diabetesresearchandclinicalpractice 209 (2024) 111561

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

A multi-state analysis of disease trajectories and mental health transitions in patients with type 2 diabetes: A population-based retrospective cohort study utilizing health administrative data

Jacopo Lenzi [a], Rossella Messina [a,*], Simona Rosa [a], Marica Iommi [b], Paola Rucci [a], Maria Pia Fantini [a], Paolo Di Bartolo [c]

[a] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[b] Department of Biomedical Sciences and Public Health, Marche Polytechnic University, Ancona, Italy
[c] Diabetes Unit, Local Healthcare Authority of Romagna, Ravenna, Italy

ARTICLE INFO

Keywords:
AGE-IT
Diabetes Mellitus, Type 2
Depression
Dementia
Epidemiology
Multi-State Survival Analysis

ABSTRACT

Aims: To investigate the risk of major depression and dementia in patients with type 2 diabetes, including dementia resulting from depression, and their impact on diabetes-related complications and mortality.
Methods: We conducted a population-based retrospective cohort study including 11,441 incident cases of diabetes in 2015–2017, with follow-up until 2022. A multi-state survival analysis was performed on a seven-state model with 15 transitions to capture disease progression and onset of mental disorders.
Results: Eight-year probabilities of depression, dementia, diabetes-related complications, and death were 9.7% (95% CI 8.7–10.7), 0.9% (95% CI 0.5–1.3), 10.4% (95% CI 9.5–11.4), and 14.8% (95% CI 13.9–15.7), respectively. Depression increased the risk of dementia up to 3.7% (95% CI 2.0–5.4), and up to 10.3% (95% CI 0.3–20.4) if coupled with diabetes complications. Eight-year mortality was 37.5% (95% CI 33.1–42.0) after depression, 74.1% (95% CI 63.7–84.5) after depression plus complications, 76.4% (95% CI 68.8–83.9) after dementia, and 98.6% (95% CI 96.1–100.0) after dementia plus complications.
Conclusions: The interconnections observed across depression, dementia, complications, and mortality underscore the necessity for comprehensive and integrated approaches in managing diabetes. Early screening for depression, followed by timely and targeted interventions, may mitigate the risk of dementia and improve diabetes prognosis.

1. Introduction

The growing evidence indicating an increased risk of major depression among individuals diagnosed with type 2 diabetes is reinforcing its recognition as a significant complication of this chronic condition [1,2]. Many authors argue that psychosocial distress arising from the threat of complications, self-management demands, unresponsive healthcare providers, and unsupportive interpersonal relationships is the primary factor contributing to depression onset in individuals with diabetes [3–5]. While cerebral microvascular dysfunction originating from hyperglycemia, obesity, insulin resistance, and hypertension may be associated with an increased risk of depression [6], the prevailing opinion is that depression is tied to the clinical diagnosis of type 2 diabetes rather than the underlying hyperglycemia defining that diagnosis [7].

Type 2 diabetes also heightens the risk of cognitive decline and dementia, including Alzheimer's disease and vascular dementia [8,9]. As discussed by Biessels et al. [10], manifestations of vascular disease and alterations in glucose, insulin, and amyloid metabolism may underlie the pathophysiology connecting diabetes and dementia. Moreover, depression has been identified as a comorbid condition potentially associated with increased cognitive dysfunction in people with diabetes [11]. Importantly, the combined association of both depression and diabetes with the risk of dementia is stronger than the additive association of each exposure individually, suggesting a complex interaction between these conditions when they co-occur [5]. However, the

* Corresponding author at: Department of Biomedical and Neuromotor Sciences, University of Bologna, Section of Hygiene, Public Health and Medical Statistics, Via San Giacomo 12, 40126 Bologna, BO, Italy.
E-mail address: rossella.messina3@unibo.it (R. Messina).

https://doi.org/10.1016/j.diabres.2024.111561
Received 15 December 2023; Received in revised form 25 January 2024; Accepted 30 January 2024
Available online 5 February 2024

mechanisms that could explain this synergistic relationship remain largely unknown [12].

Because diabetes with comorbid depression and/or dementia is widely regarded as a risk factor for worse health outcomes than diabetes alone [1,10,13,14], an integrated approach is warranted in managing these conditions, particularly considering the mediating role of depression. However, many of the findings outlined above originate from experimental designs or cross-sectional studies. This underscores the need for large population-based cohort studies to corroborate or complement existing evidence with real-world data, thereby enhancing our understanding of these diseases and informing clinical decision-making. Currently, various innovative statistical tools can be effectively employed in longitudinal observational frameworks to produce meaningful real-world evidence. Among these techniques, multi-state models offer several advantages over more conventional methods, such as standard survival analysis [15,16]. The flexibility of the multi-state approach allows for a comprehensive, "holistic" exploration of disease pathways by modeling transitions through a succession of "intermediate states" that a patient may undergo (e.g., disease progression, disease-related complications, or new clinical conditions) until reaching a certain endpoint or "absorbing state", typically mortality or censoring. The estimates obtained from multi-state survival analysis convey the probability of being in a particular state over time given an initial state. This translates into two clinically meaningful pieces of information: understanding the probability of incurring single or multiple adverse health outcomes within a specified period from disease onset, and determining whether transitioning through a state poses the patient at a higher or lower risk of further disease progression or death. Another advantage provided by multi-state analysis is the opportunity to examine the impact of patient demographic and clinical characteristics on the trajectories of the disease, which may better inform about the actual target groups for treatment and preventive strategies.

Another noteworthy aspect is that, to date, the mental health of individuals with type 2 diabetes has primarily been examined in cross-sectional samples or prevalent cohorts, i.e., among patients with a history of diabetes at baseline. However, we believe it is crucial to focus on the early stages of diabetes to gain insights into a critical phase during which patients may face a higher risk of disease progression and mental health problems, particularly among older adults [1]. This would contribute to answer an open question regarding the optimal screening frequency for mental health and cognitive impairment [10].

Taking all these premises into account, the present study aims to achieve three main objectives: (i) to investigate the risk of developing major depression and dementia in patients with type 2 diabetes, including dementia that may result from depression, using a multi-state approach; (ii) to assess the risk of acute and long-term complications of diabetes, as well as mortality associated with major depression and/or dementia; (iii) to identify baseline characteristics associated with disease trajectories, including those that may indicate disparities in the quality of care provided.

While the third study aim is, by its nature, exploratory, the hypotheses behind the first two are as follows: type 2 diabetes represents a risk factor for both depression and dementia, and the co-occurrence of depression increases the risk of dementia development.

2. Subjects, materials and methods

2.1. Setting and data sources

This retrospective cohort study included all residents in the Local Healthcare Authority (LHA) of Romagna with an estimated onset of type 2 diabetes in 2015–2017. Follow-up lasted up to eight years until December 31, 2022. Romagna's LHA in situated in Northeastern Italy and serves ~ 1,123,000 inhabitants as of January 1, 2023. Data sources, each with a unique patient identifier, included (see Supplementary Table S1 for details):

- Hospital Discharge Records (in italian, *Schede di dimissione ospedaliera* [SDO]);
- Residential Care Discharge Records (*Schede di dimissione residenziale* [SDRES]);
- Mental Health Information System (*Sistema informativo salute mentale* [SISM]);
- Integrated Home Care (*Assistenza domiciliare integrata* [ADI]);
- Residential and Semi-Residential Healthcare for the Elderly (*Assistenza residenziale e semi-residenziale anziani* [FAR]);
- Outpatient Pharmaceutical Database (*Assistenza farmaceutica territoriale* [AFT] and *Farmaci a erogazione diretta* [FED]);
- Vital Registration System (*Registro mortalità* [REM]).

2.2. Inclusion and exclusion criteria

Incident cases of type 2 diabetes were identified based on meeting either of these two inclusion criteria (sources: SDO, AFT, and FED) [1]:

- Hospital admission with a primary or secondary diagnosis of diabetes (coded as 250 according to the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]) and a filled prescription of glucose-lowering medication (coded as A10 according to the Anatomical Therapeutic Chemical [ATC] Classification System);
- Three distinct prescriptions of glucose-lowering medications.

The entry date was the hospital admission or the first filled prescription, whichever occurred first. Uncertain cases of type 2 diabetes, i.e., patients with insulin as initial and unique treatment in the first year and women with gestational diabetes (ICD-9-CM code 648.8), were not considered for inclusion in the study. Exclusion criteria were the following:

- Age < 25 years (youth);
- Current or past depression within three years before the estimated onset of diabetes;
- History of dementia within five years before the estimated onset of diabetes;
- Current or past diabetes complications within three years before the estimated onset of diabetes.

This left 11,465 eligible patients out the initial 15,946 (71.9%) for analysis (Supplementary Fig. S1).

2.3. Health outcomes

Four health outcomes—depression, dementia, diabetes complications, and death—were investigated. Depression was defined as an inpatient or outpatient visit with an ICD-9-CM diagnosis of depression or a filled prescription of antidepressant medications (ATC code N06A) (sources: SDO, SDRES, SISM, AFT, and FED) [1]. In accordance with Emilia-Romagna's surveillance algorithm [17], dementia was defined based on the following criteria (sources: SDO, ADI, FAR, AFT, and FED): (i) inpatient admission or home care with an ICD-9-CM diagnosis of dementia, including Alzheimer's disease; (ii) residential care for individuals with dementia and significant behavioral/cognitive impairment; or (iii) ≥ 2 filled prescriptions of anti-dementia medications (ATC codes N06DA02, N06DA03, N06DA04, and N06DX01).

