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# The association between the *Helicobacter pylori* infection and the occurrence of gestational diabetes: a systematic review and meta-analysis

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## Abstract

**Background** This meta-analysis aims to establish a more precise association between gestational diabetes mellitus (GDM) incidence and *H. pylori* infection by amalgamating findings from prior case–control and cohort studies.

**Methods** To identify relevant studies, we conducted a comprehensive search using the Excerpta Medica Database (Embase), PubMed (Medline), Web of Science (ISI), and Scopus from January 1990 to November 2022. The screening process involved reviewing the entire text, abstracts, and titles of retrieved articles. Subsequently, data extraction was performed from the selected articles, and their quality was assessed using the Newcastle–Ottawa Scale checklist. Version 17 of STATA software was utilized for the analysis, with relative risks (RR) calculated along with their 95% confidence intervals (CI) to quantify the impact of the included studies.

**Results** This meta-analysis included eight observational and analytical studies. The combined risk of gestational diabetes mellitus (GDM) in pregnant women with *H. pylori* infection was found to be 1.97 times higher compared to pregnant women without infection (RR: 1.97; 95% CI 1.57–2.47;  $I^2=0.00\%$ ;  $P=0.84$ ).

**Conclusion** Pregnant women with *H. pylori* infection are at an increased risk of developing gestational diabetes.

**Keywords** Gestational diabetes mellitus, *H. pylori*, Evidence synthesis

## Introduction

Diabetes is known as the third silent killer in the world. It is characterized by elevated blood glucose levels caused by deficiencies in insulin secretion or abnormalities in cellular function. To make informed clinical and public health decisions, it is crucial to carry out research in this area to identify the risk factors for illness [1, 2]. Previous studies conducted in the United States have revealed that 7% of pregnant women have diabetes, with 86% of cases being gestational diabetes mellitus (GDM), which develops during pregnancy [3, 4]. Globally, the prevalence of GDM ranges from 5 to 25.5%, depending on several factors including age, race, ethnicity, and body

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composition, in addition to the screening and diagnostic standards that have been used [1].

GDM is a high-risk pregnancy-related illness that endangers the health of both the mother and the fetus. It is also considered a primary cause of premature birth, abortion, miscarriage, and infant mortality [1]. Due to the physiological and mechanical changes that occur during pregnancy, mothers are vulnerable to a variety of opportunistic diseases, particularly common viral and bacterial infections [5–7]. *Helicobacter pylori* (*H. pylori*) is the sole kind of microorganism known to survive in the human stomach. It damages the gastric mucosa and is thought to be the primary cause of chronic stomach disorders. Serious digestive system issues, including stomach ulcers and stomach cancer, are more likely to occur when *H. pylori* infection is present [8, 9].

*H. pylori* infections affect about 50% of people worldwide, with infection rates being greater in developing countries. Studies on public health have linked *H. pylori* to several extra-gastrointestinal conditions, including neurological disorders, cardiovascular conditions, and hematologic conditions (such as idiopathic thrombocytopenic purpura and unexplained iron deficiency anemia). More recently, studies on midwifery have raised the possibility that *H. pylori* infection may affect expecting mothers [10, 11]. Pregnant women have been found to have a significantly higher level of *H. pylori* IgM test positivity than non-pregnant women in published research [12–14]. Based on the results of the *H. pylori* IgM test, which detects both recent and past infections, it is plausible to assume that many infections occur during pregnancy. Given that pregnancy induces immune adaptations to foster tolerance towards the semi-allogeneic fetus, these physiological changes could make pregnant mothers more susceptible to *H. pylori* infection [15].

