Review Article

_Helicobacter pylori_ Infection Is Associated with Type 2 Diabetes, Not Type 1 Diabetes: An Updated Meta-Analysis

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Background. Extragastric manifestations of _Helicobacter pylori_ (H. pylori) infection have been reported in many diseases. However, there are still controversies about whether _H. pylori_ infection is associated with diabetes mellitus (DM). This study was aimed at answering the question. Methods. A systematic search of the literature from January 1996 to January 2016 was conducted in PubMed, Embase databases, Cochrane Library, Google Scholar, Wanfang Data, China national knowledge database, and SinoMed. Published studies reporting _H. pylori_ infection in both DM and non-DM individuals were recruited. Results. 79 studies with 57,397 individuals were included in this meta-analysis. The prevalence of _H. pylori_ infection in DM group (54.9%) was significantly higher than that (47.5%) in non-DM group (OR = 1.69, \(P < 0.001\)). The difference was significant in comparison between type 2 DM group and non-DM group (OR = 2.05), but not in that between type 1 DM group and non-DM group (OR = 1.23, 95% CI: 0.77–1.96, \(P = 0.38\)). Conclusion. Our meta-analysis suggested that there is significantly higher prevalence of _H. pylori_ infection in DM patients as compared to non-DM individuals. And the difference is associated with type 2 DM but not type 1 DM.

1. Introduction

_Helicobacter pylori_ (H. pylori) is a gram-negative spiral bacterium, colonized in the stomach. Approximately one-half of the population over the world is infected with _H. pylori_ [1]. Many researches have proved that _H. pylori_ infection is highly associated with gastrointestinal diseases such as chronic gastritis, peptic ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma since its discovery [2]. In addition, extragastric disorders associated with _H. pylori_ infection, such as cardiovascular diseases and metabolic syndrome, have been revealed and some of them were characterized by persistent and low-grade systemic inflammation [3]. Inflammation has been demonstrated to play an important part in the pathogenesis of diabetes mellitus (DM), especially type 2 DM (T2DM) [4]. On the other hand, Kondrashova and Hyöty reviewed that some microbes served as the risk factor participating in the trigger and the development of type 1 DM (T1DM), but some microbes such as _H. pylori_ served as a protective factor by lowering the risk of T1DM [5]. Above all, _H. pylori_ infection was a factor not negligible in the process of DM.

Since Simon et al. firstly reported the association between _H. pylori_ infection and DM [6], many studies were carried out. Several case-control studies have reported a higher prevalence of _H. pylori_ infection in DM patients [7, 8]. Some cross-sectional researches also revealed a significant correlation between _H. pylori_ infection and diabetes [9–11]. Moreover, a meta-analysis carried out by Zhou et al. suggested a trend toward more frequent _H. pylori_ infection in DM patients, especially in T2DM patients [12]. However, Tamura et al. found a significantly higher DM prevalence among individuals with _H. pylori_ infection than those without, but the
difference could be mostly ascribed to older age [13]. And some studies argued that no difference in the prevalence of *H. pylori* infection was found between DM and non-DM individuals [14, 15]. Overall, this subject remains controversial now.

The present updated meta-analysis was conducted to answer if there is a difference in the prevalence of *H. pylori* infection between DM and non-DM individuals. Subgroup analyses were carried out based on the types of DM, geographical regions, and methods for *H. pylori* detection to further investigate the relationship between *H. pylori* infection and DM.

2. Methods

2.1. Search Strategy and Selection Criteria. Published guidelines for conducting meta-analyses were followed [16]. We searched PubMed, Embase databases, Cochrane Library, Google Scholar, Wanfang Data (Chinese), China national knowledge database (Chinese), and SinoMed (Chinese) for all relevant articles reported from January 1996 to January 2016, with combinations of the search terms “Helicobacter pylori,” or “*H. pylori*,” or “Campylobacter pylori,” or “*C. pylori*,” and “diabetes mellitus,” or “diabetes,” or “type 1 diabetes,” or “type 1 diabetes mellitus,” or “type 2 diabetes” or “type 2 diabetes mellitus”.

To be eligible for inclusion, studies had to meet the following criteria: (1) they were published studies which reported *H. pylori* infection in DM individuals and non-DM individuals (individuals without DM, impaired glucose tolerance, or impaired fasting glucose); (2) detailed data of *H. pylori* infection rate in both groups was provided. Studies that did not meet the inclusion criteria were not enrolled.

Studies were excluded if they were as follows: (1) duplicate publications; (2) case report, review, meta-analysis, or guideline; (3) not reporting clinically relevant outcomes; and (4) not providing enough details.

