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The association between *Helicobacter pylori* infection and diabetes mellitus: an updated meta-analysis of 45 case-control studies

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Abstract

Background Helicobacter pylori (*H. pylori*) infection is linked to various gastrointestinal and systemic diseases, including diabetes mellitus (DM). This study synthesizes evidence to determine the association between *H. pylori* infection and the risk of developing DM.

Objectives To quantify the odds ratio (OR) of DM in individuals with *H. pylori* infection and explore variations across different subgroups.

Methods A systematic review and meta-analysis were conducted following PRISMA 2020 guidelines. Databases including Medline, Web of Science, Scopus, EMBASE, Ovid, and CINHAL were searched for case-control studies from January 1990 to January 2025. Eligible studies investigated the association between *H. pylori* and DM. Data extraction was performed independently by two reviewers, and study quality was assessed using the Modified Newcastle-Ottawa Scale (NOS). Random-effects models were utilized to calculate pooled ORs, with heterogeneity assessed via I^2 statistic. Subgroup analyses included *H. pylori* detection methods, age groups, geographic regions, DM types, HbA1c levels, duration of DM, and study quality.

Results From 280 records, 45 case-control studies were included, involving 529 million diabetes cases worldwide in 2021. The pooled OR was 1.547 (95% CI: 1.243–1.926), indicating that *H. pylori* infection increases the risk of DM by approximately 1.56 times. Heterogeneity was moderate ($I^2 = 46.03\%$). Subgroup analyses showed stronger associations with non-invasive *H. pylori* detection methods (OR = 1.99), in the 40–60 age group (OR = 2.00), and for type 2 diabetes (OR = 2.25). Geographic variations were significant, with Asia showing the highest OR (2.17). No significant publication bias was detected, and sensitivity analyses confirmed the robustness of our findings.

Conclusion This meta-analysis confirms a significant association between *H. pylori* infection and an increased risk of DM, particularly type 2. The findings underscore the potential benefits of considering *H. pylori* testing in diabetes management strategies, especially in high-risk populations. Further research should focus on longitudinal studies to establish causality and explore biological mechanisms.

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Registration This review was registered in PROSPERO (CRD42025637126).
Keywords Helicobacter pylori, Diabetes mellitus, Evidence synthesis, Case-Control studies

Introduction

More than 50% of people worldwide suffer with Helicobacter pylori (*H. pylori*), a gram-negative, spiral bacterium that is common in the human stomach and one of the most common chronic infections [1, 2]. The primary cause of peptic ulcer disease is known to be *H. pylori* [3]. Beyond its impact on gastrointestinal health, emerging research suggests *H. pylori* might also play a role in non-gastrointestinal conditions like cardiovascular diseases (CVD) and metabolic syndromes, notably diabetes (5–7). In 2021, 529 million people worldwide had diabetes, with a global prevalence of 6.1%. The greatest rates were in North Africa, the Middle East (9.3%), and Oceania (12.3%), with Qatar leading nationally at 76.1% in those aged 75–79. Over 10% incidence of diabetes is predicted in 89 countries, including those in North Africa, the Middle East, and Latin America, and the number of cases might reach 1.31 billion by 2050 [4]. The association between *H. pylori* infection and DM was first noted in 1989 [5]. It is thought that *H. pylori* may increase inflammatory cytokines like as interleukin-6 and C-reactive protein (CRP), which could increase the risk of DM and CVD [5, 6, 7].

Given the focus on exploring the link between *H. pylori* infection and MD, opting for case-control studies in this meta-analysis seems justified. Other research designs like analytical cross-sectional or cohort studies present notable challenges. As an illustration, cohort studies need a significant amount of time and human resources, and they frequently face challenges like participant dropout (loss to follow-up), which might jeopardize the applicability and size of the sample. Case-control studies, on the other hand, offer quicker insights into the association. Cross-sectional studies, while simpler to execute, are less ideal for meta-analyses because they are prone to different biases, which can affect the reliability of the results. Therefore, case-control studies are particularly apt for investigating the connection between *H. pylori* and diabetes.

Various meta-analyses have been published worldwide [8, 9, 10, 11], but the continuous influx of new data allows for improved clinical decision-making and strengthens evidence-based medicine (EBM) across clinical fields, specifically in understanding the association between *H. pylori* and DM. Consequently, this systematic review and meta-analysis were undertaken to clarify and evaluate the association between *H. pylori* infection and the risk of developing DM.

Materials and methods

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12]. PROSPERO has this review registered (CRD42025637126).

Eligibility criteria

The systematic review and meta-analysis established specific eligibility criteria to ensure the inclusion of relevant research. Only case-control studies involving human participants diagnosed with DM were considered. The independent variable assessed in these studies was *H. pylori* infection (Table 1).

Several exclusion criteria were applied to refine the selection process. Case reports and case series were excluded due to their lack of comparative data necessary for this type of analysis. Similarly, reviews such as meta-analyses, rapid reviews, or other borderline review types were not included. Animal studies were also deemed irrelevant to the research question. Additionally, cohort studies, randomized controlled trials (RCTs), and other interventional study designs were excluded, as they do not align with the required case-control framework. Studies that failed to investigate the specific relationship between *H. pylori* infection and DM in humans were also omitted. Finally, any studies that did not report essential effect sizes, such as odds ratios (ORs), were excluded. Discrepancies related to data collection, compilation, or analysis were resolved through consensus among the authors to maintain the integrity and accuracy of the findings (Table 1).

Search terms and complex search syntax

A comprehensive search was conducted in several international databases, including Medline (PubMed), Web of Science, Scopus, EMBASE, Ovid, and CINHAL, covering studies from January 1990 to January 2025. The search included terms such as Diabetes, Diabetes Mellitus (type 1 and 2), Insulin Dependent, IDDM, NIDDM, Noninsulin Dependent, Insulin Sensitivity, *Helicobacter pylori*, *Campylobacter pylori*, and *H. pylori*. Following the primary search, articles were reviewed, and titles and abstracts were examined to exclude irrelevant studies. Inclusion and exclusion criteria were independently set by two researchers (Fig. 1).

Data extraction

Two authors independently extracted and recorded data from the selected studies. A structured checklist was used for data extraction, which included the following

Table 1 Eligibility criteria for studies included in the systematic review and Meta-Analysis

PECOT	Population: All population Exposure: Patients with diabetes Comparison: Patients without diabetes Outcome: Risk of Helicobacter pylori infection Type of studies: Case-control studies
Keywords	Diabetes, Diabetes Mellitus (type 1 and 2), Insulin Dependent, IDDM, NIDDM, Noninsulin Dependent, Insulin Sensitivity, Helicobacter pylori, Campylobacter pylori, H. pylori
Databases	Medline (PubMed), Web of Science, Scopus, EMBASE, Cochrane, Ovid, CINHAL
Deadline of Search	Up to January 2025
Inclusion Criteria	1. Case-control, nested case-control studies 2. Human population 3. Study population must include patients with diabetes 4. Helicobacter pylori infection as the dependent variable (outcome) 5. Studies published in peer-reviewed journals with English language
Exclusion Criteria	1.Case reports / series 2. Reviews/meta-analysis/rapid or other borderline reviews 3. Animal studies 4. Cohort studies/ Randomized control trials and other interventional studies 5. Studies not involving H. pylori infection in diabetic patients 6. studies not reported desired effect sizes (OR)

variables: (1) First author's name, (2) Date of publication, (3) Study country, (4) Study subjects, (5) Age of patients, (6) Sample size, (7) Type of DM, (8) Mean HbA1c, (9) Duration of DM, (10) Measurement of association, 11) Controlled variables, and 12) Method of bacteria detection. Additional information was extracted regarding the type of instruments used. A data extraction form was initially created based on a group discussion and piloted across 10 different studies. After modifications, it was used for data extraction. The entire process, from systematic search to data extraction, was performed independently by two research experts, with the quality agreement assessed using the Kappa statistic (0.75).

