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Systematic Review

The Main Risk Factors in Type 2 Diabetes for Cognitive Dysfunction, Depression, and Psychosocial Problems: A Systematic Review

Maarja Randväli [1,2,*], Toomas Toomsoo [2] and Jekaterina Šteinmiller [1]

[1] Nursing Department, Tallinn Health Care College, Kännu 67, 13418 Tallinn, Estonia; jekaterina.steinmiller@ttk.ee
[2] School of Natural Sciences and Health, Department of Psychology and Behavioural Sciences, Tallinn University, Narva mnt 25, 10120 Tallinn, Estonia; toomas.toomsoo@confido.ee
* Correspondence: maarja.randvali@ttk.ee

Abstract: The aim of this study is to analyze the risk factors that lead to cognitive impairment, depression, and psychosocial problems in type 2 diabetes and discern what aspects they have in common. Type 2 diabetes is associated with a higher risk of cognitive impairment, including dementia, which in turn increases the risk of hospitalization, falls, and premature mortality. In this study, we conducted a systematic review to achieve this goal, including searches on electronic databases such as PubMed, Medline, Web of Science, EBSCO Discovery, EBSCO host, Scopus, and ScienceDirect, from 2016 onwards. Additionally, we carried out manual searches in leading journals in the field. After evaluating and analyzing the articles, 60 remained, focusing on the following four main themes: disorders due to biological, psychological, social, and pharmacological causes that lead to neuropsychological complications. Based on the results, consistently analogous risk factors contributing to the onset of cognitive impairments, depression, and psychosocial predicaments encompass comorbid ailments, dysglycemia, gender, heightened levels of apprehension and anxiety, educational attainment, socio-economic standing, and pharmaceutical interventions. Furthermore, in the realm of type 2 diabetes, factors such as disease duration, adiposity, specifically overweight and obesity, and advancing age were also identified as significant contributors to cognitive impairments and depression. Concomitantly, the absence of a robust support system and social network emerged as a shared risk factor, predisposing individuals to psychosocial challenges and depressive states. These findings emphasize that the risk factors for cognitive impairments, depression, and psychosocial issues for type 2 diabetes are similar, highlighting the importance of psychosocial support, education, and patient-centered treatment to optimize outcomes and quality of life.

Keywords: type 2 diabetes; depression; cognitive; psychosocial challenges

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1. Introduction

Type 2 diabetes is a multifactorial condition that is significantly shaped by interwoven environmental, social, behavioral, and psychosocial factors, all of which collectively influence treatment outcomes, quality of life, and psychological health [1–3]. Statistically, it is estimated that 60% of older patients with type 2 diabetes have at least one other comorbidity, and 40% of these patients have no fewer than four concurrent illnesses, reflecting the complexity and challenge of managing this condition due to various demographic, psychological, social, cognitive, and cultural factors, including the influence of healthcare systems [4]. Notably, there is an established correlation between type 2 diabetes and an elevated risk of cognitive impairments, such as Alzheimer's disease. Patients with a longer duration of type 2 diabetes are at increased risk of experiencing cognitive decline, which may culminate in dementia, an increased need for institutional care, falls, and premature mortality [5,6]. Depression, which affects a significant proportion (25%) of individuals with

diabetes, often coexists with cognitive challenges [4]. In addition, in diabetes, depression can affect patient self-management and adherence to the prescribed treatment regimen [7]. Previous systematic reviews have treated cognition and depression separately, and the findings of common associations have not covered psychosocial problems. The aim of this systematic review is to describe the risk factors for cognitive impairment, depression, and psychosocial issues in type 2 diabetes and highlight the shared risk factors.

2. Methodology

2.1. Design

A comprehensive, unbiased summary of various relevant studies can be achieved through a systematic review [8,9]. This approach is particularly beneficial in examining leadership styles in healthcare, as it consolidates trustworthy information and highlights its practical use. This is crucial for healthcare professionals to understand how certain risk factors might affect neurological complications in type 2 diabetes. This systematic review is defined by its explicit objectives and the formulation of a PICO (Problem/Population, Intervention, Comparison, Outcome) question. It includes criteria for selecting and rejecting studies and conducts an extensive search for pertinent research. The assessment of study quality was performed utilizing the 'Checklist for Analytical Cross-Sectional Studies' and the 'Checklist for Qualitative Research'. In compliance with the review protocol's appropriateness criteria, studies were chosen according to their research methodology and PICO (Population, Intervention, Comparison, Outcome) elements, rather than based exclusively on their results [10,11]. This review encompasses both qualitative studies and theoretical literature.

2.2. Research Question

The PICO question, formulated based on inclusion and exclusion criteria, is as follows: What are the incidence and risk factors of cognitive dysfunction, depression, and psychosocial problems, as well as their impact on the quality of life or healthcare service utilization in adult patients diagnosed with type 2 diabetes, compared to risk factors associated with complications of type 2 diabetes? The population (P) is adult patients diagnosed with type 2 diabetes; the intervention (I) is risk factors associated with complications of type 2 diabetes; the comparator (C) is risk factors related to cognitive dysfunction, depression, and psychosocial problems in type 2 diabetes; and the outcome (O) is the incidence, severity, or changes in these conditions and their impact on quality of life.

