

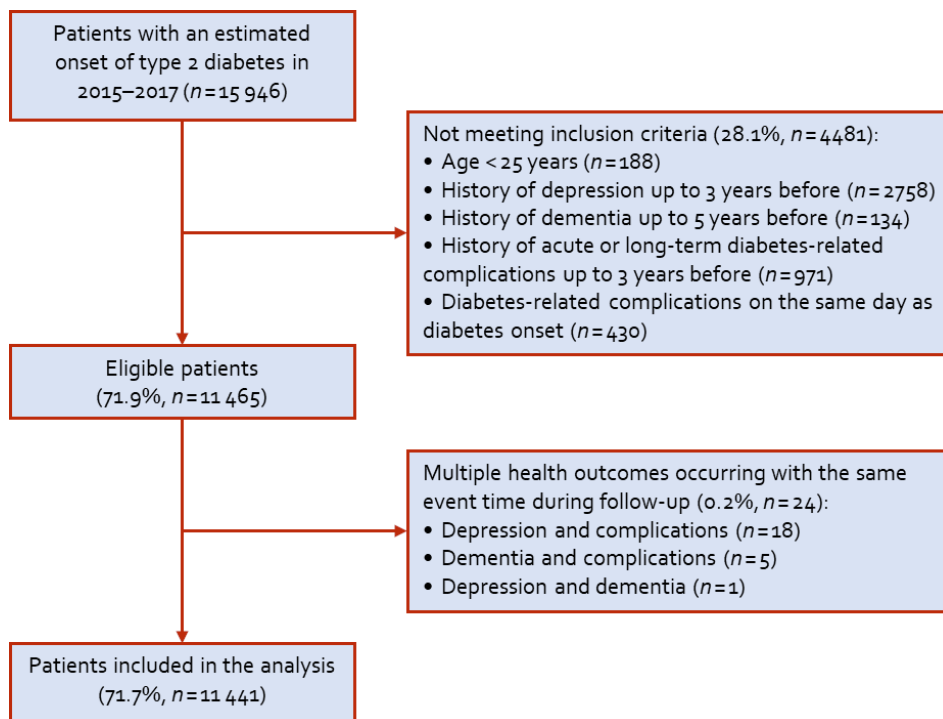
## SUPPLEMENTARY MATERIAL

**Table S1.** Description of Data Sources.

Acronym	Italian Name	English Translation	Description
SDO	<i>Schede di dimissione ospedaliera</i>	Hospital Discharge Records	In operation since 1994, the database includes demographic characteristics (age, sex and health district), admission and discharge dates, primary diagnosis, up to five secondary diagnoses, up to 11 procedures, and discharge status for each patient discharged from either public or accredited private hospitals. Diagnoses and procedures are categorized using the ICD-9-CM, version 2007. The records are submitted by all hospitals operating in Emilia-Romagna to the Regional Authority and, following data quality control, regularly sent from the Regional Authority to the Ministry of Health.
SDRES	<i>Schede di dimissione residenziale</i>	Residential Care Discharge Records	Operational since 2008, it comprises obligatory data on patients discharged from non-profit or accredited private facilities for mental health-related hospital services, including admission and discharge dates, primary diagnosis, and discharge status. Accredited facilities refer to private hospitals where fees are reimbursed by the Italian National Health Service if the patient is an official resident in Italy.
SISM	<i>Sistema informativo salute mentale</i>	Mental Health Information System	In operation since 2005 for administrative and clinical epidemiological purposes. The database records all adult patients who have at least one contact with the Community Mental Health Centers (CMHCs), including their demographic characteristics, ICD-9-CM diagnoses, and details of each type of intervention administered.
ADI	<i>Assistenza domiciliare integrata</i>	Integrated Home Care	Operational since 2002, the database records each episode of integrated home care provided to individual patients in Emilia-Romagna. It encompasses demographic characteristics, socio-health characteristics, and information related to the episode/period of home care provided.
FAR	<i>Assistenza residenziale e semi-residenziale anziani</i>	Residential and Semi-Residential Healthcare for the Elderly	Implemented in 2010 and fed with individual-level data on a quarterly basis. It pertains to non-self-sufficient individuals with chronic and/or clinically stabilized conditions admitted to accredited residential or semi-residential facilities operating in Emilia-Romagna. The database includes socio-demographic information about the care recipient and details about the admission period to the facility.
AFT/FED	<i>Assistenza farmaceutica territoriale/ Farmaci a erogazione diretta</i>	Outpatient Pharmaceutical Database	Operational since 2002, the database pertains to drugs reimbursed by the healthcare system that are prescribed by the family doctor or a specialist (AFT), or directly dispensed by hospital pharmacies (FED). It includes information on patients' demographics (age, sex and health district), prescriptions (substance name, ATC System code—V.2013, trade name, date of prescription, date of dispensation, and number of packages), as well as prescribers.
REM	<i>Registro mortalità</i>	Vital Registration System	Operational since 1995, it includes information on patients' date, place, and cause of death classified according to the ICD-10.

*Abbreviations:* ICD-9-CM, International Classification of Diseases, 9<sup>th</sup> Revision, Clinical Modification; ICD-10, International Classification of Diseases, 10<sup>th</sup> Revision.

**Figure S1.** Diagram Depicting Selection of the Study Population with Type 2 Diabetes Residing in the Local Healthcare Authority of Romagna, Italy.



*Notes:* Uncertain cases of type 2 diabetes (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 and, for this reason, are not included in the flow chart. 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.