Risk of bias

In cases of disagreement during the quality assessment process, a third author was consulted for final evaluation. The quality of the included studies was assessed using the Modified Newcastle-Ottawa (NOS) Scale for Case-Control Studies [13]. This scale is widely used to evaluate the methodological quality of observational studies, including case-control studies, based on criteria such as selection of participants, comparability of groups, and assessment of outcomes.

Statistical analysis

For the meta-analysis, logarithmic ORs and the standard error of logarithmic ORs were calculated. The DerSimonian and Laird method was used to compute the pooled OR with 95% confidence intervals (CI) using random-effects models (REM) [14]. Due to the significant heterogeneity observed in some analyses, REM were applied for estimating OR. Cochran's Q test and the I^2 statistic were used to evaluate statistical heterogeneity across studies [15]. Meta-regression, sensitivity analysis, and subgroup analyses were performed to investigate the sources of heterogeneity. Publication bias was assessed using a funnel plot and the Egger test [16]. All statistical analyses were performed using STATA 18.0 (Stata Corp, College Station, TX, USA), with statistical significance set at $p < 0.05$.

Results

The PRISMA 2020 flow diagram for this updated systematic review includes records identified through database searches and registers, along with additional records from other sources (20 records). After duplicates were removed ($n = 150$), 280 records remained for screening. These were assessed by title and abstract, leading to the evaluation of 21 full-text articles. Of these, 17 articles were excluded due to reasons such as incorrect study design ($n = 10$), wrong population ($n = 5$), or unavailable data ($n = 2$). Ultimately, 45 studies were included in the qualitative/quantities synthesis (Fig. 1).

The qualitative analysis of 45 case-control studies investigating the association between *H. pylori* infection and DM reveals mixed findings. Many studies, such as those by Bener et al. (2007) [17] and Małecki et al. (1996) [18], report varying associations between *H. pylori* and DM risk, with some suggesting a significant positive correlation (ORs ranging from 3.90 to 6.47 in certain populations) and others showing weaker or no significant associations. This variability in results is likely due to differences in study designs, population characteristics (e.g., age, sex, diabetes type), and diagnostic methods for detecting *H. pylori* infection, including serological tests, histology, and breath tests. Furthermore, many studies adjusted for potential confounders like age, BMI, and

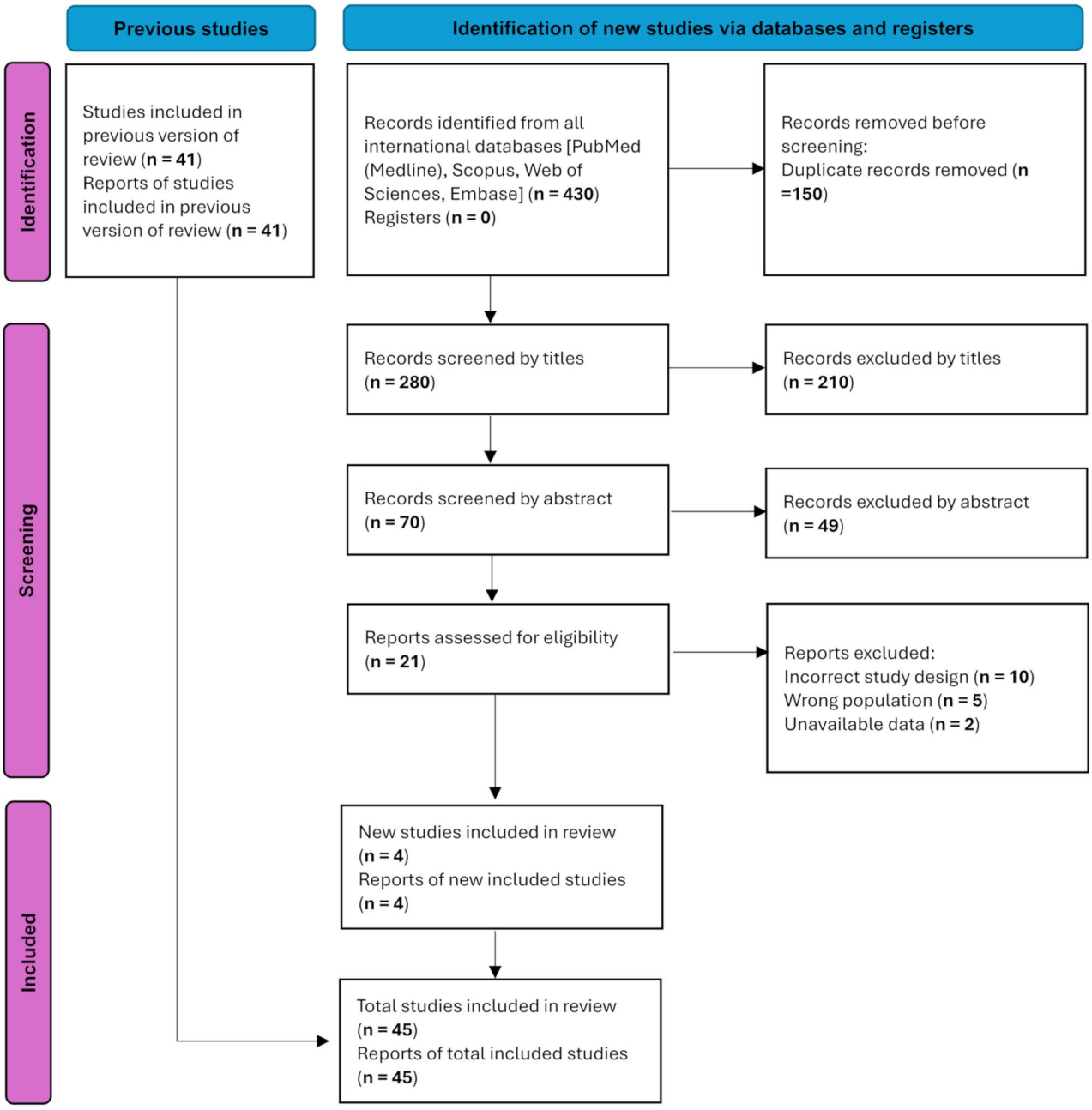

Fig. 1 PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases and registers only

socioeconomic factors, but differences in control variables may have influenced the outcomes. Despite the inconsistencies, some studies suggest a potential association between *H. pylori* infection and an increased risk of DM, particularly Type 2 Diabetes Mellitus (T2DM), while others find no such association or even hint at a protective effect in certain cases. Limitations in study quality and methodological design were also noted, with studies receiving varying NOS scores, indicating differences in the robustness of their findings (Table 2).