Diabetes complications encompassed acute and long-term conditions (source: SDO) [1]. Acute complications included coma, hyperosmolarity, hypoglycemia, and ketoacidosis, while long-term complications included cardiovascular, cerebrovascular, neuropathic, renal, ophthalmic, amputation, and other unspecified complications. Further details are provided in Supplementary Table S2.

The index date for each outcome was the date of the first event during follow-up. Post-dementia depressive events were not considered

indicative of depression, given common antidepressant use in older individuals with dementia for sundowning and neuropsychiatric symptoms. Moreover, data limitations prevented determining depression recovery or recurrence. For multiple diabetes-complication hospitalizations, only the initial episode was analyzed. Twenty-four patients experiencing depression, dementia, and/or complications simultaneously were excluded, leading to a final cohort of 11,441 individuals.

Data on deaths were retrieved from the vital registration system (REM).

2.4. Exposure variables (Covariates)

Baseline characteristics examined for their association with health outcomes were:

- o Sex (male or female);
- o Age at diabetes onset (in years);
- o Citizenship (Italian or non-Italian);
- o Year at onset (2015, 2016 or 2017);
- o Drugs within 30 days of onset (one oral antidiabetic only, ≥2 oral antidiabetics only, or insulin), as a proxy for timeliness of diagnosis and glycemic control at disease onset;
- o Thirty clinical conditions retrieved up to three years before onset (sources: SDO, AFT, and FED) and summarized using the Multisource Comorbidity Score (MCS) by summing specific weights assigned to each condition, as detailed in Supplementary Table S3 [18];
- o Health district of residence (a total of eight), to investigate potential disparities in the quality of care provided.

In Italy, health districts are responsible for providing primary care and managing local requests for specialist services, diagnostics, and applications for hospital services, both in outpatient and inpatient settings. Although LHAs aim to ensure the uniform delivery of high-quality services, variations in organizational models may exist among health districts.

2.5. Statistical analysis

Categorical variables were summarized as counts and percentages, and numerical variables (age and MCS) were summarized using mean, standard deviation, median, and interquartile range (IQR).

To address our research question, we performed a multi-state survival analysis. As illustrated in Fig. 1, we postulated a seven-state model with 15 transitions to capture disease progression and potential onset of mental disorders over time. Initially, all participants were in the "diabetes" state, which marked the study's starting point. When a first event occurred, participants transitioned to intermediate states (depression, dementia, or complications) or to the final absorbing state of death. Because only a limited number of exclusively acute complications (n = 31) were observed, we did not distinguish between acute and long-term complications in our model.

We considered all possible transitions between intermediate states, even those involving few patients. As detailed in subsection 2.3, patients could not experience multiple episodes of depression, dementia, or complications. Consequently, only the first occurrence was analyzed. For instance, if depression appeared before a complication of diabetes, it could not recur thereafter. Furthermore, post-dementia depression was not incorporated in our multi-state framework, even when mediated by a diabetes complication. The absence of multiple outcomes of the same nature led us to adopt a simplified framework, disallowing reversible transitions across states. However, to capture all depressive and dementia episodes until the final event of each patient, we differentiated between those preceding and following complications. Pre- and post-complication depressions and dementias were combined or separated based on whether the results to be presented encompassed the entire cohort or only patients with a diabetes complication.

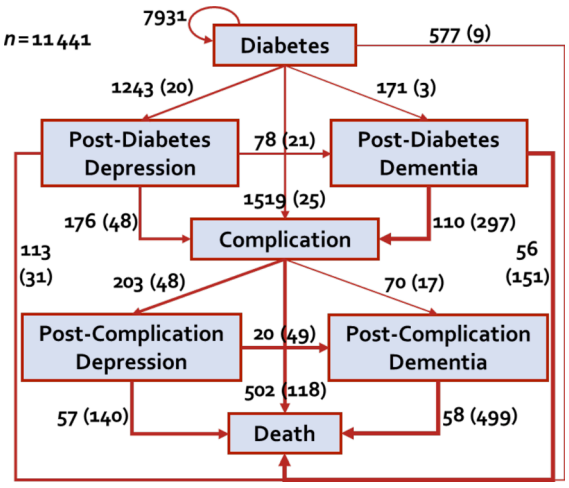

Fig. 1. Summary Plot of States and Transitions Within Eight Years of the Estimated Onset of Type 2 Diabetes. *Notes:* States are indicated by boxes, while transitions between states are indicated by arrows. Data along the arrows represent the number of transitions (incidence per 1000 person-years), with arrow widths proportional to the incidence rates. Complications of diabetes include both acute conditions (coma, hyperosmolarity, hypoglycemia, and ketoacidosis) and long-term conditions, which encompass cardiovascular, cerebrovascular, neuropathic, renal, ophthalmic, amputation, and other unspecified complications. Patients could not experience multiple episodes of depression, dementia, or complications, which means that only the first occurrence was considered in the analysis. Consequently, for example, if a patient experienced depression before a complication of diabetes, it could not reoccur after that. Moreover, post-dementia depression was never allowed in the multi-state framework, not even when mediated by diabetes complications.

Transition probabilities, a clinically relevant metric indicating the probability of being in a specific state over time given an initial state, were computed using the nonparametric Aalen–Johansen estimator [19]. Probabilities were calculated for the entire cohort and stratified by sex (males vs. females), age group (<65 vs. ≥ 65 years), and health district. Estimates were presented in tabular form at relevant timepoints, accompanied by visually informative stacked area plots. The 95 % confidence intervals (CIs) were determined using Greenwood's standard errors [20]. Transition probabilities conditional to states other than the initial one (depression, dementia, and complications) were illustrated with line charts, while 95% CIs were represented as shaded areas. This approach facilitated the assessment of excess risks associated with intermediate states in disease progression.

After the nonparametric analysis, a parametric regression approach was used to assess the independent effects of covariates on transitions, that is, adjusting for potential confounding factors. Here, "independent" denotes the effect of a specific exposure of interest after adjusting for potential confounding factors, accommodating both categorical and continuous variables. Using a separate modeling approach [21,22], we chose the best-fitting parametric distribution family for each transition based on the Akaike information criterion (AIC). The Markov assumption was relaxed for all transitions, making probabilities and intensities dependent only on the time spent in the current state (clock-reset approach) [21]. Covariates included sex, age, citizenship, health district, year, first-line therapy, and MCS.

In cases of few transition events (e.g., from depression to dementia) (Fig. 1), we reduced the set of covariates to avoid overfitting by excluding those with nonsignificant relationships with time-to-event in other models. Except for accelerated failure-time models, we initially tested the proportional hazards (PH) assumption for each covariate using Schoenfeld residuals from Cox regression. In cases of violation, interaction terms between log time and covariates were introduced into parametric models, retaining only those with statistical significance. Effect sizes from final regression models were expressed as hazard ratios

(HRs) for PH models and as time ratios (TRs) for accelerated failure-time models.

Lastly, we estimated the percentage of complications and deaths attributable to depression and dementia. To quantify the impact of removing these exposures, we used the population attributable fraction (PAF). PAF combines the risk of experiencing a health outcome associated with a factor and the occurrence of this factor in the population. The calculation involved comparing rates among patient-years unexposed to dementia and depression with those of the general cohort [23].

To address potential influences of prior cancer diagnoses on the study results, we conducted post-hoc sensitivity analyses excluding participants with a history of cancer [24]. Analyses were performed using Stata 18 [25,26]. The significance level was set to 5%, and all tests were two-tailed.

2.6. Ethics statement

The Ethics Committee of Romagna's LHA granted approval for this research on December 14, 2020 (Registration #9502/2020), with reapproval for extension on September 27, 2023 (Registration #5869/2023).

Emilia-Romagna's health administrative data are pseudonymized at the regional statistical office before analysis. Each individual is assigned a unique patient identifier, eliminating the possibility to trace the patient's identity or access other sensitive data. According to Article 9 of the General Data Protection Regulation (European Union [EU] Regulation 2016/679), pseudonymized administrative data can be used without specific written informed consent when patient information is collected for healthcare management, quality evaluation, and improvement. All procedures adhered to the 1964 Helsinki Declaration and its subsequent amendments.

3. Results

The study comprised 11,441 individuals with a mean age of 60.6 ± 15.1 years at type 2 diabetes onset; 47.6% were female, 84.8% held Italian citizenship, 85.4% were initially prescribed a single oral antidiabetic medication, and 83.4% had an MCS ≤ 4 (Supplementary Table S4). Supplementary Table S3 details conditions contributing to the MCS. Patient case mix showed no notable differences across health districts.

Over a median follow-up of 6.2 years (IQR 5.5–7.1), 1446 (12.6%) patients had a first record of depression, 339 (3.0%) had a first record of dementia, and 1805 (15.8%) had a diabetes-related complication (see Supplementary Table S5 for a breakdown of acute and long-term complications). A total of 1363 (11.9%) individuals died, while 7931 (69.3%) did not experience any of the investigated events during follow-up. Fig. 1 summarizes all states and transitions after diabetes onset, highlighting that only 577 patients (9 per 1000 person-years) died without experiencing any intermediate states, while the transitions with the highest incidence rates were from dementia to complications and from complications to death.

