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Psychiatric disorders as risk factors for the development of type 2 diabetes mellitus: an umbrella review protocol

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ABSTRACT

Introduction Numerous longitudinal studies, systematic reviews and meta-analyses have examined psychiatric disorders as risk factors for the development of type 2 diabetes mellitus. A more comprehensive overview of the area is warranted to summarise current evidence and discuss strengths and weaknesses to guide future research.

Aim The aim of this umbrella review is to determine whether and to what extent different psychiatric disorders are associated with the development of type 2 diabetes mellitus. Furthermore, the umbrella review also assesses the evidence on potential mediating mechanisms.

Methods and analysis The present umbrella review will consist of a comprehensive systematic search of published systematic reviews and meta-analyses of observational longitudinal studies investigating whether a psychiatric disorder is associated with the risk of developing type 2 diabetes. PubMed, Embase, PsychINFO and the Cochrane Database of Systematic Reviews will be searched, and the results will be screened for inclusion by two independent reviewers. Furthermore, the reference lists of included publications will be manually searched. Two independent reviewers will extract data and assess the methodological quality in the included systematic reviews and meta-analyses. Evidence on potential mediating mechanisms included in the systematic reviews and meta-analyses will also be reviewed. The implications of the overview will be discussed in light of the quality of the included studies, and suggestions for clinical practice and future research will be made.

Ethics and dissemination Ethical approval is not required for this umbrella review. Our review will be submitted for publication in a peer-reviewed international journal using open access option if available. The results will also be disseminated at international conferences.

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Strengths and limitations of this study

► To our knowledge, this is the first protocol for an umbrella review on psychiatric disorders as risk factors for type 2 diabetes.

► A broad search strategy will be used to ensure a comprehensive synthesis of existing systematic reviews and meta-analyses in this area.

► The methodological quality of the included systematic reviews and meta-analyses will be assessed.

► Assessment of data extraction and methodological quality will be performed by two independent reviewers.

► As in other umbrella reviews, the quality of the summary findings depends on the quality and content of the systematic reviews and meta-analyses that are available.

INTRODUCTION

Type two diabetes mellitus is a chronic metabolic condition that is increasingly common worldwide.[1] Nine in ten diabetes cases are diagnosed with type 2 diabetes.[2] Several factors may contribute to the increase in the number of people with type 2 diabetes, including the ageing of populations,[3] an increased number of people with a sedentary lifestyle,[3] the global obesity epidemic,[3 4] and the increase in life expectancy.[5] Furthermore, earlier and improved recognition of type 2 diabetes has increased in the number of people with diagnosed type 2 diabetes.[3]

A recent narrative review summarised evidence on different mental health problems (including psychiatric diseases, but also forms of chronic stress) as risk factors for type 2 diabetes.[6] The review concluded that longitudinal studies support an association of depression, anxiety, sleeping problems, 'general emotional stress', 'anger' and 'hostility' with increased risk of type 2 diabetes. Findings were mixed regarding 'childhood neglect', 'life events' and 'work stress'.[6] More recently, de Jonge and colleagues studied cross-sectional associations between 16 different *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV psychiatric disorders and diabetes mellitus in over 52 000 adults.[7] Depression, intermittent explosive disorder, binge eating disorder and bulimia nervosa were associated with increased risk of diabetes mellitus after adjustment for comorbidity.[7] The type of diabetes was unknown and no temporal

inferences could be made due to the cross-sectional design.[7]

Several systematic reviews and meta-analyses have also investigated whether specific psychiatric disorders are associated with the risk of developing type 2 diabetes.[8–13] Mezuk et al, for example, included 13 prospective studies and found that depression was associated with a 1.6-fold increased risk of developing type 2 diabetes during a follow-up of 3.0–15.6 years.[8] Based on 12 longitudinal studies, Smith et al found that people with a diagnosed anxiety disorder or elevated anxiety symptoms had a 1.3-fold increased risk of developing type 2 diabetes.[9] Stubbs et al investigated 25 studies and concluded that people with schizophrenia had almost double the risk of developing type 2 diabetes compared with those without that psychiatric disorder.[10] Furthermore, in two other meta-analyses of four and five studies, Vancampfort and colleagues found that people with bipolar disorder or post-traumatic stress disorder had a 1.5-fold increased risk of type 2 diabetes.[11 12] A further meta-analysis on different eating disorders found bulimia nervosa being a risk factor for type 2 diabetes, whereas people with anorexia nervosa had a reduced risk of developing type 2 diabetes, and the association of binge eating disorder with type 2 diabetes was not statistically significant.[13] However, an important limitation was the small number of included studies.[13]

