




Autoimmunity to mental health: Risk of depression in type 1 diabetes and celiac disease patients – A systematic review, meta-analysis, and bias assessment

Dagem Desalegn^{a,b}, Simone Fischer^a, Yeabsira Bedada^c, Dennis Freuer^{a,*,1} , Christa Meisinger^{a,1}

^a Epidemiology, Medical Faculty, University of Augsburg, Augsburg, Germany

^b Charité, University of Berlin, Institute of Public Health/Berlin School of Public Health, Berlin, Germany

^c University of Turku, Faculty of Medicine, Turku, Finland

ARTICLE INFO

Handling Editor: Professor C Selmi

Keywords:

Diabetes mellitus type 1
Celiac disease
Autoimmunity
Depression
Mental health
Mood disorders

ABSTRACT

Background: Depression is expected to become the world's largest disease burden by 2030. However, the incidence of depression in individuals with Type 1 diabetes mellitus (T1DM) or Celiac disease (CD) remains poorly studied. To address this gap, a systematic review and meta-analysis was carried out.

Methods: This systematic review was approved at PROSPERO on February 9, 2025, and followed the PRISMA and MOOSE guidelines. The literature search considered all peer-reviewed quantitative studies from relevant databases up to February 7, 2025. Study-specific risk of bias was assessed using the ROBINS-E tool. Inverse variance weighted random-effects models were applied on the hazard ratio (HR) scale to pool estimates of included studies. Heterogeneity was quantified by Cochran's Q and I^2 statistics. Sensitivity analyses consisted of influence, outlier, and subgroup analyses. E-values were calculated to assess the reliability of results regarding unmeasured confounding.

Results: Out of 17,095 articles screened, eight studies for T1DM and two for CD were included in the study. Both T1DM (HR = 2.77; 95 % CI: [1.82; 4.21]; $P < 0.0001$; $I^2 = 98.5\%$) and CD (HR = 1.66; 95 % CI: [1.51; 1.84]; $P < 0.0001$; $I^2 = 35.3\%$) were consistently associated with the onset of depression. Despite the high heterogeneity, which could not be fully explained for T1DM, the sensitivity analyses confirmed the results, while the E-values underscored their robustness against unmeasured confounding.

Conclusions: This meta-analysis indicates a significant increase in the incidence of depression in individuals with either T1DM or CD. Depression screening for these population is recommended. Further research is needed to clarify the underlying mechanisms for these associations.

List of abbreviations

BMI	Body mass index
CD	Celiac Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
IL-1 β	Interleukin-1 beta
IRR	Incident Rate Ratio

(continued on next column)

(continued)

IVW	Inverse-variance weighted
MOOSE	Meta-analysis of Observational Studies in Epidemiology
OR	Odds Ratio
PM	Paule-Mandel
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
ROBINS-E	Risk of Bias in Non-randomized Studies of exposure
RR	Relative Risk
SES	Socioeconomic status
T1DM	Type 1 Diabetes Mellitus

(continued on next page)

* Corresponding author.

E-mail address: dennis.freuer@med.uni-augsburg.de (D. Freuer).

¹ Contributed equally.

<https://doi.org/10.1016/j.jaut.2026.103524>

Received 1 October 2025; Received in revised form 17 December 2025; Accepted 8 January 2026

Available online 14 January 2026

0896-8411/© 2026 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

(continued)

TNF- α	Tumour Necrosis Factor alpha
WHO	World Health Organization

1. Background

According to the World Health Organization (WHO), an estimated 3.8 % of the global population is experiencing depression [1]. This condition is commonly characterized by insomnia, lack of interest in daily activities, impaired quality of life, and, in many cases, suicidal thoughts [2]. The consequences of depression can be severe. For instance, adolescents with major depression face a 30-fold higher risk of suicidality [3]. In addition, previous studies have linked major depression to an increased risk of cardiovascular diseases (CVD), as well as higher rates of morbidity and mortality [4]. Although cultural, psychological and biological factors are known to contribute to depression, its underlying pathogenesis remains complex and poorly understood [5]. Established risk factors for depression include being female, having a family history of the condition, and experiencing stressful life events [6]. Current research has further expanded our understanding by identifying additional risk factors beyond these traditional ones [7]. A recent systematic review and meta-analysis found that individuals with autoimmune diseases have a higher risk of depression, with a pooled incidence rate of 6.71 % (95 % CI 5.10 %–8.77 %) and a relative risk of 1.85 (95 % CI 1.57 to 2.19) [8]. The same study also identified higher risks of depression for a few specific autoimmune diseases [8].

Type 1 diabetes mellitus (T1DM) and celiac disease (CD) are among the most prevalent autoimmune disorders. Globally, the annual incidence rate of T1DM varies widely, with higher rates in Europe, North America, Australia and New Zealand [9]. In 2020, the global incidence of T1DM was 15 cases per 100,000 people, with a prevalence of 9.5 % [10]. For CD, the 2020 incidence rate was 21.3 per 100,000 person-years in children compared to 12.9 in adults, with a 7.5 % annual increase in incidence over recent decades [11]. Despite their prevalence, the association between T1DM or CD and incident depression remains understudied, as prior research has primarily focused on depression prevalence [12,13]. For instance, studies have reported depression prevalence ranging from 17.5 to 32.1 % in individuals with T1DM, compared to 5.7–16.0 % in non-diabetic controls [14]. Similarly, elevated depression rates are observed in individuals with CD [15], with a reported lifetime prevalence of 39 % [16]. Comparable to celiac disease findings, intestinal infectious diseases show increased risks for depression, anxiety, and other psychiatric conditions, suggesting potential shared mechanisms of gut-brain axis disruption and systemic inflammation [17].

