Diabetes Ther (2023) 14:1481–1502
https://doi.org/10.1007/s13300-023-01436-y

ORIGINAL RESEARCH

The Hidden Burden—Exploring Depression Risk in Patients with Diabetic Nephropathy: A Systematic Review and Meta-Analysis

Xiaoli Zhang · Liang Ma · Shumin Mu · Yonghui Yin

Received: May 9, 2023 / Accepted: June 13, 2023 / Published online: June 27, 2023

ABSTRACT

Introduction: Diabetic nephropathy is a common complication among patients with diabetes mellitus, and it has been linked to a higher risk of depression. However, the magnitude of this association remains unclear. This study aimed to systematically review and meta-analyse the risk of depression in patients with diabetic nephropathy compared to diabetes patients without nephropathy.

Methods: We conducted a systematic literature review, searching multiple databases from January 1964 to March 2023, and included randomized controlled trials, non-randomized controlled trials, and observational studies. We assessed the risk of bias using the Newcastle Ottawa scale for observational studies. The statistical analysis was performed using STATA version 14.2, and pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated. A total of 60 studies were included.

Results: The pooled OR for the risk of depression among patients with diabetic nephropathy was 1.78 (95% CI 1.56–2.04; I^2 = 83%; n = 56), indicating a significantly higher risk compared to diabetes patients without nephropathy ($p < 0.001$). Pooling the effect size across these studies showed that the pooled OR was 1.15 (95% CI 1.14–1.16; I^2 = 88%; n = 32). Subgroup analyses based on the type of diabetes and study region revealed no significant differences in the pooled estimates.

Conclusion: This study demonstrates that patients with diabetic nephropathy have a significantly higher risk of depression compared to diabetes patients without nephropathy. These findings highlight the importance of assessing and addressing the mental health of patients with diabetic nephropathy as part of their overall healthcare management.

Keywords: Depression; Diabetes mellitus; Meta-analysis; Nephropathy

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-023-01436-y.

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Key Summary Points
Why carry out the study?
The systematic review and meta-analysis comprised 60 studies with various designs
Patients with diabetic nephropathy have a 1.78 times higher risk of depression compared to those without nephropathy
What was learned from the study?
Subgroup analyses consistently demonstrated an increased risk of depression among diabetic nephropathy patients across diabetes types and study regions
The assessment and management of mental health are crucial for patients with diabetic nephropathy
Future research should focus on effective interventions and underlying mechanisms

INTRODUCTION

Diabetes mellitus, a chronic metabolic disorder characterized by hyperglycaemia, has become a global public health concern due to its rapidly increasing prevalence and substantial socioeconomic burden [1]. According to the International Diabetes Federation (IDF), an estimated 537 million adults were living with diabetes in 2021, with the number projected to rise to 643 million by 2030 [2]. Diabetes, particularly type 2 diabetes, is associated with various complications that affect multiple organ systems, including the cardiovascular, renal, neurological, and ocular systems [3]. One of the most severe complications of diabetes is diabetic nephropathy, a progressive kidney disease that develops in approximately 40% of individuals with diabetes and is the leading cause of end-stage renal disease (ESRD) worldwide [4].

Diabetic nephropathy not only significantly impacts the quality of life of affected individuals but also contributes to a higher risk of morbidity and mortality [5]. The complex interplay between diabetes and its complications extends beyond physical health, as it is increasingly recognized that the psychological well-being of individuals with diabetes is also adversely affected [6]. Depression, a common mental health disorder, has been identified as a significant comorbidity among individuals with diabetes. Studies have reported that the prevalence of depression in people with diabetes is approximately twice that of the general population [7]. The presence of depression in individuals with diabetes has been linked to poorer glycaemic control, increased risk of diabetes-related complications, reduced adherence to treatment regimens, and diminished quality of life [8].

The association between diabetes and depression is well-established; however, the relationship between depression and diabetic nephropathy remains relatively underexplored. Patients with diabetic nephropathy often face a multitude of challenges, including complex treatment regimens, dietary restrictions, and the need for dialysis or kidney transplantation. These factors, coupled with the knowledge that the condition is progressive and potentially life-threatening, may contribute to the development of depression in this population [9]. Identifying the risk of depression among patients with diabetic nephropathy is of paramount importance, as depression can further exacerbate the severity of the illness, compromise treatment adherence, and increase the risk of adverse outcomes.

Despite the growing awareness of the potential interrelationship between depression and diabetic nephropathy, the literature on this topic is scarce and heterogeneous. Existing studies examining the prevalence and risk factors for depression in patients with diabetic nephropathy have reported varying results, with some studies suggesting a higher prevalence of depression in this population than in individuals with diabetes without nephropathy, while others have found no significant differences [10–15]. This discrepancy in findings may

be attributed to differences in study designs, sample sizes, assessment tools, and patient populations. Consequently, there is a pressing need to synthesize and critically appraise the available evidence on the risk of depression in individuals with diabetic nephropathy to inform clinical practice, guide future research, and facilitate the development of targeted interventions for this vulnerable population.

In response to this knowledge gap, the present systematic review and meta-analysis aims to provide a comprehensive and robust summary of the existing literature on the risk of depression among patients with diabetic nephropathy. By pooling data from multiple studies, this review seeks to generate more precise estimates of the prevalence of depression in this population, identify potential risk factors associated with the development of depression, and explore the impact of depression on clinical outcomes in individuals with diabetic nephropathy. Ultimately, this review will contribute to a better understanding of the complex interplay between diabetes, diabetic nephropathy, and depression, thereby informing strategies for the prevention, early identification, and treatment of depression in this high-risk population.

METHODS

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. We developed our review protocol and research question based on the PECOS (population, exposure, comparisons, outcomes, study design) framework.

Inclusion Criteria

Study Design

There was no restriction in terms of study designs [randomized controlled trials (RCTs), non-randomized controlled trials, interventional studies, observational studies like case-control, cohort, and cross-sectional analytical studies were all eligible for review].

Study Participants

The review included studies on adult individuals aged $\geq$ 18 years with type 1 or type 2 diabetes. We performed a separate subgroup analysis for type 1 and type 2 diabetes to account for the different characteristics and treatment strategies associated with each.

Exposure and Comparison

Studies examining the risk of depression in patients with diabetic nephropathy compared to a control group of diabetes patients were included.

Outcomes

Primary outcomes included the prevalence or incidence of depression in patients with diabetic nephropathy.