While pregnancy often maintains innate and humoral immunity, it tends to decrease cellular cytotoxic immune responses. Given that *H. pylori* infection is most likely contracted before pregnancy, it is widely recognized that hormonal and immune system changes during pregnancy may contribute to the activation of a latent *H. pylori* infection [15, 16]. Although the mentioned studies suggest a potential link between *H. pylori* and the development of GDM, it remains unproven whether the combined risk of high blood sugar and *H. pylori* infection increases the likelihood of pregnancy-related illnesses and impedes fetal development [3]. During pregnancy, virulent strains of *H. pylori*, particularly the *cag+* strain, can increase insulin resistance. They do this by inducing inflammatory factors such as 71, IL6, and CRP. Moreover, chronic inflammation triggered by *H. pylori* impacts the hormones that regulate insulin production in the

stomach and duodenum. Additionally, this inflammation affects the pancreatic B cells responsible for insulin production, leading to a decrease in insulin secretion. The *cag+* strain specifically influences the gastric somatostatin hormone, resulting in reduced insulin release from the pancreas [16, 17]. Furthermore, *H. pylori* increases and decreases the levels of the ghrelin and leptin hormones, respectively, which predisposes pregnant women to diabetes [17].

This meta-analysis was conducted in response to the previously mentioned discrepancies in studies exploring the relationship between *H. pylori* infection and the incidence of GDM. It aimed to examine this association more accurately by synthesizing the results from published case-control and cohort studies. The systematic review and meta-analysis methodology used in this study contributes to the overall research question by providing a complete and robust synthesis of the available information on the relationship between *H. pylori* infection and the incidence of GDM. By combining data from different analytical observational studies, this method improves the statistical power, precision and generalizability of the results and provides valuable insights into the subject of the study.

## Methods

This study is a systematic review and meta-analysis conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, specifically following the PRISMA 2020 guidelines. It involved six fundamental steps: search syntax and strategy, screening, selection, data extraction, quality assessment, and meta-analysis [18]. The protocol of this meta-analysis is registered in Prospero (CRD42023422182).

## Search strategy and keywords

In this meta-analysis, we utilized primary search terms and their synonyms identified through Mesh, Thesaurus, and Emtree. The databases searched included PubMed (Medline), Excerpta Medica Database (Embase), Scopus, and Web of Science (ISI), covering publications from January 1, 1990, to November 30, 2022. We combined keywords related to GDM and *H. pylori* infection for the database search (Table 1). The authors conducted a grey literature search using Google Scholar and hand searching methods to locate relevant resources. All results were then compiled using Endnote software version 8. The screening process, based on titles, abstracts, and full texts, eliminated repetitive studies, considering their titles, authors, and publication years. Publications unrelated to the study's focus were excluded.

**Table 1** The inclusion criteria of presence meta-analysis and systematic search

P (Population)	Pregnant women
E (Exposure)	Presence of <i>H. pylori</i>
C (Comparison)	Non-infected pregnant women or pregnant women without <i>H. pylori</i> infection
O (Outcomes)	GDM development or GDM incidence
T (Type of studies)	Case–Control Studies Cohort Studies
PECOT question	In pregnant women (P), does <i>H. pylori</i> infection (E) compared to non-infected pregnant women (C) affect the development of GDM (O) during the pregnancy and postpartum period (T)?
Search terms	("Pregnant women"), (Pregnancy), ("Maternal health"), ("Helicobacter pylori"), (" <i>H. pylori</i> "), ("Gastric infection"), ("Stomach bacteria"), ("Gestational diabetes mellitus"), ("Glucose intolerance in pregnancy"), (GDM), ("Hyperglycemia in pregnancy"), ("Insulin resistance"), ("Glucose metabolism"), ("Maternal outcomes"), ("Fetal outcomes"), ("Pregnancy complications"), ("Perinatal outcomes")
Databases	PubMed (Medline), Excerpta Medica Database (Embase), Scopus, Web of Science (ISI)
Inclusion criteria	Human subjects were studied Studies have been published in peer-reviewed journals Studies looking into the link between GDM and <i>H. pylori</i> infection in pregnant women Studies that provide information on the prevalence, incidence, or consequences of gestational diabetes in pregnant women infected with <i>H. pylori</i> Studies are published in English
Exclusion criteria	Animal research, in vitro experiments, reviews, editorials, and letters Studies that do not investigate the link between GDM and <i>H. pylori</i> infection in pregnant women Studies containing insufficient or confusing data on GDM or <i>H. pylori</i> infection

Additionally, a manual search was conducted to include relevant studies and their references. Two independent reviewers, PK and RM, handled the screening phase.