Quantities results

The individual study results showed a wide range of ORs. Several studies, such as those by Bener et al. (2007) [17] (OR = 134.71, 95% CI: 52.46–345.90) and Vaishnav et al. (2018) [62] (OR = 4.09, 95% CI: 2.46–6.79), reported a strong positive association. Conversely, some studies, including Małecki et al. (1996) [18] (OR = 0.20, 95% CI: 0.09–0.46) and Bayrak et al. (2021) [61] (OR = 0.28, 95% CI: 0.15–0.53), suggested a protective effect or no significant association. These conflicting findings contribute to

Table 2 The main characteristics of Case – Control studies of the effect of H pylori on risk of diabetes

Authors	Years	Country	Control subjects (selection methods)	Age	Sample size	Type of Diabetic (Mean HbA1C) (Duration of disease)	Measurement of association Odds Ratio (CI 95%)	Controlled variables	Bacteria detection	NOS Score
Małecki, M. et al [18]	1996	Poland	Non-diabetic subjects	17–80	139 (Control:100 & Case: 39)	DM (-) (8 Year)	0.33 (0.18, 0.59)	Not Reported	Histology or biopsy	6
Pocecco, M. et al [19]	1997	Italy	Admitted for minor extra-abdominal surgery with no history of abdominal pain	16	379 [Control:310 & Case: 69]	DM (-) (-)	3.13 (2.08, 4.70)	Age, sex, education and economic	Rapid urease test	6
Gentile, S. [20]	1998	Italy	Non-diabetic subjects	52	328 (Control:164 & Case: 164)	T2DM (8.3 ± 1.4)	1.77 (1.35, 2.31)	Age, sex and body weight	Histology or biopsy	7
De Luis, DA [21]	1998	Spain	The control subjects were healthy volunteers, with similar age and sex-distribution that the diabetic patients	25	180 Control: 100 & Case: 80	T1DM (-) (3.1 Year)	1.36 (0.98, 1.87)	Age and sex	Anti-H. pylori antibody	6
Gasbarrini, A. et al [22]	1998	Italy	Healthy subjects	35	166 [Control: 50 & Case: 116]	DM (-) (19 year)	1.04 (0.85, 1.28)	Age and sex	13–14 C urea breath test	6
Salardi, S. et al [23]	1999	Italy	Children with minor endocrine disorders.	12	339 [Control: 236 & Case: 103]	T1DM (-) (-)	1.47 (0.99, 2.18)	Age	Anti H. pylori antibody	7
Arslan, D. et al [24]	2000	Turkey	Non-diabetic subjects	12	130 (Control: 42 & Case: 88)	T1DM (11.08 ± 3.17) (3.85 Year)	1.38 (1.08, 1.75)	Not Reported	Anti-H. pylori antibody	6
Dore, MP. et al. [25]	2000	Italy	Blood donors from the same geographic area	12–75	891 [Control: 506 & Case: 385]	DM (greater than 1 year)	1.16 (1.00, 1.35)	age and socio-economic status	Anti-H. pylori antibody	8
Senturk, O. et al. [26]	2001	Turkey	Nondiabetic patients undergoing upper diagnostic endoscopies	54.1	140 [Control: 73 & Case: 67]	T2DM (6.42 ± 0.97) (4.5 year)	1.39 (0.78, 2.48)	Age and socioeconomic	Histology or biopsy	7
Ravera, M. et al [27]	2001	Uganda	Dyspeptic patients without diabetic	Not Reported	132 [Control110: & Case: 22]	DM (-) (-)	1.22 (0.33, 4.49)	Not Reported	Histology or biopsy	6
Ko, G. T. et al [28]	2001	Chine	With upper GI symptoms in whom	49.9	118 [Control55: & Case: 63]	T2DM (8.25 ± 2.22) (6.2 year)	0.90 (0.64, 1.26)	Age and sex	Rapid urease test	6
Marrollo M. et al [29]	2001	Italy	Non diabetic dyspeptic patients	63	191 [Control: 117& Case: 74]	DM (-) (-)	1.54 (1.05, 2.27)	Age and sex	Rapid urease test and Histology or biopsy	6
Quatrini, M. et al [30]	2001	Italy	Dyspepsia patients	58	142 [Control: 71 & Case: 71]	DM (-) (-)	1.63 (1.12, 2.38)	Age and sex	13–14 C urea breath test	7
Cenerelli, S. et al [31]	2002	Italy	Control subjects were first selected on the basis of the admission criteria of the senieur protocol.	55	73 Control: 43 & Case: 30)	T2DM (6.1 ± 1.8) (3.1 Year)	1.04 (0.60, 1.80)	Not Reported	13–14 C urea breath test	7
Maule, S. et al [32]	2002	Italy	Individuals without diabetes	46–75	62 [Control:31 & Case: 31]	T2DM (7.1 ± 1.4) (-)	1.65 (0.92, 2.97)	Age	13–14 C urea breath test	8
Candelli, M. et al [33]	2003	Italy	The control Group was selected normal healthy adolescent	17	268 Control: 147 & Case: 121)	T1DM (8.2 ± 1.4) (6.7 Year)	0.97 (0.72, 1.30)	Sex, age and social class	Rapid urease test, Histology or biopsy	7

Table 2 (continued)

Authors	Years	Country	Control subjects (selection methods)	Age	Sample size	Type of Diabetic (Mean HbA1C) (Duration of disease)	Measurement of association Odds Ratio (CI 95%)	Controlled variables	Bacteria detection	NOS Score
Gulcelik, N. E. et al [34]	2005	Turkey	Dyspeptic non diabetic subjects	51.9	149 [Control: 71 & Case: 78]	T2DM (8.2 ± 1.4)	1.92 (1.29, 2.86)	Age and BMI	Histology or biopsy	7
Jaber, S. M. et al [35]	2006	Saudi Arabia	Healthy children	> 10	604 [Control:543 & Case: 61]	T1DM (-) (-)	1.60 (0.98, 2.63)	Not Reported	Anti H. pylori antibody	6
Bener, A. et al [17]	2007	Qatar	Non-diabetic subjects	48	420 (Control:210 & Case: 210)	T2DM (6.9 ± 1.4) (-)	5.03 (3.90, 6.47)	Age and sex	Anti-H. pylori antibody	7
Demir, M. et al. [36]	2008	Turkey	The control Subjects were selected in the gastroenterology clinics	52	283 Control: 142 & Case: 141	T2DM (-) (6 year)	1.07 (0.84, 1.36)	Age and sex	Rapid urease test and Histology or biopsy	7
Ariizumi, K. et al [37]	2008	Japan	non-diabetic subjects without upper GI tract disorders	62	134 [Control: 67 & Case: 67]	DM (-) (15.1 year)	0.74 (0.53, 1.03)	age and sex-matched	Anti H. pylori antibody, Rapid urease test, Histology or biopsy	8
Hamed, S. A. et al [38]	2008	Egypt	Subjects with neither history nor clinical evidence of gastrointestinal problems; vascular, inflammatory, or neurologic diseases.	47.6	140 [Control:60 & Case: 80]	DM (-) (9.2 year)	1.29 (0.83, 2.01)	Age and sex	Anti H. pylori antibody	8
Cabral, V. L. R. et al [39]	2009	Brazil	The control Group was selected normal healthy adolescent	17	45 Control: 30 & Case: 15)	T1DM (-) (-)	0.52 (0.21, 1.29)	Not Reported	Histology or biopsy	7
Lazaraki, G. et al. [40]	2009	Greece	non-smoking, non-diabetic with of dyspepsia	65	79 [Control: 30 & Case: 49]	T2DM (-) (3 year)	0.99 (0.70, 1.40)	Age, sex, H. pylori-infection, degree of gastritis	Rapid urease test and Histology or biopsy	7
Krause, I. et al. [41]	2009	Colombia	Individuals had no clinical diabetes, nor islet cell autoantibodies	16.0	180 [Control123: & Case: 57]	T1DM (-) (8.8 year)	0.44 (0.29, 0.66)	Not Reported	Anti-H. pylori antibody	6
Devrajani, BR. et al. [42]	2010	Pakistan	Non diabetic individuals with positive or negative Helicobacter pylori infection	53	148 [Control: 74 & Case: 74]	T2DM (-) (5 years)	1.64 (1.11, 2.43)	Not Reported	Stool antigen test	7
Ibrahim, A. et al [43]	2010	Egypt	Dyspeptic non diabetic subjects	45	200 [Control: 102 & Case: 98]	T2DM (8.57 ± 0.79) (-)	0.94 (0.71, 1.25)	Not Reported	Rapid urease test, Histology or biopsy	7
El-Eshmawy, M. M. et al [44]	2011	Egypt	Non-diabetic subjects	20	242 (Control:80 & Case: 162)	T1DM (8.2 ± 1.75) (7.29 Year)	1.63 (1.25, 2.11)	Age, sex, geographic area and socioeconomic status	Anti-H. pylori antibody	7
De Block, C. E. M. et al [45]	2012	Belgium	One-hundred sex- and age-matched controls were tested for H. pylori serology.	40	329 Control: 100 & Case: 229)	T1DM (7.8 ± 1.0) (18 Year)	0.86 (0.74, 1.02)	Age and sex	Anti-H. pylori antibody & Rapid urease test and Histology or biopsy	7
Candelli, M. et al. [46]	2012	Italy	Healthy children	19.8	174 [Control: 99 & Case: 75]	T1DM (8.8 ± 0.80) (-)	1.96 (1.40, 2.75)	Age, sex and socio-economic	13–14 C urea breath test	6
Jafarzadeh, A. et al [47]	2012	Iran	Healthy individuals	42.86	200 [Control: 100 & Case: 100]	T2DM (-) (-)	1.03 (0.74, 1.42)	Age	Anti H. pylori IgG	6