Exclusion Criteria

We excluded review articles, editorials, commentaries, and case reports, as these do not present original research. We focused our review on adult individuals ($\geq$ 18 years old) with either type 1 or type 2 diabetes, thus excluding studies on individuals with gestational diabetes or $<$ 18 years. Additionally, studies that did not use validated assessment tools for evaluating depression were excluded.

Search Strategy

A systematic literature review was conducted by searching multiple databases, including PubMed Central, SCOPUS, EMBASE, MEDLINE, Google Scholar, and ScienceDirect. Our search strategy was developed using a combination of MeSH terms and free-text keywords related to 'diabetes mellitus', 'diabetic nephropathy', and 'depression'. Our choice of search terms was guided by the PECOS framework and by referring to similar reviews published in the literature. Appropriate Boolean operators ("AND" and "OR" and "NOT") were used between the predefined search terms. In addition to the systematic search of the databases, we also manually screened the reference lists of the identified articles and relevant systematic reviews to locate any additional studies that

could potentially be included in our meta-analysis. This 'snowballing' technique is widely employed in systematic reviews to ensure a comprehensive literature search and can help to identify studies that might have been missed during the database search. We conducted our search from the inception of each database to March 2023. For MEDLINE, this meant beginning our search from 1964 till March 2023 without any language restrictions (Supplementary text 1).

Study Selection

During the initial stage of study selection, the title, keywords, and abstracts of the studies were screened by two independent investigators. The full texts of the studies meeting the eligibility criteria were retrieved and shortlisted for the second stage of screening. At the second stage, both investigators reviewed the full texts and selected those that met the eligibility criteria. Subsequently, these studies were included in the analysis.

Extracting Data

Once the eligible full-text articles for the review were finalized, the two investigators conducted a manual data extraction process using a predefined semi-structured data collection form that had been established during the protocol stage. For each study included in our review, we extracted the following variables using a standardized data collection form: author information and year of publication, country, study design, type of diabetes, sample size, study setting, criteria or data source used for diagnosing diabetic nephropathy, tool used for assessing depression, criteria for depression, mean age of participants, duration of diabetes, prevalence of diabetic nephropathy, prevalence of depression, co-morbidities, specific interventions and/or treatments, and any other factors that could potentially influence the association between diabetic nephropathy and depression. Risk of bias assessment was also conducted for each study. The first author recorded the data, and the second author reviewed the data entry for accuracy.

Risk of Bias

While our initial search strategy was designed to include both RCTs and observational studies, the final selection for our review comprised exclusively of observational studies. As such, we used the Newcastle-Ottawa (NO) Scale to evaluate the risk of bias within these studies [17]. The NO scale assesses the risk of bias based on selection, comparability, and outcome domains. The studies were identified to have low, high, or some concerns regarding bias risk based on the assessment criteria.

Statistical Analysis

The statistical analysis for this review was conducted using STATA version 14.2. As the outcome is binary (i.e., presence of depression), the frequency of events and participants in the diabetic nephropathy and control groups were entered, and the odds ratio (OR) with 95% confidence interval (CI) was calculated. The random-effects model with inverse variance technique was used [18]. Heterogeneity was assessed using the chi-square of heterogeneity and I^2 statistic [18]. P value < 0.05 was indicative of substantial heterogeneity. Sensitivity analysis was conducted to identify the effects of individual studies on the pooled estimates. The funnel plot and Egger's test were used to assess publication bias. P value < 0.05 indicates the possibility of presence of publication bias. Subgroup and meta-regression analyses were conducted to investigate the origin of heterogeneity.

Compliance with Ethical Guidelines

Ethics Committee Approval

Ethics committee approval was not required for this systematic review as it involved the synthesis and analysis of existing data from previously published studies. A systematic review does not involve direct contact with human subjects or the collection of new data. Instead, it entails the comprehensive and systematic analysis of data that have already been collected and reported in the literature. Therefore, obtaining ethics committee approval was deemed unnecessary for this study.

This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

RESULTS

Search Results

During the initial screening, we identified 2241 citations from different databases. After eliminating duplicates, 146 full-text studies were obtained, which were then narrowed down to 142. Moreover, we discovered four articles by examining the bibliographies of the screened studies. Following the secondary screening process, we incorporated data from 60 studies that satisfied the inclusion criteria (Fig. 1) [10–15, 19–72].

Characteristics of Studies Included

Most studies were conducted in India (9 studies), followed by Saudi Arabia (8 studies), the

