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Article

A significant Association Between Type 1 Diabetes and Helicobacter pylori Infection: A Meta-Analysis Study

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Abstract: This study aimed to present a systematic meta-analysis examining the association between *Helicobacter pylori* (*H. pylori*) infection, hemoglobin A1c levels, and the development of type 1 diabetes mellitus. The initial search identified 451 articles related to the association between *H. pylori i*nfection and T1DM. Among them, 14 articles had 2,971 participants meeting the inclusion criteria for advanced meta-analysis. A significant association was observed between *H. pylori* infection and T1DM, with an odds ratio (OR) of 1.87 (95% confidence interval [CI]: 1.27–2.78, p = 0.002). A subgroup analysis on *H. pylori* status showed that a longer duration of diabetes diagnosis and higher hemoglobin A1c levels were significantly associated with H. pylori infection ($p < 0.001$ for both). However, there was no significant association between H. pylori infection and the diagnostic age of diabetes (p = 0.306). These findings contribute to the understanding of the association between H. pylori infection and T1DM, thereby highlighting the potential role of H. pylori in influencing the duration and glycemic control of diabetes.

Keywords: Helicobacter pylori; type 1 diabetes mellitus; HbA1c; child; children; young patients; pediatrics; adolescents; meta-analysis

1. Introduction

Type 1 diabetes mellitus (T1DM) is a chronic and severe disease characterized by insufficient insulin produced by pancreatic β-cells. It generally believes that T1DM predominantly affects children and young adults. However, it can manifest at any age [1]. Recent studies have shown that the incidence of T1DM had been increasing. For example, several countries in South and Central America (e.g., Colombia, Mexico, Paraguay, Peru, and Venezuela) and East Asia (including China, Japan, Pakistan, and South Korea) reported that the incidence rates of T1DM range from 0.1 to 2.2 cases per 100,000 children per year [2]. Finland and Sardinia had relatively higher rates, with approximately 40 cases per 100,000

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children per year, thereby indicating a significant subsequent increase to 60 cases per 100,000 children per year [3,4]. The actual etiology and underlying mechanisms remain largely elusive. Approximately 85%–90% of patients with T1DM exhibit autoantibodies targeting insulin, glutamic acid decarboxylase 65, insulinoma-associated autoantigen 2, zinc transporter 8, and tyrosine phosphatase IA-2β [5, 6]. Those autoimmune destruction of β-cells may lead to the development of T1DM. Therefore, an early and accurate diagnosis is imperative to provide an appropriate management and prevent complications.

Helicobacter pylori is a common gram-negative bacterium and pathogen, infecting over 50% of the global population. Because this bacterium is associated with carcinogenesis, several invasive and noninvasive diagnostic methods have been developed in clinical practice to detect this carcinogen. The invasive procedures include upper gastrointestinal endoscopy with gastric biopsy. Meanwhile, the noninvasive tests include the urea breath test, stool antigen test, and blood antigen test. These diagnostic approaches can help accurately identify *H. pylori* infection [7]. The prevalence of *H. pylori* infection ranges from 85% to 95% developing countries and from 30% to 50% in developed countries. Moreover, there has been a remarkable decline in the prevalence of *H. pylori* infection in European countries since 2000. However, the prevalence of *H. pylori* infection in Asian countries has remained relatively stable during this period [8,9]. *H. pylori* infection can have various effects on human health, thereby affecting both gastric and extra-gastric systems. The gastric complications associated with *H. pylori* infection include gastritis, peptic ulcer disease, functional dyspepsia, reflux disease, and gastric cancer. In addition, *H. pylori* infection is associated with extra-gastric complications such as cardiopulmonary diseases (coronary artery disease and asthma), hematologic diseases (iron deficiency anemia and immune thrombocytopenic purpura), neurologic diseases (ischemic stroke, Parkinson's disease, Alzheimer's disease, Guillain-Barré syndrome and migraines), dermatologic diseases (chronic spontaneous urticaria), and metabolic diseases (metabolic syndrome and insulin resistance). These diverse effects underscore the broad impact of H. pylori infection on human health [10-12].