**Table S2.** ICD-9-CM Diagnosis Codes Used to Identify Depression, Dementia, and Diabetes-Related Complications.

Description	Code
Depression	
Major depressive disorder single episode	2962
Major depressive disorder recurrent episode	2963
Other and unspecified affective psychoses	2969
Dysthymic disorder	3004
Adjustment disorder with depressed mood	3090
Adjustment reaction with prolonged depressive reaction	3091
Depressive disorder not elsewhere classified	311
Dementia from Inpatient Care (Source: SDO)	
Jakob–Creutzfeldt disease	0461
Senile and presenile organic psychotic conditions	290
Alcohol-induced persisting dementia	2912
Drug-induced persisting dementia	29282
Other organic psychotic conditions (chronic)	294
Other cerebral degenerations (incl. Alzheimer’s disease)	331
Dementia from Integrated Home Care (Source: ADI)	
Senile and presenile organic psychotic conditions	290
Alcoholic psychoses	291
Drug psychoses	292
Other organic psychotic conditions (chronic)	294
Other cerebral degenerations (incl. Alzheimer’s disease)	331
Acute Complications	
Diabetes with ketoacidosis	2501
Diabetes with hyperosmolarity	2502
Diabetes with other coma	2503
Hypoglycemic coma	2510
Hypoglycemia unspecified	2512
Acidosis	2762
Cardiovascular and Cerebrovascular Long-Term Complications	
Diabetes with peripheral circulatory disorders	2507
Malignant hypertensive heart disease with heart failure	40201
Benign hypertensive heart disease with heart failure	40211
Unspecified hypertensive heart disease with heart failure	40291
Hypertensive heart and chronic kidney disease, malignant, with heart failure and stage I–IV kidney disease, or unspecified	40401
Hypertensive heart and chronic kidney disease, benign, with heart failure and stage I–IV kidney disease, or unspecified	40411
Hypertensive heart and chronic kidney disease, unspecified, with heart failure and stage I–IV kidney disease, or unspecified	40491
Ischemic heart disease	410–414
Heart failure	428
Myocardial degeneration	4291
Subarachnoid hemorrhage	430
Intracerebral hemorrhage	431
Other and unspecified intracranial hemorrhage	432
Occlusion and stenosis of precerebral arteries	433
Occlusion of cerebral arteries	434
Transient cerebral ischemia	435
Acute but ill-defined cerebrovascular disease	436
Other and ill-defined cerebrovascular disease	437
Atherosclerosis of native arteries of the extremities	4402
Atherosclerosis of bypass graft of the extremities	4403
Peripheral angiopathy in diseases classified elsewhere	44381
Ulcer of lower limb except decubitus	7071
Gangrene	7854
Neuropathic Long-Term Complications	

Peripheral autonomic neuropathy in disorders classified elsewhere	3371
Trigeminal nerve disorders	350
Facial nerve disorders	351
Mononeuritis of upper limb and mononeuritis multiplex	354
Mononeuritis of lower limb and unspecified site	355
Polyneuropathy in diabetes	3572
Third or oculomotor nerve palsy partial	37851
Third or oculomotor nerve palsy total	37852
Fourth or trochlear nerve palsy	37853
Sixth or abducens nerve palsy	37854
Renal Long-Term Complications	
Diabetes with renal manifestations	2504
Nephrotic syndrome in diseases classified elsewhere	58181
Acute renal failure	584
Chronic renal failure	585
Postsurgical renal dialysis status	V451
Fitting and adjustment of extracorporeal dialysis catheter	V561
Fitting and adjustment of peritoneal dialysis catheter	V562
Fitting and adjustment of peritoneal dialysis catheter	V563
Ophthalmic Long-Term Complications	
Diabetes with ophthalmic manifestations	2505
Diabetic retinopathy	3620
Toxic maculopathy of retina	36255
Rubeosis iridis	36442
Glaucoma associated with vascular disorders of eye	36563
Blindness and low vision	369
Long-Term Complications: Amputations	
Amputation of toe	8411*
Amputation through foot	8412*
Disarticulation of ankle	8413*
Other amputation below knee	8415*
Amputation above knee	8417*
Other Specified or Unspecified Long-Term Complications	
Diabetes with other specified manifestations	2508
Diabetes with unspecified complication	2509

\*ICD-9-CM procedure codes.

Abbreviations: ICD-9-CM, International Classification of Diseases, 9<sup>th</sup> Revision, Clinical Modification; SDO, *Schede di dimissione ospedaliera*; ADI, *Assistenza domiciliare integrata*.

**Table S3.** Prevalence of Individual Comorbid Conditions Included in the Multisource Comorbidity Score (MCS), Obtained From Hospital Discharge Records (HDRs) and Pharmaceutical Databases, up to Three Years Before the Estimated Onset of Type 2 Diabetes, Overall and by Health District of Residence.