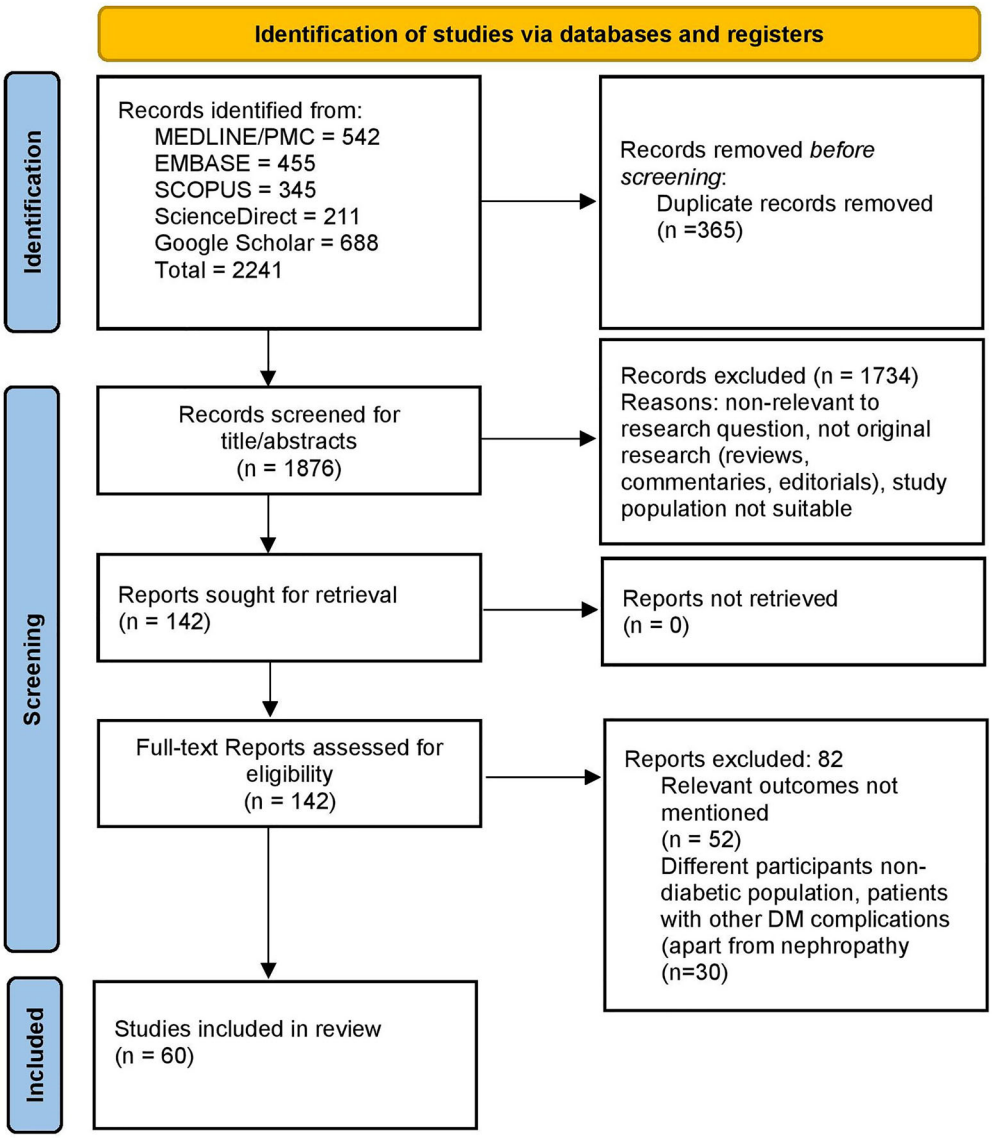

Fig. 1 Search strategy

Table 1 Characteristics of the included studies ($N = 60$)

First author and year	Country	Study design	Type of diabetes	Sample size	Study setting	Diabetic nephropathy criteria/data source	Depression tool	Depression criteria	Mean Age (in years)	Risk of bias
Abuhegazy et al. 2022	Saudi Arabia	Cross-sectional	Type 2	350	Facility	Not mentioned	PHQ-9	Score ≥ 10	61.4	High
Ahmadieh et al. 2018	Lebanon	Cross-sectional	Both type 1 and 2	436	Facility	Not mentioned	Becks depression inventory	Score ≥ 17	64.1	High
Ahmed et al. 2022	Egypt	Cross-sectional	Type 2	403	Facility	Self-reported	PHQ-9	Score ≥ 10	46	High
Ahola et al. 2010	Finland	Prospective	Type 1	1226	Facility	Macroalbuminuria or end-stage renal disease	Becks depression inventory	Score ≥ 16	45	Low
Ahola et al. 2020 (a)	4 European countries (Croatia, Finland, Lithuania, Latvia)	Cross-sectional	Type 1	1046	Facility	Macroalbuminuria or end-stage renal disease, or glomerular filtration rate below 60 ml/min per 1.73 m2	Becks depression inventory	Score ≥ 16	35	High
Ahola et al. 2020 (b)	Finland	Prospective	Type 1	3730	Facility	Baseline normal AER to microalbuminuria, macroalbuminuria or ESRD; from baseline microalbuminuria to either macroalbuminuria or ESRD; or from baseline macroalbuminuria to ESRD	ICD codes	History of diagnosed depression before/ after baseline	37	Low
Al-Ghamdi et al. 2004	Saudi Arabia	Cross-sectional	Both Type 1 and 2	200	Facility	Proteinuria or high serum urea and creatinine	Becks depression inventory	Score ≥ 17	44.1	High
Al-Ozairi et al. 2023	Kuwait	Cross-sectional	Type 2	446	Facility	Medical records	PHQ-9	Score ≥ 10	55.5	High
Al-Qusaibi et al. 2022	Saudi Arabia	Cross-sectional	Type 2	215	Facility	Self-reported	PHQ-9	Score ≥ 5	60.3	High

Table 1 continued

First author and year	Country	Study design	Type of diabetes	Sample size	Study setting	Diabetic nephropathy criteria/data source	Depression tool	Depression criteria	Mean Age (in years)	Risk of bias
AlBekairy et al. 2017	Saudi Arabia	Cross-sectional	Type 2	158	Facility	Medical records	Hospital Anxiety and Depression scale	Score $\geq$ 8	67.2	High
Albasheer et al. 2017	Saudi Arabia	Cross-sectional	Type 2	385	Facility	Not mentioned	PHQ-9	Score $\geq$ 10	47.9	High
Alhunayni et al. 2020	Saudi Arabia	Cross-sectional	Type 2	397	Facility	Medical records	PHQ-9	Score $\geq$ 5	48.8	Low
Aljohani et al. 2021	Saudi Arabia	Cross-sectional	Type 2	267	Facility	Not mentioned	PHQ-9	Not mentioned	57.9	High
Alsumry et al. 2022	Oman	Cross-sectional	Type 2	427	Facility	Medical records	PHQ-9	Score $\geq$ 10	NR	High
Aroke et al. 2020	Cameroon	Cross-sectional	Type 2	152	Facility	eGFR $<$ 90 ml/min per 1.73 m2	PHQ-9	Score $\geq$ 10	58.9	Low
Azeze et al. 2020	Ethiopia	Cross-sectional	Type 2	410	Facility	Medical records	PHQ-9	Score $\geq$ 5	47.4	High
Bai et al. 2017	Canada	Cross-sectional	Type 1	323	Community	Urine albumin to creatinine ratio (ACR) $\geq$ 2 mg/mmol) if on a (RASB) and $\geq$ 3.4 mg/mmol if otherwise, or an age-adjusted glomerular filtration rate (GFR) $<$ 60 ml/min	GDS	Score $\geq$ 5	65.5	Low
Bajaj et al. 2012	India	Case–control	Type 2	60	Facility	Raised creatinine	Becks depression inventory	Score $>$ 10	47.7	Low
Bayani et al. 2022	Iran	Cross-sectional	Type 2	400	Facility	Not mentioned	Becks depression inventory- II	Score $\geq$ 16	55.4	High
Bettegowda et al. 2019	India	Cross-sectional	Type 2	130	Facility	Urinary albumin value of $>$ 300 mg/dl	Becks depression inventory	Score $>$ 10	NR	Low
Campbell et al. 2013	USA	Cross-sectional	Type 2	5805	Community	eGFR $<$ 30 ml/min per 1.73 m2	PHQ-8	Score $\geq$ 10	NR	Low
Chen et al. 2022	Taiwan	Cohort study	Type 2	494	Community	Medical records	Center for Epidemiologic Studies Depression scale	Score $\geq$ 8	66	High