Investigating the incidence of depression in children and adolescents with T1DM or CD is critical, as depression in these populations can have severe, long-term impacts on development [18,19]. Most prior studies on T1DM, CD, and depression have not accounted for temporal relationships when calculating risk estimates, making it difficult to establish clear associations [15,20]. As a recent study on epilepsy confirms, prevalence estimates alone in patients with this condition cannot be used to draw clear conclusions about the association with mental illness [21]. Therefore, it is important to examine mental health outcomes following a disease diagnosis using large-scale, long-term follow-up studies to better clarify temporal relationships [21]. We hypothesize that individuals with T1DM or CD exhibit a higher incidence of depression compared to those without these conditions. Thus, the aim of this systematic review and meta-analysis was to separately assess the risk of developing depression in individuals with T1DM and individuals with CD.

2. Methods

2.1. Protocol registration

This systematic review and meta-analysis were carried out following the Cochrane group's recommendations and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22] and the Meta-Analyses of Observational Studies in Epidemiology (MOOSE) [23] reporting guidelines. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42025639807) and approved on February 9, 2025 [24].

2.2. Search strategy

A comprehensive literature search was performed in MEDLINE, Embase, PsycINFO, SCOPUS, and Web of Science considering all published studies until February 7, 2025. The search string combined various terms and abbreviations for T1DM, CD and depression and was adapted to the specific databases [Supplementary Table 1]. Database-controlled vocabulary was additionally used to search for subject headings in titles and abstracts.

2.3. Eligibility criteria

Based on the PICO framework, individuals with a diagnosis of either T1DM or CD (confirmed through standard diagnostic criteria) were considered as cases without age, sex, or ethnic restrictions. The general population without any autoimmune disease formed the control group. The occurrence of a diagnosed depression clearly after the diagnosis of exposure was defined as the outcome. Limiting to studies that focused exclusively on incident depression ensured that the exposure precedes the outcome in terms of evidence.

Furthermore, only peer-reviewed quantitative studies in English were included in this systematic review and the subsequent meta-analyses. Publications such as reviews, case reports, conference abstracts, commentaries, any other kind of studies with a qualitative study design, or non-peer-reviewed-articles were excluded from the analyses. The same was applied to studies, considering prevalent cases of depression or undiagnosed exposure or outcome of interest.

2.4. Selection process

Article selection occurred in two stages. Initially, after deduplication, two of five reviewers (D.D, C.M, D.F, Y.B, and S.F) worked independently to screen the titles and abstracts of the identified articles for eligibility using Rayyan, a web-based platform for systematic reviews [25]. In the second step, full-text articles of studies were assessed for relevance and reasons for inclusion and exclusion were reported based on the predefined criteria. Conflicts in article selection were resolved through discussion and involvement of a third reviewer.

2.5. Data collection

Data extraction excel form was used to collect relevant information from the included studies. Two independent reviewers (D.D and C.M) extracted the following data from each study, where available: first author's name, title and year of publication, study design, country in which the study was conducted, number of included participants with autoimmune diseases, number of incident depression cases, details about comparison group, age of participants, duration of the follow up period, time-window between diagnosis of exposure and outcome, type of extracted estimate, point estimate with 95 % confidence interval (CI) on any scale, and considered confounding factors. Discrepancies in data extraction were resolved by consensus or by consulting a third reviewer (D.F).

2.6. Risk of bias assessment

Before running the meta-analyses, each study was subjected to a risk of bias assessment using the ROBINS-E (Risk Of Bias In Non-randomized Studies - of Exposure) tool [26]. Two reviewers (D.D and D.F) decided independently the study-specific risk of bias due to the following seven domains: (1) Unmeasured confounding, (2) measurement of exposure, (3) selection of participants, (4) post-exposure interventions, (5) missing data, (6) measurement of outcome, and (7) selection of reported results. Disagreements were resolved through discussion without the need for a third reviewer.

2.7. Statistical analysis

The types of effect estimates varied between the studies as two of them present estimates as relative risk (RR) and incidence rate ratio (IRR), respectively. Since the remaining studies present their estimates in the form of hazard ratios (HR), both RR and IRR were converted to HR using the formula below to ensure a common scale for calculating meta-analytic estimates [27].

$$HR = \frac{\ln(1 - RR \cdot p)}{\ln(1 - p)}$$

where p denotes the incidence rate of depression in the unexposed group and RR the respective risk measure (i.e. RR or IRR).

Inverse-variance weighted (IVW) random effects models were used for calculating the pooled HRs. Between-study heterogeneity was quantified and evaluated by the Higgins' I^2 , τ^2 (calculated by the with the Paule-Mandel (PM) estimator), and Cochran's Q statistics.

2.8. Sensitivity analyses

To investigate potential sources of heterogeneity for an association, influence, outlier, and subgroup analyses were performed. The influence analysis, consisting of the Baujat Diagnostics and a leave-one-out analysis, attempted to identify studies that disproportionately contributed to the heterogeneity and affected the overall estimate. The outlier analysis calculated a pooled effect estimate after excluding studies that differed statistically from the overall estimate prior to exclusion. Subgroup