Several studies have shown a significant association between *H. pylori* infection and elevated hemoglobin A1c (HbA1c) levels, particularly in individuals with type 2 diabetes [13-18]. Moreover, previous studies have reported higher serological prevalence rates of *H. pylori* infection among patients with T1DM [19]. Therefore, the current study aimed to conduct a systematic meta-analysis to determine the overall effect size of the association between *H. pylori* infection, HbA1c levels, and the development of T1DM in pediatric patients.

2. Material and Methods

2.1. Data Collection

All original articles were searched from international databases, including NCBI (PubMed), ISI Web of Science, EMBASE, and Cochrane Library, without language limitations. The search strategy was conducted using the PICOS tool, which uses data on population (children), intervention (diabetes), outcomes (*H. pylori* infection), and study type (case-control study). The complete list of searched keywords were Diabetes, Diabetes Mellitus (type 1 and 2), Insulin Dependent, IDDM, NIDDM, Noninsulin Dependent, Insulin Sensitivity, Helicobacter pylori, campylobacter pylori, H Pylori, Child, Children, Young patients, Pediatric, and Adolescents.

The articles meeting the following inclusion criteria were evaluated: (1) case-control studies, (2) those with patients aged <20 years, (3) those that used *H. pylori* as an exposure variable. Case reports, reviews, meta-analyses, cross-sectional studies, and cohort studies were excluded from the analysis.

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2.2. Statistical Analysis

Odds ratio (OR) and standard error were used in the meta-analysis. MedCalc was used to calculate the estimated odds ratio with 95% confidence interval. Differences in terms of means and standard deviations were used for subgroup analysis. The random-effect model was used to combine the estimated effects [20]. Statistical heterogeneity among studies was evaluated using I^2 statistics [21].

All statistical analyses were performed using the Comprehensive Meta-Analysis (CMA) 4.0 software, and a *p*-value of <0.05 was considered statistically significant.

3. Results

3.1. Characteristics and Methodologies of the Included Studies

The initial search yielded 451 articles examining the association between *H. pylori* infection and T1DM. Further examination excluded 437 articles, including 106 duplicate articles, 265 articles with unrelated outcomes, 66 reviews, letters, meta-analysis studies, and case reports. The remaining 14 articles were selected for an advanced meta-analysis (Figure 1). One study was conducted on children without information regarding age, and other studies included patients aged 10–20 years. Table 1 shows the characteristics of the included articles. In total, 2,971 participants were selected in this meta-analysis, and the total number of cases and controls in the study was 1190 and 1781, respectively. In six studies, *H. pylori* infection was diagnosed using the enzyme-linked immunosorbent assay. The remaining studies used other methods such as the ^{13}C urea breath test, RIBASIA, rapid urease test, enzyme immunoassay (EIA), and stool antigen test. Most studies are case-control studies regarding T1DM and *H. pylori* infection. To assess publication bias, a funnel plot was constructed using the logarithm and logarithm standard error of the odds ratio (OR) values for *H. pylori* infection. The funnel plot exhibited a symmetrical distribution, and it was analyzed using the Begg's rank correlation method. Results showed that the association was not statistically significant ($Pr > |z| = 0.656 > 0.05$), thereby indicating the absence of publication bias (Figure 2)

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Table 1. Primary characteristics of the included studies and the association between *H. pylori* infection and diabetes.

