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**Psychiatric disorders as risk factors for type 2 diabetes
an umbrella review of systematic reviews with and without meta-analyses**

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Review

Psychiatric disorders as risk factors for type 2 diabetes: An umbrella review of systematic reviews with and without meta-analyses



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ABSTRACT

Having a psychiatric disorder may increase the risk of developing type 2 diabetes [T2D] and this umbrella review aims to determine whether people with a psychiatric disorder have an increased risk of developing T2D and to investigate potential underlying mechanisms. A literature search was performed to identify systematic reviews of longitudinal studies investigating different psychiatric disorders as risk factors for incident T2D in humans (≥ 18 years). A total of 8612 abstracts were identified, 180 full-text articles were read, and 25 systematic reviews were included. Six categories of psychiatric disorders were identified. Except for eating disorders, all psychiatric disorders were associated with increased risk of incident T2D ranging from RR = 1.18 [95% CI 1.12–1.24] to RR = 1.60 [95% CI 1.37–1.88] for depression; from RR = 1.27 [95% CI 1.19–1.35] to OR = 1.50 [95% CI 1.08–2.10] for use of

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antidepressant medication; from OR = 1.93 [1.37–2.73] to OR = 1.94 [1.34–2.80] for use of antipsychotic medication; from RR = 1.55 [95% CI 1.21–1.99] to RR = 1.74 [95% CI 1.30–2.34] for insomnia, and finally showed OR = 1.47 [95% CI 1.23–1.75] for anxiety disorders. Plausible underlying mechanisms were discussed, but in most reviews corrections for mechanisms did not explain the association. Notable, only 16% of the systematic reviews had a high methodological quality.

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1. Introduction

A large number of risk factors may play a role in the epidemic of type 2 diabetes, ranging from biological characteristics (e.g. genetic disposition and obesity) and health-related behaviors (e.g. physical inactivity) to environmental factors (e.g. neighborhood deprivation) [1]. In addition, an increasing number of systematic reviews [2–6] suggest that psychiatric disorders may contribute to the development of type 2 diabetes. However, due to heterogeneity in study designs of the included primary studies and variance in the methodological quality of the systematic reviews, a standardized, pre-registered overview with comprehensive quality assessment is needed.

Several behavioral and biological mechanisms could link psychiatric disorders with the development of type 2 diabetes. People with a psychiatric disorder more frequently appear to display adverse health behaviors, such as physical inactivity, smoking, and high-risk alcohol consumption than those without such disorders [7,8]. Medications that are used to treat psychiatric disorders may have metabolic side-effects, such as weight gain, that increase the risk of type 2 diabetes [9,10]. Biological changes, such as an increased stress response activating the nervous system, and release of epinephrine and norepinephrine, could also increase the risk of type 2 diabetes [11–15]. Furthermore, shared genotypes could explain the association [16,17].

The main objective of this umbrella review is to determine to what extent people with a psychiatric disorder have an increased risk of developing type 2 diabetes compared with

a reference group without psychiatric disorder. Furthermore, we review evidence on underlying mechanisms.

2. Methods

2.1. Search strategy and selection criteria

An umbrella review, in essence is a systematic review of systematic reviews, by systematically collecting and evaluating existing summary information [18,19]. This umbrella review was conducted according to PRISMA guidelines and followed an a priori defined protocol [20] as pre-registered in PROSPERO (registration no: CRD42018096362). The protocol can be found here, however in short:

Four electronic databases (PubMed, Embase, PsycINFO, and the Cochrane Database of Systematic Reviews) were searched from inception to the 23rd of March 2021. A comprehensive search strategy covered the following three domains: psychiatric disorders, diabetes, systematic review (Supplementary file 1). No date or language restrictions were used.

We set the following five inclusion criteria:

- (1) A systematic review with or without a meta-analysis, describing both a systematic search string and eligibility criteria.
- (2) The review described longitudinal studies in adult humans (≥ 18 years).

- (3) Type 2 diabetes was included as an outcome. Systematic reviews describing studies with no information available on subtypes of diabetes were also included as we expected that the majority of the sample had type 2 diabetes. Type 2 diabetes was determined by: 1) medical record documentation, 2) diabetes screening, 3) a medical prescription for the treatment of diabetes, or 4) self-reported by persons with diabetes.
- (4) Psychiatric disorder at baseline was determined by: 1) a diagnostic interview (resulting in International Statistical Classification of Diseases and Related Health Problems [ICD]- or Diagnostic and Statistical Manual of Mental Disorders [DSM] classifications), 2) data from medical record documentation or registries, 3) medication prescription as a proxy measurement, 4) self-report of psychiatric problems, or 5) elevated levels of clusters of psychiatric symptoms (e.g. questionnaires).
- (5) Inclusion of a group with a psychiatric disorder and a control group without a psychiatric disorder at baseline, all without type 2 diabetes at baseline.

Screening of titles/abstracts and full-texts for inclusion was carried out by two independent reviewers (NL and FR/FP) and if necessary, a third reviewer (FP or GN) was consulted. Finally, the reference lists of the included publications were manually screened to identify eligible systematic reviews.

2.2. Data analysis

Information from the included systematic reviews was extracted independently by two authors (NL and FR/GN/FP) using a predesigned data extraction form. A translator was contacted when an included systematic review was in a language not spoken by the reviewers. For all included systematic reviews we extracted: name of first author, year of publication, type of study (with or without meta-analyses), name of the psychiatric disorder studied as a risk factor, type of assessment of risk factor, type of assessment of type 2 diabetes, the number of longitudinal studies included, number of follow-up years (range), and total number of participants at baseline without diabetes at baseline that were included in the systematic review. If the systematic review included different types of primary studies (e.g. cross-sectional and longitudinal designs) only data regarding the longitudinal studies were extracted. For systematic reviews with meta-analyses, summary effect sizes (random effect size and/or fixed effect size, 95% CI), significance levels, between-study heterogeneity (Cochrane Q statistic or I^2), and small-study effects where extracted when available. If for some reason not all longitudinal studies identified in the systematic review were included in the meta-analysis (often due to too large heterogeneity in the design), this was noted. Finally, descriptions of potential mechanisms linking psychiatric disorders with type 2 diabetes risk were extracted. A descriptive analysis was carried out to summarize the findings from the systematic reviews.

