna were considered.

Data were retrieved from regional HUDs, by linking the unique anonymized identification code of HDR, the MHIS, RMHC, Pharmaceutical Prescriptions databases, and the regional mortality register.

Two cohorts of people with type 2 diabetes at 01/01/2020 (2020 cohort) and at 01/01/2019 (2019 cohort) were identified, based on having at least one HDR claim with a primary or secondary diagnosis of diabetes (ICD-9-CM: 250.xx), or at least two distinct prescriptions of GLM (ATC: A10) in the two years preceding the date of cohort entry. The two cohorts were then followed up for 12 months or until the date of death if this occurred earlier.

During the follow-up, the new onset of depression was ascertained as at least one prescription of antidepressant drugs (ATC: N06A), one hospitalization with a primary or secondary diagnosis of depression, or outpatient service with a diagnosis of depression (Supplementary material 2). Patients with a history of depression in the previous 10 years from the date of cohort entry were excluded from the analysis.

5.2.2 Statistical analysis

For the two cohorts, the annual incidence rate (IR) of depression per 1,000 person-years and 95% confidence interval (95% CI) were estimated. Depression incidence rates were analysed by sex, age groups (18–49, 50–59, 60-74, ≥75 years), number of comorbidities (0, 1, 2 or more), duration of diabetes (≤1 year, 2-4 years, 5-9 years, ≥10 years), and drug therapy in the last 5 years (1 oral GLM, 2 or more oral GLM, only insulin, oral GLM and insulin). The incidence-rate ratio (IRR) of depression with 95% CI was calculated as the ratio between the IR of 2020 cohort and the IR of 2019 cohort.

To consider the evolution of the pandemic and the alternation of containment interventions, the IR of the two cohorts and the IRR were also calculated for four subperiods: pre-pandemic phase (P1: January 1 – March 9), first wave (P2: March 10, beginning of national lockdown in Italy - May 3), slowdown phase of restrictions (P3: May 4, first phase of reopening from Lockdown – September 30), and second wave (P4: October 1 - December 31).

Lastly, a multiple Cox regression model was used to evaluate the impact of COVID-19 on the incidence of new cases of depression, adjusting by sex, age, number of comorbidities, duration of diabetes, and drug therapy of the last 5 years, stratified by pandemic subperiods. Results were provided as Hazard Ratio and 95% CI.

For all tests, significance was set as $p<0.05$; statistical analyses were performed using Stata 15.

5.3 Results

The 2020 and 2019 cohorts comprised 44,194 and 42,961 people with type 2 diabetes without a history of depression in the previous 10 years, respectively.

In the 2020 cohort, 59.5% were males, the mean age was 68.6 (SD=13.4), 46.8% had more than 10 years of history of diabetes, 40% had only one GLM drug therapy in the previous five years, and 80% had no comorbidities at the date of cohort entry.

5.3.1 Annual incidence of depression

The annual incidence rate of depression significantly decreased in 2020, from 27.0 cases in 2019 cohort per 1,000 person-years to 24.0 cases per 1,000 person-years in 2020 cohort; the IRR was 0.89 (95% CI 0.81-0.97, p=0.006) (Table 3).

Table 3 – Incidence of depression in people with type 2 diabetes per 1,000 person-years (95% CI) by demographic and clinical features. The Incidence Rate Ratio is the ratio of IR in the 2020 cohort to the IR of 2019 cohort.

	2019			**2020**			**IRR (95% CI)**	**p-value**
	Cases	*py*	*IR / 1,000 py*	*Cases*	*py*	*IR / 1,000 py*		
Total cohort	*1125*	*41,637*	*27.0*	*1028*	*42,890*	*24.0*	0.89 (0.81-0.97)	**0.006**
Sex								
Female	569	16,777	33.9	491	17,342	28.3	0.83 (0.74-0.94)	**0.003**
Male	556	24,860	22.4	537	25,549	21.0	0.94 (0.83-1.1)	0.305
Age groups								
18-39	16	1,315	12.2	13	1,351	9.6	0.79 (0.35-1.75)	0.536
40-59	95	8,292	11.5	91	8,480	10.7	0.94 (0.69-1.26)	0.656
60-74	350	17,557	19.9	289	18,006	16.1	0.81 (0.69-0.94)	**0.006**
>74	664	14,474	45.9	635	15,053	42.2	0.92 (0.82-1.03)	0.131
N. of comorbidities								
0	741	33,464	22.1	674	34,672	19.4	0.88 (0.79-0.98)	**0.014**
1	143	3,765	38.0	131	3,842	34.1	0.90 (0.70-1.15)	0.373
2+	241	4,408	54.7	223	4,376	51.0	0.93 (0.77-1.12)	0.450
Duration of type 2 diabetes (years)								
≤1	107	4,515	23.7	79	4,857	16.3	0.69 (0.51-0.93)	**0.011**
2-4	147	7,110	20.7	154	7,488	20.6	0.99 (0.79-1.26)	0.963
5-9	277	11,917	23.2	231	10,623	21.7	0.94 (0.78-1.12)	0.455
10+	594	18,095	32.8	564	19,922	28.3	0.86 (0.77-0.97)	**0.012**
Drug therapy of the last 5 years								
1 oral GLM	422	16,724	25.2	377	17,240	21.9	0.87 (0.75-1.00)	0.043
2 or more oral GLM	350	13,251	26.4	315	13,540	23.3	0.88 (0.75-1.03)	0.102
Insulin	80	2,741	29.2	58	2,802	20.7	0.71 (0.50-1.01)	0.050
Insulin plus oral GLM	273	8,921	30.6	278	9,307	29.9	0.98 (0.82-1.16)	0.776

IR: Incidence Rate per 100,000 person-years; **IRR**: Incidence Rate Ratio; **95% CI**: 95% confidence interval
py: person-years; **GLM**: glucose lowering medications