Different psychiatric disorders may increase the risk of the development of type 2 diabetes through several pathways involving both behavioural and physiological mechanisms, including, for example, less healthy eating behaviours in terms of quality and quantity of food, physical inactivity, smoking and higher alcohol consumption.[14] These factors, in turn, are associated with an increased risk of type 2 diabetes.[15] Furthermore, the pharmacological treatment of various psychiatric disorders may affect type 2 diabetes risk.[16 17] For example, the association between antipsychotic drug use and development of type 2 diabetes is suggested to be attributable to weight gain implicated by hormones, neurotransmitters and neuropeptides that regulate appetite stimulation and consequently increase food consumption (eg, leptin, histamine H1 receptor and melanocortin 4 receptor).[16] Weight-independent insulin resistance and insulin secretion may also contribute to the association.[16] Further potential physiological mechanisms are hypercortisolism, resulting from long-term activation of the hypothalamic–pituitary–adrenal axis,[18] changes in the immune function[19] and inflammatory markers, such as elevated levels of interleukin-6 and C reactive protein,[20] altered levels of specific cytokines and chemokines[21] and changes in the number and activation state of various leucocyte populations,[21] all of which might impair glucose metabolism.

In sum, the number of systematic reviews and meta-analyses is increasing but has applied different methodologies and thus has not led to a coherent overview on psychiatric disorders as risk factors for type 2 diabetes. A novel method for a higher level synthesis of evidence is the so-called 'umbrella review', also known as 'review of reviews'. An umbrella review contributes to a comprehensive overview and aims to compile all the evidence in a specific area. These field synopses have the ability to clarify what is still unknown and require future research.[22 23] Furthermore, umbrella reviews typically include a methodological assessment of the included systematic reviews and meta-analyses, which contributes to a quality assessment of the existing evidence.[22 23] Obviously, the findings of umbrella reviews are dependent on the quality of the included systematic reviews and meta-analyses, which is an important methodological limitation.[22 23]

A recent umbrella review by Bellou and colleagues was the first of its kind to summarise risk factors for the development of type 2 diabetes.[24] A broad range of risk factors was explored, including specific biomarkers, dietary factors, lifestyle and environmental factors, as well as medical history, including psychiatric disorders. Although the umbrella review by Bellou and colleagues had a broad and general focus, it did not discuss psychiatric disorders or potential pathways in detail. A comprehensive umbrella review with focus on specific psychiatric disorders and potential pathways is therefore needed for a synthesis of the numerous systematic reviews and meta-analyses in this area. By clarifying the strengths and weaknesses of the existing evidence, an umbrella review will contribute to a more thorough understanding of the associations and potential underlying pathways and enhance the needs for future research. Our umbrella review will emphasise the methodological quality assessment of already conducted systematic reviews and meta-analyses.
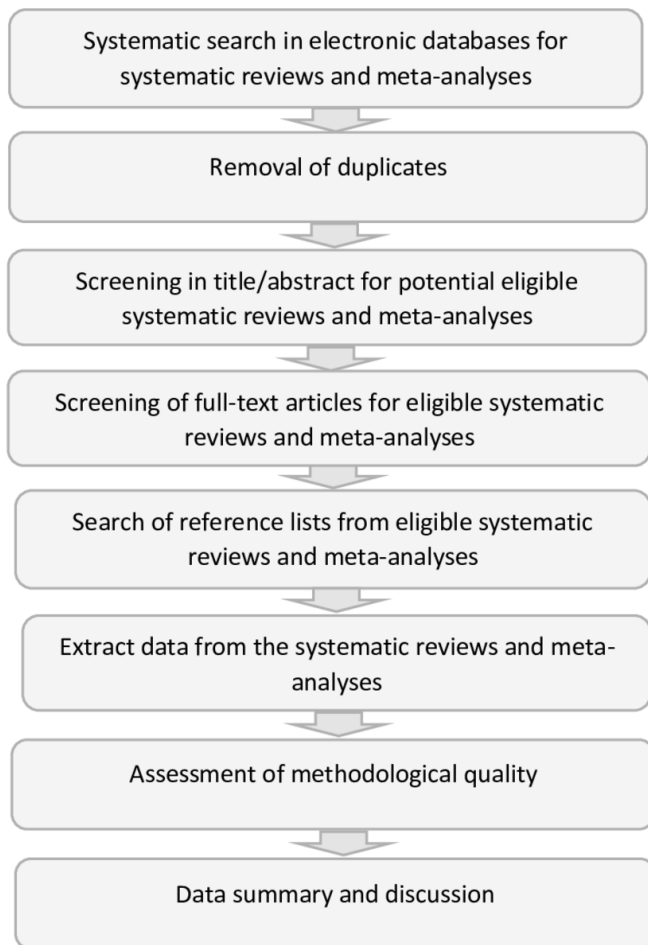
OBJECTIVE

