Systematic Review and Meta-Analysis

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Helicobacter pylori infection and increased diabetes prevalence were the risks of colorectal adenoma for adults

A systematic review and meta-analysis (PRISMA-compliant article)

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Abstract

Background: *Helicobacter pylori* infection and hyperglycemia are associated with an increased risk of colorectal neoplasm, and may have a synergistic effect in combination. However, these 2 factors that affect colorectal neoplasm remain controversial. We aimed to carry out a meta-analysis to evaluate the study population diabetes prevalence rate and *H pylori* infection rate with colorectal adenoma risk for adults.

Methods: We conducted systemic research through English databases for medical reports. We also recorded the diabetes prevalence and *H pylori* infection prevalence in each study. We classified these studies into 4 subgroups as their background population diabetes prevalence <6% (Group 1); between 6% and 8% (Group 2); between 8% and 10% (Group 3), and more than 10% (Group 4). The random-effects model had used to calculate pooled prevalence estimates with 95% confidence interval (CI).

Results: Twenty-seven studies were finally eligible for meta-analysis. The random-effects model of the meta-analysis was chosen, showing pooled odds ratio (OR) equal to 1.51 (95% CI 1.39–1.63). The subgroup meta-analyses showed in Group 1 the *H pylori* infection associated colorectal adenoma risk OR was 1.24 (95% CI 0.86–1.78). As the diabetes rate exceed 6%, the *H pylori* infection became the more significant increased risk of colorectal adenoma (Group 2: OR 2.16 (95% CI 1.61–2.91); Group 3: OR 1.40 (95% CI 1.24–1.57); and Group 4: OR 1.52 (95% CI 1.46–1.57)).

Conclusions: The results of this meta-analysis showed elevated diabetes prevalence combined *H pylori* infection increasing the risks of colorectal adenoma in the adult population.

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The authors have no conflicts of interest to disclose.

The data supporting this systematic review and meta-analysis are from previously reported studies and datasets, which have been cited. The processed data are available from the corresponding author upon reasonable request. The protocol of this meta-analysis has been registered with PROSPERO (no. CRD42020199442).

All data generated or analyzed during this study are included in this published article [and its supplementary information files]. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Abbreviations: CIs = confidence intervals, CLO = Campylobacter-like organism test, CRC = colorectal carcinoma, DM = diabetes mellitus, *H pylori* = *Helicobacter pylori*, HbA_{1c} = glycosylated hemoglobin, IL = interleukin, OR = odds ratio, UBT = urea breath test.

Keywords: colorectal adenoma, diabetes prevalence, *Helicobacter pylori*

1. Introduction

Helicobacter pylori is a Gram-negative bacterium that has infected almost 50% of the world's population.[1] Since 1994, *H pylori* has been recognized as a human carcinogen by the International Agency for Research on Cancer due to its strong correlation with gastric cancer.[2] Except for intragastric malignancy disease, many scientists have noted that this bacterium is also related to colon neoplasms and colorectal carcinoma (CRC) formation and have shown that infection with *H pylori* confers a 1.3- to 1.97-fold increased risk of colon adenoma or adenoma with high-grade dysplasia in the past 2 decades.[3–5] However, some Asian studies did not show consistent results. Early studies showed that *H pylori* infection may have a trend of increased colon adenoma but no significant difference.[6,7] Recent studies have demonstrated a positive association between *H pylori* infection and colon adenoma formation.[8,9] In these studies, Sonnenberg and Genta[3] established the largest study, which included 156,000 patients, and showed that *H pylori* gastritis was positively associated with colon adenomas (odds ratio [OR]=1.52). Even with this impressive study result, Plummer also commented and queried several key points.[10] The most important question that needs to be answered is how to explain why some areas had a high prevalence of *H pylori* infection but a low CRC risk. Several meta-analysis studies have shown that *H pylori* infection increases the risk of colorectal neoplasm formation.[11–13] However, these studies did not address Plummer query.

