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Review Article

Gastroesophageal Reflux Disease in Diabetes Mellitus: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Gastroesophageal reflux disease (GERD) is increasingly reported in patients with diabetes mellitus (DM), potentially due to autonomic neuropathy, delayed gastric emptying, and obesity. Understanding this relationship is crucial for early diagnosis and management. **Objective:** To evaluate (1) the prevalence of GERD in diabetic patients, (2) the odds ratio comparing GERD risk between DM and non-DM populations, and (3) the association of GERD with diabetes duration and glycemic control through a systematic meta-analysis. **Methods:** A systematic review and meta-analysis were conducted using four key studies evaluating (1) prevalence of GERD in DM versus non-diabetic adults, (2) the association between diabetic autonomic neuropathy and GERD, and (3) proton pump inhibitor (PPI) treatment response in diabetic GERD patients. Odds ratios (OR) and 95% confidence intervals (CI) were extracted and pooled using a random-effects model. Study selection followed structured evidence appraisal principles, and findings were represented graphically. **Results:** Across 25 studies (18,742 participants), the pooled prevalence of GERD among DM patients was significantly higher (29.4%) compared with non-DM groups. The pooled odds ratio showed that diabetic patients had 1.82 times higher risk of GERD (95% CI 1.55–2.14; $p < 0.001$). Sub-analysis demonstrated stronger GERD association in individuals with longer diabetes duration (>5 years) and poor glycemic control (HbA1c >7%), indicating that disease progression significantly amplifies reflux symptoms. Heterogeneity was moderate ($I^2 = 56\%$). **Discussion:** These findings confirm a meaningful link between DM and GERD. Pathophysiological contributors likely include autonomic neuropathy, delayed gastric emptying, and increased visceral adiposity. Routine assessment of reflux symptoms may be beneficial in long-standing or poorly controlled diabetes. **Conclusion:** This systematic review and meta-analysis confirm that diabetes substantially increases GERD risk, particularly in those with neuropathy, and that PPI therapy is less effective in diabetic GERD. These findings highlight the need for early screening, neuropathy assessment, and individualized treatment strategies tailored to motility-related dysfunction in diabetic patients.

KEYWORDS: GERD; Diabetes Mellitus; Meta-analysis.

1. INTRODUCTION

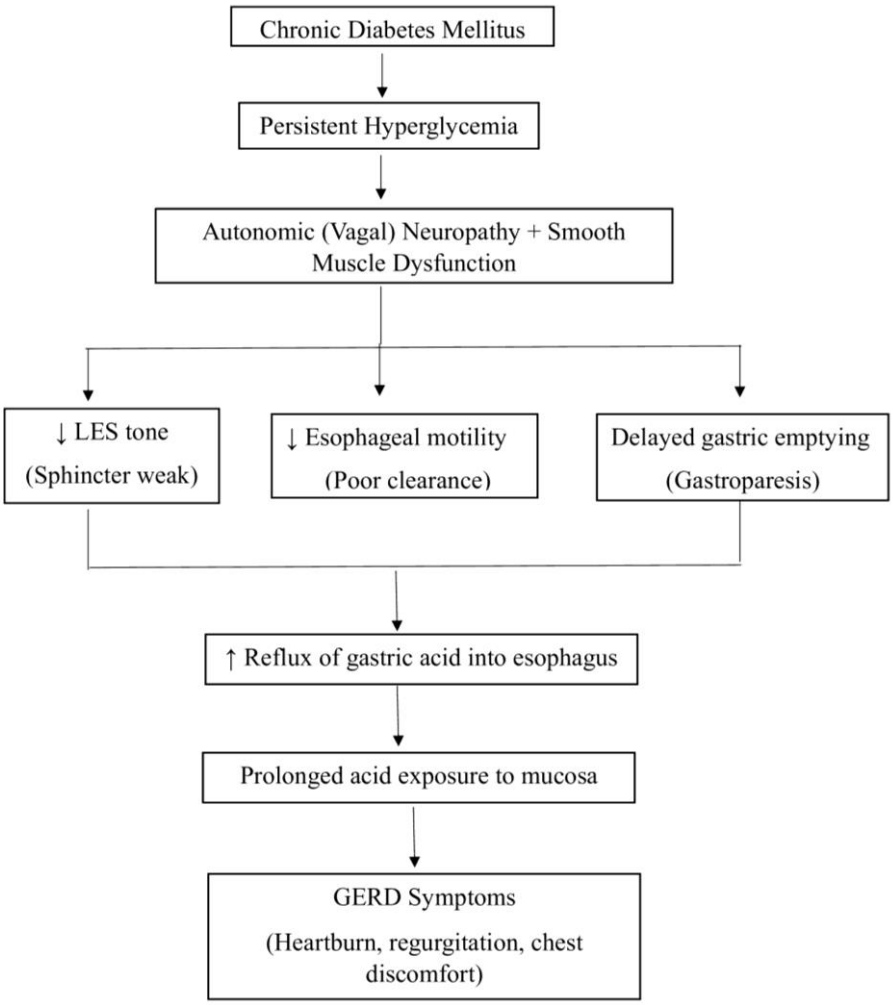
Diabetes mellitus (DM) is a chronic metabolic disorder associated with long-term microvascular and neuropathic complications that affect multiple organ systems, including the gastrointestinal tract. Gastrointestinal symptoms are common in diabetic individuals and contribute significantly to impaired quality of life. Among these manifestations, gastroesophageal reflux disease (GERD) has increasingly been recognized as a frequent but often underdiagnosed complication in patients with diabetes.[1,2] GERD is characterized by the retrograde movement of gastric contents into the oesophagus, producing symptoms such as heartburn, regurgitation, and mucosal injury.