Table 1 continued

First author and year	Country	Study design	Type of diabetes	Sample size	Study setting	Diabetic nephropathy criteria/data source	Depression tool	Depression criteria	Mean Age (in years)	Risk of bias
D'Amato et al. 2016	Italy	Prospective	Both type 1 and 2	181	Facility	Macroalbuminuria > 300 mg	Becks depression inventory—II	Score ≥ 14	60.7	Low
Egila et al. 2022	Egypt	Cross-sectional	Type 2	102	Facility	Self-reported	Zung Self-Rating Depression Scale	Score ≥ 50	61	High
Gupta et al. 2020	India	Cross-sectional	Type 2	300	Facility	Medical records	PHQ-9	Score ≥ 7	55.5	High
Habtewold et al. 2016	Ethiopia	Cross-sectional	Type 2	264	Facility	Medical records	PHQ-9	Score ≥ 5	55.9	High
Han et al. 2023	China	Prospective cohort study	Type 2	2040	Facility	Microalbuminuria (30 but < 300 mg/24 h or 20 but < 200 mg/min), macroalbuminuria (300 mg/24 h or 200 lg/min), and kidney failure (received a kidney transplantation or undergoing dialysis)	Hospital Anxiety and Depression scale	Score ≥ 8	60.2	Low
Hirai et al. 2012	USA	Cross-sectional analysis of cohort study	Type 1	484	Community	History of kidney transplant, being on renal dialysis, or having gross proteinuria (defined as urine concentration of ≥ 0.30 g/l measured by reagent strip)	Center for Epidemiologic Studies Depression scale	Score ≥ 16	49.1	Low
Horiba et al. 2022	Japan	Prospective cohort study	Type 2	486	Facility	Progression to ESRD, defined as the necessity of dialysis or pre-emptive renal transplantation, and pre-ESRD death	PHQ-9	Score ≥ 5	67	Low
Ishizawa et al. 2016	Japan	Cross-sectional	Both type 1 and 2	4290	Facility	Self-reported—whether undergoing dialysis for ESRD	PHQ-9	Score ≥ 5	73	High
Karpha et al. 2022	India	Cross-sectional	Type 2	152	Facility	Self-reported	PHQ-9	Score ≥ 5	55.1	High
Katon et al. 2009	USA	Prospective	Both type 1 and 2	2759	Facility	Automated data	PHQ-9	Score ≥ 10	NR	Low

Table 1 continued

First author and year	Country	Study design	Type of diabetes	Sample size	Study setting	Diabetic nephropathy criteria/data source	Depression tool	Depression criteria	Mean Age (in years)	Risk of bias
Khan et al. 2019	Pakistan	Cross-sectional	Type 2	142	Facility	Self-reported	Hospital Anxiety and Depression scale	Score ≥ 10	57	High
Khodabandehloo et al. 2020	Iran	Cross-sectional	Type 2	100	Facility	Higher than 30–299 µg/dl albumin excretion in 24-h urine, which must be positive two or three tests at 3–6 months of interval	Hamilton 24-question questionnaire	Score more than 7	69	Low
Le Floch et al. 2013	France	Prospective observational study	Type 2	987	Facility	eGFR < 30 ml/min per 1.73 m2	GDS	Score more than 0	77	Low
Madkhali et al. 2019	Saudi Arabia	Cross-sectional	Both type 1 and 2	480	Facility	Self-reported	BDI-II	Score ≥ 20	49.9	High
Maimaitituerxun et al. 2023	China	Cross-sectional	Type 2	496	Facility	Medical records	Hospital Anxiety and Depression scale	Score ≥ 8	59.6	Low
Mut-Vitcu et al. 2016	Romania	Cross-sectional	Type 2	184	Community	Either positive markers markers of kidney damage or decreased glomerular filtration rate, both present for a duration longer than 3 months	PHQ-9	Score ≥ 10	64	Low
Novak et al. 2016	USA	Prospective cohort	Type 2	933,211	Community	eGFR levels,60 ml/min/1.73 m2 separated by 90 days	ICD-9	ICD-9 diagnostic criteria	64	Low
Pal et al. 2021	India	Cross-sectional	Type 2	290	Facility	eGFR less than 60 ml/min per 1.73 m^2	DSM-5 criteria	DSM-5 diagnostic criteria	58.2	Low
Pan et al. 2017	China	Cross-sectional	Type 2	288	Facility	Urinary albumin excretion ≥ 200 ug/min twice during hospitalization or urine protein > 0.5 g/24 h	Hamilton 24-question questionnaire	Score ≥ 8	63.2	Low
Poongothai et al. 2011	India	Cross-sectional	Type 2	847	Community	Urinary albumin excretion was ≥ 300 mg/mg creatinine	PHQ-12	Score > 4	50	Low

Table 1 continued

First author and year	Country	Study design	Type of diabetes	Sample size	Study setting	Diabetic nephropathy criteria/data source	Depression tool	Depression criteria	Mean Age (in years)	Risk of bias
Pouwer et al. 2010	The Netherlands	Cross-sectional	Both type 1 and 2	461	Facility	Medical records	Center for Epidemiologic Studies Depression scale	Score ≥ 16	61	High
Rajput et al. 2016	India	Cross-sectional	Type 2	410	Facility	Microalbuminuria and creatinine levels	Hamilton Depression Rating scale	Score ≥ 8	54.7	Low
Raval et al. 2010	India	Cross-sectional	Type 2	300	Facility	Higher than 30–299 µg/dl of albumin excretion in 24-h urine, which must be positive two or three tests or urine protein > 0.5 g/24 h	PHQ-9	Score ≥ 10	54.2	Low
Roky et al. 2023	Bangladesh	Cross-sectional	Type 2	102	Facility	Self-reported	PHQ-9	Score ≥ 5	62.5	High
Roy et al. 2012	Bangladesh	Cross-sectional	Type 2	417	Facility	Self-reported	PHQ-9	Score ≥ 10	53.2	High
Salinero-Fort et al. 2018	Spain	Cross-sectional	Type 2	2955	Facility	History of renal disease due to DM or requiring dialysis	Mini-International Neuropsychiatric Interview	As per MINI criteria	70.2	Low
Sharif et al. 2019	Pakistan	Cross-sectional	Type 2	100	Facility	Specialist evaluation	PHQ-9	Score ≥ 6	58.3	Low
Takasaki et al. 2016	Japan	Cross-sectional	Both type 1 and 2	2212	Facility	Joint Committee on Diabetic Nephropathy	PHQ-9	Score ≥ 5	60.9	Low
Tran et al. 2021	Vietnam	Cross-sectional	Type 2	216	Facility	Self-reported	PHQ-9	Score ≥ 10	64.7	Low
Van Steenbergen-Weijenburg et al. 2010	The Netherlands	Cross-sectional	Type 2	596	Facility	Medical records	PHQ-9	Score ≥ 10	63.2	High
Victoria et al. 2019	Phillipines	Cross-sectional	Type 2	476	Facility	Self-reported	PHQ-9	Score ≥ 5	58.3	High
Vidyulatha et al. 2022	India	Cross-sectional	Type 2	333	Facility	Micro (30–299 ml/min per 1.73 m2) or macroalbuminuria (> 300 ml/min per 1.73 m2)	DASS-21	Score ≥ 10	50	Low