Author	Year	Nation	Study Design	Sample Size	Gender(Male/Female)	Age	Control Group	Measurement of association Odds Ratio(95% C.I.)	Type of diabetes (Mean of HbA1c) (Duration)	H. Pylori Test Method	Control Var.
M Pocecco, et al.	1997	Italy	Case-Control Study	379 (Control:310; Case:69)	213/166	16	Admitted for minor extra-abdominal surgery with no history of abdominal pain	6.08 (2.94, 12.58)	DM (-) (-)	ELISA	Age, sex, education and economic status
S Salardi, et al.	1999	Italy	Case-Control Study	339 (Control:236; Case:103)	N/A	12	Patients attending the hospital for minor endocrine disorders	1.79 (0.93, 3.44)	T1DM (-) (4.96±3.22 years)	RIBASIA	Age
Arslan D., et al.	2000	Turkey	Case-Control Study	130 (Control:42; Case:88)	N/A	12	Healthy children	2.80 (1.29 to 6.10)	T1DM (11.08 ± 3.17) (3.85 Years)	ELISA	-
Marcello Candelli, et	2003	Italy	Case-Control Study	268 (Control:147 ; Case:121)	145/123	14.96	Healthy participants	0.98 (0.58, 1.66)	T1DM (8.2 ± 1.4) (79.7 ± 55.5 months)	C-UBT	Age, sex, and social class
Krause I, et al.	2009	Colombia	Case-Control Study	197 (Control: 140; Case:57)	N/A	16	Healthy subjects	3.35 (1.72, 6.53)	T1DM (-) (8.8 ± 8.7 years)	ELISA	-
Cabral VL, et al.	2009	Brazil	Case-Control Study	45 (Control:30; Case:15)	N/A	17.6	Adolescents with the histological findings of gastric and duodenal biopsies with normal mucosal architecture	0.38 (0.10, 1.39)	T1DM (-) (8 ± 3.6 years)	Rapid Urease Test	-
El-Eshmawy M.M., e	2011	Egypt	Case-Control Study	242 (Control:80; Case:162)	108/134	19.49	Healthy subjects	3.58 (2.01, 6.39)	T1DM (8.2 ± 1.75) (7.29 ± 7.9 years)	ELISA	Age, sex and socioeconomic status
Candelli M, et al.	2012	Italy	Case-Control Study	168 (Control:99; Case:69)	96/72	19.8	Healthy subjects	1.96 (1.67, 11.04)	T1DM (-) (-)	C-UBT	Age, sex and social class
Zekry O.A., et al.	2013	Egypt	Case-Control Study	120 (Control:60; Case:60)	N/A	12.53	Healthy children who were selected from among relatives	2.4 (1.25,4.58)	T1DM (-) (-)	ELISA	Age, sex and socioeconomic
Agata Chobot, et al.	2014	Poland	Case-Control Study	447 (Control:298; Case:149)	201/246	13.4	Healthy children and adolescents	0.65 (0.36, 1.18)	T1DM (7.69±1.63) (4.6±3.5 years)	C-UBT	Age and sex
Samah M Osman, et	2016	Sudan	Case-Control Study	180 (Control:90; Case:90)	96/84	1-18	Healthy children	0.95 (0.51, 1.76)	T1DM (-) (duration < 6 month)	ELISA	Age and sex
Hassan Bazmamoun	2016	Iran	Case-Control Study	160 (Control:80; Case:80)	63/97	9.37	Non-Diabetic children from the same	2.25 (1.20 to 4.24)	T1DM (-) (2.14 ±0.43)	EIA Test	Age, sex and socioeconomic status
Vorontsova L., et al.	2018	Russia	Case-Control Study	128 (Control:64; Case:64)	N/A	N/A	Healthy children	1.43 (0.68, 3.03)	T1DM (-) (-)	Rapid Urease Test	-
Esmaeili Dooki MR, (	2020	Iran	Case-Control Study	168 (Control:105 ; Case:63)	81/87	10.44	Children without Diabetes Mellitus	1.18 (0.58, 2.42)	T1DM (-) (at least 6 months)	Stool Test	Age and gender