The methodological quality was assessed for each included systematic review by two independent reviewers (NL and FR/GN/FP) using the 11-item AMSTAR checklist (A Measurement Tool to Assess Systematic Reviews) [21,22]. In accordance with

guidelines, an overall score was calculated by summarizing scores for each item, 0–3 defined as “low quality”, 4–7 as “medium quality”, and 8–11 as “high quality” [23].

3. Results

In total, 8612 abstracts were identified, 180 full-text articles were read, and 25 systematic reviews (of which 14 also reported results of meta-analyses) were included (Fig. 1). The systematic reviews included 101 unique longitudinal studies describing different psychiatric disorders as risk factors for incident type 2 diabetes which could be categorized into six categories: 1) depression, 2) use of antidepressant medication, 3) use of antipsychotic medication, 4) eating disorders, 5) insomnia, and 6) anxiety disorders (Table 1). Psychiatric disorders were measured with diagnostic and self-reported measurements. Supplementary file 2 lists which longitudinal studies were included in the systematic reviews. The overall AMSTAR-score of methodological quality for each systematic review is shown in Table 1 (a detailed description is available on request for the first author). The median AMSTAR score was 5 out of 11 (mean 4.9; range 0–9; interquartile range 4). Eight systematic reviews (32%) were rated as “low quality”, 11 systematic reviews (52%) as “medium quality”, and only two (16%) were rated as “high quality” systematic reviews.

Thirteen systematic reviews (five with and eight without meta-analysis) focused on depression [2,24–35](Table 1). Their methodological quality varied from low to medium (AMSTAR score: median 4, range 0–8). The median number of longitudinal studies included in the systematic reviews was 6 (range 1–23) and the number of reported participants without diabetes at baseline ranged from 8722 to 424,557. In the five systematic reviews including meta-analyses, the relative risk of depression associated with incident type 2 diabetes was 1.18 to 1.60 (Graham: RR = 1.18 [95% CI 1.12–1.24]; Knol: RR = 1.37 [95% CI 1.14–1.63]; Mezuk: RR = 1.60 [95% CI 1.37–1.88]; Hasan: RR = 1.41 [95% CI: 1.13–1.76], and Rotella: OR = 1.56 [95% CI 1.37–1.77]) [2,25,30,31,34]. Heterogeneity was present to varying degree ($Q = 18.3$ – 37.6 ; $I^2 = 87\%$).

Four systematic reviews with meta-analysis and one systematic review without meta-analysis investigated use of antidepressant medication as a risk factor for incident type 2 diabetes [36–40](Table 1). The median number of longitudinal studies included in the systematic reviews was 12 (range 7–17). All the systematic reviews were based on large samples of participants without diabetes at baseline (n ranged from 351,695 to 528,312). The methodological quality ranged from low to high (AMSTAR score: median 7, range 3–8). In all five systematic reviews, evidence suggested a link between the use of antidepressant medication and incident type 2 diabetes. In the four systematic reviews with meta-analysis, the risk associated with antidepressant medication use varied between 1.27 and 1.50 (Bhattacharjee: OR = 1.50 [95% CI 1.08–2.10]; Yoon: RR = 1.49 [95% CI 1.29–1.71]; Salvi: RR = 1.27 [95% CI 1.19–1.35]; Yao: OR = 1.38 [95% CI 1.24–1.54]) [37–40]. Considerable heterogeneity was detected in all four systematic reviews with meta-analysis ($I^2 = 53$ – 87%).

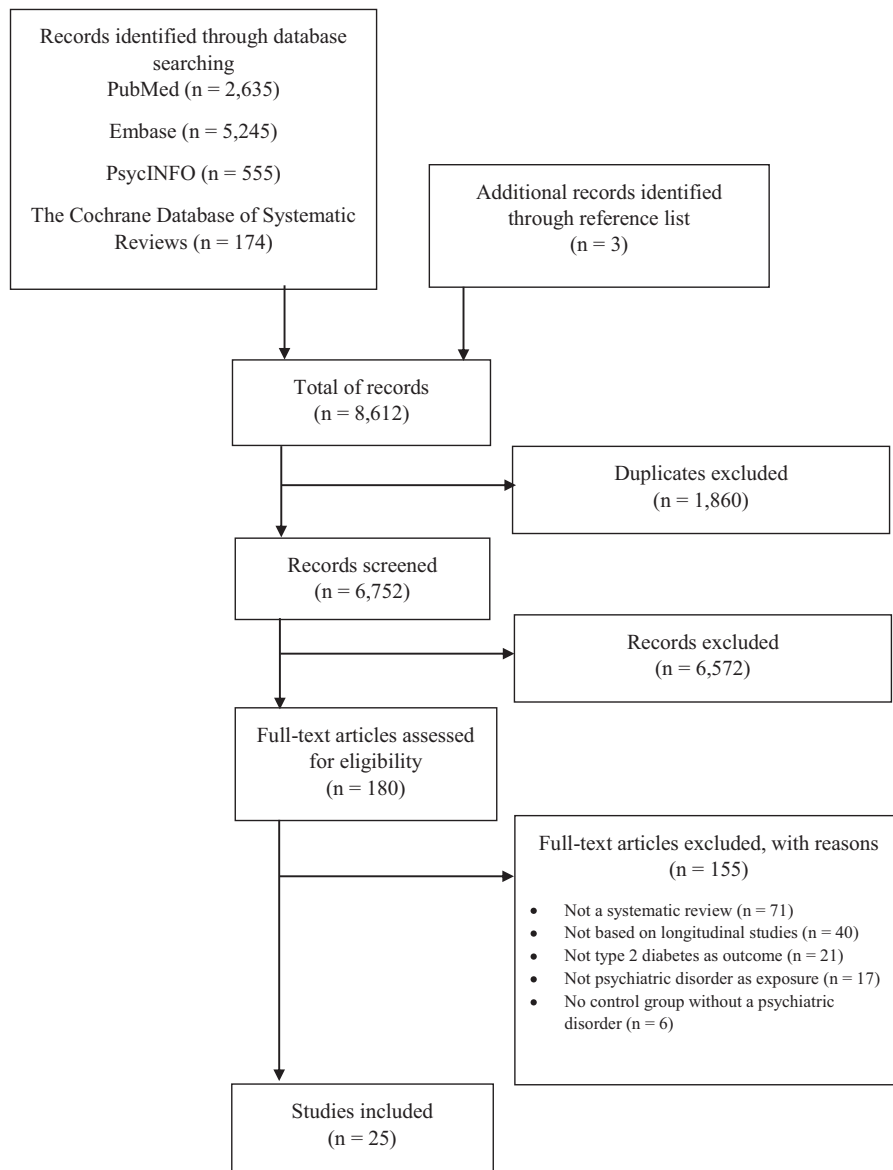


Fig. 1 – PRISMA Flowchart diagram.

