Association of type 2 diabetes according to the number of risk factors within the recommended range with incidence of major depression and clinically relevant depressive symptoms: a prospective analysis

April C E van Gennip, Miranda T Schram, Sebastian Köhler, Abraham A Kroon, Annemarie Koster, Simone J P M Eussen, Bastiaan E de Galan, Thomas T van Sloten, Coen D A Stehouwer**

Summary

Background Type 2 diabetes is associated with an increased risk of depression, but the extent to which risk factor modification can mitigate this risk is unclear. We aimed to examine the association between the incidence of major depression and clinically relevant depressive symptoms among individuals with type 2 diabetes, according to the number of risk factors within the recommended target range, compared with individuals without diabetes.

Methods We did a prospective analysis of population-based data from the UK Biobank and the Maastricht Study. Individuals with type 2 diabetes were categorised according to the number of risk factors within the recommended target range (non-smoking, guideline-recommended levels of glycated haemoglobin (HbA_{1c}), blood pressure, BMI, albuminuria, physical activity, and diet). The primary outcome, based on data from the UK Biobank, was the incidence of major depression ascertained from hospital records; the secondary outcome, based on data from the UK Biobank and the Maastricht Study, was clinically relevant depressive symptoms based on a score of 10 or higher on the Patient Health Questionnaire (PHQ-9).

Findings The study population of the UK Biobank comprised 77 786 individuals (9047 with type 2 diabetes and 68 739 without diabetes; median age 59 years [IQR 51–64]; 34 136 [43·9%] women and 43 650 [56·1%] men). A median of 12·7 years (IQR 11·8–13·4) after recruitment (between March 13, 2006, and Oct 1, 2010), 493 (5·5%) of 9047 individuals with type 2 diabetes and 2574 (3·7%) of 68 739 individuals without diabetes developed major depression. Compared with individuals without diabetes, those with type 2 diabetes had a higher risk of major depression (hazard ratio [HR] 1·61 [95% CI 1·49–1·77]). Among individuals with type 2 diabetes, the excess risk of depression decreased stepwise with an increasing number of risk factors within the recommended target range (HR 2·04 [95% CI 1·65–2·52] for up to two risk factors within the recommended target range; 1·95 [1·65–2·30] for three risk factors within the recommended target range; 1·38 [1·16–1·65] for four risk factors within the recommended target range; and 1·34 [1·12–1·62] for five to seven risk factors within the recommended target range). In the UK Biobank dataset, a median of 7·5 years (IQR 6·8–8·2) after the baseline examination, 147 (7·5%) of 1953 individuals with type 2 diabetes and 954 (4·5%) of 21 413 individuals without diabetes had developed clinically relevant depressive symptoms. The study population of the Maastricht Study comprised 4530 individuals (1158 with type 2 diabetes and 3372 without diabetes; median age 60 years [IQR 53–66]; 2244 [49·5%] women and 2286 [50·1%] men). A median of 5·1 years (IQR 4·1–6·1) after recruitment (between Sept 1, 2010, and Dec 7, 2017), 170 (14·7%) of 1158 individuals with type 2 diabetes and 227 (6·7%) of 3372 individuals without diabetes developed clinically relevant depressive symptoms. Similarly, in both the UK Biobank dataset and the Maastricht Study cohort, among individuals with type 2 diabetes, the excess risk of clinically relevant depressive symptoms decreased stepwise with an increasing number of risk factors within the recommended target range.

Interpretation Among individuals with type 2 diabetes, the excess risk of major depression and clinically relevant depressive symptoms decreased stepwise with an increasing number of risk factors within the recommended target range. This study provides further evidence to promote risk factor modification strategies in individuals with type 2 diabetes and to encourage the adoption of a healthy lifestyle.

Funding ZonMW, Hartstichting, and Diabetes Fonds.

Lancet Healthy Longev 2023; 4: e63–71

*Contributed equally as senior authors

Department of Internal Medicine (A C E van Gennip MD, M T Schram PhD, Prof A A Kroon MD, Prof B E de Galan MD, Prof C D A Stehouwer MD) **and Heart and Vascular Centre** (M T Schram), **Maastricht University Medical Centre, Maastricht, Netherlands; School for Cardiovascular Diseases CARIM** (A C E van Gennip, M T Schram, Prof A A Kroon, S J P M Eussen PhD, Prof B E de Galan, Prof C D A Stehouwer), **School for Mental Health and Neuroscience MHENS** (M T Schram, S Köhler PhD), **Department of Psychiatry and Neuropsychology** (S Köhler), **Care and Public Health Research Institute CAPHRI** (A Koster PhD, S P J M Eussen), **Department of Social Medicine** (A Koster), **and Department of Epidemiology** (S P J M Eussen), **Maastricht University, Maastricht, Netherlands; Department of Vascular Medicine, University Medical Centre Utrecht, Utrecht, Netherlands** (T T van Sloten MD); **Department of Internal Medicine, Radboud University Medical Centre, Nijmegen, Netherlands** (Prof B E de Galan)

Correspondence to:
Dr Thomas T van Sloten, Department of Vascular Medicine, University Medical Centre Utrecht, Utrecht 3508 GA, Netherlands
t.t.vansloten@umcutrecht.nl