2.2. Data Extraction and Quality Assessment. Data were extracted by one investigator, verified by another investigator, and recorded in a well-designed form developed for this study. The data items included authors, year of publication, country, study design, methods of *H. pylori* detection, strains of *H. pylori*, types of DM, age, and sample size. The Newcastle-Ottawa scale (NOS) scoring system was used to assess the quality of the studies [17].

2.3. Statistical Analysis. To obtain pooled effect estimates, the random effects model or fixed effects model was used for meta-analysis, according to the heterogeneity among studies. If there was no statistically significant heterogeneity (two-tailed *P* value >0.05) among the pooled studies, the fixed effect model would be applied; otherwise, the random effect model would be applied [18]. Odds ratio (OR) with 95% confidence interval (CI) was used for the case-control and cross-sectional studies, while risk ratio (RR) was for the cohort studies. The presence of between-study heterogeneity was estimated using *Q*-test and *I*² statistics. Sources of heterogeneity were explored by conducting subgroup analyses based on types of DM, geographical regions, and methods of *H. pylori* detection. The two-sided tests with significance level of 0.05 were conducted in pooled analyses and subgroup analyses using RevMan software (Version 5.3 for Windows, Cochrane Collaboration, Oxford, UK). Publication bias was evaluated graphically by the funnel plots and statistically by Begg’s test and Egger’s test with the STATA software (Version 14.0; STATA Corporation, College Station, TX, US). *Pr* and *P* value less than 0.05 were considered representative of no statistically significant publication bias. If publication bias was indicated, the trim and fill method procedure was performed to identify and correct the publication bias [19]. The basis of the method was to (1) “trim” (remove) the studies causing funnel plot asymmetry, (2) use the trimmed funnel plot to estimate the true “centre” of the funnel, and then (3) replace the removed studies and their missing “counterparts” around the centre (filling). An estimate of the number of missing studies was provided; an adjusted OR is derived by performing a meta-analysis including the filled studies.

3. Results

3.1. Description of Studies. A total of 783 studies were retrieved from PubMed, Embase databases, Cochrane Library, Google Scholar, Wanfang Data (Chinese), China national knowledge database (Chinese), and SinoMed (Chinese). According to the criteria for inclusion and exclusion, 79 studies were included in this meta-analysis (Figure 1). The included study characteristics were summarized in Table 1. All of the articles were qualified to be pooled with quality score of NOS over 5. 76 studies were either case-control or cross-sectional studies, and 3 were prospective cohort ones.

A total of 57,397 individuals were enrolled in these studies, with a total *H. pylori* infection prevalence of 49.7% (28,542/57,397). The pooled *H. pylori* infection rate was 54.9% (9434/17,187) in DM group and 47.5% (19,108/40,210) in non-DM group. The OR was 1.69 (95% CI: 1.47–1.95, *P* < 0.001) for the two groups. There was high heterogeneity among the studies (*I*² = 86%). The forest plot for pooled prevalence is shown in Figure 2. Each study was sequentially removed from the analysis, and the adjusted ORs (1.63–1.73) were approximate to the initial ones. Especially, the study of Han et al. [20] recruited a total of 6395 patients in DM group and 24,415 in non-DM group, which accounted for nearly one-third of the enrolled individuals in this analysis. However, after removing the data of Han et al. and re-analyzing, the adjusted odds (OR = 1.71) and heterogeneity (*I*² = 83%) were still approximate to the initial ones in spite of its overweight scale.

3.2. Subgroup Analysis. We found a significant association between *H. pylori* infection and DM but the pooled analysis was with high heterogeneity (*I*² = 86%). Subgroup analyses based on the types of DM, geographical regions, and methods for *H. pylori* detection were conducted to detect the sources of heterogeneity.
(1) Types of DM

12 studies with 3175 individuals were assigned to the T1DM subgroup, while 42 studies with 41,684 individuals were to the T2DM subgroup. No significant difference was found between T1DM group and non-DM group in *H. pylori* infection rate (OR = 1.23, 95% CI: 0.77–1.96, *P* = 0.38; Figure 3). On the contrary, the pooled data indicated that the prevalence of *H. pylori* infection in T2DM was significantly higher than that in non-DM group (OR = 2.05, 95% CI: 1.67–2.52, *P* < 0.001; Figure 3). Each study including the study by Han et al. with overweight scale was sequentially removed in the subgroups and the adjusted ORs (1.93–2.10 in T2DM and 1.10–1.42 in T1DM) approximated to the initial ones.