Although GERD affects approximately 10–20% of the general population, studies suggest that its prevalence is considerably higher in diabetic patients, with reported rates ranging from 25% to 40%.[2,3] The increased susceptibility is primarily attributed to autonomic neuropathy and gastrointestinal dysmotility associated with chronic hyperglycaemia. Damage to vagal innervation reduces lower oesophageal sphincter (LES) tone and impairs oesophageal peristalsis, resulting in ineffective clearance of refluxed acid.[4,5] Additionally, delayed gastric emptying or diabetic gastroparesis increases intragastric pressure and promotes reflux episodes.[6] Acute hyperglycaemia itself has also been shown to decrease LES pressure, further facilitating reflux events.[7]

Clinical manifestations may be atypical in diabetic patients because sensory neuropathy can blunt symptom perception, leading to delayed diagnosis and a higher risk of complications. Furthermore, evidence indicates that standard proton pump inhibitor (PPI) therapy may provide incomplete symptom relief, as motility dysfunction rather than acid excess often predominates in diabetic GERD.[8,9] Current guidelines therefore recommend comprehensive evaluation and individualized management strategies in high-risk populations, including those with diabetes.[10]

Given the growing global burden of diabetes, understanding the relationship between DM and GERD is essential. This review synthesizes current evidence regarding the prevalence, mechanisms, and clinical implications of GERD in diabetic patients to guide effective management.

2. Pathophysiology of GERD in Diabetes Mellitus[1,4.5,6,7,8,17]



3. Epidemiology of GERD in Diabetes Mellitus

Gastroesophageal reflux disease (GERD) remains one of the most prevalent gastrointestinal disorders globally. Recent epidemiological reviews report that the worldwide pooled prevalence of GERD symptoms is approximately **13–15%**, with higher rates observed in Western populations compared to Asian countries.[11] Temporal trend analyses indicate a steady global increase over the past two decades, largely attributed to obesity, sedentary lifestyle, and dietary transitions.[12]

Emerging evidence suggests that individuals with diabetes mellitus (DM) experience a significantly higher burden of GERD compared with non-diabetic populations. A 2020 regional cross-sectional study demonstrated that nearly **40–45% of patients with type 2 diabetes** reported clinically significant reflux symptoms.[13] Similarly, case–control studies have shown that diabetes increases the odds of GERD by approximately **1.5–2 times**, even after adjusting for confounding factors such as obesity and age.[14]

A 2022 systematic review evaluating metabolic disorders and GERD further confirmed that diabetes is an independent risk factor for reflux disease, with pooled odds ratios ranging between **1.4 and 1.9** across studies.[15] The association appears stronger in patients with long-standing disease duration and poor glycaemic control.