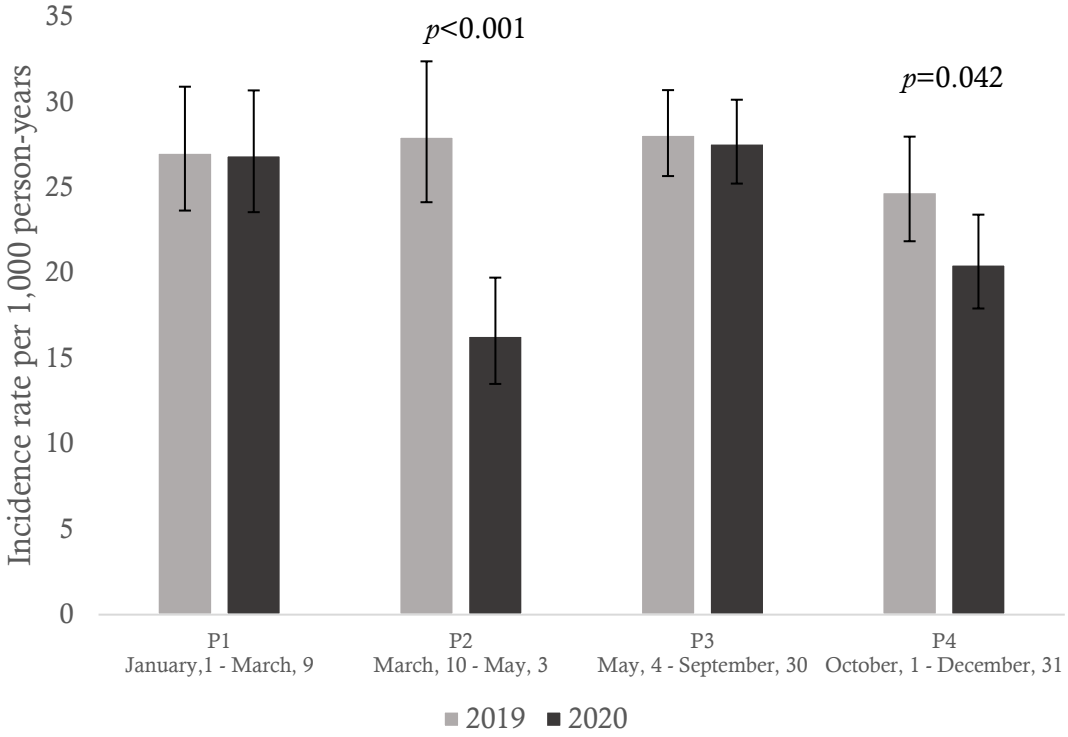
When IRR were investigated in the different strata, a significant decrease in the annual incidence rate of depression in 2020 vs. 2019 was observed in females (IRR=0.83, 95% CI 0.74-0.94, p=0.003), in the age group 60-74 years (IRR=0.81, 95% CI 0.69-0.94, p=0.006), in those with no comorbidities at the date of cohort entry (IRR=0. 88, 95% CI 0.79-0.98, p=0. 014), and in people with type 2 diabetes whose drug therapy in the last 5 years was of 1 oral GLM (IRR=0.69, 95% CI 0.51-0.93, p=0.011).

5.3.2 Incidence of depression by subperiod

Figure 5 shows the incidence rates of depression in 2020 cohort and 2019 cohort of each subperiod.

Different incident rates of depression were found in the subperiod P2 (March 10 – May 3, 2020, corresponding to the Italian national lockdown), as in 2020 cohort it was significantly lower (IR=16.3/1,000 py) than in 2019 cohort (IR=27.9/1,000 py), with an IRR of 0.58 (95% CI 0.45-0.75, p<0.001). In addition, in the last subperiod (P4, October 1– December 31) there was a slight reduction in the new cases of depression in 2020 cohort compared to 2019 cohort (IRR=0.83, 95% CI 0.69-0.99, p=0.042).

Figure 5 - Comparison of the 2019 and 2020 incidence rate of depression per 1,000 person-years in people with diabetes stratified by the four subperiods.



The incidence rate reduction in subperiod P2 was also confirmed when stratifying by sex (Males: IRR=0.58, 95%CI 0.40-0.82; Females: IRR=0.59, 95%CI 0.42-0.83), age class (Age group 60-74 years: IRR=0.62, 95%CI 0.39-0.97; age group ≥75 years: IRR=0.60, 95%CI 0.43-0.82), duration of diabetes (≤1 years: IRR=0.30, 95%CI 0.12-0.68; ≥10 years: IRR=0.66, 95%CI 0.47-0.93), drug treatment (1 GLM: IRR=0.46, 95%CI 0.29-0.72), and by number of comorbidities at baseline (no comorbidities: IRR=0.53, 95%CI 0.38-0.74; 1 comorbidity: IRR=0.45, 95%CI 0.21-0.93).

5.3.3 Multiple Cox regression model

The multiple Cox regression model (Table 4) confirmed a significant reduction in the HR of depression in 2020 cohort compared to 2019 cohort in the P2 subperiod

(HR=0.59, 95%CI 0.46-0.75, p<0.001) and in the P4 subperiod (HR=0.81, 95%CI 0.68-0.97, p=0.025) after adjusting for demographic and clinical characteristics.

Table 4 – Multiple Cox regression model to evaluate the impact of COVID-19 on the incidence of depression stratified by four subperiods, adjusting by sex, age, number of comorbidities, duration of diabetes, and drug therapy in the last 5 years.

	P1	**P2**	**P3**	**P4**
	HR (95% CI)	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
Cohort				
2019	*Ref.*			
2020	1 (0.83-1.21)	0.59 (0.46-0.75)***	0.98 (0.86-1.11)	0.81 (0.68-0.97)*
Sex				
Female	*Ref.*			
Male	0.73 (0.6-0.88)***	0.67 (0.53-0.84)***	0.78 (0.69-0.89)***	0.79 (0.66-0.95)*
Age group				
18-39	0.86 (0.39-1.88)	0.46 (0.16-1.29)	0.57 (0.32-1.04)	0.55 (0.24-1.28)
40-59	0.67 (0.46-0.98)*	0.57 (0.36-0.91)*	0.63 (0.49-0.81)***	0.73 (0.53-1.02)
60-74	*Ref.*			
>74	2.42 (1.94-3.02)***	1.86 (1.42-2.42)***	2.26 (1.96-2.62)***	1.98 (1.61-2.43)***
N. of comorbodities				
0	*Ref.*			
1	1.87 (1.42-2.46)***	1.8 (1.26-2.57)***	1.48 (1.22-1.8)***	1.22 (0.9-1.65)
2+	2.3 (1.82-2.91)***	2.85 (2.16-3.77)***	1.73 (1.46-2.04)***	1.72 (1.35-2.2)***
Duration of diabetes				
≤1	1.12 (0.79-1.6)	1.3 (0.86-1.95)	0.79 (0.61-1.02)	0.73 (0.51-1.07)
2-4	1.11 (0.83-1.48)	0.92 (0.63-1.35)	0.88 (0.72-1.08)	0.84 (0.63-1.13)
5-9	1.06 (0.83-1.35)	1.04 (0.77-1.4)	0.86 (0.73-1.01)	0.9 (0.71-1.13)
≥10	*Ref.*			
Drug therapy				
1 oral GLM	*Ref.*			
2 or more oral GLM	1.12 (0.89-1.43)	1.13 (0.83-1.53)	0.93 (0.79-1.09)	1.07 (0.86-1.35)
Insulin	1.04 (0.66-1.64)	2.09 (1.34-3.25)***	1.09 (0.81-1.47)	1.09 (0.72-1.67)
Insulin plus oral GLM	1.21 (0.93-1.57)	1.21 (0.87-1.69)	1.18 (0.99-1.4)	1.05 (0.81-1.36)

* p<0.05; *** p<0.001

P1: January, 1 – March, 9; **P2**: March, 10 – May, 3; **P3**: May, 4 – September, 30; **P4**: October, 1 – December, 31

HR: Hazard ratio; **95% CI**: Confidence interval 95%

Ref.: Reference category; **GLM**: glucose lowering medications

5.4 Discussion

This population-based study investigated the impact of COVID-19 pandemic on the incidence of depression in a large, unselected population of people with type 2 diabetes, using HUDs.