(2) Geographical regions

Subgroup studies stratified by geographical regions were performed. The recruited individuals were mostly from Asia (75.8%, 43,523/57,397). The infection rate was 51.7% (22,503/43,523), 39.7% (2969/7479), 47.3% (2562/5411), and 48.7% (499/1024) in group Asia, group Europe, group America, and group Africa, respectively. No significant difference of *H. pylori* infection rate between DM and non-DM individuals was found in group America and group Africa (OR = 0.36 for America; *P* = 0.38 for Africa). However, in group Asia and group Europe, significantly higher *H. pylori* infection rate was detected in DM individuals (OR = 2.04 and OR = 1.40, resp.). But there was still high heterogeneity within these subgroups (*I^2* = 68%–90%; Figure 4).

(3) Methods for *H. pylori* detection

Methods for *H. pylori* detection displayed different power in accuracy, which consequently might affect the detection rate of *H. pylori* infection. Methods for diagnosis of *H. pylori* were classified as invasive tests and noninvasive tests [21]. Invasive tests included rapid urease test, histology, and culture, and the noninvasive tests included 13C or 14C urea breath test, stool antigen detection, and serological approaches for antibodies of *H. pylori*. For the serological tests of anti-*H. pylori* IgG or/and IgA antibody in serum, high rates of false-positive results may happen and they cannot identify the differences between the current infection and past infection [21,22]. So we typically sorted the studies with detection method of serological test into one subgroup and others into the other subgroup as they could identify the current infection precisely.

The studies of current infection group comprised of 51 articles and showed a significant higher prevalence of *H. pylori* infection in DM patients as compared to that in non-DM individuals with OR = 1.92 (95% CI: 1.57–2.34, *P* < 0.001). Similarly, by enrolling 21 articles in serological test group, we found that the infection rate was 53.7% (1956/3640) in DM group while 46.4% (4097/8829) in the non-DM one (OR = 1.40, 95% CI: 1.10–1.79, *P* < 0.001; Figure 5). The heterogeneities in both groups were high among studies with *I^2* = 89% and *I^2* = 81%, respectively (Figure 5).

3.3. Publication Bias. Funnel plot analysis did not show significant evidences of publication bias (Figure 6). Most of the studies were concentrated symmetrically. No significant publication bias was detected by Begg’s test with Pr = 0.411.
Table 1: Characteristics of the included studies.