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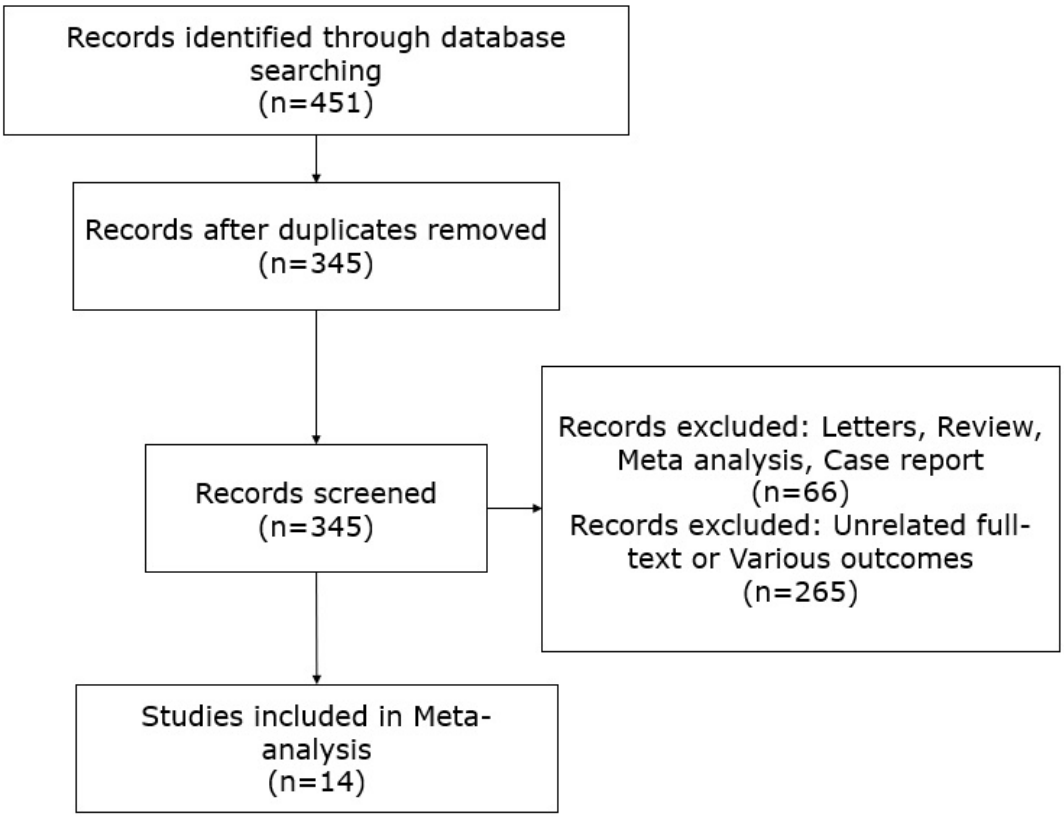

Figure 1. Flow chart of the systematic literature review.

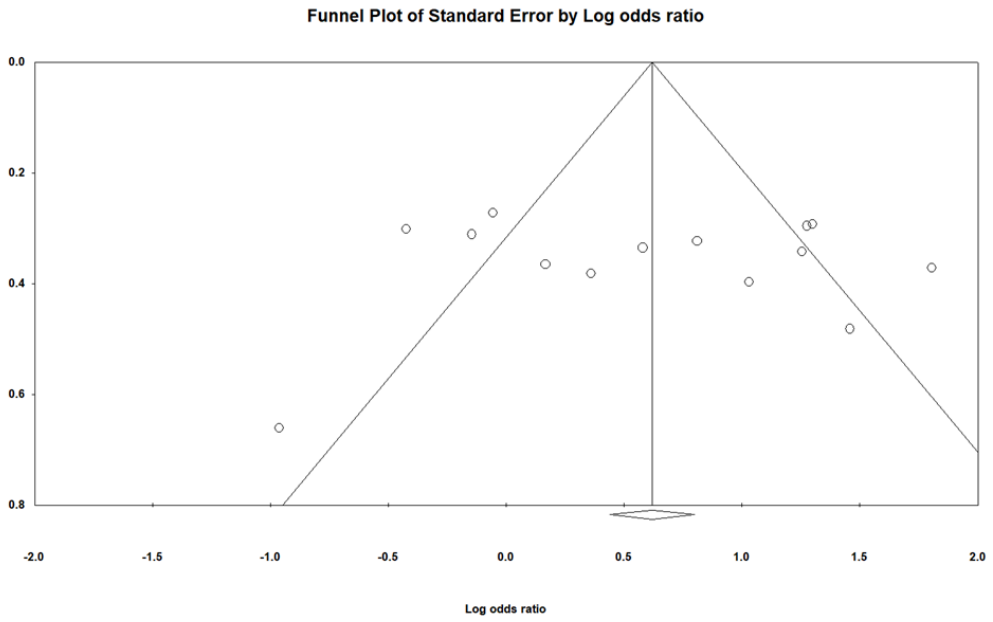

Figure 2. Funnel plot analysis of *H. pylori* infection and type 1 diabetes mellitus.

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3.2. Meta-Analysis Results

In total, 578 (44.74%) and 420 (23.32%) participants in the diabetes and healthy groups had *H. pylori* infection, respectively. The OR of the association between *H. pylori* infection and diabetes was 1.87 (95% CI: 1.27–2.78, p = 0.002) (Figure 3).