Pts	MCS Conditions	All (n=11,441)	Ravenna (n=2379)	Lugo (n=1207)	Faenza (n=953)	Forlì (n=1650)	Cesena* (n=1193)	Rimini (n=2063)	Riccione (n=1074)	Rubicone (n=922)
..	<i>Infectious and Parasitic Diseases</i>									
10	Tuberculosis	10 (0.1%)	1 (0.0%)	2 (0.2%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)	2 (0.2%)
..	<i>Neoplasms</i>	496 (4.3%)	110 (4.6%)	53 (4.4%)	32 (3.4%)	81 (4.9%)	45 (3.8%)	86 (4.2%)	47 (4.4%)	42 (4.6%)
5	Lymphoma	21 (0.2%)	3 (0.1%)	1 (0.1%)	1 (0.1%)	9 (0.5%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	4 (0.4%)
18	Metastatic cancer	134 (1.2%)	27 (1.1%)	9 (0.7%)	9 (0.9%)	20 (1.2%)	15 (1.3%)	28 (1.4%)	15 (1.4%)	11 (1.2%)
10	Cancer without metastasis	391 (3.4%)	86 (3.6%)	42 (3.5%)	27 (2.8%)	61 (3.7%)	31 (2.6%)	74 (3.6%)	40 (3.7%)	30 (3.3%)
5	Malignancy medication	218 (1.9%)	36 (1.5%)	22 (1.8%)	13 (1.4%)	39 (2.4%)	26 (2.2%)	36 (1.7%)	24 (2.2%)	22 (2.4%)
..	<i>Endocrine, Nutritional, Metabolic, and Immunity Disorders</i>	2259 (19.7%)	537 (22.6%)	298 (24.7%)	187 (19.6%)	326 (19.8%)	224 (18.8%)	325 (15.8%)	181 (16.9%)	181 (19.6%)
1	Hypothyroidism	1146 (10.0%)	293 (12.3%)	163 (13.5%)	94 (9.9%)	155 (9.4%)	123 (10.3%)	135 (6.5%)	82 (7.6%)	101 (11.0%)
1	Obesity	73 (0.6%)	9 (0.4%)	7 (0.6%)	8 (0.8%)	17 (1.0%)	4 (0.3%)	8 (0.4%)	15 (1.4%)	5 (0.5%)
6	Weight loss	3 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)	1 (0.1%)	0 (0.0%)
4	Disorders of fluid, electrolyte, and acid–base balance	34 (0.3%)	12 (0.5%)	2 (0.2%)	1 (0.1%)	10 (0.6%)	4 (0.3%)	2 (0.1%)	1 (0.1%)	2 (0.2%)
2	Gout	1183 (10.3%)	276 (11.6%)	155 (12.8%)	100 (10.5%)	169 (10.2%)	106 (8.9%)	197 (9.5%)	92 (8.6%)	88 (9.5%)
..	<i>Diseases of the Blood and Blood-Forming Organs</i>	93 (0.8%)	21 (0.9%)	8 (0.7%)	4 (0.4%)	18 (1.1%)	11 (0.9%)	14 (0.7%)	7 (0.7%)	10 (1.1%)
5	Coagulation defects	17 (0.1%)	7 (0.3%)	2 (0.2%)	1 (0.1%)	3 (0.2%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	1 (0.1%)
3	Anemias	80 (0.7%)	15 (0.6%)	8 (0.7%)	3 (0.3%)	16 (1.0%)	10 (0.8%)	12 (0.6%)	7 (0.7%)	9 (1.0%)
..	<i>Mental Disorders</i>	96 (0.8%)	15 (0.6%)	8 (0.7%)	6 (0.6%)	10 (0.6%)	10 (0.8%)	24 (1.2%)	11 (1.0%)	12 (1.3%)
8	Psychosis	88 (0.8%)	14 (0.6%)	8 (0.7%)	6 (0.6%)	10 (0.6%)	9 (0.8%)	20 (1.0%)	11 (1.0%)	10 (1.1%)
11	Alcohol abuse	2 (0.0%)	1 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
6	Anxiety medication	8 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	4 (0.2%)	0 (0.0%)	2 (0.2%)
..	<i>Diseases of the Nervous System</i>	446 (3.9%)	89 (3.7%)	51 (4.2%)	32 (3.4%)	56 (3.4%)	43 (3.6%)	94 (4.6%)	45 (4.2%)	36 (3.9%)
5	Hemiplegia and hemiparesis	10 (0.1%)	1 (0.0%)	3 (0.2%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	3 (0.1%)	1 (0.1%)	0 (0.0%)
3	Other neurological diseases	18 (0.2%)	5 (0.2%)	2 (0.2%)	1 (0.1%)	2 (0.1%)	3 (0.3%)	3 (0.1%)	1 (0.1%)	1 (0.1%)
2	Epilepsy	368 (3.2%)	71 (3.0%)	39 (3.2%)	24 (2.5%)	50 (3.0%)	37 (3.1%)	83 (4.0%)	35 (3.3%)	29 (3.1%)
5	Parkinson’s disease	84 (0.7%)	21 (0.9%)	12 (1.0%)	11 (1.2%)	6 (0.4%)	8 (0.7%)	8 (0.4%)	9 (0.8%)	9 (1.0%)
..	<i>Diseases of the Circulatory System</i>	2839 (24.8%)	582 (24.5%)	290 (24.0%)	198 (20.8%)	441 (26.7%)	280 (23.5%)	536 (26.0%)	293 (27.3%)	219 (23.8%)
4	Heart failure	1361 (11.9%)	261 (11.0%)	141 (11.7%)	80 (8.4%)	220 (13.3%)	135 (11.3%)	298 (14.4%)	134 (12.5%)	92 (10.0%)
1	Arrhythmia	220 (1.9%)	50 (2.1%)	25 (2.1%)	17 (1.8%)	29 (1.8%)	21 (1.8%)	37 (1.8%)	17 (1.6%)	24 (2.6%)
1	Valvular diseases	38 (0.3%)	8 (0.3%)	5 (0.4%)	2 (0.2%)	5 (0.3%)	3 (0.3%)	8 (0.4%)	3 (0.3%)	4 (0.4%)
2	Vascular diseases	18 (0.2%)	4 (0.2%)	2 (0.2%)	1 (0.1%)	2 (0.1%)	2 (0.2%)	2 (0.1%)	1 (0.1%)	4 (0.4%)
3	Cerebrovascular diseases	3 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	1 (0.1%)	0 (0.0%)
1	Coronary and peripheral vascular disease	1923 (16.8%)	409 (17.2%)	196 (16.2%)	143 (15.0%)	295 (17.9%)	185 (15.5%)	344 (16.7%)	199 (18.5%)	152 (16.5%)
..	<i>Diseases of the Respiratory System</i>									
2	Chronic pulmonary diseases	2526 (22.1%)	554 (23.3%)	274 (22.7%)	210 (22.0%)	409 (24.8%)	305 (25.6%)	391 (19.0%)	197 (18.3%)	186 (20.2%)
..	<i>Disease of the Digestive System</i>	1314 (11.5%)	282 (11.9%)	152 (12.6%)	102 (10.7%)	192 (11.6%)	93 (7.8%)	263 (12.7%)	146 (13.6%)	84 (9.1%)
2	Peptic ulcer	1233 (10.8%)	270 (11.3%)	146 (12.1%)	99 (10.4%)	169 (10.2%)	78 (6.5%)	251 (12.2%)	141 (13.1%)	79 (8.6%)
8	Liver diseases	97 (0.8%)	12 (0.5%)	9 (0.7%)	6 (0.6%)	26 (1.6%)	15 (1.3%)	14 (0.7%)	8 (0.7%)	7 (0.8%)

..	<i>Diseases of the Genitourinary System</i>									
4	Kidney diseases	6 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	1 (0.0%)	2 (0.2%)	0 (0.0%)
..	<i>Diseases of the Musculoskeletal System and</i>									
..	<i>Connective Tissue</i>									
3	Rheumatologic conditions	75 (0.7%)	19 (0.8%)	9 (0.7%)	4 (0.4%)	10 (0.6%)	5 (0.4%)	15 (0.7%)	8 (0.7%)	5 (0.5%)

\*Short for Cesena - Valle del Savio.

Notes: Each condition is assigned a specific weight (pts) that contributes to the total sum of the MCS. Of note, diabetes, dementia, and acute myocardial infarction are not included in the MCS calculation because our study population, by definition, did not have any of these conditions before their entry into the study.