Although reviews and meta-analyses found a high prevalence in 2020 of depressive disorders in the general population [62], [67], [68], and two longitudinal studies observed an increase of depressive symptoms in people with diabetes [69], [70], the results of this study showed a statistically significant decrease of the incidence rate of depression in 2020 compared to 2019. This difference can be accounted by the decrease of antidepressant prescriptions, mental health services and hospital admissions with a diagnosis of depression during the 2020 lockdown period and during the second wave of COVID-19. This reduction might also be due to the limited access to healthcare services rather than a decrease in the depression incidence, linked to a disruption in regular monitoring and integrated care [71]. In fact, this apparent "decline" was also observed for other diseases/conditions not related to depression in people with type 2 diabetes, such as hypothyroidism, gout, glaucoma, Parkinson's disease, arrhythmia, Crohn's and ulcerative colitis, and pain and inflammation (additional analyses reported in Supplementary Material 5), suggesting a lack of access to healthcare of all types during this period.

Another possible explanation of the discrepancy with previous studies may be found in the tools used to detect depression: in this study, depression was identified through ICD-9-CM diagnoses and ATC codes present in HUDs while in the other studies it was assessed with self-report questionnaires such as the Patient Health Questionnaire. The pandemic may have increased self-reported depressive symptoms without an increase in clinically diagnosed depression.

Anyway, the results of this study are consistent with those of Kowall et al. [72], who reported a lower incidence rate of depressive disorders per 1000 person-years in 2020 (IR=23.3, 95% CI 22.3–24.3) than in 2019 (IR=26.5, 95% CI: 25.5–27.5) in people with type 2 diabetes in Germany. Two other studies that evaluated the incidence of depression in the general population also found a reduction in new cases of depression in 2020 compared with 2019 [73], [74].

A study exploring the psychological effects of COVID-19 pandemic and lockdown on a sample of the Italian population, reported higher scores of depressive symptoms in females, younger adults, people reporting professional uncertainty and in those who could not leave home for going to work [75]. On the other hand, in this study the investigated cohort consisted of predominantly elderly subjects (the mean age was 69 years) not affected by home-based work or fear of job loss.

An Italian study, evaluating the COVID-19 pandemic impact, found out that people with diabetes reported more frequently an improvement of lifestyles than healthy older people, such as physical activity, drinks/week reduction, and increased consumption of fruit and vegetables [76]. The development of depression may have been curtailed by the pandemic in people with type 2 diabetes, who seized the opportunity to improve health behaviours.

Other explanations for the reduction of new cases of depression can be sought in the reduction of general practitioner or diabetologist visits due to restrictive measures or to fear of contracting the virus, leading to unnoticed or underestimated psychiatric disorders [77]. To mitigate these unintended implications of lockdowns/containment interventions, policymakers should adopt a more holistic approach in order to prevent patients with health needs from disengaging from health services.

COVID-19 pandemic put a huge strain on health systems ability to respond and provide regular care especially to the most vulnerable people. To confirm mental health unmet needs of people with diabetes during the first and the second pandemic waves further research are necessary, ensuring that healthcare services are prepared to address the needs of this this segment of the population.

6. CONCLUSION

In this thesis, carried out in the framework of PSIGE-DIAB project, I explored and evaluated the role of depression in people with type 2 diabetes and how depression can negatively influence the natural history of diabetes, increasing the risk of diabetes complications.

The first population-based study suggests that being a woman, being over 65 years, living in rural areas, and having comorbid conditions are important risk factors for the onset of depression in this population. Knowing the risk factors of depression in people with type 2 diabetes may help healthcare professionals identify timely patients at high risk, thus improving screening activities regarding the evaluation of psychological aspects and introducing targeted personalized treatment in diabetes care settings. As recommended by the standards of medical care in diabetes of the American Diabetes Association [78], the evaluation for depressive symptoms should be integrated into diabetes care as initial and annual screenings, and as suggested by the PsychoSocial Aspects of Diabetes study group of the European Association for the Study of Diabetes, person-centred outcomes should be used longitudinally and integrated into diabetes registers for clinical management and risk stratification [79]. The first study also confirms that depression is not only associated with an increased risk for chronic diabetes complications and all-cause mortality in patients with diabetes, but it provides new evidence of the impact of depression on acute complications.

Having ascertained the fragility of people with diabetes and depression, in the context of the pandemic I investigated the impact of COVID-19 on depression in people with type 2 diabetes. The incidence of depression decreased in 2020 compared to 2019, particularly during the first and the second waves of the pandemic, where people with

diabetes may have had difficulty to reach healthcare services. The number of Emergency Department accesses for acute and long-term diabetes-related complications during the COVID-19 pandemic was higher in people with type 2 diabetes and a history of depression compared to those without history of depression, but this discrepancy was also observed in a previous pre-pandemic period.

Healthcare Utilization Databases proved to be an important data source for epidemiological studies, allowing to design longitudinal observational studies, correctly assessing temporal sequence of exposures and outcomes in large population-based cohorts with chronic conditions; real-world evidences will help healthcare professionals identify timely patients at high risk of developing depression and introduce targeted and personalized treatment in diabetes healthcare pathways.

Future research is needed to evaluate the impact of a structured depression screening and comprehensive treatment in people with type 2 diabetes and depression on acute and long-term complications and mortality. Furthermore, the assessment of the effects of the COVID-19 pandemic on depression in people with type 2 diabetes might inform policy makers, healthcare facilities managers and clinicians and let them be prepared to maintain key health systems functioning during crisis periods.

References

[1] R. Messina *et al.*, "Is it time to consider depression as a major complication of type 2 diabetes? Evidence from a large population-based cohort study," *Acta Diabetol.*, vol. 59, no. 1, pp. 95–104, Jan. 2022, doi: 10.1007/s00592-021-01791-x.

[2] R. Messina *et al.*, "Emergency department accesses for diabetes-related complications during COVID-19 pandemic in people with type 2 diabetes and depression," *Acta Diabetol.*, vol. 59, no. 9, pp. 1247–1249, Sep. 2022, doi: 10.1007/s00592-022-01894-z.

[3] C. Miani, E. Robin, V. Horvath, C. Manville, J. Cave, and J. Chataway, "Health and Healthcare: Assessing the Real World Data Policy Landscape in Europe.," *Rand Heal. Q.*, vol. 4, no. 2, p. 15, 2014, [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/28083344.