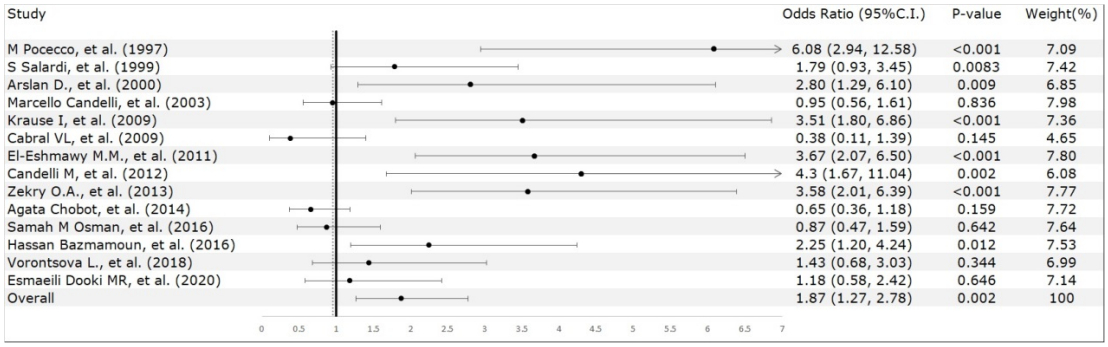

Figure 3. Correlation analysis of *H. pylori* infection and type 1 diabetes mellitus.

Data, including diagnostic age, HbA1c levels, and duration of diabetes, were comprehensively collected from patients with diabetes for an advanced subgroup analysis. The participants were divided into the *H. pylori* positive (HP+) and *H. pylori* negative (HP-) groups. This division allowed for the analysis of the association between *H. pylori* infection and these respective subgroups (Table 2).

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Table 2. Characteristics of patients with diabetes.

Author	Year	Nation	Study Design	Number of diabetic patients	Gender of diabetic patients (Male/Female)	Number of HP+ in diabetic patients	Number of HP- in diabetic patients	Diabetic-age(year)		Diabetic-HbA1c(%)		Diabetic-Duration(year)	
								HP+	HP-	HP+	HP-	HP+	HP-
M Pocecco, et al.	1997	Italy	Case-Control Study	69	42/27	18	51	16	11	7.6	7.1	3	2
S Salardi, et al.	1999	Italy	Case-Control Study	103	N/A	18	85	13.2±3.4	11.2±3.4	N/A	N/A	6±3.4	4.3±3.2
Arslan D., et al.	2000	Turkey	Case-Control Study	88	N/A	49	39	N/A	N/A	N/A	N/A	N/A	N/A
Marcello Candelli, et al.	2003	Italy	Case-Control Study	121	65/56	34	87	16± 5.6	14.3± 5.5	8.05± 4.52	7.9± 10	8.05± 4.52	5.35± 4.09
Krause I, et al.	2009	Colombia	Case-Control Study	57	24/33	26	31	N/A	N/A	N/A	N/A	N/A	N/A
Cabral VL, et al.	2009	Brazil	Case-Control Study	15	6/9	5	10	18	17	N/A	N/A	7	10
El-Eshmawy M.M., et al.	2011	Egypt	Case-Control Study	162	72/90	99	63	20.1± 4.6	19.8± 4.34	8.3 ± 1.58	6.8 ± 2.3	8.9 ± 8.6	4.22 ± 2.35
Candelli M, et al.	2012	Italy	Case-Control Study	69	41/28	17	52	N/A	N/A	8.8± 0.8	8.4± 0.7	N/A	N/A
Zekry O.A., et al.	2013	Egypt	Case-Control Study	60	N/A	128	34	12.0±2.4	12.89±2.29	7.75±1.67	5.72±1.2	9.25±2.73	6.11±1.78
Agata Chobot, et al.	2014	Poland	Case-Control Study	149	67/82	17	132	13.3±3.3	13.9±3.6	7.82±1.42	7.60±1.66	5.3±3.9	4.4±3.4
Samah M Osman, et al.	2016	Sudan	Case-Control Study	90	50/40	56	34	N/A	N/A	N/A	N/A	N/A	N/A
Hassan Bazmamoun, et al.	2016	Iran	Case-Control Study	80	32/48	48	32	7.7±0.86	7.58 ±0.65	8±0.65	7.9 ±0.40	2.72 ±0.55	1.26 ±0.13
Vorontsova L., et al.	2018	Russia	Case-Control Study	64	18/46	46	18	N/A	N/A	N/A	N/A	N/A	N/A
Esmaeili Dooki MR, et al.	2020	Iran	Case-Control Study	63	34/29	17	46	8.84±2.03	7.45±2.9	8.08±1.51	7.9 ±0.40	2.74±1.62	9.08±1.87