2.3. Search Strategy

The systematic literature review process involves several steps [10]: pinpointing the issue, conducting a literature search, assessing the gathered data, analyzing these data, and then reporting the results. Search terms included "*type 2 diabetes*", "*cognitive disorders*", "*depression*", "*psychosocial problems*", and "*risk factors*", combined using the Boolean operators "OR" and "AND". The initial search in electronic databases (PubMed, Medline, Web of Science, EBSCO Discovery, EBSCO host, Scopus, and ScienceDirect) yielded 589 results. After removing duplicates and review articles, 387 studies were excluded for being published earlier than 2016, focusing on type 1 diabetes (n = 98), being in a foreign language (n = 67), or lacking full-length articles (n = 35). Study inclusion was based on a checklist assessing the reliability of outcomes, ethical conformity, research design appropriateness, data completeness, and control of confounders. 'Yes' markings were required for clarity in population description and statistical methodology to ensure methodological soundness [12]. Titles and abstracts were screened based on inclusion criteria (see Tables 1 and 2).

Table 1. Results of the literature search and selection process.

Databases from 2013 to 2023	Records Retrieved	Records after Title and Abstract Screening	Full-Text Articles Assessed for Eligibility	Studies Included after Quality Appraisal *
PubMed	112	97	38	30
Medline	58	11	3	3
EBSCOhost	110	69	2	2
EBSCO Discovery Service	68	68	5	3
Scopus	82	32	2	2
ScienceDirect	49	1	0	0
Web of Science	115	88	15	10
Total from all databases	589	387	65	60

* Quality assessment was based on a checklist evaluating each study's methodology, data reporting, and bias risk. Studies were included if they met a minimum of five out of eight criteria.

Table 2. Process of the systematic review on the modelling of risk factors in type 2 diabetes for cognitive dysfunction, depression, and psychosocial challenges.

Aspect	Description
Reviewers	Maarja Randväli, Toomas Toomsoo, Jekaterina Šteinmiller
Review aims and questions	Research Aim: The aim of this systematic review is to comprehensively examine and synthesize the existing international literature on the modeling of risk factors in type 2 diabetes for cognitive dysfunction, depression, and psychosocial challenges, focusing on an adult patient and understanding what similarities there are of the risk factors together. Revised Research Questions: 1. What are the main risk factors for complications in type 2 diabetes?Can these risk factors be categorized? 2. Which risk factors are mainly associated with neurological complications?What are these complications related to? 3. What are the risk factors for cognitive impairment in type 2 diabetes? 4. What risk factors are associated with depression in type 2 diabetes? 5. How is depression related to diabetes? What are the influencing factors? 6. What risk factors are associated with the development of psychological problems in type 2 diabetes? What are the most common problems? 7. What risk factors are associated with psychosocial problems in type 2 diabetes? 8. Do risk factors share common characteristics? What are these similarities? 9. What role does the healthcare professional play in identifying these risk factors? 10. Is it possible for healthcare workers to use appropriate metrics effectively? By addressing these research questions, this systematic review aims to provide a comprehensive overview of the main risk factors in these constructs and what similarities they have.
Review type	A systematic review of the international literature.
Language	English
Study designs	Studies based on original research employing qualitative, quantitative, or mixed methods approaches will be considered for inclusion. Exclusions will be made for reviews, commentaries, letters, case reports, case studies, and books. Grey literature encompasses existing guidelines and profiles utilized in diverse healthcare environments, available online and retrievable through Google and other standard search engines.
PICO statement	Population (P): Adult patients, who had diagnosed with type 2 diabetes. Interest (I): Risk factors associated with complications of type 2 diabetes. Context (Co): Risk factors related to the association between cognitive dysfunction, depression, and psychosocial challenges in type 2 diabetes. The incidence, severity, or changes in cognitive dysfunction, depression, and psychosocial challenges and their impact on quality of life.

Table 2. *Cont.*

Aspect	Description
Literature search	Assistance will be sought from a librarian, through consultation, to help ensure the accuracy and precision of the search process. The following search terms were used: "type 2 diabetes" AND "cognitive disorders" AND "depression" AND "psychosocial problems" AND "risk factors". These terms were combined using Boolean operators "OR" and "AND". Comprehensive research and evidence on the main risk factors emerged from electronic databases. Electronic databases such as PubMed [including MEDLINE], Scopus, Cinahl, ProQuest, Web of Science, and Ebsco will be searched to retrieve studies published without time limits. Cross-referencing from the bibliographies of retrieved articles will be conducted, and current review papers will be considered to enhance the comprehensiveness of the search. Population Keywords: type 2 diabetes * OR risk factors * OR complications * Concept 1: Cognitive impairment: Cognitive dysfunction or mild cognitive problems or general cognitive problems. Risk factors for cognitive impairment OR causes of cognitive dysfunction*. Concept 2: Depression: Risk factors for depression in type 2 diabetes OR causes of depression in diabetes*. Concept 3: Psychosocial problems: Risk factors for psychosocial problems in type 2 diabetes OR causes of psychosocial problems in diabetes*. Search Strings: (Population Keywords) AND (Concept 1: Cognitive impairment Keywords). (Concept 2: depression in type 2 diabetes) AND (Concept 3: Psychosocial problems Setting Keywords).
Literature selection	The research team will independently review the titles, abstracts, and full texts of all original studies. Together, they will determine whether to include or exclude these studies, making their decisions in accordance with the established eligibility criteria. The inclusion criteria for original and scientific content are as follows: studies must be focused on the phenomenon in question; conducted within the context of medical services; involve medical personnel operating in a multidisciplinary team that addresses type 2 diabetes complications; and be published in peer-reviewed journals in English. Methodological checklists based on each article's research design: Tools for Critical Appraisal—Systematic Reviews and Other Reviews. Types—Research Guides at Temple University.
Research synthesis	A data extraction table will be created to organize and import information from the chosen studies, categorizing their specifics. Additionally, an analytical framework will be established using tables to aggregate, summarize, and contrast the findings of these studies in the context of the review topic. The results of the review will be aligned with a theoretical framework that focuses on the primary risk factors associated with type 2 diabetes.
Equator guideline	The process of reporting the review will be guided by the methodological checklist of the extension of PRISMA for scoping reviews (PRISMA): http://www.equator-network.org/reporting-guidelines/prisma/ (accessed on 10 October 2023)
Funding sources/sponsors	This research received no funding to carry it out, but will obtain funding for publication in an open-access journal.
Conflicts of interest	The authors affirm that this research was conducted without any commercial or financial ties that might be interpreted as a conflict of interest. They retain copyright to this article and hold the intellectual property rights for this study and any other concepts derived from it.