Use of antipsychotic medication was investigated as risk factor for the development of type 2 diabetes in one systematic review with meta-analysis and one systematic review without meta-analysis [41,42] (Table 1). The methodological quality of these two systematic reviews were medium and high (AMSTAR-score 4 and 8, respectively). None of the systematic reviews reported the number of participants without diabetes at baseline. In the systematic review with meta-analysis an increased risk of incident type 2 diabetes was reported for users of second generation of antipsychotics [SGA] and Quetiapine respectively (SGA: OR = 1.93 [1.37–2.73] and Quetiapine: OR = 1.94 [1.34–2.80]), whereas heterogeneity was detected to a varying degree (0% and 50.6%) [42].

Eating disorders were investigated in one systematic review with meta-analysis and one systematic review without meta-analysis [43,44] (Table 1). In these two systematic reviews with medium and low methodological quality (AMSTAR score 5 and 3, respectively), only two to three longi-

tudinal studies were included (Supplementary file 2). The number of participants without diabetes at baseline in the systematic reviews ranged from 11,978 to 54,847. The findings regarding eating disorders as risk factor for incidence of type 2 diabetes were inconsistent. In the systematic review with meta-analysis only a single longitudinal study reported bulimia nervosa as factor with increased risk of incident type 2 diabetes (RR = 1.7 [95% CI 1.2–2.5]). For binge eating disorder as risk factor, the association with type 2 diabetes was not significant (OR = 3.34, 95% CI 0.85–13.12), whereas anorexia nervosa was significantly associated with decreased risk of developing type 2 diabetes (RR = 0.71, 95% CI 0.52–0.98) [43]. For binge eating disorder large heterogeneity was detected ($I^2 = 84\%$), but no heterogeneity was detected for anorexia nervosa ($I^2 = 0\%$).

In two systematic reviews with meta-analysis, insomnia was defined using two symptoms: problems initiating and maintaining sleep [45,46] (Table 1). The number of longi-

Table 1 – Characteristics and main findings of the included systematic reviews (n = 25).

First author (year) Type of study	Risk factor(s)	Type of assessment of risk factor	Assessment of type 2 diabetes	No of included longitudinal studies	Range of follow-up	Number of participants without DM2 at baseline	Summary effect size	Heterogeneity and small study-effects	A M S T A R	Main findings
Depression (n = 13)										
Camus et al., (2004) SR	Depression, vascular depression, depressive disorders	Not reported	Not reported	2	5–10 years	Not reported	Not reported	Not reported	1	Adult subjects with moderate to severe symptoms of depression at a baseline assessment were at increased risk to develop type 2 diabetes during 5–10-year follow-up.
Knol et al., (2006) MA	Depression, depressive symptoms	Diagnostic interview, self-reported questionnaire, MRD	Self-report, screening, MRD	9	3–16 years	n = 174,035	Pooled RR Fixed effect models: 1.26 (95% CI 1.13–1.39) Random effects models: 1.37 (95% CI 1.14–1.63)	Q = 18.26, p = 0.02	6	Adults with depression or high-depressive symptoms have a 37% increased risk of developing type 2 diabetes compared with those who are not depressed or have low-depressive symptoms.
Mezuk et al., (2008) MA	Depression, depressive symptoms	Diagnostic interview, self-reported questionnaire	Self-report, screening (incl.: OGTT; FPG), MRD, medication	13	3–15.6 years	n = 222,019	Pooled RR of 1.60 (95% CI 1.37–1.88)	Q = 37.63, p = 0.001 Small study effects not reported	6	There is a strong and robust association between depression and incidence of type 2 diabetes. Depression is associated with a 60% increased risk of type 2 diabetes
Renn et al., (2011) SR	Depression, depressive symptoms	Diagnostic interview, self-reported questionnaire	Not reported	2	2–5 years	n = 8722	Not reported	Not reported	3	Rates of new-onset T2DM were higher for people with elevated baseline depressive symptoms, even after adjusting for demographic variables. Clinically significant depression is associated with an increased risk of new-onset diabetes mellitus.
Roy et al., (2012) SR	Depression, depressive symptoms	Self-reported questionnaire, diagnostic interview	Self-report, MRD	5	Not reported	Not reported	Not reported	Not reported	2	Current research suggests that the risk of developing depression is increased in people with diabetes. However, further studies are required in order to establish the nature of the relationship.
Stuart et al., (2012) SR	Depression, depressive symptoms	Self-reported questionnaire, medication, MRD	Self-report, screening (incl.: OGTT; FPG), MRD, medication	15	Not reported	Not reported	Not reported	Not reported	2	Depression may increase the risk of developing T2DM; however, the mechanisms via which this may occur still require investigation.

