Association of Helicobacter pylori infection with diabetes mellitus: A Meta-analysis of Case Control Studies

Kamyar Mansori
Zanjan University of Medical Sciences
Yousef Moradi (Yousefmoradi211@yahoo.com)
Iran University of Medical Sciences https://orcid.org/0000-0002-2936-5930
Sara Naderpour
Iran University of Medical Sciences
Roya Rashti
Kurdistan University of Medical Sciences
Ali Baradaran Moghaddam
Iran University of Medical Sciences
Lotfolah Saed
Kurdistan University of Medical Sciences
Hedye Mohammadi
Kurdistan University of Medical Sciences

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Abstract

Background Results of previous studies were showed that the association between H. pylori infection and the risk of diabetes is still controversies. Therefore, this systematic review and meta-analysis study was designed and implemented aimed to determine the association between H. pylori infection and the risk of diabetes.Methods All case control articles were searched in international databases, including Medline (PubMed), Web of sciences, Scopus, EMBASE, and CINHAL. Search was done from January 1990 to March 2019 without language limitations. Also, logarithm and standard error logarithm odds ratio (OR) were used for meta-analysis.Results A total of 41 studies were included in this meta-analysis. The range of association with odds ratio in case control studies which published between 1990 to 2019 was 0.21 to 6.08. The pooled estimate of the association between H. pylori infection with diabetes was 1.27 (95% CI 1.11 to 1.45, P = 0.0001, I 2 = 86.6%). The effect of H. pylori infection on diabetes mellitus, type 1 and type 2 diabetes was 1.17 (95% CI 0.94 to 1.45), 1.19 (95% CI 0.98 to 1.45), and 1.43 (95% CI 1.11 to 1.85) respectively. Subgroup analysis by the geographical regions showed in Asian population risk of the effect of H. pylori infection on diabetes was higher than other population, but in the American, this was a protective relationship.Conclusion In conclusion, this systematic review & meta-analysis study suggested that H. pylori infection was associated with the risk of diabetes as compared to non- diabetes individual.

Background

Helicobacter pylori (H. pylori) is a gram-negative spiral bacterium which is found abundantly in the stomach. The H. pylori infection is one of the most common chronic infections in the world, so that more than 50% of the world's population are infected with this infection (1, 2). It is now known that H. pylori is responsible for most cases of peptic ulcer disease. Also, the different studies highlighted that it is associated with other important gastrointestinal diseases such as chronic gastritis, gastric adenocarcinoma, and MALT lymphoma which are recognized as a major public health concern in the world (3, 4). In addition to the role of H. pylori in gastrointestinal disorders, some researches have suggested the potential role of this bacterium in the development of non-gastrointestinal disorders such as cardiovascular diseases and metabolic syndrome especially diabetes (5-7). Diabetes is the most common metabolic disease in the world and responsible for about 4 million deaths per year. The global prevalence of diabetes was 4.6% equivalent to 285 million in adults for 2010, which this number has reached 371 million in 2012, and is expected to reach 552 million by 2030(8-10).

As mentioned above, one of the factors that may affect incidence of diabetes is H. pylori. The relationship between H.pylori infection and diabetes was introduced in 1989 (11). It has been suggested that the H. pylori may be contributed to the incidence of cardiovascular disease and diabetes through elevations in inflammatory cytokines levels such as C-reactive protein (CRP) and interleukin-6 (11-13). In general, various studies have investigated the role of H. pylori in the pathogenesis of diabetes and its complications, but the results are inconsistent with each other. For example, some case-control studies have reported higher prevalence of H. pylori in patients with diabetes (14, 15). Also, several cross-sectional studies have shown a significant statistical association between H. pylori and diabetes (3, 15). However, some studies in this regard have shown that there is no significant association between diabetes and prevalence H. pylori infection (2, 16, 17).

Therefore, the association between H. pylori infection and the risk of diabetes is still controversies. Hence, this systematic review and meta-analysis study was designed and implemented aimed to determine the association between H. pylori infection and the risk of diabetes.

Methods

This systematic review and Meta-analysis was performed according to the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) and Strengthening the Reporting of Observationally Studies in Epidemiology (STROBE) guidelines for reviews of analytical observational studies (case-control) (18-20).