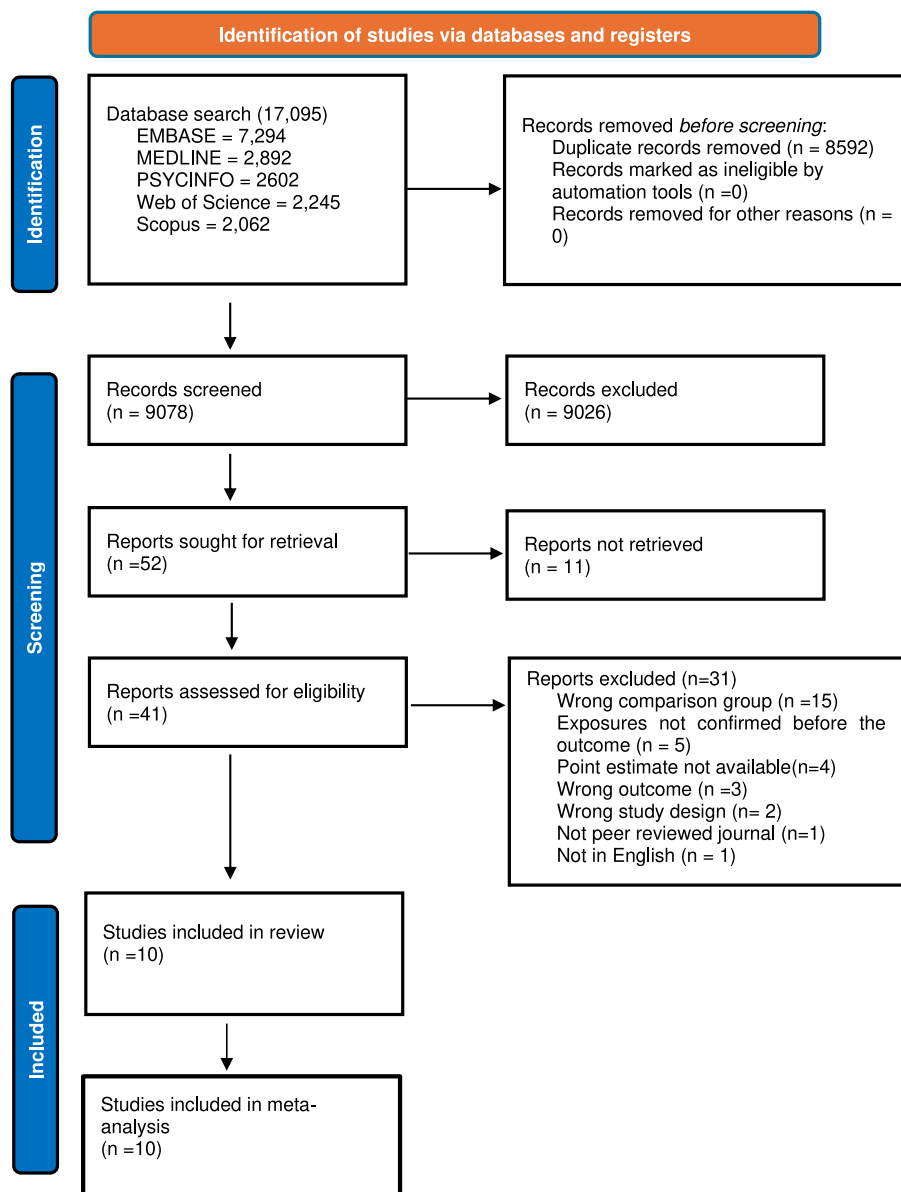


Fig. 1. PRISMA flow diagram of the study-selection process.

analyses were conducted to assess differences in study-specific estimates due to the study region, the number of participants with an autoimmune disease, the mean age of the participants, and the follow-up time of a study. Finally, the reliability of pooled estimates regarding the bias caused by unmeasured confounding, which is a common issue in observational studies, was evaluated by calculating E-values. An E-value quantifies the minimum strength of an association (on the risk ratio scale) that unmeasured confounding would need to have with both the exposure and the outcome to fully explain away a found association [28].

In the context of depression risk in people with T1DM and CD, an HR greater than 1 suggests an increased instantaneous risk of developing depression compared to those without Type 1 diabetes and CD, while a value less than 1 indicates a reduced instantaneous risk. Statistical tests were performed two-sided with a Bonferroni corrected significance level of 0.025. Data handling and statistical analyses were performed in R (version: 4.4.2) primarily using the packages dplyr (version: 1.1.4), meta (version: 8.0–1), metafor (version: 4.6–0), dmetar (version: 0.1.0), and EValue (version: 4.1.3). The Risk of bias was visualized using the robnis web application [29].

3. Results

The literature search initially yielded 17,095 publications [Fig. 1]. After deduplication, the titles and abstracts of 9078 publications were screened, and 52 full texts were assessed against the inclusion and exclusion criteria. Finally, 8 and 2 studies were included for the associations with T1DM and CD, respectively.

3.1. Main results

The characteristics of included studies are detailed in Table 1. The studies were published as cohort studies between 2007 and 2024, and conducted in European (Austria, Czech, Denmark, Sweden, and the United Kingdom) or Asian countries (South Korea and Taiwan). Sample sizes for T1DM and depression ranged from 28,833 to 2,263,311 and for CD and depression from 63,660 to 80,591. Mean age of participants varied from about 8 to 57 years, with an overall almost equal proportion

of men (50.77 %) and women. Follow up duration varied across studies, ranging from 1 to 34 years. The studies used different standard diagnostic criteria to diagnose T1DM, CD and depression [Supplementary Table 2].

Of the 10 studies included in meta-analyses, 9 studies had a high risk of bias and 1 study had a moderate risk of bias. The risk of bias could mainly be attributed to the first domain (i.e. unmeasured confounding) of the ROBINS-E tool [Supplementary Fig. 1].

Based on 8 included studies, the inverse variance weighted random-effects model revealed a positive association between T1DM and depression (HR = 2.77; 95 % CI: [1.82; 4.21]; P < 0.0001) [Fig. 2]. Despite large heterogeneity across the specific estimates ($I^2 = 98.5\%$, P < 0.0001), all studies consistently reported notable positive associations. Similarly, the evaluation of two studies, whose estimates did not differ considerably ($I^2 = 35.3\%$, P = 0.2138), revealed a positive association between CD and the occurrence of depression (HR = 1.66; 95 % CI: [1.51; 1.84]; P < 0.0001) [Fig. 3].