Table 2 (continued)

Authors	Years	Country	Control subjects (selection methods)	Age	Sample size	Type of Diabetic (Mean HbA1C) (Duration of disease)	Measurement of association Odds Ratio (CI 95%)	Controlled variables	Bacteria detection	NOS Score
Keramat, F. et al [48]	2013	Iran	Non-diabetic subjects	51	158 (Control: 79 & Case: 79)	DM (8.96 ± 1.82) (2.78 Year)	1.29 (0.89, 1.88)	Age and sex	Anti-H. pylori antibody & Rapid urease test and Histology or biopsy	8
Zekry, O. A. et al [49]	2013	Egypt	Healthy children and adolescents	12.53	120 [Control: 60 & Case: 60]	T1DM (7.75 ± 1.67) (9.25 year)	1.69 (1.21, 2.35)	Age and sex	Anti-H. pylori antibody	8
Chobot, A. et al [50]	2014	Poland	This group was enrolled from a large cohort of children	13.4	447 [Control: 298 & Case: 149]	T1DM (7.69 ± 1.63) (4.6 year)	0.74 (0.48, 1.15)	Age- and sex	13–14 C urea breath test	8
Fayed, SB. et al [51]	2014	Egypt	healthy normal volunteers	12.2	106 [Control:53 & Case: 53]	T1DM (9.6 ± 1.6) (12.2 year)	1.80 (1.14, 2.84)	Age and sex	Anti H. pylori antibodies	7
Zhou, F. et al [52]	2015	China	Non-diabetic subjects with dyspepsia symptoms	45	253 (Control:65 & Case: 188)	T2DM (8.2 ± 1.9)	1.15 (0.99, 1.33)	Age and sex	Anti-H. pylori antibody & Rapid urease test	9
Bajaj, S. et al [53]	2015	India	The control group comprised of age, sex, socioeconomic status, and education matched normal healthy volunteers	> 18	140 Control: 60 & Case: 80)	T2DM (8.2 ± 1.2) (4.2 Year)	1.53 (1.04, 2.24)	Age, sex, socioeconomic status, and education	Anti-H. pylori antibody & Rapid urease test and Histology or biopsy	8
Bazmamoun, H. et al [54]	2016	Iran	Non-diabetic subjects	10	160 (Control: 80 & Case: 80)	T1DM (8.00 ± 0.65) (2.72 Year)	1.50 (1.09, 2.07)	Age, sex, socioeconomic status	Anti-H. pylori antibody	8
Osman, S. M. et al [55]	2016	Sudan	Healthy children	1–18	180 [Control: 90 & Case: 90]	T1DM (-) (6 month)	0.97 (0.71, 1.33)	age and sex	Anti-H. pylori antibody	8
Alzahrani, S. et al [56]	2017	Saudi Arabia	Non-diabetic subjects	49	842 (Control:421 & Case: 421)	DM (6.1 ± 0.6)	1.01 (0.88, 1.16)	Age, sex, race, DPP intervention, length of follow-up time, body mass index, alcohol consumption, physical activity and smoking	Anti-H. pylori antibody & Rapid urease test	9
Vaishnav, B. et al. [57]	2018	India	Non diabetic with dyspepsia	56	287 [Control: 140 & Case: 147]	T2DM (8.4 ± 1.0) (7.59 year)	1.89 (1.51, 2.36)	Not Reported	Rapid urease test	8
Wang, S. J. et al [58]	2024	Taiwan	Patients who had not tested positive for or been diagnosed with H. pylori infection within three months prior to the initial documentation of pregnancy	36.9	10,232 [Control: 5116 & Case: 5116]	DM (-) (-)	0.98 (0.83,1.16)	Age, race, pre-gestational diabetes, pre-pregnancy BMI, GERD, nausea, and vomiting	Urea breath tests, Stool, immunoassays detecting H. pylori antigen, Serum anti-H. pylori antibodies (IgG)	9

Table 2 (continued)

Authors	Years	Country	Control subjects (selection methods)	Age	Sample size	Type of Diabetic (Mean HbA1C) (Duration of disease)	Measurement of association Odds Ratio (CI 95%)	Controlled variables	Bacteria detection	NOS Score
Li, J. et al. [59]	2024	China	Healthy individuals who underwent annual health checkups at Xian GEM Flower Changqing Hospital from January 2019 to December 2021	48.8	4406 [Control: 2353 & Case: 2053]	DM (-) (-)	1.59 (1.17, 2.15)	Age, gender, BMI, FBG, TG, TC, HDLC, and LDL-C	Urea breath tests	8
Li, Z. et al. [60]	2024	China	Patients with T2D who received H. pylori testing between January 2016 and December 2021	58.8	960 [Control: 479 & Case: 481]	DM (8.81) (9.65 years)	1.16 (1.06, 1.26)	Gender, Smoking history, and Alcohol intake	C-urea breath test (C-UBT), or the rapid urease test (RUT), or serological testing	8
Bayrak, N. A. [61]	2021	Turkey	Children who underwent esophago-gastro-duodenoscopy (EGD) were studied. CD diagnosis was established by favorable histology and serology	9.1	783 [Control: 505 & Case: 278]	T1DM (-) (-)	1.43 (1.09, 2.12)	Age, gender, and socioeconomic status	Histology and the rapid urease test	7

the observed heterogeneity and highlight the complexity of the relationship between *H. pylori* infection and DM.