Table 1 continued

First author and year	Country	Study design	Type of diabetes	Sample size	Study setting	Diabetic nephropathy criteria/data source	Depression tool	Depression criteria	Mean Age (in years)	Risk of bias
Wang et al. 2017	China	Cross-sectional	Type 2	210	Facility	Microalbuminuria (30 but < 300 mg/24 h or 20 but < 200 mg/min), macroalbuminuria (300 mg/24 h or 200 lg/min), and kidney failure (received a kidney transplantation or undergoing dialysis)	Hospital Anxiety and Depression scale	Score more than 11	57.7	Low
Wu et al. 2019	China	Cross-sectional	Type 2	615	Facility	Self-reported	PHQ-9 and Hamilton depression rating scale (HADS)	PHQ-9—score ≥ 5 with HADS score ≥ 8	53.8	High
Yoshida et al. 2009	Japan	Cross-sectional	Both type 1 and 2	129	Facility	Presence of persistent proteinuria	Zung Self-Rating Depression Scale	Score ≥ 40	52.7	High
Yu et al. 2013	USA	Cross-sectional	Both type 1 and 2	4082	Facility	Microalbuminuria	PHQ-9	Score ≥ 10	59.7	High
Yu et al. 2014	USA	Prospective cohort study	Both type 1 and 2	3886	Facility	Require dialysis or kidney transplant	PHQ-9	Score ≥ 10	59.3	Low
Zuberi et al. 2011	Pakistan	Cross-sectional	Type 2	286	Facility	Renal failure	Hospital Anxiety and Depression scale	Score ≥ 8	NR	Low

ESRD end-stage renal disease, *PHQ-9* Patient Health Questionnaire-9, *DASS* Depression Anxiety Stress Score, *NR* note reported

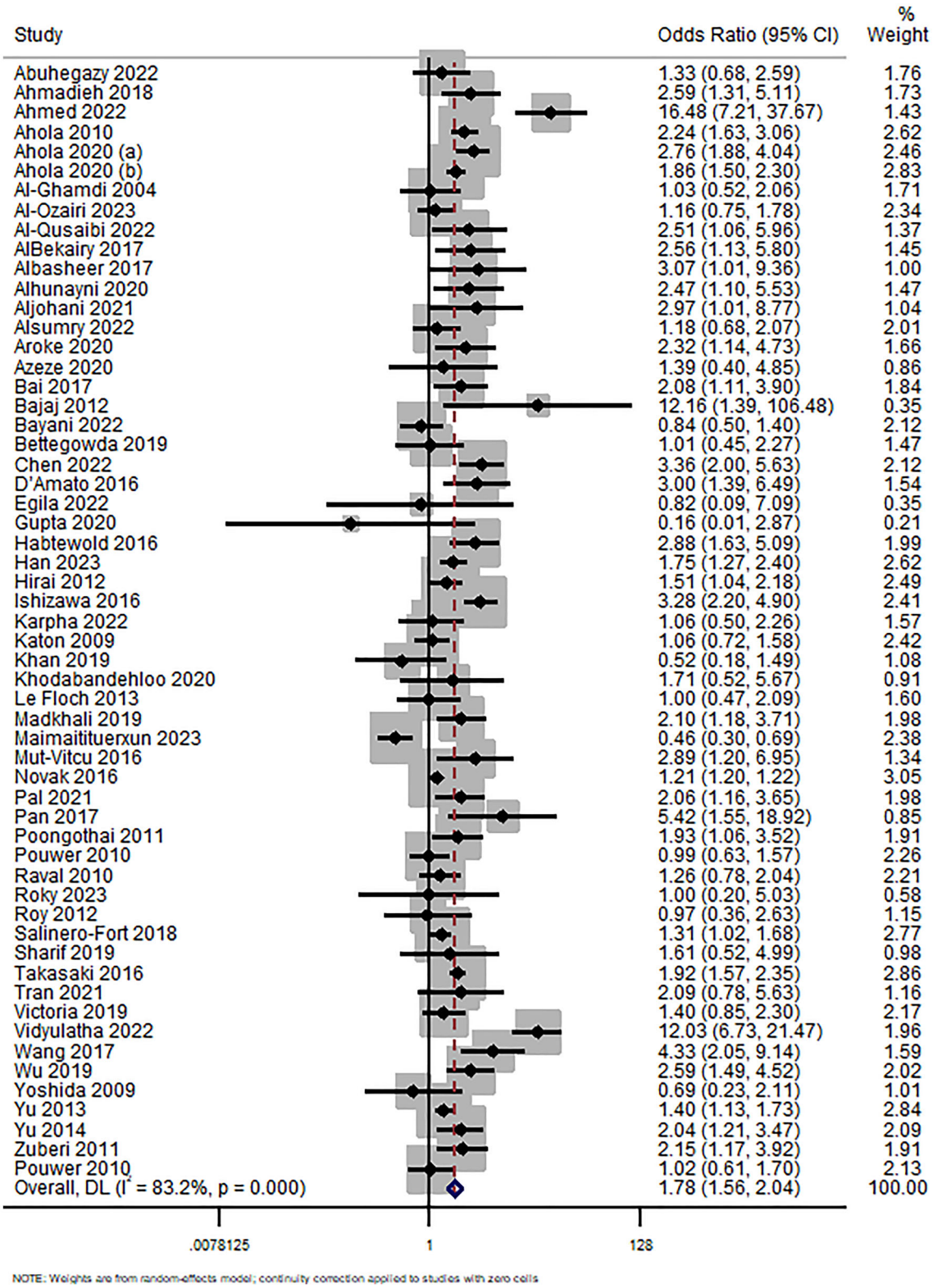

Fig. 2 Forest plot showing the risk of depression between diabetic nephropathy and non-nephropathy diabetic patients