Search Terms and Complex Search Syntax

All original published articles were searched in international databases, including Medline (PubMed), Web of sciences, Scopus, EMBASE, Cochrane, Ovid and CINHAL. Search was done from January 1990 to March 2019 without language limitations. The keywords were Diabetes, Diabetes Mellitus (type 1 and 2), Insulin Dependent, IDDM, NIDDM, Noninsulin Dependent, Insulin Sensitivity, Helicobacter pylori, Campylobacter pylori, and H Pylori. The primary search results were reviewed, and some of the articles were eliminated after reviewing their title and an abstract. Inclusion and exclusion criteria were set by 2 researchers separately (YM and RR) (Figure 1).

Eligibility Criteria:

A published study had to meet the following inclusion criteria:

(1) case-control, nested case control studies, (2) human population, (3) study population were patients with diabetes, and (4) Helicobacter pylori infection was independent variable. Case reports, reviews, animal studies, and cohort studies were removed from the tabulation. The authors resolved all disputes during the collection, compilation, and analysis of data.

Data Extraction

Two review authors (YM and RR) independently extracted and entered study data. A structured checklist was used for the extraction of information on the 1) name of first author, 2) date of publication, 3) country, 4) study subjects, 5) age of patients, 6) sample size, 7) type of diabetes, 8) mean of HbA1C, 9) duration of diabetes, 10) measurement of association, 11) controlled variables, 12) and method of bacteria detection. Additional information on the study results was extracted with respect to the type of instruments. A data extraction form was created based on our group discussion and piloted according to 10 different types of studies. Then, it was modified and used by the data extractor. All process from systematic search to final data extraction were followed independently by two research experts (Kappa statistic for agreement for quality assessment; 0.75). Any disagreement was assessed by both and if a consensus was not reached, a third author (LS) would evaluate the study. The qualities of all studies were assessed by Modified Newcastle-Ottawa Scale for Case Control studies (21).

Statistical Analysis

Logarithm and standard error logarithm odds ratio (OR) were used for the meta-analysis. DerSimonian and Laird method was used to compute the pooled estimate of odds ratio (OR) with confidence interval (CI 95%) using random models (22). Because the test for heterogeneity was statistically significant in some analyses, the random effects models were used to estimate OR. In this study, w Cochran's Q test and I2 statistic were used to evaluate statistical heterogeneity between studies (23). In addition, a meta-regression and subgroup analysis was performed to assess the source of heterogeneity between studies. Moreover, publication bias was assessed by funnel plot and Egger test (24, 25). Statistical analysis was performed using STATA 14.0 (Stata Corp, College Station, TX, USA), and statistical significance was set at $p < 0.05$.

Results

Study Characteristics

The first step of search in electronic databases yielded 2027 publications and 200 studies identified through other sources. In the final step, after removing the duplicates, reviewing by title, abstract and full text and considering the inclusion and exclusion criteria, 41 studies were selected for the meta-analysis of pooled association between H. pylori infection and the risk of diabetes (**Figure 1**). Studies characteristics of each study included in the meta-analysis are reported in **Table 1**. The total sample size in the 41 studies that reported the association between H. pylori infection and the risk of diabetes in case and control was 4445 and 5416, respectively. Also, 11 studies reported association between H. pylori infection with DM. Other primary studies reported association between H. pylori infection with type 1 and 2 diabetes. A total of 41 studies were included in this meta-analysis, of which 20 were conduct in European, 12 were in Asian, 7 studies done in African and 2 in American (Table 2). The range of association with odds ratio in case control studies which published between 1990 to 2019 was 0.21 to 6.08. Of the 41 studies, 18 showed statistically significant between H. pylori infection and the risk of diabetes.

The pooled estimate of the association between H. pylori infection with diabetes mellitus was 1.27 (95% CI 1.11 to 1.45, P = 0.0001, I^2 = 86.6%) (**Figure 2**), but since the CI of test (Egger's test) included zero, no significant bias occurred in the publication of the results (Egger's test = 1.579, P = 0.073, 95% CI -0.154 to 3.312) (**Figure 3**).

Subgroup analysis

Based on the random effect model, the effect of H. pylori infection on diabetes mellitus, type 1 and type 2 diabetes was 1.17 (95% CI 0.94 to 1.45), 1.19 (95% CI 0.98 to 1.45), and 1.43 (95% CI 1.11 to 1.85) respectively. Effect size of H. pylori infection on type 2 diabetes was higher than type 1 and diabetes mellitus (**Table 2**).