[4] A. Makady, A. de Boer, H. Hillege, O. Klungel, and W. Goettsch, "What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews," *Value Heal.*, vol. 20, no. 7, pp. 858–865, Jul. 2017, doi: 10.1016/j.jval.2017.03.008.

[5] E. Skrami *et al.*, "Availability of Real-World Data in Italy: A Tool to Navigate Regional Healthcare Utilization Databases," *Int. J. Environ. Res. Public Health*, vol. 17, no. 1, p. 8, Dec. 2019, doi: 10.3390/ijerph17010008.

[6] G. Corrao and G. Mancia, "Generating Evidence From Computerized Healthcare Utilization Databases," *Hypertension*, vol. 65, no. 3, pp. 490–498, Mar. 2015, doi: 10.1161/HYPERTENSIONAHA.114.04858.

[7] D. Gibertoni *et al.*, "Developing and validating an algorithm to identify incident chronic dialysis patients using administrative data," *BMC Med. Inform. Decis. Mak.*, vol. 20, no. 1, p. 185, Dec. 2020, doi: 10.1186/s12911-020-01206-x.

[8] M. Iommi *et al.*, "Occurrence of Idiopathic Pulmonary Fibrosis in Italy: Latest Evidence from Real-World Data," *Int. J. Environ. Res. Public Health*, vol. 19, no. 5, p. 2510, Feb. 2022, doi: 10.3390/ijerph19052510.

[9] M. Iommi, S. Rosa, M. Fusaroli, P. Rucci, M. P. Fantini, and E. Poluzzi, "Modified-Chronic Disease Score (M-CDS): Predicting the individual risk of death using drug prescriptions," *PLoS One*, vol. 15, no. 10, p. e0240899, Oct.

2020, doi: 10.1371/journal.pone.0240899.

[10] J. Lenzi, V. M. Avaldi, P. Rucci, G. Pieri, and M. P. Fantini, "Burden of multimorbidity in relation to age, gender and immigrant status: a cross-sectional study based on administrative data," *BMJ Open*, vol. 6, no. 12, p. e012812, Dec. 2016, doi: 10.1136/bmjopen-2016-012812.

[11] F. Swart *et al.*, "Risk of hospitalization from drug-drug interactions in the Elderly: real-world evidence in a large administrative database," *Aging (Albany. NY).*, vol. 12, no. 19, pp. 19711–19739, Oct. 2020, doi: 10.18632/aging.104018.

[12] D. Tedesco *et al.*, "Impact of rehabilitation on mortality and readmissions after surgery for hip fracture," *BMC Health Serv. Res.*, vol. 18, no. 1, p. 701, Dec. 2018, doi: 10.1186/s12913-018-3523-x.

[13] P. Rucci *et al.*, "Medical Costs of Patients with Type 2 Diabetes in a Single Payer System: A Classification and Regression Tree Analysis," *PharmacoEconomics - Open*, vol. 4, no. 1, pp. 181–190, Mar. 2020, doi: 10.1007/s41669-019-0166-8.

[14] L. Connelly, G. Fiorentini, and M. Iommi, "Supply-side solutions targeting demand-side characteristics: causal effects of a chronic disease management program on adherence and health outcomes," *Eur. J. Heal. Econ.*, vol. 23, no. 7, pp. 1203–1220, Sep. 2022, doi: 10.1007/s10198-021-01421-x.

[15] M. Yurkovich, J. A. Avina-Zubieta, J. Thomas, M. Gorenchtein, and D. Lacaille, "A systematic review identifies valid comorbidity indices derived from administrative health data," *J. Clin. Epidemiol.*, vol. 68, no. 1, pp. 3–14, Jan. 2015, doi: 10.1016/j.jclinepi.2014.09.010.

[16] Ministero della Salute, "Nuovo sistema informativo sanitario - NSIS," 2022. https://www.salute.gov.it/portale/temi/p2_4.jsp?lingua=italiano&area=sistemaInformativo (accessed Oct. 15, 2022).

[17] Regione Emilia-Romagna, "Sistema Informativo Politiche per la Salute e Politiche Sociali," 2022. https://salute.regione.emilia-romagna.it/siseps/ (accessed Oct. 15, 2022).

[18] L. Fisher, J. S. Gonzalez, and W. H. Polonsky, "The confusing tale of depression and distress in patients with diabetes: a call for greater clarity and precision," *Diabet. Med.*, vol. 31, no. 7, pp. 764–772, Jul. 2014, doi:

10.1111/dme.12428.

[19] S. S. Hasan, A. A. Mamun, A. M. Clavarino, and T. Kairuz, "Incidence and Risk of Depression Associated with Diabetes in Adults: Evidence from Longitudinal Studies," *Community Ment. Health J.*, vol. 51, no. 2, pp. 204–210, Feb. 2015, doi: 10.1007/s10597-014-9744-5.

[20] C. Lunghi, J. Moisan, J.-P. Grégoire, and L. Guénette, "Incidence of Depression and Associated Factors in Patients With Type 2 Diabetes in Quebec, Canada," *Medicine (Baltimore).*, vol. 95, no. 21, p. e3514, May 2016, doi: 10.1097/MD.0000000000003514.

[21] A. Simayi and P. Mohemaiti, "Risk and protective factors of co-morbid depression in patients with type 2 diabetes mellitus: a meta analysis," *Endocr. J.*, vol. 66, no. 9, pp. 793–805, 2019, doi: 10.1507/endocrj.EJ18-0579.

[22] R. S. Bergmans, A. Rapp, K. M. Kelly, D. Weiss, and B. Mezuk, "Understanding the relationship between type 2 diabetes and depression: lessons from genetically informative study designs," *Diabet. Med.*, vol. 38, no. 2, Feb. 2021, doi: 10.1111/dme.14399.

[23] B. Chireh, M. Li, and C. D'Arcy, "Diabetes increases the risk of depression: A systematic review, meta-analysis and estimates of population attributable fractions based on prospective studies," *Prev. Med. Reports*, vol. 14, p. 100822, Jun. 2019, doi: 10.1016/j.pmedr.2019.100822.

[24] M. Khaledi, F. Haghighatdoost, A. Feizi, and A. Aminorroaya, "The prevalence of comorbid depression in patients with type 2 diabetes: an updated systematic review and meta-analysis on huge number of observational studies," *Acta Diabetol.*, vol. 56, no. 6, pp. 631–650, Jun. 2019, doi: 10.1007/s00592-019-01295-9.

[25] J. S. Gonzalez, L. Fisher, and W. H. Polonsky, "Depression in Diabetes: Have We Been Missing Something Important?," *Diabetes Care*, vol. 34, no. 1, pp. 236–239, Jan. 2011, doi: 10.2337/dc10-1970.

[26] E. H. B. Lin *et al.*, "Relationship of Depression and Diabetes Self-Care, Medication Adherence, and Preventive Care," *Diabetes Care*, vol. 27, no. 9, pp. 2154–2160, Sep. 2004, doi: 10.2337/diacare.27.9.2154.

