Risk factors associated with mortality among individuals with type 2 diabetes and depression across two cohorts

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Abstract

Objective: Depression has been linked to excess mortality in individuals with type 2 diabetes, but it remains unclear what drives this association. We examined if the association depends on unhealthy lifestyle and medical comorbidity.
Methods: We followed a clinically recruited cohort of Danish people with type 2 diabetes (n = 8175) with fine-grained clinical information and a population-wide register-based cohort of Danish individuals with HbA1c-defined type 2 diabetes (n = 87 500) representing everyday clinical practice. Antidepressant drug use prior to the onset of type 2 diabetes was used as a proxy for preexisting depression. In both cohorts, we first estimated the association between depression and 5-year mortality following type 2 diabetes, using a Cox proportional hazards model, yielding sex- and age-adjusted mortality rate ratios (MRRs). We subsequently examined how further adjustment for markers of unhealthy lifestyle (smoking, physical inactivity, obesity, alcohol abuse, and marital status) and medical comorbidity affected the association.
Results: Preexisting depression was associated with an approximately 50% increased age- and sex-adjusted all-cause mortality rate in both the clinically recruited- (5-year MRR: 1.46; 95% CI: 1.12–1.90) and the register-based type 2 diabetes cohort (5-year MRR: 1.51; 95% CI: 1.45–1.57). The excess mortality associated with depression almost disappeared when the analyses were adjusted for unhealthy lifestyle and medical comorbidity in both the clinically recruited- (MRR: 1.05; 95% CI: 0.72–1.52) and the register-based type 2 diabetes cohort (MRR: 1.14, 95% CI: 1.09–1.19).
Conclusions: A large fraction of the excess mortality associated with preexisting depression in type 2 diabetes is attributable to the unhealthy lifestyle and medical comorbidity accompanying depression.

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Introduction

One in six individuals with type 2 diabetes is affected by depression (1, 2, 3, 4). Converging evidence suggests that all-cause mortality is substantially higher among individuals with type 2 diabetes and comorbid depression than among individuals with type 2 diabetes without depression (34–110% increased mortality rate) (5, 6, 7, 8). However, the mechanism underlying the association between depression comorbid to type 2 diabetes and excess mortality is not well established.

Depression in the context of type 2 diabetes has been linked to increased cortisol levels and inflammation and suboptimal treatment adherence, all of which may contribute to metabolic dysregulation (3, 9, 10). Accordingly, as the long-term prognosis of type 2 diabetes

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depends on good metabolic control, it has been suggested that individuals with depression prior to the onset of type 2 diabetes have excess all-cause mortality due to poor metabolic control (11, 12). However, recent studies seem to counter this theory, as they report that preexisting depression in type 2 diabetes is linked neither to suboptimal glucose – or lipid control – nor to delayed initiation of – or lack of adherence to – antidiabetic treatment (13, 14, 15, 16, 17). This suggests that other factors may be driving the excess mortality observed for individuals with depression and type 2 diabetes. Here, the known relationship between depression and other medical comorbidities than type 2 diabetes (18, 19) as well as unhealthy lifestyle – including smoking, alcohol consumption, physical inactivity, poor diet, and obesity (20, 21, 22, 23) – is of particular interest.

Although the relationship between depression and increased mortality in type 2 diabetes has been previously described (6, 8), only a few studies have aimed at quantifying the influence of unhealthy lifestyle and medical comorbidities in this context (24, 25, 26), and even fewer studies have focused on preexisting depression at the time of diabetes diagnosis (27, 28). Generally, these recently published studies have shown that adjusting for unhealthy lifestyle and medical comorbidities attenuates the association between preexisting depression and excess mortality in type 2 diabetes (27, 28). However, these studies have been marred by several limitations, including (i) the use of selected study samples, for example, with the exclusion of individuals with diabetic complications (27) or cardiovascular disease (28), which limits generalizability, (ii) lack of comprehensive information on lifestyle factors (27), and (iii) no clarification of which specific depression-related lifestyle factors may drive the excess mortality in the context of type 2 diabetes (27, 28).

In the present study, we aimed to overcome these limitations by leveraging the potential of two large type 2 diabetes cohorts, each with distinct advantages, namely a clinically recruited type 2 diabetes cohort with fine-grained information available at baseline and a population-wide register-based type 2 diabetes cohort representing everyday clinical practice. Our study had two sequential aims: (i) to examine the magnitude of excess all-cause mortality associated with preexisting depression across the two type 2 diabetes cohorts and (ii) to examine if the association between preexisting depression and excess mortality in type 2 diabetes depends on unhealthy lifestyle and medical comorbidity.

Methods

Study cohorts

The following two cohorts were used to address the aims of the study. There was likely a minor overlap between the two cohorts (estimated at 3%). See the Supplementary Methods (see section on supplementary materials given at the end of this article) for the calculation underlying this estimation.

Clinically recruited type 2 diabetes cohort

This cohort included all participants with type 2 diabetes from the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) project (29). The DD2 project was initiated on January 1, 2009, to establish a national cohort of individuals with recently diagnosed type 2 diabetes for deep phenotyping. All individuals with recently diagnosed type 2 diabetes in Denmark were eligible for inclusion and were recruited by hospital departments and general practitioners on a feasibility basis. At baseline, questionnaire information (e.g. family history of diabetes and lifestyle factors such as physical activity, alcohol consumption, and smoking), data from clinical examination (including waist and hip circumference, height, and resting heart rate) and blood and urine samples for a biobank were collected. The DD2 participants were subsequently followed prospectively via linkage to various Danish registers, including the Danish Diabetes Database for Adults (DDDA) and the Danish health and administrative registers (30). For the present study, we included DD2 participants enrolled from January 1, 2009, to August 20, 2018.