Diabetes mellitus type 2 (DM) is one of the most common metabolic disorders in the world, and the prevalence of DM has been increasing quickly in recent decades.[14] The prevalence of DM also has significant regional variability. According to the latest report, the highest prevalence of DM was found in North America and the Caribbean region, and the prevalence in this region was approximately 11.0%. The Western Pacific region (including Australia, China, Indonesia, Japan, Taiwan, Korea, and Vietnam) has a DM prevalence of approximately 8.1%.[15] However, as socioeconomic growth and industrialization are rapidly occurring in this area, the increasing prevalence of diabetes was also noted in these countries.[16] DM is also considered a risk factor for colon adenoma and carcinoma. Several studies have shown that subjects with DM had an OR of 1.45 for colon adenoma and a relative risk of 1.38 for colorectal adenocarcinoma.[17,18] Our previous study demonstrated that combined hyperglycemia and *H pylori* infection was involved in colon adenoma formation and had a synergistic effect.[19] The risk of colorectal adenoma might decrease after *H pylori* is successfully eradicated.[20] This means that hyperglycemia and *H pylori* infection might interact and affect colorectal adenoma formation.

Therefore, we carried out a systematic review and meta-analysis of published studies to evaluate the association between *H pylori* infection and colorectal adenoma formation. Furthermore, we surveyed the DM prevalence in each published study as a subgroup analysis and tried to determine the relationship between *H pylori* infection and DM prevalence in the risk of colon adenoma formation. We tried to use different DM prevalence rates to classify subgroups of these studies to answer Plummer question and discuss the relationship between the DM prevalence rate and *H pylori* infection involvement in colorectal adenoma formation.

2. Materials and methods

2.1. Data sources and searches

Preferred reporting items for systematic reviews and meta-analyses statement guidelines were followed for conducting and reporting meta-analysis data. The participants, intervnetions, comparison, outcomes, and study design scheme was followed for reporting inclusion criteria. A systematic search was conducted using PubMed/MEDLINE, EMBASE, and the Cochrane Library for medical reports published until the end of August 2020 without language or date restrictions. The following search terms were used: "*Helicobacter pylori*" AND ("colorectal OR "colonic" OR "colon" OR "large intestine") AND ("neoplasms" OR "polyp" OR "adenoma" OR "cancer"). Abstracts of articles from the literature search were individually evaluated independently for possible inclusion by the 3 authors (CMJ, WMS, and YHW). For all databases, the last search was run on 3 September 2020. The study protocol was registered in PROSPERO (CRD42020199442).

2.2. Study selection

The eligible studies enrolled in the meta-analysis satisfied the following criteria: (i) English-language abstract; (ii) full manuscript publication; (iii) study design: clinical trials including cohort studies, cross-sectional studies, and case–control studies; (iv) reported OR estimates with corresponding 95% confidence intervals (CIs) for the relationship between *H pylori* and colorectal adenoma or provided sufficient raw data to calculate crude ORs and 95% CIs; and (v) results: the prevalence of patients with colorectal adenoma due to *H pylori* infection or the risk of colorectal adenoma in *H pylori* infection. Studies were excluded if they (i) reported duplicate results that were published in other articles, (ii) investigated only the gastrin level or the recurrence of colorectal neoplasia, or (iii) included a pediatric population.

2.3. Data extraction

Three reviewers (CCC, LCJ, and SSC) independently extracted data using a predefined form, and disagreements were resolved by discussion and consensus. Information was collected in each selected study as possible, concerning first author, publication year, research type, publication type, the number of subjects, the country of origin, the prevalence of DM rate of origin, the matching variables, the location of neoplasia, the *H pylori* detection method, the sample characteristics (age and sex), the

reported OR for colorectal adenoma with 95% CIs, and the covariates adjusted for in the analysis.

2.4. Statistical analysis

Three reviewers (LYC, YLY, and KHJ) independently assessed the quality of all eligible studies using the risk of bias in non-randomized studies of interventions scale. The ORs were collected for analysis. Heterogeneity between studies was assessed using both the χ^2 test with a P value <.10 and inconsistency index (I^2) with a cutoff of 50%. Pooled effects with 95% CIs were derived using a fixed-effect model unless significant heterogeneity was present, in which case a random-effects model was applied. When a study provided different OR estimates based on hospital-based controls and population-based controls, the latter estimates were selected for the combined analysis. We also calculated and presented a summary of the adjusted ORs for the studies that provided adjusted results. Publication bias was evaluated with a funnel plot and Egger test.