3.1. Nonparametric Multi-State analysis

Table 1, Supplementary Fig. S2, and Fig. 2 display the transition probabilities for our multi-state process, overall and by sex and age group. At eight years, probabilities of depression, dementia, diabetes-

Table 1
Aalen–Johansen Probabilities and 95% Confidence Intervals (%) of Being in Each State for Patients with Type 2 Diabetes up to Eight Years After Onset, Overall and by Sex and Age Group.

Time Since Diabetes Onset	Diabetes Only	Depression	Dementia	Complication	Death
All					
1 year	92.3 (91.8, 92.8)	2.6 (2.3, 2.8)	0.3 (0.2, 0.5)	2.7 (2.4, 3.0)	2.1 (1.9, 2.4)
2 years	87.2 (86.6, 87.8)	4.1 (3.8, 4.5)	0.6 (0.4, 0.7)	4.5 (4.1, 4.9)	3.6 (3.2, 3.9)
4 years	78.8 (78.1, 79.6)	6.7 (6.2, 7.1)	0.8 (0.6, 0.9)	6.9 (6.5, 7.4)	6.8 (6.4, 7.3)
6 years	71.0 (70.1, 71.8)	8.4 (7.8, 8.9)	1.0 (0.8, 1.2)	8.6 (8.1, 9.1)	11.0 (10.4, 11.6)
8 years	64.2 (62.8, 65.5)	9.7 (8.7, 10.7)	0.9 (0.5, 1.3)	10.4 (9.5, 11.4)	14.8 (13.9, 15.7)
Males					
1 year	92.1 (91.4, 92.8)	1.9 (1.6, 2.3)	0.3 (0.1, 0.4)	3.3 (2.9, 3.8)	2.4 (2.0, 2.8)
2 years	86.8 (85.9, 87.6)	2.9 (2.5, 3.3)	0.4 (0.2, 0.5)	5.8 (5.2, 6.4)	4.1 (3.6, 4.6)
4 years	77.8 (76.7, 78.8)	5.1 (4.5, 5.6)	0.5 (0.3, 0.7)	8.9 (8.2, 9.6)	7.7 (7.1, 8.4)
6 years	69.8 (68.6, 71.0)	6.2 (5.6, 6.9)	0.7 (0.4, 0.9)	10.9 (10.0, 11.7)	12.5 (11.6, 13.3)
8 years	63.4 (61.7, 65.0)	7.5 (6.5, 8.5)	0.4 (0.1, 0.7)	12.7 (11.3, 14.1)	16.0 (14.9, 17.2)
Females					
1 year	92.5 (91.8, 93.2)	3.3 (2.8, 3.7)	0.5 (0.3, 0.6)	2.0 (1.6, 2.4)	1.8 (1.4, 2.2)
2 years	87.6 (86.7, 88.5)	5.5 (4.9, 6.1)	0.8 (0.6, 1.0)	3.1 (2.6, 3.6)	3.0 (2.5, 3.4)
4 years	80.0 (78.9, 81.0)	8.4 (7.7, 9.2)	1.1 (0.8, 1.3)	4.8 (4.2, 5.3)	5.8 (5.2, 6.4)
6 years	72.2 (71.0, 73.4)	10.7 (9.9, 11.6)	1.5 (1.1, 1.8)	6.1 (5.4, 6.8)	9.5 (8.7, 10.3)
8 years	65.0 (62.7, 67.3)	12.3 (10.7, 13.9)	1.4 (0.7, 2.0)	7.9 (6.7, 9.2)	13.4 (12.1, 14.8)
Adults (25–64 y)					
1 year	95.8 (95.3, 96.3)	2.0 (1.7, 2.4)	0.0 (0.0, 0.1)	1.3 (1.1, 1.6)	0.8 (0.5, 1.0)
2 years	93.0 (92.4, 93.6)	3.5 (3.1, 4.0)	0.1 (0.0, 0.1)	2.1 (1.8, 2.5)	1.3 (1.0, 1.6)
4 years	88.1 (87.3, 88.9)	5.7 (5.1, 6.2)	0.2 (0.1, 0.2)	3.9 (3.4, 4.4)	2.2 (1.9, 2.6)
6 years	82.9 (82.0, 83.9)	7.6 (6.9, 8.2)	0.2 (0.1, 0.4)	5.7 (5.2, 6.3)	3.5 (3.1, 4.0)
8 years	78.5 (77.2, 79.9)	9.0 (8.0, 10.0)	0.2 (0.1, 0.4)	7.7 (6.6, 8.7)	4.6 (4.0, 5.2)
Older Adults (≥65 y)					
1 year	87.7 (86.7, 88.6)	3.2 (2.7, 3.7)	0.7 (0.5, 1.0)	4.5 (3.9, 5.0)	3.9 (3.4, 4.5)
2 years	79.6 (78.5, 80.7)	5.0 (4.4, 5.6)	1.2 (0.9, 1.5)	7.7 (6.9, 8.4)	6.5 (5.8, 7.2)
4 years	66.7 (65.4, 68.0)	8.0 (7.2, 8.7)	1.6 (1.2, 1.9)	10.9 (10.1, 11.8)	12.8 (11.9, 13.8)
6 years	55.3 (53.9, 56.7)	9.4 (8.6, 10.2)	2.1 (1.7, 2.5)	12.4 (11.4, 13.3)	20.9 (19.7, 22.0)
8 years	45.1 (42.5, 47.8)	10.5 (8.7, 12.2)	1.9 (0.9, 2.8)	14.2 (12.5, 16.0)	28.3 (26.5, 30.1)

Notes: Complications of diabetes include both acute conditions (coma, hyperosmolarity, hypoglycemia, and ketoacidosis) and long-term conditions, which encompass cardiovascular, cerebrovascular, neuropathic, renal, ophthalmic, amputation, and other unspecified complications. Cases of depression occurring before and after complication were added together to form a single state, as well as cases of pre- and post-complication dementia. Patients in the "diabetes-only" state may have experienced clinical conditions different from depression, dementia, and diabetes complications. The slight decrease in dementia figures at eight years of follow-up is possibly related to small sample sizes and high mortality rates.

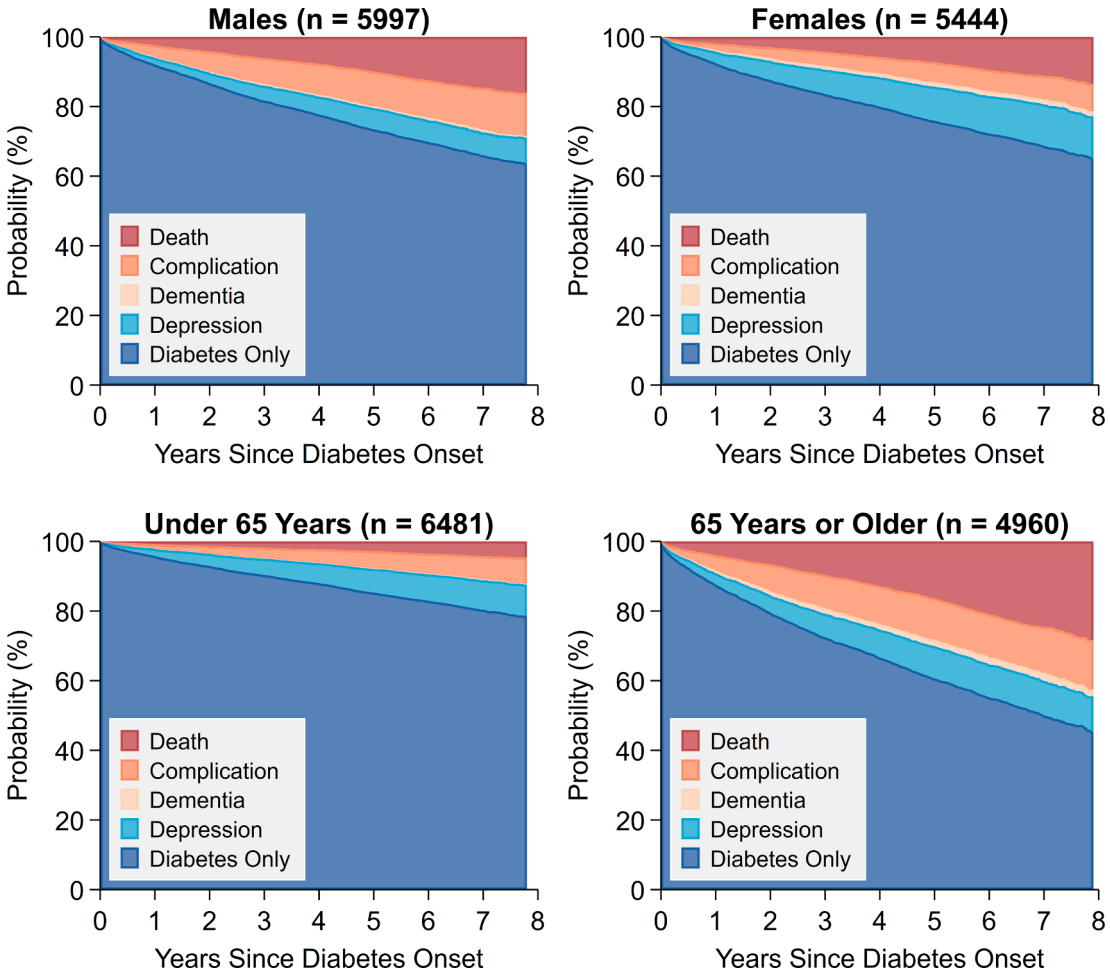

Fig. 2. Aalen–Johansen Stacked Probabilities of Being in Each State for Patients with Type 2 Diabetes up to Eight Years After Onset, by Sex and Age Group. *Notes:* Complications of diabetes include both acute conditions (coma, hyperosmolarity, hypoglycemia, and ketoacidosis) and long-term conditions, which encompass cardiovascular, cerebrovascular, neuropathic, renal, ophthalmic, amputation, and other unspecified complications. Cases of depression occurring before and after complication were added together to form a single state, as well as cases of pre- and post-complication dementia. Patients in the "diabetes-only" state may have experienced clinical conditions different from depression, dementia, and diabetes complications.