**Table S4.** Baseline Characteristics of the Study Cohort of Patients With an Estimated Onset of Type 2 Diabetes Between 2015 and 2017 in Romagna, Italy, Overall and by Health District of Residence.

	All (n=11,441)	Ravenna (n=2379)	Lugo (n=1207)	Faenza (n=953)	Forlì (n=1650)	Cesena* (n=1193)	Rimini (n=2063)	Riccione (n=1074)	Rubicone (n=922)
Female Sex	5444 (47.6%)	1133 (47.6%)	587 (48.6%)	467 (49.0%)	779 (47.2%)	586 (49.1%)	954 (46.2%)	470 (43.8%)	468 (50.8%)
Age at Onset, y									
Mean±SD	60.6±15.1	59.7±15.9	60.0±15.6	58.9±16.0	62.5±14.1	59.4±15.6	61.9±14.5	62.3±13.4	58.4±15.5
Median [IQR]	62 [51–72]	61 [49–71]	61 [49–71]	61 [48–70]	63 [54–73]	61 [48–71]	63 [52–73]	63 [54–72]	60 [47–70]
Grouped Age at Onset									
25–34 y	732 (6.4%)	184 (7.7%)	84 (7.0%)	92 (9.7%)	65 (3.9%)	90 (7.5%)	97 (4.7%)	33 (3.1%)	87 (9.4%)
35–44 y	1137 (9.9%)	264 (11.1%)	144 (11.9%)	106 (11.1%)	118 (7.2%)	148 (12.4%)	174 (8.4%)	73 (6.8%)	110 (11.9%)
45–54 y	1841 (16.1%)	408 (17.2%)	177 (14.7%)	153 (16.1%)	261 (15.8%)	194 (16.3%)	328 (15.9%)	181 (16.9%)	139 (15.1%)
55–64 y	2771 (24.2%)	512 (21.5%)	295 (24.4%)	224 (23.5%)	437 (26.5%)	268 (22.5%)	510 (24.7%)	307 (28.6%)	218 (23.6%)
65–74 y	2772 (24.2%)	571 (24.0%)	284 (23.5%)	198 (20.8%)	427 (25.9%)	274 (23.0%)	529 (25.6%)	271 (25.2%)	218 (23.6%)
75–84 y	1736 (15.2%)	353 (14.8%)	170 (14.1%)	142 (14.9%)	270 (16.4%)	167 (14.0%)	343 (16.6%)	168 (15.6%)	123 (13.3%)
≥85 y	452 (4.0%)	87 (3.7%)	53 (4.4%)	38 (4.0%)	72 (4.4%)	52 (4.4%)	82 (4.0%)	41 (3.8%)	27 (2.9%)
Citizenship									
Italy	9704 (84.8%)	2038 (85.7%)	1012 (83.8%)	796 (83.5%)	1426 (86.4%)	996 (83.5%)	1757 (85.2%)	934 (87.0%)	745 (80.8%)
Rest of Europe	866 (7.6%)	185 (7.8%)	88 (7.3%)	86 (9.0%)	92 (5.6%)	82 (6.9%)	156 (7.6%)	95 (8.8%)	82 (8.9%)
Africa	546 (4.8%)	92 (3.9%)	83 (6.9%)	52 (5.5%)	82 (5.0%)	78 (6.5%)	69 (3.3%)	28 (2.6%)	62 (6.7%)
Asia	268 (2.3%)	57 (2.4%)	21 (1.7%)	16 (1.7%)	43 (2.6%)	33 (2.8%)	58 (2.8%)	8 (0.7%)	32 (3.5%)
America or Oceania	57 (0.5%)	7 (0.3%)	3 (0.2%)	3 (0.3%)	7 (0.4%)	4 (0.3%)	23 (1.1%)	9 (0.8%)	1 (0.1%)
Year at Onset									
2015	3756 (32.8%)	830 (34.9%)	378 (31.3%)	300 (31.5%)	552 (33.5%)	411 (34.5%)	643 (31.2%)	309 (28.8%)	333 (36.1%)
2016	3675 (32.1%)	740 (31.1%)	391 (32.4%)	310 (32.5%)	514 (31.2%)	381 (31.9%)	705 (34.2%)	343 (31.9%)	291 (31.6%)
2017	4010 (35.0%)	809 (34.0%)	438 (36.3%)	343 (36.0%)	584 (35.4%)	401 (33.6%)	715 (34.7%)	422 (39.3%)	298 (32.3%)
Drugs within 30 Days of Onset									
One oral antidiabetic	9772 (85.4%)	1993 (83.8%)	1038 (86.0%)	826 (86.7%)	1421 (86.1%)	1013 (84.9%)	1722 (83.5%)	934 (87.0%)	825 (89.5%)
Two or more antidiabetics	854 (7.5%)	118 (5.0%)	46 (3.8%)	48 (5.0%)	114 (6.9%)	136 (11.4%)	220 (10.7%)	100 (9.3%)	72 (7.8%)
Insulin	339 (3.0%)	129 (5.4%)	60 (5.0%)	26 (2.7%)	43 (2.6%)	8 (0.7%)	48 (2.3%)	16 (1.5%)	9 (1.0%)
Oral drugs and insulin	476 (4.2%)	139 (5.8%)	63 (5.2%)	53 (5.6%)	72 (4.4%)	36 (3.0%)	73 (3.5%)	24 (2.2%)	16 (1.7%)
MCS									
Mean±SD	2.6±5.1	2.6±4.7	2.6±4.8	2.3±4.8	2.8±5.4	2.5±5.2	2.7±5.2	2.7±5.5	2.5±5.2
Median [IQR]	0 [1–3]	0 [1–3]	0 [1–3]	0 [0–3]	0 [1–3]	0 [1–3]	0 [1–3]	0 [1–3]	0 [1–3]
Grouped MCS									
≤4	9537 (83.4%)	1987 (83.5%)	997 (82.6%)	819 (85.9%)	1366 (82.8%)	1008 (84.5%)	1685 (81.7%)	895 (83.3%)	780 (84.6%)
5–9	1230 (10.8%)	242 (10.2%)	130 (10.8%)	91 (9.5%)	174 (10.5%)	126 (10.6%)	261 (12.7%)	121 (11.3%)	85 (9.2%)
10–14	361 (3.2%)	92 (3.9%)	51 (4.2%)	23 (2.4%)	48 (2.9%)	29 (2.4%)	59 (2.9%)	29 (2.7%)	30 (3.3%)
15–19	128 (1.1%)	28 (1.2%)	17 (1.4%)	5 (0.5%)	29 (1.8%)	9 (0.8%)	21 (1.0%)	7 (0.7%)	12 (1.3%)
≥20	185 (1.6%)	30 (1.3%)	12 (1.0%)	15 (1.6%)	33 (2.0%)	21 (1.8%)	37 (1.8%)	22 (2.0%)	15 (1.6%)

\*Short for Cesena - Valle del Savio.