2.4. Screening and Quality Control

The review's reliability and uniformity were ensured by setting strict criteria for selecting or excluding articles, limited to peer-reviewed studies published in English from 2016 to 2023. These studies provided insights into medical risk factors in type

2 diabetes related to brain function and mental health. In this systematic review, we limited our sources to published peer-reviewed literature, excluding grey literature such as unpublished studies and conference papers. This approach was chosen to ensure data reliability and verifiability, though we recognize it may introduce a potential for publication bias due to the exclusion of unpublished studies with possibly negative or inconclusive results. The initial researchers meticulously screened all 589 titles and abstracts twice, following pre-established criteria, narrowing down to 60 potentially relevant sources. The JBI Critical Appraisal Tool supported the review's coherence and thoroughness [13]. The quality evaluation of selected articles was conducted using both the 'Checklist for analytical cross-sectional studies' and the 'Checklist for qualitative research'. Articles were considered for inclusion if they met at least five criteria with a 'yes'. The review's quality and assessment procedure were further validated by the second author through critical discussion, ensuring the selected literature's appropriateness for the review. In the end, 60 sources were finalized for the study (see Figure 1). The PRISMA checklist can be found at Supplementary File S1.

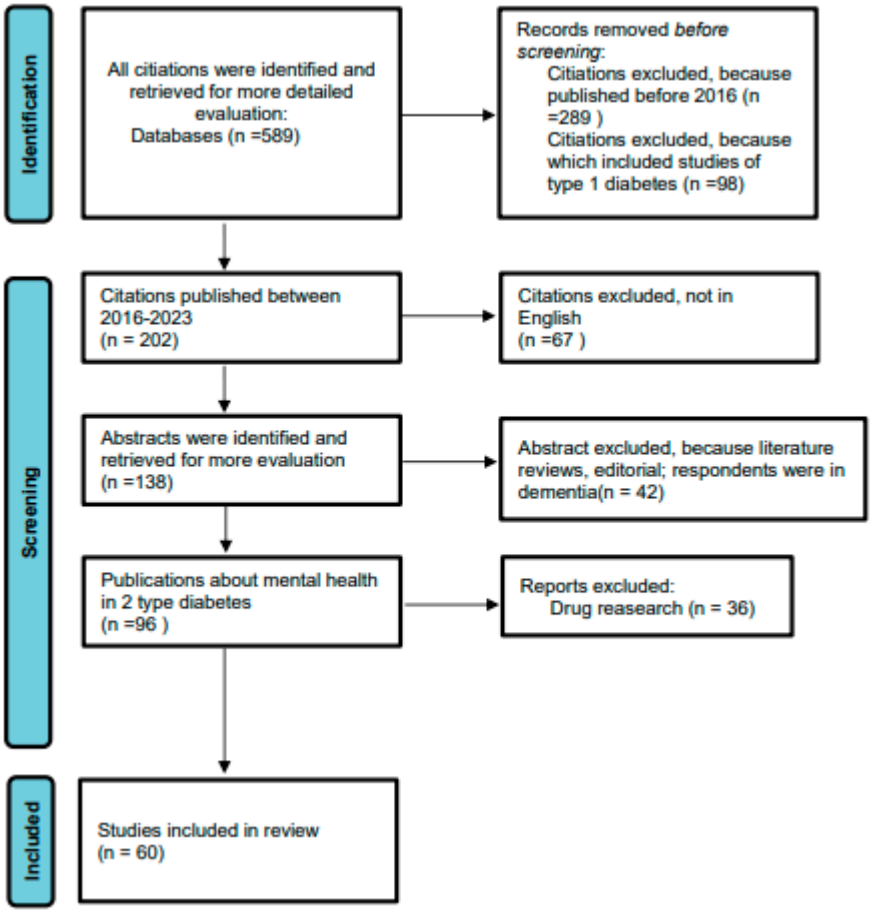

Figure 1. PRISMA, source screening.

In our systematic review, we utilized EndNote for reference organization and Rayyan QCRI for preliminary screenings, accompanying these tools with detailed manual reviews. This combination helped us to thoroughly assess a wide array of studies, minimizing oversights. To combat manual methods' subjectivity, we balanced them with these digital tools for a more objective analysis. Our approach, a synergy of technological precision and human discernment, was designed to be both systematic and transparent, ensuring an unbiased and comprehensive literature review.