related complications, and death were 9.7% (95% CI 8.7–10.7), 0.9% (95% CI 0.5–1.3), 10.4% (95% CI 9.5–11.4), and 14.8% (95% CI 13.9–15.7), respectively, with 64.2% (95% CI 62.8–65.5) expected event-free survival. Compared to men, women had higher eight-year depression rates (12.3% [95% CI 10.7–13.9] vs. 7.5% [95% CI 6.5–8.5]), but lower diabetes complications (7.9% [95% CI 6.7–9.2] vs. 12.7% [95% CI 11.3–14.1]) and death rates (13.4% [95% CI 12.1–14.8] vs. 16.0% [95% CI 14.9–17.2]). Dementia rates showed no appreciable sex difference (females: 1.4% [95% CI 0.7–2.0]; males: 0.4% [95% CI 0.1–0.7]). Individuals aged $\geq$ 65 years were more likely to be in the dementia state (1.9% [95% CI 0.9–2.8] vs. 0.2% [95% CI 0.1–0.4]), complications state (14.2% [95% CI 12.5–16.0] vs. 7.7% [95% CI 6.6–8.7]), and death state (28.3% [95% CI 26.5–30.1] vs. 4.6% [95% CI 4.0–5.2]) than those aged 25–64. Supplementary Table S6 and Fig. S3 reveal consistent probability estimates across all health districts.

Fig. 3 depicts transition probabilities conditional to diabetes and intermediate states. As shown in the upper-left panel, a diabetes complication appeared as a potential risk for higher depression rates but lacked statistical significance, as the 95 % CIs included depression probability from state #1 (diabetes onset) for most of the follow-up. Moving to the upper-right panel, depression and complications significantly increased the risk of dementia development. Following depression, the probability peaked at $\sim$ 2 years (3.7%, 95% CI 2.0–5.4), surpassing the risk of dementia with diabetes alone after eight years (2.5% [95% CI 1.2–3.9] vs. 0.9% [95% CI 0.5–1.3]). A diabetes complication increased dementia risk for much of the follow-up, peaking at $\sim$ 2 years (2.6%, 95% CI 0.8–4.4), as did a complication followed by depression (10.3%, 95% CI 0.3–20.4).

As shown in the lower-left panel, depression and dementia were significant risk factors for diabetes-related complications. The overall eight-year complication risk of 10.4% rose to 16.8% (95% CI 14.5–19.1) when preceded by depression and 17.0% (95% CI 11.5–22.5) when preceded by dementia. The risk of complications following dementia peaked at 37.5% (95% CI 23.7–51.4) within just one year of follow-up, exceeding the overall complication rate of 10.4% by more than three-fold. The lower-right panel illustrates that the overall eight-year death risk of 14.8% increased to 37.5% (95% CI 33.1–42.0) if preceded by depression, 76.4% (95% CI 68.8–83.9) if preceded by dementia, 77.0% (95% CI 70.9–83.0) if preceded by diabetes complications, and 74.1% (95% CI 63.7–84.5) if preceded by complications plus depression. Diabetes complications followed by dementia virtually nullified eight-year survival, with a morality rate of 98.6% (95% CI 96.1–100.0).

3.2. *Parametric Multi-State analysis*

Supplementary Table S7 lists AIC values for survival distributions fitted to the 15 multi-state transitions, while Table 2 presents the best-fitting survival models with independent covariate effects across

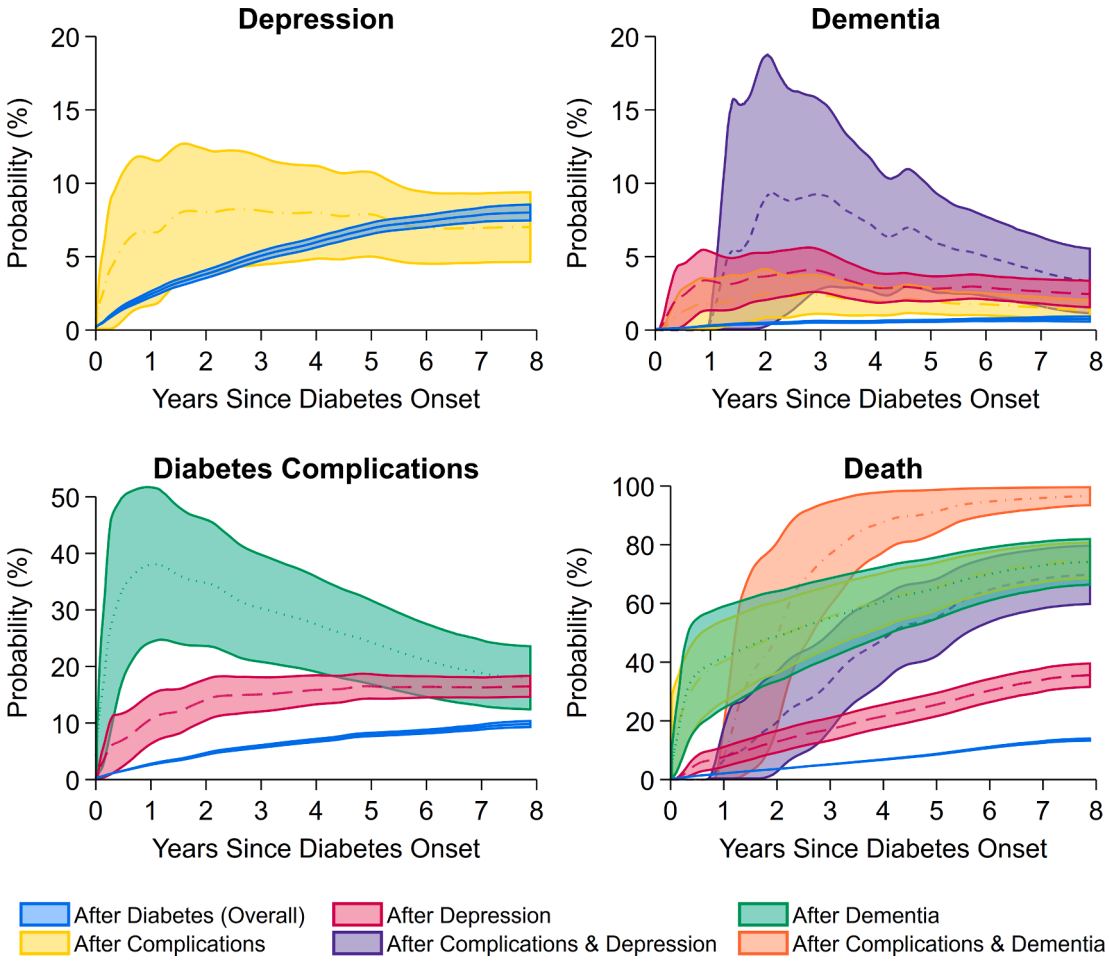

Fig. 3. Aalen–Johansen Transition Probabilities (and 95% Confidence Intervals) to Depression, Dementia, Complications, and Death Conditional to the Initial State (Type 2 Diabetes) and to the Intermediate States of the Multi-State Process. *Notes:* Complications of diabetes include both acute conditions (coma, hyperosmolarity, hypoglycemia, and ketoacidosis) and long-term conditions, which encompass cardiovascular, cerebrovascular, neuropathic, renal, ophthalmic, amputation, and other unspecified complications. Cases of depression occurring before and after complication were analyzed separately, as well as cases of pre- and post-complication dementia. For clarity, all estimates were smoothed over time using a running mean with a 0.1 bandwidth and a tricube weighting function.

transitions. Increasing age strongly correlated with all transitions, showing significant HRs and TRs, depending on the model, for one-year age increments. Females, compared to males, had a higher risk of transitioning from diabetes to depression but a better prognosis for complications and death, both before and after depression. The health district of residence, except for a potential spurious decreased risk of post-complication depression in Riccione, was unrelated to disease trajectories. Non-Italian residents had a significantly decreased risk of depression and dementia following diabetes onset.

Therapies indicating poor glycemic control at disease onset were associated with higher risks of transitioning to diabetes-related complications and death, as were elevated MCS values indicating multiple serious comorbid conditions at baseline. Increasing MCS was also linked to significantly shorter transitions to depression and dementia. Lastly, the year of disease onset showed no association with outcomes for each transition, suggesting an absence of trends in disease epidemiology and management over the study period.

3.3. Adverse health outcomes attributable to depression and dementia

Supplementary Table S8 shows that 10.3% (95% CI 8.5–12.1) of the 1805 diabetes-related complications within eight years of disease onset could be attributed to post-diabetes depression and/or dementia. When examining depression and dementia individually, PAFs were 6.1% (95% CI 4.5–7.6) and 5.6% (95% CI 4.4–6.7), respectively. Dementia PAF was higher in females than in males, and notably higher in older patients compared to adults.