The aim of this umbrella review is to determine to what extent people with a psychiatric disorder have an increased risk of developing type 2 diabetes mellitus (compared with a reference group without psychiatric disorder). Furthermore, the umbrella review also aims to review evidence on mediating mechanisms.

METHODS AND ANALYSIS

This protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines (see online supplementary file 1). In accordance with these guidelines, the present umbrella review protocol has been registered in the International Prospective Register of Systematic Reviews. Protocol amendments will be documented in PROSPERO. The procedure of the planned umbrella review is shown in figure 1.

Patient and public involvement

The patients or the public have not been involved in developing the present protocol nor will they be involved in conducting the umbrella review.

Figure 1 Flowchart of the umbrella review.

with a librarian and initially targeted PubMed, and will subsequently be adapted for the other databases. Date and language restrictions will not be used in the search strategy. Online supplementary file 2 shows the complete search string.

Eligibility criteria
Study design
The present umbrella review will include systematic reviews and meta-analyses of observational longitudinal studies in adult humans (≥18 years).

Inclusion and exclusion criteria
We set the following inclusion and exclusion criteria:
► The study is a full systematic review with or without a meta-analysis, describing both a systematic search string and eligibility criteria.
► The papers that will be included in the systematic review/meta-analysis describe observational longitudinal studies in adult humans (≥18 years) and include results based on longitudinal data.
► Type 2 diabetes and diabetes in general is included as an outcome determined , for example, by a diagnosis, medical reports, medical prescription or self-reported measurement (It is estimated that more than 90 % of cases with diabetes mellitus have type 2 diabetes.[2] Therefore, we will include adult samples with 'diabetes in general, where no information is available on subtypes of diabetes' as we expect that the majority of the sample will actually have type 2 diabetes. We are aware of potential bias and will discuss this accordingly). However, papers reporting only on type 1 diabetes, latent autoimmune diabetes in adults or maturity-onset diabetes of the young and other specific types of diabetes except type 2 diabetes will be excluded.
► Distinct psychiatric disorders are studied as a risk factor for type 2 diabetes. The presence of a psychiatric disorder at baseline can be determined, for example, by a diagnostic interview (ICD or DSM classifications), data from medical charts, registries, medication prescription as a proxy measurement or by self-reported psychiatric diagnoses or elevated levels of clusters of psychiatric symptoms (eg, questionnaires measuring psychiatric disorders).
► Inclusion of a group with psychiatric disorder and a control group without a psychiatric disorder at baseline, all without having type two diabetes at baseline.