3.2. Sensitivity analyses

Regarding the association with T1DM, the influence and outlier analyses found that the studies of Chen et al. [30] and Ni et al. [37] differed notably from the other studies. Both of them were among the most influential studies contributing relatively strongly to the overall heterogeneity [Supplementary Fig. 2]. The leave-one-out analysis showed that omitting Chen et al. led to a slightly lower and more precise overall estimate [Supplementary Fig. 3]. Removing both studies attenuated the estimate to HR = 2.36; 95 % CI: [1.96; 2.85] [Supplementary Fig. 4]. However, even the exclusion of the outliers was not able to explain away a considerable proportion of the heterogeneity.

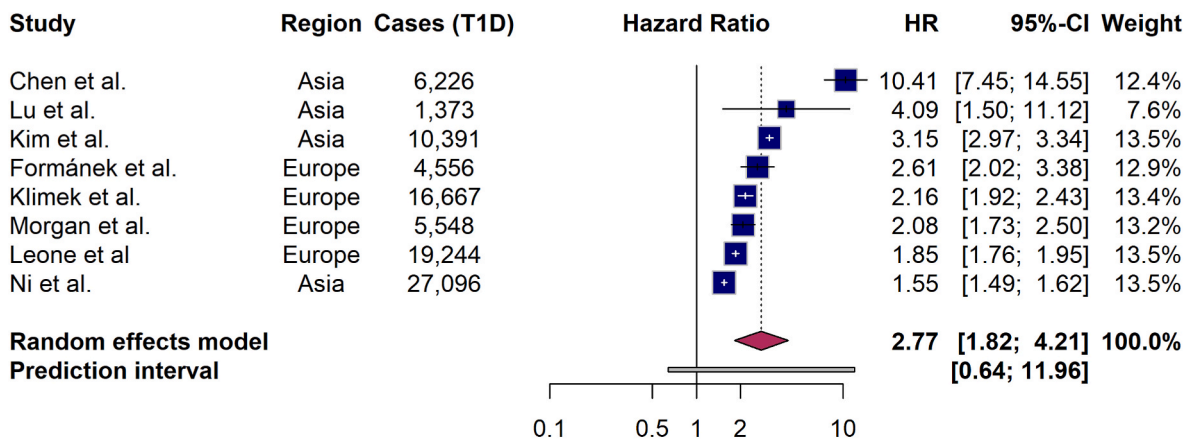
To further explore potential sources of heterogeneity, subgroup analyses were performed regarding the regional differences (European vs. Asian studies) and the number of individuals with T1DM (<10,000 vs. ≥ 10,000 participants). Despite larger effect estimates in Asian studies (HR_{Asia} = 3.73; 95 % CI: [1.68; 8.27] vs. HR_{Europe} = 2.09; 95 % CI: [1.83; 2.37]) and studies with fewer than 10,000 participants with T1DM (HR < 10k = 3.85; 95 % CI: [1.86; 7.94] vs. HR > 10k = 2.10; 95 % CI: [1.56; 2.83]), no notable subgroup differences could be detected

Table 1

Characteristics and references of included studies for the associations between Type 1 diabetes mellitus (T1DM) and Celiac disease (CD) with the incidence of depression.

Author (Year)	Country	Cases AD/ Controls	Depression in AD/Controls	Age (years)	Follow up time (years)	Point estimate (95 %CI)	Adjusted variables
T1DM							
Chen et al. (2022) [30]	Taiwan	6226/62,260	69/75	Mean = 23.7 SD = 15.2	Mean = 5.83	HR = 10.41 (7.45–14.56)	age, sex, income, residence, family history, freq. of psychiatrist visits
Formánek et al. (2024) [31]	Czech	4556/45,560	73/280	Mean = 8.66 SD = 3.89	Range: 10–24	HR = 2.61 (2.02–3.38)	age, sex, population stratification, time at discharge from hospitalization
Kim et al. (2024) [32]	South Korea	10,391/ 51,995	2246/3962	Mean = 56.9 SD = 12.9	Median = 7.9	HR = 3.15 (2.97–3.34)	age, sex, BMI, income, smoking, alcohol, activity, hypert, dyslipidemia, CVD, cancer
Klimek et al. (2015) [33]	Austria	16,667/ 1,862,258	not reported	Range: 0–95	2	RR = 1.94 (1.76–2.73)	none
Leone et al. (2022) [34]	Sweden	19,244/ 2,244,067	1737/116,314	Born: 1973–1996 Mean = 12.3	Median = 27	HR = 1.85 (1.76–2.73)	sex, birth year, sibling type
Lu et al. (2017) [35]	Taiwan	1373/27,460	15/146	Mean = 12.3	≤ 5	IRR = 3.09 (1.82–5.26)	age, index year, hypertension, CVD, CKD, thyroid diseases
Morgan et al. (2014) [36]	United Kingdom	5548/10,657	315/343	Mean = 17.7 SD = 9.3	Mean = 4.8	HR = 2.08 (1.73–2.50)	age, sex, general practice
Ni et al. (2024) [37]	Taiwan	27,096/ 108,116	4014/10,095	Mean = 55.7 SD = 18.1	7	HR = 1.55 (1.48–1.61)	age, sex, year of Diabetes diagnosis
Celiac disease							
Hansen et al. (2023) [38]	Denmark	6329/63,287	810/5452	Mean = 27 SD = 21	18	HR = 1.61 (1.49–1.73)	age, sex, calendar period, follow up time
Ludvigsson et al. (2007) [15]	Sweden	13,776/ 66,815	181/529	Range: 0–94	Median = 9.6	HR = 1.8 (1.6–2.2)	age, sex, calendar period, county; SES, diabetes, thyroid disease