#### Inclusion and exclusion criteria

The PECOT framework was utilized to define the inclusion criteria for this study. All case–control and cohort studies that identified a relationship between *H. pylori* infection and GDM in pregnant women were eligible for inclusion. The criteria, structured on the PECOT framework, are outlined in Table 1. Also the exclusion criteria listed in Table 1. In cases where the full text of a study that met the inclusion criteria was not available, we initially contacted the authors via email. If there was no response, those studies were excluded from the analysis. The selection and screening of articles for this meta-analysis were independently conducted by two authors, RM and PK.

#### Data extraction

Following the screening phases according to the inclusion and exclusion criteria, an information extraction checklist was created to extract data from the final articles based on the checklist. This information included details about the studies (such as the authors' names, publication years, types of studies, countries, and sample sizes), the intended population (such as the age of pregnant mothers, gestational age, and type of population investigated

in the studies), the outcome (such as the desired effect size in the studies along with the 95% confidence interval (CI)), and information related to the desired exposure (such as the diagnosis method of *H. pylori* infection).

#### Quality assessment

Two of the authors (PK/MS and YM) conducted a qualitative evaluation of studies based on the Newcastle–Ottawa Quality Assessment Scale (NOS) checklist. This checklist is designed to evaluate the quality of observational studies, especially case–control and cohort studies.

#### Statistical analysis

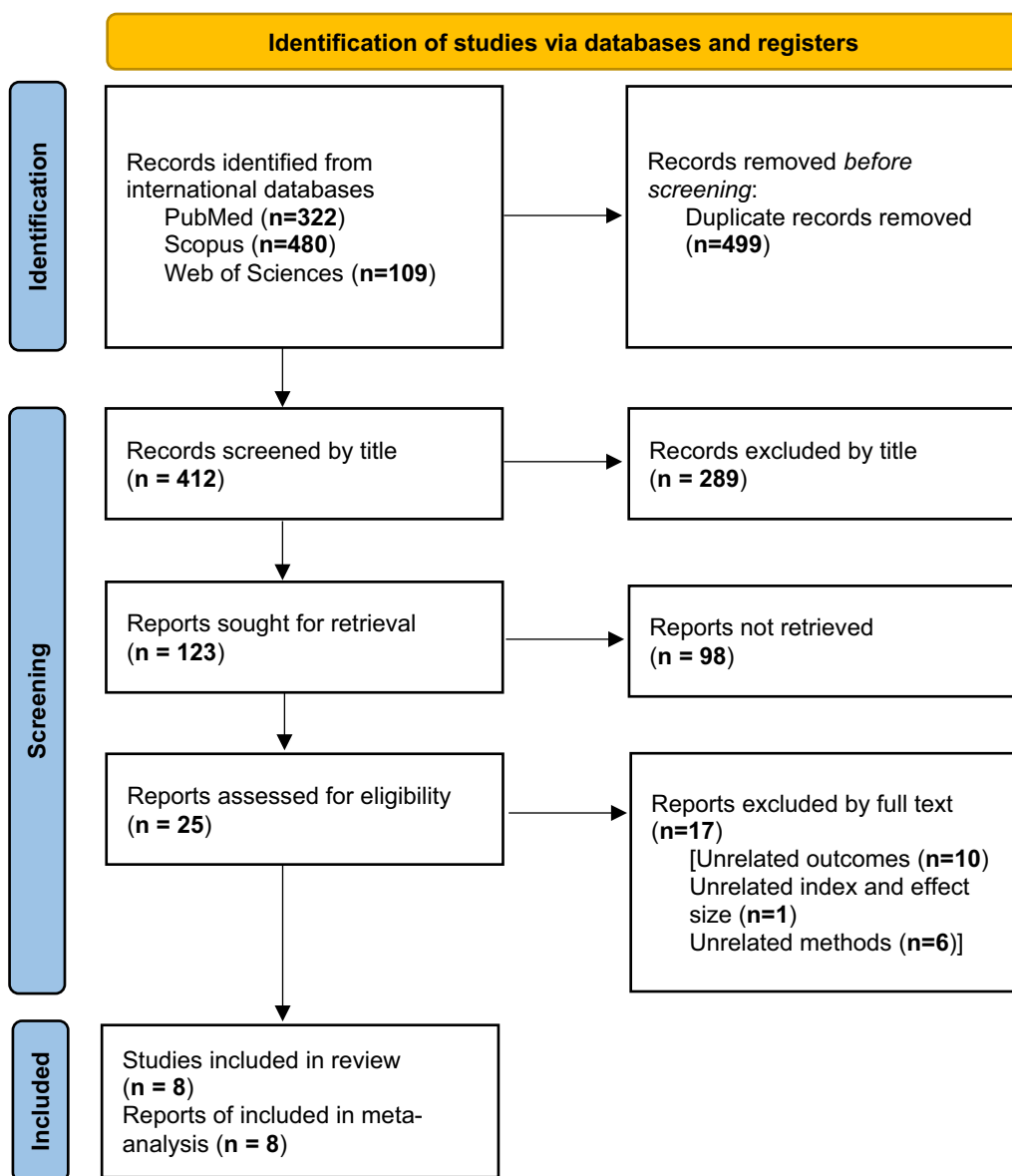
To calculate the pooled relative risk (RR) with a 95% CI, authors utilized the Meta set package, which accounted for the logarithm and standard deviation of the RR logarithm. The choice of RR as the general effect size was based on the low prevalence of GDM in the exposed groups (pregnant women with *H. pylori*), which is less than 5% [19]. In this meta-analysis, we combined odds ratio (OR) values from case–control studies with risk ratio (RR) values from cohort studies, reporting them collectively as RR effect sizes. Study heterogeneity was assessed using  $I^2$  and Cochrane's Q test, where 0–25% indicates minimal heterogeneity, and 75–100% indicates high heterogeneity. Also, authors utilized the random-effects model (REM) for