[27] A. Nouwen *et al.*, "Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis," *Diabet. Med.*,

vol. 36, no. 12, pp. 1562–1572, Dec. 2019, doi: 10.1111/dme.14054.

[28] F. Wang *et al.*, "Prevalence of comorbid major depressive disorder in Type 2 diabetes: a meta-analysis of comparative and epidemiological studies," *Diabet. Med.*, vol. 36, no. 8, pp. 961–969, Aug. 2019, doi: 10.1111/dme.14042.

[29] J. S. Gonzalez *et al.*, "Symptoms of depression prospectively predict poorer self-care in patients with Type 2 diabetes," *Diabet. Med.*, vol. 25, no. 9, pp. 1102–1107, Aug. 2008, doi: 10.1111/j.1464-5491.2008.02535.x.

[30] C. Devarajooh and K. Chinna, "Depression, distress and self-efficacy: The impact on diabetes self-care practices," *PLoS One*, vol. 12, no. 3, p. e0175096, Mar. 2017, doi: 10.1371/journal.pone.0175096.

[31] S. M. Danna, E. Graham, R. J. Burns, S. S. Deschênes, and N. Schmitz, "Association between Depressive Symptoms and Cognitive Function in Persons with Diabetes Mellitus: A Systematic Review," *PLoS One*, vol. 11, no. 8, p. e0160809, Aug. 2016, doi: 10.1371/journal.pone.0160809.

[32] J. S. Gonzalez, M. L. Tanenbaum, and P. V. Commissariat, "Psychosocial factors in medication adherence and diabetes self-management: Implications for research and practice.," *Am. Psychol.*, vol. 71, no. 7, pp. 539–551, Oct. 2016, doi: 10.1037/a0040388.

[33] C. Lunghi, J. Moisan, J.-P. Grégoire, and L. Guénette, "The Association between Depression and Medication Nonpersistence in New Users of Antidiabetic Drugs," *Value Heal.*, vol. 20, no. 6, pp. 728–735, Jun. 2017, doi: 10.1016/j.jval.2016.09.2399.

[34] J. F. Scherrer *et al.*, "Increased Risk of Myocardial Infarction in Depressed Patients With Type 2 Diabetes," *Diabetes Care*, vol. 34, no. 8, pp. 1729–1734, Aug. 2011, doi: 10.2337/dc11-0031.

[35] C.-S. Wu, L.-Y. Hsu, and S.-H. Wang, "Association of depression and diabetes complications and mortality: a population-based cohort study," *Epidemiol. Psychiatr. Sci.*, vol. 29, p. e96, Jan. 2020, doi: 10.1017/S2045796020000049.

[36] D. Mollaioli *et al.*, "Benefits of Sexual Activity on Psychological, Relational, and Sexual Health During the COVID-19 Breakout," *J. Sex. Med.*, vol. 18, no. 1, pp. 35–49, Jan. 2021, doi: 10.1016/j.jsxm.2020.10.008.

[37] A. Sansone, D. Mollaioli, G. Ciocca, E. Limoncin, E. Colonnello, and E. A. Jannini, "Sexual Dysfunction in Men and Women with Diabetes: A Reflection of their Complications?," *Curr. Diabetes Rev.*, vol. 18, no. 1, Jan. 2022, doi: 10.2174/1573399817666210309104740.

[38] G. Corona, C. B. Giorda, D. Cucinotta, P. Guida, and E. Nada, "Sexual Dysfunction at the Onset of Type 2 Diabetes: The Interplay of Depression, Hormonal and Cardiovascular Factors," *J. Sex. Med.*, vol. 11, no. 8, pp. 2065–2073, Aug. 2014, doi: 10.1111/jsm.12601.

[39] E. A. Jannini, "SM = SM: The Interface of Systems Medicine and Sexual Medicine for Facing Non-Communicable Diseases in a Gender-Dependent Manner," *Sex. Med. Rev.*, vol. 5, no. 3, pp. 349–364, Jul. 2017, doi: 10.1016/j.sxmr.2017.04.002.

[40] L. E. Egede, D. Zheng, and K. Simpson, "Comorbid Depression is Associated With Increased Health Care Use and Expenditures in Individuals With Diabetes," *Diabetes Care*, vol. 25, no. 3, pp. 464–470, Mar. 2002, doi: 10.2337/diacare.25.3.464.

[41] J.-H. Jeong *et al.*, "Depression and Mortality in People with Type 2 Diabetes Mellitus, 2003 to 2013: A Nationwide Population-Based Cohort Study," *Diabetes Metab. J.*, vol. 41, no. 4, p. 296, 2017, doi: 10.4093/dmj.2017.41.4.296.

[42] F. E. P. van Dooren, G. Nefs, M. T. Schram, F. R. J. Verhey, J. Denollet, and F. Pouwer, "Depression and Risk of Mortality in People with Diabetes Mellitus: A Systematic Review and Meta-Analysis," *PLoS One*, vol. 8, no. 3, p. e57058, Mar. 2013, doi: 10.1371/journal.pone.0057058.

[43] A. Farooqi, K. Khunti, S. Abner, C. Gillies, R. Morriss, and S. Seidu, "Comorbid depression and risk of cardiac events and cardiac mortality in people with diabetes: A systematic review and meta-analysis," *Diabetes Res. Clin. Pract.*, vol. 156, p. 107816, Oct. 2019, doi: 10.1016/j.diabres.2019.107816.

[44] C. Lunghi, A. Zongo, I. Tardif, É. Demers, J. D. R. Diendéré, and L. Guénette, "Depression but not non-persistence to antidiabetic drugs is associated with mortality in type 2 diabetes: A nested case-control study," *Diabetes Res. Clin. Pract.*, vol. 171, p. 108566, Jan. 2021, doi:

10.1016/j.diabres.2020.108566.

[45] G. Nefs, V. J. M. Pop, J. Denollet, and F. Pouwer, "Depressive symptoms and all-cause mortality in people with type 2 diabetes: A focus on potential mechanisms," *Br. J. Psychiatry*, vol. 209, no. 2, pp. 142–149, Aug. 2016, doi: 10.1192/bjp.bp.114.154781.

[46] D. G. Bruce, W. A. Davis, S. E. Starkstein, and T. M. E. Davis, "A prospective study of depression and mortality in patients with type 2 diabetes: the Fremantle Diabetes Study," *Diabetologia*, vol. 48, no. 12, pp. 2532–2539, Dec. 2005, doi: 10.1007/s00125-005-0024-3.

[47] L. C. Brown, S. R. Majumdar, S. C. Newman, and J. A. Johnson, "Type 2 diabetes does not increase risk of depression.," *CMAJ*, vol. 175, no. 1, pp. 42–6, Jul. 2006, doi: 10.1503/cmaj.051429.