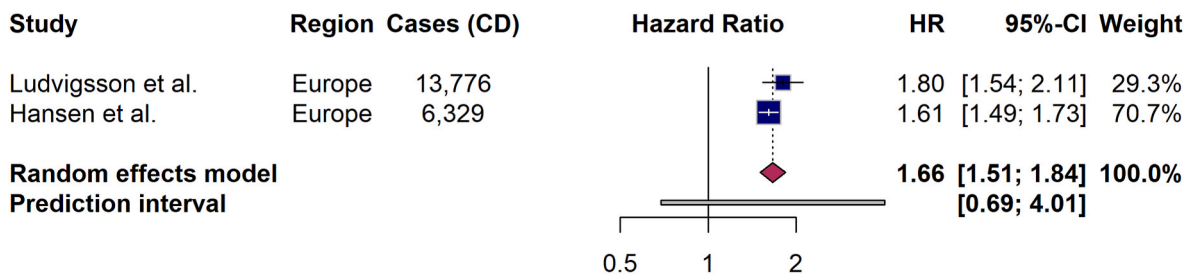
Abbreviations: AD, autoimmune disease; BMI, Body Mass Index; CI, confidence interval; CKD, Chronic Kidney Disease; CVD, cardiovascular disease HR, Hazard Ratio; IRR, Incident Rate Ratio; RR, Relative Risk; T1DM, type 1 diabetes mellitus.



Heterogeneity: $I^2 = 98.5\%$, $\tau^2 = 0.3370$, $p < 0.0001$

Fig. 2. Forest plot of associations between Type 1 diabetes and depression.

The pooled hazard ratio (HR) and corresponding 95 % confidence interval (CI) were derived using an inverse-variance weighted random-effects model. Statistical significance was assessed using a Bonferroni-corrected threshold of $\alpha = 0.025$.



Heterogeneity: $I^2 = 35.3\%$, $\tau^2 = 0.0022$, $p = 0.2138$

Fig. 3. Forest plot of associations between celiac disease and depression.

The pooled hazard ratio (HR) and corresponding 95 % confidence interval (CI) were derived using an inverse-variance weighted random-effects model. Statistical significance was assessed using a Bonferroni-corrected threshold of $\alpha = 0.025$.

[Supplementary Figs. 5 and 6]. Also, no differences between the studies could be found regarding the average age of participants or the follow-up time [Supplementary Figs. 7 and 8]. Moreover, heterogeneity remained high in all subgroups (I^2 between 74.8 % and 99.5 %) and could therefore not be explained by any of the subgroup analyses. Meta-regression and small-study bias assessment could not be performed with the view on the number of studies included per association.

Due to the limited number of studies included, no sensitivity analyses could be performed on the association between CD and depression.

With regard to the risk of bias due to unmeasured confounding factors, E-values revealed that these factors must be associated with the exposure and outcome with RRs of at least 4.98 (lower 95 % CI = 3.04) and 2.71 (lower 95 % CI = 2.39), respectively, to explain away the associations with T1DM and CD obtained from the main analysis.

4. Discussion

Our results revealed that individuals with T1DM or CD have an increased risk of depression compared to individuals without these conditions. The studies examining the link between T1DM and depression showed high heterogeneity, which persisted despite excluding two outlier studies or conducting subgroup analyses. However, all eight studies included in the meta-analysis confirmed a statistically significant positive association between T1DM and depression, thus, an association can hardly be doubted.

In contrast to the present study, prior research in this field has primarily relied on cross-sectional study designs, limiting the ability to assess temporal relationships. Previous systematic reviews and meta-analyses have demonstrated a higher prevalence of depression among individuals with T1DM compared to non-diabetic individuals. For example, a systematic review and meta-analysis including 44 studies found a significantly elevated prevalence of depression diagnoses or symptoms in T1DM individuals (OR = 2.10, 95 % CI 1.23 to 3.52, $I^2 = 78.9\%$) [12]. Another systematic review and meta-analysis reported a pooled prevalence of depressive symptoms in individuals with T1DM of 30.04 % (95 % CI 16.33 to 43.7, $I^2 = 97\%$) [39].

This systematic review and meta-analysis are the first to evaluate the relationship between CD and incident depression. A previous systematic review and meta-analysis investigating the association between CD and neuropsychiatric disorders, reported a significantly high odds of depression in CD patients compared to controls (OR = 1.60; 95 % CI 1.37 to 1.86, $I^2 = 47\%$) [40]. However, that study, based on seven studies, differed methodologically from the present analysis by (1) excluding cohort studies, which limited the ability to establish temporality between CD and depression, and (2) including case-control studies, better suited for prevalence rather than incidence assessments [40].

Both T1DM and CD are immune-mediated diseases with shared genetic predispositions, particularly involving HLA (Human Leukocyte Antigen) class II genes DQ2 and DQ8, present in approximately 95 % of T1DM patients and 99 % of CD patients, compared to 40 % of the general

population [41]. This genetic overlap represents a significant risk factor and suggests shared pathogenic mechanisms, such as tissue damage resulting from autoimmunity or dietary antigen intolerance [42,43]. Additionally, both conditions are influenced by common environmental factors, including breastfeeding duration, early gluten exposure, and viral infections [42–44].

The link between T1DM and depression may be explained by shared pathophysiological mechanisms, including autoimmune processes, insulin deficiency, chronic hyperglycemia, and hypothalamic-pituitary-adrenal axis dysfunction [45,46]. Inflammatory cytokines, such as tumor necrosis factor alpha (TNF- α), interleukin-1 β (IL-1 β), and interferon-gamma (IFN- γ), play a crucial role in T1DM and depression, and thus potentially serve as mediators between the two conditions [47]. The neurological mechanisms underlying CD remain under investigation [48,49]. The biological connection to depression may involve impaired central monoaminergic metabolism, pro-inflammatory cytokines, bacterial compounds like lipopolysaccharides, and potential imbalances in adaptive responses [50]. These factors are thought to contribute to serotonin depletion, which may lead to depression [50]. Additionally, the link between CD and depression may be influenced by reduced quality of life following a CD diagnosis [51], dissatisfaction with sexual life [52], and challenges in managing the chronic nature of the disease [53].