Subgroup analysis by the geographical regions showed in Asian population risk of the effect of H. pylori infection on diabetes was higher than other population, but in the American, this was a protective relationship. In addition, the relationship between H. pylori and the risk of

diabetes according to age showed that risk in individual with 30 to 60 year was 1.34 (95% CI 1.09, 1.65), in 10 to 30 years, and upper 60 years was 1.34 (95% CI 1.05, 1.62) and 1.03 (95% CI 0.93, 3.23), respectively (**Table 2**).

Based on methods of detecting H. pylori infection, the effect of H. pylori infection on diabetes mellitus in detect by rapid urease test was higher than other methods, but this effect not significant (**Table 2**).

Discussion

The purpose of this systematic review and meta-analysis study was to determine the association between H. pylori infection and the risk of diabetes. In the present study, the range of OR for case-control studies included in meta-analysis was 0.21 to 6.08. The results showed a significant statistical association between H. pylori infection and the risk of diabetes (overall OR: 1.27; 95% CI: 1.11 – 1.45). The results of subgroup analysis by type of diabetes revealed a significant association between H. pylori infection and the risk of type 2 diabetes (OR: 1.43; 95% CI: 1.11 – 1.85), however, there was no significant relationship between H. pylori and the risk of type 1 diabetes (OR: 1.19; 95% CI: 0.98– 1.45) and diabetes mellitus (OR: 1.17; 95% CI: 0.94 – 1.45). Subgroup analysis by the geographical regions showed a significant direct relationship between H. pylori and the risk of diabetes in Asian, Europe and Africa but in the American, this was a protective relationship. In addition, in subgroup analysis, the relationship between H. pylori and the risk of diabetes was different according to age, level of HbA1C, duration of diabetes and methods for H. pylori detection. This suggests that these factors could be an important source of heterogeneity in the studies included in the meta-analysis.

Our meta-analysis suggests that H. pylori infection can increase the risk of diabetes by up to 27%. These findings are consistent with the results of several meta-analysis studies that have been done in this field. The meta-analysis study by Jun-Zhen Li et al. showed a significant statistical association between H. pylori infection and the risk of diabetes mellitus (OR: 1.69; 95% CI: 1.47 – 1.95) and type 2 diabetes (OR: 2.05; 95% CI: 1.67 – 2.52), but did not show a significant relationship between risk of type 1 diabetes and H. pylori infection (OR: 1.23; 95% CI: 0.77 – 1.96) (2). The another study by Wang F et al. indicated that the H. pylori is related with an increased risk of each type of diabetes mellitus (OR: 2; 95% CI: 1.82 – 2.20) also related with increased risks of type 1 (OR: 1.99; 95% CI: 1.52 – 2.60) and type 2 diabetes (OR: 2.15; 95% CI: 1.81 – 2.55) (26). Zhou et al. in meta-analysis with 41 articles and 14080 participants reveled difference significant between H. pylori infection and increased risks of diabetes (OR: 1.33; 95% CI: 1.08 – 1.64) (27). However, some studies did support significant association between H. Pylori infection and the risk of diabetes (16, 28).

The Several mechanisms have been proposed for the relationship between H. pylori infection and risk of diabetes. Inflammatory cytokine may lead to induce phosphorylation of serine residues on the insulin receptor substrate and subsequently this phenomenon may impair the interaction between the substrate and the insulin receptors due to impaired insulin function (7, 29). Also, Lipopolysaccharides from gram-negative bacteria such as H. pylori may activate Toll-like receptors and subsequently insulin resistance occurs (30). All of these events can lead to reduced blood sugar control and consequently diabetes mellitus. In addition, the presence of bacterial infections can lead to microvascular failure and eventually incidence of atherosclerosis (31).

