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Diabetic complications and risk of depression and anxiety among adults with type 2 diabetes

Running title: Diabetic complications and mental health

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Novelty statement

What is already known?

- Individuals with type 2 diabetes are at increased risk for mental health issues.
- A few prospective studies show that diabetic complications increase the risk for depression, but they have important methodological limitations.

What this study has found?

- Having diabetic complications increases the risk of depression and/or anxiety among individuals with type 2 diabetes.
- This is both the case for cardiovascular disease, amputation of lower extremities, neuropathy, nephropathy, and retinopathy.

What are the implications of the study?

- Health care professionals should have an increased focus on mental well-being among individuals with type 2 diabetes and complications.

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Abstract

Aims: To investigate if diabetic complications increase the risk of depression and/or anxiety among adults with type 2 diabetes.

Methods: This register-based, prospective study included 265,799 adult individuals diagnosed with type 2 diabetes between 1997 and 2017 without a recent history of depression or anxiety. Diabetic complications included cardiovascular disease, amputation of lower extremities, neuropathy, nephropathy, and retinopathy. Both diabetic complications and depression and anxiety were defined by hospital contacts and prescription-based medication. All individuals were followed from the date of type 2 diabetes diagnosis until date of incident depression or anxiety, emigration, death, or 31 December 2018, whichever occurred first.

Results: The total risk time was 1,915,390 person-years. The incidence rate of depression and/or anxiety was 3,368 per 100,000 person-years among individuals with diabetic complications, and 1,929 per 100,000 person-years among those without.

Having or developing any diabetic complication was associated with increased risk of depression and/or anxiety (HR 1.77, 95% CI 1.73-1.80). The risk for depression and/or anxiety was increased for all types of diabetic complications. The strongest association was found for amputation of lower extremities (HR 2.16, 95% CI 2.01-2.31), and the weakest for retinopathy (HR 1.13, 95% CI 1.09-1.17).

Conclusion: Individuals with type 2 diabetes and diabetic complications are at increased risk of depression and anxiety. This points towards the importance of an increased clinical focus on mental well-being among individuals with type 2 diabetes and complications.

KEYWORDS: Diabetic complications, depression, anxiety, diabetes mellitus, type 2, epidemiology

INTRODUCTION

It is estimated that 463 million people have diabetes worldwide, and the prevalence is increasing.¹ Approximately one-third of patients with type 2 diabetes have diabetic complications at time of diagnosis,² while more develop complications over time.

It is well documented that the risk for mental health issues and psychiatric diagnoses is increased among individuals with type 2 diabetes,^{3,4} while the co-existence of diabetes and mental health issues have been associated with inadequate treatment adherence⁵ and increased risk of complications.⁶ However, the association may be bi-directional, as diabetic complications may also induce an increased risk of mental health issues.

Existing studies on diabetic complications and mental health are primarily cross-sectional.⁷⁻¹¹ However, a recent systematic review assessing the associations between diabetic complications and depression identified six prospective studies on the subject.⁶ Two of the studies were suitable for meta-analysis (N=234,628),^{12,13} showing that diabetic complications increased the risk for incident depression (HR 1.14, 95% CI 1.07-1.21). The remaining four studies¹⁴⁻¹⁷ showed similar results of increased risk for depression among individuals with diabetic complications. However, none of the studies took death into account as a competing event, even though diabetic complications are associated with increased mortality. Moreover, most of the studies only considered complications at baseline and ignored diabetic complications appearing during follow-up. Lastly, most of the studies did not adjust for socioeconomic factors, which is an important confounder to consider as it is associated with both diabetic complications and depression. Studies addressing these issues are warranted. To the best of our knowledge, no studies have previously assessed whether diabetic complications increase the risk of anxiety. Cross-sectional studies have found an association between complications and anxiety,⁸⁻¹¹ but the direction of the association is unknown.

The aims of this study were to investigate if having diabetic complications increases the risk of depression and/or anxiety among adults with type 2 diabetes.

METHODS

In this prospective study, all included individuals were followed from the date of type 2 diabetes diagnosis until date of incident depression or anxiety, emigration, death, or 31 December 2018, whichever occurred first.

The reporting of the study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

Study population

The study population consisted of individuals diagnosed with type 2 diabetes during the period of 1997 to 2017, when they were at least 18 years old and residing in Denmark.