calculating overall pooled estimates and the fixed-effects model (FEM) for reporting and conducting subgroup analyses. Publication bias was evaluated using Egger’s test and the funnel plot. All statistical analyses were conducted using STATA 17.0, with a *P*-value of less than 0.05 considered significant. Subgroup analyses were based on the age of pregnant mothers, gestational age, and different *H. pylori* diagnosis methods. Furthermore, Meta-regression analysis was also performed to establish the linear association between various parameters such as maternal age and gestational

age and the strength of the correlation between *H. pylori* infection and GDM.

**Results**

In this meta-analysis, 8 observational and analytical studies were evaluated, as shown in Fig. 1 and Table 2. After searching and retrieving papers from international databases, 322 articles from PubMed, 480 from Scopus, and 109 from Web of Science were discovered for this meta-analysis. Initially, 499 items were excluded for duplication. Subsequently, 412 articles were subjected to title screening, and 289 articles were deleted owing



**Fig. 1** A flow diagram demonstrating the study selection process

**Table 2** The characteristics of selected analytical observational studies

Authors	Country	Type of study	Study population	Age (years)	Sample size	GDM test	HP test	Effect size (OR/RR)	Gestational age (week)	NOS score
Li et al. [3]	China	Case-control	Pregnant women	C = 29.02 ± 2.75 GDM = 29.40 ± 2.9	T = 294 NC = 208 GDM = 86	75-g oral glucose tolerance test	ELISA	1.82 (1.08, 3.06)	24 (time of GDM test)	8
Cardaropoli et al. [19]	Italy	Cohort	Pregnant women	32.2 (4.5)	T = 2820	100 g, 3-h oral glucose tolerance test	ELISA	1.655 (1.133, 2.416)	13.3 (2.4)	8
Alshareef et al. [20]	Sudan	Case-control	Pregnant Sudanese women	26.5	20	FBG and 75-g oral glucose tolerance test	ELISA	2.8 (1.1-7.5)	26	7
Kuo et al. [10]	China	Cohort	Pregnant women	HP+ 29.24 ± 4.59 HP- 29.14 ± 4.49	346	NR	HPSA	1.15 (0.34-3.92)	HP+ 38.57 ± 1.17 HP- 38.45 ± 1.42	8
Ahmed et al. [34]	Sudan	Case-control	Preeclampsia and healthy pregnant women	Case = 28.4 (6.3) Control = 28.1 (6.5)	166 GDM+ 20 GDM- 146	NR	ELISA	2.66 (1.03-6.85)	GDM 37.6 (1.1) Healthy 37.6 (1.3)	7
Li and Yang [35]	China	Cohort	Pregnant women	NR	110 HP+ 55 HP- 55	NR	UBT	1.81 (0.61-5.40)	NR	7
Guijing et al. [36]	China	Case-control	Pregnant women	NR	255 HP+ 119 HP- 170	NR	WB	2.37 (1.39-4.03)	NR	7
Xia et al. [11]	China	Cohort	Pregnant women	27.1	320 HP+ 78 HP- 242	NR	UBT	2.64 (1.29-5.39)	12	8