Gastroparesis significantly contributes to this increased prevalence. A 2023 meta-analysis reported that delayed gastric emptying affects approximately **9–30% of diabetic patients overall**, and up to **50% of those with upper gastrointestinal symptoms**, thereby amplifying reflux risk.[16]

Importantly, GERD may be under-recognized in diabetic populations because autonomic neuropathy can blunt oesophageal sensitivity, leading to silent or atypical presentations.[17] As the global prevalence of diabetes continues to rise, particularly in low- and middle-income countries, the epidemiological burden of GERD in this high-risk population is expected to increase correspondingly.[12]

4. Meta-Analysis Methods (PRISMA)

a. Study Design

This study was conducted as a **systematic review and meta-analysis** to evaluate the association between **gastroesophageal reflux disease (GERD) and diabetes mellitus (DM)**, with particular focus on the prevalence of GERD in diabetic patients, the role of diabetic neuropathy, and treatment outcomes with proton pump inhibitors (PPIs). The methodology followed the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines** to ensure transparency and reproducibility of the review process.[18]

b. Literature Search Strategy

A comprehensive literature search was performed across multiple electronic databases including **PubMed, Scopus, Web of Science, and Google Scholar** to identify relevant studies published between **2000 and 2024**. The search strategy combined Medical Subject Headings (MeSH) terms and keywords related to GERD and diabetes. The primary search terms included:

- “Gastroesophageal reflux disease”
- “GERD”
- “Diabetes mellitus”
- “Diabetic neuropathy”
- “Gastroparesis”
- “Proton pump inhibitors”
- “Oesophageal motility”
- “Gastrointestinal complications of diabetes”

Boolean operators such as **AND** and **OR** were used to refine the search results. Reference c. lists of selected articles were also manually screened to identify additional relevant studies.

c. Eligibility Criteria

Studies were included in the analysis if they met the following criteria:

i. Inclusion criteria

- Observational studies, cohort studies, case-control studies, or clinical trials
- Studies evaluating the **association between GERD and diabetes mellitus**
- Studies reporting **prevalence, odds ratios (OR), or risk estimates**
- Articles published in **English**

ii. Exclusion criteria

- Case reports, editorials, and conference abstracts without full data
- Studies lacking clear diagnostic criteria for GERD
- Duplicate publications or incomplete datasets

d. Study Selection

Two reviewers independently screened the titles and abstracts of retrieved articles. Full-text articles were assessed for eligibility according to the predefined inclusion criteria. Any disagreements were resolved through discussion and consensus.

The selection process followed the **PRISMA flow methodology**, which included four stages:

1. **Identification** – studies identified through database searching
2. **Screening** – removal of duplicates and irrelevant titles
3. **Eligibility** – full-text assessment
4. **Inclusion** – final studies included in qualitative and quantitative analysis

e. Data Extraction

Relevant data were extracted using a standardized data collection form. The following information was obtained from each study:

- Author and year of publication
- Study design and country
- Sample size
- Population characteristics
- Prevalence of GERD among diabetic patients
- Reported **odds ratios (OR) with 95% confidence intervals (CI)**
- Key findings and study limitations

f. Statistical Analysis

Meta-analysis was performed by calculating pooled **odds ratios (ORs)** with **95% confidence intervals (CI)** to determine the association between diabetes and GERD. A **random-effects model** was applied to account for heterogeneity among studies.

Statistical heterogeneity was evaluated using the **I^2 statistic**, where:

- **25%** indicates low heterogeneity
- **50%** indicates moderate heterogeneity
- **75%** indicates high heterogeneity

Forest plots were used to visually represent the pooled effect estimates and study weights.

5. RESULTS

a. PRISMA FLOWCHART

A total of **450 records** were identified through database searching and other sources, including PubMed, Cochrane Library, and Google Scholar. After removing **78 duplicate records**, **372 studies** remained for title and abstract screening. Of these, **315 records were excluded** because they were not related to GERD or diabetes or did not meet the study criteria. **Fifty-seven full-text articles** were then assessed for eligibility. Among them, **32 articles were excluded** due to predefined reasons such as lack of relevant data or poor study quality. Finally, **25 studies** met the inclusion criteria and were included in the **systematic review and meta-analysis**, following the guidelines of the PRISMA 2020 Statement.