[48] CINECA SID, "Osservatorio ARNO Diabete. Il profilo assistenziale della popolazione con diabete. Volume XXXI," Bologna, Italy, 2019. [Online]. Available: https://www.siditalia.it/clinica/linee-guida-societari/send/80-linee-guida-documenti-societari/5025-rapporto-arno-diabete-2019.

[49] A. Elixhauser, C. Steiner, D. Harris, and R. Coffey, "Comorbidity Measures for Use with Administrative Data," *Med. Care*, vol. 36, no. 1, pp. 8–27, Jan. 1998, doi: 10.1097/00005650-199801000-00004.

[50] L. E. Levesque, J. A. Hanley, A. Kezouh, and S. Suissa, "Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes," *BMJ*, vol. 340, no. mar12 1, pp. b5087–b5087, Mar. 2010, doi: 10.1136/bmj.b5087.

[51] O. M. Dekkers and R. H. H. Groenwold, "When observational studies can give wrong answers: the potential of immortal time bias.," *Eur. J. Endocrinol.*, vol. 184, no. 1, pp. E1–E4, Jan. 2021, doi: 10.1530/EJE-20-1124.

[52] P.-C. Chen, Y.-T. Chan, H.-F. Chen, M.-C. Ko, and C.-Y. Li, "Population-Based Cohort Analyses of the Bidirectional Relationship Between Type 2 Diabetes and Depression," *Diabetes Care*, vol. 36, no. 2, pp. 376–382, Feb. 2013, doi: 10.2337/dc12-0473.

[53] C. E. Lloyd *et al.*, "Prevalence and correlates of depressive disorders in people with Type 2 diabetes: results from the International Prevalence and Treatment of Diabetes and Depression (INTERPRET-DD) study, a

collaborative study carried out in 14 countries," *Diabet. Med.*, vol. 35, no. 6, pp. 760–769, Jun. 2018, doi: 10.1111/dme.13611.

[54] N. M. H. Tran, Q. N. L. Nguyen, T. H. Vo, T. T. A. Le, and N. H. Ngo, "Depression Among Patients with Type 2 Diabetes Mellitus: Prevalence and Associated Factors in Hue City, Vietnam," *Diabetes, Metab. Syndr. Obes. Targets Ther.*, vol. Volume 14, pp. 505–513, Feb. 2021, doi: 10.2147/DMSO.S289988.

[55] Emerging Risk Factors Collaboration *et al.*, "Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies.," *Lancet (London, England)*, vol. 375, no. 9733, pp. 2215–22, Jun. 2010, doi: 10.1016/S0140-6736(10)60484-9.

[56] J. L. Harding, M. E. Pavkov, D. J. Magliano, J. E. Shaw, and E. W. Gregg, "Global trends in diabetes complications: a review of current evidence," *Diabetologia*, vol. 62, no. 1, pp. 3–16, Jan. 2019, doi: 10.1007/s00125-018-4711-2.

[57] A. M. Meraya and M. Alwhaibi, "Health related quality of life and healthcare utilization among adults with diabetes and kidney and eye complications in the United States," *Health Qual. Life Outcomes*, vol. 18, no. 1, p. 85, Dec. 2020, doi: 10.1186/s12955-020-01336-w.

[58] P. E. Greenberg, A.-A. Fournier, T. Sisitsky, C. T. Pike, and R. C. Kessler, "The Economic Burden of Adults With Major Depressive Disorder in the United States (2005 and 2010)," *J. Clin. Psychiatry*, vol. 76, no. 02, pp. 155–162, Feb. 2015, doi: 10.4088/JCP.14m09298.

[59] R. I. G. Holt *et al.*, "Correlates of psychological care strategies for people with diabetes in the second Diabetes Attitudes, Wishes and Needs (DAWN2 ™) study," *Diabet. Med.*, vol. 33, no. 9, pp. 1174–1183, Sep. 2016, doi: 10.1111/dme.13109.

[60] F. Senese *et al.*, "Measuring costs of community mental health care in Italy: A prevalence-based study," *Eur. Psychiatry*, vol. 51, pp. 34–41, Jun. 2018, doi: 10.1016/j.eurpsy.2018.02.001.

[61] T. Vos *et al.*, "Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019," *Lancet*, vol. 396, no. 10258, pp. 1204–1222, Oct. 2020, doi:

10.1016/S0140-6736(20)30925-9.

[62] D. F. Santomauro *et al.*, "Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. COVID-19 Mental Disorders Collaborators.," *Lancet*, vol. 398, no. 10312, pp. 1700–1712, Nov. 2021, doi: 10.1016/S0140-6736(21)02143-7.

[63] M. M. Hossain *et al.*, "Epidemiology of mental health problems in COVID-19: a review," *F1000Research*, vol. 9, p. 636, Jun. 2020, doi: 10.12688/f1000research.24457.1.

[64] Italian Civil Protection Department, "Official Italian data about COVID-19," 2020. https://github.com/pcm-dpc/COVID-19 (accessed Jul. 07, 2022).

[65] C. Bosetti *et al.*, "A real world analysis of COVID-19 impact on hospitalizations in older adults with chronic conditions from an Italian region.," *Sci. Rep.*, vol. 12, no. 1, p. 13704, Aug. 2022, doi: 10.1038/s41598-022-17941-2.

[66] A. Nath, K. L. Sudarshan, G. K. Rajput, S. Mathew, K. R. R. Chandrika, and P. Mathur, "A rapid assessment of the impact of coronavirus disease (COVID- 19) pandemic on health care & service delivery for noncommunicable diseases in India.," *Diabetes Metab. Syndr.*, vol. 16, no. 10, p. 102607, Sep. 2022, doi: 10.1016/j.dsx.2022.102607.

[67] N. Salari *et al.*, "Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis.," *Global. Health*, vol. 16, no. 1, p. 57, 2020, doi: 10.1186/s12992-020-00589-w.

[68] M. Necho, M. Tsehay, M. Birkie, G. Biset, and E. Tadesse, "Prevalence of anxiety, depression, and psychological distress among the general population during the COVID-19 pandemic: A systematic review and meta-analysis.," *Int. J. Soc. Psychiatry*, vol. 67, no. 7, pp. 892–906, Nov. 2021, doi: 10.1177/00207640211003121.

[69] A. M. Chao *et al.*, "Changes in the Prevalence of Symptoms of Depression, Loneliness, and Insomnia in U.S. Older Adults With Type 2 Diabetes During the COVID-19 Pandemic: The Look AHEAD Study.," *Diabetes Care*, vol. 45, no. 1, pp. 74–82, 2022, doi: 10.2337/dc21-1179.

[70] J. W. Sacre *et al.*, "Impact of the COVID-19 pandemic and lockdown

restrictions on psychosocial and behavioural outcomes among Australian adults with type 2 diabetes: Findings from the PREDICT cohort study.," *Diabet. Med.*, vol. 38, no. 9, p. e14611, 2021, doi: 10.1111/dme.14611.