A total of 45 case-control studies were included in this meta-analysis to evaluate the association between *H. pylori* infection and DM. The overall pooled OR using a random-effects model was 1.547 (95% confidence interval [CI]: 1.243–1.926), indicating a significant positive association. This suggests that individuals with *H. pylori* infection are approximately 1.56 times more likely to develop DM compared to those without the infection. Heterogeneity among the included studies was substantial, with $I^2 = 46.03\%$, $tau^2 = 0.04$, $Q = 5.02$, and $P = 0.549$. These results indicate moderate variability in the study findings, potentially due to differences in population characteristics, diagnostic methods, or other confounding factors. However, the moderate level of heterogeneity suggests that the overall positive association between *H. pylori* infection and DM is consistent across many studies, supporting the potential link between the two (Fig. 2).

Publication bias and sensitivity analysis

To assess potential small-study effects (publication bias), a regression-based Egger test for publication bias was performed using a random-effects model with the hypothesis that there are no small-study effects. The regression coefficient was 0.98, with a standard error (SE) of 1.162. The z-value was 0.84, and the corresponding *p*-value was 0.398. Given that the *p*-value is greater than the conventional threshold of 0.05, the null hypothesis cannot be rejected (Fig. 3).

A sensitivity analysis was conducted to assess the robustness of the overall effect size by sequentially excluding individual studies and recalculating the pooled estimate. The overall OR for the *H. Pylori's* effect on the DM was 1.558 (95% confidence interval [CI]: 1.168–2.076), which remained statistically significant. Excluding studies such as **Zhou, F. et al. (2015)** [52], **Gentile, S. et al. (1998)** [63], and **Małecki, M. et al. (1996)** [18] led to only minimal changes in the pooled OR, with *p*-values remaining significant. However, the removal of **Alzahrani, S. et al. (2017)** [56] resulted in a noticeable change in the effect size, suggesting that this study may have a more substantial influence on the overall findings. The results of the sensitivity analysis indicate that the meta-analysis findings are generally robust (Fig. 3).

Subgroup analysis

H. Pylori Detection Methods The odds ratio (OR) for invasive methods of detecting H. pylori was 1.27, with a confidence interval from 0.97 to 1.25, showing a moderate effect but with quite a bit of variation between studies ($I^2 = 44.81\%$). On the other hand, non-invasive methods had a higher OR of 1.99, with a confidence interval from 1.35 to 2.93, indicating a stronger effect with moderate

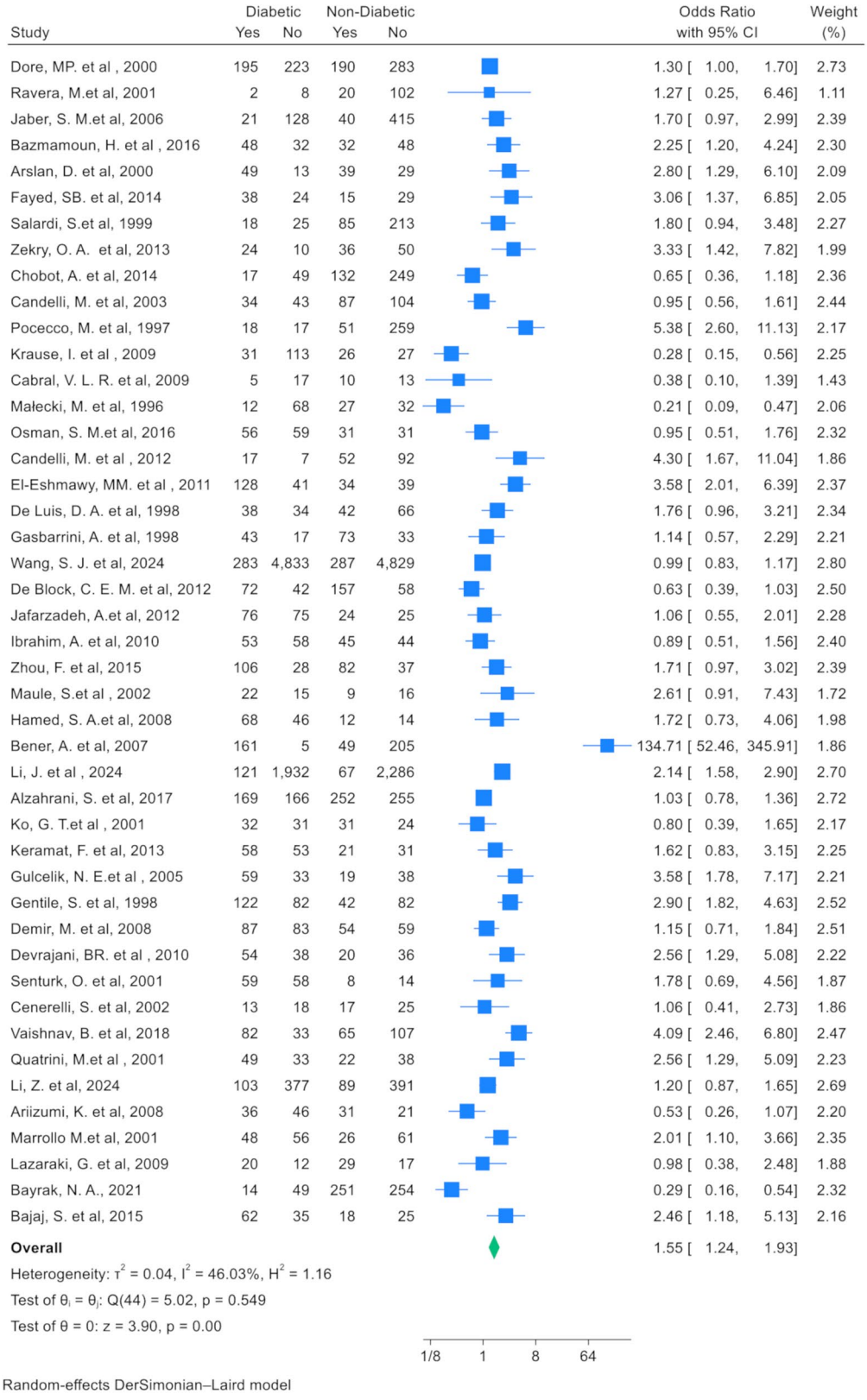

Fig. 2 Forest plot of the he association between H. Pylori and Diabetes Mellitus by combining case-control studies