Those with a recent history of depression or anxiety were excluded from the study. This was defined as having redeemed a prescription for anxiolytics or antidepressants (ATC: N06A or N05B) or having been recorded with a diagnosis of depression and anxiety (ICD 10: F32, F33, F41 or F43.2) in an in- or outpatient hospital contact within two years prior to their type 2 diabetes diagnosis. The information was obtained from the National Prescription Register covering all redeemed prescriptions from Danish pharmacies since 1995,¹⁸ and from the Psychiatric Central Research Register including all inpatient and outpatient contacts at psychiatric departments since 1995.¹⁹

In Denmark, most type 2 diabetes care (>80 %) take place in general practice, except from patients with severe complications, which are treated in hospital outpatient clinics. Thus, we used a carefully developed algorithm combining several national health registers to identify

individuals with type 2 diabetes.²⁰ A person was considered as having diabetes at the first date of one of the following registrations to occur:

- A diabetes diagnosis in the Danish Adult Diabetes Database²¹ or a hospital-treated diabetes diagnosis in the National Patient Register²² (ICD-10: E10-11)
- A prescription of any anti-diabetic drug (A10A; insulins and A10B; oral antidiabetics) in the Danish National Prescription Registry¹⁸
- Use of podiatry for patients with diabetes in the Danish National Health Service Register²³
- An eye examination recorded in The Danish Registry of Diabetic Retinopathy²⁴

All diabetes outpatient clinics have been obliged to report to the Danish Adult Diabetes Database²¹ since 2004. From 2006 data from general practice was also included and became mandatory from 2014. Information on each patient is reported annually. Further, Danish hospitals have an obligation to report information on all inpatient (since 1977) and outpatient (since 1995) hospital contacts to The Danish National Patient Register.²²

Individuals were classified as having type 1 diabetes and excluded from this study, if they met any of the following criteria: 1) Purchase of insulin before age 30 or 2) Classified as having type 1 diabetes in >50% of the records in the Danish Adult Diabetes Database or in the National Patient Register.²⁰ In Denmark, individuals with type 1 diabetes are treated in hospital outpatient clinics and registered in the National Patient Register. The approach with the algorithm is to identify persons with type 1 diabetes with reasonably high specificity and classify the rest as having type 2 diabetes.²⁰

Diabetic complications

We identified groups of macrovascular and microvascular diseases that potentially are diabetic complications. Macrovascular complications comprised the following cardiovascular

diseases: Peripheral vascular disease, cerebrovascular disease, ischemic heart disease, heart failure, hypertensive heart and renal disease, and atrial fibrillation and flutter. Microvascular complications included amputation of lower extremities, neuropathy, nephropathy, and retinopathy. Amputation differs from the other complications, as it reflects a treatment decision rather than a condition. It represents individuals with long-term foot ulcer problems, and in some cases also neuropathy, nephropathy, and/or cardiovascular disease.²⁵

Presence of the conditions was identified by hospital-based diagnoses (ICD10) and procedures, and use of prescription-based medications (Supplementary Table S1). This information was obtained from the Danish National Patient Register,²² and the National Prescription Register.¹⁸

The diseases were categorized as diabetic complications if they were recorded from five years prior to type 2 diabetes diagnosis and onwards. This was considered a reasonable time frame to capture complications arising from undiagnosed type 2 diabetes. For those individuals where a diabetic complication appeared before type 2 diabetes diagnosis (baseline in the study), the date of complication was recorded as the same as the date of type 2 diabetes diagnosis.

Depression and/or anxiety

We constructed a measure of depression and/or anxiety based on information from the Psychiatric Central Research Register,¹⁹ and the National Prescription Register.¹⁸ It was defined as having redeemed at least two prescriptions of antidepressants (ATC code N06A) and/or anxiolytics (ATC code N05B) within a year, and/or being recorded with a diagnosis of depression (ICD 10: F32 and F33) and/or anxiety (ICD 10: F41 and F43.2) at an in- or outpatient hospital contact. The date of event was the first occurring one. This combination of depression and/or anxiety served as the primary outcome of the study, because indications for

antidepressants and anxiolytics overlap. Antidepressants are in some cases used for treatment of anxiety, and conversely anxiolytics are in some cases used as part of treatment of depression. This complicates separation of the two conditions, when using information on medication.