Table 1 – (continued)

First author (year) Type of study	Risk factor(s)	Type of assessment of risk factor	Assessment of type 2 diabetes	No of included longitudinal studies	Range of follow-up	Number of participants without DM2 at baseline	Summary effect size	Heterogeneity and small study-effects	A M S T A R	Main findings
Wagner et al., (2012) SR	Depression, depressive symptoms	Diagnostic interview, self-reported questionnaire, MRD, medication	Screening, self-report, self-reported questionnaire	6	2.5–12 years	n = 87,648	Not reported	Not reported	1	Depression seems to be a risk for the manifestation of type 2 diabetes mellitus.
Hasan et al., (2013) MA	Depression, depressive symptoms	self-reported questionnaire, self-report, MRD, medication	Self-report, screening (incl.: OGTT; FPG), MRD, medication	15	3–15.6 years	n = 208,056	RR = 1.41 (95% CI: 1.13–1.76; for binary point estimates; based on 8 studies) HR = 1.24 (95% CI: 1.05–1.47; based on 6 studies)	RR: Q = 25.95, p = .00; I ² = 73% HR: Q = 6.68, p = .25; I ² = 25%	7	This study provides evidence that depression results in a small increase in relative risk for the development of T2DM.
Rotella et al., (2013) MA	Depression, depressive symptoms	Diagnostic interview, self-reported questionnaire, medication, MRD (In one paper not reported)	Self-report, screening (incl.: OGTT; FPG), medication, MRD (In two papers not reported)	23 (24 datasets, however 1 dataset with focus on DM1)	2.3–34 years	n = 424,557	Unadjusted OR: 1.56 (95% CI 1.37–1.77; based on 20 datasets) Adjusted HR: 1.38 (95% CI 1.23–1.55; based on 18 datasets)	I ² = 86.5%, p = .001 Small study effects not reported	5	Depressive symptoms are associated with a significantly increased risk for incident diabetes.
Bastidas-Bilbao et al., (2014) SR	Depression	Not reported	Not reported	2	13 (In one paper not reported,)	Not reported	Not reported	Not reported	0	Longitudinal studies show that depression can predict the onset of diabetes
Walsan et al., (2018) SR	Depression	MRD	MRD, medication	1	7 years	n = 336,340	Not reported	Not reported	5	Depression increase the risk of T2DM
Graham et al., (2020) MA	Depression, depressive symptoms	Diagnostic interviews, self-reported questionnaire, medication, MRD	self-report, screening (incl.: OGTT; FPG), medication, MRD	21 (25 datasets)	1–18 years	Not reported	RR = 1.18 (95% CI 1.12–1.24)	I ² = 45.4% t ² = 0.004). Results showed heterogeneity and evidence of publication bias.	8	Significant association and results suggest that various measures of depression may be used to identify individuals at higher risk of type 2 diabetes.
Bergmans et al., (2021) SR	Depression	Structured interview	OGTT, impaired fasting glucose, Impaired glucose tolerance	1	Not reported	Not reported	Not reported	Not reported	4	Major depression was associated incident type 2 diabetes: OR = 1.22, (95% CI 1.01–1.47, p = 0.04)
Antidepressant medication use (n = 5) Barnard et al., (2013) SR	Antidepressant medication	Medication	MRD, screening (incl.: OGTT; FPG), medication, self-report	12	4.75–18 (In three papers not reported)	Not reported	Not reported	Not reported	3	The evidence suggests a link between antidepressant use and diabetes. Studies have shown that diabetes is more common in those using antidepressants in a higher dose or for longer duration, or both.

Table 1 – (continued)

First author (year) Type of study	Risk factor(s)	Type of assessment of risk factor	Assessment of type 2 diabetes	No of included longitudinal studies	Range of follow-up	Number of participants without DM2 at baseline	Summary effect size	Heterogeneity and small study-effects	A M S T A R	Main findings
Bhattacharjee et al., (2013) MA	Antidepressant medication	Medication	Self-report, medication, MRD	8 (10 datasets in total)	2–18 years	n = 504,836	OR = 1.50 (95% CI, 1.08–2.10; based on 4 datasets) HR = 1.20 (95% CI, 1.10–1.31; based on 6 datasets)	OR: $I^2 = 76.2\%$, $p = .006$ (based on 4 datasets) HR: $I^2 = 45.6\%$, $p = 0.102$ based on 6 datasets) Small study effects not reported	7	Antidepressant use is associated with an increased risk for new-onset diabetes in adults.
Yoon et al., (2013) MA	Antidepressant medication	MRD, self-report	Not reported	12 (14 datasets in total)	Not reported	n = 528,312, (In one paper not reported)	Fixed-effect model: RR = 1.31 (95% CI 1.26–1.37) Random-effect model: RR = 1.49 (95% CI 1.29–1.71) Pooled RR = 1.27 (95% CI 1.19–1.35, $p = 0.001$)	$I^2 = 85.8\%$	7	The results suggest that the use of antidepressants is associated with an increased risk of diabetes There was an association between exposure to antidepressants and new-onset diabetes.
Salvi et al., (2017) MA	Antidepressant medication	Medication, MRD, structured interviews, self-report	MRD, Self-report, medication	17 (20 datasets in total)	1–18 years	Not reported	Pooled OR = 1.38 (95% CI 1.24–1.54)	$I^2 = 71\%$ $p < .001$ Small study effects not reported	8	This meta-analysis provides evidence of a significant positive association between SSRIs use and risk of T2DM
Yao et al., (2018) MA	SSRIs	Not reported	Not reported	7 (9 datasets in total)	4–16 years	n = 351,695	Pooled OR = 1.38 (95% CI 1.24–1.54)	$I^2 = 52.8\%$; $p = .031$	6	This meta-analysis provides evidence of a significant positive association between SSRIs use and risk of T2DM
Antipsychotic medication use (n = 2) Hirsh et al., (2017) SR	Antipsychotic medication	Medication	MRD, medication	10	1–8 years	Not reported	Not reported	Not reported	8	Clozapine and olanzapine were most strongly associated with type 2 diabetes mellitus. Evidence was mixed for a moderate association between type 2 diabetes mellitus and risperidone or quetiapine. Mixed and limited findings for Ziprasidone and aripiprazole, respectively Different types if antipsychotic medication are significantly associated with incident T2DM compared to placebo
Rotella et al., (2020) MA	Antipsychotic medication	Medication	Not reported	14	>52 weeks	Not reported	Quetiapine vs. placebo (MH –OR: 1.94 [1.34 –2.80]) SGAs vs placebo (MH –OR: 1.93 [1.37 –2.73])	I^2 scores ranged between 0% and 50.6%. Small study effects not reported	4	Different types if antipsychotic medication are significantly associated with incident T2DM compared to placebo
Eating disorders (n = 2) Nieto-Martinez et al., (2017) MA	Eating disorders, BED, BN, AN	Diagnostic interview, MRD	Not reported	3 (4 datasets in total)	Not reported	n = 54,847	BED: OR = 3.34 (95% CI 0.849–13.118; based on 2 datasets) AN: RR = 0.712 (95% CI 0.520–0.975; based on 2 datasets) BN: RR = 1.7 (95% CI 1.2–2.5; based on 1 dataset)	BED: $I^2 = 84\%$, $p = .012$ AN: $I^2 = 0\%$, $p = .0779$ Small study effects not reported	5	In a single longitudinal study BN increased the risk of development of type 2 diabetes. In longitudinal studies, BED did not significantly increase the risk of type 2 diabetes. However, in longitudinal studies AN decreased the incidence type 2 diabetes.