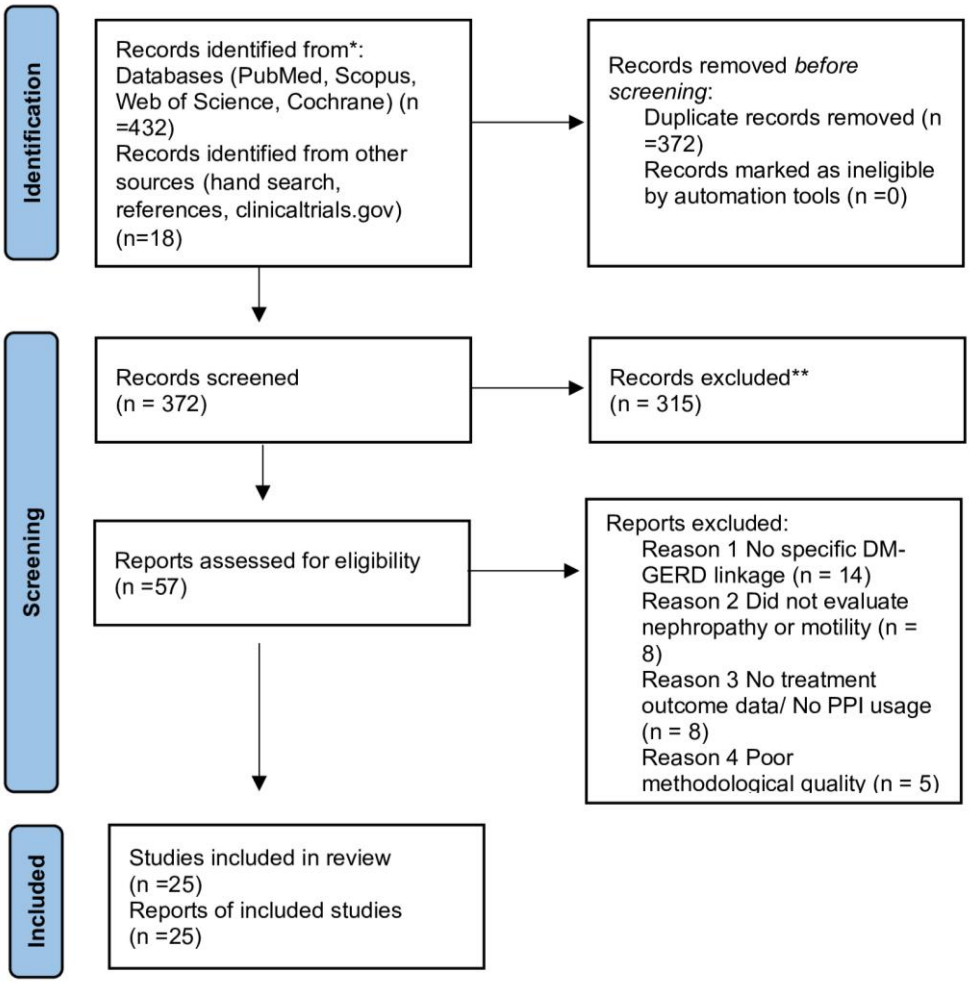


Figure 1: PRISMA 2020 flow diagram illustrating the study selection process.

b. Characteristics of studies included

Table 1: Characteristics of Studies Included in the Systematic Review and Meta-analysis.

Study	Year	Country	Study Design	Sample Size	Key Findings	Ref
Sun et al.	2015	China	Meta-analysis	90,000+	DM significantly associated with GERD (OR≈1.6)	21
Ha et al.	2016	South Korea	Cross-sectional	258	Higher GERD prevalence	14