Register-based type 2 diabetes cohort

This cohort was identified via linkage of data from the Danish health and administrative registers, using the unique 10-digit personal identification number (assigned to all individuals living in Denmark) from the Danish Civil Registration System (DCRS) as key (31). For the identification of individuals with incident type 2 diabetes, we used information from the Clinical Laboratory Information System (LABKA) database containing laboratory data from all general practitioners and hospitals in Central and Northern Denmark (complete data from the early 2000s) (32), the Danish National Prescription Register (DNPreR) containing information on all prescriptions redeemed at Danish Pharmacies Denmark since 1995 (33), and the Danish National Patient Registry (DNPatR) containing

discharge diagnoses from all admissions to Danish hospitals (since 1977 for nonpsychiatric hospitals and since 1969 for psychiatric hospitals) as well as discharge diagnoses from all contacts to emergency rooms and outpatient hospital services since 1995 (34). Consistent with prior studies (4, 13), incident type 2 diabetes was defined by the first hemoglobin A1C (HbA1c) value of ≥6.5% (48 mmol/mol) in LABKA in the period from January 1, 2000, to October 31, 2016. Individuals who (i) were registered with their first elevated HbA1c before the age of 30, (ii) prior to the first registration of an elevated HbA1c had redeemed a prescription for a glucose-lowering drug, or (iii) were registered with a diagnosis of diabetes in the DNPatR were excluded to reduce the number of individuals with type 1 diabetes in the cohort and because we aimed to focus on incident diagnoses of type 2 diabetes (4, 13). The Anatomical Therapeutic Chemical (ATC) and International Classification of Diseases (ICD) codes used in the definition of incident type 2 diabetes are available in Supplementary Table 1.

Exposure (depression)

Depression was operationalized based on redeemed prescriptions for antidepressants (definition according to ATC codes is available in Supplementary Table 1). Specifically, depression preceding type 2 diabetes was defined as having redeemed at least one prescription for an antidepressant in the year leading up to inclusion in the DD2 project or incident type 2 diabetes (register-based cohort), respectively. While antidepressants are also used for other medical indications than depression (anxiety disorders in particular, and occasionally pain), Musliner *et al*. have demonstrated that the majority of antidepressants prescribed in Denmark are used for the treatment of depression (≈88% of the prescriptions with an indication code) (35). Less than 0.1% of antidepressants are prescribed for neuropathic pain. Focusing on prescriptions redeemed before the type 2 diabetes index date should further reduce the risk of the antidepressants being prescribed to manage pain associated with diabetic neuropathy rather than for treatment of depression (35).

Outcome (mortality)

The date of death was obtained from the DCRS (31).

Covariates

For the clinically recruited type 2 diabetes cohort, data – from the time of recruitment to the DD2 project – on sex, age, medical comorbidity (no, one, or ≥two diseases according to the Charlson comorbidity index (CCI)) (36), macro- and microvascular complications (in the 5 years leading up to inclusion in the DD2 project), redeemed drug prescriptions (in the 6 months leading up to inclusion in the DD2 project), and markers of lifestyle (self-reported alcohol abuse (above 14/21 units per week (female/male)), waist circumference, marital status, self-reported physical activity (number of active days per week), and smoking status (current, former, or never) were extracted from the DD2 project, the DDDA, the DNPatR, and the DNPreR. Data for lifestyle variables in the clinically recruited type 2 diabetes cohort were complete, except for smoking status (43.8% missing) where we relied on data linkage with the DDDA. The definition of the variables according to ATC and ICD codes is available in Supplementary Table 1.

For the register-based type 2 diabetes cohort, data – from the time of incident type 2 diabetes – on sex, age, medical comorbidity (no, one, or ≥ two diseases according to the CCI), micro- and macrovascular complications, redeemed prescriptions, and markers of lifestyle (alcohol abuse, obesity, marital status, and smoking status (see definitions below)) was extracted from LABKA, the DNPreR, the DNPatR, and the DCRS. The definition of the variables according to ATC and ICD codes is available in Supplementary Table 1. As for the clinically recruited type 2 diabetes cohort, information on these variables was extracted for the 5-year period preceding incident type 2 diabetes, whereas drug prescriptions were ascertained 6 months before incident type 2 diabetes. As the registers do not contain direct information on alcohol abuse, medical obesity, and smoking status, we used available data from the registers to create proxies for these aspects. For example, a cohort member was considered as having alcohol abuse if he/she was registered with a hospital contact, leading to a diagnosis of an alcohol-related disorder or a redeemed prescription for disulfiram (Antabuse). A similar approach was used for obesity and smoking status (for the specific operationalization, please see Supplementary Table 1).

Statistical analysis

The clinically recruited type 2 diabetes cohort members were followed from baseline until either 5 years after inclusion in the DD2 project, death, emigration, or end of follow-up (August 22, 2018), whichever came first. Mortality rates were compared between individuals with and without preexisting depression using the Cox proportional hazards model adjusted for age and sex, yielding the mortality rate ratio (MRR). Subsequently, we included adjustment for each of

the individual lifestyle (alcohol abuse, waist circumference, marital status, physical activity, and smoking status) and medical comorbidity markers (macro- and microvascular complications, use of analgesics (as proxy for diabetic neuropathy and other types of pain), and CCI) – one at a time. Finally, we ran the analysis, including adjustment for all of the markers of lifestyle and medical comorbidity listed above – as well as age and sex. As we deemed valid smoking data essential, all analyses involving smoking were made as a complete case analysis, i.e. only including individuals without missing data on smoking status.

The register-based type 2 diabetes cohort members were followed from incident type 2 diabetes until either 5 years after incident type 2 diabetes, death, emigration, or end of follow-up (October 31, 2017), whichever came first. Mortality rates were compared between individuals with and without preexisting depression using the Cox proportional hazards model adjusted for age and sex, yielding the MRR. Subsequently, we included adjustment for each of the individual lifestyle (alcohol abuse, medical obesity, marital status, and smoking status) and medical comorbidity markers (macro- and microvascular complications, use of analgesics, and CCI) – one at a time. Finally, we ran the analysis, including adjustment for all of the markers of lifestyle and medical comorbidity listed above – as well as age and sex.