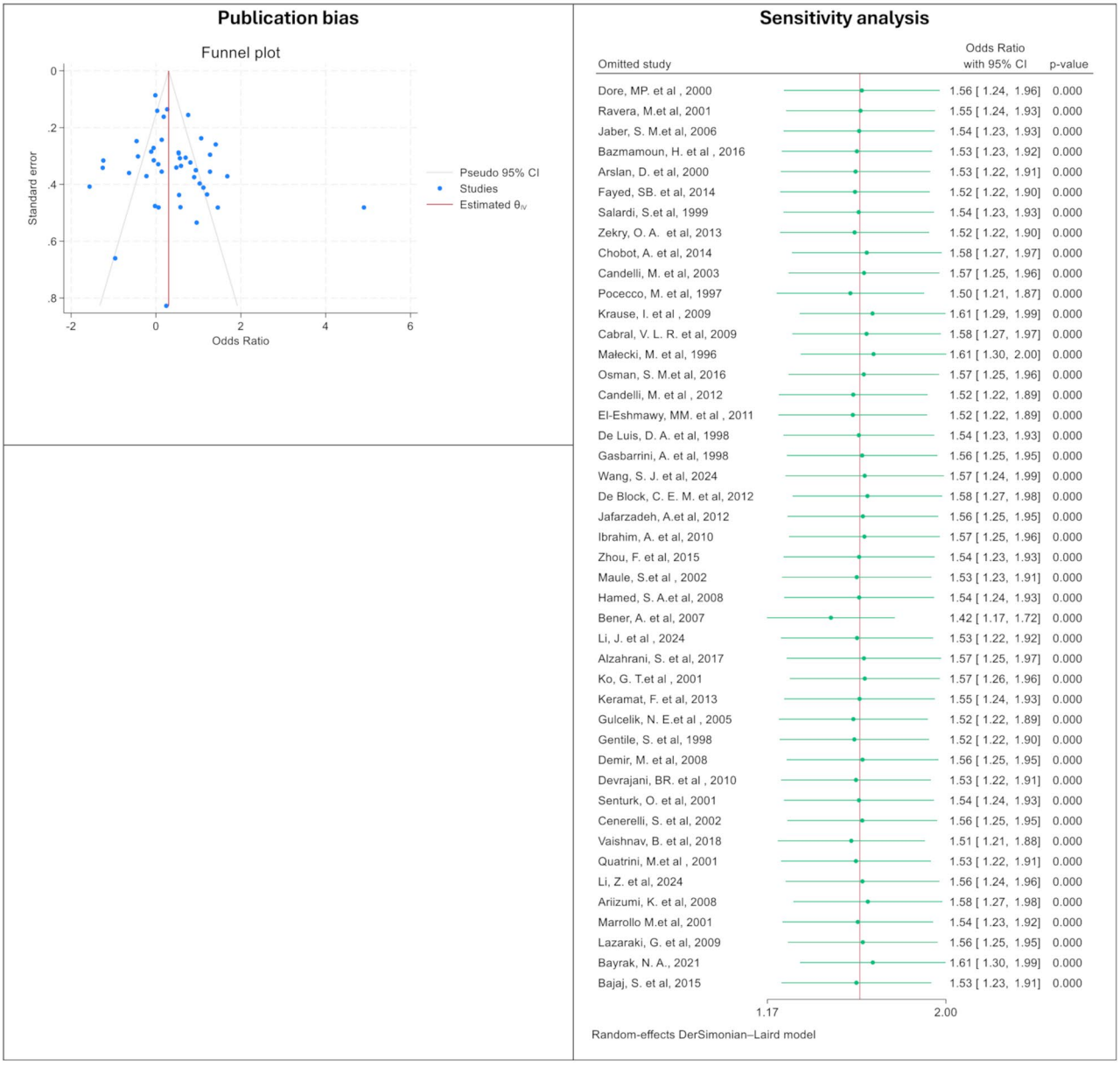

Fig. 3 Publication bias and sensitivity analysis of the association between H. Pylori and Diabetes Mellitus by combining case-control studies

variation ($I^2 = 59.93\%$). Despite these differences in OR, there was no significant distinction between the two detection methods ($Z = 3.57$, $P = 0.068$), which could suggest that non-invasive methods might be more effective for detecting H. pylori (Table 3).

Age categories The study showed different ORs for different age groups. For young people aged 10 to 20, the OR was 1.55, with a confidence interval from 0.98 to 2.47, and moderate heterogeneity ($I^2 = 33.09\%$), suggesting a moderate impact. Moving to the 20 to 40 age group, the OR dropped to 1.14, with a confidence interval from 0.38 to 1.39, and moderate heterogeneity ($I^2 = 50.01\%$). The 40- to 60-year-olds had a higher OR of 2.00, with a confidence interval from 1.32 to 3.04, and lower heterogeneity ($I^2 = 44.33\%$), indicating a more significant effect in this group. For those over 60, the OR was 1.29, with a confidence interval from 0.63 to 2.63, showing higher heterogeneity ($I^2 = 56.99\%$). Overall, no significant differences were found between age categories ($Z = 1.80$, $P = 0.621$), indicating that age does not significantly influence the outcome (Table 3).

Continents We noticed a significant variation in the outcomes across different continents. In Africa, the OR was 1.84, with a confidence interval from 1.10 to 3.08, showing high heterogeneity ($I^2 = 69.08\%$), which suggests a moderate impact of H. pylori detection in this region.

Table 3 Subgroup analysis of the association between Helicobacter pylori infection and diabetes

Variables	Subgroups	OR (%95 CI)	Heterogeneity assessment				
			Between studies			Between subgroups	
			I^2 (%)	Q	*P* value	Z	*P* value
H. Pylori detection methods	Invasive	1.27 (0.97–1.25)	44.81	4.33	0.601	3.57	0.068
	Non-invasive	1.99 (1.35–2.93)	59.93	5.02	0.048		
Age categories	10–20 years	1.55 (0.98–2.47)	33.09	10.04	0.552	1.80	0.621
	20–40 years	1.14 (0.38–1.39)	50.01	12.02	0.503		
	40–60 years	2.00 (1.32–3.04)	44.33	9.33	0.320		
	60 < years	1.29 (0.63–2.63)	56.99	10.02	0.055		
Continents	Africa	1.84 (1.10–3.08)	69.08	19.41	0.001	28.98	0.001
	America	0.30 (0.17–0.66)	0.00	0.16	0.690		
	Asian	2.17 (1.23–3.83)	71.30	26.52	0.001		
	European	1.54 (1.14–2.07)	78.32	37.62	0.001		
Type of diabetes	DM	1.30 (0.88–1.92)	60.05	10.13	0.001	3.04	0.22
	T1DM	1.43 (0.96–2.13)	71.45	15.47	0.001		
	T2DM	2.25 (1.36–3.71)	68.11	17.76	0.001		
HbA1C (Mean)	6–8	2.25 (1.00–5.05)	90.08	45.90	0.001	0.01	0.920
	8 <	2.15 (1.54–3.00)	68.93	19.00	0.001		
Duration of diabetes (Years)	0–3	1.37 (1.13–1.66)	0.00	5.53	0.480	0.05	0.982
	4–7	1.40 (0.92–2.13)	75.83	37.23	0.001		
	8 <	1.28 (0.63–2.61)	90.95	48.42	0.001		
NOS score	6	1.25 (0.74–2.12)	85.45	39.73	0.001	3.09	0.38
	7	2.07 (1.33–3.22)	87.26	44.94	0.001		
	8	1.62 (1.01–2.62)	82.35	40.23	0.001		
	9	1.24 (0.77–2.01)	59.25	2.45	0.12		

In contrast, the Americas had a much lower OR of 0.30, with a confidence interval from 0.17 to 0.66, and no heterogeneity ($I^2 = 0.00\%$). Over in Asia, the OR was higher at 2.17, with a confidence interval from 1.23 to 3.83, and high heterogeneity ($I^2 = 71.30\%$), pointing to a stronger effect there. Europe's OR was 1.54, with a confidence interval from 1.14 to 2.07, but with very high heterogeneity ($I^2 = 78.32\%$). Significant differences were found across continents ($Z = 28.98$, $P = 0.001$), indicating regional variations in the effectiveness of H. pylori detection (Table 3).