to irrelevant titles. In the following phase, 123 articles were evaluated based on their abstracts, with 25 articles remaining for additional study. Following full-text screening, 17 articles were removed because they were irrelevant to the outcome and effect size or the methodology used. Finally, the meta-analysis included eight publications from case–control and cohort studies. The 17 publications were excluded because of their lack of relevance to the outcome and effect size, as well as the methodology used (Fig. 1).

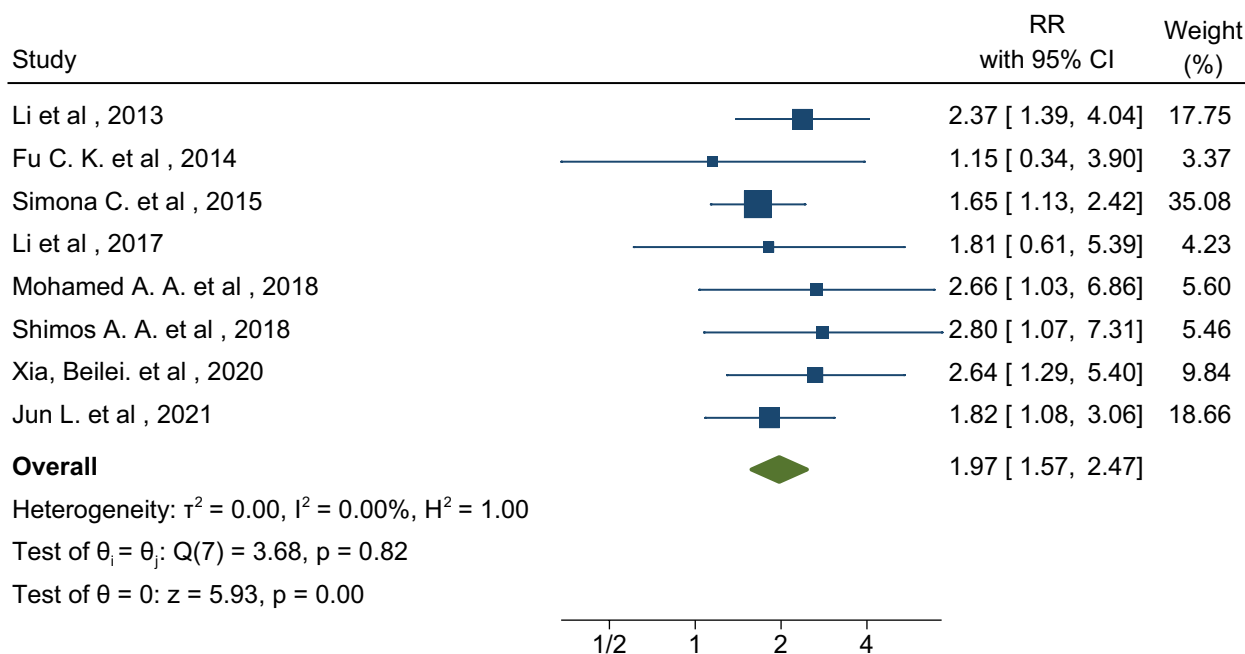
The sample sizes of these studies ranged from 20 to 2820 pregnant women. The highest and lowest effect sizes, related to the presence of *H. pylori* infection and the occurrence of GDM, were observed in the studies by Shimos et al. [20] and Fu et al. [10], respectively. When these studies' results were combined, the pooled RR of GDM in pregnant women with *H. pylori* infection was found to be 1.97 times higher than in those without this infection. The CI for this pooled RR was 1.57–2.47, indicating a significant association with high precision due to the narrow CI (RR: 1.97; 95% CI 1.57–2.47) (Fig. 2). The analysis of heterogeneity in this meta-analysis revealed that all the combined studies were homogeneous, with a heterogeneity percentage of 0% and a significance level of 0.81 ( $I^2$ : 0.00%;  $P$ : 0.82) (Figs. 2 and 3).