To capture the effects on depression and anxiety separately, we focused on hospital contacts for each of the conditions.

Covariates

Information on gender, age, and country of origin was extracted from the Danish Civil Registration System. Cohabitation status was obtained from the Danish Population Register, and highest obtained educational level from the Danish Education Register at the year of diabetes diagnosis. Further, we took calendar year into account, as diagnostics and treatments may have changed within the follow-up period.

Statistical analyses

The association between diabetic complications and depression and/or anxiety was assessed in Cox proportional hazards regression models, where all individuals were followed from the date of type 2 diabetes until date of incident depression and/or anxiety, emigration, death, or 18 December 2018, whichever occurred first. Analyses were conducted with any diabetic complication as exposure, and separately with cardiovascular disease, amputation of lower extremities, neuropathy, nephropathy, and retinopathy as exposures. Information on diabetic complications were handled as time-dependent variables, so unexposed individuals (without complications) could change status to exposed (with complications) during follow-up.

All models were adjusted for age, gender, and calendar period, and fully adjusted models were further adjusted for country of origin, cohabitation status, and educational level.

The adjusted models were performed as complete case analyses, as the amount of missing information on covariates was modest (Table 1).

Since death was an important competing risk in the analyses, we also completed Fine and Gray's competing risk regression analyses to estimate the association between diabetic complications and depression and/or anxiety in the presence of death as competing risk. Finally, we applied Cox proportional hazards regression models to study the association between of any diabetic complication and hospital contacts for depression and anxiety separately.

The proportional hazards assumption was evaluated by assessing log-minus-log survivor curves.

We also computed sensitivity analyses. First, we computed analyses where depression and/or anxiety were only defined by hospital contacts to examine if the association remained the same when only focusing on clinical depression and/or anxiety. Second, all analyses were performed separately on those without complications at time of type 2 diabetes diagnosis to examine if the associations were similar, when solely focusing on complications appearing during follow-up after type 2 diabetes diagnosis.

All analyses were performed using Stata version 17.

Ethical approvals

According to Danish acts, informed consent from included persons and ethical review of study protocol are not required in register-based studies. The study was approved by the Danish Data Protection Agency (record number REG-118-2019).

RESULTS

In all, 352,259 individuals were registered with a type 2 diabetes diagnosis in Denmark between 1997 and 2017. We excluded 790 individuals due to registration errors in the registers. Further, 85,670 were excluded because they had a recent history of depression or anxiety prior to type 2 diabetes diagnosis. Finally, 265,799 individuals with type 2 diabetes were included in the study, of which 66,123 (25%) already had at least one diabetic complication at date of type 2 diabetes diagnosis, the majority being cardiovascular diseases (Table 1).

Any diabetic complications

The total risk time was 1,915,390 person-years. The incidence rate of depression and/or anxiety was 3,368 per 100,000 person-years among individuals with diabetic complications. Correspondingly, the incidence rate was 1,929 per 100,000 person-years among those without complications.

Having or developing diabetic complications were associated with increased risk of depression and/or anxiety (adjusted HR 1.77, 95% CI 1.73-1.80) (Table 2).

Results from the competing risk analysis were similar to that of the Cox regression analyses.

Death was an important competing risk (Figure 1), but it did not affect the results of the association between complications and depression and/or anxiety markedly (adjusted HR 1.67, 95% CI 1.64-1.71).

Having or developing diabetic complications were associated with increased risk of hospital contacts for depression (HR 1.55, 95% CI 1.43-1.67) and anxiety (HR 1.75, 95% CI 1.59-1.93) (Table 3). Among those that had hospital contacts for anxiety and/or depression (N=4,325), 14% had contacts for both conditions.

Specific types of diabetic complications

The risk of depression and/or anxiety was increased for all types of diabetic complications. Person-years with cardiovascular disease was most frequent. The risk of depression and/or anxiety was increased the most for amputation of lower extremities (adjusted HR 2.16, 95% CI 2.01-2.31), whereas it was increased the least for retinopathy (adjusted HR 1.13, 95% CI 1.09-1.17) (Table 2).

Supplementary analyses

When only focusing on hospital contacts for depression and anxiety as outcome, the risk was still increased for those with complications compared to those without (adjusted HR 1.63, 95% CI 1.53-1.74).