Supplementary Tables S9 and S10 present PAF for deaths occurring before and after diabetes complications, respectively. Overall, 17.5% (95% CI 14.3–20.7) of pre-complication mortality was attributable to depression and/or dementia, a value rising to 28.9% (95% CI 23.8–33.6) for post-complication mortality. Depression alone had similar PAFs for pre- and post-complication mortality, while dementia PAF for pre-complication mortality was lower than for post-complication mortality.

A sensitivity analysis excluding 496 patients with a history of cancer did not yield substantial changes in the results (data not shown).

4. Discussion

In this cohort study, the first to use a multi-state analytic approach for exploring disease trajectories and mental health transitions in type 2 diabetes, we estimated that 14.8% of patients would die within eight years of disease onset, while 10.4% would develop diabetes-related complications. The relatively low rates of complications, compared to recent data from the literature [27], suggest effective disease control and management within our study cohort. Moreover, the observed depression rate of 9.7% exceeds the national average of 6.4% reported by the Italian National Institute of Health during the COVID-19 pandemic [28]. This finding supports prior research [8,10], including a large population-based study in Italy that highlights the role of major

Table 2
Results of Parametric Survival Models Showing Independent Covariate Effects Across All Transitions of the Multi-State Process.

Covariate	Diabetes → Depression		Diabetes → Dementia		Diabetes → Complication		Diabetes → Death		Depression → Dementia	
	#1: 1243 Uncensored Events		**#2:** 171 Uncensored Events		**#3:** 1519 Uncensored Events		**#4:** 577 Uncensored Events		**#5:** 78 Uncensored Events	
	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value	TR† (95 % CI)	*p*-value
Female Sex	1.55 (1.38, 1.74)	<0.001***	1.23 (0.90, 1.68)	0.19	0.57 (0.51, 0.63)	<0.001***	0.62 (0.53, 0.74)	<0.001***	1.71 (0.80, 3.66)	0.17
Age, y	1.02 (1.02, 1.03)	<0.001***	1.14 (1.12, 1.16)	<0.001***	1.06 (1.05, 1.06)	<0.001***	1.07 (1.07, 1.08)	<0.001***	0.82 (0.78, 0.87)	<0.001***
Non-Italian Citizenship	0.82 (0.67, 0.99)	0.04*	0.21 (0.05, 0.84)	0.03*	0.89 (0.72, 1.09)	0.26	0.76 (0.51, 1.15)	0.20	*(omitted)*	*(omitted)*
Health District of Residence										
Ravenna	Ref.		Ref.		Ref.		Ref.			
Lugo	1.10 (0.90, 1.35)	0.36	0.84 (0.44, 1.62)	0.61	0.94 (0.77, 1.15)	0.57	0.90 (0.65, 1.24)	0.51	*(omitted)*	*(omitted)*
Faenza	1.09 (0.86, 1.37)	0.48	0.96 (0.48, 1.92)	0.90	1.14 (0.93, 1.41)	0.21	1.22 (0.87, 1.70)	0.25	*(omitted)*	*(omitted)*
Forlì	1.03 (0.85, 1.25)	0.74	1.40 (0.85, 2.30)	0.19	1.13 (0.95, 1.33)	0.17	1.04 (0.79, 1.37)	0.77	*(omitted)*	*(omitted)*
Cesena - Valle del Savio	0.96 (0.77, 1.19)	0.69	1.14 (0.63, 2.08)	0.66	1.18 (0.97, 1.42)	0.10	1.15 (0.84, 1.57)	0.38	*(omitted)*	*(omitted)*
Rimini	1.09 (0.91, 1.30)	0.36	1.44 (0.90, 2.31)	0.13	1.15 (0.98, 1.35)	0.10	1.08 (0.83, 1.40)	0.59	*(omitted)*	*(omitted)*
Riccione	0.96 (0.77, 1.21)	0.73	1.43 (0.81, 2.52)	0.22	1.04 (0.85, 1.27)	0.71	1.09 (0.79, 1.49)	0.60	*(omitted)*	*(omitted)*
Rubicone	1.15 (0.92, 1.44)	0.23	0.78 (0.34, 1.78)	0.56	1.09 (0.88, 1.37)	0.42	1.03 (0.72, 1.48)	0.88	*(omitted)*	*(omitted)*
Year at Onset (2015–17)	1.03 (0.96, 1.10)	0.43	0.86 (0.72, 1.04)	0.12	0.94 (0.88, 1.00)	0.05	0.98 (0.88, 1.08)	0.67	1.47 (0.84, 2.58)	0.18
First-Line Therapy										
One oral antidiabetic	Ref.		Ref.		Ref.		Ref.		Ref.	
Two or more antidiabetics	1.02 (0.82, 1.27)	0.86	1.47 (0.88, 2.44)	0.14	1.48 (1.25, 1.76)	<0.001***	0.95 (0.68, 1.33)	0.76	0.86 (0.20, 3.67)	0.84
Insulin	1.03 (0.82, 1.31)	0.79	1.16 (0.57, 2.38)	0.68	1.79 (1.49, 2.14)	<0.001***	1.64 (1.22, 2.21)	0.001**	0.41 (0.08, 2.15)	0.29
MCS‡	1.23 (1.17, 1.29)	<0.001***	0.80 (0.67, 0.94)	0.007**	1.26 (1.20, 1.32)	<0.001***	1.66 (1.54, 1.78)	<0.001***	1.09 (0.78, 1.52)	0.61
Insulin × ln(Time)	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	0.73 (0.66, 0.81)	<0.001***	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*
MCS‡ × ln(Time)	*(omitted)*	*(omitted)*	0.83 (0.76, 0.90)	<0.001***	*(omitted)*	*(omitted)*	0.89 (0.86, 0.93)	<0.001***	*(omitted)*	*(omitted)*

Covariate	Depression → Complication		Depression → Death		Dementia → Complication		Dementia → Death		Complication → Depression	
	#6: 176 Uncensored Events		**#7:** 113 Uncensored Events		**#8:** 110 Uncensored Events		**#9:** 56 Uncensored Events		**#10:** 203 Uncensored Events	
	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value
Female Sex	0.56 (0.41, 0.76)	<0.001***	0.44 (0.30, 0.64)	<0.001***	0.45 (0.30, 0.67)	<0.001***	0.40 (0.24, 0.69)	0.001**	1.24 (0.93, 1.67)	0.15
Age, y	1.06 (1.04, 1.07)	<0.001***	1.05 (1.04, 1.07)	<0.001***	1.06 (1.03, 1.09)	<0.001***	1.05 (1.02, 1.09)	0.002**	1.03 (1.01, 1.04)	<0.001***
Non-Italian Citizenship	0.85 (0.40, 1.79)	0.67	0.72 (0.25, 2.02)	0.53	1.60 (0.33, 7.82)	0.56	*(omitted)*	*(omitted)*	1.39 (0.80, 2.44)	0.24
Health District of Residence										
Ravenna	Ref.		Ref.		Ref.				Ref.	
Lugo	1.03 (0.56, 1.90)	0.92	0.76 (0.41, 1.43)	0.39	0.58 (0.25, 1.35)	0.20	*(omitted)*	*(omitted)*	1.11 (0.66, 1.85)	0.70
Faenza	1.88 (1.05, 3.39)	0.04*	0.73 (0.34, 1.60)	0.43	1.72 (0.77, 3.82)	0.19	*(omitted)*	*(omitted)*	1.04 (0.62, 1.75)	0.89
Forlì	1.62 (0.96, 2.75)	0.07	0.59 (0.30, 1.15)	0.12	1.39 (0.71, 2.69)	0.33	*(omitted)*	*(omitted)*	1.12 (0.72, 1.73)	0.62
Cesena - Valle del Savio	1.59 (0.86, 2.94)	0.14	0.72 (0.33, 1.58)	0.41	0.79 (0.36, 1.72)	0.55	*(omitted)*	*(omitted)*	0.85 (0.49, 1.46)	0.56
Rimini	1.51 (0.91, 2.52)	0.11	1.14 (0.67, 1.94)	0.64	0.79 (0.41, 1.54)	0.49	*(omitted)*	*(omitted)*	0.85 (0.54, 1.32)	0.46
Riccione	1.87 (1.03, 3.38)	0.04*	0.48 (0.18, 1.23)	0.13	0.86 (0.38, 1.97)	0.73	*(omitted)*	*(omitted)*	0.40 (0.19, 0.82)	0.01*
Rubicone	1.20 (0.63, 2.31)	0.58	0.72 (0.34, 1.54)	0.40	1.36 (0.45, 4.11)	0.59	*(omitted)*	*(omitted)*	0.95 (0.52, 1.74)	0.88
Year at Onset (2015–17)	1.01 (0.84, 1.22)	0.90	0.80 (0.63, 1.01)	0.06	0.79 (0.61, 1.00)	0.05	0.88 (0.64, 1.22)	0.45	1.09 (0.93, 1.29)	0.29
First-Line Therapy										
One oral antidiabetic	Ref.		Ref.		Ref.				Ref.	
Two or more antidiabetics	1.09 (0.62, 1.90)	0.77	0.63 (0.27, 1.46)	0.28	0.80 (0.39, 1.62)	0.53	*(omitted)*	*(omitted)*	0.96 (0.59, 1.55)	0.86
Insulin	1.82 (1.02, 3.26)	0.04*	1.64 (0.81, 3.30)	0.17	0.58 (0.18, 1.91)	0.37	*(omitted)*	*(omitted)*	0.85 (0.51, 1.44)	0.55
MCS‡	1.24 (1.09, 1.42)	0.002**	1.26 (1.06, 1.49)	0.009**	1.04 (0.89, 1.22)	0.61	1.18 (0.95, 1.45)	0.14	1.04 (0.91, 1.18)	0.57
Sex × ln(Time)	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	0.59 (0.40, 0.85)	0.005**
MCS‡ × ln(Time)	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	1.14 (1.04, 1.26)	0.008**	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*