Abbreviations: SD, standard deviation; IQR, interquartile range; MCS, Multisource Comorbidity Score.

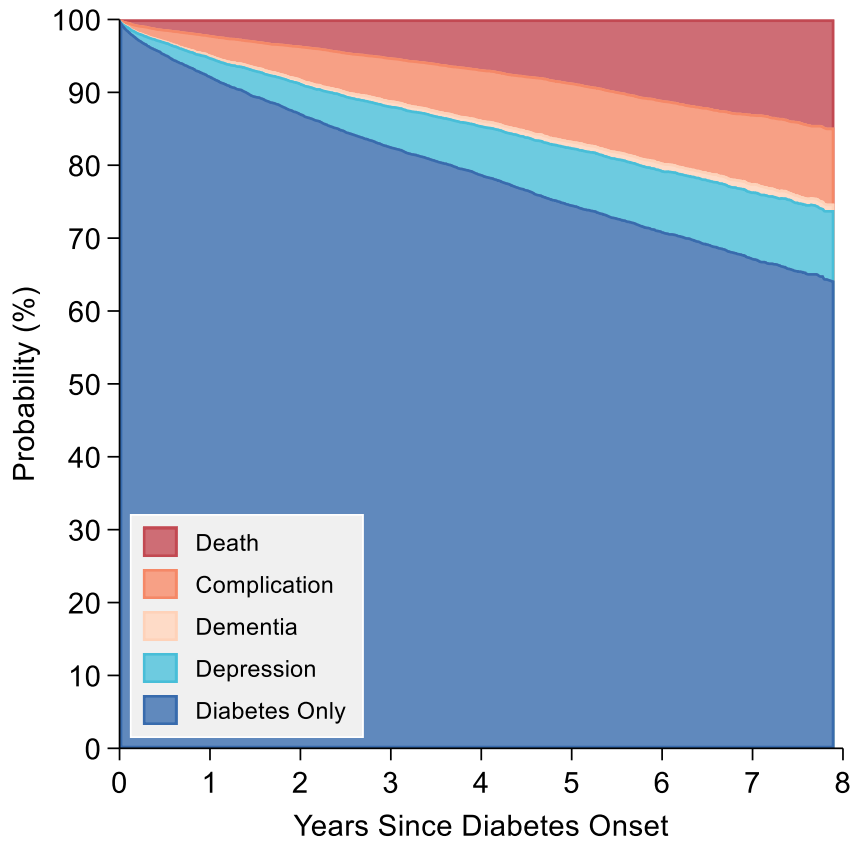
**Table S5.** Frequency Distribution of the Acute and Long-Term Complications of Diabetes Observed on 1805 Patients During the Follow-Up Period.

<i>n</i>	%	Acute Complications	Long-Term Complications				
			Cardiovascular/ Cerebrovascular	Neuropathic	Renal	Ophthalmic	Other/ Unspecified
1339	74.2		✓				
236	13.1				✓		
87	4.8		✓		✓		
37	2.0			✓			
31	1.7	✓					
18	1.0					✓	
15	0.8				✓		
11	0.6		✓			✓	
11	0.6	✓	✓				
4	0.2		✓			✓	
4	0.2	✓			✓		
3	0.2		✓		✓	✓	
3	0.2		✓	✓			
2	0.1				✓	✓	
2	0.1		✓	✓	✓		
1	0.1		✓	✓	✓	✓	
1	0.1	✓		✓			
<i>Complications Taken Singularly</i>		47 (2.4%)	1461 (75.3%)	44 (2.3%)	335 (17.3%)	22 (1.1%)	32 (1.6%)

*Notes:* Complications of multiple kinds (e.g., 87 cardiovascular and renal) occurred simultaneously during the follow-up period. In cases where multiple complications occurred on different dates, only the first one was considered in the analysis (incident events). Acute complications include coma, hyperosmolarity, hypoglycemia, and ketoacidosis.



**Figure S2.** Aalen–Johansen Stacked Probabilities of Being in Each State for Patients with Type 2 Diabetes up to Eight Years After Onset.