In subgroup analysis of geographical regions by the type of continent, we explored a significant direct relationship between H. pylori and the risk of diabetes in Asian, Europe and Africa but in the American, this was a protective relationship, but there was still high heterogeneity within these subgroups. It was consistent with study of Jun-Zhen Li et al. that have shown H. pylori infection is significantly higher in diabetic patients residing in Asia and Europe than in Africa and the American (32). Also, Wang F et al. reported H. pylori can increase the risk of diabetes in European, Middle East and South Asia (26). But, study of Zhou et al. found H. pylori infection is significantly higher in diabetic patients residing in only Asia (27). This difference in various continents may be due to differences in sample size, different diagnostic methods and different medical care conditions. However, to determine the precise effect of geographical location on the association between H. pylori and diabetes risk, it seems useful migrants study to distinguish between the role of genetic and environmental factors.

Also, in subgroup analysis, we found significant direct relationship between H. pylori and the risk of diabetes in mean of HbA1C >8. This result was in line with the results of other studies in this field. For example, the study by Ming-Chia Hsieh et al. displayed patients with higher levels of HbA1c had higher prevalence of H. pylori infection than patients with lower levels of HbA1c and this association was significant statistically (33). Another study in China revealed individuals with H. pylori infection had a higher level HbA1C than those who did not (34). Considering the HbA1c is a valid and reliable indicator for estimating average blood sugar in long-term, it seems to be more valid to evaluate the effect of chronic H. pylori infection on blood glucose regulation (35-37). So, pay attention to HbA1c in assessing the relationship between H. pylori and the risk of diabetes can be important, although there was still high heterogeneity within these subgroups in our study. In addition, in subgroup analysis relationship between H. pylori and the risk of diabetes was different by age. This

finding was consistent with results of other studies, because the different studies have shown that the prevalence of H. pylori infection varies with age (38).

Finally, association between H. pylori and the risk of diabetes was different by methods for H. pylori detection in subgroup analysis. This suggests that this factor could be an important source of heterogeneity in the studies included in the meta-analysis, because different methods of detection for H. pylori have different accuracy and precision. The studies have shown that the serological tests of anti-H. Pylori IgG or/and IgA antibody in serum may be report many false positives (39, 40). As a results, association H. pylori and the risk of diabetes may be different according to the method of diagnosis of infection.

Strengths And Limitations

This study also has several limitation and strengths. The first strength of this study is deal with heterogeneity through a subgroups analysis based on Type of diabetes, geographical regions, age, and level of HbA1C, duration of diabetes and methods for H. pylori detection. Another strength was considerable number of studies included in the meta-analysis (41 study) that would be possible to investigate the exact effect of the publication bias on the results. Also, this study has several limitations. Firstly, missing potential studies e.g. limiting full- text review to English language articles may be lead to some degree of selection bias. Secondly, all studies included in meta-analysis were case-control, hence, the design and implementation of cohort studies are essential for detailed assessment of the association between H. pylori infection and diabetes. Thirdly, personal judgments may be effect on search of articles, data extraction and assessment of included articles in meta-analysis.

Conclusions

In conclusion, this systematic review & meta-analysis study suggested that H. pylori infection was associated with the risk of diabetes as compared to non- diabetes individual. However, in subgroup analysis by type of diabetes, this association was only significant for type 2 diabetes.

Abbreviations

CI: Confidence Interval

OR: Odds Ratio

IDDM: Insulin-Dependent Diabetes Mellitus

NIDDM: Non-Insulin-Dependent Diabetes Mellitus

CINAHL: Cumulative Index to Nursing and Allied Health Literature

EMBASE: Excerpta Medica dataBASE

STROBE: Strengthening the Reporting of Observationally Studies in Epidemiology

PRISMA: Preferred reporting items for systematic reviews and meta-analyses

H. pylori: Helicobacter Pylori

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

Input data for the analyses are available from the corresponding author on request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

YM conceptualized the idea for this review, formulated the review question, and objectives, assisted with the development of the final search strategy, contributed to the data analysis/ interpretation, and writing the manuscript. KM, SN, LS, HM and RR contributed to the conceptualization of the final review question, formulation of the review objectives, data analysis/interpretation, and writing the manuscript. HM, LS, and ABM contributed to the conducting the searches, data extraction and data analysis/interpretation. All authors read and approved the final manuscript.