The screening and quality assessment tasks were systematically allocated among the research team. Maarja Randväli and Toomas Toomsoo carried out the initial screening of

titles and abstracts independently, rigorously applying our inclusion and exclusion criteria. Jekaterina Šteinmiller subsequently re-evaluated the articles selected for inclusion and contributed to the quality assessment. The concordance between Randväli and Toomsoo's evaluations was 85%, indicating substantial agreement, albeit with minor divergences primarily attributed to different interpretations of the inclusion criteria. Disagreements were collaboratively discussed between Randväli and Toomsoo to reach a consensus. When a consensus could not be achieved, Šteinmiller acted as a third reviewer to provide an impartial adjudication, thus preserving the methodological soundness of our review. This teamwork fortified the reliability of our study selection process and ensured an impartial examination of the literature pertinent to risk factors for cognitive dysfunction, depression, and psychosocial problems in type 2 diabetes.

2.5. Data Analysis

The 60 studies included (Figure 1) were published between 2016 and 2023. The categories were categorized based on biological, psychological, social, and pharmacological causes. In the process of analyzing the articles, the author considered it important to assess the metrics used in the studies. MoCa (Montreal Cognitive Assessment) (n = 4), MMSE (Mini Mental State Examination) (n = 10), PHQ-9 (Patient Health Questionnaire) (n = 5), and other verbal word and memory tests were used to assess cognitive ability. These metrics aim to assess cognitive functioning and identify cognitive changes that may be associated with various diseases, such as Alzheimer's disease or other forms of dementia. Mental health (including depression) has been evaluated in studies using the following metrics, which were related to the assessment of psychological well-being and the measurement of emotional states such as depression, anxiety, stress, and self-efficacy. Most study types were large- and small-scale cohort and cross-sectional studies. Cohort studies allow the study of different outcomes and risk factors. Cross-sectional studies are often useful as primary studies to assess associations between risk factors and disease. They help researchers gather raw data and generate hypotheses [14].

Content analysis was employed to examine the data, which we then organized into categories based on similarity in content and the authors' definitions in the studies [13]. Four categories identified risk factors for cognitive impairment, five for depression, and four for psychosocial problems in type 2 diabetes. These findings, including study characteristics and results, are detailed in the following tables, and our comprehensive database is registered in the PROSPERO environment (CRD42023451300).

The certainty of evidence for each outcome was assessed using the GRADE approach [15]. For example, the evidence for the risk of cognitive impairment in type 2 diabetes was rated 'moderate' due to the presence of some inconsistency in study results and minor concerns about publication bias. Upon application of the approach, the certainty of evidence for the association between type 2 diabetes and the risk of depression was determined to be 'moderate'. This rating was due to variabilities in study methodologies and some degree of inconsistency in results, alongside considerations of potential publication bias. Regarding socio-economic factors influencing type 2 diabetes outcomes, the assessment yielded a 'low' certainty of evidence. This was attributed to limited studies with diverse methodologies, the varying quality of data, and some inconsistencies in how socio-economic variables were measured and reported across studies. As a result of this systematic review, it was revealed that several clinical parameters and comorbid conditions, and psychological, socioeconomic, pharmacological, and behavioral factors are risk factors for cognitive disorders related to type 2 diabetes.

3. Results

3.1. Risk Factors for Cognitive Impairment in Type 2 Diabetes

Biological causes are multifactorial (Table 3). Obesity, high BMI, and waist circumference play an important role. A larger waist circumference is considered a risk factor for dementia in diabetes studies (OR: 1.057, $p = 0.011$) [16]. The effect of diabetes on brain

atrophy can begin in early middle age. Cognitive impairment is most common in type 2 diabetes between the ages of 40 and 80, and especially between the ages of 60 and 80 [17,18]. Gender also plays an important role. Gender differences in dementia risk are unclear, but some studies have found a higher risk for women (45%) compared to men of the same age (40%) [19,20]. Men have been found to have a higher risk of developing vascular dementia, which is associated with anxiety disorders [21].

Type 2 diabetes can be associated with a number of comorbidities and complications including micro- and macrovascular diseases (hypertonia, cardiac arrhythmias, dyslipidemia, nephropathy, retinopathy, stroke, etc.) [22–24]. Vascular factors increase the risk of cerebrovascular damage to small blood vessels associated with vascular cognitive impairment and vascular dementia [24,25]. Elevated fasting glucose and high HbA1c levels are associated with cognitive impairment in high-age patients with type 2 diabetes [17]. One reason is the presence of an acute phase protein in the body. A cohort study conducted in Israel (n = 224) found that higher HbA1c levels in elderly people with type 2 diabetes are associated with smaller hippocampal volume in haptoglobin (Hp) 1-1 carriers. The findings of the study suggest that Hp 1-1 carriers may be more vulnerable to the adverse effects of high HbA1c levels on cognitive function [26].

Inadequate glucose monitoring and control (HbA1c $\geq$ 7.5%;) is associated with a double risk of dementia and its progression [22,27]. The risk is also increased by increased systemic inflammation in the body [27]. Studies show that in type 2 diabetes $\geq$ HbA1c 7% significant changes take place in verbal fluency and performance memory [28].

The core symptoms of depression are a decline in mood, interest, and energy over a period of at least two weeks, more common in those with longer-standing type 2 diabetes. In studies using the Depression Symptom Questionnaire (PHQ-9), up to 37% of participants are at risk of severe depression [5,22,29]. Depression is an important risk factor for dementia in people with type 2 diabetes [30]. The prospective cohort study points out that 10% of those who develop dementia are primarily elderly (69.4 years old) and are more likely to develop depression (21.0% vs. 10.8%) compared to those who do not have dementia [30].

Various studies have shown that low levels of education are a potential risk factor for dementia. Low educational attainment is not an isolated factor but should be considered in routine cognition assessment in type 2 diabetes, in addition to age, duration of disease, hypertension, BMI, gender and depression symptoms [17,20,22,28]. Studies suggest a negative correlation between education and the incidence of dementia, possibly explained by the fact that people with a higher level of education have a higher synaptic density in the cerebral cortex, which increases the brain's memory capacity and thus delays the onset of dementia symptoms by around 4–5 years [17]. Economic situation significantly predicts cognitive functioning [6,20,31].