Table 1 – (continued)

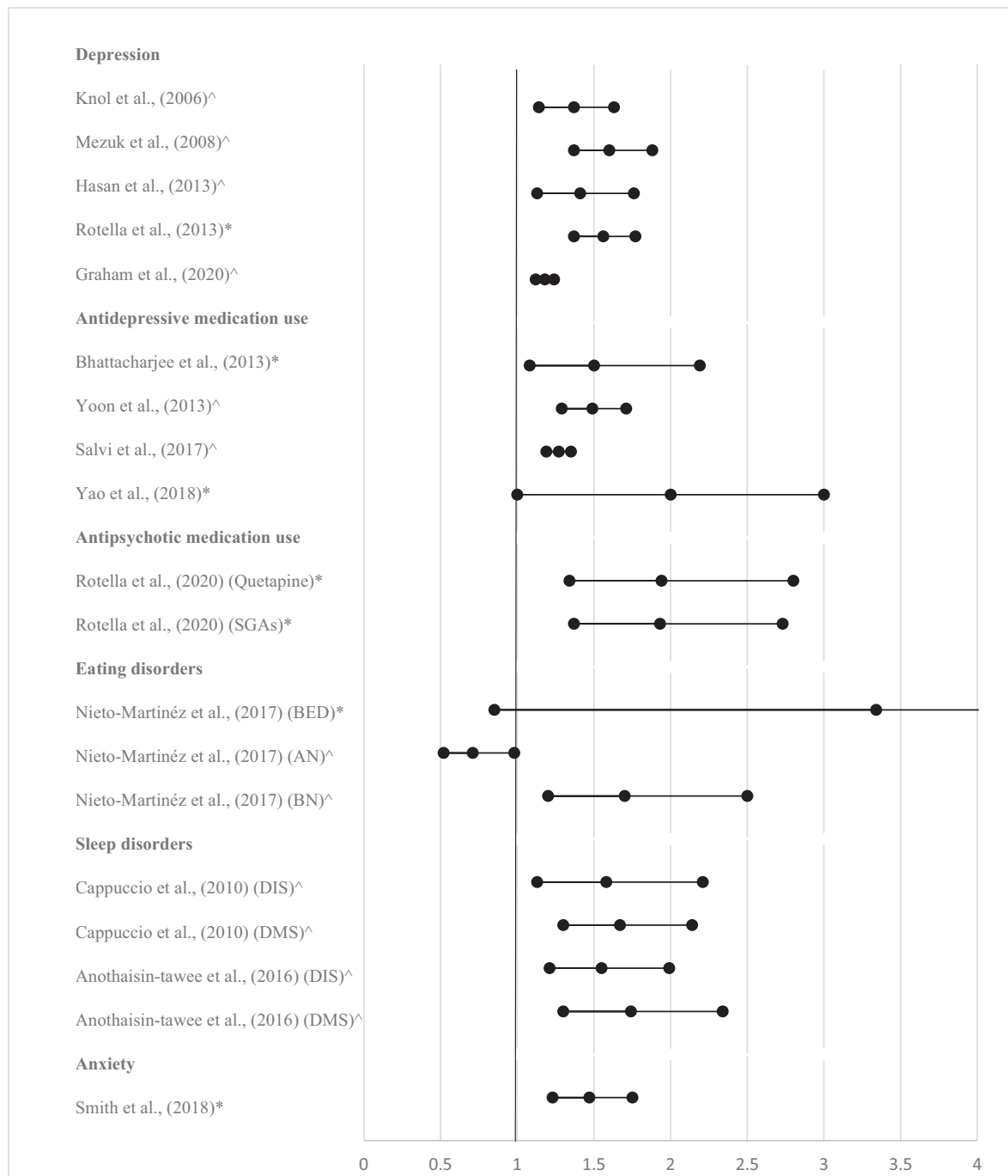
First author (year) Type of study	Risk factor(s)	Type of assessment of risk factor	Assessment of type 2 diabetes	No of included longitudinal studies	Range of follow-up	Number of participants without DM2 at baseline	Summary effect size	Heterogeneity and small study-effects	A M S T A R	Main findings
Olguin et al., (2017) SR	BED non-purging BN	MRD (In one paper not reported)	Not reported	2	5–16 years	n = 11,978	Not reported	Not reported	3	The review has mixed results. However, the preliminary findings indicate that a focus on diabetes in patients with BED is meaningful.
Insomnia (n = 2) Cappuccio et al., (2010) MA	Insomnia symptoms DIS DMS	Self-reported questionnaire	MRD, self-reported questionnaire, screening (incl. FPG), self-report, multiple methods	5	4.2–15.2 years	Not reported	DIS: RR = 1.58 (95% CI 1.13–2.21), p = 0.0082, based on 4 studies). DMS: RR = 1.67 (95% CI 1.30–2.14) p = 0.0001, based on 4 studies)	No heterogeneity was present. Small study effects were not reported.	6	Insomnia symptoms consistently and significantly predicted the risk of the development of type 2 diabetes.
Anothaisin-tawee et al., (2016) MA	Insomnia symptoms DIS DMS	Self-report, MRD, self-reported questionnaire	(incl.: OGTT; FPG), MRD, self-report, medication, self-reported questionnaire	11	3–22 years	n = 289,588	DIS: Pooled RR = 1.55 (95% CI: 1.21–1.99) DMS: Pooled RR = 1.74 (95% CI: 1.30–2.34)	DIS: I ² = 30.1% DMS: I ² = 67.4% Small study effects not reported.	7	Insomnia symptoms increase in the risk of developing diabetes. DIS increases the risk with 55% and DMS 74%. Insomnia symptoms should be considered in clinical guidelines for type 2 diabetes screening.
Anxiety disorders (n = 1) Smith et al., (2018) MA	Anxiety disorders, anxiety symptoms	Diagnostic interview, self-reported questionnaire, MRD	Screening (incl.: OGTT; FPG), medication, self-report, MRD	14 (16 datasets)	2–20 years	n = 1,760,800	Pooled OR = 1.47 (95% CI: 1–23–1.75; based on 15 datasets)	I ² = 98.13% Small study effects not reported	9	Most analyses indicated a significant association between baseline anxiety and incidence diabetes.