As we only had proxies for lifestyle in the register-based cohort, which may leave the analyses sensitive to residual confounding, we repeated the analyses described for the register-based type 2 diabetes cohort above while including a record-level quantitative bias analysis (QBA) (37) informed by the results from the analysis of the clinically recruited type 2 diabetes cohort. In brief, we estimated the prevalence of alcohol abuse, increased waist circumference, physical inactivity, and smoking status (current or former) according to depression status and estimated 5-year MRR for these lifestyle factors in the clinically recruited type 2 diabetes cohort. We then used the prevalence and the 95% CI for the MRR for each of these lifestyle factors to run the record-level QBA in the register-based type 2 diabetes cohort. For a detailed description of the QBA, please see Supplementary Table 2.

The proportional hazard assumption was tested for all analyses by plotting the observed survival curves with the estimated survival curves.

Sensitivity analyses

For the register-based type 2 diabetes cohort, the analyses were repeated using hospital diagnoses to define preexisting depression, as a hospital diagnosis of depression most likely is a proxy for more severe depression (the clinically recruited type 2 diabetes cohort was too small to allow for this analysis). Specifically, in these analyses, preexisting depression was defined as being registered with a clinical diagnosis of depression (ICD-10 codes: F32–-33) in the DNPatR in relation to an inpatient contact, an outpatient contact, or an emergency room visit to a Danish psychiatric hospital in the 2 years leading up to incident type 2 diabetes. For the clinically recruited type 2 diabetes cohort where the analyses involving smoking were based only on the 56.1% without missing data on smoking, we ran a *post hoc* sensitivity analysis in which we explored potential differences between the complete case cohort (i.e. with no missing data on smoking) and the full cohort. We also reran the regression models adjusting for all covariates except smoking in the complete case cohort and in the full clinically recruited cohort, to examine if the association between preexisting depression and mortality was similar between the two.

Results

The clinically recruited type 2 diabetes cohort

A total of 8175 individuals with type 2 diabetes were identified in the DD2 project, and 1214 (14.9%) of those had preexisting depression, according to the study definition. Table 1 shows the characteristics of the individuals with and without preexisting depression, respectively. Those with preexisting depression were slightly younger, were more likely to be women, were more likely to have an unhealthy lifestyle (higher waist circumference, physical inactivity, and smoking), and had more medical comorbidity.

The median follow-up time for the cohort members was 4.7 years (25th–75th percentile: 3.1–5.0). We observed 68 deaths (5.6%) among individuals with depression and 331 deaths (4.8%) among individuals without depression, corresponding to crude mortality rates per 1000 person-years of 14.1 in those with depression and 12.2 in those without depression. Figure 1 shows the association between preexisting depression and all-cause mortality in the clinically recruited type 2 diabetes cohort. Preexisting depression was associated with an increased mortality rate (MRR adjusted for age and sex: 1.46, 95% CI: 1.12–1.90). Adjustment for either physical activity (MRR: 1.35, 95% CI: 1.03–1.76), smoking status (MRR: 1.34, 95% CI: 0.96–1.86), analgesic use (MRR: 1.35, 95% CI: 1.03–1.82), or CCI (MRR: 1.27, 95% CI: 0.97–1.65), all attenuated the strength of the association between preexisting depression and mortality.

Table 1 Characteristics of the clinically recruited type 2 diabetes cohort, stratified by depression status. Data are presented as *n* (%), mean ± S.D. or as median (Q1–Q3).

	No preexisting depression	Preexisting depression
n	6961	1214
Time from diabetes to inclusion in DD2, years	2.1	2.1
Lifestyle		
Male	4257 (61.2%)	526 (43.3%)
Age, mean (S.D.)	60.9 ± 11.3	58.6 ± 11.8
Waist circumference	106.9 ± 15.2	108.7 ± 14.9
BMI, mean	31.5± 6.3 (*n* = 4,018)	32.1 ± 6.3 (*n* = 674)
Hip circumference		
Male	107.6 ± 11.7	109.0 ± 10.9
Female	111.4 ± 14.4	113.2 ± 14.3
Physical activity (pr. week)		
None	988 (14.2%)	288 (23.7%)
1–3 days	2315 (33.3%)	426 (35.1%)
4–7 days	3658 (52.5%)	500 (41.2%)
Alcohol abuse		
Less than 14/21 units	6509 (93.5%)	1154 (95.1%)
More than 14/21 units	452 (6.5%)	60 (4.9%)
Smoking status		
Current	656 (9.4%)	192 (15.8%)
Former	1314 (18.9%)	210 (17.3%)
Never	1934 (27.8%)	286 (23.6%)
Missing	3057 (43.9%)	526 (43.3%)
Systolic blood pressure	133 ± 15 (*n* = 4010)	130 ± 14 (*n* = 692)
Civil status		
Married/partner	4305 (61.8%)	662 (54.5%)
Unmarried, divorced, or widowed	2540 (36.5%)	525 (43.2%)
Medical comorbidity		
Charlson comorbidity index		
0	5306 (76.2%)	849 (69.9%)
1	1250 (18.0%)	249 (20.5%)
≥2	405 (5.8%)	116 (9.6%)
Macrovascular complications	1006 (14.5%)	238 (19.6%)
Microvascular complications	718 (10.3%)	158 (13.0%)
Medication use*		
Use of prescription drugs		
0	993 (14.3%)	156 (12.9%)
1	1354 (19.5%)	219 (18.0%)
≥2	4614 (66.3%)	839 (69.1%)
Glucocorticoid use	252 (3.6%)	78 (6.4%)
Analgesic use	1288 (18.5%)	463 (38.1%)
Antipsychotic use	59 (0.8%)	154 (12.7%)
Biomarkers (from Biobank samples)		
Fasting glucose	7.1 (6.4–8.2) (*n* = 4019)	7.1 (6.2–8.3) (*n* = 703)
HbA1c	6.6 (6.2–7.3) (*n* = 4156	6.6 (6.2–7.3) (*n* = 726)
LDL	2.4 ± 0.9 (*n* = 4055)	2.4 ± 0.9 (*n* = 698)
C-peptide	1270 ± 642 (*n* = 4846)	1407 ± 750 (*n* = 870)
C-reactive protein	3.8 ± 6.7 (*n* = 6163)	5.2 ± 8.0 (*n* = 1082)
Albuminuria (mg/g)		
Mean	38.7	32.9
<30 mg/g	3533 (50.8%)	629 (51.8%)
30–300 mg/g	750 (10.8%)	119 (9.8%)
>=300 mg/g	92 (1.3%)	14 (1.2%)
Missing	2586 (37.1%)	452 (37.2%)
Diabetes medication use		
No use	1656 (23.8%)	263 (21.7%)
Oral use	4934 (70.9%)	855 (70.4%)
Insulin use	371 (5.3%)	96 (7.9%)

DD2, Danish Centre for Strategic Research in Type 2 Diabetes.
*Use of beta blockers, ACE-related drugs, calcium Ca channel blockers, diuretics, lipid-modifying agents, and antithrombotics.