| Author                  | Year | Country | Study design       | Type of DM | Age (years)* | Method of detection* | NOS |
|-------------------------|------|---------|--------------------|------------|--------------|----------------------|-----|
| Han et al. [20]         | 2016 | China   | Cross-sectional    | T2DM       | 64.1 ± 8.6   |                      | 1   |
| Kayar et al. [7]        | 2015 | Turkey  | Case-control       | T2DM       | 18–65        |                      | 2   |
| Vafaieimanesh et al. [10] | 2015 | Iran    | Cross-sectional    | T2DM       | 52.84 ± 8.82 |                      | 3   |
| Zhou et al. [14]        | 2015 | China   | Case-control       | T2DM       | 42.4 ± 9.8   |                      | 3, 4|
| Qiao et al. [45]        | 2015 | China   | Case-control       | T2DM       | 52.5 ± 1.7   |                      | 1   |
| Ji et al. [46]          | 2015 | China   | Case-control       | T2DM       | 51.6 ± 12.5  |                      | 1, 3|
| Bajaj et al. [9]        | 2014 | India   | Case-control       | T2DM       | ≥18          |                      | 3, 4, 8|
| Chobot et al. [47]      | 2014 | Poland  | Case-control       | T1DM       | 13.4 ± 3.4   |                      | 1   |
| Sotuneh et al. [15]     | 2014 | Iran    | Cross-sectional    | DM         | Elderly      |                      | 3   |
| Yang et al. [11]        | 2014 | Taiwan  | Cross-sectional    | T2DM       | 59.6 ± 10.0  |                      | 5, 9|
| Zhang et al. [48]       | 2014 | China   | Case-control       | DM         | 52.14 ± 10.25|                      | 1   |
| Wei et al. [49]         | 2014 | China   | Case-control       | T2DM       | 52.79 ± 12.86|                      | 1   |
| Ye and Xu [50]          | 2014 | China   | Case-control       | T2DM       | 54.2 ± 2.0   |                      | 1   |
| Liu et al. [51]         | 2014 | China   | Case-control       | T2DM       | 51–65        |                      | 1   |
| Zhou et al. [52]        | 2014 | China   | Case-control       | T2DM       | 57.8 ± 11.7  |                      | 1   |
| Wang F and Wang XF [53] | 2014 | China   | Case-control       | T2DM       | 54.6 ± 1.4   |                      | 1   |
| Bai et al. [54]         | 2014 | China   | Case-control       | T2DM       | 52.5 ± 14.2  |                      | 1   |
| Jia et al. [55]         | 2014 | China   | Case-control       | DM         | 61.0 ± 10.0  |                      | 1   |
| Jafarzadeh et al. [56]  | 2013 | Iran    | Cross-sectional    | DM         | 42.86 ± 6.42 |                      | 3   |
| Keramat et al. [57]     | 2013 | Iran    | Case-control       | DM         | 51.20 ± 11.60|                      | 3, 4, 5|
| Xue et al. [58]         | 2013 | China   | Case-control       | T2DM       | 57.03 ± 11.29|                      | 1   |
| Luo H [59]              | 2013 | China   | Case-control       | DM         | 51.5 ± 4.9   |                      | 4   |
| Candelli et al. [60]    | 2012 | Italy   | Prospective cohort | T1DM       | 19.8 ± 4.3   |                      | 1   |
| Jeon et al. [32]        | 2012 | USA     | Prospective cohort | DM         | 67.9 (64.1–71.3)|                      | 3   |
| Oluyemi et al. [61]     | 2012 | Nigeria | Cross-sectional    | T2DM       | 56.4 ± 10.4  |                      | 2   |
| Hao et al. [62]         | 2012 | China   | Case-control       | DM         | 47.24 ± 8.49 |                      | 1   |
| Xu et al. [63]          | 2012 | China   | Case-control       | T2DM       | 61.0 ± 10.96 |                      | 3   |
| El-Eshmawy et al. [40]  | 2011 | Egypt   | Case-control       | T1DM       | 19.35 ± 2.6  |                      | 3   |
| Wang et al. [64]        | 2011 | China   | Case-control       | T2DM       | 53.4 ± 1.8   |                      | 1   |
| Chen et al. [65]        | 2011 | China   | Case-control       | DM         | 53.0 ± 5.6   |                      | 1   |
| Agrawal et al. [66]     | 2010 | India   | Case-control       | T2DM       | —            |                      | 5   |
| Devrajani et al. [8]    | 2010 | Pakistan| Case-control       | T2DM       | >35          |                      | 2   |
| Ibrahim et al. [44]     | 2010 | Egypt   | Case-control       | T2DM       | 45 ± 5.4     |                      | 4, 5, 6|
| Sfarti et al. [37]      | 2010 | Romania | Case-control       | T1DM       | 49.5 ± 14.2  |                      | 1, 4, 5|
| Xu et al. [67]          | 2010 | China   | Case-control       | T2DM       | 51.5 ± 13.0  |                      | 1   |
| Cabral et al. [68]      | 2009 | Brazil  | Case-control       | T1DM       | 17.6 ± 1.5   |                      | 5   |
| Ciortescu et al. [69]   | 2009 | Romania | Case-control       | DM         | —            |                      | 1, 3, 5|
| Krause et al. [38]      | 2009 | Israel  | Case-control       | T1DM       | 16.0 ± 8.7   |                      | 3   |
| Lazaraki et al. [70]    | 2009 | Greece  | Case-control       | T2DM       | 65.32 ± 8.56 |                      | 4, 5, 6|
| Zhang LQ and Zhang MQ [71]| 2009 | China   | Case-control       | T2DM       | 56.5 ± 1.1   |                      | 1   |
| Yu [72]                 | 2009 | China   | Case-control       | T2DM       | 52.5 ± 13.4  |                      | 1   |
| Ariizumi et al. [73]    | 2008 | Japan   | Case-control       | DM         | 62.5 ± 11.5  |                      | 3, 4, 5|
| Demir et al. [74]       | 2008 | Turkey  | Case-control       | T2DM       | 52 ± 8.2     |                      | 5   |
| Hamed et al. [75]       | 2008 | Egypt   | Case-control       | DM         | 47.65 ± 1.2  |                      | 3   |
| Nicholas et al. [76]    | 2008 | Nigeria | Case-control       | T2DM       | 29–72        |                      | 3   |
| Yan et al. [77]         | 2008 | China   | Case-control       | T2DM       | 32–85        |                      | 1   |
| Wang et al. [78]        | 2008 | China   | Case-control       | T2DM       | 47.1 ± 6.37  |                      | 5   |
| Ji YF et al. [79]       | 2008 | China   | Case-control       | T2DM       | 55.2 ± 13.5  |                      | 5   |
but a significant bias was detected by Egger’s test with $P < 0.001$ (Figure 7). As Egger’s test indicated the possibility of publication bias, the trim and fill procedure was performed to identify and correct the publication bias. There was 14 hypothetical missing studies indicated by the trim and fill procedure, and the imputed pooled estimate was $1.366$ (95% CI: $1.181–1.580$, $P < 0.001$). There still existed a statistically significant association between $H. pylori$ infection and DM after adjusting for the publication bias, which suggested that our result was credible. Adjusted funnel plot by the trim and fill method was symmetrical and shown in Figure 8.