AN = Anorexia nervosa; BED = Binge eating disorder; BN = Bulimia nervosa; DIS = difficulty initiating sleep; DMS = difficulty maintaining sleep; DM1 = Type 1 diabetes mellitus; DM2 = Type 2 diabetes mellitus; FPG = fasting plasma glucose; HR = hazard ratio; MA = systematic review with a meta-analysis; MH-OR = Mantel-Haenszel Odds Ratio; MRD = medical record documentation; OGTT = oral glucose tolerance test; RR = relative risk; SGA = second generation antipsychotics; SR = systematic review without a meta-analysis

nal studies included in the systematic reviews were five and 11, respectively, and only in the latter review, the number of participants without diabetes at baseline was reported, $N = 289,588$. The methodological quality of the two systematic reviews with meta-analysis was medium (AMSTAR-score 6 and 7). The insomnia symptoms “difficulty initiating sleep” and “difficulty maintaining sleep” were associated with a 1.55- to 1.74-fold increased risk of incident type 2 diabetes

(difficulty initiating sleep: $RR = 1.55$ [95% CI: 1.21–1.99]; $RR = 1.58$ [95% CI 1.13–2.21] and difficulty maintaining sleep: $RR = 1.67$ [95% CI 1.30–2.14]; $RR = 1.74$ [95% CI 1.30–2.34]) [45,46]. One of the systematic reviews detected moderate heterogeneity ($I^2 = 30$ –67%) whereas the other detected no heterogeneity.

One systematic review with meta-analysis investigated the association between anxiety disorders and incident type



AN: anorexia nervosa; BED: binge eating disorder; BN: bulimia nervosa; DIS: difficulties initiating sleep; DMS: difficulties maintaining sleep, SGA: second generation antipsychotics, *: odds ratio, [^]: relative risks

Fig. 2 – Forest Plot showing risk of incident type 2 diabetes in systematic reviews with meta-analyses.

2 diabetes [47], as described in Table 1. The review included several types of anxiety disorders (generalized anxiety disorder, panic disorder, phobic disorders, posttraumatic stress disorder, other anxiety disorders, social anxiety disorder, and elevated level of anxiety symptoms) and was based on 14 longitudinal studies and 1,760,800 participants without diabetes at baseline. The systematic review was of high methodological quality (AMSTAR score: 9) and it concluded that people with anxiety disorder had a 1.5-fold increased risk of type 2 diabetes (OR = 1.47 [95% CI 1.23–1.75]) [47]. However, large heterogeneity in study-specific estimates was detected ($I^2 = 98\%$).

Many of the systematic reviews focusing on the same risk factor category were based on overlapping longitudinal studies (Supplementary file 2). Due to this overlap, a second order meta-analysis (summary estimate for each psychiatric disorder based on all systematic review with meta-analyses) was not possible [48]. Instead, we have provided a forest plot showing the odds ratios or relative risks that have been reported in the included systematic reviews with meta-analysis (Fig. 2).

In the majority of the systematic reviews with meta-analysis (8 out of 14), adjusted sub-analyses were performed

to explore the role of potential underlying mechanisms [2,30,31,38–40,46,47]. Besides demographic potentially confounding factors (age, gender, and ethnicity), potential behavioral mechanisms (lifestyle, physical activity, drugs, and alcohol consumption) and biological mechanisms (body weight, body mass index [BMI], cardiometabolic/adiposity, medical comorbidity, psychopathology) were investigated. In most reviews the association between psychiatric disorder and incident type 2 diabetes remained significant after controlling for behavioral or biological covariates. However, the association between anxiety disorders and incident type 2 diabetes was attenuated and became statistically non-significant after adjustment for sociodemographic, cardiometabolic/adiposity, and lifestyle factors [47].

In addition, all 25 systematic reviews discussed plausible mechanisms that could explain the link between different psychiatric disorders and incident type 2 diabetes and the possibility that several mechanisms might interact and have bidirectional effects. However, no empirical evidence was available to determine the temporal order of the mechanisms. In general, the mechanisms discussed can be divided into three main groups: 1) behavioral, 2) biological, and 3) cognitive (Fig. 3).