[71] E. Coma *et al.*, "Primary care in the time of COVID-19: monitoring the effect of the pandemic and the lockdown measures on 34 quality of care indicators calculated for 288 primary care practices covering about 6 million people in Catalonia.," *BMC Fam. Pract.*, vol. 21, no. 1, p. 208, 2020, doi: 10.1186/s12875-020-01278-8.

[72] B. Kowall, K. Kostev, R. Landgraf, H. Hauner, R. Bierwirth, and W. Rathmann, "Effects of the COVID-19 pandemic on clinically diagnosed psychiatric disorders in persons with type 2 diabetes.," *Diabet. Med.*, vol. 39, no. 8, p. e14852, 2022, doi: 10.1111/dme.14852.

[73] A. Sisó-Almirall, B. Kostov, E. Sánchez, J. Benavent-Àreu, and L. González de Paz, "Impact of the COVID-19 Pandemic on Primary Health Care Disease Incidence Rates: 2017 to 2020.," *Ann. Fam. Med.*, vol. 20, no. 1, pp. 63–68, doi: 10.1370/afm.2731.

[74] K. Wikström, M. Linna, and T. Laatikainen, "The impact of the COVID-19 pandemic on incident cases of chronic diseases in Finland.," *Eur. J. Public Health*, Aug. 2022, doi: 10.1093/eurpub/ckac107.

[75] M. Delmastro and G. Zamariola, "Depressive symptoms in response to COVID-19 and lockdown: a cross-sectional study on the Italian population," *Sci. Rep.*, vol. 10, no. 1, p. 22457, Dec. 2020, doi: 10.1038/s41598-020-79850-6.

[76] G. Pietro Vigezzi *et al.*, "COVID-19 pandemic impact on people with diabetes: results from a large representative sample of Italian older adults.," *Prim. Care Diabetes*, vol. 16, no. 5, pp. 650–657, Oct. 2022, doi: 10.1016/j.pcd.2022.06.001.

[77] A. Somma *et al.*, "A longitudinal study on clinically relevant self-reported depression, anxiety and acute stress features among Italian community-dwelling adults during the COVID-19 related lockdown: Evidence of a predictive role for baseline dysfunctional personality dime," *J. Affect. Disord.*, vol. 282, pp. 364–371, 2021, doi: 10.1016/j.jad.2020.12.165.

[78] American Diabetes Association, "Standards of Medical Care in Diabetes-

2020 Abridged for Primary Care Providers.," *Clin. Diabetes*, vol. 38, no. 1, pp. 10–38, Jan. 2020, doi: 10.2337/cd20-as01.

[79] J. Speight *et al.*, "Data on diabetes-specific distress are needed to improve the quality of diabetes care," *Lancet*, vol. 397, no. 10290, p. 2149, Jun. 2021, doi: 10.1016/S0140-6736(21)00633-4.

[80] Corrao G *et al.*, "Developing and validating a novel multisource comorbidity score from administrative data: a large population-based cohort study from Italy," *BMJ Open*, vol. 7, issue 12, Dec. 2017, doi:10.1136/bmjopen-2017-019503

Supplementary Materials

Supplementary material 1 - ICD-9-CM diagnosis and surgery procedure codes of acute and long-term diabetes complications.

Diabetes complications	**ICD-9-CM diagnosis and surgery procedure codes**
Acute	coma (250.3, 251.0) hyperosmolarity (250.2) hypoglycaemia (251.2) ketoacidosis (250.1, 276.2)
Long-term	
Cardio-Cerebrovascular	acute myocardial infarction (410) cerebrovascular disease (433, 435-437) diabetes circulatory complications (250.7) gangrene (785.4) hischemic/emorragic stroke (430-432, 434) hypertension (402.01; 402.11; 402.91; 404.01; 404.11; 404.91) ischemic heart disease (411-414) other hearth disease (428, 429.1) peripheral artery disease, (440.2; 440.3; 443.81) ulcers (707.1)
Neuropathy	disorders of the peripheral nervous system (354-355, 357.2) neuropathy (350; 351; 378.51; 378.52; 378.53; 378.54) peripheral autonomic neuropathy (337.1)
Renal	acute renal kidney (584) chronic renal disease, nephritic syndrome (585, 581.81) diabetes renal complications (250.4) dialysis (V45.1; V56.1; V56.2; V56.3)
Ophthalmic	diabetes ophthalmic complications (250.5) disorders of the eye and adnexa (362.0; 362.01; 362.02; 362.55, 364.42, 365.63, 369) maculopathy (362.07)
Amputations	surgery procedure code (84.11; 84.12; 84.13; 84.15; 84.17)
Diabetes with other specified or unspecified complications	diabetes with other specified manifestations (250.8) diabetes with unspecified complication (250.9)

Supplementary material 2 - ICD-9-CM diagnosis codes of depression.

ICD-9-CM diagnosis codes of depression	
Depression	296.2, 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.3, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.9, 296.90, 296.99, 300.4, 309.0, 309.1, 311.

Supplementary material 3 - ICD-9-CM diagnosis and ATC codes of comorbid conditions.

Comorbidity	ICD-9-CM and ATC codes
Other mental disorders	**ATC:** Anxiety/obsessive-compulsive disorder (N05B), Bipolar disorders (N05AN), Psychosis (N05A) excluding (N05AN), Addictive Disorders (N07B) **ICD-9-CM:** Psychoses (293.8, 295, 296.04, 296.14, 296.44, 296.54, 297, 298), Drug Abuse (292, 304, 305.2, 305.3, 305.4, 305.5, 305.6, 305.7, 305.8, 305.9, V65.42), Alcohol Abuse (265.2, 291.1, 291.2, 291.3, 291.5, 291.8, 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0, 571.1, 571.2, 571.3, 980, V11.3)
Neurological disorders	**ATC:** Epilepsy (N03A, N05CD08) excluding (N03AA02, N03AE01, N03AF01, N03AG02, N03AX09, N03AX12, N03AX16, N03AX21), Dementia (N06D, N06BX13), Parkinson disease (N04) excluding (N04BC01) **ICD-9-CM:** Dementia (290, 290.0, 290.1, 290.10, 290.11, 290.12, 290.13, 290.2, 290.20, 290.21, 290.3, 290.4, 290.40, 290.41, 290.42, 290.43, 290.8, 290.9, 294.1, 294.10, 294.11, 331.2, 331.0, 293.0, 293.1, 293.9, 294.0, 294.8, 294.9, 310.0, 310.1, 310.2, 310.8, 310.9), Other Neurological Disorders (331.9, 332.0, 332.1, 333.4, 333.5, 333.92, 334, 335, 3362, 340, 341, 345, 348.1, 348.3, 780.3, 784.3)
Respiratory illness	**ATC :** R03 **ICD-9-CM:** 416.8, 416.9, 490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505, 506.4, 508.1, 508.8
Hypothyroidism	**ATC:** H03A **ICD-9-CM:** 240.9, 243, 244, 246.1, 246.8
Cancer	**ATC:** H01CB, L01, L02, L03AC, L03AX, L04AX02, L04AX04, L04AX06, V03AF excluding H01CB01, L01AA01, L01DB07, L01XC02, L01XE31, L01XX05, L01XX14, L02AB01, L03AX13 **ICD-9-CM:** Lymphoma (200, 201, 202, 203.0, 238.6), Metastatic Cancer (196, 197, 198, 199), Solid Tumor without Metastasis (140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195)

Supplementary material 4 - Initial antidepressant therapy of patients with diabetes and depression (n=5,146).