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Tables

Table 1: 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(41)	1996	Poland	Non-diabetic subjects	17-80	139 (Control:100 & Case: 39)	DM (-) (8 Year)	0.33 (0.18, 0.59)	-	Histology or biopsy	6
Pocecco, M. et al(42)	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. (43)	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(44)	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(45)	1998	Italy	Healthy subjects	35	166 [Control: 50 & Case: 116]	DM (-) (19 year)	1.04 (0.85, 1.28)	Age and sex	13C or 14C urea breath test	6
Salardi, S.et al(46)	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(47)	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)	-	Anti-H. pylori antibody	6
Dore, MP. et al (48)	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 socioeconomic status	Anti-H. pylori antibody	8
Senturk, O. et al (49)	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(50)	2001	Uganda	Dyspeptic patients without diabetic	-	132 [Control110: & Case: 22]	DM (-) (-)	1.22 (0.33, 4.49)	-	Histology or biopsy	6
Ko, G. T.et al (51)	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(52)	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 (53)	2001	Italy	Dyspepsia patients	58	142 [Control: 71 & Case: 71]	DM (-) (-)	1.63 (1.12, 2.38)	Age and sex	13C or 14C urea	7

									breath test	
Cenerelli, S. et al(54)	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)	-	13C or 14C urea breath test	7
Maule, S.et al **(55)**	2002	Italy	Individuals without diabetes	46-75	62 [Control:31 & Case: 31]	T2DM (7.1 ± 1.4) (-)	1.65 (0.92, 2.97)	Age	13C or 14C urea breath test	8
Candelli, M. et al(56)	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
Gulcelik, N. E.et al **(57)**	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**(58)**	2006	Saudi Arabia	Healthy children	>10	604 [Control:543 & Case: 61]	T1DM (-) (-)	1.60 (0.98, 2.63)	-	Anti H. pylori antibody	6
Bener, A. et al(59)	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 **(60)**	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**(61)**	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**(62)**	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(63)	2009	Brazil	The control Group was selected normal healthy adolescent	17	45 Control: 30 & Case: 15)	T1DM (-) (-)	0.52 (0.21, 1.29)	-	Histology or biopsy	7
Lazaraki, G. et al **(64)**	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 **(65)**	2009	Colombia	Individuals had	16.0	180	T1DM	0.44	-	Anti-H.	6

			no clinical diabetes, nor islet cell autoantibodies		[Control123: & Case: 57]	(-) (8.8 year)	(0.29, 0.66)		pylori antibody	
Devrajani, BR. et al (66)	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)	-	Stool antigen test	7
Ibrahim, A. et al(67)	2010	Egypt	Dyspeptic non diabetic subjects	45	200 [Control: 102 & Case: 98]	T2DM (8.57 ± 0.79) (-)	0.94 (0.71, 1.25)	-	Rapid urease test, Histology or biopsy	7
El-Eshmawy, M. M. et al(68)	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(69)	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 (70)	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	13C or 14C urea breath test	6
Jafarzadeh, A.et al (71)	2012	Iran	Healthy individuals	42.86	200 [Control: 100 & Case: 100]	T2DM (-) (-)	1.03 (0.74, 1.42)	Age	Anti H. pylori IgG	6
Keramat, F. et al(72)	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(73)	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(74)	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	13C or 14C urea breath test	8
Fayed, SB. et al(75)	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(17)	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	2015	India	The control	>18	140	T2DM (8.2	1.53	Age, sex,	Anti-H.	8

al(3)			group comprised of age, sex, socioeconomic status, and education matched normal healthy volunteers		Control: 60 & Case: 80)	± 1.2) (4.2 Year)	(1.04, 2.24)	socioeconomic status, and education	pylori antibody & Rapid urease test and Histology or biopsy	
Bazmamoun, H. et al(76)	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(77)	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(78)	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 (79)	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)	-	Rapid urease test	8

Table 2: Summary odds Ratio (OR) Estimates [95 % confidence intervals (CIs)] for Case–Control studies Conducted on the Association Between Helicobacter pylori and Risk of diabetes by Type of diabetes, Continent, Mean of HbA1C, Duration of Diabetes, Method of detection bacteria, NOS score and Age.