4.1. Implications

The significant association of depression with T1DM and CD indicates the need for routine depression screening among these individuals. Depression screening should therefore be integrated into routine primary care services. To enhance screening, multilevel approaches are advised, such as eliminating financial and access barriers, utilizing health professionals to provide outreach services and awareness creation programs, and promoting depression screening adherence through psychosocial support. Depression prevention and management strategies should be incorporated within policies and guidelines focused on T1DM and CD.

Future research on mental health issues in patients with autoimmune diseases should focus on temporal relationships and incident cases (new-onset cases after disease diagnosis) rather than prevalent cases (depression present at or before the time of autoimmune disease diagnosis). This approach helps avoid potential immortal time bias in observational designs, ensuring clearer insights into causality and risk [54]. Furthermore, it is important to evaluate the quality and impact of studies using more comprehensive metrics that account for the integrity and reproducibility of the research. Greater sensitivity and vigilance toward scientific misconduct when selecting articles for future systematic reviews and meta-analyses are essential to obtain valid research evidence [55].

4.2. Strengths and limitations

Our work has several strengths. It is the first comprehensive systematic review with meta-analytical focusing explicitly on the incidence of depression in individuals with T1DM and those with CD by taking temporal relation into account. The analyses included studies with large sample sizes from diverse populations, enhancing the generalizability of the findings. The rigorous systematic approach was followed by a total of three reviewers per task in accordance with recommended checklists and guidelines. Robust statistical methods, a series of sensitivity analyses, and a risk of bias assessment were applied to pool and evaluate studies, considering their influence and contribution to heterogeneity. Finally, the reliability of the estimates obtained was investigated with regard to unmeasured confounding.

However, this study also has some limitations. Publication bias could not be assessed due to the limited number of included studies that met our inclusion criteria. Between-study heterogeneity in case of T1DM

could not be fully ruled out, suggesting the pooled estimates should be interpreted cautiously. The same applies to the results for CD patients, which were based on only two studies. Most of the studies included were rated as having a high risk of bias, particularly in terms of unmeasured confounding. ICD-8, ICD -9 and ICD-10 coding systems for disease diagnoses might carry a potential risk of misclassification, potentially leading to bias and affecting the final effect estimate.

4.3. Conclusions

In conclusion, this study reveals a significant association between T1DM, CD, and depression. These findings have important implications for research, clinical practice, and patient care. Future studies should explore the mechanisms driving these associations. Clinicians should prioritize targeted depression screening for individuals with T1DM or CD. Finally, public health initiatives should focus on increasing awareness and implementing preventive strategies to address the risk of depression in these populations.

CRediT authorship contribution statement

Dagem Desalegn: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Simone Fischer:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Yeabsira Bedada:** Writing – review & editing, Investigation. **Dennis Freuer:** Writing – review & editing, Visualization, Supervision, Methodology, Formal analysis, Conceptualization. **Christa Meisinger:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Data sharing statement

This study is based on previously published data available in the original studies.

Funding

No specific funding was received for this study.

Declaration of competing interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jaut.2026.103524>.

Data availability

Data is available in the original studies.

References

- [1] Depressive disorder (depression). [August 18, 2025]; Available from: <https://www.who.int/news-room/fact-sheets/detail/depression>.
- [2] O. Caliyurt, Sleep and quality of life in depression, in: J.C. Verster, S.R. Pandi-Perumal, D.L. Streiner (Eds.), *Sleep and Quality of Life in Clinical Medicine*, Humana Press, Totowa, NJ, 2008, pp. 251–260.
- [3] A. Stringaris, Editorial: what is depression? *Child Psychology Psychiatry* 58 (12) (2017) 1287–1289.
- [4] F. Seligman, C.B. Nemeroff, The interface of depression and cardiovascular disease: therapeutic implications, *Ann. N. Y. Acad. Sci.* 1345 (1) (2015) 25–35.
- [5] C. Ménard, G.E. Hodes, S.J. Russo, Pathogenesis of depression: insights from human and rodent studies, *Neuroscience* 321 (2016) 138–162.
- [6] C. Hammen, Risk factors for depression: an autobiographical review, *Annu. Rev. Clin. Psychol.* 14 (2018) 1–28.