In analyses of individuals without diabetic complications at time of type 2 diabetes diagnosis, the association between developing diabetic complications and risk of depression and/or anxiety was stronger than in analyses of the entire population. Those that developed any type of diabetic complication during follow-up had a twice as high risk of depression and/or anxiety than those that did not (adjusted HR 2.11, 95% CI 2.05-2.16) (Supplementary Table S2).

DISCUSSION

In this nationwide, register-based cohort study we showed that having diabetic complications are associated with increased risk for depression and/or anxiety. This was the case for any complications, as well as specifically for cardiovascular disease, amputation of lower extremities, neuropathy, nephropathy, and retinopathy.

The previously mentioned meta-analysis of two prospective studies showed that the risk for incident depression was higher in the presence of microvascular (neuropathy, nephropathy,

and retinopathy) (HR 1.24, 95% CI 1.12-1.37) than macrovascular complications (cardiovascular disease) (HR 1.09, 95% CI 1.02-1.17).⁶ We did not see the same tendency in our study, as the relative estimates were similar for all complications (HR 1.81-1.94), except than for retinopathy where the association was weaker (HR 1.12, 95% CI 1.08-1.16), and for amputation where the association was slightly stronger (HR 2.16, 95% CI 2.01-2.31).

In general, most associations found in our study are stronger than in those from the meta-analysis. These discrepancies might be explained by differences in definitions of diabetic complications in the two studies in the meta-analysis and this present study. For example, one of the studies from the meta-analysis solely used information on diabetic complications from primary care physicians.¹² Thus, the severity of the complications may have been higher in our study, where we only used hospital-based diagnoses, as this comprises conditions severe enough to lead to a hospital contact, and most likely also more strongly associated with depression and anxiety. The other study in the meta-analysis solely used information on depression from hospital-based diagnoses,¹³ and when we restricted our analyses to hospital-based contacts, the associations also slightly weakened. Further, in that study only complications appearing before diabetes diagnosis were considered, and those occurring during follow-up were ignored.¹³ This might have led to misclassification of the exposure and an underestimation of the association between diabetic complications and depression.

In this present study, we found amputation to be a particular strong risk factor for depression and/or anxiety. Amputation differs from the other complications examined, since it reflects a treatment decision rather than a condition. Individuals with type 2 diabetes that go through lower extremity amputation might have suffered from long-term foot ulcer problems, and they are also likely to have neuropathy, nephropathy, and cardiovascular disease.²⁵ Thus, they represent a population with a severe disease and symptom burden, which most likely contribute to the observed increased risk of depression and/or anxiety. Further, going through

lower extremity amputation have been found to negatively affect social activities, and psychological wellbeing.²⁶

Retinopathy was not as strongly associated with depression and/or anxiety as the other complications examined. A previous cross-sectional study showed that severe retinopathy and moderate to severe vision impairment are associated with depressive symptoms among individuals with diabetes, whereas mild or moderate retinopathy and mild vision impairment are not.⁹ In our study, the codes for diagnoses and procedures related to retinopathy did not allow for differentiation between levels of seriousness. Thus, for some of the individuals recorded with retinopathy, the condition may have been at an asymptomatic stage, not affecting their vision considerably.

Most existing prospective studies on diabetic complications and mental health issues have focused solely on depression. This study contributes with results on anxiety, and we show that having or developing diabetic complications increases the risk of hospital contacts for anxiety. Actually, the association between diabetic complications and hospital contacts for anxiety tended to be stronger than for contacts for depression. It seemed that this was only the case for cardiovascular disease and amputation of lower extremities. However, when examining specific diabetic complications and hospital contacts for depression or anxiety, the number of events were rather small, leading to unprecise estimates with broad confidence intervals.