Introduction

Major depression is increasingly recognised as an important complication associated with type 2 diabetes. The risk of depression in individuals with type 2 diabetes is 1·5–2·0 times higher than that in the general population.[1] Moreover, type 2 diabetes is associated with

Research in context

Evidence before this study

We searched PubMed, Google Scholar, and the reference lists of relevant articles for studies published from database inception to Sept 27, 2022, in any language, using the search terms (including synonyms and related terms): "diabetes" AND "depression" OR "depressive symptoms" AND "treatment" OR "risk factors". We identified no previous observational studies that investigated whether the excess risk of major depression or clinically relevant depressive symptoms among individuals with type 2 diabetes compared with individuals without diabetes might be associated with the number of risk factors within the target range recommended by guidelines for the management of diabetes and prevention of cardiovascular disease.

Added value of this study

Using prospective data from the UK Biobank, we show that the excess risk of major depression among individuals with type 2 diabetes compared with individuals without diabetes is progressively lower for an increasing number of seven selected risk factors within the recommended target range (non-smoking, guideline-recommended levels of glycated haemoglobin [HbA_{1c}], blood pressure, BMI, albuminuria, physical activity, and diet). Similarly, the risk of clinically relevant depressive symptoms decreased stepwise with an increasing number of risk factors within the recommended target range in individuals with type 2 diabetes compared with individuals without diabetes. To increase the validity of our findings, we replicated the results on clinically relevant depressive symptoms in 4530 participants from the Maastricht Study. Together, these findings suggests that multifactorial risk factor modification might reduce the excess risk of depression associated with type 2 diabetes.

Implications of all the available evidence

In addition to previous studies showing that multifactorial risk modification might reduce the excess risk of cardiovascular disease, mortality, and dementia associated with type 2 diabetes, the present study suggests that such an approach might also reduce the excess risk of major depression related to type 2 diabetes. This study provides important further evidence to promote multifactorial risk factor treatment strategies in individuals with type 2 diabetes and to encourage the facilitation and adoption of a healthy lifestyle in this population.

an increased risk of clinically relevant depressive symptoms.[2] Depression and depressive symptoms are associated with a lower quality of life and a higher risk of diabetes-related complications and mortality.[3]

Treatment of type 2 diabetes consists of multifactorial risk modification strategies to reduce adverse outcomes. Observational studies[4–6] have shown that individuals with type 2 diabetes who had various risk factors within the recommended target range (eg, glycated haemoglobin [HbA_{1c}], cholesterol, blood pressure, BMI, albuminuria, physical activity, diet, and not smoking) had little or no excess risk of death or cardiovascular disease compared with the general population. Another study[7] has suggested that a multifactorial risk modification approach might also reduce the excess risk of structural brain abnormalities (ie, higher white matter hyperintensity volume, lower total brain volume, and lacunar infarcts), lower cognitive performance, and dementia in individuals with type 2 diabetes. However, whether the excess risk of major depression and depressive symptoms in individuals with type 2 diabetes compared with individuals without diabetes is associated with the number of risk factors within the guideline-recommended target range remains unclear.

Using data from the UK Biobank, we aimed to evaluate the associations between the risk of major depression and clinically relevant depressive symptoms and the number of risk factors within the recommended target range among individuals with type 2 diabetes, relative to individuals without diabetes. To increase the validity of our findings, analyses were replicated with data from the Maastricht Study, a Dutch population-based cohort.

Methods

Data sources

We did a complete-case analysis based on data from the UK Biobank and the Maastricht Study. These cohort studies were selected because of the high number of individuals with type 2 diabetes enrolled. The primary analysis, of the risk of major depression, was based on data from the UK Biobank,[8] a population-based cohort of more than 500 000 participants aged 40–69 years who were recruited from across the UK between March 13, 2006, and Oct 1, 2010. Participants in the UK Biobank are continuously followed up for incident major depression. The secondary analysis, of clinically relevant depressive symptoms, was based on data from the UK Biobank and the Maastricht Study.[9] The Maastricht Study is an ongoing cohort study comprising approximately 9200 individuals aged 40–79 years from the southern part of the Netherlands. Individuals are recruited from the general population, with an oversampling of individuals with type 2 diabetes.[9] For this analysis, prospective data from the Maastricht Study were available for 7689 participants who were recruited between Sept 1, 2010, and Dec 7, 2017.

The UK Biobank received ethical approval from the North-West Multi-centre Research Ethics Committee (reference 21/NW/0157), and the Maastricht Study received ethical approval from the Medical Research Ethics Committee of the Maastricht University Medical Centre and Maastricht University (reference NL31329.068.10) and from the Ministry of Health, Welfare, and Sports of the Netherlands (permit 131088-105234-PG). All participants gave written informed consent.