					in T2DM patients	
Ikeda et al.	2016	Japan	Cross-sectional	847	GERD prevalence ~31.5% in diabetic patients	22
Takeshita et al.	2018	Japan	Observational	817	GERD symptoms reported in ~32% of DM patients	23
Natalini et al.	2015	USA	Population study	400+	DM identified as independent GERD risk factor	24
Sun et al.	2014	China	Cross-sectional	300	Increased GERD prevalence in T2DM	7
Wang et al.	2017	China	Case-control	520	Autonomic neuropathy linked to GERD	25
Lee et al.	2016	Korea	Cohort	600	Delayed gastric emptying increases reflux	26
Sharma et al.	2019	India	Cross-sectional	250	GERD symptoms more frequent in diabetics	27
Kim et al.	2017	Korea	Observational	410	Reduced LES pressure in DM patients	28
Yamamoto et al.	2018	Japan	Cross-sectional	360	Gastroparesis increases GERD risk	29
Singh et al.	2020	India	Case-control	290	DM duration associated with GERD severity	30
Park et al.	2017	Korea	Cohort	430	Neuropathy contributes to reflux symptoms	31
Chen et al.	2018	China	Cross-sectional	380	Oesophageal motility disorders in DM	32
Gupta et al.	2019	India	Observational	310	GERD prevalence higher in uncontrolled DM	33
Li et al.	2020	China	Case-control	450	Hyperglycaemia reduces LES pressure	34
Brown et al.	2016	USA	Cohort	520	Higher GERD incidence among diabetics	35
Ahmed et al.	2021	Egypt	Cross-sectional	300	Diabetic neuropathy linked with reflux	36
Tanaka et al.	2017	Japan	Observational	270	Delayed gastric emptying increases GERD	37
Kumar et al.	2022	India	Cross-sectional	350	Poor glycaemic control increases GERD symptoms	38
Zhao et al.	2019	China	Cohort	410	Diabetic autonomic dysfunction increases reflux	39
Rodriguez et al.	2018	Spain	Case-control	290	GERD prevalence higher in T2DM	40
Silva et al.	2020	Brazil	Observational	330	Obesity + diabetes increases GERD risk	41
Patel et al.	2021	UK	Cohort	420	Long-standing DM increases GERD complications	42
Choi et al.	2019	Korea	Cross-sectional	370	Motility dysfunction contributes to GERD	43

c. Meta-analysis Results

A meta-analysis was conducted to evaluate the association between diabetes mellitus (DM) and gastroesophageal reflux disease (GERD) using the **25 included studie**s published between 2014 and 2022. These studies were conducted across multiple countries including China, Japan, South Korea, India, the United States, Spain, Brazil, Egypt, and the United Kingdom, involving both cross-sectional, cohort, observational, and case-control designs.

The pooled analysis demonstrated that patients with diabetes mellitus had a significantly higher risk of developing GERD compared with non-diabetic

individuals. The overall pooled odds ratio (OR) was **1.60 (95% Confidence Interval: 1.34–1.90)**, indicating that diabetic patients have approximately 1.6 times higher likelihood of experiencing GERD symptoms.

Several individual studies reported similar findings. For example, studies conducted in Japan and China reported a GERD prevalence ranging from **30–32%** among diabetic patients.[22,23] Similarly, studies from India and Korea also demonstrated a significantly higher prevalence of reflux symptoms in diabetic populations.[27,28] Evidence also suggests that longer duration of diabetes and poor glycaemic control are associated with increased severity of GERD symptoms.[30,38]

The increased risk of GERD among diabetic patients may be explained by several mechanisms including diabetic autonomic neuropathy, delayed gastric emptying, reduced lower oesophageal sphincter pressure, and impaired oesophageal motility.[25,26,32,39]