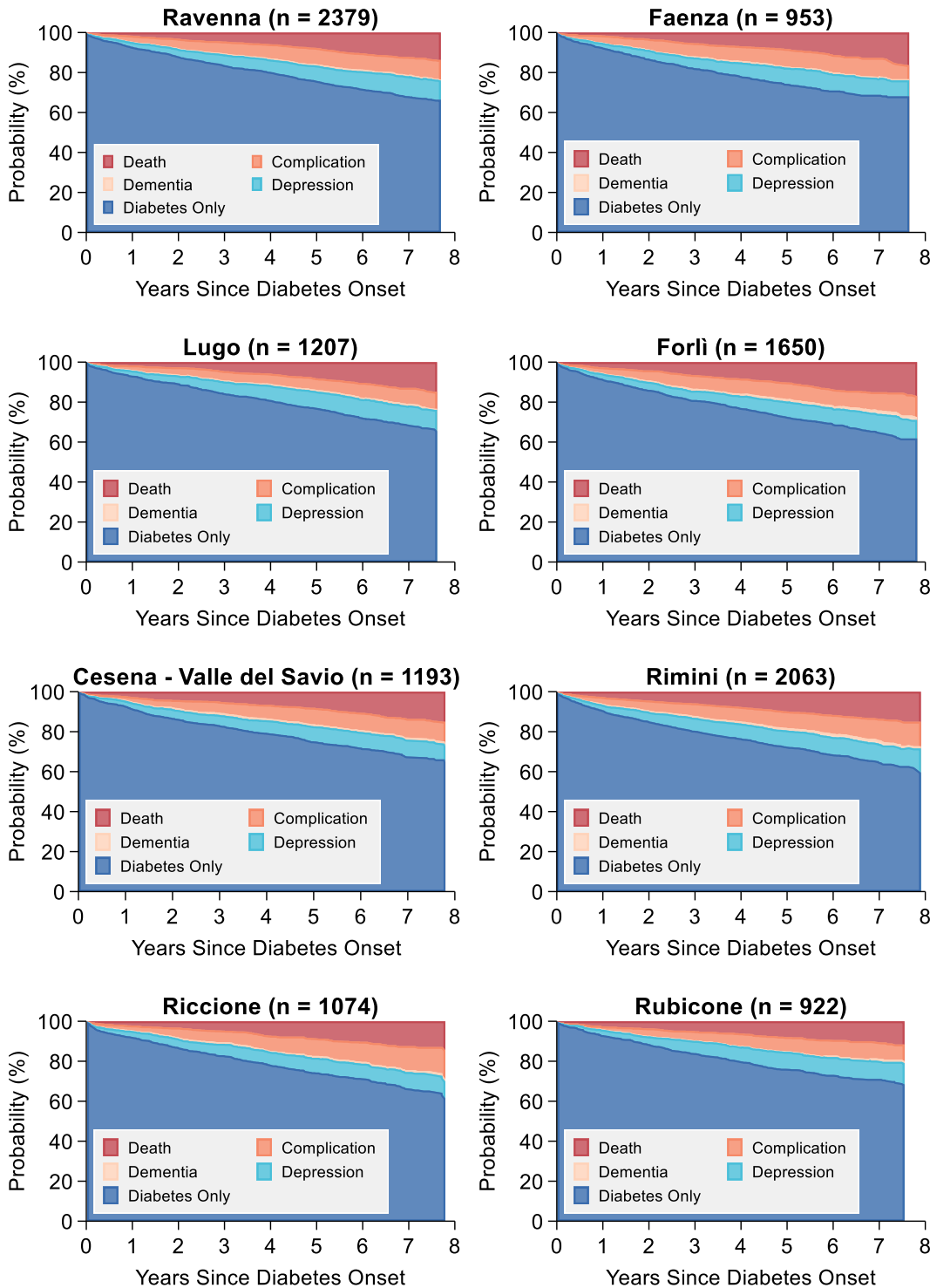
*Notes:* The Aalen–Johansen can be considered an extension of the Kaplan–Meier approach suitable for time-inhomogeneous, right-censored Markov processes with a finite number of states. Complications of diabetes include both acute conditions (coma, hyperosmolarity, hypoglycemia, and ketoacidosis) and 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.

**Table S6.** Aalen–Johansen Probabilities and 95% Confidence Intervals (%) of Being in Each State for Patients with Type 2 Diabetes up to Eight Years After Onset, by Health District of Residence.