In a case–control study (n = 8276), insulin therapy (basal and bolus insulin) was found to be associated with an increased risk of developing dementia (OR: 1.34) [32]. The PREDIMED Plus cohort study (n = 6874) showed that the use of insulin therapy was inversely associated with cognitive function [$\beta = -0.31$ (95% CI -0.44, -0.18)]. This may be because these individuals tend to have poorer glycemic control and a higher risk of hypoglycemia, which in turn is associated with a risk of cognitive decline and dementia [33]. Cardiovascular problems (hypertension) are common among people with type 2 diabetes [23,24]. The treatment of hypertension with beta-blockers in diabetes was associated with an increased risk of cardiovascular events. The incidence of severe hypoglycemia was significantly higher in patients taking beta-blockers than in patients not taking beta-blockers (HR, 1.30; 95% CI, 1.03–1.64; p = 0.02) [34]. The use of beta-blockers is associated with an increased longitudinal risk of vascular dementia in older people, regardless of cardiovascular risk factors [35].

Table 3. Risk factors for cognitive dysfunction in type 2 diabetes.

Category	Subcategory	Substantive Code
Biological causes		
	Comorbidities [16,22–25]	Micro- and macrovascular diseases, complications, hypertension, cardiovascular diseases, heart rhythm disorders, diabetic retinopathy, dyslipidemia, systemic inflammation, diabetic nephropathy, stroke, and sleep apnea
	Disease duration [5,28,36,37]	Long-term diabetes, disease duration, disease duration over five years, and disease progression
	Overweight, obesity [16,23,38–41]	Overweight, obesity, body mass index (BMI), high BMI, and high waist circumference
	Age [18,35–37,42]	Elderly, age $\leq$ 65 years, advanced age, middle-aged and older people
	Dysglycemia [17,24,28,43,44]	Hypoglycemia, hyperglycemia, low blood sugar, blood sugar fluctuation, hypoglycemia episodes, fasting glucose, high HbA1c, glycemic control, insulin resistance, and chronic hyperglycemia
	Sex [19–21,23]	Female, male and gender differences
Psychological causes		
	Fear, anxiety [5,22,30]	Symptoms of depression, stress, anxiety, and fear
Socio-economic causes	Education level [5,17,22,28]	Education level, schooling under 6 years, and low education level
	Economic status [6,20,31]	Social status, economic capability, socioeconomic status, unemployment, and access to resources
Pharmacologic causes	Medications [32–35]	Insulin, beta blockers, polypharmacy, drug side effect, drug interaction, drug effect, time of drug use, and long-term use

3.2. Risk Factors for Depression in Type 2 Diabetes

Elderly people with an average age of 70.1 with type 2 diabetes (n = 550) showed an increased risk of depression with high BMI indicating obesity [7,45]. The incidence of depression in patients with type 2 diabetes is 28–35.6%. Studies show that obese patients with type 2 diabetes are 2.19 times more likely to develop depression. The link between obesity and depression can be explained by the fact that the two diseases share common biological pathways [46].

High glycosylated hemoglobin (HbA1c $\geq$ 7%) is a risk factor for depression (9.15 $\pm$ 4.27) and anxiety disorders, increased by the occurrence of complications due to diabetes [47]. The frequency of hypoglycemia can be a risk factor and a symptom of depression at the same time [48]. The risk of depression is 57% higher if type 2 diabetes begins at a younger age and the disease has been present for a long time [48]. These patients are likely to represent a metabolic and genetically heterogeneous group, require early insulin therapy, and suffer from severe complications [49,50]. Depression has also been found to be related to age [51–53]. Due to the gender difference, men have a lower risk of depression, anxiety, and stress than women with type 2 diabetes. In women, depression is more common (prevalence 50–60%) [54].

Comorbidity (more than two diseases) predicts a higher risk of depression [7,47]. The prevalence of symptoms of depression and anxiety is significantly increased in type 2

diabetes with polyneuropathy. The risk is increased by the presence of pain and the severity of neuropathy [55]. In a study conducted in China, it was found that diabetic retinopathy is mainly associated with depression (25%) and anxiety (13.5%) [56]. Genetic predispositions to metabolic and psychiatric disorders may overlap. The polygenic risk of type 2 diabetes affects the microstructural integrity of white matter networks. The PGS (polygenic risk score) can help to identify people with depression in the early stages of a more severe disease course, as indicated by a deterioration in brain structural connectivity and cognitive performance [57]. The risks of a single nucleotide polymorphism in the NR3C1 gene are associated with depressive disorder and/or type 2 diabetes, and epigenetic changes in this gene affect vulnerability to coping styles and depression [58].

Several lifestyle factors increase the risk of depression. Depression occurs more often in people with diabetes who have a history of obesity, alcohol abuse, and smoking [59]. Sleep disorders, along with fluctuations in glucose levels, increase the risk of depression, which is associated with severe fatigue and exhaustion [48]. Alcohol abuse increases the risk of depression by 3.6 times in people with diabetes compared to non-consumers. Inactivity also increases the likelihood of depression risk (p = 0.083) [50]. Lack of exercise also affects the quality of sleep, which in turn is associated with a deterioration in mental health [60].