Covariate	Complication → Dementia		Complication → Death		Depression → Dementia		Depression → Death		Dementia → Death	
	#11: 70 Uncensored Events		**#12:** 502 Uncensored Events		**#13:** 20 Uncensored Events		**#14:** 57 Uncensored Events		**#15:** 58 Uncensored Events	
	TR† (95 % CI)	*p*-value	HR (95 % CI)	*p*-value	TR† (95 % CI)	*p*-value	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value
Female Sex	0.53 (0.25, 1.12)	0.10	1.04 (0.86, 1.24)	0.71	4.65 (0.76, 28.6)	0.10	0.51 (0.29, 0.88)	0.02*	0.48 (0.27, 0.84)	0.01*
Age, y	0.89 (0.85, 0.93)	<0.001***	1.07 (1.06, 1.08)	<0.001***	0.86 (0.77, 0.96)	0.007**	1.05 (1.02, 1.09)	<0.001***	1.06 (1.02, 1.09)	0.002**

(*continued on next page*)

Table 2 (*continued*)

Covariate	Complication → Dementia		Complication → Death		Depression → Dementia		Depression → Death		Dementia → Death	
	#11: 70 Uncensored Events		**#12:** 502 Uncensored Events		**#13:** 20 Uncensored Events		**#14:** 57 Uncensored Events		**#15:** 58 Uncensored Events	
	TR† (95 % CI)	*p*-value	HR (95 % CI)	*p*-value	TR† (95 % CI)	*p*-value	HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value
Non-Italian Citizenship	*(omitted)*	*(omitted)*	0.53 (0.28, 1.01)	0.05	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*
Health District of Residence										
Ravenna			Ref.							
Lugo	*(omitted)*	*(omitted)*	1.21 (0.86, 1.70)	0.27	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*
Faenza	*(omitted)*	*(omitted)*	1.05 (0.73, 1.52)	0.77	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*
Forlì	*(omitted)*	*(omitted)*	1.26 (0.94, 1.69)	0.13	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*
Cesena - Valle del Savio	*(omitted)*	*(omitted)*	1.35 (0.97, 1.88)	0.08	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*
Rimini	*(omitted)*	*(omitted)*	1.06 (0.79, 1.42)	0.71	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*
Riccione	*(omitted)*	*(omitted)*	1.10 (0.76, 1.58)	0.61	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*
Rubicone	*(omitted)*	*(omitted)*	1.14 (0.77, 1.70)	0.52	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*
Year at Onset (2015–17)	0.86 (0.51, 1.43)	0.55	0.90 (0.81, 1.00)	0.06	*(omitted)*	*(omitted)*	1.07 (0.79, 1.46)	0.65	0.85 (0.60, 1.20)	0.36
First-Line Therapy										
One oral antidiabetic			Ref.							
Two or more antidiabetics	*(omitted)*	*(omitted)*	0.91 (0.67, 1.25)	0.56	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*
Insulin	*(omitted)*	*(omitted)*	0.93 (0.64, 1.33)	0.68	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*
MCS‡	1.25 (0.90, 1.74)	0.18	1.04 (0.96, 1.13)	0.36	*(omitted)*	*(omitted)*	1.18 (0.95, 1.47)	0.12	1.03 (0.82, 1.29)	0.82
Age × ln(Time)	*(omitted)*	*(omitted)*	1.01 (1.00, 1.01)	0.005**	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*	*(omitted)*

Notes: Depression and dementia from transition #10 onwards occur after acute or long-term complications of diabetes, and involve patients with no prior history of depression or dementia before the onset of complications (incident events). Using a separate modeling approach, we applied the best fitting parametric model to each transition based on the Akaike information criterion (see Supplementary Table S7 for details). When the number of uncensored events was small, we reduced the set of covariates to avoid overfitting and spurious associations. In this process, we sacrificed covariates with no significant relationships with time-to-event in other models, marking them as "omitted". With the exception of lognormal models, we initially tested the proportional-hazard assumption using Schoenfeld residuals from Cox regression. In case of violation, interaction terms between log time and covariates were introduced into the parametric models, retaining only those exhibiting statistical significance.

*p-value < 0.05; **p-value < 0.01; ***p-value < 0.001.

†Time ratio (TR) is the effect size resulting from accelerated failure-time models such as the lognormal used to parametrize most transitions to dementia (#5, #11 and #13). If TR > 1, the effect of the covariate acts to increase the patient's survival; if TR < 1, the patient's survival is reduced.

‡Transformed using the inverse hyperbolic sine to mitigate severe right-skewness while preserving zero values. The analysis of martingale residuals, however, did not suggest the need for transforming numeric variables (MCS and age).

Abbreviations: HR, hazard ratio; CI, confidence interval; TR, time ratio; MCS, Multisource Comorbidity Score.

depression as a complication of type 2 diabetes [1].

Notably, dementia accounted for 0.9% of transition probabilities at the end of the follow-up period. This low figure originates from a case-definition algorithm that captures only cases with medium-to-severe cognitive impairment [17]. However, we observed that dementia was associated with elevated mortality rates at eight years, particularly when co-occurring with depression and/or complications (>50%), leading to substantial attributable fractions in the population.

In line with previous research [1,5,6,9,27,29], we found a differential effect of sex and age on various health outcomes, with women showing a higher susceptibility to depression but a lower likelihood of experiencing diabetes complications and mortality compared to men. Individuals aged $\geq$ 65 years exhibited elevated probabilities of experiencing depression, dementia, complications, and mortality when compared with the younger members of the cohort. We also observed that non-Italian residents had lower rates of depression and dementia following diabetes onset, possibly due to lower healthcare access compared to Italian citizens [30]. On the contrary, no significant differences were found across health districts, suggesting a substantially uniform healthcare provision to residents with type 2 diabetes in the LHA of Romagna.

When referring to the third objective of our study, the absence of positive deviants (i.e., health districts consistently showing high performance in survival rates) discourages the need for mixed-methods investigations to extrapolate specific local characteristics that might have an impact on the health outcomes of the patient population [31]. However, further multi-state analysis may focus on contextual variables retrieved at a smaller territorial level, such as general practice organizational models and proximity to green areas—variables that may still play a prognostic role in shaping the disease trajectories of individuals with type 2 diabetes.

Our multi-state analysis provides valuable insights into the pathways that link type 2 diabetes, mental health outcomes, and complications, emphasizing the role of depression and dementia in molding the clinical course of the disease. Consistent with findings from other studies [1,32], individuals with depression were more likely to experience diabetes complications at eight years (16.8%) than those with diabetes alone (10.4%). This underscores the need for integrated physical and mental healthcare to foster medication adherence and glucose control, aiming to prevent the negative impact of major depression on self-care and self-efficacy [13,14]. While the use of information and communication technologies has been shown to be effective in reducing depression symptoms, their impact on glycemic control remains unclear and deserves further investigation [33]. The analysis also identifies depression as a significant risk factor for subsequent dementia development, especially two years after diabetes onset (3.7%), suggesting shared pathophysiological mechanisms, such as inflammation and neurodegeneration, that are involved in both conditions [5,6,12,34].

A bidirectional relationship was found between post-diabetes dementia and diabetes-related complications, with dementia leading to a complication risk of 37.5% after only one year of diabetes onset, and complications being in turn associated with increased incidence of dementia for most of the follow-up, peaking at 2.6% after two years. Another result highlighting the interconnection and potentially multiplicative effect between mental conditions and diabetes is that complications coupled with depression were associated with an impressive dementia rate of 10.3% within two years of diabetes onset.

Encouraging findings from the literature recognize metformin, a first-line oral therapy in a significant proportion of patients [35], as a neuroprotective agent effective in slowing down cognitive decline in patients with type 2 diabetes [36,37]. Glucagon-like peptide-1 (GLP-1) receptor agonists have also shown impressive clinical potential for the treatment of dementia, Alzheimer's disease, and Parkinson's disease [38,39]. Although further research is needed, these treatment options have the potential to address cognitive decline in patients with type 2 diabetes, especially those dealing with major depression and aging.

Our study further emphasizes the significant impact of depression, dementia, and diabetes complications on mortality in individuals with type 2 diabetes. The overall eight-year mortality rate of 14.8% significantly increased when these mental health conditions were present (37.5% for depression and 76.4% for dementia), especially when dementia occurred in conjunction with diabetes complications (98.6%). We also found that complications, whether alone or in conjunction with depression, were associated with a mortality rate of ~ 75%. These results reinforce the cruciality of integrating early prevention and treatment strategies for optimal diabetes control, reduced diabetes distress, and preserved cognitive function [34,40]. Collaborative care models involving both primary and specialist care professionals could enhance the management of these complex comorbidities through the introduction of early psychosocial screening activities, mental health interventions, and targeted treatments within diabetes care pathways [1,41,42].