**Publication bias**

The funnel plot and Egger's test were utilized to evaluate publication bias. The results of the funnel plot have been shown in Fig. 3, indicating the absence of publication bias in the results. The results of the Eggers test were not statistically significant, which indicated the absence of publication bias in the results ( $B$ : 0.400;  $SE$ : 0.951;  $P$ : 0.671) (Fig. 3).

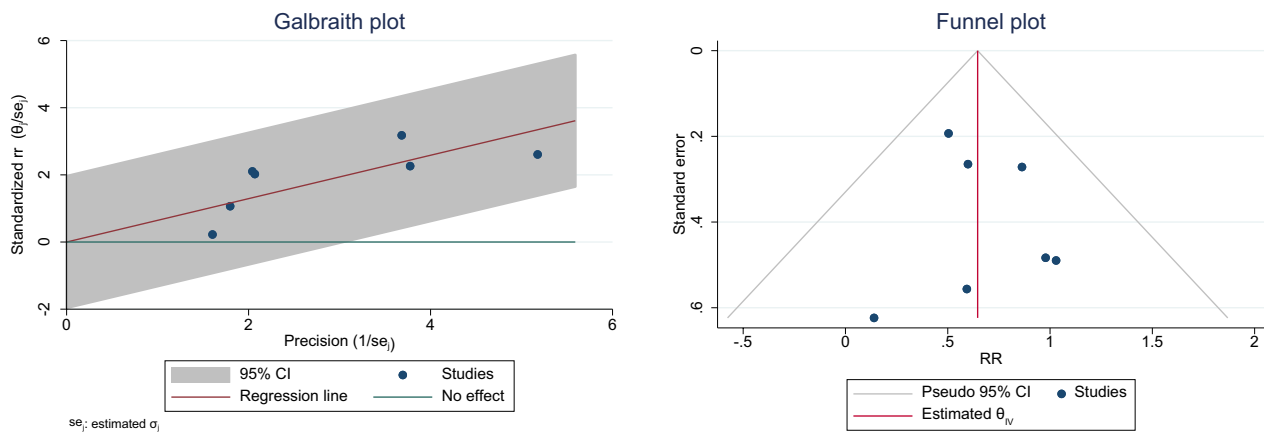
**Subgroup analyses**

Subgroup analyses in this meta-analysis were conducted based on the age of pregnant mothers, gestational age, type of studies, and various *H. pylori* diagnostic methods. The results, detailed in Table 3, reveal differences in the impact of *H. pylori* infection on the occurrence of GDM, depending on the diagnostic method used. Additionally, the analysis showed that the likelihood of *H. pylori* infection causing GDM decreased as the age of pregnant mothers increased. Specifically, the infection was 2.728 (RR: 2.728; 95% CI 1.390–5.354) times more likely to cause GDM in women under the age of 29, whereas, for women older than 29, the risk was 1.671 (RR: 1.671; 95% CI 1.242–2.248) (Table 3). The meta-regression analysis further confirmed this inverse association. However, the association between *H. pylori* infection and the occurrence of GDM with increasing maternal age was not statistically significant ( $B$ : -0.071;  $SE$ : 0.046;  $P$ : 0.221; 95% CI -0.220, 0.076), as shown in Table 3.