We examined the roles of several potential sources of heterogeneity using restricted maximum likelihood-based random-effects meta-regression analysis and subgroup analyses according to geographic location, prevalence of diabetes (DM) rate, the prevalence of *H pylori* infection rate, study design, the sample size for the cases, subsite of the neoplasia, *H pylori* detection method and sex. The estimated DM prevalence rate of each study was referenced from the International Diabetes Federation Atlas and local country government data or study results (by WHY and HCT). We used the mean year of study duration as the DM prevalence rate. According to the diabetes prevalence rate of the study population, we classified the studies into 4 groups: Group 1: DM prevalence <6%; Group 2: DM prevalence from 6% to 8%, Group 3: DM prevalence from 8% to 10%; and Group 4: DM prevalence >10%. Statistical analyses were performed by STATA version 11.0 (STATA Corporation, College Station, TX, USA) and RevMan version 5.3 (The Cochrane Collaboration, Oxford, UK).

2.5. Ethical statements

No ethical approval is required since this is a literature-based study.

3. Results

3.1. Search results and study characteristics

After initial screening, the full text of 281 potentially eligible articles was retrieved for detailed assessment, and 27 studies were eligible for analysis.[3,6,8,9,19,21–42] All of the eligible studies presented OR for colorectal adenoma related to *H pylori* infection.[3,6,8,9,19,21–42] Nineteen of them are cross-sectional studies,[3,6,8,19,21–24,25–28,30,31,35,37–40] and the remaining 8 are case–control studies.[9,29,32–34,36,41,42] Serology was utilized as the detection method for *H pylori* in 14 studies,[8,9,21,23,25–27,31–35,38,39] pathology in 4,[3,22,40,42] urea breath test (UBT) in 4,[6,37] Campylobacter-like organism test (CLO) in 6,[19,24,30,36] and combining UBT and CLO in 2.[28,29] Gender and age are reported in 22[3,6,8,9,19,21–30,34–40] and 27[3,6,8,9,19,21–35,37–39,41,42] studies, respectively. Most studies were carried out in Asia (7 in Korea, 3 in Taiwan, 3 in Japan, 1 in Thailand, and 1 in China) and the remaining in the Americas (5 in the United States of America and 1 in Brazil) and in Europe (2 in Germany, 1 in Turkey, 1 in Greece, and 1 in Israel). All included studies had assessed the quality of all eligible studies using the risk of bias in non-randomized studies of interventions scale and no serious risk of bias after survey (in Appendix).

A flow chart describing the process of study selection is shown in Figure 1. For the meta-analysis, data were extracted from 27 studies with a total of 68,410 patients, and the pooled OR for colorectal adenoma related to *H pylori* infection was 1.51 (95% CI 1.39–1.63), although there was significant heterogeneity ($P<.001$) (Table 1 and Fig. 2). Because of geographic and time differences in DM prevalence rate,[14,43–51] subgroup analysis for the studies was performed by classifying them into 4 groups: Group 1: DM prevalence <6%; Group 2: DM prevalence from 6% to 8%, Group 3: DM prevalence from 8% to 10%, and Group 4: DM prevalence >10% (Table 1 and Fig. 2).

In the subgroup analysis, the background population DM prevalence <6% studies had 3 studies with a total of 886 patients. Meta-analysis of these studies revealed that the *H pylori*-infected patients have an increased risk of having colorectal adenoma with a pooled OR of 1.24 (95% CI 0.86–1.78) but no significant difference. There was no significant heterogeneity in Group 1 studies ($P=.279$). Since the study background population DM prevalence increased more than 6%, the *H pylori*-infected patients have a significantly increased risk of having colorectal adenoma. This upturn was more significant when the background population DM prevalence was approximately 6% to 8%. After a meta-analysis of these studies, the *H pylori*-infected people had a higher risk of colorectal adenoma than noninfected people. The pooled OR was 2.16 (95% CI 1.61–2.91), and a total of 11,655 patients were included. In these studies, Lin study noted the DM prevalence in his study participants, and males had an 8.1% prevalence of DM, and females had a 6.1% prevalence of DM. Due to Lin study population, 6.94% of patients had DM and were thus classified into Group 2 for subgroup analysis. There was significant heterogeneity in the Group 2 studies ($P<.01$)