Notably, the latest "Standards of Care in Diabetes" published in 2023 by the American Diabetes Association (ADA) recommend, with strong support from high-grade research evidence, the screening of all patients with type 2 diabetes for depression and anxiety using validated tools during the initial visit and at regular annual check-ups. When indicated, the guidelines further advise collaborative referrals to qualified behavioral or mental health professionals for comprehensive evaluation and targeted treatment [43,44]. Moreover, the ADA proposes a similar screening approach to assess cognitive performance in individuals aged 65 or older [43,45]. In case of altered, declining or absent ability to perform diabetes self-care behaviors, a lay care professional should be involved to serve the capacities of day-to-day monitoring, and alternative teaching approaches to diabetes education should be considered [44]. The guidelines also emphasize the importance of simplifying diabetes treatment plans in the presence of cognitive impairment to minimize the risk of hypoglycemia [43].

To reduce the significant share of complications and mortality attributable to post-diabetes depression and dementia, it is imperative to integrate the ADA's standards of care into clinical practice and promote their widespread adoption across diabetes care pathways.

4.1. Study Limitations

This study has several limitations. First, our analyses used strict inclusion criteria, potentially limiting the generalizability of results to a broader population of individuals with type 2 diabetes. However, our study was designed to focus on the early stages of diabetes within the first years of disease onset. These initial years are critical, as they are expected to be associated with a higher risk of disease progression and mental health problems. Effectively managing the disease during this period requires active involvement of both patients and healthcare professionals.

Second, health administrative data did not allow us to track the actual dates of diagnosis for diabetes, dementia, and depression. Instead, we estimated disease onset using secondary information based on healthcare consumption, such as hospitalizations and drug dispensations. This limitation hindered our ability to disentangle the etiopathogenesis of mental conditions and diabetes complications. For instance, we could not distinguish isolated depression events from depression-like prodromal manifestations of dementia, or determine the extent to which cases of dementia observed during follow-up were already present, albeit latently, at the study's onset. Another limitation inherent to administrative data is the inability to identify patients recovering from depression or from sequelae of diabetes complications.

Third, we did not have access to electronic medical records from general practice and diabetes clinics, nor to the roster of residents with medical exemption certificates for diabetes and dementia to claim free prescriptions. This information would have greatly improved the accuracy of our case-definition algorithms. Furthermore, the criteria we adopted, in line with our previous work on depression and Emilia-

Romagna's dementia surveillance [1,17], might suffer from suboptimal specificity for depression and suboptimal sensitivity for dementia.

Fourth, we developed a relatively simplified multi-state model that did not account for reverse transitions, cause-specific mortality, and, most importantly, physical disability, cancer, and other chronic conditions that play a key role in the loss of independence and increased impairment in daily life. We chose this simplification based on the understanding that adding states and transitions would complicate data analysis and interpretation, partly due to sparse data that arise when considering a larger number of states. Nevertheless, parametric regression analysis was adjusted for baseline comorbidities, and results obtained after restricting the cohort to patients with no history of cancer fully confirmed our primary study findings. Another simplification of the model is that all states were considered mutually exclusive, although complications of diabetes can coexist with depression or dementia.

Fifth, we lacked access to relevant information on social determinants (e.g., poor education, un- and underemployment, social exclusion, etc.) and behavioral risk factors (e.g., alcohol and tobacco use, diet, physical activity, etc.) that negatively influence both physical and mental health outcomes. These variables, along with clinical data not available in administrative databases (e.g., body mass index), would have strengthened risk adjustment when comparing sexes, age groups and health districts, and would have provided further insights into individual characteristics affecting the disease trajectory and prognosis of type 2 diabetes.

Lastly, we did not distinguish long-term complications into micro- and macro-vascular events. Similarly, we were unable to provide distinct transition probabilities for acute complications, in particular hypoglycemia, due to very low numbers that suggest the virtual impossibility of tracking such events from hospitalizations.

4.2. Conclusions

The study's focus on the early stages of type 2 diabetes and its multi-state approach contribute to the growing body of real-world evidence on the interwoven relationships between type 2 diabetes, mental health outcomes, and complications. The bidirectional associations observed among depression, dementia, and diabetes complications, along with their substantial impact on mortality, underscore the necessity for a comprehensive and integrated approach in managing patients with type 2 diabetes. Early screening for depression, followed by timely and targeted interventions, may not only enhance patients' mental well-being but also mitigate the risk of dementia and reduce the incidence of diabetes-related complications.

This study also introduces semi-Markov multi-state analysis as a versatile tool with the potential to contribute valuable insights to diabetes research [46]. This is achieved by estimating transition probabilities conditional on baseline characteristics and intermediate states that shape the trajectories of the disease. Further applications of multi-state modeling are warranted, particularly in investigating secondary and tertiary prevention strategies for type 2 diabetes. This may include exploring the modifying effects of specific antidiabetic medications on the association between early glycemic exposure and long-term outcomes, a phenomenon commonly referred to as "metabolic memory" [47], as well as testing the effectiveness of regular screening activities and medication persistence.

CRediT authorship contribution statement

Jacopo Lenzi: Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Rossella Messina:** Writing – review & editing, Validation, Methodology, Conceptualization. **Simona Rosa:** Validation, Data curation. **Marica Iommi:** Validation, Data curation. **Paola Rucci:** Writing – review & editing, Validation, Methodology, Conceptualization. **Maria Pia Fantini:** Validation, Data curation. **Paolo Di Bartolo:** Writing – review & editing, Validation, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Prof. Gianluca Fiorentini from the University of Bologna for providing valuable insights and assistance in conceptualizing the practical implications of our work.

Funding

This study received support as part of the Next Generation EU Project titled "*PE8 - AGE-IT: A Novel Public-Private Alliance to Generate Socio-economic, Biomedical and Technological Solutions for an Inclusive Italian Ageing Society*" (Grant #PE0000015). This project represents a hub-and-spoke enlarged partnership involving 27 universities, institutes, and agencies operating in Italy. It is funded under Mission #4 ("*Istruzione e ricerca*"), Component #2 ("*Dalla ricerca all'impresa*"), Investment #1.3 ("*Partenariati allargati estesi a nuiversità, centri di ricerca, imprese e finanziamento progetti di ricerca di base*") of the National Recovery and Resilience Plan (NRRP). Prof. Lenzi leads Task #4.1 ("Integrating datasets on healthcare consumption, organizational settings and economic incentives for health promotion and prevention programs") within Work Package #4 ("Policies to improve the compliance with organizational and clinical guidelines in programs of health promotion and prevention for aging adults") of the AGE-IT Spoke #10 ("Mainstreaming ageing by building institutional mechanisms for better and future-oriented policy making"). Dr. Messina is supported by an AGE-IT NRRP research fellowship (Project #J33C22002900006).

The study funder had no role in the study design, data collection, data analysis, data interpretation, report writing, or decision to submit the paper for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2024.111561.

References

[1] Messina R, Iommi M, Rucci P, Reno C, Fantini MP, Lunghi C, 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 2022;59(1):95–104. https://doi.org/10.1007/s00592-021-01791-x.

[2] van Gennip ACE, Schram MT, Köhler S, Kroon AA, Koster A, Eussen SJPM, et al. Association of type 2 diabetes according to the number of risk factors within the recommended range with incidence of major depression and clinically relevant depressive symptoms: a prospective analysis. Lancet Healthy Longev 2023;4(2):e63–71. https://doi.org/10.1016/S2666-7568(22)00291-4.

[3] Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of comorbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. Diabet Med 2006;23(11):1165–73. https://doi.org/10.1111/j.1464-5491.2006.01943.x.

[4] Fisher L, Skaff MM, Mullan JT, Arean P, Glasgow R, Masharani U. A longitudinal study of affective and anxiety disorders, depressive affect and diabetes distress in adults with Type 2 diabetes. Diabet Med 2008;25(9):1096–101. https://doi.org/10.1111/j.1464-5491.2008.02533.x.

[5] Katon WJ, Lin EH, Williams LH, Ciechanowski P, Heckbert SR, Ludman E, et al. Comorbid depression is associated with an increased risk of dementia diagnosis in patients with diabetes: a prospective cohort study. J Gen Intern Med 2010;25(5):423–9. https://doi.org/10.1007/s11606-009-1248-6.

[6] van Sloten TT, Sedaghat S, Carnethon MR, Launer LJ, Stehouwer CDA. Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. Lancet Diabetes Endocrinol 2020;8(4):325–36. https://doi.org/10.1016/S2213-8587(19)30405-X.

[7] Bergmans RS, Rapp A, Kelly KM, Weiss D, Mezuk B. Understanding the relationship between type 2 diabetes and depression: lessons from genetically informative study designs. Diabet Med 2021;38(2):e14399.

[8] Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review [published correction appears in Lancet Neurol. 2006 Feb;5(2):113]. Lancet Neurol. 2006;5(1):64-74. doi: 10.1016/S1474-4422(05)70284-2.

[9] Dao L, Choi S, Freeby M. Type 2 diabetes mellitus and cognitive function: understanding the connections. Curr Opin Endocrinol Diabetes Obes 2023;30(1):7–13. https://doi.org/10.1097/MED.0000000000000783.

[10] Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nat Rev Endocrinol 2018;14(10):591–604. https://doi.org/10.1038/s41574-018-0048-7.