Type of diabetes For diabetes in general, the odds ratio (OR) was 1.30, with a confidence interval from 0.88 to 1.92, and there was high heterogeneity ($I^2 = 60.05\%$). In people with Type 1 Diabetes Mellitus (T1DM), the OR was 1.43, with a confidence interval from 0.96 to 2.13, showing very high heterogeneity ($I^2 = 71.45\%$). The most pronounced effect was seen in those with Type 2 Diabetes Mellitus (T2DM), where the OR reached 2.25, with a confidence interval from 1.36 to 3.71, and high heterogeneity ($I^2 = 68.11\%$). Despite these variations, no significant differences were found between the diabetes types ($Z = 3.04$, $P = 0.22$), indicating that the type of diabetes does not significantly alter the outcome (Table 3).

HbA1C (Mean) The analysis of HbA1C levels revealed no significant differences across groups. For people with HbA1C levels ranging from 6 to 8, the OR was 2.25, with a 95% CI from 1.00 to 5.05, and high heterogeneity ($I^2 = 90.08\%$), suggesting a significant effect. For those with HbA1C levels above 8, the OR was 2.15, with a CI from 1.54 to 3.00, showing moderate heterogeneity ($I^2 = 68.93\%$). No significant difference was found between the HbA1C subgroups ($Z = 0.01$, $P = 0.920$), indicating that HbA1C levels do not influence the outcome significantly (Table 3).

Duration of diabetes (Years) The analysis regarding how long someone has had diabetes showed that there are not significant differences among different groups. For people with DM for 0 to 3 years, the OR was 1.37, with a 95% CI from 1.13 to 1.66, and no heterogeneity ($I^2 = 0.00\%$). For those with DM for 4 to 7 years, the OR was 1.40, with a 95% CI from 0.92 to 2.13, but with high heterogeneity ($I^2 = 75.83\%$). Among individuals who had diabetes for 8 or more years, the OR was 1.28, with a 95% CI from 0.63 to 2.61, and very high heterogeneity ($I^2 = 90.95\%$). No significant differences were found across these subgroups ($Z = 0.05$, $P = 0.982$), indicating that the duration of DM does not significantly impact the results (Table 3).

NOS score The analysis examined how study quality might affect results, using the NOS. For studies scoring 6 on the NOS, an OR of 1.25 was found, with a 95% CI from 0.74 to 2.12, and very high heterogeneity at 85.45%. Studies with an NOS score of 7 had an OR of 2.07, with

a 95% CI from 1.33 to 3.22, again showing very high heterogeneity at 87.26%. For studies scoring 8 on the NOS, the OR was 1.62, with a 95% CI of 1.01 to 2.62, and high heterogeneity at 82.35%. The top-scoring studies with an NOS of 9 had an OR of 1.24, with a 95% CI of 0.77 to 2.01 and moderate heterogeneity at 59.25%. Despite these variations in OR across different quality levels, statistical tests showed no significant differences between the groups ($Z = 3.09$, $P = 0.38$), suggesting that study quality does not significantly influence the results (Table 3).

Discussion

The primary goal of this meta-analysis was to look into the link between *H. pylori* infection and the prevalence of DM (type 1, type 2, or total diabetes) in the general population. To do this, all case-control studies published until January 2025 were rigorously evaluated and analyzed. The data show that people infected with *H. pylori* are 1.56 times more likely to develop diabetes. These findings are consistent with recent research indicating that chronic inflammation, changes in stomach hormone levels, and insulin resistance could mediate the link between *H. pylori* infection and diabetes [9, 10, 64, 65].

However, it is vital to evaluate how lifestyle factors affect this association. Lifestyle influences both the risk of *H. pylori* infection and the development of diabetes. Poor eating habits, smoking, and excessive alcohol consumption have all been linked to an increased chance of *H. pylori* infection, as well as a higher risk of developing T2DM. In contrast, a nutritious diet rich in fruits, vegetables, and whole grains may minimize these risks by strengthening immune function and lowering inflammation [66, 67, 68, 69]. Physical activity is another critical factor that can modulate the relationship between *H. pylori* infection and DM. Regular exercise has been shown to improve insulin sensitivity, reduce systemic inflammation, and enhance overall metabolic health, potentially counteracting some of the adverse effects of *H. pylori* infection. Sedentary behavior, on the other hand, exacerbates insulin resistance and may amplify the impact of *H. pylori* induced metabolic disturbances. Other contributing factors, such as obesity, stress, and socioeconomic status, also warrant consideration. Obesity, for example, is a known risk factor for both *H. pylori* infection and DM, while chronic stress may exacerbate inflammation and impair glucose metabolism [8, 70, 71, 72]. Socioeconomic disparities can further influence access to healthcare, nutrition, and opportunities for physical activity, thereby indirectly affecting the strength of the association between *H. pylori* and DM [9, 10, 64, 65]. While there is some variability among studies, this consistent link across different research indicates *H. pylori* might indeed be a factor in DM development, possibly by causing ongoing inflammation or altering gut health, which impacts metabolism [73]. This opens up discussions about whether treating *H. pylori* could help prevent DM, particularly in at-risk or infected individuals [74].

An essential aspect of this analysis was the notably low heterogeneity among the included studies, measured at 46%. This reduced variability can largely be attributed to the meticulous application of specific article selection criteria using the PECOT framework customized for this meta-analysis. The population considered had no restrictions, the exposure was defined by the presence of DM, the comparator by its absence, the outcome focused on the incidence of *H. pylori* infection, and the study design was restricted to case-control studies. Articles that deviated from these criteria or those reporting effect sizes other than ORs were omitted from the analysis.

One of the key strengths of this meta-analysis was the implementation of subgroup analyses based on variables crucial to understanding the association. These analyses were segmented by age groups: 10–20, 20–40, 40–60, and 60 and above. The choice of these groups was to cover the entire age spectrum and explore how the association might vary with age. This approach marks a significant departure from the 2019 meta-analysis, which overlooked such age-specific stratifications [8]. The findings from this meta-analysis indicated that the association between diabetes and *H. pylori* infection was most pronounced in the 40–60 age group, with a notable relationship also observed in the 10–20 age group. This suggests that age plays a pivotal role in how these conditions might interact, providing valuable insights for both research and healthcare practices.

Recent research has shed light on how *H. pylori* impact different age groups when it comes to DM. For younger folks (10–20 years), the bacteria might mess with growth and metabolism, leading to early insulin resistance. The noticeable effect here could be due to their shorter exposure time to *H. pylori*, yet their bodies are more sensitive during growth phases. In the 20–40 age range, we see a lower impact, perhaps because lifestyle choices like diet haven not fully taken hold, which might offset some effects of *H. pylori* on diabetes. For middle-aged individuals (40–60), there is a stronger association, likely because long-term *H. pylori* can lead to chronic inflammation and insulin resistance, contributing to DM [11, 75]. Older adults (60+) show varied responses, possibly due to a lifetime of accumulated health factors, including changes in how their immune systems deal with infection. However, the consistency across age groups indicates that while age might tweak the effect, *H. pylori's* link to diabetes holds steady [76, 77, 78].