- [7] M. Kozyra, M. Nowińska, J. Klas, M. Pytko, U. Łopuszańska, The latest research on risk factors and pathomechanisms of depression – review, *J Educ Health Sport* 10 (11) (2020) 50–60.
- [8] Y. Li, C. Zhao, S. Sun, G. Mi, C. Liu, G. Ding, et al., Elucidating the bidirectional association between autoimmune diseases and depression: a systematic review and meta-analysis, *BMJ Ment Health* 27 (1) (2024) e301252.
- [9] Wang Du, X. Hou, J. Huang, J. Sun, T. Kadowaki, M.-K. Lee, et al., Incidence and trends of type 1 diabetes before and after 2000 in the Western Pacific region: a systematic review and meta-analysis, *Diabetes Res. Clin. Pract.* 207 (2024) 111055.
- [10] M. Mobasser, M. Shirmohammadi, T. Amiri, N. Vahed, H. Hosseini Fard, M. Ghajzadeh, Prevalence and incidence of type 1 diabetes in the world: a systematic review and meta-analysis, *Health Promot. Perspect.* 10 (2) (2020) 98–115.
- [11] J.A. King, J. Jeong, F.E. Underwood, J. Quan, N. Panaccione, J.W. Windsor, et al., Incidence of celiac disease is increasing over time: a systematic review and meta-analysis, *Am. J. Gastroenterol.* 115 (4) (2020) 507–525.
- [12] A. Farooqi, C. Gillies, H. Sathanapally, S. Abner, S. Seidu, M.J. Davies, et al., A systematic review and meta-analysis to compare the prevalence of depression between people with and without type 1 and type 2 diabetes, *Primary Care Diabetes* 16 (1) (2022) 1–10.
- [13] E. Clappison, M. Hadjivassiliou, P. Zis, Psychiatric manifestations of coeliac disease, a systematic review and meta-analysis, *Nutrients* 12 (1) (2020) 142.
- [14] N. Gendelman, J.K. Snell-Bergeon, K. McFann, G. Kinney, R. Paul Wadwa, F. Bishop, et al., Prevalence and correlates of depression in individuals with and without type 1 diabetes, *Diabetes Care* 32 (4) (2009) 575–579.
- [15] J.F. Ludvigsson, J. Reutfors, U. Ösby, A. Ekblom, S.M. Montgomery, Coeliac disease and risk of mood disorders — a general population-based cohort study, *J. Affect. Disord.* 99 (1–3) (2007) 117–126.
- [16] N.J. van Hees, W. van der Does, E.J. Giltay, Coeliac disease, diet adherence and depressive symptoms, *J. Psychosom. Res.* 74 (2) (2013) 155–160.
- [17] C. Kang, S.W. Lee, H. Jung, Y. Bae, Psychiatric morbidity following intestinal infectious diseases: a nationwide cohort study in South Korea, *Stress and health journal of the International Society for the Investigation of Stress* 41 (5) (2025) e70103.
- [18] M. Monaghan, C. Singh, R. Streisand, F.R. Cogen, Screening and identification of children and adolescents at risk for depression during a diabetes clinic visit, *Diabetes Spectr.* 23 (1) (2010) 25–31.
- [19] H. Jericho, N. Khan, J. Cordova, N. Sansotta, S. Guandalini, K. Keenan, Call for action, *JPGN rep* 2 (3) (2021).
- [20] M. Grey, R. Whittemore, W. Tamborlane, Depression in type 1 diabetes in children, *J. Psychosom. Res.* 53 (4) (2002) 907–911.
- [21] S.W. Lee, C. Kang, U. Choi, H. Jung, Y. Bae, Risk of anxiety disorders after epilepsy diagnosis: a nationwide retrospective cohort study, *Epilepsy & behavior E&B* 171 (2025) 110602.
- [22] D. Moher, L. Shamseer, M. Clarke, D. Ghera, A. Liberati, M. Petticrew, et al., Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement, *Syst. Rev.* 4 (1) (2015).
- [23] D.F. Stroup, J.A. Berlin, S.C. Morton, I. Olkin, G.D. Williamson, D. Rennie, et al., Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in Epidemiology (MOOSE) group, *JAMA* 283 (15) (2000) 2008–2012.
- [24] Dagem Desalegn, Christine Meisinger, Dennis Freuer. The Association of Type 1 Diabetes Mellitus(T1DM), Celiac Disease (CD) and the Subsequent Development of Depression: a Systematic Review and Meta-Analysis.
- [25] M. Ouzzani, H. Hammady, Z. Fedorowicz, A. Elmagarmid, Rayyan—A web and mobile app for systematic reviews, *Syst. Rev.* 5 (1) (2016).
- [26] J.P. Higgins, R.L. Morgan, A.A. Rooney, K.W. Taylor, K.A. Thayer, R.A. Silva, et al., A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E), *Environ. Int.* 186 (2024) 108602.
- [27] E. Shor, D. Roelfs, Z.M. Vang, The “Hispanic mortality paradox” revisited: meta-analysis and meta-regression of life-course differentials in Latin American and Caribbean immigrants’ mortality, *Soc. Sci. Med.* 186 (2017) 20–33.
- [28] T.J. VanderWeele, P. Ding, Sensitivity analysis in observational research: introducing the E-Value, *Annals of internal medicine* 167 (4) (2017) 268–274.
- [29] L.A. McGuinness, J.P.T. Higgins, Risk-of-bias VISualization (robvis): an R package and shiny web app for visualizing risk-of-bias assessments, *Res. Synth. Methods* 12 (1) (2021) 55–61.
- [30] M.-H. Chen, S.-J. Tsai, Y.-M. Bai, K.-L. Huang, T.-P. Su, T.-J. Chen, et al., Type 1 diabetes mellitus and risks of major psychiatric disorders: a nationwide population-based cohort study, *Diabetes & Metabolism* 48 (1) (2022) 101319.
- [31] T. Formánek, D. Chen, Z. Šumník, K. Mladá, J. Hughes, S. Burgess, et al., Childhood-onset type 1 diabetes and subsequent adult psychiatric disorders: a nationwide cohort and genome-wide Mendelian randomization study, *Nat. Mental Health* 2 (9) (2024) 1062–1070.