[11] Geijselaers SLC, Sep SJS, Stehouwer CDA, Biessels GJ. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review [published correction appears in Lancet Diabetes Endocrinol. 2015 Jan;3(1):e1]. Lancet Diabetes Endocrinol. 2015;3(1):75-89. doi: 10.1016/S2213-8587(14)70148-2.

[12] Carr AL, Sluiman AJ, Grecian SM, Forster R, McLachlan S, Strachan MWJ, et al. Depression as a risk factor for dementia in older people with type 2 diabetes and the mediating effect of inflammation. Diabetologia 2021;64(2):448–57. https://doi.org/10.1007/s00125-020-05301-6.

[13] Jiang R, Ta X, Xu M, Luo Z, Du Y, Zhong X, et al. Mediating Role of Depression Between Diabetes Management Self-Efficacy and Diabetes Self-Care Behavior Among Elderly Type 2 Diabetes Mellitus Patients in China. Psychol Res Behav Manag 2023;16:1545–55. https://doi.org/10.2147/PRBM.S396916.

[14] Yorke E, Boima V, Ganu V, Tetteh J, Twumasi L, Ekem-Ferguson G, et al. The mediating role of quality of life on depression and medication adherence among patients with type 2 diabetes mellitus: A cross-sectional study. Health Sci Rep 2023;6(9):e1539.

[15] Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26(11):2389–430. https://doi.org/10.1002/sim.2712.

[16] Meira-Machado L, de Uña-Alvarez J, Cadarso-Suárez C, Andersen PK. Multi-state models for the analysis of time-to-event data. Stat Methods Med Res 2009;18(2):195–222. https://doi.org/10.1177/0962280208092301.

[17] Agenzia Sanitaria e Sociale Regionale dell'Emilia-Romagna. Epidemiologia della demenza in Emilia-Romagna nel 2017 – Analisi attraverso dati amministrativi, https://assr.regione.emilia-romagna.it/pubblicazioni/rapporti-documenti/report-demenza-rer-2017; 2018 [accessed September 27, 2023].

[18] Corrao G, Rea F, Di Martino M, De Palma R, Scondotto S, Fusco D, et al. Developing and validating a novel multisource comorbidity score from administrative data: a large population-based cohort study from Italy. BMJ Open 2017;7(12):e019503.

[19] Aalen OO, Johansen S. An empirical transition matrix for nonhomogeneous Markov-chains based on censored observations. Scand J Stat 1978;5(3):141–50.

[20] Allignol A, Schumacher M, Beyersmann J. Empirical transition matrix of multi-state models: The etm package. J Stat Softw 2011;38(4):1–15. https://doi.org/10.18637/jss.v038.i04.

[21] Crowther MJ, Lambert PC. Parametric multistate survival models: Flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences. Stat Med 2017;36(29):4719–42. https://doi.org/10.1002/sim.7448.

[22] Hill M, Lambert PC, Crowther MJ. Relaxing the assumption of constant transition rates in a multi-state model in hospital epidemiology. BMC Med Res Methodol 2021;21(1):16. https://doi.org/10.1186/s12874-020-01192-8.

[23] Greenland S, Drescher K. Maximum likelihood estimation of the attributable fraction from logistic models. Biometrics 1993;49(3):865–72.

[24] Neumann JT, Thao LTP, Callander E, Carr PR, Qaderi V, Nelson MR, et al. A multistate model of health transitions in older people: a secondary analysis of ASPREE clinical trial data. Lancet Healthy Longev 2022;3(2):e89–97. https://doi.org/10.1016/s2666-7568(21)00308-1.

[25] StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC.

[26] Crowther MJ, Lambert P. 2016. MULTISTATE: Stata module to perform multi-state survival analysis. Statistical Software Components S458207, Boston College Department of Economics, 2016; revised January 18, 2023.

[27] An J, Nichols GA, Qian L, Munis MA, Harrison TN, Li Z, et al. Prevalence and incidence of microvascular and macrovascular complications over 15 years among patients with incident type 2 diabetes. BMJ Open Diabetes Res Care 2021;9(1):e001847.

[28] Istituto Superiore di Sanità. Sorveglianza PASSI (Progressi delle Aziende Sanitarie per la Salute in Italia), https://www.epicentro.iss.it/passi/dati/depressione#dati; 2023 [accessed November 24, 2023].

[29] Tachkov K, Mitov K, Koleva Y, Mitkova Z, Kamusheva M, Dimitrova M, et al. Life expectancy and survival analysis of patients with diabetes compared to the non diabetic population in Bulgaria. PLoS One 2020;15(5):e0232815.

[30] Rucci P, Piazza A, Perrone E, Tarricone I, Maisto R, Donegani I, et al. Disparities in mental health care provision to immigrants with severe mental illness in Italy. Epidemiol Psychiatr Sci 2015;24(4):342–52. https://doi.org/10.1017/S2045796014000250.

[31] O'Hara JK, Grasic K, Gutacker N, Street A, Foy R, Thompson C, et al. Identifying positive deviants in healthcare quality and safety: a mixed methods study. J R Soc Med 2018;111(8):276–91. https://doi.org/10.1177/0141076818772230.

[32] Lin EH, Rutter CM, Katon W, Heckbert SR, Ciechanowski P, Oliver MM, et al. Depression and advanced complications of diabetes: a prospective cohort study. Diabetes Care 2010;33(2):264–9. https://doi.org/10.2337/dc09-1068.

[33] Varela-Moreno E, Carreira Soler M, Guzmán-Parra J, Jódar-Sánchez F, Mayoral-Cleries F, Anarte-Ortíz MT. Effectiveness of eHealth-Based Psychological Interventions for Depression Treatment in Patients With Type 1 or Type 2 Diabetes Mellitus: A Systematic Review. Front Psychol 2022;12:746217. https://doi.org/10.3389/fpsyg.2021.746217.

[34] Lyu F, Wu D, Wei C, Wu A. Vascular cognitive impairment and dementia in type 2 diabetes mellitus: An overview. Life Sci 2020;254:117771. https://doi.org/10.1016/j.lfs.2020.117771.

[35] Fischer J, Ganellin CR. Analogue-based Drug Discovery II. Hoboken, NJ: Wiley; 2010. doi:10.1002/9783527630035.

[36] Campbell JM, Stephenson MD, de Courten B, Chapman I, Bellman SM, Aromataris E. Metformin Use Associated with Reduced Risk of Dementia in Patients with Diabetes: A Systematic Review and Meta-Analysis. J Alzheimers Dis 2018;65(4):1225–36.

[37] Sood A, Capuano AW, Wilson RS, Barnes LL, Kapasi A, Bennett DA, et al. Metformin, age-related cognitive decline, and brain pathology. Neurobiol Aging 2024;133:99–106. https://doi.org/10.1016/j.neurobiolaging.2023.10.005.

[38] Kuate Defo A, Bakula V, Pisaturo A, Labos C, Wing SS, Daskalopoulou SS. Diabetes, antidiabetic medications and risk of dementia: A systematic umbrella review and meta-analysis. Diabetes Obes Metab. 2023. doi: 10.1111/dom.15331. Epub ahead of print.

[39] Nowell J, Blunt E, Gupta D, Edison P. Antidiabetic agents as a novel treatment for Alzheimer's and Parkinson's disease. Ageing Res Rev 2023;89:101979. https://doi.org/10.1016/j.arr.2023.101979.

[40] Srikanth V, Sinclair AJ, Hill-Briggs F, Moran C, Biessels GJ. Type 2 diabetes and cognitive dysfunction-towards effective management of both comorbidities. Lancet Diabetes Endocrinol 2020;8(6):535–45. https://doi.org/10.1016/S2213-8587(20)30118-2.

[41] Markowitz SM, Gonzalez JS, Wilkinson JL, Safren SA. A review of treating depression in diabetes: emerging findings. Psychosomatics 2011;52(1):1–18. https://doi.org/10.1016/j.psym.2010.11.007.

[42] Sharma G, Parihar A, Talaiya T, Dubey K, Porwal B, Parihar MS. Cognitive impairments in type 2 diabetes, risk factors and preventive strategies. J Basic Clin Physiol Pharmacol. 2020;31(2):/j/jbcpp.2020.31.issue-2/jbcpp-2019-0105/jbcpp-2019-0105.xml. doi: 10.1515/jbcpp-2019-0105.

[43] ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al., on behalf of the American Diabetes Association. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes-2023. Diabetes Care. 2023;46(Suppl 1):S49-S67. doi: 10.2337/dc23-S004.

[44] ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. on behalf of the American Diabetes Association. 5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: Standards of Care in Diabetes-2023. Diabetes Care 2023;46(Suppl 1):S68–96. https://doi.org/10.2337/dc23-S005.

[45] ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al., on behalf of the American Diabetes Association. 13. Older Adults: Standards of Care in Diabetes-2023. Diabetes Care. 2023;46(Suppl 1):S216-S229. doi: 10.2337/dc23-S013.

[46] Le-Rademacher JG, Therneau TM, Ou FS. The utility of multistate models: a flexible framework for time-to-event data. Curr Epidemiol Rep 2022;9(3):183–9. https://doi.org/10.1007/s40471-022-00291-y.

[47] Ceriello A, Lucisano G, Prattichizzo F, La Grotta R, Frigé C, De Cosmo S, et al., AMD Annals study group. The legacy effect of hyperglycemia and early use of SGLT-2 inhibitors: a cohort study with newly-diagnosed people with type 2 diabetes. Lancet Reg Health Eur. 202312;31:100666. doi: 10.1016/j.lanepe.2023.100666.