In Groups 3 and 4, similar results were observed. Compared to that of Group 2 studies, the pooled OR of Groups 3 and 4 was mildly decreased but still had a significantly elevated risk of colorectal adenoma in *H pylori*-infected patients. For the *H pylori*-infected patients, the risk of colorectal adenoma in Group 3 was 1.40 (95% CI 1.24–1.57), and the Group 4 OR was 1.52 (95% CI 1.46–1.57). The Group 3 studies included 28,431 patients, and the heterogeneity across studies was marginal ($I^2=58.6\%$, $P=.013$). There were 27,438 participants included in Group 4 studies, and there was no significant heterogeneity ($I^2=0.0\%$, $P=.704$). We also checked other variables, including gender, detection methods of *H pylori* infection, and study designs, and there was no evidence of statistical relevance to OR for adenoma with *H pylori* infection.

3.2. Test of heterogeneity and publication bias

Heterogeneity was assessed by chi-square and I-square for the included studies. The value of χ^2 was <0.01, and the I^2 was 61.9%. Due to the heterogeneity noted in our analysis, a random-effects model was used. The shape of the funnel plots for studies on the association between *H pylori* infection and the risk of colorectal adenoma appeared asymmetrical (Fig. 3A), which indicated that studies with positive correlation are reported more often. The *P*-value for Egger linear regression method ($P<.01$)