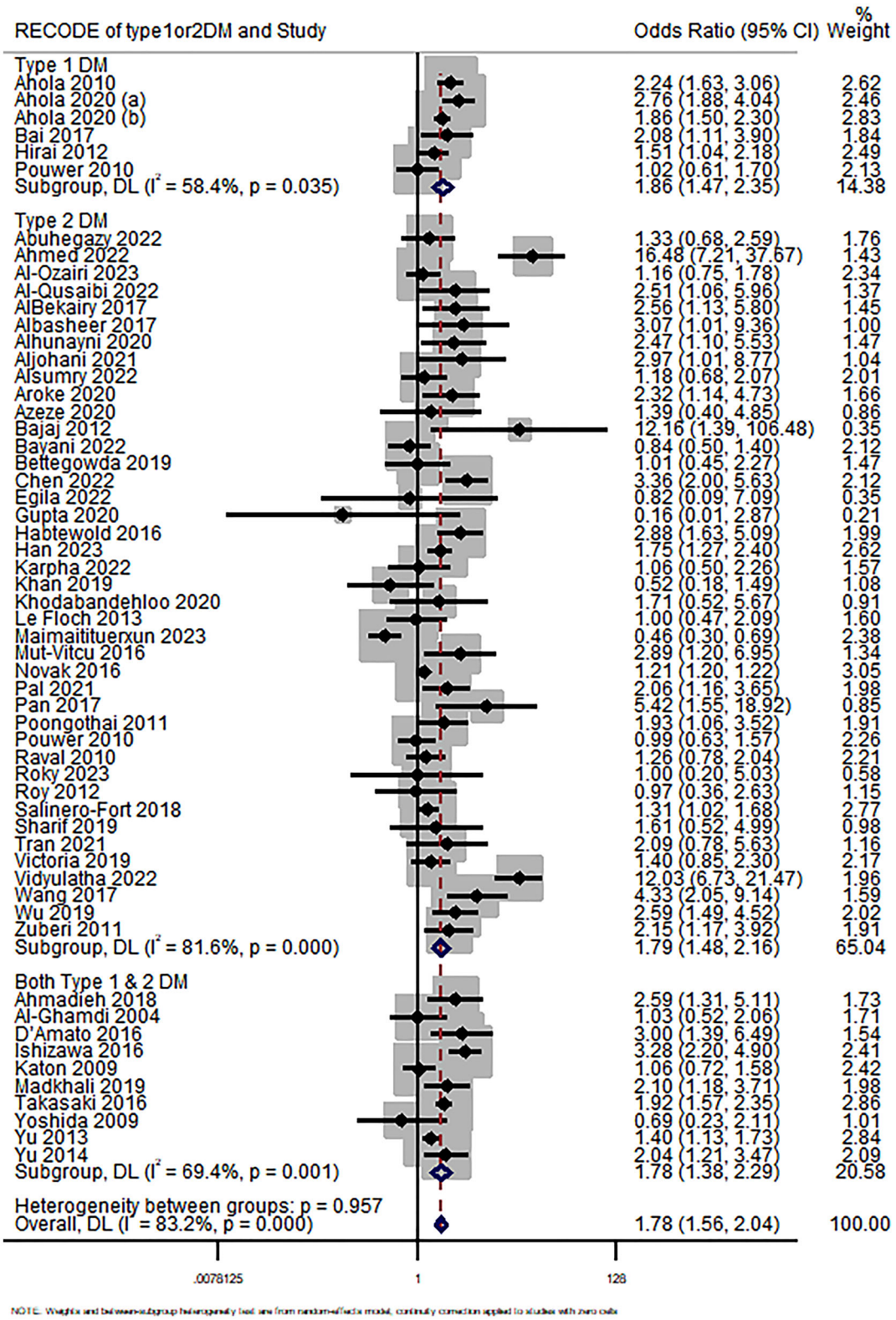

Fig. 3 Subgroup analysis based on the type of diabetes mellitus

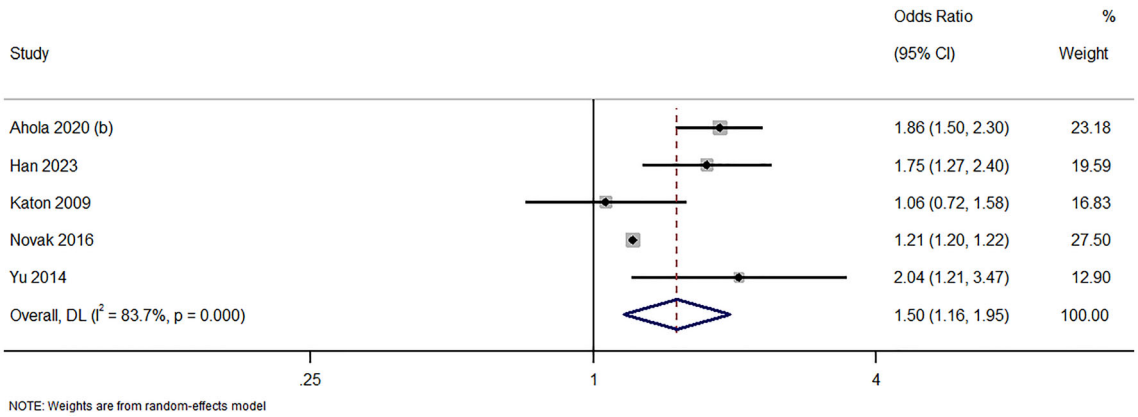

Fig. 4 Forest plot showing the longitudinal risk of depression between diabetic nephropathy and non-nephropathy diabetic patients

USA (6 studies), and China (5 studies). The majority of the studies included in our review (48 in total) employed a cross-sectional design, while the remainder were prospective cohort studies. However, in a few of these cohort studies, we only utilized the cross-sectional data, as the longitudinal data were collected with a different objective in mind. Forty-five out of 60 studies were conducted amongst type 2 diabetes mellitus patients, while rest were conducted amongst type 1 diabetes mellitus patients or both type 1 and 2. Patient Health Questionnaire (PHQ) was the most common scale used for assessing the depression. Medical records or self-reported data were the most common form of diagnosis for diabetic nephropathy. As all the studies included in our review turned out to be observational studies, we used the Newcastle-Ottawa Scale (NOS) for assessing their quality and risk of bias. There was almost equal distribution of high and low risk of bias studies (Table 1).

Risk of Depression Amongst Patients with Diabetic Nephropathy

A total of 60 studies were included in our systematic review, with some reporting data as the number of events and participants and others reporting it as odds ratios. In total, 56 studies reported the aggregate data on number of events and participants. The pooled OR was 1.78)95% CI 1.56–2.04; I^2 = 83%). This indicates that the patients with diabetic nephropathy had significantly higher odds of developing depression compared to those diabetes patients without nephropathy ($p < 0.001$) (Fig. 2). Thirty-two studies reported the risk of depression in terms of odds ratio/risk ratio. Pooling the effect size across these studies showed that the pooled OR was 1.15 (95% CI 1.14–1.16; I^2 = 88%; $p < 0.001$) (Supplementary Fig. 1).