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In the diabetic group, further subgroup analysis was performed with the random effect model. The association between *H. pylori* infection and the diagnostic age of diabetes was not significant (p = 0.306) (Figure 4). Our results revealed that a longer diabetes diagnosis duration and high HbA1c levels were significantly associated with the *H. pylori* infection (p < 0.001 and p < 0.001, respectively) (Figures 5 and 6).

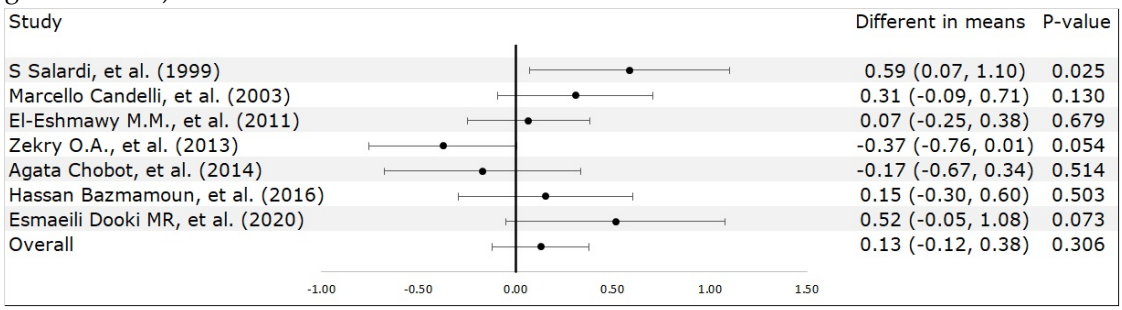

Figure 4. Correlation analysis of *H. pylori* infection and diagnostic age.

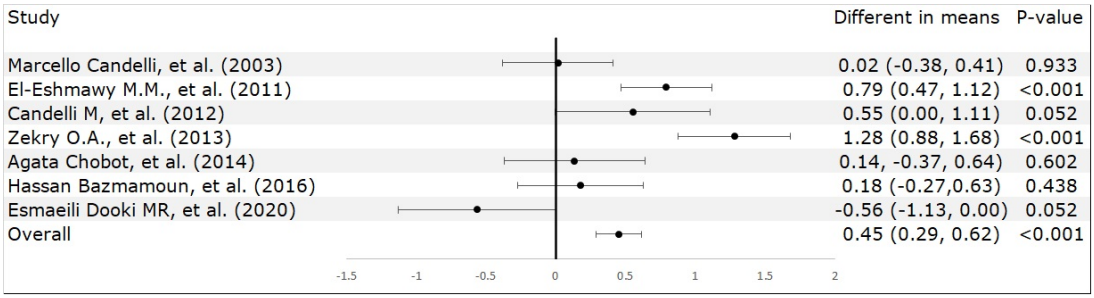

Figure 5. Correlation analysis of *H. pylori* infection and hemoglobin A1c levels.

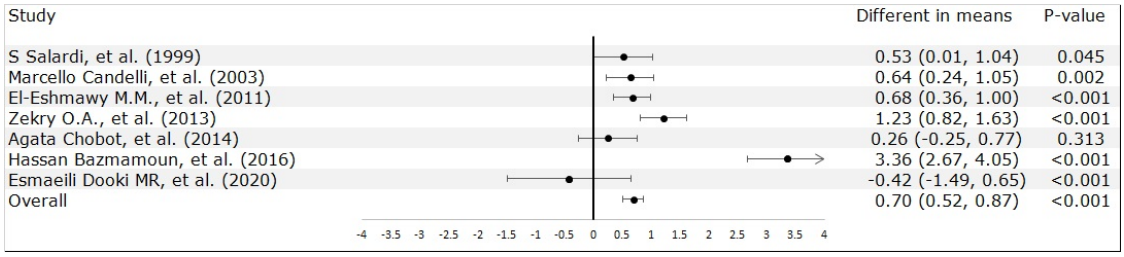

Figure 6. Correlation analysis of *H. pylori* infection and diabetes duration.