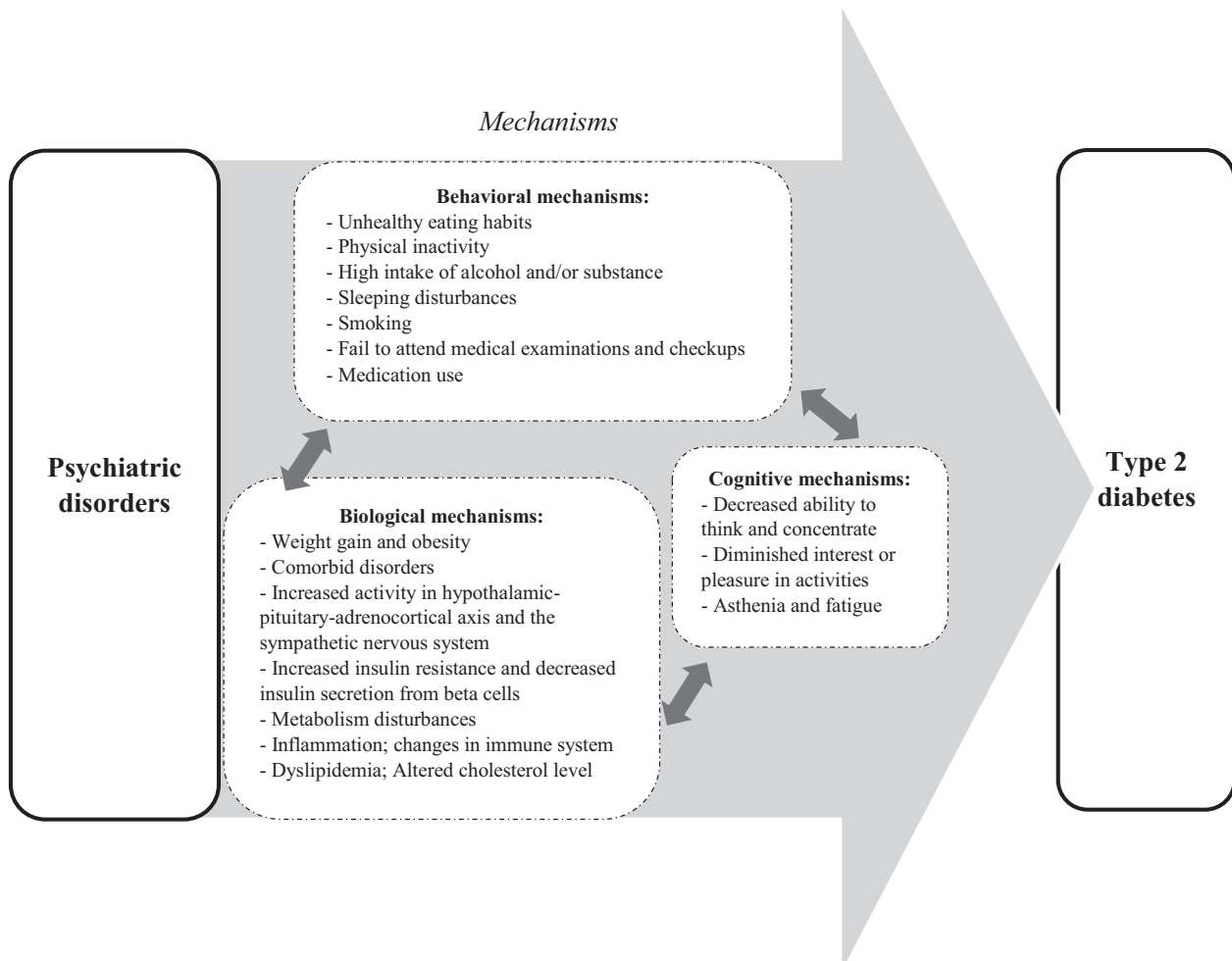


Fig. 3 – Potential mechanisms explaining the associations between psychiatric disorders and type 2 diabetes.

First, behavioral mechanisms such as adverse health behavior involved “unhealthy eating”, overeating (e.g. high intake of food with a high glycemic index), and low intake (or impaired metabolism) of ω -3 polyunsaturated fatty acids [25–27,33,39,46]. Physical inactivity, sleeping disturbances, smoking, high alcohol intake, and substance abuse were also suggested to explain the observed associations [25–27,31,38,39,45–47]. Further explanations included the notion that people with a psychiatric disorder may not attend medical examinations or follow medical treatment recommendations [39]. These behavioral mechanisms were often quoted as bidirectional.

Second, multiple biological mechanisms, including “weight gain and obesity”, were described as key mediating factors [25–27,31,36,38]. Medications that induce weight gain as a side effect were also often described [2,32,36,38]. Other suggested biological mechanisms included dysregulation of the hypothalamic-pituitary-adrenocortical axis (HPA-axis) and the sympathetic nervous system, [25,26,29,30,32], systemic inflammation [25,26,29,32,39,43,46,47], increased insulin resistance and decreased insulin secretion from beta cells [26,27,32,36,38,40], and comorbid disorders, both somatic and psychopathological [31,32,37,38,43,44,46,47].

Third, cognitive mechanisms were raised as potential mediators, including decreased ability to think and concentrate, anhedonia, fatigue, and lack of motivation [26,39]. Interactions between cognitive mechanisms and behaviors were suggested as well. For example, unhealthy lifestyle may lead to decreased ability to concentrate or a lack of motivation, which, in turn, can negatively influence the likelihood of attending medical examination and checkups or maintaining physically active lifestyle [26].

4. Discussion

Our umbrella review identified 25 systematic reviews, 14 with and 11 without meta-analysis, that included 101 unique longitudinal studies on psychiatric disorders and type 2 diabetes risk. They covered six categories of psychiatric disorders: depression, use of antidepressant medication, use of antipsychotic medication, eating disorders, insomnia, and anxiety disorders. The relative risk ratio or odds ratio for type 2 diabetes was found to vary between 1.18 (RR) and 1.60 (RR) for individuals with depression, between 1.27 (RR) and 1.50 (OR) for those treated with antidepressant medication, between 1.93 (OR) and 1.94 (OR) for use of antipsychotic medication, between 1.55 (RR) and 1.74 (RR) for individuals with insomnia, and was 1.47 (OR) for individuals with anxiety disorders. No robust associations between eating disorders and type 2 diabetes were observed.

The methodological quality of the systematic reviews was low to medium with only four of the 25 systematic reviews being of high quality. The four reviews with high methodological quality were focused on depression, antidepressant medication use, antipsychotic use, and anxiety disorders, respectively [34,39,41,47]. Findings relating to eating disorders should be interpreted cautiously due to the limited number and low quality of the systematic reviews [43,44]. Overall, the results of the AMSTAR quality assessment suggest that

there is room for improvement in the methodological quality of the systematic reviews to date. Higher quality of future systematic reviews will strengthen the evidence within the field and be able to guide future research questions.

We also reviewed hypothetical and empirical evidence on potential underlying mechanisms in the included systematic reviews. Several behavioral, biological, and cognitive mechanisms were identified, although some potentially important mechanisms were not noted. A shared genotype has been suggested as a common denominator of schizophrenia, mood disorders and type 2 diabetes [16,17], however, this was not investigated in any of the included systematic reviews. Results from the Swedish twin registry showed that the association between depression and type 2 diabetes were primarily attributed to genetic effects in women but not in men [49]. In the same article, similar analyses of the Danish twin registry showed that genetic effects accounted for the majority of the covariance in both males and females [49].