### 4. Discussion

DM is a chronic disease characterized by a long-term inflammation mechanism. Guo et al. demonstrated that diabetes was a risk factor for $H. pylori$ infection [23]. Several meta-analyses aiming to investigate the association between $H. pylori$ infection and DM have been carried out. Zhou et al. recruited 41 studies involving 14,080 patients, and the analysis reported higher risk of $H. pylori$ infection among DM patients with $OR = 1.33$ (95% CI: $1.08–1.64$) [12]. Wang et al. retrieved 39 studies involving more than 20,000 participants, with the $OR = 1.59$ (95% CI: $1.33–1.90$) [24]. Our meta-analysis was an updated one and included more studies and individuals. Consistently, we found that the prevalence of $H. pylori$ infection was significantly higher in DM patients. But we brought more robust result with higher OR ($OR = 1.69$, 95% CI: $1.47–1.95$; Figure 2). Moreover, we explored more databases and recruited 25 studies reported in Chinese with high-quality score of NOS (all of them were >5). In addition, in subgroup analysis, we found no significant difference in prevalence of $H. pylori$ infection.
FIGURE 2: Forest plot for pooled prevalence of *H. pylori* infection in DM group and non-DM group.
| Study or subgroup | DM Events | Non-DM Events | Weight | Odds ratio M-H, Random, 95% CI | Year | Odds ratio M-H, Random, 95% CI |
|------------------|-----------|---------------|--------|--------------------------------|------|--------------------------------|
| T2DM             |           |               |        |                                |      |                                |
| Han et al. 2016  | 3254      | 6395          | 12.041 | 24.415                         | 3.0% | 1.06 (1.01, 1.12)               | 2016 |
| Ji et al. 2015   | 83        | 125           | 73     | 142                            | 2.6% | 1.87 (1.14, 3.07)               | 2015 |
| Vafeimaneh et al. 2015 | 139    | 211           | 110    | 218                            | 2.7% | 1.90 (1.28, 2.80)               | 2015 |
| Qiao et al. 2015 | 25        | 42            | 9      | 20                             | 1.7% | 1.80 (0.61, 5.27)               | 2015 |
| Zhou et al. 2015 | 106       | 188           | 28     | 65                            | 2.5% | 1.71 (0.97, 3.02)               | 2015 |
| Kayar et al. 2015 | 40       | 62            | 31     | 71                            | 2.2% | 2.35 (1.16, 4.73)               | 2015 |
| Bai et al. 2014  | 102       | 150           | 80     | 150                           | 2.6% | 1.86 (1.16, 2.97)               | 2014 |
| Yang et al. 2014 | 147       | 238           | 358    | 729                           | 2.9% | 1.67 (1.24, 2.26)               | 2014 |
| Basu et al. 2014 | 62        | 80            | 35     | 60                            | 2.2% | 2.46 (1.18, 5.13)               | 2014 |
| Wang F and Wang XF 2014 | 52   | 80            | 40     | 60                            | 2.4% | 1.86 (0.98, 3.50)               | 2014 |
| Zhou et al. 2014 | 148       | 200           | 71     | 180                           | 2.7% | 4.37 (2.83, 6.75)               | 2014 |
| Liu et al. 2014  | 240       | 281           | 41     | 86                            | 2.5% | 6.42 (3.75, 11.00)              | 2014 |
| Wei et al. 2014  | 68        | 109           | 51     | 106                           | 2.5% | 1.79 (1.04, 3.08)               | 2014 |
| Ye and Xu 2014   | 84        | 110           | 50     | 120                           | 2.5% | 3.95 (2.24, 6.97)               | 2014 |
| Xue et al. 2013  | 79        | 120           | 60     | 120                           | 2.5% | 1.93 (1.15, 3.24)               | 2013 |
| Xu et al. 2012   | 58        | 130           | 18     | 50                            | 2.3% | 1.43 (0.73, 2.81)               | 2012 |
| Olyemli et al. 2012 | 18  | 100           | 13     | 100                           | 2.1% | 1.47 (0.68, 3.19)               | 2012 |
| Wan et al. 2011  | 92        | 120           | 59     | 130                           | 2.5% | 3.95 (2.29, 6.83)               | 2011 |
| Agrawal et al. 2010 | 50      | 80            | 32     | 80                            | 2.4% | 2.50 (1.32, 4.72)               | 2010 |
| Xu et al. 2010   | 430       | 768           | 65     | 172                           | 2.8% | 2.09 (1.49, 2.94)               | 2010 |