It is well-known that individuals with type 2 diabetes are at increased risk for mental health issues and psychiatric diagnoses.^{3,4} The results from this study indicate that appearance of diabetic complications may be one of the contributing factors to this. The mechanisms behind are not within the content of this study. However, speculations could be that some of the complications themselves lead to increased risk of depression and anxiety. It is for example well-established that depression and anxiety are common among individuals with severe

cardiovascular disease.²⁷ Further, being diagnosed with a diabetic complication may for many be perceived as a stressful life event, and such stressors have been found to be associated with risk for depression among individuals with type 2 diabetes.²⁸ Another contributing mechanism could be distress related to diabetic complications. One third of people with type 2 diabetes are affected by diabetes distress, which is distinct from clinical depression and anxiety, as it directly results from the emotional burden of living with and managing type 2 diabetes. Diabetes distress comprises worry about existing or future complications, stress related to the disease-management, fear of hypoglycaemia, and feelings of guilt or shame with regard to obesity or lifestyle.²⁹ Diabetic complications have been found to be risk factors of increased diabetes distress,³⁰ and a cross-sectional study have shown that diabetic complications and diabetes distress have an additive interaction effect on depression.³¹ Thus, a mechanism could be that individuals with diabetic complications are more likely to experience diabetes distress which contributes to an increased risk of depression and anxiety.

Strengths and limitations

The major strengths of this study are the prospective design, and the linkage of high-quality national registers allowing us to provide closely and long-term follow-up of complications, anxiety, and depression. Further, we used a comprehensive algorithm to identify individuals with type 2 diabetes combining several health registers including information from the hospital sector and general practice. The Danish health care system is universal and government-funded, ensuring free access to healthcare at both hospitals and general practitioners for all inhabitants. Thus, register-based data ensures a comprehensive measure of type 2 diabetes, that do not depend on membership of an insurance scheme. Based on all these features, we are confident that the risk of selection bias in this study is minimal. Lastly, the nationwide design secures a high level of generalizability.

However, using register-based data also has limitations. Even though we have applied a comprehensive and extensive algorithm to distinguish between type 1 and 2 diabetes, there is a risk that some patients with type 1 diabetes erroneously are classified as having type 2 diabetes and included in this study. However, based on the available data sources, we believe that this algorithm is the most accurate way to identify individuals with type 2 diabetes, and to distinguish between type 1 and 2 diabetes.²⁰

Further, we considered hospital contacts for depression and anxiety and use of antidepressant and anxiolytics as a proxy for depression and anxiety. A considerable proportion of individuals with symptoms of depression and anxiety are not treated in hospital or do not receive medical treatment for their condition. Thus, our results reflect the most severe cases of depression and anxiety. Also, even though antidepressants and anxiolytics are only prescribed by physicians in Denmark, all patients treated with these types of medication may not suffer from clinical depression and anxiety, but for example chronic pain. However, we believe that most individuals who are prescribed these types of medication suffer from depression and/or anxiety, and we also showed an association between diabetic complications and hospital contacts for depression and anxiety.

Likewise, the definition of diabetic complications has similar limitations, since we only capture those treated at hospital or with medications, again leading to an underestimation of the association. Furthermore, it is complicated to define diabetic complications, as especially cardiovascular disease share some of the same risk factors as type 2 diabetes. Thus, in some cases, the complications are more likely to represent comorbidity than complications caused by type 2 diabetes. However, we also show similar associations to depression and/or anxiety for specific complications like neuropathy, amputation of lower extremities, and nephropathy that are more likely to be consequences of type 2 diabetes.

Lastly, there are additional possible confounders that we did not have information about. This includes glycaemic control, as inadequate treatment adherence has been found to be associated with mental health issues,⁸ and is also a risk factor for diabetic complications.

Also, lifestyle factors could be possible confounders, as they are associated with development of diabetic complications and depression.³²

To conclude, having diabetic complications increases the risk of depression and anxiety among individuals with type 2 diabetes. This is both the case for presence of any complications, as well as specifically for cardiovascular disease, amputation of lower extremities, neuropathy, nephropathy, and retinopathy.

The results point towards the importance of an increased clinical focus on mental well-being among individuals with type 2 diabetes and complications.

FUNDING

This study was funded by Steno Diabetes Center Sjaelland.

CONFLICTS OF INTEREST

No potential conflicts reported.

AUTHOR CONTRIBUTIONS

TAH, LCT, SHH, ABT, and SR were involved in designing the study. TAH and LCT performed data-management and analyses. All authors contributed to interpretation of the results. TAH and SHH drafted the first version of the manuscript, and all authors edited, reviewed, and approved the final version. The guarantors for this work are LCT and TAH.

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FIGURE LEGENDS

Figure 1 Cumulative incidence of depression and/or anxiety and death based on Fine and Gray's competing risk regression models.