Selection criteria

In both studies, we excluded individuals who, at baseline, had major depression or clinically relevant depressive symptoms (ie, 9-item Patient Health Questionnaire [PHQ-9] score ≥10; baseline data on depressive symptoms were available only in the Maastricht Study) or were using antidepressant medication. After exclusion of participants with prediabetes or diabetes other than type 2, we selected individuals with type 2 diabetes and compared them with all individuals without diabetes. Participants were classified as having type 2 diabetes, prediabetes, or no diabetes as described in the appendix (p 2). We excluded individuals with prediabetes a priori from the reference group in the main analysis because the results of previous studies on prediabetes and incident depression have been inconsistent (appendix p 2).[2,10,11]

Risk factors

Risk factors were assessed in individuals with and without type 2 diabetes. Seven risk factors were selected on the basis of recommendations in clinical guidelines from the European Society of Cardiology, the European Association for the Study of Diabetes, American College of Cardiology, and the American Heart Association for the management of diabetes and prevention of cardiovascular disease,[12–15] and were defined as being within the target range on the basis of guideline-recommended levels: HbA_{1c} concentration (cutoff <53 mmol/mol [<7%]), blood pressure (cutoff <130/80 mm Hg), BMI (cutoff ≥20 kg/m² and <25 kg/m²), smoking status (non-smoker), albuminuria (absence of albuminuria), physical activity (cutoff ≥150 min/week of moderate to vigorous physical activity), and diet (optimal as defined by the American Heart Association healthy diet score; for a detailed definition of risk factors see the appendix [p 4]). We did not consider cholesterol as a risk factor a priori because the association between cholesterol levels and depression is inconsistent.[16,17]

Incident major depression and clinically relevant depressive symptoms

In the UK Biobank, incident major depression was ascertained from hospital records according to the International Classification of Diseases 10th Revision codes F32 (single episode major depression) and F33 (recurrent major depression) only.[18] Follow-up was until Jan 1, 2022. In the Maastricht Study, major depression was assessed solely at baseline, with the Mini-International Neuropsychiatric Interview.[19] Clinically relevant depressive symptoms were defined as a PHQ-9 score of 10 or higher in both cohorts, as described in the appendix (p 3).[20] With a cutoff score of 10 or higher, the PHQ-9 has high sensitivity (88%) and specificity (85%) compared with a structured interview for the diagnosis of major depression.[20] In the UK Biobank, depressive symptoms were assessed in a subsample during an online mental health questionnaire, a median of 7·5 years (IQR 6·8–8·2) after initial recruitment, but not at baseline (appendix p 3).[18] In the Maastricht Study, depressive symptoms were assessed at baseline and annually during follow-up until Dec 7, 2017 (appendix p 3).

Statistical analysis

The Maastricht Study oversampled individuals with type 2 diabetes (1893 [24·8%] of 7639 individuals had type 2 diabetes), and the UK Biobank included a large study population (n=502 412), of which 31 836 (6·3%) had type 2 diabetes. The flowchart for the derivation of the study populations is provided in the appendix (p 24). In the UK Biobank, 369 012 individuals were excluded due to missing data on diabetes status (n=68 922) or risk factors (n=300 090), largely due to missing data on albuminuria (n=290 764). In the Maastricht Study, 1456 individuals were excluded due to missing data on risk factors (n=1159) or depressive symptoms (n=297). We did not do a formal power calculation a priori. We evaluated the association between the incidence of major depression (the primary outcome) and the incidence of clinically relevant depressive symptoms (the secondary outcome) among individuals with type 2 diabetes, according to the number of risk factors within the recommended target range, compared with individuals without diabetes. The following categories were retained in the analysis to include groups of individuals with type 2 diabetes that were sufficiently large and as defined in a previous study:[7] up to two risk factors within the recommended target range; three risk factors within the recommended target range; four risk factors within the recommended target range; and five to seven risk factors within the recommended target range.

We used Cox regression to estimate hazard ratios (HRs) and 95% CIs to estimate the association of the incidence of major depression in the UK Biobank and incidence of clinically relevant depressive symptoms in the Maastricht Study with the number of risk factors within the recommended target range among individuals with type 2 diabetes, compared with individuals without diabetes, with time in study as the time scale. We used the baseline examination as the origin and start time for the survival analysis in both cohorts. In the UK Biobank, follow-up time was calculated from the UK Biobank baseline examination (2006–10) to the incidence of major depression, death, or Jan 1, 2022, whichever came first. Participants who died during the follow-up were censored at the date of death to account for the competing risk of death by use of cause-specific hazard models. In the Maastricht Study, follow-up time was calculated from the Maastricht Study baseline examination (2010–17) to the incidence of clinically relevant depressive symptoms or time of the last examination, whichever came first. Data on mortality or reasons for censoring were not available in the Maastricht Study at the time of the present study. The proportional hazards assumption was verified by visual inspection of the log-log survival curves (appendix p 23), and the linearity assumption was verified by a test for