| Ibrahim et al. 2010 | 53   | 98            | 58     | 102                           | 2.5% | 0.89 (0.51, 1.56)               | 2010 |
| Devaraju et al. 2010 | 54  | 74            | 38     | 74                            | 2.3% | 2.56 (1.29, 5.08)               | 2010 |
| Yu 2009          | 135       | 180           | 80     | 150                           | 2.6% | 2.63 (1.65, 4.18)               | 2009 |
| Zhang LQ and Zhang MQ 2009 | 100 | 160           | 76     | 160                           | 2.7% | 1.84 (1.18, 2.88)               | 2009 |
| Lazarakis et al. 2009 | 20 | 49            | 12     | 29                            | 1.9% | 0.98 (0.38, 2.48)               | 2009 |
| Wang et al. 2008  | 65        | 103           | 72     | 175                           | 2.6% | 2.45 (1.48, 4.04)               | 2008 |
| Yan et al. 2008  | 113       | 150           | 36     | 70                            | 2.4% | 2.88 (1.59, 5.24)               | 2008 |
| Nicholas et al. 2008 | 21  | 60            | 17     | 60                            | 2.1% | 1.36 (0.63, 2.95)               | 2008 |
| Ji YF et al. 2008 | 81        | 120           | 76     | 110                           | 2.5% | 0.93 (0.53, 1.62)               | 2008 |
| Demir et al. 2008 | 87        | 141           | 83     | 142                           | 2.6% | 1.15 (0.71, 1.84)               | 2008 |
| Bener et al. 2007 | 161       | 210           | 136    | 210                           | 2.7% | 1.79 (1.17, 2.74)               | 2007 |
| Sun et al. 2007  | 76        | 230           | 54     | 150                           | 2.7% | 0.88 (0.57, 1.35)               | 2007 |
| Lu et al. 2006   | 74        | 132           | 5      | 24                            | 1.7% | 4.85 (1.71, 13.76)              | 2006 |
| Gulcelik et al. 2005 | 59   | 78            | 33     | 71                            | 2.3% | 3.58 (1.78, 7.17)               | 2005 |
| Candelli et al. 2003 | 34   | 121           | 43     | 147                           | 2.5% | 0.95 (0.56, 1.61)               | 2003 |
| Maula et al. 2002 | 22        | 31            | 15     | 31                            | 1.7% | 2.61 (0.91, 7.43)               | 2002 |
| Cenedelli et al. 2002 | 13  | 30            | 18     | 43                            | 1.8% | 1.06 (0.41, 2.73)               | 2002 |
| Zhao 2001        | 230       | 370           | 19     | 255                           | 2.6% | 20.41 (12.22, 34.07)            | 2001 |
| Ko et al. 2001   | 32        | 63            | 31     | 55                            | 2.2% | 0.80 (0.39, 1.65)               | 2001 |
| Senturk et al. 2001 | 59  | 67            | 58     | 72                            | 1.9% | 1.78 (0.69, 4.56)               | 2001 |
| Gövener et al. 1999 | 41   | 51            | 14     | 25                            | 1.7% | 3.2 (1.13, 9.20)                | 1999 |
| Gentile et al. 1998 | 122  | 164           | 82     | 164                           | 2.6% | 2.90 (1.82, 4.63)               | 1998 |
| Total (95% CI)   | 12,271    | 29,413        | 100.0% | 100.0%                        | 2.05 (1.67, 2.52) |  |
in comparison between T1DM patients and non-DM patients, which was inconsistent with what was reported by Wang et al. In a subgroup analysis of geographical regions, we found significant higher \textit{H. pylori} infection rate among DM individuals in group Asia and group Europe but not in group Africa or group America. It was inconsistent with the Zhou et al. study which reported that the \textit{H. pylori} effect only happened in Asian people. In this meta-analysis, we found no publication bias with Begg’s test, while Egger’s test showed a possibility of publication bias. But we performed the trim and fill method and found 14 hypothetical missing studies. The imputed pooled result still supported our original one. Therefore, no publication bias was shown in our meta-analysis and the result we got was credible. In this meta-analysis, the study of Han et al., even though with a total of 30,810 participants, did not affect the significance of the pooled results. Maybe it was because the other studies recruited as enough individuals (a total of 26,587 participants) as to be commensurate to the scale of the Han et al. study. Furthermore, the quality score of NOS for the study Han et al. was 9, which was high. Hence, despite the over-weight scale, the study of Han et al. should not be neglected.