The level of anxiety disorder is significantly associated with socio-demographic variables (standard of living, level of education), satisfaction with treatment, adherence to treatment, and family history of mental health problems [61]. The risk of occurrence of depression is increased if there is a history of depression [62]. Diabetes diagnosed at a younger age is associated with lower self-esteem, isolation, and excessive worry [63]. Studies have confirmed that stress and emotional strain associated with treatment procedures can be important factors affecting the psychological state and general well-being of people with type 2 diabetes [64,65].

Socio-economic aspects that increase the risk of depression are a low level of education (basic education), small family ($\leq$7 members), unemployment, and lack of support from loved ones [46,54]. Low levels of education are associated with a poor understanding of the disease, medication adherence, and nutrition, thus increasing the risk of complications [47,52,62]. People with strong social support have a lower risk of depression [56]. Insulin users have a higher risk of depression (OR = 3.77, 95% CI = (1.50–9.44)) [51] and anxiety (OR = 4.27, 95% CI = (2.05–8.91)) [51] compared to those who do not use insulin [47,51]. Studies of adaptive difficulties assess the effects of insulin treatment on mental health. Such studies show that patients under insulin treatment experience more severe disease management [66]. A summary of the risk factors can be found in Table 4.

Table 4. Risk factors for depression in type 2 diabetes.

Category	Subcategory	Substantive Code
Biological causes	Overweight, obesity [7,45,46]	Overweight, waist circumference, obesity, and body mass index (BMI)
	Dysglycemia [47–49]	Hypo- and hyperglycemia, HbA1c, blood sugar fluctuation, and effect of hyperglycemia
	Comorbidities [20,47,55,56]	Micro- and macrovascular complications, hippocampal atrophy, damage to the HPA axis, inflammatory processes, immune inflammation, dyslipidemia, cardiac arrhythmias, overweight, obesity, dementia, pain, and sleep apnea
	Age [51–54]	Elderly, age groups, age over 65, and age at onset of illness
	Genetics [57,58]	Genetic predisposition, genetics, and NR3C1 gene
	Sex [47,50,53,54]	Female gender, more common in women, and gender difference
	Disease duration [48–50]	Duration of the disease, length of the disease, course of the disease, and duration of the disease for more than five years

Table 4. *Cont.*

Category	Subcategory	Substantive Code
Behavioral causes		
	Lifestyle aspects [48,50,59]	Sleep disorders, disturbed circadian rhythm, fatigue, alcohol consumption, alcoholism, and lack of exercise
Psychological causes		
	Anxiety, stress, distress [60,61,64,65]	Anxiety, fear of coping with the disease, anxiety about complications, fatigue, inability to take care of yourself, difficulty with self-care, anxiety about treatment, excessive worry, self-management when coping with the disease, anger and guilt, feelings of helplessness, adaptation problems, and negative attitude towards the disease
Socio-economic causes		
	Support [50,52,56]	Family support, family size, social support, lack of support and need for support
	Economic status [31,46,47]	Low economic status, inequality, few opportunities, socioeconomic deficit, unemployment, and underemployment
	Education level [52,54,62]	Low level of education, incomplete level of education, and level of education

3.3. Risk Factors for Psychosocial Problems in Type 2 Diabetes

Women with type 2 diabetes experience a higher risk of depression and need more social support [67–69]. High HbA1c levels (≥10%) increase the need for social support [70]. Poor glucose control, complications, especially cardiovascular diseases, and hypoglycemia predict difficulties in coping with the disease [49,71]. Erectile dysfunction is associated with comorbidities, the duration of diabetes, and age, affecting sexual life and increasing mental health risks [72]. Neuropathy and thyroid dysfunction also increase the risk of depression [73]. Anxiety about complications is associated with a lack of knowledge and weak social support, which in turn affects the risk of mortality [67,74].

Personality traits affect adherence to treatment. Higher neuroticism is associated with a poorer lifestyle and adaptation to the disease. The patient's coping ability is also affected by the personality traits of loved ones, i.e., the support network [75]. A type D personality, characterized by negative affectivity and social inhibition, is associated with lower self-efficacy and social support [76]. Economic situation and work capacity affect the ability to cope with diabetes, as high HbA1c levels (≥10%) increase the risk of unemployment [70,77]. The support of family and friends has a significant impact on coping with diabetes and mental health [67,78–81]. Low social support increases the risk of physical complications and therefore the occurrence of psychiatric disorders [69,81].

The level of education of patients has a significant impact on the ability to cope with the disease, which is related to skills and knowledge on how to avoid fluctuations in glucose levels and how to adapt medications. A skills and self-efficacy survey revealed that individuals with higher education demonstrate greater proficiency in managing treatment than those who have completed secondary education or vocational training [82]. Insulin used for treatment requires continuous self-management, including the regular monitoring of blood sugar, insulin injections, and related dietary adjustments. The stress associated with these processes can affect psychosocial well-being [49,71,73]. The summary of risk factors is given in Table 5.

Table 5. Risk factors for psychosocial problems in type 2 diabetes.