See Online for appendix

	Individuals without diabetes*	Individuals with type 2 diabetes and with complete data on the number of risk factors*				
		Overall	0–2 risk factors on target	3 risk factors on target	4 risk factors on target	5–7 risk factors on target
Participants	68 739 (100·0%)	9047 (100·0%)	1350 (14·9%)	2324 (25·7%)	2801 (31·0%)	2572 (28·4%)
Age, years	58 (50–64)	61 (56–65)	60 (54–64)	61 (55–65)	62 (56–66)	62 (57–66)
Sex						
Female	31 286 (45·5%)	2850 (31·5%)	332 (24·6%)	583 (25·1%)	891 (31·8%)	1044 (40·6%)
Male	37 453 (54·5%)	6197 (68·5%)	1018 (75·4%)	1741 (74·9%)	1910 (68·2%)	1528 (59·4%)
Educational attainment						
No college or university level education	45 668 (66·4%)	6666 (73·7%)	1031 (76·4%)	1749 (75·3%)	2056 (73·4%)	1830 (71·2%)
College or university level education	23 071 (33·6%)	2381 (26·3%)	319 (23·6%)	575 (24·7%)	745 (26·6%)	742 (28·9%)
Ethnicity						
White	64 862 (94·4%)	7999 (88·4%)	1141 (84·5%)	2027 (87·2%)	2504 (89·4%)	2327 (90·5%)
Other	3655 (5·3%)	1005 (11·1%)	200 (14·8%)	287 (12·4%)	282 (10·1%)	236 (9·2%)
Unknown	222 (0·3%)	43 (0·5%)	9 (0·7%)	10 (0·4%)	15 (0·5%)	9 (0·4%)
Previous cardiovascular disease	3820 (5·6%)	1542 (17·1%)	277 (20·6%)	426 (18·4%)	460 (16·5%)	379 (14·8%)
Duration of diabetes, years	..	3 (0–8)	5 (1–11)	4 (1–9)	3 (0–8)	2 (0–6)
Glycated haemoglobin, mmol/mol	35·3 (4·2)	52·5 (15·2)	63·2 (16·2)	56·8 (15·7)	50·5 (13·7)	43·9 (9·3)
Glycated haemoglobin, %	5·4% (0·4)	6·9% (1·4)	7·9% (1·5)	7·4% (1·4)	6·8% (1·3)	6·2% (0·9)
Glycated haemoglobin <53 mmol/mol (<7%)	68 672 (99·9%)	5564 (61·5%)	277 (20·5%)	1014 (43·6%)	1900 (67·8%)	2373 (92·3%)
Non-smokers	60 975 (88·7%)	8084 (89·4%)	930 (68·9%)	2010 (86·5%)	2624 (93·7%)	2520 (98·0%)
BMI, kg/m²	27·8 (4·8)	31·3 (5·6)	33·4 (6·0)	32·3 (5·3)	31·4 (5·2)	29·3 (5·5)
BMI ≥20 and <25 kg/m²	18 649 (27·1%)	878 (9·7%)	21 (1·6%)	74 (3·2%)	165 (5·9%)	618 (24·0%)
Systolic blood pressure, mm Hg	141·4 (19·9)	144·1 (18·3)	147·6 (17·3)	146·6 (17·6)	145·3 (17·7)	138·8 (19·1)
Diastolic blood pressure, mm Hg	84·4 (10·9)	83·1 (10·3)	85·7 (10·1)	84·6 (10·1)	83·5 (9·9)	79·8 (10·1)
Systolic <130 mm Hg and diastolic <80 mm Hg	15 135 (22·0%)	1457 (16·1%)	59 (4·4%)	194 (8·4%)	330 (11·8%)	874 (34·0%)
Absence of albuminuria	53 959 (78·5%)	5486 (60·6%)	290 (21·5%)	955 (41·1%)	1882 (67·2%)	2359 (91·7%)
Estimated glomerular filtration rate, mL/min	87·6 (14·7)	52·2 (15·2)	83·1 (19·9)	82·9 (19·3)	84·0 (17·0)	43·9 (9·3)
LDL cholesterol, mmol/L	3·6 (0·9)	2·9 (0·9)	2·9 (0·9)	2·9 (0·9)	2·9 (0·9)	2·9 (0·9)
Use of lipid-modifying medication	8074 (11·8%)	3722 (43·9%)	576 (48·1%)	1049 (49·4%)	1152 (43·3%)	945 (37·8%)
Use of antihypertensive medication	9562 (13·9%)	3327 (39·2%)	513 (42·8%)	934 (44·0%)	1059 (39·8%)	821 (32·8%)
Use of renin–angiotensin–aldosterone system inhibitors	8262 (12·0%)	3990 (44·1%)	650 (48·2%)	1122 (48·3%)	1259 (45·0%)	959 (37·3%)
Moderate to vigorous physical activity, min/week	840 (240–2160)	560 (80–1680)	0 (0–340)	260 (0–1270)	720 (240–1860)	1112 (480–2240)
Moderate to vigorous physical activity ≥150 min/week	54 214 (78·9%)	6416 (70·9%)	404 (29·9%)	1361 (58·6%)	2228 (79·5%)	2423 (94·2%)
Dietary habits at optimal level†	43 683 (63·4%)	6188 (68·4%)	396 (29·3%)	1364 (58·7%)	2075 (74·1%)	2353 (91·5%)
Incident major depression	2574 (3·7%)	493 (5·5%)	90 (6·7%)	150 (6·5%)	132 (4·7%)	121 (4·7%)
Clinically relevant depressive symptoms‡	954 (4·5%)	147 (7·5%)	32 (13·8%)	44 (9·8%)	44 (7·0%)	27 (4·2%)

Data are n (%), mean (SD), or median (IQR). *The median number of risk factors within the recommended target range was 4 (IQR 3–5) among individuals with type 2 diabetes and 5 (4–5) among individuals without diabetes. †Dietary habits at optimal level was defined as a score of 3 or more on a 4-item healthy diet score as defined by the American Heart Association,[13] with one point each given for the following items: two or more servings of fruit or vegetables per day; two or more servings of fish per week; 15 or more slices of bread or bowls of cereal per week; and never, rarely, or sometimes adding salt to food. ‡Data available for a subsample of 23 366 individuals.