Furthermore, effects on waist circumference, waist/hip ratio, and visceral adiposity were not acknowledged in the systematic reviews even though these have been postulated as important type 2 diabetes risk factors on pair with BMI [50,51]. Likewise, microvascular dysfunction was not mentioned as potential mechanisms even though different microvascular dysfunctions such as endothelial dysfunction and arterial stiffness have been hypothesized as underlying mechanisms [52]. In this umbrella review, there are several potential biases that need to be discussed. First, use of antidepressant medication and antipsychotic medication were viewed as a proxy for psychiatric disorders and were therefore included as potential risk factors. However, the use of antidepressant medication or antipsychotic medication may have side-effects such as weight gain which itself may increase the risk of incident type 2 diabetes and thus could mediate the association between psychiatric disorders and incident type 2 diabetes. Furthermore, there is a high level of comorbidity between psychiatric disorders in general [53] and this might explain why several psychiatric disorders seems to be associated with type 2 diabetes. Future studies adjusting for psychopathology are needed. Second, psychiatric disorders may affect detection of type 2 diabetes, introducing ascertainment bias because people with psychiatric disorders more often have their health checked. However, the opposite could also be true as people with psychiatric disorders often fail to attend medical examinations [26] and may have limited access to the general healthcare system due to unavailable care or inexpedient interactions with health care providers [54,55]. Third, psychiatric disorders and type 2 diabetes were measured in different ways (e.g. diagnostic interviews and self-reports). Our umbrella review is dependent on the measurements that were conducted in the longitudinal studies that were included in the systematic reviews. Only few systematic reviews stratified analyses based on measurement type [31,34,45,47] precluding us to analyze this evidence at a higher level. For example, self-report measures may lead to overestimation of psychiatric disorders [56]. Furthermore, the diagnostic criteria for ascertainment of psychiatric disorders also varied, including definitions from DSM-IV and DSM-5; no comparisons of the differences between the classifica-

tion systems were available. Fourth, a bias regarding the age of the participants may have affected results. On average the participants included in the primary longitudinal studies were limited to older people with the exception of studies on eating disorders (>16 years). Eating disorders are highly present in younger age group and thus post risk of type 2 diabetes. Importantly, both systematic reviews on eating disorders were able to ascertain type 2 diabetes (and not diabetes in general) [43,44]. Finally, variation in the designs of the primary studies included in the systematic reviews could be a source of bias. Although most of the systematic reviews were based on longitudinal cohort studies, some systematic reviews also included studies with case-control designs or randomized controlled trials which could result in heterogeneity, although sensitivity analyses did not provide consistent evidence of the effects of heterogeneity of study designs on heterogeneity of the results [39,40]. Furthermore, to be able to provide the highest level of evidence in our umbrella review, we only included systematic reviews based on longitudinal studies. However, in the screening process we also identified several systematic reviews using cross-sectional data (e.g. on psychiatric disorders such as bipolar, schizophrenia and posttraumatic stress disorder [4–6] with positive associations observed. When further research accumulates, future systematic reviews should extend the focus on these disorders in longitudinal studies.

The findings from this umbrella review have important implications for general practitioners and care providers. People with different types of psychiatric disorders are at moderately increased risk of developing type 2 diabetes. The associations of depression, use of antidepressant medication, use of antipsychotic medication, insomnia or anxiety disorders with type 2 diabetes raise the question about special needs for prevention of type 2 diabetes in these vulnerable groups. To date, several interventions addressing medical conditions and health-risk behaviors have been successful in preventing type 2 diabetes [57]. Metformin and behavioral interventions have beneficial effects via weight loss, whereas bupropion and varenicline may help in quitting tobacco smoking [57]. Further intervention studies are needed to assess whether these findings are generalizable to those with psychiatric disorders and how the interventions should be adapted to maximize benefits for these specific groups. Furthermore, several psychiatric disorders are treated with medication with the side-effect of weight gain [9,10]. These metabolic influences should be carefully considered when deciding on treatments for people with psychiatric disorders. Routine screening for type 2 diabetes may improve detection rates. For general practitioners and care providers, a focus on minimizing use of psychotropic medication that can impair glucose metabolism, and a preventive focus on optimizing health behaviors may optimize the treatment of people with a psychiatric disorder and potential minimizing the risk of developing type 2 diabetes.

This umbrella review approach had a pre-registered design which facilitated a comprehensive search on a broad area. We used a systematic search strategy of four literature databases with independent study selection, data extraction and quality assessment by two reviewers. However, an umbrella review can only be as strong as the existing systematic reviews are.

For example, definitions of psychiatric disorders tend to be vague due to the multiple diagnostic criteria and operationalizations used in the field (ICD or DSM classification). Umbrella reviews are also affected by publication delays as recently published longitudinal studies are not yet included in an existing systematic review. In addition, due to the lack of systematic reviews that fulfilled our inclusion criteria, some psychiatric disorders were not covered (e.g. schizophrenia, stress-related disorders).

The results of this umbrella review suggest that people with depression, antidepressant medication use, antipsychotic medication use, insomnia and anxiety disorders are at moderately increased risk of developing type 2 diabetes. This finding should be interpreted cautiously as the quality of the summary evidence was diverse and only 16% of the systematic reviews were of high quality. Future longitudinal studies and systematic reviews with high methodological quality are needed to increase understanding of the role of psychiatric disorders in the etiology of type 2 diabetes.

5. Contributors

NL had full access to all the data in the study and FP had final responsibility for the decision to submit for publication. NL and FP were responsible for the conception and design of the study. NL, FR, GN and FP were responsible for acquisition of data. NL, FR and FP were responsible for analysis and interpretation of data. NL wrote the first draft of the manuscript with input from FP and FR, JEH, ML, MTS, KHR, MK, GN and FP were responsible for revisions of the manuscript with important intellectual content. All authors approved the final version prior to submission.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2021.108855>.

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