Time Since Diabetes Onset	Ravenna ( <i>n</i> =2379)				Lugo ( <i>n</i> =1207)			
	Depression	Dementia	Complication	Death	Depression	Dementia	Complication	Death
1 year	2.4 (1.7, 3.0)	0.2 (0.0, 0.4)	3.0 (2.3, 3.7)	1.6 (1.1, 2.1)	2.5 (1.6, 3.4)	0.3 (0.0, 0.7)	2.3 (1.5, 3.2)	1.7 (0.9, 2.4)
2 years	3.7 (2.9, 4.4)	0.4 (0.2, 0.7)	4.7 (3.9, 5.6)	3.1 (2.4, 3.8)	3.9 (2.8, 5.0)	0.5 (0.1, 0.9)	3.6 (2.6, 4.7)	2.6 (1.7, 3.5)
4 years	6.1 (5.2, 7.1)	0.7 (0.3, 1.0)	7.0 (6.0, 8.0)	5.9 (4.9, 6.8)	7.5 (6.0, 8.9)	0.7 (0.3, 1.2)	5.1 (3.8, 6.3)	5.7 (4.4, 7.0)
6 years	8.8 (7.6, 10.0)	0.9 (0.5, 1.3)	8.2 (7.0, 9.3)	10.3 (9.1, 11.6)	9.2 (7.5, 10.9)	0.8 (0.2, 1.3)	7.4 (5.8, 8.9)	10.4 (8.6, 12.1)
8 years	9.6 (8.0, 11.2)	0.5 (0.1, 0.9)	9.8 (8.0, 11.7)	13.7 (12.0, 15.4)	10.7 (8.4, 13.1)	0.5 (0.0, 1.1)	8.5 (6.2, 10.9)	14.8 (12.2, 17.5)
Time Since Diabetes Onset	Faenza ( <i>n</i> =953)				Forlì ( <i>n</i> =1650)			
	Depression	Dementia	Complication	Death	Depression	Dementia	Complication	Death
1 year	2.2 (1.3, 3.1)	0.2 (0.0, 0.5)	3.6 (2.4, 4.7)	1.5 (0.7, 2.2)	2.7 (1.9, 3.4)	0.4 (0.1, 0.7)	2.8 (2.0, 3.6)	2.6 (1.8, 3.4)
2 years	4.4 (3.1, 5.7)	0.3 (0.0, 0.7)	5.1 (3.7, 6.5)	3.1 (2.0, 4.3)	4.0 (3.1, 4.9)	0.7 (0.3, 1.1)	5.1 (4.0, 6.2)	4.1 (3.2, 5.1)
4 years	6.8 (5.2, 8.4)	0.7 (0.2, 1.3)	7.3 (5.7, 9.0)	6.8 (5.2, 8.4)	6.1 (4.9, 7.2)	1.0 (0.5, 1.4)	7.6 (6.4, 8.9)	8.3 (7.0, 9.6)
6 years	8.2 (6.4, 10.1)	0.7 (0.1, 1.4)	9.0 (7.1, 10.9)	11.1 (9.0, 13.1)	7.7 (6.4, 9.1)	1.3 (0.7, 2.0)	8.3 (6.9, 9.7)	13.6 (11.9, 15.3)
8 years	8.0 (5.7, 10.2)	0.6 (0.0, 1.3)	6.9 (4.1, 9.7)	16.4 (12.9, 19.9)	9.2 (7.3, 11.2)	1.4 (0.0, 2.9)	10.5 (8.0, 13.0)	17.0 (14.7, 19.3)
Time Since Diabetes Onset	Cesena - Valle del Savio ( <i>n</i> =1193)				Rimini ( <i>n</i> =2063)			
	Depression	Dementia	Complication	Death	Depression	Dementia	Complication	Death
1 year	2.5 (1.6, 3.4)	0.4 (0.1, 0.8)	1.8 (1.1, 2.6)	2.3 (1.4, 3.1)	2.7 (2.0, 3.4)	0.6 (0.3, 0.9)	3.3 (2.5, 4.1)	2.7 (2.0, 3.4)
2 years	4.4 (3.3, 5.6)	0.8 (0.3, 1.4)	3.7 (2.6, 4.8)	4.2 (3.1, 5.3)	4.7 (3.8, 5.6)	0.7 (0.4, 1.1)	4.9 (4.0, 5.8)	4.4 (3.5, 5.3)
4 years	6.3 (4.9, 7.7)	0.9 (0.4, 1.5)	6.8 (5.4, 8.2)	6.5 (5.1, 7.9)	7.4 (6.2, 8.5)	1.0 (0.6, 1.5)	7.2 (6.1, 8.3)	7.7 (6.5, 8.8)
6 years	7.8 (6.2, 9.4)	1.0 (0.4, 1.6)	8.7 (7.0, 10.3)	10.6 (8.8, 12.3)	8.7 (7.4, 9.9)	1.6 (1.1, 2.2)	9.5 (8.1, 10.8)	11.6 (10.2, 13.1)
8 years	7.8 (5.7, 9.9)	1.1 (0.4, 1.8)	11.3 (7.3, 15.3)	15.1 (12.4, 17.7)	12.1 (9.0, 15.2)	1.1 (0.2, 2.0)	12.3 (9.8, 14.8)	15.0 (13.1, 17.0)
Time Since Diabetes Onset	Riccione ( <i>n</i> =1074)				Rubicone ( <i>n</i> =922)			
	Depression	Dementia	Complication	Death	Depression	Dementia	Complication	Death
1 year	2.9 (1.9, 3.9)	0.4 (0.0, 0.7)	2.4 (1.5, 3.3)	2.1 (1.3, 3.0)	2.7 (1.7, 3.8)	0.2 (0.0, 0.5)	1.4 (0.6, 2.2)	2.6 (1.6, 3.6)
2 years	4.3 (3.1, 5.5)	0.7 (0.2, 1.1)	4.8 (3.6, 6.1)	3.2 (2.1, 4.2)	3.9 (2.7, 5.2)	0.3 (0.0, 0.7)	3.6 (2.4, 4.8)	3.6 (2.4, 4.8)
4 years	6.4 (5.0, 7.9)	0.5 (0.1, 0.9)	7.6 (6.0, 9.2)	7.2 (5.6, 8.7)	7.3 (5.6, 8.9)	0.3 (0.0, 0.7)	6.3 (4.7, 7.9)	6.1 (4.5, 7.6)
6 years	7.3 (5.7, 8.8)	0.9 (0.3, 1.5)	10.1 (8.2, 11.9)	10.2 (8.4, 12.1)	8.9 (7.0, 10.8)	0.8 (0.1, 1.4)	7.8 (6.0, 9.6)	9.4 (7.5, 11.3)
8 years	8.5 (6.4, 10.6)	1.3 (0.1, 2.4)	14.4 (10.4, 18.4)	14.5 (10.6, 18.5)	10.6 (7.8, 13.5)	1.1 (0.2, 1.9)	8.3 (5.7, 10.9)	11.6 (9.1, 14.1)

*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.

**Figure S3.** Aalen–Johansen Stacked Probabilities of Being in Each State for Patients with Type 2 Diabetes up to Eight Years After Onset, by Health District of Residence.



*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.

**Table S7.** Akaike Information Criterion (AIC) Values for Selecting the Parametric Family that Best Describes Survival Times in Each Transition of the Multi-State Model.

Distribution Family	Diabetes → Depression #1: 1243 Uncensored Events	Diabetes → Dementia #2: 171 Uncensored Events	Diabetes → Complication #3: 1519 Uncensored Events
Exponential	12 166.03	2353.81	14 257.78
Weibull	12 103.09*	2333.98*	14 211.40
Gompertz	12 130.86	2349.30	14 242.90
Log-normal	12 104.74	2334.11	14 217.81
Log-logistic	12 136.05	2339.55	14 302.63
Generalized gamma	12 104.40	2335.85	14 208.71
Royston–Parmar with 2 df	12 105.07	2334.56	14 206.54*
Royston–Parmar with 3 df	12 103.83	2334.36	14 208.03
Royston–Parmar with 4 df	12 104.47	2336.39	14 209.40
Royston–Parmar with 5 df	12 105.26	2335.73	14 210.76
Distribution Family	Diabetes → Death #4: 577 Uncensored Events	Depression → Dementia #5: 78 Uncensored Events	Depression → Complication #6: 176 Uncensored Events
Exponential	6534.16	758.53	1422.60
Weibull	6482.98	731.95	1408.38
Gompertz	6513.99	735.69	1418.71
Log-normal	6483.77	731.61	1409.60
Log-logistic	6492.98	729.15*	1414.73
Generalized gamma	6484.27	730.70	1409.52
Royston–Parmar with 2 df	6484.84	731.60	1410.37
Royston–Parmar with 3 df	6474.61*	733.58	1407.79*
Royston–Parmar with 4 df	6475.73	735.57	1409.61
Royston–Parmar with 5 df	6476.47	737.42	1411.46
Distribution Family	Depression → Death #7: 113 Uncensored Events	Dementia → Complication #8: 110 Uncensored Events	Dementia → Death #9: 56 Uncensored Events
Exponential	1014.23	488.90	325.49
Weibull	965.81	313.97	291.08
Gompertz	987.13	419.29	311.84
Log-normal	965.47	309.54	291.06
Log-logistic	962.19	299.25	288.94
Generalized gamma	963.80	281.60	290.91
Royston–Parmar with 2 df	963.13	293.78	290.18
Royston–Parmar with 3 df	962.75	246.21*	283.76
Royston–Parmar with 4 df	960.21	249.71	282.03*
Royston–Parmar with 5 df	958.03*	250.12	283.75
Distribution Family	Complication → Depression #10: 203 Uncensored Events	Complication → Dementia #11: 70 Uncensored Events	Complication → Death #12: 502 Uncensored Events
Exponential	1641.72	716.48	3147.85
Weibull	1609.76*	702.24	2299.66
Gompertz	1624.02	704.92	2885.30
Log-normal	1610.21	702.08	2304.10
Log-logistic	1617.80	700.77*	2295.72
Generalized gamma	1611.71	(convergence not achieved)	2297.62
Royston–Parmar with 2 df	1611.71	703.28	2301.50
Royston–Parmar with 3 df	1613.13	704.87	2262.06
Royston–Parmar with 4 df	1612.71	701.88	2232.53
Royston–Parmar with 5 df	1613.59	703.60	2125.89*
Distribution Family	Depression → Dementia #13: 20 Uncensored Events	Depression → Death #14: 57 Uncensored Events	Dementia → Death #15: 58 Uncensored Events
Exponential	162.57	340.22	198.61
Weibull	152.44	320.53	186.02
Gompertz	157.92	333.28	198.45
Log-normal	152.42	320.48	192.86
Log-logistic	152.39*	317.72	194.50
Generalized gamma	154.32	319.02	184.79
Royston–Parmar with 2 df	154.34	319.96	186.70
Royston–Parmar with 3 df	156.24	309.08*	179.97*
Royston–Parmar with 4 df	158.18	310.38	181.79
Royston–Parmar with 5 df	159.30	312.31	180.64