Table 1: **Characteristics of individuals without diabetes and individuals with type 2 diabetes from the UK Biobank**

trend. We used Poisson regression to calculate age-adjusted, sex-adjusted, and education-adjusted incidence rates and absolute rate differences per 1000 person-years and 95% CIs for major depression in the UK Biobank and clinically relevant depressive symptoms in the Maastricht Study, according to the number of risk factors within the

recommended target range. Additionally, we used Poisson regression with robust error variance to estimate risk ratios (RRs) and 95% CIs for the association with clinically relevant depressive symptoms in the UK Biobank.

Potential confounders were identified from the literature and incorporated into a directed acyclic graph (appendix p 25), which was used to guide the modelling strategy. All analyses were adjusted for baseline age, sex, and education. In the UK Biobank dataset, analyses with clinically relevant depressive symptoms as the outcome were additionally adjusted for time between baseline examination and assessment of depressive symptoms.

We did several additional analyses in both the UK Biobank and the Maastricht Study. First, we evaluated whether the associations differed by age, sex, and education by testing interaction on a multiplicative (testing interaction terms) and additive scale (calculating the relative excess risk due to interaction). Second, analyses were repeated with different cutoff values for HbA_{1c} (≥42 mmol/mol [≥6%] and <53 mmol/mol [<7%]), blood pressure (<140/90 mm Hg), and BMI (≥20 and ≤30 kg/m²). Additionally, we used 24 h ambulatory blood pressure instead of office blood pressure (cutoff <130/80 mm Hg; data available only in the Maastricht Study). Third, we additionally adjusted for diabetes duration, use of renin–angiotensin–aldosterone system inhibitors, and estimated glomerular filtration rate (appendix p 25). Adjustment for diabetes duration was done by centralising the duration of diabetes around the grand mean (the mean duration among all individuals) for individuals with diabetes and setting diabetes duration to 0 years for individuals without diabetes. Fourth, analyses were repeated considering LDL cholesterol concentrations as an additional risk factor (cutoff <2·5 mmol/L). Fifth, analyses were repeated by defining the reference group as individuals without diabetes who had up to three risk factors within the recommended target range (low number of risk factors within the recommended target range), five risk factors within the recommended target range (median number of risk factors within the recommended target range among individuals without diabetes), and six to seven risk factors within the recommended target range (high number of risk factors within the recommended target range); and by defining the reference group as individuals without diabetes, including individuals with prediabetes. Sixth, analyses were repeated after excluding individuals who had a lifetime history of depression (appendix p 3), and again after additional adjustment for baseline PHQ-9 score (data available in the Maastricht Study only). Seventh, analyses were repeated after the consecutive exclusion of each of the seven risk factors. Eighth, because risk factor levels might be affected by the preclinical phase of depression,[10] the analysis of major depression in the UK Biobank dataset was repeated with consecutive exclusion of the first 5 years of follow-up. Ninth, given that in the Maastricht Study the presence of clinically relevant depressive symptoms was known each year at examination waves and therefore the exact date of the incidence of depressive symptoms was not ascertained (ie, the time to disease onset is interval censored), the analysis in the Maastricht Study was repeated by use of Poisson regression with robust error variance and logistic regression. Tenth, in analyses restricted to individuals with type 2 diabetes, we evaluated the association of each individual risk factor with the outcomes and the association of the number of risk factors within the recommended target range as a count from zero to seven with the outcomes. Finally, because 290 764 (58%) of 502 412 individuals from the UK Biobank dataset were excluded due to missing data on albuminuria, we repeated the analysis among individuals with missing data on albuminuria and excluding albuminuria as a risk factor.

Statistical analyses were done with Stata (version 17). A p-value less than 0·05 was considered statistically significant in all analyses.

Role of the funding source

The funders of the study had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of this manuscript.

Results

The study population of the UK Biobank included 9047 individuals with type 2 diabetes and 68 739 individuals without diabetes who had complete data on all seven risk factors and did not have major depression or used antidepressant medication at baseline (appendix p 24). The median age was 59 years (IQR 51–64); 34 136 (43·9%) of participants were women and 43 650 (56·1%) were men (table 1). The characteristics of individuals excluded from the present analysis were similar to the characteristics of those who were included (appendix p 5).