Category	Subcategory	Substantive Code
Psychological causes		
	Fear, anxiety, stress [74,80,81]	Fear of complications, fear of hypoglycemia, fear of meeting treatment goals, depression, anxiety, fear of changing lifestyle, anxiety disorders, phobias, anxiety about complications, anxiety about lack of knowledge, emotional experiences, emotional distress, concern about disease management, support, emotional burden, and health care services' availability
	Personality characteristics [75,76]	Personality, personality traits, D-type personality, neuroticism, and temperament
Social causes		
	Economic status [47,70,77]	Social inequality, economic difficulties, expensive treatment, regional location, and lack of health insurance
	Support [69,78,81,83]	Support, family involvement, support from healthcare professionals, social isolation, support from support networks (family and friends, spouse), and psychological support
	Education level [22,28,82]	Few skills and knowledge about coping with the disease, use of new technologies, knowledge about diabetes, lack of information, insufficient information, ineffective teaching method, economic opportunities, level of education, ability to find information, information on the web, understanding information, literacy and numeracy, and level of education
Biological causes		
	Comorbidities [73,84]	Psychiatric diseases, dementia, obsessive compulsive behavior, sleep disorders, sleep apnea, depression, eating disorders, micro- and macrovascular complications, disease duration, obesity, malignant tumors, stroke, erectile dysfunction, and sexual dysfunction
	Sex [49,67–69]	Female gender, woman, and gender differences
	Dysglycemia [49,70–72]	Hyper- and hypoglycemia, blood sugar fluctuations, low blood sugar control, and HbA1c level
Pharmacologic causes		
	Medications [49,71,73]	Drug administration, injection, drug side effects, duration of insulin treatment, and insulin

4. Discussion

4.1. Factors Influencing the Development of Diabetic Cognitive Impairment

The pathophysiology of cognitive impairment associated with diabetes is multifaceted and is likely to include disruptions in insulin signaling, heightened inflammatory responses, alterations in oxidative stress levels, and anomalies in metabolic regulation [85–87]. Risk factors for cognitive impairment in individuals with type 2 diabetes include a longer duration of the disease, advanced age, and fluctuations in glucose levels, all of which are associated with an increased risk of developing cognitive issues, which are associated with a higher risk of cognitive impairment. Elderly patients are at higher risk for cognitive impairment, especially if they have comorbid conditions such as hypertension and depres-

sion [17,42]. Similarly, previous systematic reviews have shown that brain aging processes are up to 26% faster in people with type 2 diabetes than in those without the disease. In addition, the disease is associated with an increased risk of geriatric conditions [5,40]. The aging process of the brain is accelerated by hyperglycemia, hyperinsulinemia, and repeated hypoglycemic episodes. Hypoglycemia is largely associated with insulin therapy [4,27,88].

Among comorbid conditions, hypertension and microvascular diseases increase the risk of dementia. Furthermore, the thickening of the capillary basement membrane, a hallmark of diabetic microangiopathy, has been found in the brains of patients with diabetes [27,87,89–91]. Factors can include low income and poor levels of education. One's education level is not an independent factor in type 2 diabetes. Age, disease duration, arterial hypertension, BMI, gender, and symptoms of depression must be taken into account when assessing cognitive abilities [22,28]. Cognitive dysfunction in the elderly is related to age, income, and the ability to perform daily activities, and it may play an important role in the early detection of dementia among elderly people with low income and poor self-care ability [6,20]. Cognition is most affected by insulin therapy and beta-blockers are used to treat arterial hypertension. With insulin treatment, the elderly have a higher risk of hypoglycemia [33]. A decrease in cognitive function is primarily related to the use of long-acting beta-blockers [92].

Our systematic review underscores the complex interplay between biological and psychosocial factors in diabetic cognitive impairment, with disturbances in insulin signaling and inflammatory processes exacerbated by type 2 diabetes playing a critical role (Figure 2). We found that not only do clinical factors like disease duration and glucose fluctuations contribute to this impairment, but socio-economic and psychological aspects are also deeply intertwined with these biological pathways [17,20,22,27,33]. This insight points to the necessity of a holistic approach to managing diabetic cognitive impairment, emphasizing the need for future research to focus on personalized treatments and lifestyle interventions, such as addressing obesity, alongside regular mental health screenings to potentially slow cognitive decline. Our review offers detailed insights, but it is constrained by diverse study designs and the omission of grey literature, potentially introducing publication bias. Additionally, the varied methodologies and participant demographics across studies restrict how broadly our conclusions can be applied, warranting a careful and measured interpretation of the results.

4.2. Factors Influencing the Onset of Depression in Diabetes Patients

Research has confirmed that the effects of depression are bidirectional. The co-occurrence of depression and elevated anxiety in diabetes impairs coping with the disease, increases non-compliance with treatment, worsens the overall quality of life, and increases mortality [93]. Depression increases the risk of developing type 2 diabetes by 60%, and vice versa [94–96]. The risk of depression is similarly increased by factors that contribute to cognitive impairment. These are often overweight and obesity, which studies have linked to a higher risk of depression. Increased levels of glycated hemoglobin (HbA1c) and complications arising from diabetes also serve as risk factors. In diabetic patients, research has observed a reduction in brain volume, specifically in the hippocampus. Additionally, there is a noted inverse correlation between blood glucose control and the volume of the hippocampus. In a similar vein, depression is linked to neurodegenerative changes, predominantly affecting the prefrontal cortex and the hippocampus [96].

Taking into account factors such as an unbalanced diet, excessive alcohol consumption, smoking, poor sleep quality, and a lack of physical activity, the activation and disruption of the stress system may be a key factor in the common pathway [97]. People with type 2 diabetes often have sleep disorders and sleep apnea as comorbidities. Sleep disturbances often co-exist with symptoms of depressive disorders. Chronic insomnia has been considered a predictor and trigger factor for a group of depressive illnesses [98]. Our findings corroborate the bidirectional nature of depression and type 2 diabetes, as previously reported. However, our review goes further by elucidating the underlying biological mechanisms,

such as neurodegenerative changes in the hippocampus, that are triggered by diabetic conditions. The convergence of lifestyle factors such as diet and physical activity with these biological changes points to a compounded risk, calling for a more integrated treatment approach. Our review confirms the bidirectional relationship between depression and type 2 diabetes, while further uncovering the underlying biological mechanisms, like hippocampal neurodegenerative changes, influenced by diabetic conditions. This interaction, combined with lifestyle factors such as diet and physical activity, amplifies the risk, emphasizing the need for an integrated treatment approach. Addressing depression in diabetes effectively requires interdisciplinary treatment strategies, including coordinated care among healthcare professionals and policy interventions to enhance patient education and support [47,52,62,94–96].