- [32] S. Kim, G. Kim, S.H. Cho, R. Oh, J.Y. Kim, Y.-B. Lee, et al., Increased risk of incident mental disorders in adults with new-onset type 1 diabetes diagnosed after the age of 19: a nationwide cohort study, *Diabetes & Metabolism* 50 (1) (2024) 101505.
- [33] P. Klimek, A. Kautzky-Willer, A. Chmiel, I. Schiller-Frühwirth, S. Thurner, Quantification of diabetes comorbidity risks across life using nation-wide big claims data, *PLoS Comput. Biol.* 11 (4) (2015) e1004125.
- [34] M. Leone, R. Kujala-Halkola, A. Leval, A. Butwická, J. Skov, R. Zhang, et al., Genetic and environmental contribution to the Co-Occurrence of endocrine-metabolic disorders and depression: a nationwide Swedish study of siblings, *Aust. J. Pharm.* 179 (11) (2022) 824–832.
- [35] M.-C. Lu, C.-Y. Juan, M. Koo, N.-S. Lai, Higher incidence of psychiatrist-diagnosed depression in Taiwanese female school-age children and adolescents with type 1 diabetes: a nationwide, population-based, retrospective cohort study, *J. Child Adolesc. Psychopharmacol.* 27 (3) (2017) 281–284.
- [36] E. Morgan, C.C. Patterson, C.R. Cardwell, General practice - recorded depression and antidepressant use in young people with newly diagnosed type 1 diabetes: a cohort study using the clinical practice research datalink, *Diabet. Med.* 31 (2) (2014) 241–245.
- [37] M.-H. Ni, Y.-S. Yang, J.-Y. Huang, S.-C. Lo, C.-N. Huang, E. Kornelius, The association of depression and sleep disorders in patients with type 1 diabetes in Taiwan, *Medicine* 103 (29) (2024) e38969.
- [38] S. Hansen, M. Osler, S.M. Thysen, J.J. Rummessen, A. Linneberg, L.L. Kårhus, Celiac disease and risk of neuropsychiatric disorders: a nationwide cohort study, *Acta Psychiatr. Scand.* 148 (1) (2023) 60–70.
- [39] B. Buchberger, H. Huppertz, L. Krabbe, B. Lux, J.T. Mattivi, A. Siafarikas, Symptoms of depression and anxiety in youth with type 1 diabetes: a systematic review and meta-analysis, *Psychoneuroendocrinology* 70 (2016) 70–84.
- [40] N. Sharma, K. Singh, S. Senapati, Celiac disease poses significant risk in developing depression, anxiety, headache, epilepsy, panic disorder, dysthymia: a meta-analysis, *Indian J. Gastroenterol.* 40 (5) (2021) 453–462.
- [41] A. Cohn, A.M. Sofia, S.S. Kupfer, Type 1 diabetes and celiac disease: clinical overlap and new insights into disease pathogenesis, *Curr Diab Rep* 14 (8) (2014).
- [42] G.V. Flores Monar, H. Islam, S.M. Puttagunta, R. Islam, S. Kundu, S.B. Jha, et al., Association between type 1 diabetes mellitus and celiac disease: autoimmune disorders with a shared genetic background, *Cureus* 14 (3) (2022).
- [43] F. Bao, L. Yu, S. Babu, T. Wang, E.J. Hoffenberg, M. Rewers, et al., One third of HLA DQ2 homozygous patients with type 1 diabetes express celiac disease-associated transglutaminase autoantibodies, *J. Autoimmun.* 13 (1) (1999) 143–148.
- [44] A. Ivarsson, O. Hernell, H. Stenlund, L.Å. Persson, Breast-feeding protects against celiac disease, *Am. J. Clin. Nutr.* 75 (5) (2002) 914–921.
- [45] S.V. Bădescu, C. Tătaru, L. Kobylinska, E.L. Georgescu, D.M. Zăhău, A.M. Zăgrean, et al., The association between diabetes mellitus and depression, *Journal of medicine and life* 9 (2) (2016) 120–125.
- [46] D.J. Korczak, S. Pereira, K. Koulijian, A. Matejcek, A. Giacca, Type 1 diabetes mellitus and major depressive disorder: evidence for a biological link, *Diabetologia* 54 (10) (2011) 2483–2493.
- [47] K. Wang, F. Li, Y. Cui, C. Cui, Z. Cao, K. Xu, et al., The association between depression and type 1 diabetes mellitus: inflammatory cytokines as ferryman in between? *Mediat. Inflamm.* 2019 (2019) 1–11.
- [48] M.H.-E. Moawad, I. Serag, M.M. Shalaby, M.S. Aissani, M.A. Sadeq, N.I. Hendi, et al., Anxiety and depression among adults and children with celiac disease: a meta-analysis of different psychiatry scales, *Psych Res and Clin Practice* 6 (4) (2024) 124–133.
- [49] R. Alkhiari, Psychiatric and neurological manifestations of celiac disease in adults, *Cureus* 15 (3) (2023).
- [50] E. Brietzke, R.O. Cerqueira, R.B. Mansur, R.S. McIntyre, Gluten related illnesses and severe mental disorders: a comprehensive review, *Neurosci. Biobehav. Rev.* 84 (2018) 368–375.
- [51] C. Hallert Cgcs, Quality of life of adult coeliac patients treated for 10 years, *Scand. J. Gastroenterol.* 33 (9) (1998) 933–938.
- [52] C. Ciacci, C. D’Agate, A. de Rosa, C. Franzese, S. Errichiello, V. Gasperi, et al., Self-rated quality of life in celiac disease, *Dig. Dis. Sci.* 48 (11) (2003) 2216–2220.
- [53] T. Fera, B. Cascio, G. Angelini, S. Martini, C.S. Guidetti, Affective disorders and quality of life in adult coeliac disease patients on a gluten-free diet, *Eur. J. Gastroenterol. Hepatol.* 15 (12) (2003) 1287–1292.
- [54] M.S. Kim, D.K. Yon, S.W. Lee, M. Rahmati, M. Solmi, A.F. Carvalho, et al., Quantifying the impact of immortal time bias: empirical evidence from meta-analyses, *J. R. Soc. Med.* 118 (9) (2025) 293–303.
- [55] S.Y. Hwang, D.K. Yon, S.W. Lee, M.S. Kim, J.Y. Kim, L. Smith, et al., Causes for retraction in the biomedical literature: a systematic review of studies of retraction notices, *J. Kor. Med. Sci.* 38 (41) (2023) e333.