In the UK Biobank dataset, a median of 12·7 years (IQR 11·8–13·4) after recruitment (2006–10), 493 (5·5%) of 9047 individuals with type 2 diabetes and 2574 (3·7%)

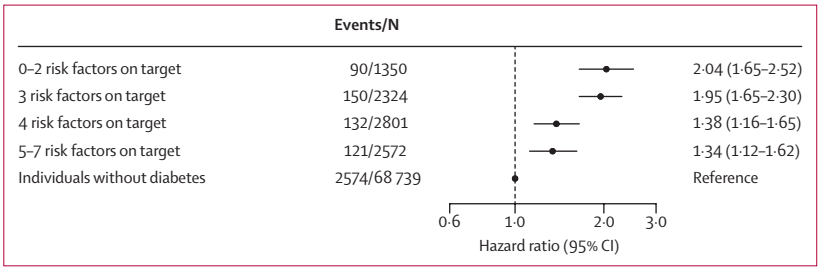

Figure 1: **Incidence of major depression according to the number of risk factors within the recommended target range* among individuals with type 2 diabetes compared with those without diabetes in the UK Biobank**

Adjusted hazard ratios are shown for the risk of major depression among individuals with type 2 diabetes according to the number of risk factors within the recommended target range compared with individuals without diabetes. All analyses were adjusted for age, sex, and education. The p value for the linear trend was less than 0·0001. *Risk factors and their cutoff values are defined in the appendix (p 4).

	Events (n/N)	Person-years	Incidence rate† (95% CI)	Absolute rate difference† (95% CI)
Individuals without diabetes	2574/68 739	840 239	3·04 (2·92–3·16)	Reference
Individuals with type 2 diabetes				
Total subsample	493/9047	105 172	4·88 (4·44–5·31)	1·84 (1·38–2·29)
0–2 risk factors on target	90/1350	15 096	6·17 (4·89–7·45)	3·13 (1·84–4·41)
3 risk factors on target	150/2324	26 703	5·90 (4·95–6·85)	2·86 (1·90–3·81)
4 risk factors on target	132/2801	32 894	4·19 (3·48–4·91)	1·15 (0·42–1·19)
5–7 risk factors on target	121/2572	30 478	4·10 (2·26–4·83)	1·05 (0·31–1·18)

*Risk factors and their cutoff values are defined in the appendix (p 4). †Age-adjusted, sex-adjusted, and education-adjusted incidence rates and absolute rate differences per 1000 person-years.

Table 2: **Incidence rates for major depression among individuals without diabetes and individuals with type 2 diabetes from the UK Biobank according to the number of risk factors within the recommended target range***

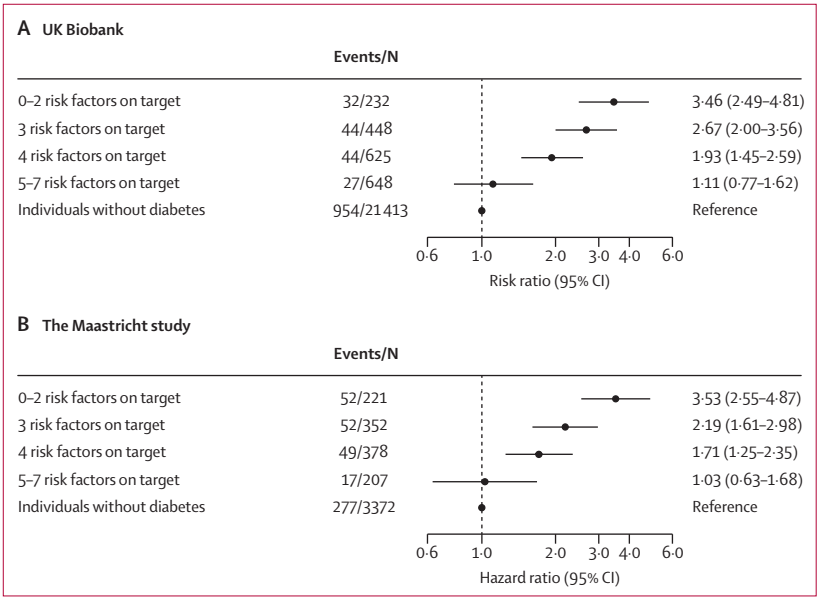

Figure 2: **Incidence of clinically relevant depressive symptoms according to the number of risk factors within the recommended target range* among individuals with type 2 diabetes compared with those without diabetes in the UK Biobank (A) and the Maastricht Study (B)**
Adjusted effect estimates are shown for the risk of clinically relevant depressive symptoms among individuals with type 2 diabetes according to the number of risk factors within the recommended target range compared with individuals without diabetes. All analyses were adjusted for age, sex, and education. The analysis in the UK Biobank dataset was additionally adjusted for time between baseline examination and assessment of depressive symptoms. The p value for the linear trend was less than 0·0001 in the UK Biobank dataset and 0·00081 in the Maastricht Study. *Risk factors and their cutoff values are defined in the appendix (p 4).

of 68 739 individuals without diabetes developed major depression. 74 719 (96·1%) of 77 786 individuals were censored. Reasons for censoring included end of follow-up (n=67 593), death (n=6924), or loss to follow-up (n=202). Figure 1 shows the adjusted HRs and table 2 shows the incidence rates and absolute rate differences for major depression for individuals with type 2 diabetes compared with individuals without diabetes, and according to the number of risk factors within the recommended target range. Compared with individuals without diabetes, those with type 2 diabetes had a higher risk of major depression (HR 1·61 [95% CI 1·49–1·77]). The excess risk of major depression decreased stepwise in individuals with type 2 diabetes with an increasing number of risk factors within the recommended target range (figure 1).