Subgroup analyses based on DM type also demonstrated that *H. pylori* infection had a stronger association with the occurrence of T2DM. However, it should

be noted that the association varied depending on the type of diabetes. For T1DM, the connection is complex, potentially involving *H. pylori* in the autoimmune attack on insulin-producing cells. The inconsistency in findings might be due to differences in how studies define and diagnose T1DM or genetic factors at play [79, 80, 81]. In contrast, for T2DM, there's a clearer link, with *H. pylori* contributing to inflammation and insulin resistance, central to T2DM onset. Recent research has shown that *H. pylori* can influence insulin production and sensitivity through changes in both inflammation and gut hormones [82, 83, 84, 85, 86]. Even though the strength of association differs, *H. pylori* seem to play a role in both types of DM, just through different pathways.

This analysis highlights the need for further investigations in the future, as different types of DM play varying roles in increasing the risk of *H. pylori* infection. Conducting studies using genetic methods could be a valuable option for obtaining more precise results. The relationship between *H. pylori* and DM shows considerable geographic variation, influenced by factors like the types of *H. pylori* strains present, dietary habits, socioeconomic status, and genetics. In Africa, where *H. pylori* infection is common, there's a moderate effect, possibly due to the virulence of strains and nutritional factors [87, 88, 19, 20]. In the Americas, the association is less pronounced, which might reflect different diets or effective public health measures against *H. pylori* [21, 22]. In Asia, the effect is stronger, likely because of high infection rates and possibly more aggressive *H. pylori* strains, alongside widespread metabolic issues [23]. Europe falls somewhere in between, with diversity in results possibly due to a mix of cultural and dietary differences across countries. This regional variation highlights the need for tailored approaches to managing *H. pylori* related to diabetes risk.

Non-invasive methods for detecting *H. pylori*, like breath tests or stool tests, show a stronger link to diabetes than invasive ones, perhaps because they are easier to use, leading to more widespread testing. This suggests that these studies may detect more cases, especially in persons without visible symptoms, giving us a more complete picture of how H. pylori connect to diabetes [24, 25, 26]. However, the data does not significantly differ between methods, suggesting both are useful for understanding this relationship, with non-invasive methods just being more practical for screening. Recent improvements in non-invasive test accuracy have likely played a role in these findings.

The updated meta-analysis builds on the 2020 study by Mansori K et al. [8], which explored the relationship between *H. pylori* and DM based on data from 41 studies conducted up to 2019. By extending the literature review to January 2025, this analysis provides a more contemporary perspective on this health relationship. The primary objective of this update is to highlight the importance of this association and to refine existing clinical guidelines. New findings incorporated in this study illuminate the complex connection between *H. pylori* infection and DM risk. Moreover, the inclusion of large-sample case-control studies has enhanced the reliability of the conclusions, offering a more thorough and credible understanding. Thus, this meta-analysis not only reinforces the potential link but also establishes a foundation for future research and updates in clinical practice.

The case-control studies in this meta-analysis have both strengths and limitations. Their advantages include efficient design, suitability for studying rare outcomes, and the capacity to assess multiple risk factors. However, they are vulnerable to biases, such as recall and selection bias, and encounter challenges in establishing temporality. While case-control studies cannot definitively prove causality, they effectively identify potential associations, especially when the studies, as in this meta-analysis, demonstrate high methodological quality, scoring between 7 and 9 on the NOS.

The analysis revealed heterogeneity among the included studies. Subgroup analyses were performed to investigate further variation. The analyses were based on factors such as *H. pylori* detection methods, age groups, geographic regions, types of DM, HbA1c levels, and study quality (assessed using the NOS). The results showed that subgroups varied in heterogeneity; for instance, non-invasive detection methods exhibited greater variability than invasive methods. Effect sizes and heterogeneity levels varied by continent. Though some heterogeneity sources were identified, variability persisted in subgroups. This indicates unmeasured factors or study/population differences may influence results. Also, observational studies especially case-control studies cannot rule out confounding, so findings should be interpreted with caution.

Future directions

To understand the temporal relationship between *H. pylori* infection and DM development, longitudinal studies are needed. Long-term, prospective studies that clarify whether *H. pylori* infection precedes or follows DM onset would help establish causality. It is crucial to investigate the biological mechanisms by which *H. pylori* may affect gut microbiota, immune response, and metabolic pathways, as this exploration offers significant insights. It is essential to analyze both the host and the *H. pylori* strain. Investigating the virulence factors of various *H. pylori* strains shows which aspects are tested, with most linked to diabetes. Review intervention studies to determine if eliminating *H. pylori* reduces the onset or advancement of diabetes, particularly in individuals at

elevated risk. Expanding global health studies to include diverse populations allows examination of how socioeconomic, dietary, and cultural factors influence the *H. pylori*-DM relationship. Advances in technology and diagnostics, particularly with non-invasive methods, improve detection accuracy and understanding of *H. pylori's* role in DM risk.

Recommendations

Incorporate *H. pylori* testing into diabetic recommendations, particularly in locations with high *H. pylori* prevalence or in at-risk groups. Early detection and treatment of *H. pylori* infections may help reduce the incidence of DM. Encourage public health activities that incorporate *H. pylori* testing and treatment into diabetes preventive efforts, especially among high-risk groups. Inform healthcare professionals and patients about the dangers of untreated *H. pylori* infection, emphasizing the benefits of early detection and treatment through educational programs. Encourage research collaborations amongst domains such as endocrinology, gastrointestinal, microbiology, and epidemiology to gain a complete grasp of this relationship. Conduct cost-effectiveness analyses to determine the financial benefits of *H. pylori* screening and treatment in DM prevention, informing policy decisions. Investigate the links between nutrition, lifestyle, and *H. pylori* infection in order to find non-drug alternatives to diabetes management or prevention.

Conclusion

The meta-analysis has revealed a significant association between *H. pylori* infection and the development of DM, indicating that individuals with *H. pylori* are approximately 1.56 times more likely to develop the condition. This relationship appears to be mediated by mechanisms such as chronic inflammation, changes in gastric hormone levels, and increased insulin resistance. However, the observed variability across studies underscores the complexity of this association and highlights the need for further research to fully elucidate the underlying pathways and contributing factors. In addition to addressing *H. pylori* infection, lifestyle interventions play a critical role in mitigating the risk of diabetes and its associated complications. Regular physical activity has been shown to improve insulin sensitivity, reduce systemic inflammation, and enhance metabolic health, potentially counteracting some of the adverse effects of *H. pylori* infection. Similarly, eating a well-balanced diet high in fruits, vegetables, whole grains, and lean meats can help manage blood sugar, boost immunological function, and reduce inflammation. Public health programs that improve these modifiable lifestyle variables may dramatically lower the burden of both *H. pylori*-related diseases and DM, emphasizing the importance of a holistic approach to prevention and management.

Abbreviations

RR	Risk Ratio
OR	Odds Ratio
NOS	Newcastle-Ottawa Scale
PRISMA	The Preferred Reporting Items for Systematic Reviews and Meta-Analyses
BMI	Body Mass Index
CI	Confidence Interval

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YM, PM, and HH: concept development (provided idea for the research). RRD, KA, and HH: search strategy. HH, PM, and YM: data extraction. YM: supervision. RRD, KA, HH, and YM: analysis/interpretation. All authors: writing (responsible for writing a substantive part of the manuscript).

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Competing interests

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