4. Discussion

This meta-analysis aimed to investigate the association between *H. pylori* infection and T1DM. Results showed a significant association between *H. pylori* infection and the risk of elevated HbA1c levels and diabetic duration in patients with T1DM. These results are in accordance with those of previous studies conducted worldwide, thereby providing further support for the above mentioned association. The seroprevalence of *H. pylori* in patients diagnosed with T1DM was significantly elevated compared with that in healthy control individuals [22-24]. The prevalence of positive *H. pylori* cases was slightly higher in patients with diabetes who were aged over 12 years and who had longer disease duration. However, the result did not significantly differ [24]. Another study showed that *H. pylori*-positive patients with higher HbA1c levels exhibited a significantly longer diabetes duration [24]. *H. pylori* infection has a substantial negative impact on metabolic control in children and adolescents diagnosed with type 1 diabetes mellitus [25,26]. In patients infected with *H. pylori*, impaired glycemic control may be attributed to the high production of pro-inflammatory cytokines triggered by gastric infection [27]. Conversely, disturbances in glucose metabolism could facilitate the colonization of *H. pylori* [28].

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A meta-analysis conducted by Feng Wang, including 39 eligible studies from 1997 to 2012, showed a significant association between *H. pylori* infection and an elevated risk of both T1DM and type 2 diabetes mellitus (T2DM) [29]. Kamyar Mansori performed a meta-analysis on 41 studies with 9,559 individuals from 1990 to 2019. Results showed a significant statistical association between *H. pylori* infection and the risk of developing diabetes. Subgroup analysis based on the type of diabetes revealed a significant association between *H. pylori* infection and the risk of T2DM. However, this meta-analysis found a positive association between T1DM and *H. pylori* infection. However, the result was not statistically significant [14]. Another study revealed that the presence of *H. pylori* infection was not significantly associated with diabetes in children with T1DM, and there was no difference in terms of glycemic control between patients with T1DM who developed *H. pylori* infection and those without [30]. The potential association between *H. pylori* infection and T1DM remains a topic of debate, particularly concerning factors such as glycemic control, gastrointestinal symptoms, infection prevalence, eradication and reinfection rates, and sanitary condition [22]. Our current study performed a meta-analysis of 14 studies with 2,971 individuals from 1997 to 2020. Results showed a positive correlation between *H. pylori* infection and HbA1c levels as well as diabetic duration in patients with T1DM. This study performed an extensive and up-to-date literature search, which identified a significant number of studies. These studies provided sufficient data to pool information from nearly 2,971 pediatric subjects, thereby indicating relatively large sample sizes. Importantly, no individual study had a substantial influence on the overall results.

An alternative inference can be made based on our findings regarding the impact of diabetes mellitus on the incidence of *H. pylori* infection. Hence, this infection might be a complication rather than a cause of DM. This result could be attributed to reduced gastric motility and peristaltic activity in individuals with diabetes, which could facilitate the colonization of *H. pylori* [28]. Furthermore, chemical changes in the gastric mucosa, such as non-enzymatic glycosylation of mucins and elevated sialic acid levels, may act as receptors on cell surfaces, thereby facilitating the adhesion of *H. pylori* to gastric mucosa cells. [31-33]. In addition, impaired non-specific immunity further contributes to the risk of *H. pylori* infection in patients with diabetes [31]. Further, several mechanisms that can explain the association between *H. pylori* infection and the risk of diabetes have been proposed. One mechanism involves inflammatory cytokines, which can induce the phosphorylation of serine residues on the insulin receptor substrate. This phosphorylation may impair the interaction between the substrate and the insulin receptors, leading to impaired insulin function [34]. Furthermore, *H. pylori* infection induces inflammation, which affects pancreatic β-cells, leading to a decrease in insulin secretion. In particular, cag+ strains of *H. pylori* can further reduce insulin secretion by affecting the production of somatostatin [14,35]. Another mechanism involves lipopolysaccharides (LPS) produced by gram-negative bacteria such as *H. pylori*. These LPS can activate Toll-like receptors, resulting in insulin resistance [36]. Moreover, *H. pylori* infection is associated with elevated leptin and ghrelin levels, which can contribute to obesity and increase the risk of developing diabetes [37]. These events collectively contribute to poor blood sugar control and the development of diabetes mellitus.