In the UK Biobank dataset, a median of 7·5 years (IQR 6·8–8·2) after the baseline examination, 147 (7·5%) of 1953 individuals with type 2 diabetes and 954 (4·5%) of 21 413 individuals without diabetes developed clinically relevant depressive symptoms. Compared with individuals without diabetes, those with type 2 diabetes had a higher risk of clinically relevant depressive symptoms (RR 2·02 [95% CI 1·70–2·39]). The excess risk of clinically relevant depressive symptoms decreased stepwise in individuals with type 2 diabetes with an increasing number of risk factors within the recommended target range (figure 2).

The study population of the Maastricht Study included 1158 individuals with type 2 diabetes and 3372 without diabetes (appendix p 24). The median age was 60 years (IQR 53–66); 2244 (49·5%) of participants were women and 2286 (50·1%) were men (appendix p 7). A median of 5·1 years (IQR 4·1–6·1) after recruitment (2010–17), 170 (14·7%) of 1158 individuals with type 2 diabetes and 227 (6·7%) of 3372 individuals without diabetes developed clinically relevant depressive symptoms. 4083 (90·1%) of 4530 individuals were censored at the date of their last examination. The adjusted HRs are shown in figure 2; the appendix (p 9) shows the incidence rates and absolute rate differences for clinically relevant depressive symptoms for individuals with type 2 diabetes compared with individuals without diabetes, and according to the number of risk factors within the recommended target range. Compared with individuals without diabetes, those with type 2 diabetes had a higher risk of clinically relevant depressive symptoms (HR 1·98 [95% CI 1·60–2·43]). Similarly to what was observed in the UK Biobank dataset, the excess risk of clinically relevant depressive symptoms decreased stepwise among individuals with type 2 diabetes with an increasing number of risk factors within the recommended target range (figure 2).

No consistent multiplicative or additive interactions with age, sex, or education were noted (appendix pp 10–12). Results were similar in all additional analyses (appendix pp 13–20, 26). Results were similar when the reference group was defined as individuals without diabetes with a low (zero to three), median (four), or high (six or seven) number of risk factors within the recommended target range (appendix pp 13–16). Of the individual risk factors among individuals with type 2 diabetes, being a non-smoker and absence of albuminuria were most strongly associated with a lower risk of major depression or clinically relevant depressive symptoms in both cohorts (appendix p 21). In the UK Biobank dataset, a higher number of risk factors within

the recommended target range among individuals with type 2 diabetes was associated with a lower risk of major depression (HR 0·87 [95% CI 0·81–0·94] per additional risk factor within the recommended target range) and clinically relevant depressive symptoms (RR 0·74 [95% CI 0·66–0·84]; appendix p 22). A similar association was found in the Maastricht Study (HR 0·75 [95% CI 0·66–0·85]; appendix p 22).

Discussion

In this analysis of 77 786 individuals from the UK Biobank, the excess risk of major depression in individuals with type 2 diabetes compared with individuals without diabetes decreased stepwise with an increasing number of risk factors within the recommended target range. Similarly, the risk of clinically relevant depressive symptoms decreased stepwise among individuals with type 2 diabetes with an increasing number of risk factors within the recommended target range. Results for clinically relevant depressive symptoms were replicated in 4530 individuals from the Maastricht Study. In both cohorts, individuals with type 2 diabetes who had between five and seven risk factors within the recommended target range had no significant excess risk of clinically relevant depressive symptoms.

To the best of our knowledge, no other observational study has investigated the association between multiple risk factors and the risk of depression in individuals with type 2 diabetes. Additionally, randomised controlled trials investigating the effect of multifactorial risk intervention in individuals with type 2 diabetes with depressive symptoms as the outcome are scarce. The Look Action for Health in Diabetes (Look AHEAD) trial was a multisite, randomised clinical trial that enrolled 5145 individuals with type 2 diabetes. Consistent with our findings, an intensive lifestyle intervention involving decreased caloric intake and increased physical activity had beneficial effects on clinically relevant depressive symptoms.[21] Additionally, most other lifestyle intervention studies among individuals with diabetes found beneficial effects on clinically relevant depressive symptoms.[22] By contrast, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which evaluated the effect of targeting isolated risk factors in 2053 individuals with type 2 diabetes, did not find a beneficial effect of targeting HbA_{1c}[23] or blood pressure[24] on clinically relevant depressive symptoms.