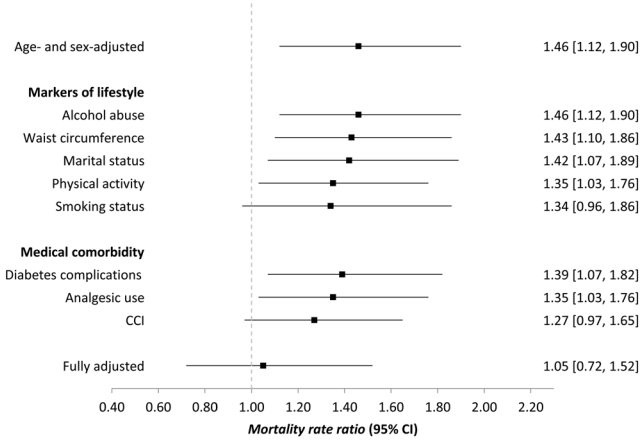

Figure 1

Comparison of all-cause mortality between individuals with and without preexisting depression in the clinically recruited type 2 diabetes cohort. Depression mortality rate ratios (MRRs) are shown with adjustment for each single lifestyle factor or comorbidity, in addition to age and sex. For example, the MRR estimate next to 'Alcohol abuse' shows the depression MRR, adjusted for sex, age, and alcohol abuse. The MRR next to 'Waist circumference' shows the depression MRR, adjusted for sex, age, and waist circumference. The fully adjusted MRR is adjusted for age, sex, and all factors displayed, i.e. alcohol abuse, waist circumference, marital status, physical activity, smoking status, diabetes complications, analgesic use, and Charlson comorbidity index (CCI).

When adjusting the analysis for all markers of lifestyle and medical comorbidity as well as age and sex, the MRR approached 1 (MRR: 1.05, 95% CI: 0.72–1.52).

The register-based type 2 diabetes cohort

A total of 87 500 individuals with incident type 2 diabetes were identified, of whom 12 162 (13.9%) had preexisting depression according to the definition employed in this study. Table 2 shows the characteristics of the individuals with and without preexisting depression, respectively. Those with depression were 1 year older, were more likely to be women, were more likely to have an unhealthy lifestyle (alcohol abuse, medical obesity, and smoking-related disorders), and had more medical comorbidity.

The median follow-up time for the cohort members was 5.0 years (25th–75th percentile: 2.8–5.0). A total of 3101 (25.5%) individuals with and 12 606 (16.7%) without depression died during follow-up, corresponding to crude mortality rates per 1000 person-years of 68.3 in those with depression and 42.2 in those without depression. Figure 2 shows the association between preexisting depression and all-cause mortality in the register-based cohort. Preexisting depression was associated with a mortality rate increase of a magnitude very similar to that observed in the clinically recruited type 2 diabetes cohort (MRR adjusted for age and sex: 1.51, 95% CI: 1.45–1.57). Adjustment for either smoking status (MRR: 1.42, 95% CI: 1.37–1.49), analgesic use (MRR: 1.35, 95% CI: 1.30–1.40), or CCI (MRR: 1.25, 95% CI: 1.20–1.30), all attenuated the strength of the association between preexisting depression and mortality. When adjusting the analysis for all markers of lifestyle and medical comorbidity as well as age and sex, the MRR approached 1 (MRR: 1.14, 95%CI: 1.09–1.19) – even more so in the QBA (fully adjusted MRR: 1.05, 95%CI: 1.00–1.09).

Sensitivity analyses

The findings from the sensitivity analyses using hospital diagnoses to define preexisting depression are reported in Supplementary Fig. 2 and are consistent with those from the main analyses reported above. Our comparison of individuals in the complete case cohort (i.e. with no missing data on smoking) and the full clinically recruited cohort (see Supplementary Table 3) generally showed no differences in the characteristics (physical activity, waist circumference, alcohol use, marital status, CCI, macrovascular complications, and analgesic use (all $P > 0.10$)), with the only exception being the prevalence of microvascular complications (12.6% and 10.7% in the complete case cohort and full clinically recruited cohort, respectively ($P < 0.01$)), suggesting that information on smoking was likely to be missing at random. Accordingly, when rerunning the fully adjusted model without including smoking status in the complete case cohort and the full cohort, the adjusted MRRs for the association between preexisting and depression were similar, at 1.09 (0.76–1.58) and 1.14 (0.85–1.52), respectively.

Discussion

Main findings

In this longitudinal study of two large cohorts of clinically recruited- and register-based individuals with type 2 diabetes, we found that preexisting depression was associated with an approximately 50% increased age- and sex-adjusted all-cause mortality rate. This increase, however, virtually disappeared following adjustment for higher medical comorbidity and adverse lifestyle factors assessed at the time of incident type 2 diabetes.

Table 2 Characteristics of the register-based type 2 diabetes cohort, stratified by depression status. Data are presented as *n* (%), mean ± S.D. or as median (Q1–Q3).