Subgroup	Number of studies	Summery Odds Ratio (95% CI)	Between studies			Between subgroups	
			I^2	P heterogeneity	Q	Q	P heterogeneity
Type of diabetes							
Diabetes Mellitus	11	1.17 (0.94– 1.45)	82.5 %	0.0001	1.43	3.59	0.0001
Type 1 Diabetes	15	1.19 (0.98– 1.45)	81.6 %	0.0001	1.75		
Type 2 Diabetes	15	1.43 (1.11 – 1.85)	90.0 %	0.0001	2.72		
Continent	12	1.41 (1.05 – 1.88)	93.2%	0.0001	2.29	3.59	0.001
Asian	2	0.45 (0.31 – 0.66)	0.0%	0.728	4.12		
American	7	1.32 (1.05 – 1.66)	61.0%	0.018	2.40		
African	20	1.26 (1.08 – 1.47)	80.3%	0.0001	2.94		
European							
Mean of HbA1C*	9	1.40 (0.92 – 2.13)	95.0 %	0.001	1.55	3.59	0.0001
6 – 8	13	1.41 (1.20 – 1.64)	73.7 %	0.001	4.33		
8 <							
Duration of Diabetes*	7	1.18 (1.06 – 1.31)	0.0 %	0.450	3.07	3.59	0.001
0 – 3 Y	10	1.15 (0.95 – 1.38)	69.1 %	0.001	1.45		
4 – 7 Y	9	1.09 (0.79 – 1.51)	91.0 %	0.0001	0.55		
8 < Y							
Method of detection bacteria	2	1.08 (0.95 – 1.22)	35.0 %	0.215	1.14	3.59	0.0001
Anti-H. pylori antibody & Rapid urease test	6	1.04 (0.58 – 1.84)	85.0 %	0.0001	0.12		
Histology or biopsy	14	1.40 (1.07 – 1.85)	91.2 %	0.0001	2.44		
Anti-H. pylori antibody	4	1.03 (0.76 – 1.40)	76.0 %	0.006	0.21		
Anti-H. pylori antibody & Rapid urease test & Histology or biopsy	5	1.06 (0.91 – 1.23)	18.3 %	0.298	0.74		
Rapid urease test & Histology or biopsy	6	1.27 (0.94 – 1.72)	73.4 %	0.002	1.56		
13C or 14C urea breath test	3	1.73 (0.93 – 3.23)	91.3 %	0.0001	2.49		
Rapid urease test	1	-	-	-	-		
Stool antigen test							
Age*	15	1.30 (1.05 – 1.62)	81.9 %	0.0001	2.37	3.59	0.0001
10-30 Y	18	1.34 (1.09 – 1.65)	91.3 %	0.0001	2.77		
30-60 Y	3	1.03 (0.68 – 1.57)	76.4 %	0.014	0.15		
60< Y							
NOS Score	11	1.14 (0.85 – 1.53)	87.7 %	0.0001	0.86	3.59	0.0001
6	16	1.42 (1.10 – 1.82)	89.0 %	0.0001	2.72		
7	12	1.24 (1.00 – 1.53)	81.6 %	0.0001	1.96		
8	2	1.08 (0.95 – 1.22)	35.0 %	0.216	1.14		
9							

Largely diabetes mellitus

All statistical tests were 2-sided.