We found that there existed an association between \textit{H. pylori} infection and DM in this meta-analysis. Several possible mechanisms might explain the association.

Hyperglycemic condition in diabetic individuals could result in immune dysfunction, including damage to the neutrophil function, depression of antioxidant system, and impaired humoral immunity [25]. Moreover, abnormal enteric neuropathy caused by high blood sugar can modulate immune-cell function and stimulate proinflammatory cytokine production, resulting in neurodegeneration [26]. It leads to delay gastric emptying and lacking of acid secretion, which promotes bacterial colonization or overgrowth in gastrointestinal tract [27]. On the other hand, \textit{H. pylori} infection in diabetic patients may worsen glycemic control [28], which leads to the difficulty of DM treatment, forming the vicious circle.

In this meta-analysis, we found that DM patients had a higher prevalence of \textit{H. pylori} infection. But we could not come to the result whether and what role \textit{H. pylori} infection plays on the pathogenesis or development of DM. It was reported that patients could be connected with \textit{H. pylori} and some other pathogens like herpes simplex virus 1, cytomegalovirus, and Epstein-Barr virus, some of whom were also associated with DM [29–31]. But the number of researches on this issue was limited. We could not know whether other pathogens affect the effect of \textit{H. pylori} on DM, either. Jeon et al. firstly carried out a prospective cohort study of 782 Latino elderly aged >60 years and

Figure 4: Forest plot for subgroup analysis based on geographic regions. (India, Japan, China, Qatar, Pakistan, Saudi Arabia Iran, Hong Kong, and Taiwan were included in group Asia. Greece, Turkey, Italy, Poland, Romania, Belgium, Spain, Croatia, Israel, UK, and Czech Republic were included in group Europe, as well as Australia because it comprises similar races and people who lived in similar lifestyle with these countries. Brazil and USA were included in group America. Egypt and Nigeria were included in group Africa.)
| Study or subgroup | Non-DM Events | Total | Weight | Odds ratio M-H, Random, 95% CI | Year |
|------------------|--------------|-------|--------|-------------------------------|------|
| Han et al. 2016  | 5529         | 12695 | 42,415 | 2.5%                          | 2016 |
| Qin et al. 2015  | 25           | 42     | 1      | 1.3%                          | 2015 |
| Roy et al. 2015  | 40           | 62     | 31     | 1.9%                          | 2015 |
| Liu et al. 2014  | 240          | 281    | 41     | 2.1%                          | 2014 |
| Zhou et al. 2014 | 245          | 271    | 78     | 2.3%                          | 2014 |
| Liu et al. 2014  | 102          | 170    | 80     | 2.2%                          | 2014 |
| Yang et al. 2014 | 147          | 238    | 358    | 2.4%                          | 2014 |
| Schwab et al. 2014| 9            | 54     | 120    | 2.1%                          | 2014 |
| Li et al. 2013   | 69           | 49     | 118    | 2.1%                          | 2014 |
| Sall et al. 2013 | 71           | 74     | 145    | 2.1%                          | 2014 |
| Xu et al. 2013   | 18           | 100    | 120    | 2.2%                          | 2014 |
| Xia et al. 2013  | 18           | 100    | 120    | 2.2%                          | 2014 |
| Xu et al. 2013   | 18           | 100    | 120    | 2.2%                          | 2014 |
| Ye et al. 2013   | 18           | 100    | 120    | 2.2%                          | 2014 |
| Zhang et al. 2013| 18           | 100    | 120    | 2.2%                          | 2014 |
| Zeng et al. 2013 | 18           | 100    | 120    | 2.2%                          | 2014 |
| Total            |              | 195    | 230    | 34%                           | 2014 |

**Forest plot for subgroup analysis of methods for H. pylori detection.**

**Gastroenterology Research and Practice**
After following up over 10 years, the authors demonstrated that *H. pylori* seropositive patients experienced a greater rate of incident DM than individuals without DM (hazard ratio 2.69, 95% CI: 1.10–6.60), whereas those who were seropositive for herpes simplex virus 1, varicella virus, cytomegalovirus, and *Toxoplasma gondii* did not show an increased rate of DM. It indicated that *H. pylori* infection might play an unknown role in the pathogenesis of DM, which implicated a potential step for preventing DM by eradication of *H. pylori* infection. Moreover, it also suggested that other pathogens such as cytomegalovirus and herpes simplex virus 1 might not
have the similar effect on the DM like *H. pylori*. But our meta-analysis just revealed the association between *H. pylori* and DM, but could not suggest the effect of *H. pylori* on DM pathogenesis. More researches are needed to find out the actually effect of *H. pylori* infection on DM.