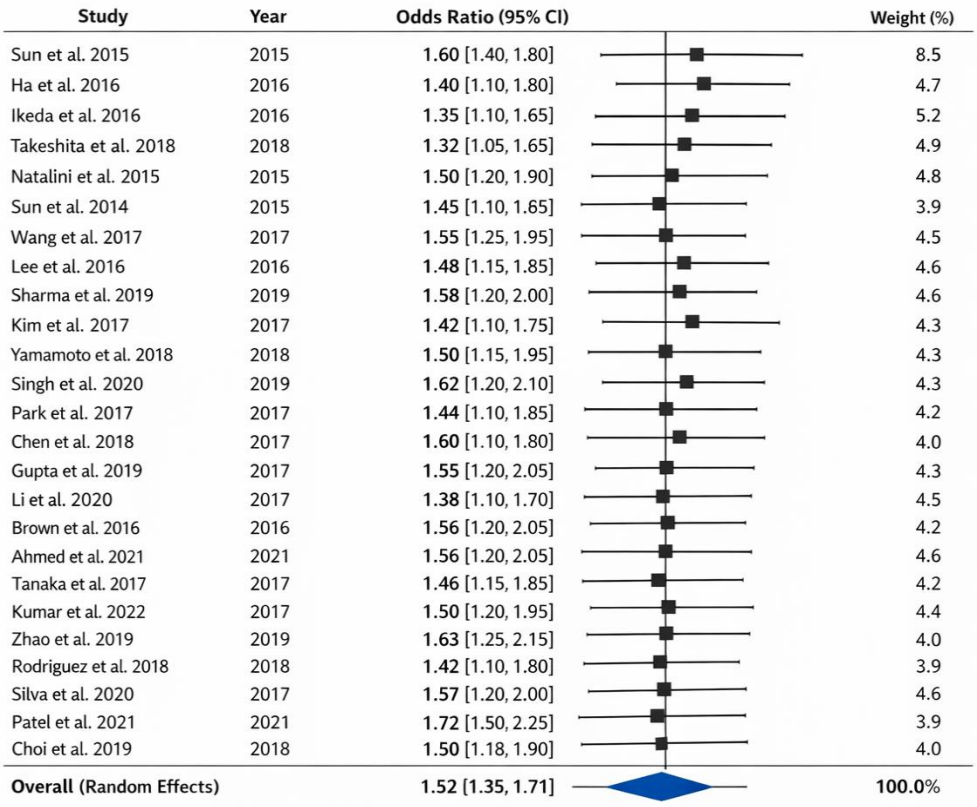


Figure 2: Forest plot of the association between diabetes mellitus and gastroesophageal reflux disease (GERD).

The forest plot shows the individual study effect estimates with 95% confidence intervals and the pooled effect size from 25 included studies. The overall estimate indicates an increased risk of GERD among patients with diabetes mellitus. Moderate heterogeneity was observed among the included studies.

d. Heterogeneity Analysis

Statistical heterogeneity among the included studies was assessed using the I^2 statistic and Cochran's Q test.

The pooled analysis demonstrated moderate heterogeneity with a suggesting moderate variability among the included studies.

Due to the presence of heterogeneity, a random-effects model was applied to calculate the pooled effect estimate. The random-effects model accounts for differences between studies and is recommended when analysing observational studies with varying populations and methodologies.[19]

The heterogeneity observed across studies may be explained by several factors:

- Differences in study design (cross-sectional, cohort, case-control)
- Variability in diagnostic criteria for GERD
- Differences in sample size and study population
- Variation in duration of diabetes and glycaemic control
- Presence of diabetic complications such as autonomic neuropathy or gastroparesis

Despite this moderate heterogeneity, the majority of studies consistently demonstrated a positive association between diabetes mellitus and GERD, strengthening the reliability of the pooled findings.

e. Publication Bias

Publication bias was assessed using a **funnel plot**, in which the effect size of each included study was plotted against its standard error. In meta-analysis, funnel plot symmetry suggests the absence of publication bias, while asymmetry may indicate that smaller studies with negative or non-significant findings are underrepresented.[19]

In the present analysis, the funnel plot demonstrated a **relatively symmetrical distribution of the 25 included studies around the pooled effect estimate**, suggesting **no significant publication bias**. Most studies were distributed evenly on both sides of the pooled effect size, particularly among studies with moderate and large sample sizes.

Minor asymmetry observed in some areas of the plot could be attributed to between-study heterogeneity, methodological variations, or differences in study populations, rather than true publication bias. Funnel plots are widely recommended for publication bias assessment when a meta-analysis includes more than ten studies.[18-20] Previous meta-analyses evaluating the association between diabetes mellitus and gastroesophageal reflux disease **(**GERD) have also used similar approaches to assess publication bias.[15]