	No preexisting depression	Preexisting depression
n	75 488	12 162
Lifestyle		
Male	44 004 (58.3%)	5206 (42.8%)
Age	64.1 ± 13.3	65.3 ± 14.2
Obesity[†]	3323 (4.4%)	868 (7.1%)
Alcohol abuse[*]	1266 (1.7%)	543 (4.5%)
Smoking status (current/former)[‡]	4396 (5.8%)	1293 (10.6%)
Dyslipidemia[§]	21 029 (27.9%)	4346 (35.7%)
Hypertension[‖]	27 998 (37.1%)	5283 (43.4%)
Civil status		
Married/partner	52 273 (69.2%)	7546 (62.0%)
Unmarried, divorced, or widowed	20 823 (27.6%)	4232 (34.8%)
Medical comorbidity		
Charlson comorbidity index		
0	54 612 (72.3%)	7141 (58.7%)
1	13 962 (18.5%)	2989 (24.6%)
≥2	6914 (9.2%)	2032 (16.7%)
Macrovascular complications	12 479 (16.5%)	3002 (24.7%)
Microvascular complications	5555 (7.4%)	1210 (9.9%)
Medication use		
Use of prescription drugs[‡‡]		
0	26 697 (35.4%)	2853 (23.5%)
1	12 595 (16.7%)	2209 (18.2%)
≥2	36 196 (47.9%)	7100 (58.4%)
Glucocorticoid use	7269 (9.6%)	1883 (15.5%)
Analgesic use	17 422 (23.1%)	5566 (45.8%)
Antipsychotic use	1108 (1.5%)	1470 (12.1%)
Biomarkers (from routine care tests)		
Fasting glucose	6.9 (6.0–8.2) (*n* = 20 235)	6.7 (5.8–7.9) (*n* = 3876)
HbA1c	6.8 (6.6–7.9)	6.8 (6.6–7.4)
LDL	3.1 ± 1.0 (*n* = 59 273)	3.0 ± 1.1 (*n* = 9627)
eGFR	79.7± 22.7 (*n* = 73 282)	77.6 ± 24.4 (*n* = 11 991)

eGFR, estimated glomerular filtration rate.

[†]Diagnosis of obesity or prescriptions for an anti-obesity agent. *Alcohol-related disorder or prescriptions for disulfiram (Antabuse)). [‡]Smoking-related disorder or prescriptions for an inhalant used for chronic obstructive lung diseases or a smoking cessation agent. [§]Diagnosis of dyslipidemia or prescriptions for a lipid-modifying agent. [‖]Diagnosis of essential hypertension or prescriptions for at least two agents used in the treatment of hypertension. [‡‡]Use of beta blockers, ACE-related drugs, calcium channel blockers, diuretics, lipid-modifying agents, and antithrombotics.

Depression and excess mortality in type 2 diabetes

Our findings from a population-based setting corroborate meta-analyses showing that depression in type 2 diabetes is associated with approximately 50% increased risk of all-cause and cardiovascular mortality (6, 8). Notably, our results indicate that in individuals with diabetes and preexisting depression, this association may be almost entirely attributable to the unhealthy lifestyle and medical comorbidity accompanying depression. This was also suggested in two recently published large population-based studies from Taiwan (27) and Korea (28). Specifically, it was reported that the association between preexisting depression and excess all-cause mortality was much attenuated when the results were adjusted for all lifestyle factors and comorbidity in individuals with type 2 diabetes without diabetes-related complications (27) or cardiovascular disease (28). Unlike these two prior studies, we were, however, also able to determine which lifestyle factors were the main drivers of this excess mortality, namely physical inactivity and smoking, as well as medical comorbidity accompanying depression. Our findings contradict the common belief that preexisting depression *per se* necessarily impacts the clinical course of type 2 diabetes (6, 7, 8, 38). This is in line with a growing body of evidence suggesting that preexisting depression in type 2 diabetes is linked to neither suboptimal glucose – or lipid control – nor delayed initiation of – or lack of adherence to – antidiabetic treatment (13, 14, 15, 16, 17). In contrast, studies of incident depression occurring

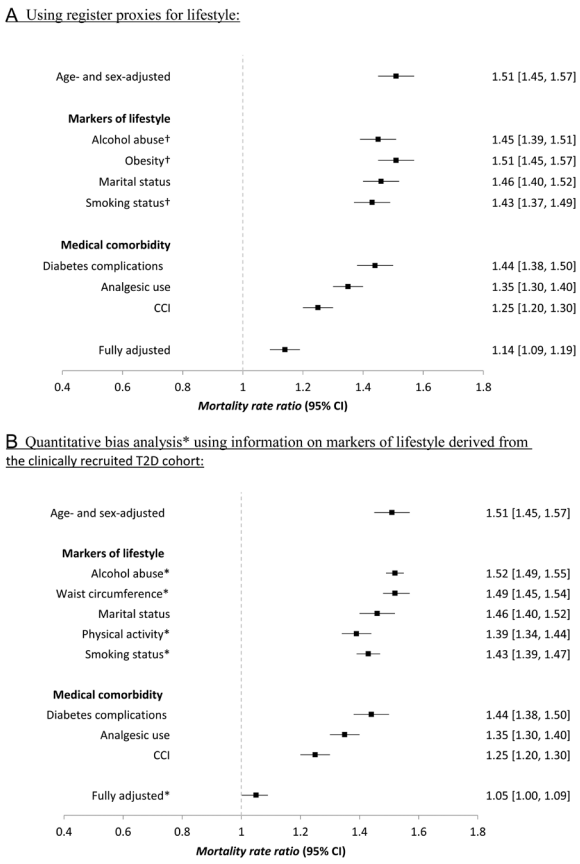

Figure 2

Comparison of all-cause mortality between individuals with and without preexisting depression in the register-based type 2 diabetes (T2D) cohort. (A) Using register proxies for lifestyle. (B) Quantitative bias analysis using information on markers of lifestyle derived from the clinically recruited T2D cohort. Depression mortality rate ratios (MRRs) are shown with adjustment for each single lifestyle factor or comorbidity, in addition to age and sex. For example, the MRR estimate next to 'Obesity' shows the depression MRR, adjusted for sex, age, and obesity. The MRR next to 'Marital status' shows the depression MRR, adjusted for sex, age, and marital status. The fully adjusted MRR is adjusted for age, sex, and all factors displayed, i.e. alcohol abuse, waist circumference/obesity, marital status, physical activity, smoking status, diabetes, analgesic use, and Charlson comorbidity index (CCI). †Data on alcohol abuse, obesity, and smoking status based on hospital contacts, leading to diagnoses of lifestyle-related disorders and/or redeemed prescriptions for disulfiram, anti-obesity agents, inhalants used for chronic obstructive lung diseases, or smoking cessation agents. *Quantitative bias analysis was performed when adjusting for alcohol abuse, waist circumference, physical activity, smoking status, and when adjusting for these variables in the fully adjusted model.

during the course of diabetes suggest that depression may increase mortality risk, even after adjustment for various lifestyle factors (24, 25, 26).