The present study appears to support the more direct causal evidence, from the aforementioned randomised trials, that multifactorial risk modification might reduce the excess risk of depression in individuals with type 2 diabetes. The pathophysiology of diabetes-related depression is complex and likely to be multifactorial. Potential biological mechanisms underlying depression in diabetes include inflammation,[25] neurodegeneration,[26] glucotoxicity,[10] insulin resistance,[25] and cerebral vascular or microvascular disease.[1] The seven risk factors investigated here have each been associated with one or more of these mechanisms.[1] However, the higher risk of major depression but not of clinically relevant depressive symptoms remained partially unexplained after taking into account the number of risk factors within the recommended target range. Major depression possibly reflects a different entity that might have underlying mechanisms different from those of clinically relevant depressive symptoms in individuals with diabetes. Additionally, in the UK Biobank, major depression was defined on the basis of hospital records, which might reflect a severe form of depression that could be less strongly related to the seven selected risk factors. The remaining association with major depression might potentially be due to risk factors that we did not take into account, including diabetes severity that is not reflected by the risk factors we studied, the presence of diabetes-related complications,[27] type of treatment,[28] and psychological factors such as personality[29] and diabetes-related burden and distress.[1]

Key strengths of this study are the large sample size, which enabled study of the combination of risk factors in type 2 diabetes, the replication of findings for clinically relevant depressive symptoms in an independent cohort, and the large range of additional analyses that allowed us to explore the influence of potential bias.

This study has several limitations. First, the observational design precludes definitive causal conclusions and a complete comparison of the effect of treating risk factors, and we cannot exclude the possibility of residual confounding. Second, in the UK Biobank, major depression was defined on the basis of hospital records, which might reflect a severe form of depression. Additionally, the use of hospital records could induce information bias because individuals with diabetes might be more likely to be admitted for hospital care. However, the results for incident clinically relevant depressive symptoms were consistent with those for major depression. Third, in the UK Biobank, clinically relevant depressive symptoms were assessed at a single follow-up examination only, and not at baseline. Additionally, in both cohorts, the use of antidepressant medication was only assessed at the baseline examination. Fourth, antidepressant medication can also be prescribed for conditions other than depression, and this might have led to misclassification of depression at the baseline examination. Fifth, not all individual categories of the number of risk factors within the recommended target range could be examined due to low numbers in some categories. Sixth, our median follow-up time of 12·7 years is relatively short, and some of the differences in the risk of depression might be due to built-in selection bias in HRs when estimating effects in short follow-up periods.[30] Additionally, interventions for risk factor modification are known to be less effective in individuals at high risk of depression.[3] Therefore, our results might have been affected by risk factor levels in individuals in the preclinical phase of depression (ie, reverse causality) or

with onset of depression earlier in life. However, when we repeated the analysis after consecutively excluding the first 5 years of follow-up and after excluding individuals with a lifetime diagnosis of depression, the results did not change. Seventh, in the Maastricht Study, data on mortality or reasons for censoring were not available at the time of the present study. Eighth, data were not available on change in diabetes status and risk factors over time, and we did not evaluate trajectories of change in depressive symptoms over time. Ninth, in the UK Biobank dataset, the number of individuals excluded from the present analysis due to missing data was high (n=369 012), and largely due to missing data on albuminuria (n=290 764). This could increase the risk of selection bias and limit the generalisability of the results. However, the characteristics of individuals excluded from the present analysis were similar to the characteristics of those included. Additionally, when we repeated the analysis among individuals with missing data on albuminuria, the results were similar to those obtained in the main analysis. Lastly, both studies were done in high-income countries and the study populations consisted mostly of White individuals. Although we did not find interactions with education, further research is required to evaluate the extent to which these results can be generalised to other socioeconomic or ethnic groups.

In conclusion, this study shows that the excess risk of major depression and clinically relevant depressive symptoms among individuals with type 2 diabetes decreased stepwise with an increasing number of risk factors within the recommended target range. These findings provide further evidence to promote current multifactorial risk modification strategies in individuals with diabetes and to encourage the facilitation and adoption of a healthy lifestyle.

Contributors

TTvS and CDAS conceived and supervised the study. ACEvG and TTvS developed the statistical analysis and drafted the manuscript. ACEvG and TTvS directly accessed and verified the underlying data reported in the manuscript and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in data acquisition, had full access to all the data in the study, critically reviewed the manuscript for important intellectual content, and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The UK Biobank is a public open database from which data are available to researchers after acceptance of a formal research proposal. Data from the Maastricht Study are available to any researcher who meets the criteria for access to confidential data; the corresponding author of the present study can be contacted to request the data used in the present analysis.

Acknowledgments

The Maastricht Study was supported by the European Regional Development Fund via OP-Zuid (grant 31O.041), the Province of Limburg, the Dutch Ministry of Economic Affairs (grant 31O.041), Stichting De Weijerhorst, the Pearl String Initiative Diabetes, CVC Maastricht, CARIM Maastricht, CAPHRI Maastricht, NUTRIM Maastricht, Stichting Annadal, Health Foundation Limburg, Netherlands Organization for Health Research and Development (ZonMW), Netherlands Consortium of Dementia Cohorts, and the Memorabel program. TTvS is supported by the ZonMW Veni research grant (916.19.074) and by a Diabetes Fonds Junior Fellowship grant (2021.81.004). TTvS and ACEvG are supported by a Dutch Heart Foundation research grant (2018T025). This research has been done under the UK Biobank Resource application number 81410 and the Maastricht Study application number 484.

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