Random-effects DerSimonian–Laird model

**Fig. 2** The forest plot of effect of *H. pylori* on the risk of GDM in pregnant women



**Fig. 3** The Galbraith and Funnel plot of effect of *H. pylori* on the risk of GDM in pregnant women for determining heterogeneity and publication bias

**Table 3** The subgroup analysis of effect of *H. pylori* on the risk of GDM in pregnant women based on gestational age, type of detect *H. pylori*, and pregnant women age

Categories	No. of studies	Pooled relative risk (% 95 CI)	Between groups			Between subgroup	
			I <sup>2</sup> (%)	Q	P value	Q	P value
<i>H. pylori</i> test							
ELISA	4	1.852 (1.402–2.447)	0.00	1.62	0.656	0.15	0.694
Other methods	4	2.058 (1.318–3.213)	0.00	1.19	0.55		
Pregnant women age							
< 29 years	3	2.728 (1.390–5.354)	0.00	0.01	0.941	1.7	0.192
≤ 29 years	3	1.671 (1.242–2.248)	0.00	0.47	0.792		
Gestational age							
< 30 weeks	4	1.790 (1.337–2.396)	0.00	1	0.605	0.04	0.843
30 weeks ≤	2	1.942 (0.918–4.106)	11.45	1.13	0.288		
Type of studies							
Case–control	4	2.212 (1.590–3.064)	0.00	0.98	0.819	0.89	0.342
Cohort	4	1.788 (1.300–2.423)	0.00	1.8	0.612		

The subgroup analysis focusing on gestational age revealed that the risk of GDM in pregnant women with *H. pylori* infection increases as the gestational age progresses. Specifically, the analysis, as detailed in Table 3, indicated that the risk of developing gestational diabetes in women with *H. pylori* infection was 1.790 (RR: 1.790; 95% CI 1.337–2.396) for those with a gestational age of less than 30 weeks. This risk increased to 1.942 (RR: 1.942; 95% CI 0.918–4.106) in women with a gestational age of more than 30 weeks, as shown in Table 3. Additionally, the meta-regression analysis supported this direct association between *H. pylori* infection and an increased risk of GDM with advancing gestational age, although this finding was not statistically

significant (B: 0.081; SE: 0.345; P: 0.829; 95% CI – 1.018, 1.181).

The subgroup analysis results indicated that the association between *H. pylori* infection and the occurrence of GDM, when combining the case–control studies, was 2.122 (RR: 2.122; 95% CI 1.590, 3.064). However, after combining the cohort studies, the effect size was found to be 1.788 (RR: 1.788; 95% CI 1.300, 2.423) (Table 3).

### Discussion

This study primarily aimed to explore the link between *H. pylori* infection and the incidence of GDM in pregnant women. Our findings indicated that pregnant mothers with *H. pylori* infection were 91% more likely to develop



GDM than pregnant mothers without *H. pylori* infection. This result was derived from combining entirely homogeneous studies, exhibiting no heterogeneity. Furthermore, the calculated CI, ranging from 1.51 to 2.42, signifies the high accuracy of our estimate, as evidenced by the narrowness of this interval. Previous studies have indicated that pregnancy may heighten sensitivity to *H. pylori*, making expectant mothers more susceptible to this infection. This increased susceptibility is likely due to immunological adaptations during pregnancy, which are essential for the mother's tolerance of the semi-allogeneic embryo [1, 11, 19].

Generally, pregnancy is known to reduce cellular cytotoxic immune responses in both innate and humoral immunity. This reduction potentially creates favorable conditions for *H. pylori* infection [21–23]. Moreover, due to a variety of physiological and immunological changes occurring during pregnancy, there is an increased risk of gastrointestinal infections, with *H. pylori* being particularly noteworthy [24]. There is also a possibility that these conditions cause the activation of latent *H. pylori* infections during pregnancy [11]. Previous studies have identified several factors contributing to the reduction of IgG levels during pregnancy. These factors include decreased cellular immunity, the excretion of proteins through urine, the hemodilution of IgG transferred from the mother to the fetus via the placenta, and the impact of pregnancy-related hormones, particularly steroid hormones, on protein synthesis [25].