Table 1 Descriptive statistics for the entire cohort and separately for individuals with and without diabetic complications at time of diabetes diagnosis.

	No complications		Complications		All	
	N	%	N	%	N	%
Total	199,676		66,123		265,799	
Gender						
Male	116,293	58	43,287	65	159,580	60
Female	83,383	42	22,836	35	106,219	40
Age group						
≤50	48,446	24	4,832	7	53,278	20
51-70	110,352	55	31,528	48	141,880	53
>70	40,878	21	29,763	45	70,641	27
Origin						
Danish	174,442	87	60,695	92	235,137	88
Immigrant/descendant from a western country	5,727	3	1,724	3	7,451	3
Immigrant/descendant from a non-western country	19,507	10	3,704	6	23,211	9
Cohabitation status						
Living with others	131,858	66	39,491	60	171,349	64
Living alone	67,818	34	26,632	40	94,450	36
Educational level						
Elementary school	78,511	39	28,653	43	107,164	40
Upper secondary education	6,265	3	1,198	2	7,463	3
Vocational education	71,720	36	21,345	32	93,065	35
Higher education	32,104	16	7,812	12	39,916	15
Unknown	11,075	6	7,115	11	18,190	7
Income						
1. quartile (lowest income)	43,233	22	19,053	29	62,286	23
2. quartile	44,887	22	17,895	27	62,782	24
3. quartile	51,077	26	15,554	23	66,631	25
4. quartile (highest income)	58,594	29	13,361	20	71,955	27
Unknown	1,885	1	260	0	2,145	1
Hypertension^a	110,908	56	57,193	86	168,101	63
Complications at time of diabetes diagnosis*						
Cardiovascular disease			60,971	92		
Amputation			803	1		
Neuropathy			4,495	7		
Nephropathy			1,961	3		
Retinopathy			1,799	3		

^a Assessed from 5 years prior to and until diabetes diagnosis.

Table 2 Results from cox regression analyses comparing hazard for depression and/or anxiety among persons with and without diabetic complications (time-dependent variables).

	Events	Person years (PY)	IR per 100.000 PY	HR ^a	95% CI	HR ^b	95% CI
Any complication							
No	23,201	1,202,710	1929	1.00		1.00	
Yes	24,004	712,680	3368	1.78	1.75 - 1.82	1.77	1.73 - 1.80
Cardiovascular disease							
No	26,119	1,325,700	1970	1.00		1.00	
Yes	21,086	589,690	3576	1.83	1.79 - 1.86	1.81	1.77 - 1.84
Amputation							
No	46,394	1,900,060	2442	1.00		1.00	
Yes	811	15,330	5290	2.21	2.06 - 2.37	2.16	2.01 - 2.31
Neuropathy							
No	44,544	1,854,340	2402	1.00		1.00	
Yes	2661	61,050	4359	1.93	1.86 - 2.01	1.94	1.86 - 2.02
Nephropathy							
No	45,733	1,879,490	2433	1.00		1.00	
Yes	1472	35,900	4100	1.83	1.73 - 1.92	1.82	1.72 - 1.91
Retinopathy							
No	43,517	1,772,790	2455	1.00		1.00	
Yes	3688	142,590	2586	1.13	1.09 - 1.17	1.13	1.09 - 1.17

^a Adjusted for age, gender, and calendar time.

^b Adjusted for age, gender, calendar time, origin, educational level, and cohabitation status.

Table 3 Results from cox regression analyses comparing hazard for severe depression (hospital contacts for depression ICD 10: F32, F33) and/or severe anxiety (hospital contacts for ICD 10: F41 and F43.2) among persons with and without diabetic complications (time-dependent variables).