If unhealthy lifestyle and medical comorbidity constitute the decisive link between preexisting depression and excess mortality in individuals with type 2 diabetes, the best way to ameliorate survival in this vulnerable population might be through smoking cessation, increased physical activity, and early detection and treatment of medical comorbidity (39, 40). Accordingly, in their recent meta-analysis, Machado *et al.* suggested that promoting a healthy lifestyle and treating comorbid medical conditions may be the best way to decrease mortality in individuals with coexisting type 2 diabetes and depression, beyond the treatment targeting type 2 diabetes and depression more specifically (41). This, however, remains an open question that should be addressed empirically via clinical trials.

Limitations

The results of this study must be interpreted in light of its limitations. First, the design of our study leaves uncertainties regarding the order of events in time, i.e. whether a primary depression caused unhealthy lifestyle and medical comorbidity or vice versa. Accordingly, we cannot draw firm conclusions regarding the causality of the associations between preexisting depression, unhealthy lifestyle, medical comorbidity, and excess mortality in type 2 diabetes. Therefore, Mendelian randomization studies allowing for causal inference would be of great interest in this regard. Relatedly, recent Mendelian randomization studies have established that depression is a causal risk factor for type 2 diabetes and vice versa (42, 43). Assessment of whether depression is a causal risk factor for mortality in type 2 diabetes would be an interesting next step in this line of research. Second, we used redemption of prescriptions for antidepressants as a proxy for depression. Antidepressants are, however, used for other indications than depression, such as anxiety disorder and neuropathic pain. However, depression is the prime indication for prescription of antidepressants in Denmark (35), and our results were similar when we used hospital contacts to operationalize depression rather than redemption of prescriptions for antidepressants. On the other hand, we could not identify untreated depression or depression treated exclusively nonpharmacologically (e.g. using psychotherapy), which will have led us to include some people with depression in the reference populations, likely biasing our estimates toward the null. Third, we

focused specifically on the association between preexisting depression and excess mortality in type 2 diabetes (T2D). Consequently, it remains uncertain whether our findings will generalize to individuals with T2D and incident depression. This possibility should be addressed in future studies. Fourth, we had no information on lifestyle factors such as sleep and food/energy intake.

Conclusion

In conclusion, the results of this study suggest that a large fraction of the excess mortality associated with preexisting depression in the context of type 2 diabetes is attributable to the unhealthy lifestyle and medical comorbidity accompanying depression. To ameliorate survival in people with depression and type 2 diabetes, special points of attention should include smoking cessation, increased physical activity, and early detection and treatment of medical comorbidities.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EJE-22-0466.

Declaration of interest
C R received the 2020 Lundbeck Foundation Talent Prize. S D Ø received the 2020 Lundbeck Foundation Young Investigator Prize. Furthermore, Østergaard owns units of mutual funds with stock tickers DKIGI and WEKAFKI, as well as units of exchange-traded funds with stock tickers TRET, IQQH, QDV5, and EUNL.

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Data sharing
According to Danish data protection legislation, linked individual-level register data analyzed in the study cannot be shared or made publicly available. Register data are stored at the Danish Health Data Authority Data and can be made available for research on reasonable request and with permission from the Danish Data Protection Agency.

Ethics approval
As per Danish Law, ethical approval is not required for studies based solely on data from registries. The study was approved by the Danish Health Data Authority and Registered with the Danish Data Protection Agency.

Author contribution statement
C R, J S K, J S N, R W T, and S D Ø designed the study. J S K and C R reviewed the literature. R W T and S D Ø directed the analyses, which were carried out by C R. All authors participated in the discussion and interpretation of the results. C R organized the writing and wrote the initial draft. All authors critically revised the manuscript for intellectual content and approved the final version. C R is the guarantor.