Since *H. pylori* infection is most likely acquired before pregnancy, it is widely believed that hormonal and immunological changes during pregnancy can activate latent *H. pylori* [15, 26]. In addition, the decrease in gastric acid production in early pregnancy as a result of increased fluid accumulation in the pregnant mother's body, steroid hormonal changes, and immune tolerance can lead to the activation of a latent *H. pylori* infection [26, 27]. The link between *H. pylori* infection and insulin resistance can be attributed to several biological mechanisms. Firstly, changes in glucose metabolism might lead to alterations in the gastric mucosa's chemical makeup, facilitating the diagnosis of *H. pylori* infection. Secondly, *H. pylori* infection in the stomach triggers an increase in pro-inflammatory cytokines, causing structural changes in insulin-binding agents and subsequently hindering their interaction with insulin. These effects may become more pronounced as gestational age increases in mothers, potentially strengthening the link between *H. pylori* infection and GDM in pregnant women [28–31].

The subgroup analysis in our meta-analysis revealed that a gestational age of 30 weeks or more could intensify the association between *H. pylori* infection

and GDM in pregnant women. Additionally, a stronger correlation between *H. pylori* infection and GDM was observed in younger pregnant mothers, specifically those under 29 years of age. However, this finding should be interpreted with caution due to the limited number of studies in this subgroup, which numbered only two. Consequently, the reliability of these results might be limited, and further research in this area is necessary.

The findings of the subgroup analysis revealed that when data from case–control studies were coupled with cohort studies, the effect size, which reflects the magnitude of the observed treatment impact, increased. This shows that the findings from the case–control studies had a stronger association or treatment impact than the cohort studies. It is crucial to remember that case–control studies have inherent limitations and are prone to bias, particularly in terms of participant selection and data collection on exposure and outcome variables [32, 33].

One of the limitations of our study is the small number of studies included in some subgroup analyses. Future research, with a larger number of studies in this field, could facilitate more comprehensive meta-analyses or cohort studies with extensive sample sizes. Although we performed subgroup analyses based on infection diagnosis method, gestational age, and maternal age, the lack of data on key variables like body mass index, history of diabetes or *H. pylori* infection before pregnancy, and various treatments for diabetes and infection, limited our ability to conduct subgroup analyses on these factors. To assess the impact of these variables and their role in the relationship between *H. pylori* infection and GDM, designing and implementing large-scale cohort studies is essential.

## Conclusion

The results of this meta-analysis unequivocally show that pregnant women with *H. pylori* infection have a higher chance of developing gestational diabetes. Given these findings, it is imperative that both developed and developing countries create and execute comprehensive healthcare standards to inform and prevent *H. pylori* infection in expectant mothers. Care strategies that prioritize early detection and adequate treatment of *H. pylori* infection before, during, and following pregnancy should be part of this. Additionally, considering the high probability of latent *H. pylori* activation during pregnancy, which can lead to the development of GDM, prompt action for identifying and eliminating this infection before pregnancy is imperative.

## Abbreviations

CI	Confidence interval
OR	Odds ratio
RR	Risk ratio/relative risk



GDM	Gestational diabetes mellitus
I <sup>2</sup>	I Square
NOS	Newcastle ottawa scale
PRISMA	Preferred reporting items for systematic reviews and meta-analyses

### Acknowledgements

Not applicable.

### Author contributions

YM identified the review topic and designed the search strategy. PK and MS performed the initial search, and both authors were involved in the screening data extraction, risk of bias assessment and certainty of evidence grading. YM performed the meta-analyses. HGK, RM, HRB, YM, and PK wrote the first draft of the manuscript, and both authors provided substantial intellectual input to the subsequent edits and have read and approved the final manuscript. YM is the guarantor of the work and has primary responsibility for the content presented in this manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

### Availability of data and materials

Data and materials are available by request to the corresponding author (Dr. Yousef Moradi).

### Declarations

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

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