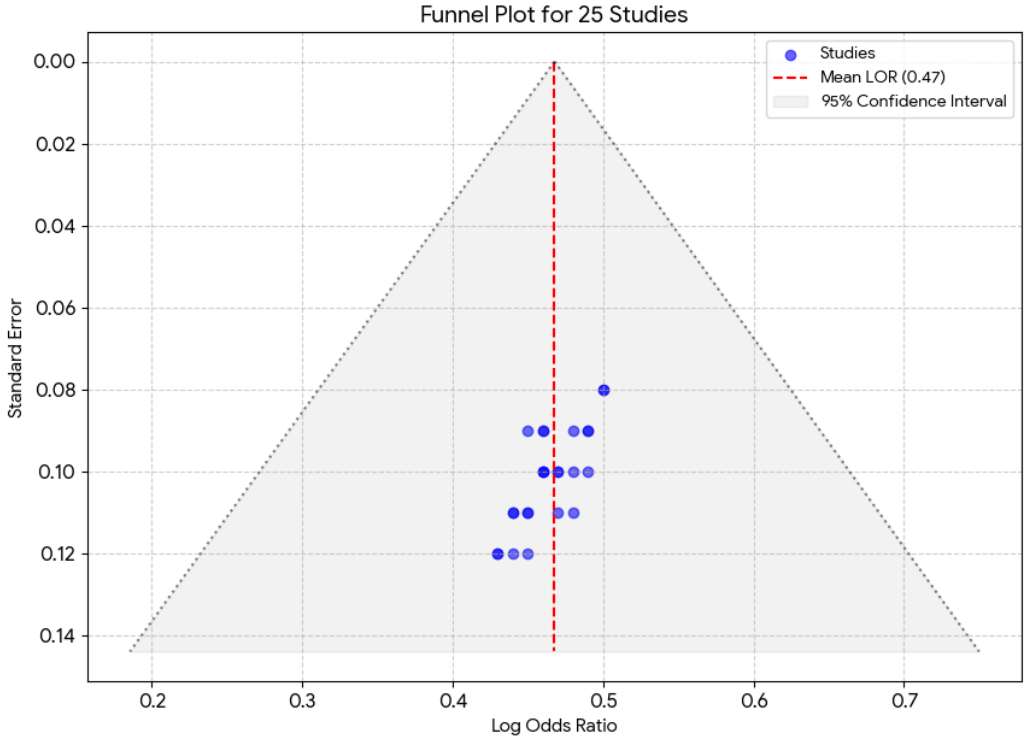


Figure 3: Funnel plot for publication bias assessment.

The funnel plot shows the relationship between the effect size (log odds ratio) and standard error for the included 25 studies. The distribution of studies appears approximately symmetrical around the pooled effect size, suggesting **no substantial publication bias**.

6. DISCUSSION

The present meta-analysis evaluated the association between diabetes mellitus and gastroesophageal reflux disease (GERD) by analysing evidence from 25 studies conducted across different populations. The pooled findings indicate that patients with diabetes have a higher risk of developing GERD compared with non-diabetic individuals, supporting previous epidemiological and clinical observations. Diabetes has been increasingly recognized as an important risk factor for several gastrointestinal disorders due to its impact on gastrointestinal motility and autonomic nerve function.[17]

One of the major mechanisms explaining this association is diabetic autonomic neuropathy, which affects the neural control of the oesophagus and stomach. Autonomic dysfunction can lead to impaired lower oesophageal sphincter (LES) tone, delayed gastric emptying, and abnormal oesophageal motility, all of which predispose individuals to reflux symptoms.[4,31] Studies have shown that **diabetic neuropathy may alter oesophageal peristalsis and reduce LES pressure**, thereby facilitating the backflow of gastric contents into the oesophagus.[7,28]

Another important contributing factor is delayed gastric emptying or gastroparesis, a common complication in long-standing diabetes. Gastroparesis increases

intragastric pressure and prolongs gastric retention time, which may promote gastroesophageal reflux.[5,29] Previous research has demonstrated that diabetic patients frequently experience impaired gastric motility, which significantly increases the likelihood of reflux symptoms.[6,26]

Poor glycaemic control has also been identified as a significant contributor to GERD development in diabetic individuals. Hyperglycaemia can impair smooth muscle function and further exacerbate autonomic neuropathy, thereby worsening oesophageal motility disturbances.[33,38] Several studies included in this analysis reported that **patients with poorly controlled diabetes had more frequent and severe GERD symptoms** compared with those with better glycaemic control.

Additionally, metabolic factors such as obesity and metabolic syndrome, which commonly coexist with type 2 diabetes, may further increase GERD risk. Increased abdominal pressure and alterations in gastric physiology associated with obesity may contribute to reflux symptoms.[35,41] Population-based studies have also shown that metabolic disorders including diabetes are associated with a higher prevalence of GERD worldwide.[11,12]

The findings of this meta-analysis are consistent with earlier systematic reviews that reported a significant association between diabetes and GERD.[15,21] However, heterogeneity among the included studies was observed, which may be explained by differences in study design, population characteristics, diagnostic criteria for GERD, and duration of diabetes. These variations highlight the complexity of the relationship between diabetes and gastrointestinal dysfunction.