Figure 2. The main risk factors in type 2 diabetes for cognitive dysfunction, depression, and psychosocial problems.

4.3. Socio-Economic Aspects

A low level of education, a small family, unemployment, and a lack of social support increase the likelihood of developing depression. The guidelines of the American Diabetes Association (ADA) emphasize that owing to the escalation in adverse health effects and

complications, it is imperative to concurrently acknowledge and treat both diabetes and depression in individuals. This integrated approach aims to mitigate depression and enhance the management of diabetes [99]. Several psychosocial issues in type 2 diabetes can affect patients' quality of life and ability to cope with the disease, and need to be addressed. These issues include stress, anxiety, depression, self-esteem and body image challenges, social isolation, coping with stress, poor adherence to treatment, fear of complications, and socio-economic factors. Interestingly, this review found that the ability to cope with the illness is influenced by personality, which is largely understudied, but recent articles suggest that neuroticism and a type D personality are important contributors [75,76]. Negative emotions associated with mental health problems are directly related to a poorer ability to cope with diabetes. The relationship between personality and health is comprehensive and is influenced by various circumstances (support network, level of education, economic status, and access to health services) [75]. This finding provides evidence that a more positive and adaptive personality type can promote a better ability to cope with chronic illness. People with a positive mindset may be more motivated to follow healthy lifestyles, such as a balanced diet, regular physical activity, and monitoring blood sugar.

Diabetes management involves ongoing self-care behaviors, including adjusting medication dosages and frequencies, monitoring blood glucose levels, regulating food intake, and maintaining physical activity. The progression of the disease, whether potential or actual, can be influenced by the stress experienced by individuals with diabetes. Additionally, psychosocial factors that impact self-management and treatment outcomes include attitudes towards the illness, expectations from medical services and their outcomes, the availability of resources (financial, social, and emotional), and the individual's psychiatric history [78,100].

Similar to risk factors for cognitive impairment and depression, glucose fluctuations and comorbid conditions are important for psychosocial problems [70,71]. Comorbidities in turn increase mental health problems, affect the ability to cope with the disease, and increase excessive anxiety. In diabetes, anxiety is also related to treatment (injection and fear of hypoglycemia). Previous studies show that fear of hypoglycemia and ignorance about hypoglycemia often occur together. Fear of hypoglycemia may explain the avoidance of lowering blood glucose levels by manipulating insulin therapy and glucose monitoring [101].

Socio-economic factors like education level and income are critical in type 2 diabetes, serving not merely as risk factors but as integral elements that intertwine with biological and psychological pathways, significantly impacting the disease's progression and patients' management capabilities. Recognizing this, it is essential to provide comprehensive support, including education and professional assistance, to enhance patients' coping mechanisms, mental well-being, and effective disease management. The American Diabetes Association (ADA) [99] underscores the importance of collaborative and patient-centered psychosocial care, focusing on improving treatment outcomes and overall quality of life. Such care includes assessing patients' attitudes toward diabetes, expectations from medical care, mood variations, life quality, and available support resources, all of which are pivotal in diabetes management.

The discernible heterogeneity among the studies we reviewed has necessitated a careful interpretation of our results. The diversity in methodologies, participant characteristics, and outcome variables reflects the multifaceted nature of type 2 diabetes and imposes limitations on the generalizability of our findings. Future research, benefiting from an accumulation of more standardized data, may allow for meta-analytical approaches that could yield more granular insights and enhance our ability to predict and stratify risk with greater precision.

5. Conclusions

This study comprehensively demonstrates that the management of type 2 diabetes, particularly concerning mental health, involves a complex interplay of various risk factors.

Common determinants for cognitive impairment, depression, and psychosocial problems include comorbidities, dysglycemia, gender, excessive fear and anxiety, educational level, economic status, and medication usage. Notably, disease duration, increased weight, obesity, and age emerged as shared risk factors for cognitive disorders and depression. The absence of a support network and inadequate psychosocial support were identified as critical factors exacerbating both psychosocial and depression risks. Distinctively, personality traits significantly contribute to psychosocial challenges, while lifestyle choices and genetic predispositions play a crucial role in depression.

The findings emphasize the imperative of a holistic approach in the management of type 2 diabetes. This approach should transcend mere glycemic control to include comprehensive monitoring and treatment of associated physical and mental health conditions, along with a strong consideration of socio-economic factors. It is evident that economic status and education level not only influence the progression of the disease but also the effectiveness of its management. Ensuring equitable access to education and social services is essential to mitigating these socio-economic disparities. Furthermore, this study underscores the substantial impact of psychosocial factors such as stress, anxiety, depression, and social isolation on the quality of life of individuals with type 2 diabetes. This underscores the importance of considering personality traits and promoting healthier lifestyle activities, such as balanced nutrition and regular physical activity, in diabetes care. A more personalized and tailored treatment approach, addressing these multifaceted aspects, could be pivotal in enhancing patient outcomes and overall quality of life.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/diabetology5010004/s1, File S1: PRISMA 2020 Checklist. Reference [102] is cited in the Supplementary Materials.

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