In subgroup analysis based on the types of DM, we demonstrated that 56.5% T2DM individuals were infected with *H. pylori*, but only 36.2% T1DM carried the bacterium (Figure 3). T2DM was more significantly prone to the infection of *H. pylori*. As to T2DM, insulin resistant (IR) is one of its characteristics. Aydemir et al. showed that IR was significantly higher in *H. pylori* infection group [33]. And Esraghian et al. also supported that *H. pylori* infection was a risk factor for IR [34, 35]. Furthermore, it was reported that IR in T2DM patients could be improved after successful eradication of *H. pylori* [4]. It might partly explain the higher *H. pylori* infection rate in T2DM patients. On the other hand, we found no significant difference in prevalence of *H. pylori* infection in comparison between T1DM patients and non-DM people (*P* = 0.38), consistently with the report by Candelli et al. [27]. Whether this outcome is caused by the different pathogenesis or the onset age of T1DM and T2DM remains unclear. In the T1DM group, the mean age in most studies was not over 20, except for the studies of De Block et al. [36] and Sfarti et al. [37], while in T2DM group, the mean age was usually over 50 years old (Table 1). Epidemiological studies suggested that the prevalence of *H. pylori* infection increases with age [34]. As T1DM mainly onsets during childhood or young age, T1DM patients probably have less chance to be exposed to *H. pylori* infection. Consistently, Krause et al. showed a significantly lower positive rate of antibodies against *H. pylori* in T1DM patients [38]. But some studies held the contrary view that T1DM individuals were also prone to *H. pylori* infection [39, 40]. However, our meta-analysis with pooled estimate favored that T2DM rather than T1DM was associated with *H. pylori* infection. But the sample size of T1DM subgroup was not as large as that of T2DM. Larger sample size is needed to further verify the association between *H. pylori* infection and DM, especially T1DM.

The prevalence of *H. pylori* infection varies in different regions. We found significant higher *H. pylori* infection rate among DM individuals in group Asia and group Europe but not in group Africa or group America (Figure 4). Firstly, it was to be noted that there were much bigger sample size in group Asia and group Europe, respectively. This might be due to the more accurate detection methods and in group Africa and group America; the sample size might be too small to draw robust conclusion. Secondly, it might be explained by that the condition of medical care in developing countries from group Asia was too poor for DM patients to get good control of DM and prevent infectious complications. On the other hand, the epidemiology and different strains of *H. pylori* infection might attribute to the part of the result. Epidemiology studies revealed that almost all the Asians are infected with the strain of *H. pylori* carrying cytotoxin-associated gene A (CagA) but only nearly 60% of western people carried this stain [41, 42]. It was reported that *H. pylori* infection in Asians was predominated by CagA iceA1 genotypes while Americans and Africans by CagA iceA2 genotypes [41, 43]. CagA is a major virulence factor of *H. pylori* and has been reported to be associated with diabetic complications [44]. CagA-positive strain of *H. pylori* could cause poor glycemic control in T2DM and difficulty in eradication, which might result in the visible *H. pylori* effect among Asian but not African DM patients. However, due to the lack of data, we could not carry out the subgroup analysis based on different strains of *H. pylori*.

A number of testing methods are available for *H. pylori* detection. Serological test, namely, anti-*H. pylori* IgG and/or IgA test, is not affected by acid suppression therapy or recent antibiotic use. But seropositivity could not confirm current *H. pylori* infection, and anti-*H. pylori* IgG titre usually remains elevated for a long period even after clearance or eradication. Some study using anti-*H. pylori* IgG as the diagnosis of *H. pylori* infection might overestimate

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**Figure 8:** Adjusted funnel plot in the trim and fill method of this meta-analysis.
the infection rate. We typically conducted the analysis of serological test group and current infection group and found that in both subgroups, DM patients had higher prevalence of H. pylori infection than non-DM people (Figure 5). As a result, the association between H. pylori infection and DM was verified despite of different methods for H. pylori detection.

Despite the robust result, there existed limitations in our study. The studies were highly heterogeneous. Variables like age, sex, race, economic status, DM prevalence, and strains of H. pylori infection in the included studies varied. For the lack of enough detailed data, subgroup analysis stratified by age, sex, different stages of DM, and strains of H. pylori, which might bring up heterogeneity, could not be carried out. Furthermore, most of the articles meeting the inclusive criteria were case-control or cross-sectional ones, and only 3 were prospective ones. More well-designed and prospective cohort studies are needed for clarifying the association between H. pylori infection and DM.

In conclusion, despite the limitations, our meta-analysis suggested that there is significantly higher prevalence of H. pylori infection in DM when compared with the non-DM individuals. And the difference is associated with type 2 DM but not type 1 DM.

Abbreviations

H. pylori: Helicobacter pylori
DM: Diabetes mellitus
T2DM: Type 2 DM
T1DM: Type 1 DM
NOS: Newcastle-Ottawa scale
OR: Odds ratio
CI: Confidence interval
RR: Risk ratio
IR: Insulin resistant
CagA: Cytoxin-associated gene A
MALT: Mucosa-associated lymphoid tissue.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Authors’ Contributions

Jun-Zhen Li and Jie-Yao Li contributed equally to this work.

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