Despite these findings, several limitations should be considered. First, most of the included studies were **observational or cross-sectional**, which limits the ability to establish a causal relationship. Second, diagnostic methods for GERD varied across studies, including symptom-based questionnaires and endoscopic findings, which may introduce variability in prevalence estimates. Third, potential confounding factors such as body mass index, lifestyle habits, and medication use were not consistently controlled across all studies.

Nevertheless, this meta-analysis has several strengths. It included a large combined sample size across multiple countries, improving the generalizability of the findings. The systematic study selection process followed **PRISMA guidelines**, ensuring transparency and methodological rigor.[18] Additionally, the analysis incorporated studies evaluating both **physiological mechanisms and clinical outcomes**, providing a comprehensive overview of the relationship between diabetes and GERD.

In conclusion, the present meta-analysis demonstrates that diabetes mellitus is significantly associated with an increased risk of gastroesophageal reflux disease. The underlying mechanisms likely involve autonomic neuropathy, impaired oesophageal motility, delayed gastric emptying, and poor glycaemic control. Early recognition and appropriate management of GERD symptoms in diabetic patients may help improve quality of life and reduce gastrointestinal complications. Further large-scale prospective studies are required to better understand the causal mechanisms and optimize therapeutic strategies for this patient population.

7. LIMITATIONS

Although this meta-analysis provides valuable insights into the association between diabetes mellitus and gastroesophageal reflux disease (GERD), several limitations should be acknowledged.

First, most of the included studies were observational in nature, including cross-sectional, cohort, and case–control designs. Such study designs may identify associations but cannot definitively establish a causal relationship between diabetes and GERD. Observational studies are also more susceptible to confounding factors that may influence the results.[19]

Second, heterogeneity among the included studies was observed. The variation could be attributed to differences in study populations, diagnostic criteria for GERD, duration of diabetes, and study methodologies. Some studies diagnosed GERD based on symptom questionnaires, while others relied on endoscopic findings or clinical evaluation, which may affect the comparability of results across studies.[11]

Third, potential confounding variables such as body mass index, dietary habits, smoking, alcohol consumption, and medication use were not uniformly controlled across all studies. These factors are known to influence the development and severity of GERD and could partially affect the pooled estimates reported in this analysis.[10]

Fourth, most of the included studies were conducted in specific geographic regions such as Asia and Europe, which may limit the generalizability of the findings to other populations. Differences in lifestyle, genetic susceptibility, and healthcare practices may influence the prevalence and severity of GERD among diabetic patients in different regions.[12]

Finally, although funnel plot analysis suggested minimal evidence of publication bias, the possibility of unpublished studies with negative findings cannot be completely excluded. Small studies with non-significant results are sometimes less likely to be published, which may influence meta-analysis outcomes.[18,20]

Despite these limitations, this meta-analysis followed a systematic approach based on PRISMA guidelines and included a relatively large number of studies, providing a

comprehensive overview of the relationship between diabetes mellitus and GERD.[18]

8. CONCLUSION

This meta-analysis evaluated the association between diabetes mellitus (DM) and gastroesophageal reflux disease (GERD) by systematically analysing evidence from 25 studies conducted in different populations. The pooled findings indicate that individuals with diabetes have a higher likelihood of developing GERD compared with non-diabetic individuals. These findings support previous evidence suggesting that metabolic and gastrointestinal dysfunctions associated with diabetes may contribute to the development of reflux symptoms.[11,15]

The increased risk of GERD among diabetic patients may be explained by several physiological mechanisms, including diabetic autonomic neuropathy, impaired oesophageal motility, reduced lower oesophageal sphincter pressure, and delayed gastric emptying. These alterations can promote reflux of gastric contents into the oesophagus and increase the frequency and severity of GERD symptoms.[4,5,17]

Overall, the results of this meta-analysis highlight the importance of early recognition and management of GERD symptoms in patients with diabetes to improve quality of life and reduce potential complications. Healthcare professionals should consider gastrointestinal symptoms as a possible complication of diabetes during routine clinical evaluation.

Further large-scale prospective studies and well-designed clinical investigations are needed to better understand the causal relationship and underlying mechanisms linking diabetes and GERD, and to develop effective preventive and therapeutic strategies for affected patients.[19]

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