Classes of antidepressant drugs	**n**	**%**
No antidepressant drugs	68	1.3%
Tricyclic antidepressants (TCAs)	491	9.5%
Selective serotonin reuptake inhibitors (SSRIs)	2923	56.8%
Serotonin–norepinephrine reuptake inhibitors (SNRIs)	533	10.4%
Other antidepressant drugs	1131	22.0%

Supplementary material 5 – Additional analysis conducted to compare the incidence of different diseases or conditions in people with type 2 diabetes in four subperiods between 2020 and 2019.

Disease or condition	P1	P2	P3	P4
	HR (95% CI)	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
2020 cohort vs. 2019 cohort				
Neoplasms	0.99 (0.80-1.23)	0.77 (0.59-1.00)	**0.81 (0.70-0.93)***	**0.69 (0.59-0.80)*****
Hypothyroidism	0.84 (0.59-1.18)	**0.63 (0.42-0.95)***	0.86 (0.66-1.10)	0.89 (0.65-1.23)
Gout	**1.56 (1.31-1.85)*****	**0.61 (0.49-0.77)*****	0.98 (0.88-1.10)	1.05 (0.90-1.22)
Coagulation defects	0.87 (0.33-2.25)	0.46 (0.20-1.07)	0.95 (0.56-1.59)	0.84 (0.45-1.58)
Dementia	1.03 (0.73-1.48)	1.02 (0.72-1.45)	1.01 (0.84-1.22)	1.02 (0.82-1.26)
Other neurological diseases	**1.79 (1.05-3.04)***	0.60 (0.35-1.04)	0.97 (0.72-1.29)	0.79 (0.56-1.10)
Glaucoma	1.08 (0.85-1.37)	**0.27 (0.17-0.43)*****	**0.81 (0.66-0.98)***	1.03 (0.83-1.29)
Epilepsy	**1.59 (1.31-1.92)*****	0.83 (0.65-1.05)	**1.15 (1.01-1.31)***	0.90 (0.76-1.06)
Parkinson's disease	1.38 (0.93-2.05)	**0.50 (0.29-0.87)***	1.16 (0.89-1.51)	1.36 (0.97-1.91)
Arrhythmia	1.00 (0.83-1.21)	**0.58 (0.46-0.73)*****	**0.86 (0.75-0.99)***	0.94 (0.81-1.10)
Cystic fibrosis	0.90 (0.46-1.74)	1.15 (0.52-2.58)	0.86 (0.54-1.37)	1.02 (0.60-1.72)
Liver diseases	0.85 (0.57-1.27)	0.81 (0.48-1.38)	0.94 (0.70-1.25)	0.95 (0.67-1.34)
Crohn's and ulcerative colitis	1.50 (1.00-2.25)	**0.43 (0.26-0.69)*****	0.92 (0.72-1.17)	1.13 (0.81-1.56)
Kidney disease	**0.77 (0.61-0.96)***	0.96 (0.74-1.24)	**0.86 (0.74-1.00)***	0.86 (0.72-1.02)
Pain and inflammation	1.00 (0.9-1.11)	**0.78 (0.68-0.88)*****	**0.89 (0.82-0.96)***	0.95 (0.86-1.05)

* p<0.05; *** p<0.001; **P1**: January, 1 – March, 9; **P2**: March 10 – May, 3; **P3**: May, 4 – September, 30; **P4**: October, 1 – December, 31; **HR**: Hazard ratio; **95% CI**: Confidence interval 95%

Footnote: For the two cohorts of people with type 2 diabetes (2020 cohort and 2019 cohort), the new onset of each disease or condition was ascertained using the Hospital Discharge Records and/or Pharmaceutical Prescriptions databases; for each disease or condition, patients with a history of that specific disease or condition in the 3 years preceding the date of cohort entry were excluded.

The Hazard Ratio with 95% CI was calculated as the ratio between the probability of developing each disease or condition between 2020 cohort and 2019 cohort in the four pandemic subperiods. The list of codes of each disease and condition are reported as follow [80]:

Disease or condition	**HUDs used to detect diseases or conditions**	
	HDR	*Pharmaceutical Prescriptions*
2020 vs. 2019		
Neoplasms	140.0x-172.9x, 174.0x-175.9x,179.x-195.8x, 196.0x-199.1x, 200.00-202.38, 202.50-203.01, 203.8x, 238.6x, 273.3x, V10.0x-V10.9x, V10.71, V10.72, V10.79	L01, C07AB05, L03AC, L03AA, A04
Hypothyroidism	243.x-244.2, 244.8x, 244.9x	H03A, H03B
Gout	274.x	M04AC01, M04AA, M04AB
Coagulation defects	286.0x-286.9x, 287.1x, 287.3x-287.5x	
Dementia	290.x	
Other neurological diseases	331.9x, 332.0x, 333.4x, 333.5x, 334.0x-335.9x, 340.x, 341.1x-341.9x, 345.00-345.11, 345.40-345.51, 345.80-345.91, 348.1x, 348.3x, 780.3x, 784.3x	
Glaucoma	365.x	S01E
Epilepsy	345.x	N03AA, N03AB02, N03AB05, N03AB52, N03AX
Parkinson's disease	332x	N04B, N04BD01
Arrhythmia	426.10, 426.11, 426.13, 426.20-426.53, 426.60-426.89, 427.0x, 427.2x, 427.31, 427.60,427.9x, 785.0x, V45.0x, V53.3x	C01BA, C01BC, C01BD
Cystic fibrosis	277.0	R05CB, R05FB01, R05FA01, A09AA02
Liver diseases	070.32, 070.33, 070.54, 456.0x, 456.1x, 456.20, 456.21, 571.0x, 571.2x, 571.3x, 571.40-571.49, 571.5x, 571.6x, 571.8x, 571.9x, 572.3x, 572.8x, V42.7x	A06AD
Crohn’s and ulcerative colitis	555.x-556.x	A07EC01, A07EC03, A07EC02
Kidney disease	582.x, 583.0, 583.1, 583.4, 583.7, 583.8, 584.6, 585.x, 586.x, 588.x	V01AE01
Pain and inflammation		N02, M01A

HUDs: Healthcare Utilization Databases; **HDR**: Hospital Discharge Records