References

1 Lindekilde N, Scheuer SH, Diaz LJ, Rubin KH, Plana-Ripoll O, Henriksen JE, Lasgaard M, Andersen GS & Pouwer F. Risk of developing type 2 diabetes in individuals with a psychiatric disorder: a nationwide register-based cohort study. *Diabetes Care* 2022 **45** 724–733. (https://doi.org/10.2337/dc21-1864)
2 Lindekilde N, Scheuer SH, Rutters F, Knudsen L, Lasgaard M, Rubin KH, Henriksen JE, Kivimäki M, Andersen GS & Pouwer F. Prevalence of type 2 diabetes in psychiatric disorders: an umbrella review with meta-analysis of 245 observational studies from 32 systematic reviews. *Diabetologia* 2022 **65** 440–456. (https://doi.org/10.1007/s00125-021-05609-x)
3 Semenkovich K, Brown ME, Svrakic DM & Lustman PJ. Depression in type 2 diabetes mellitus: prevalence, impact, and treatment. *Drugs* 2015 **75** 577–587. (https://doi.org/10.1007/s40265-015-0347-4)
4 Rohde C, Schmitz N, Thomsen RW & Østergaard SD. Incident psychopharmacological treatment and psychiatric hospital contact in individuals with newly developed type 2 diabetes – a register-based cohort study. *Acta Neuropsychiatrica* 2021 **33** 72–84. (https://doi.org/10.1017/neu.2020.39)
5 Hayashino Y, Okamura S, Tsujii S, Ishii H & Diabetes Distress and Care Registry at Tenri Study Group. The joint association of diabetes distress and depressive symptoms with all-cause mortality in Japanese individuals with type 2 diabetes: a prospective cohort study (Diabetes Distress and Care Registry in Tenri [DDCRT 20]). *Diabetologia* 2020 **63** 2595–2604. (https://doi.org/10.1007/s00125-020-05274-6)
6 Farooqi A, Khunti K, Abner S, Gillies C, Morriss R & Seidu S. Comorbid depression and risk of cardiac events and cardiac mortality in people with diabetes: a systematic review and meta-analysis. *Diabetes Research and Clinical Practice* 2019 **156** 107816. (https://doi.org/10.1016/j.diabres.2019.107816)
7 Naicker K, Johnson JA, Skogen JC, Manuel D, Øverland S, Sivertsen B & Colman I. Type 2 diabetes and comorbid symptoms of depression and anxiety: longitudinal associations with mortality risk. *Diabetes Care* 2017 **40** 352–358. (https://doi.org/10.2337/dc16-2018)
8 van Dooren FE, Nefs G, Schram MT, Verhey FR, Denollet J & Pouwer F. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. *PLoS ONE* 2013 **8** e57058. (https://doi.org/10.1371/journal.pone.0057058)
9 Majd M, Saunders EFH & Engeland CG. Inflammation and the dimensions of depression: a review. *Frontiers in Neuroendocrinology* 2020 **56** 100800. (https://doi.org/10.1016/j.yfrne.2019.100800)
10 Krass I, Schieback P & Dhippayom T. Adherence to diabetes medication: a systematic review. *Diabetic Medicine* 2015 **32** 725–737. (https://doi.org/10.1111/dme.12651)
11 Gaede P, Lund-Andersen H, Parving HH & Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *New England Journal of Medicine* 2008 **358** 580–591. (https://doi.org/10.1056/NEJMoa0706245)

12 Svensson E, Baggesen LM, Johnsen SP, Pedersen L, Nørrelund H, Buhl ES, Haase CL & Thomsen RW. Early glycemic control and magnitude of HbA(1c) reduction predict cardiovascular events and mortality: population-based cohort study of 24,752 metformin initiators. *Diabetes Care* 2017 **40** 800–807. (https://doi.org/10.2337/dc16-2271)

13 Rohde C, Knudsen JS, Schmitz N, Østergaard SD & Thomsen RW. The impact of hospital-diagnosed depression or use of antidepressants on treatment initiation, adherence and HbA(1c)/LDL target achievement in newly diagnosed type 2 diabetes. *Diabetologia* 2021 **64** 361–374. (https://doi.org/10.1007/s00125-020-05303-4)

14 Hoogendoorn CJ, Schechter CB, Llabre MM, Walker EA & Gonzalez JS. Distress and type 2 diabetes self-care: putting the pieces together. *Annals of Behavioral Medicine* 2021 **55** 938–948. (https://doi.org/10.1093/abm/kaaa070)

15 Shrestha M, Ng A, Al-Ghareeb A, Alenazi F & Gray R. Association between subthreshold depression and self-care behaviors in people with type 2 diabetes: a systematic review of observational studies. *Systematic Reviews* 2020 **9** 45. (https://doi.org/10.1186/s13643-020-01302-z)

16 Van Buren DJ, Wilfley DE, Marcus MD, Anderson B, Abramson NW, Berkowitz R, Ievers-Landis C, Trief P, Yasuda P, Hirst K *et al.* Depressive symptoms and glycemic control in youth with type 2 diabetes participating in the TODAY clinical trial. *Diabetes Research and Clinical Practice* 2018 **135** 85–87. (https://doi.org/10.1016/j.diabres.2017.11.008)

17 Ismail K, Moulton CD, Winkley K, Pickup JC, Thomas SM, Sherwood RA, Stahl D & Amiel SA. The association of depressive symptoms and diabetes distress with glycaemic control and diabetes complications over 2 years in newly diagnosed type 2 diabetes: a prospective cohort study. *Diabetologia* 2017 **60** 2092–2102. (https://doi.org/10.1007/s00125-017-4367-3)

18 Steffen A, Nübel J, Jacobi F, Bätzing J & Holstiege J. Mental and somatic comorbidity of depression: a comprehensive cross-sectional analysis of 202 diagnosis groups using German nationwide ambulatory claims data. *BMC Psychiatry* 2020 **20** 142. (https://doi.org/10.1186/s12888-020-02546-8)

19 Koyanagi A, Kohler-Forsberg O, Benros ME, Munk Laursen T, Haro JM, Nordentoft M & Hjorthoj C. Mortality in unipolar depression preceding and following chronic somatic diseases. *Acta Psychiatrica Scandinavica* 2018 **138** 500–508. (https://doi.org/10.1111/acps.12899)

20 Schuch FB, Vancampfort D, Firth J, Rosenbaum S, Ward PB, Silva ES, Hallgren M, Ponce De Leon A, Dunn AL, Deslandes AC *et al.* Physical activity and incident depression: a meta-analysis of prospective cohort studies. *American Journal of Psychiatry* 2018 **175** 631–648. (https://doi.org/10.1176/appi.ajp.2018.17111194)

21 Weinberger AH, Kashan RS, Shpigel DM, Esan H, Taha F, Lee CJ, Funk AP & Goodwin RD. Depression and cigarette smoking behavior: a critical review of population-based studies. *American Journal of Drug and Alcohol Abuse* 2017 **43** 416–431. (https://doi.org/10.3109/00952990.2016.1171327)

22 Bonnet F, Irving K, Terra JL, Nony P, Berthezène F & Moulin P. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. *Atherosclerosis* 2005 **178** 339–344. (https://doi.org/10.1016/j.atherosclerosis.2004.08.035)

23 Zhang YB, Pan XF, Chen J, Cao A, Xia L, Zhang Y, Wang J, Li H, Liu G & Pan A. Combined lifestyle factors, all-cause mortality and cardiovascular disease: a systematic review and meta-analysis of prospective cohort studies. *Journal of Epidemiology and Community Health* 2021 **75** 92–99. (https://doi.org/10.1136/jech-2020-214050)