Subgroup Analysis

Subgroup analysis was performed for studies focusing on type 1 diabetes and type 2 diabetes separately to account for the distinct characteristics and disease profiles of each population. Analysis based on type of diabetes did not reveal a significant difference in terms of pooled estimate. The pooled OR for risk of depression amongst type 1 diabetes mellitus was 1.86 (95% CI 1.47–2.35; I^2 = 59%; n = 6) and amongst type 2 diabetes mellitus was 1.78 (95% CI 1.48–2.16; I^2 = 82%; n = 41), respectively (Fig. 3). Analysis including only longitudinal study data still revealed a significant association between depression and diabetic nephropathy (pooled OR = 1.50; 95% CI 1.16–1.95; I^2 = 84%; n = 5; p = 0.002) (Fig. 4). Subgroup analysis based on study region also revealed that the effect size was almost similar across all the regions (Fig. 5). Analysis based on depression tool was not possible given the wide variation in the tool utilized by the individual studies.

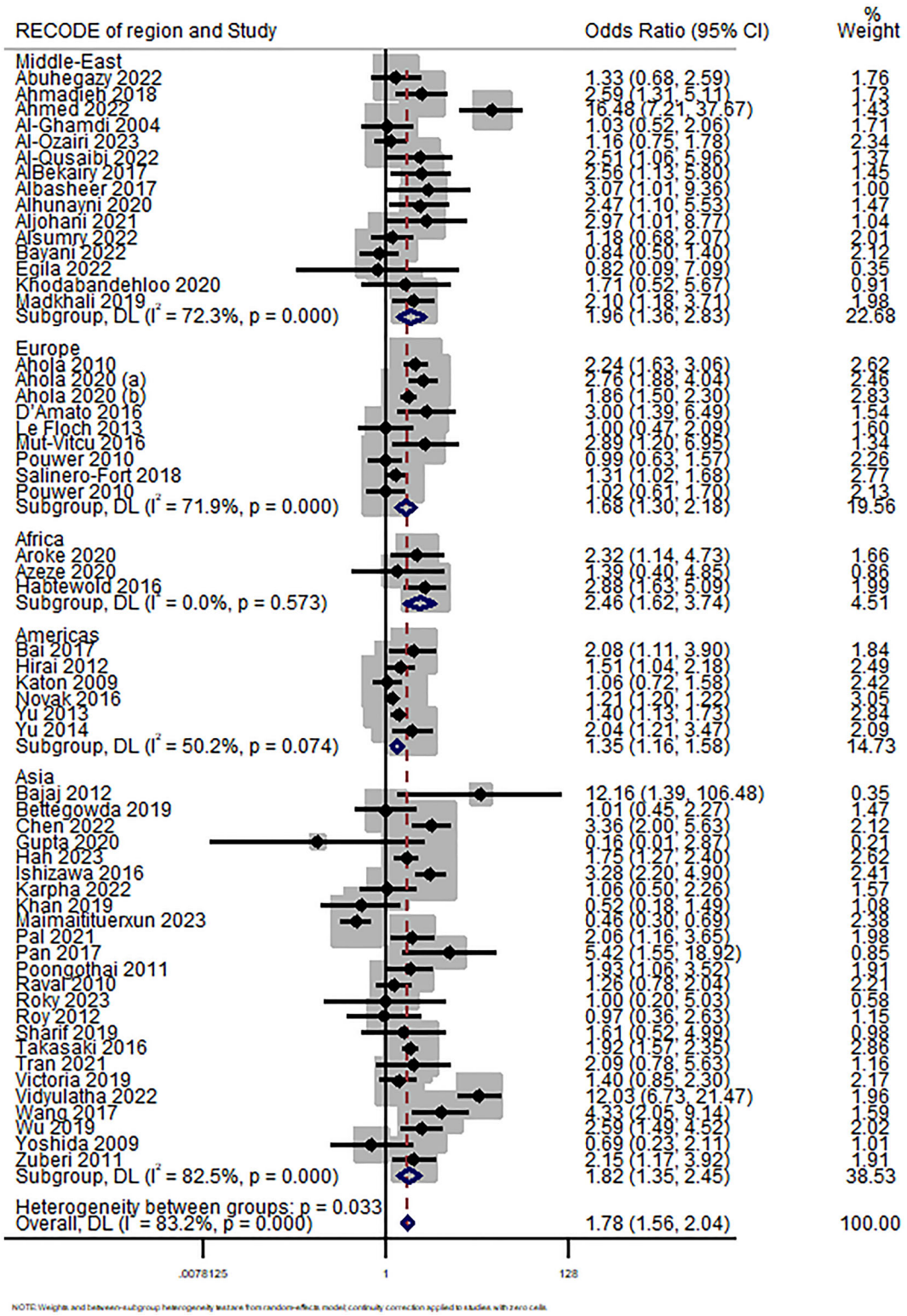

Fig. 5 Subgroup analysis based on study region

Additional Analysis

Publication bias assessment showed that the funnel plot was asymmetrical with statistically significant Egger's test ($p < 0.001$) (Supplementary Fig. 2). Meta-regression was performed using the covariates such as study design, region, setting, diagnostic tool for depression, sample size, mean age, type of diabetes mellitus patients, and quality of the studies to explore the high heterogeneity. However, none of these factors were found to be a source of heterogeneity. Sensitivity analysis did not show any difference in terms of effect size or direction for any of the above outcomes. This suggests that there were no single-study effects with respect to any outcomes (Supplementary Fig. 3).

DISCUSSION

This systematic review and meta-analysis aimed to evaluate the risk of depression in patients with diabetic nephropathy. By incorporating data from 60 studies, the results revealed a significantly increased risk of depression in patients with diabetic nephropathy compared to diabetes patients without nephropathy. This finding highlights the importance of addressing mental health concerns in patients with diabetic nephropathy, given the potential impact on overall well-being and treatment adherence.

Our study found that the odds of developing depression in patients with diabetic nephropathy were 1.78 times higher than in those without nephropathy. The increased risk persisted across different types of diabetes (type 1 and type 2), study designs, and regions. The association remained significant even when considering only longitudinal studies, suggesting a temporal relationship between diabetic nephropathy and depression risk. These findings are consistent with previous literature reporting a higher prevalence of depression among individuals with complications from diabetes, including nephropathy, retinopathy, and neuropathy [73–75]. However, the wide variation in depression assessment tools utilized by the individual studies precluded a meaningful subgroup analysis based on the diagnostic methods.