Study selection
The study selection will be handled in EndNote and in the software programme Covidence; in 2015, Covidence was selected by Cochrane to become the standard production platform for Cochrane Reviews.[28] The initial search and the removal of duplicates will be performed by the first author. In all the identified publications, a screening of titles and abstracts for inclusion and exclusion criteria will be carried out by two independent

Search strategy
Database search
The following four electronic databases will be searched: PubMed (1966–present), Embase (1974–present), PsychINFO (1967–present) and the Cochrane Database of Systematic Reviews (1992–present). Furthermore, a manual screening of the reference lists of the included publications will be completed.

Search terms
In the four electronic databases, we will conduct a systematic search using search words and Medical Subject Headings (MeSH) terms combined using the Boolean logic operators (OR and AND). The search strategy will be based on three overall domains: psychiatric disorder, diabetes and systematic review/meta-analysis. Specific search words and MeSH terms within each domain will be combined using OR terms, and the domains will be combined by using AND terms. The domain of psychiatric disorders is coved by a comprehensive search string including terms and categories from the DSM-III or DSM-IV-TR (axis I and axis II)[25 26] and the International Classification of Diseases, 10th Revision (ICD-10), Classification of Mental Disorders (F00-F99).[27] The search strategy has been generated in collaboration

reviewers. If eligibility of the publication is unsure, the publication will be identified as potentially relevant and will be enrolled in the next selection step. All publications identified as potentially relevant by at least one reviewer will be retrieved in full text and assessed for eligibility by two independent reviewers. In case of disagreement, the two reviewers will discuss this and, if necessary, a third reviewer will be included. Finally, the reference lists of the included publications are manually screened to identify publications, which fulfil the inclusion criteria. If both an original version and an updated version on a systematic review are identified, both papers will be included and discussed in the umbrella review. In the final umbrella review, a PRISMA flow diagram will show the selection flow and the number of included publications.

Data extraction

The included systematic reviews and meta-analyses will be independently reviewed by two reviewers, and information will be extracted using a predesigned data extraction form. Any discrepancies will be discussed until consensus is achieved. If any included papers are published in a non-English language not spoken by the reviewers, Google Translate will be used and a translator will be contacted if needed. Extracted information will include first author, year of publication, type of study, risk factor(s), type of assessment of risk factor(s), assessment of type 2 diabetes, the number of studies included, range of follow-up, total number of participants at baseline without diabetes mellitus, gender distribution and range of age of cases/controls. Furthermore, the description of and primary conclusions about potential mechanisms (eg, lifestyle behaviour and medication use) that link psychiatric disorders with diabetes risk will also be extracted. For meta-analyses, we will extract summary effect sizes (random effect size and/or fixed effect size, 95% CI) and significance levels. When available, information of between-study heterogeneity (Cochrane Q statistic or I^2 and small-study effects will also be extracted.

Assessment of methodological quality

The methodological quality of each of the included systematic reviews and meta-analyses will be assessed independently by two reviewers using A MeaSurement Tool to Assess systematic Reviews,[29 30] which consists of an 11-item checklist. Disagreements will be resolved by discussion. The assessment of methodological quality will be included in the discussion of the findings from the respective systematic reviews and meta-analyses.

DISCUSSION

In the umbrella review, we will provide a high-level field synthesis and also discuss the results from the systematic reviews and meta-analyses for each psychiatric disorder as a potential risk factor for type 2 diabetes. Furthermore, mechanisms identified in the included systematic reviews and meta-analyses will be described and addressed. We will also focus on several methodological aspects,

including the use of self-report versus diagnostic interview and the differences among psychiatric diagnoses and clusters of psychiatric symptoms. Furthermore, the characteristics of included primary studies in the systematic reviews and meta-analyses will be discussed. The results will be discussed in relation to the methodological quality assessment.

ETHICS AND DISSEMINATION

According to Danish law, formal ethical approval is not required for the present study, as primary data will not be collected. For the same reason, the project does not have to be reported to the Danish Data Protection Agency. The umbrella review will be submitted for publication in a peer-reviewed journal using open access option, if available, and results will also be disseminated at international conferences.

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