*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). The Weibull model was found to be the most suitable for transitions #1 (diabetes to depression), #2 (diabetes to dementia), and #10 (complication to depression), indicating that the individual hazard continually increased over time. The lognormal model was the best choice for transitions #5 (depression to dementia before complications), #11 (complication to dementia), and #13 (depression to dementia after complications), signifying that the individual hazard initially rose and then declined after a certain point. For all other transitions, the Royston–Parmar (RP) model with various degrees of freedom was the most appropriate. In this model, the logarithm of the baseline cumulative hazard function is modeled as a restricted cubic spline to approximate a flexible yet continuous function on the proportional-hazard scale.

\*Lowest AIC value for each transition.

**Table S8.** Percentage of Complications of Type 2 Diabetes Attributable to Depression and Dementia, Both Taken Singularly and Combined, Overall and by Sex and Age Group.

	Depression		Dementia		Depression or Dementia	
	PAF	95%CI	PAF	95%CI	PAF	95%CI
All	6.1%	4.5%, 7.6%	5.6%	4.4%, 6.7%	10.3%	8.5%, 12.1%
Sex						
Male	5.2%	3.4%, 6.9%	4.3%	3.0%, 5.5%	8.2%	6.2%, 10.2%
Female	8.5%	5.6%, 11.4%	7.8%	5.7%, 9.9%	14.7%	11.3%, 18.0%
Age Group						
Adult (25–64 y)	3.0%	0.6%, 5.4%	0.5%	–0.2%, 1.1%	3.5%	1.0%, 6.0%
Older adult ( $\geq 65$ y)	6.2%	4.2%, 8.2%	7.1%	5.6%, 8.6%	11.6%	9.3%, 13.9%

*Notes:* Deaths were treated as censored events. The 95% CIs were obtained using the normalizing and variance-stabilizing transformation  $\log(1 - \text{PAF})$ .

*Abbreviations:* PAF, population attributable fraction; CI, confidence interval.

**Table S9.** Percentage of Deaths Following Type 2 Diabetes Onset Attributable to Depression and Dementia, Both Taken Singularly and Combined, Overall and by Sex and Age Group.

	Depression		Dementia		Depression or Dementia	
	PAF	95%CI	PAF	95%CI	PAF	95%CI
All	12.4%	9.4%, 15.2%	7.0%	5.1%, 8.9%	17.5%	14.3%, 20.7%
Sex						
Male	12.6%	8.9%, 16.1%	5.8%	3.5%, 8.0%	16.8%	12.8%, 20.7%
Female	12.7%	7.8%, 17.3%	8.8%	5.4%, 12.0%	19.2%	13.7%, 24.4%
Age Group						
Adult (25–64 y)	14.9%	8.6%, 20.9%	1.0%	–0.6%, 2.6%	16.1%	9.5%, 22.1%
Older adult ( $\geq 65$ y)	10.4%	7.1%, 13.7%	8.3%	5.8%, 10.6%	16.6%	12.7%, 20.3%

*Notes:* Complications were considered as censored events, which means that PAFs were calculated exclusively for deaths not preceded by a diabetes complication. The 95%CIs were obtained using the normalizing and variance-stabilizing transformation  $\log(1 - \text{PAF})$ .

*Abbreviations:* PAF, population attributable fraction; CI, confidence interval.

**Table S10.** Percentage of Deaths Following Complications of Type 2 Diabetes Attributable to Depression and Dementia, Both Taken Singularly and Combined, Overall and by Sex and Age Group.

	Depression		Dementia		Depression or Dementia	
	PAF	95%CI	PAF	95%CI	PAF	95%CI
All	13.2%	8.9%, 17.3%	18.9%	15.4%, 22.4%	28.9%	23.8%, 33.6%
Sex						
Male	16.1%	10.7%, 21.2%	18.6%	14.1%, 22.9%	29.8%	23.6%, 35.5%
Female	7.0%	-0.4%, 13.9%	18.8%	12.7%, 24.4%	25.5%	16.4%, 33.6%
Age Group						
Adult (25–64 y)	10.2%	-1.2%, 20.4%	4.6%	-0.7%, 9.7%	14.1%	1.8%, 24.9%
Older adult ( $\geq 65$ y)	12.4%	7.6%, 16.9%	19.8%	15.7%, 23.6%	29.1%	23.5%, 34.4%

*Notes:* The calculation of PAFs was limited to patients who experienced a diabetes complication. The 95% CIs were obtained using the normalizing and variance-stabilizing transformation  $\log(1 - \text{PAF})$ .

*Abbreviations:* PAF, population attributable fraction; CI, confidence interval.