Our findings call for additional research to explore the underlying biological mechanisms that may contribute to the increased risk of depression in patients with diabetic nephropathy. Potential mechanisms could include the role of inflammatory processes, oxidative stress, and neuroendocrine dysregulation in the development of both diabetes complications and depression [76]. A better understanding of these mechanisms may pave the way for novel therapeutic targets and strategies to address depression in the context of diabetic nephropathy.

Nonetheless, the observed association between diabetic nephropathy and depression may be explained by various factors. Patients with diabetic nephropathy often experience physical discomfort, fatigue, and sleep disturbances, which are known to contribute to depressive symptoms [77]. Additionally, the burden of managing a complex chronic illness such as diabetic nephropathy, including the need for strict dietary and medication regimens, frequent medical appointments, and possible dialysis, may lead to feelings of helplessness and hopelessness, which are hallmarks of depression [78]. Moreover, the bidirectional relationship between diabetes and depression has been previously reported [73], suggesting that the presence of depression may exacerbate diabetic nephropathy, thus creating a vicious cycle.

The high heterogeneity observed in our meta-analysis can be attributed to the diverse methodologies and tools employed in the included studies. Differences in diagnostic criteria for depression, study settings, and patient populations might have contributed to the variation in the reported effect sizes. However, the high heterogeneity observed in our meta-analysis warrants further investigation, as we were unable to identify any specific factors contributing to the observed variability through meta-regression. Nonetheless, the overall effect estimate remained significant and robust in sensitivity analyses, indicating that our findings are unlikely to be affected by single-study effects.

Our study has several implications for clinical practice and future research. First, healthcare providers should be aware of the increased

risk of depression among patients with diabetic nephropathy and should consider incorporating routine mental health screening into the management of these patients. Timely identification and treatment of depression can improve patients' quality of life and may enhance adherence to diabetic care, potentially reducing the risk of further complications. Second, multidisciplinary care teams, including mental health professionals, should be involved in the management of patients with diabetic nephropathy to ensure a comprehensive approach to care. Third, future research should investigate the effectiveness of targeted interventions aimed at reducing depression risk in patients with diabetic nephropathy, such as psychoeducation, cognitive-behavioral therapy, and psychopharmacological treatments.

Furthermore, our study underscores the need for increased awareness and education among patients with diabetic nephropathy regarding the potential risks associated with depression. Patient empowerment through self-management support programmes and psychoeducation can help individuals better understand their condition, cope with emotional challenges, and actively engage in their treatment plan. Involving family members and caregivers in the education process may also help create a supportive environment that fosters emotional well-being.

There are several notable strengths of our review that contribute to the robustness and reliability of our findings. We employed a rigorous and comprehensive search strategy across multiple databases to ensure a broad representation of the available literature, which minimized the risk of missing relevant studies. The inclusion of studies from various countries and settings provides a global perspective on the association between diabetic nephropathy and depression risk. The inclusion of data from 60 studies with a large total number of participants increases the statistical power of our analysis and improves the precision of our effect estimates, lending more confidence to our conclusions. We conducted several subgroup analyses based on factors such as type of diabetes, study design, and geographic region, which allowed us to explore potential sources of heterogeneity and examine the robustness of our findings across various contexts. Sensitivity analyses further confirmed the stability of our results, indicating that no single study had an undue influence on the pooled effect estimates. We systematically evaluated the risk of bias in the included studies using established tools for different study designs, providing a transparent appraisal of the quality of the evidence contributing to our review. These strengths bolster the credibility of our review findings and their implications for clinical practice and future research.

There are some limitations to our study. First, the majority of included studies were cross-sectional in design, limiting our ability to infer causality. Second, the high heterogeneity across studies may have affected the precision of our effect estimates. Third, potential publication bias was detected, which might have led to an overestimation of the association between diabetic nephropathy and depression risk. Fourth, inability to adjust for potential confounding variables in our meta-analysis, such as disease duration, socioeconomic status, and the presence of other diabetes-related complications, and stage of diabetic nephropathy, all of which could independently influence the risk of depression. Future research should aim to investigate the association between depression and different stages of chronic kidney disease (CKD) more comprehensively, considering the potential impact of treatment regimens, lifestyle modifications, and other factors specific to each CKD stage. Additionally, exploring the underlying reasons for depression in individuals with early-stage CKD, beyond the direct influence of diabetic nephropathy, would provide valuable insights into the multifaceted nature of depression in this population. Finally, inclusion of a diverse range of study designs might introduce methodological heterogeneity. However, this approach was adopted to capture the broadest possible range of available evidence linking diabetic nephropathy and depression.

CONCLUSION

Our systematic review and meta-analysis demonstrate a significant increase in the risk of depression among patients with diabetic nephropathy. Given the potential impact of depression on patients' quality of life and treatment adherence, healthcare providers should be vigilant in identifying and addressing mental health concerns in this population. Comprehensive, multidisciplinary care, including mental health support, is essential for managing both the physical and psychological aspects of diabetic nephropathy. Future research should focus on developing and evaluating targeted interventions to reduce depression risk and improve overall well-being in patients with diabetic nephropathy.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

Author Contributions. Xiaoli Zhang: Acquisition, analysis, and interpretation of data, Drafting the manuscript, Critical revision of the manuscript for important intellectual content, Final approval of the version to be published. Liang Ma: Acquisition, analysis, and interpretation of data, Drafting the manuscript, Critical revision of the manuscript for important intellectual content, Final approval of the version to be published. Shumin Mou: Acquisition, analysis, and interpretation of data, Drafting the manuscript, Critical revision of the manuscript for important intellectual content, Final approval of the version to be published. Yonghui Yin: Conception and design of the study, Acquisition, analysis, and interpretation of data, Drafting the manuscript, Critical revision of the manuscript for important intellectual content, Final approval of the version to be published.

Disclosures. Xiaoli Zhang, Liang Ma, Shumin Mou, Yonghui Yin has nothing to disclose.

Compliance with Ethical Guidelines. Ethics committee approval was not required for this systematic review as it involved the synthesis and analysis of existing data from previously published studies. A systematic review does not involve direct contact with human subjects or the collection of new data. Instead, it entails the comprehensive and systematic analysis of data that have already been collected and reported in the literature. Therefore, obtaining ethics committee approval was deemed unnecessary for this study. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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