	Events	Person years (PY)	IR per 100.000 PY	HR ^a	95% CI	HR ^b	95% CI
Hospital contacts for depression							
Any complication							
No	1573	1,307,870	120	1.00		1.00	
Yes	1339	846,150	158	1.58	1.46 - 1.71	1.55	1.43 - 1.67
Cardiovascular disease							
No	1800	1,452,530	124	1.00		1.00	
Yes	1112	701,500	159	1.62	1.50 - 1.76	1.59	1.47 - 1.72
Amputation							
No	2872	2,133,160	135	1.00		1.00	
Yes	40	20,860	192	1.54	1.12 - 2.10	1.51	1.10 - 2.06
Neuropathy							
No	2726	2,069,280	132	1.00		1.00	
Yes	186	84,750	219	1.67	1.43 - 1.94	1.65	1.42 - 1.93
Nephropathy							
No	2829	2,109,270	134	1.00		1.00	
Yes	83	44,760	185	1.59	1.27 - 1.98	1.56	1.25 - 1.94
Retinopathy							
No	2622	1,982,510	132	1.00		1.00	
Yes	290	171,510	169	1.21	1.07 - 1.37	1.19	1.05 - 1.35
Hospital contacts for anxiety							
Any complication							
No	111	1,309,740	85	1.00		1.00	
Yes	872	848,950	103	1.81	1.64 - 1.99	1.75	1.59 - 1.93
Cardiovascular disease							
No	1285	1,454,840	88	1.00		1.00	
Yes	698	703,840	99	1.89	1.71 - 2.09	1.83	1.66 - 2.03
Amputation							
No	1949	2,137,700	91	1.00		1.00	
Yes	34	20,980	162	2.10	1.49 - 2.95	1.92	1.36 - 2.70
Neuropathy							
No	1861	2,073,540	90	1.00		1.00	
Yes	122	85,140	143	1.69	1.40 - 2.05	1.68	1.39 - 2.03
Nephropathy							
No	1933	2,113,760	91	1.00		1.00	
Yes	50	44,920	111	1.58	1.19 - 2.10	1.53	1.15 - 2.03
Retinopathy							
No	1782	1,986,420	90	1.00		1.00	
Yes	201	172,260	117	1.18	1.02 - 1.37	1.18	1.01 - 1.37

^a Adjusted for age, gender, and calendar time.

^b Adjusted for age, gender, calendar time, origin, educational level, and cohabitation status.

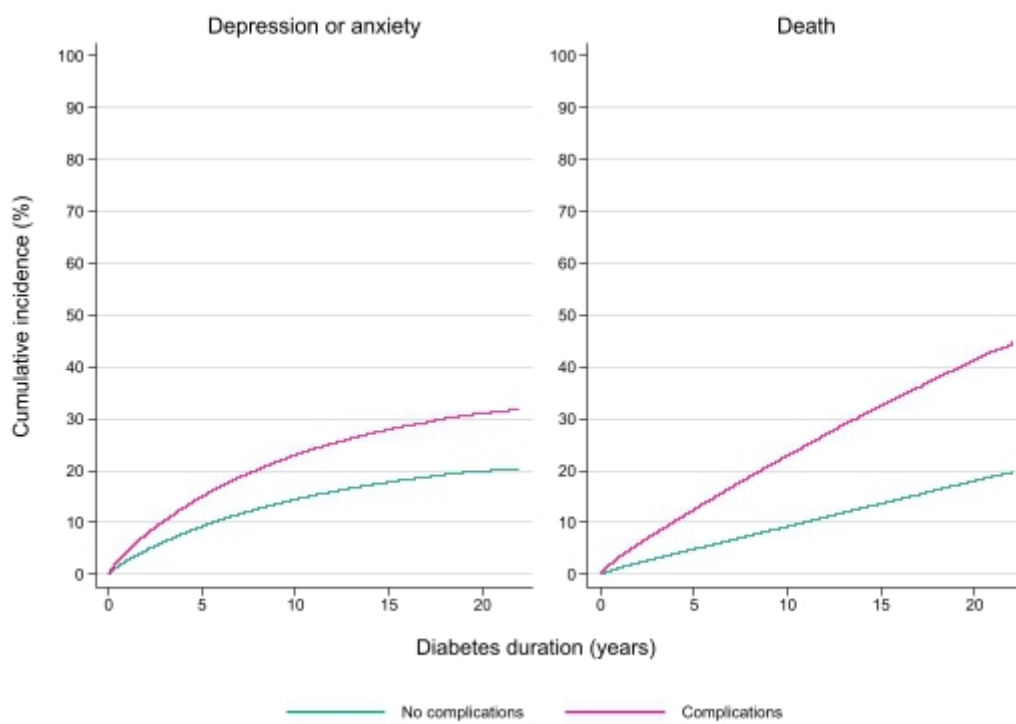


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