*other studies not reported HbA1C, duration of diabetes,

Figures

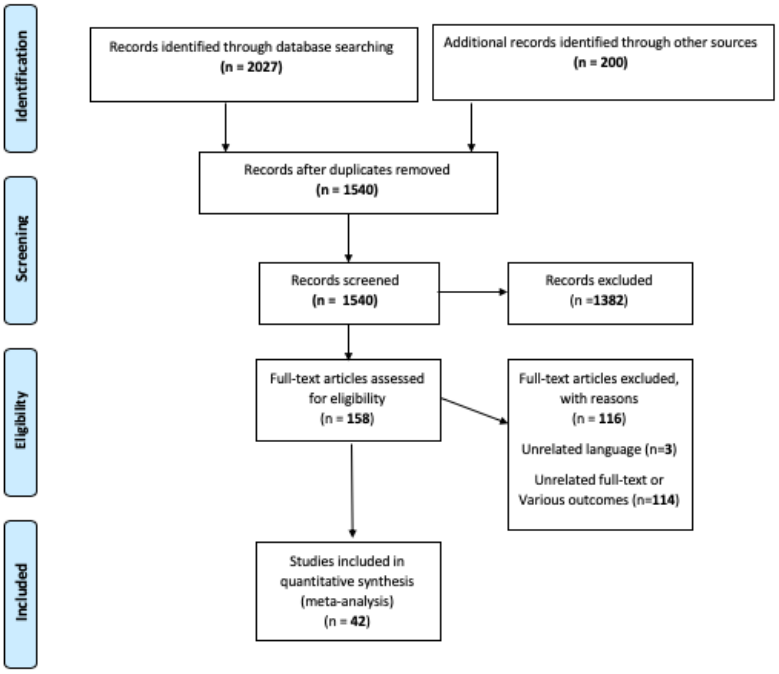

Figure 1

Flow Diagram of the Literature Search and Study Selection

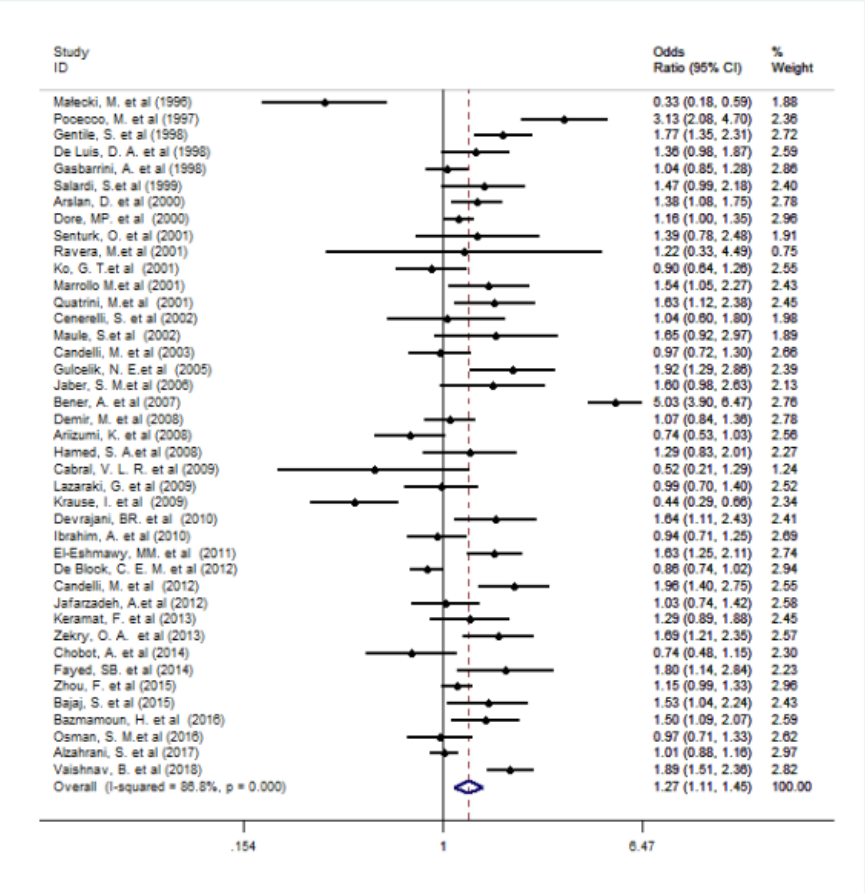

Figure 2

Association between Helicobacter pylori and Risk of diabetes (DM, T2DM and T1DM)

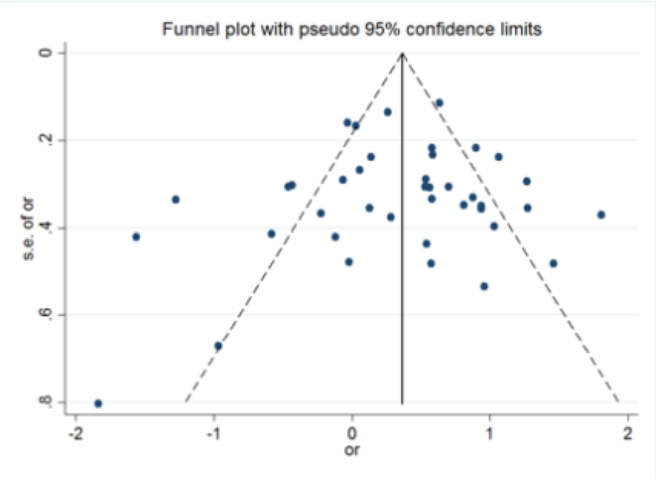

Figure 3

Funnel plot of association between Helicobacter pylori and Risk of diabetes