Differences in the prevalence of infection can be attributed to several factors, including the inclusion of study populations with various age and sample size. Age is an important factor as it influences *H. pylori* exposure over time, and similar age groups should be compared when examining the prevalence of infection. Furthermore, the diagnostic methods used for assessing *H. pylori* infection varied. These included the urea breath test, measurement of anti-*H. pylori* IgA, IgG, and IgM antibodies, detection of *H. pylori* antigen in stool samples, and measurement of anti-CagA IgG antibodies. These methods contribute to the divergent findings on this topic. In the current study, the assessment of fecal *H. pylori* antigens was performed, which may offer a greater relevance for identifying active gastrointestinal infection in specific patients with diabetes [38]. Notably, serologic methods cannot differentiate between recent and previous infections. Therefore, future studies should include multiple tests to provide more comprehensive and reliable results. The current study had several limitations. First, there was no information regarding the history of drug or non-drug treatments in patients with *H. pylori* infection. Such treatments can affect the presence of *H. pylori* infection and the development of metabolic syndrome and insulin resistance. Future studies should

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consider evaluating the impact of different treatments on these outcomes in individuals *with H. pylori* infection. Second, gastrointestinal co-morbidities, such as coeliac disease, were not considered; hence, these should be addressed in future studies. Third, the current study focused on patients with T1DM patients, which limited the ability to compare the association between *H. pylori* infection and HbA1c levels between patients with T1DM and those with T2DM. Therefore, future studies should include patients with T2DM to facilitate a more comprehensive analysis and provide valuable insights on the differences and similarities in the association between *H. pylori* infection and HbA1c levels across different types of diabetes. However, our study does not have access to a dataset from Asian populations, thereby limiting the generalizability of our findings to this specific demographic. To further investigate the association between H. *pylori* infection and HbA1c levels in patients with diabetes mellitus, future research should include datasets from Asian populations. This could provide a more comprehensive understanding of the association and help determine any regional variations or specific considerations that must be considered in clinical practice and the management of patients with diabetes worldwide. Notably, in this meta-analysis, all studies had a case-control design. Case-control studies can provide valuable insights about associations. However, they have inherent limitations, such as recall, and selection biases. Therefore, the design and implementation of cohort studies could be essential for a more comprehensive and detailed assessment of the association between *H. pylori* infection and diabetes. By incorporating cohort study designs, researchers can establish temporal associations, follow-up participants over time, and gather longitudinal data, which can enhance our understanding of the causal association between *H. pylori* infection and diabetes. Further, they can examine potential confounding factors and provide more robust evidence. In addition, it is important to acknowledge that personal judgments may have influenced various stages of the meta-analysis, including the search for articles, data extraction, and the assessment of included articles. To minimize bias, rigorous, and systematic methods, such as predefined search criteria, independent data extractions, and quality assessment, were used. To further advance our understanding of the association between *H. pylori* infection and diabetes, future research should prioritize the inclusion of well-designed cohort studies. These studies should adhere to transparent and rigorous methodologies to minimize biases and increase the validity and generalizability of the findings. Moreover, data on important variables including weight loss, socioeconomic status, and household size were not collected. Nevertheless, future studies should include such details as they can contribute to a more comprehensive understanding of the topic.

5. Conclusions

The subgroup analysis revealed a significant positive association between *H. pylori* infection and HbA1c levels as well as the duration of diabetes diagnosis. Therefore, chronic conditions characterized by dysregulated glycemic control and prolonged disease onset may increase the risk of *H. pylori* infection. Hence, large-scale cohort studies with a substantial sample size should be performed to further assess this association. This can provide more robust evidence and a better understanding of the association between *H. pylori* infection and the outcomes of interest.

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Data Availability Statement

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