24 Katon WJ, Rutter C, Simon G, Lin EH, Ludman E, Ciechanowski P, Kinder L, Young B & Von Korff M. The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care* 2005 **28** 2668–2672. (https://doi.org/10.2337/diacare.28.11.2668)

25 Zhang X, Norris SL, Gregg EW, Cheng YJ, Beckles G & Kahn HS. Depressive symptoms and mortality among persons with and without diabetes. *American Journal of Epidemiology* 2005 **161** 652–660. (https://doi.org/10.1093/aje/kwi089)

26 Egede LE, Nietert PJ & Zheng D. Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. *Diabetes Care* 2005 **28** 1339–1345. (https://doi.org/10.2337/diacare.28.6.1339)

27 Wu CS, Hsu LY & Wang SH. Association of depression and diabetes complications and mortality: a population-based cohort study. *Epidemiology and Psychiatric Sciences* 2020 **29** e96. (https://doi.org/10.1017/S2045796020000049)

28 Jung I, Kwon H, Park SE, Han KD, Park YG, Kim YH, Rhee EJ & Lee WY. Increased risk of cardiovascular disease and mortality in patients with diabetes and coexisting depression: a nationwide population-based cohort study. *Diabetes and Metabolism Journal* 2021 **45** 379–389. (https://doi.org/10.4093/dmj.2020.0008)

29 Christensen DH, Nicolaisen SK, Berencsi K, Beck-Nielsen H, Rungby J, Friborg S, Brandslund I, Christiansen JS, Vaag A, Sørensen HT *et al.* Danish Centre for Strategic Research in Type 2 Diabetes (DD2) project cohort of newly diagnosed patients with type 2 diabetes: a cohort profile. *BMJ Open* 2018 **8** e017273. (https://doi.org/10.1136/bmjopen-2017-017273)

30 Thomsen RW, Friborg S, Nielsen JS, Schroll H & Johnsen SP. The Danish Centre for Strategic Research in Type 2 Diabetes (DD2): organization of diabetes care in Denmark and supplementary data sources for data collection among DD2 study participants. *Clinical Epidemiology* 2012 **4** 15–19. (https://doi.org/10.2147/CLEP.S30082)

31 Pedersen CB. The Danish civil registration system. *Scandinavian Journal of Public Health* 2011 **39** (7 Supplement) 22–25. (https://doi.org/10.1177/1403494810387965)

32 Grann AF, Erichsen R, Nielsen AG, Frøslev T & Thomsen RW. Existing data sources for clinical epidemiology: the Clinical Laboratory Information System (LABKA) Research Database at Aarhus University, Denmark. *Clinical Epidemiology* 2011 **3** 133–138. (https://doi.org/10.2147/CLEP.S17901)

33 Kildemoes HW, Sørensen HT & Hallas J. The Danish national prescription registry. *Scandinavian Journal of Public Health* 2011 **39** (7 Supplement) 38–41. (https://doi.org/10.1177/1403494810394717)

34 Lynge E, Sandegaard JL & Rebolj M. The Danish national patient register. *Scandinavian Journal of Public Health* 2011 **39** (7 Supplement) 30–33. (https://doi.org/10.1177/1403494811401482)

35 Musliner KL, Liu X, Gasse C, Christensen KS, Wimberley T & Munk-Olsen T. Incidence of medically treated depression in Denmark among individuals 15–44 years old: a comprehensive overview based on population registers. *Acta Psychiatrica Scandinavica* 2019 **139** 548–557. (https://doi.org/10.1111/acps.13028)

36 Thygesen SK, Christiansen CF, Christensen S, Lash TL & Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of patients. *BMC Medical Research Methodology* 2011 **11** 83. (https://doi.org/10.1186/1471-2288-11-83)

37 Lash TL, Fox MP & Fink AK. *Applying Quantitative Bias Analysis to Epidemiologic Data*. Springer Publishing Company, Incorporated, 2009.

38 Reeves GC, Alhurani AS, Frazier SK, Watkins JF, Lennie TA & Moser DK. The association of comorbid diabetes mellitus and symptoms of depression with all-cause mortality and cardiac rehospitalization in patients with heart failure. *BMJ Open Diabetes Research and Care* 2015 **3** e000077. (https://doi.org/10.1136/bmjdrc-2014-000077)

39 Belvederi Murri M, Folesani F, Zerbinati L, Nanni MG, Ounalli H, Caruso R & Grassi L. Physical activity promotes health and reduces cardiovascular mortality in depressed populations: a literature overview. *International Journal of Environmental Research and Public Health* 2020 **17** 5545. (https://doi.org/10.3390/ijerph17155545)

40 Pirie K, Peto R, Reeves GK, Green J & Beral V. The 21st century hazards of smoking and benefits of stopping: a prospective study of one

million women in the UK. *Lancet* 2013 **381** 133–141. (https://doi.org/10.1016/S0140-6736(12)61720-6)

41 Machado MO, Veronese N, Sanches M, Stubbs B, Koyanagi A, Thompson T, Tzoulaki I, Solmi M, Vancampfort D, Schuch FB *et al.* The association of depression and all-cause and cause-specific mortality: an umbrella review of systematic reviews and meta-analyses. *BMC Medicine* 2018 **16** 112. (https://doi.org/10.1186/s12916-018-1101-z)

42 Yuan S & Larsson SC. An atlas on risk factors for type 2 diabetes: a wide-angled Mendelian randomisation study. *Diabetologia* 2020 **63** 2359–2371. (https://doi.org/10.1007/s00125-020-05253-x)

43 Xuan L, Zhao Z, Jia X, Hou Y, Wang T, Li M, Lu J, Xu Y, Chen Y, Qi L *et al.* Type 2 diabetes is causally associated with depression: a Mendelian randomization analysis. *Frontiers of Medicine* 2018 **12** 678–687. (https://doi.org/10.1007/s11684-018-0671-7)

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