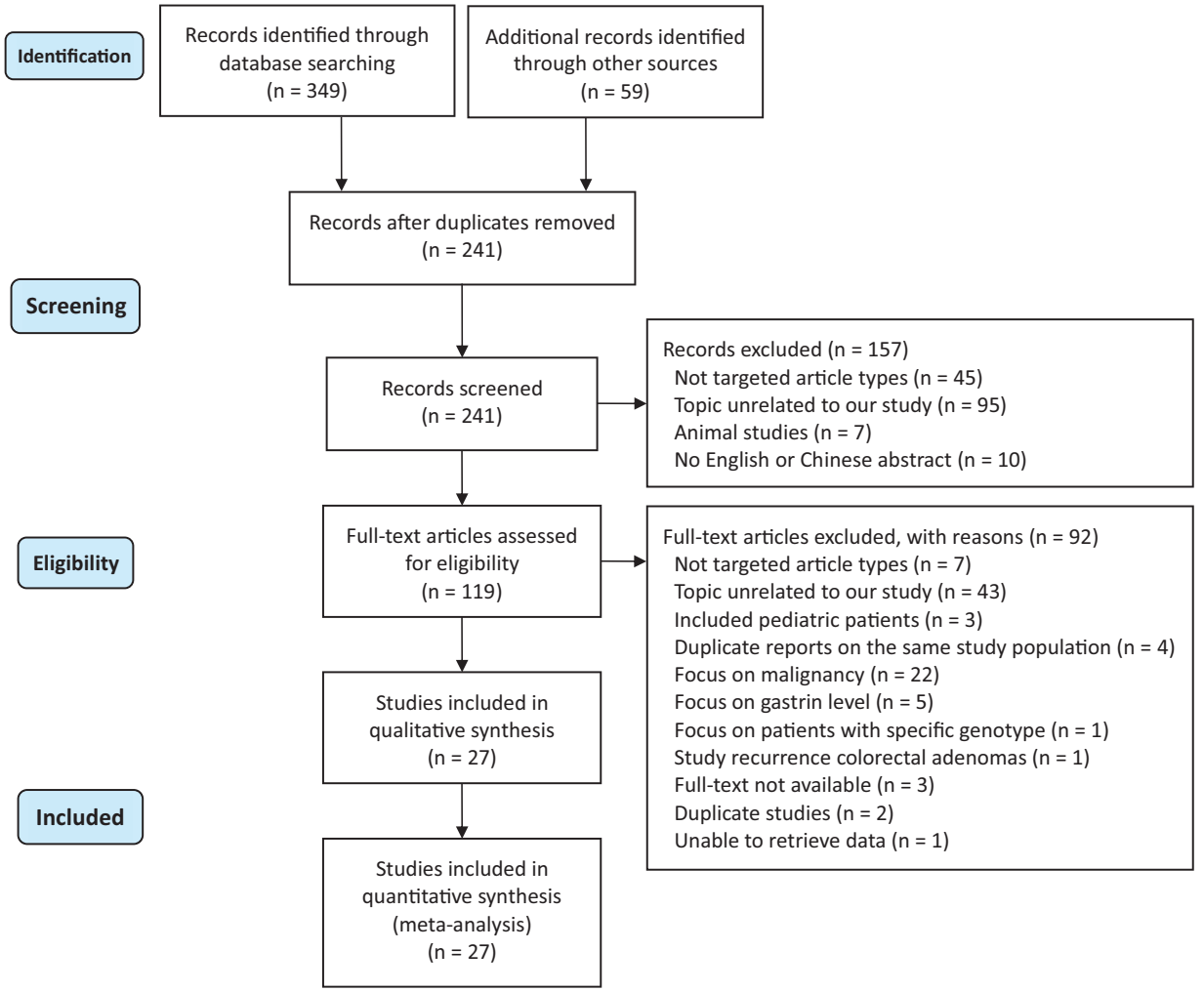

Figure 1. Flow diagram of the studies identified in this meta-analysis.

suggested that there was statistical evidence of publication bias (Fig. 3B).

4. Discussion

Since the discovery of *H pylori* as a cause of peptic ulcer disease in 1983, this bacterial infection continues to be a major public health issue worldwide. The prevalence of *H pylori* infection varies by geographic area, age, ethnicity, and socioeconomic status; in fact, the prevalence is higher in developing countries and in those in poor socioeconomic conditions.[52] Traditionally, Western and Eastern countries have different *H pylori* infection rates in their general populations. The prevalence is highest in Africa (79.1%), Latin America, and Asia (54.7%). On the other hand, the *H pylori* infection rate is lowest in Northern America (37.1%) and Oceania (24.4%).[53,54]

As an infectious disease, *H pylori* can be cured with a course of antibiotics and its infection rate decreased due to public health improvement in developed countries and some developing countries. However, as the prevalence rate of *H pylori* infection remains high in most developing countries and is generally related to socioeconomic status, it remains one of the most important diseases in these areas.[54] Hong et al. published a meta-analysis of *H pylori* infection and increased the risk of colorectal adenoma formation. In this study, he focused on Eastern or Western studies for subgroup analysis and found that the ORs of these 2 groups were similar.[25] This means that even the *H pylori* infection prevalence was different in Eastern and Western countries, and this bacterial infection still increased colorectal adenoma formation. Although the detailed mechanism of the relation between *H pylori* infection and colorectal adenoma formation was not clear. Butt and Epplein stated *H pylori* infection might contribute to colorectal carcinogenesis by direct or indirect effect. In direct effect, *H pylori* might secrete toxins and present in the respective colorectal tissue. On the other hand, the indirect effect included several hypotheses. First, *H pylori* infection could lead to changes in the colonization of the gut with other bacteria and then could induce colorectal carcinogenesis. Second, the gastrin level might increase after *H pylori* infection and gastrin might act as a mitogen. Third, *H pylori* was found to be associated with metabolic diseases that are associated with CRC risk.[55] It also hints at a link between *H pylori* infection and colorectal adenoma formation, which may be due to the third factor in this connection.

Table 1

Demographics and outcome characteristics of included Groups 1 to 4 studies.

First author	Study duration	Study location	Study design	*H. pylori* detection	Sample size	Mean age (years)*	Gender (% male)	Odds ratio†	95% CI	*H pylori* infection rate (%)	Estimate DM prevalence (%)‡	DM prevalence Reference	Reference
Group 1 (DM prevalence < 6%)													
Siddheshwar RK	1997–1999	UK	Cross-section	Serology	236	62.21 (10–94)	44.92	1.08	0.58–1.99	35.5	3.8	49	27
Liou JM	2005	Taiwan	Cross-section	UBT(C13)	462	49.97 0.74	57.79	1.06	0.69–1.62	53.9	5.56	46	6
Buso AG	2005–2007	Brazil	Case-control	Serology	188	59.79 12.25	46.88	1.98	0.82–3.15	71.2	5.8	45	34
Group 2 (DM prevalence: 6%–8%)													
Lin YL	2004–2006	Taiwan	Cross-section	CLO test	9311	52.84§	41.95	1.366	1.23–1.517	53.9	6.94	24	24
Georgopoulos S. D	2000–2001	Greece	Case-control	Serology	156	64.25 (37–80)	NA	1.83	0.88–3.78	52.1	6.9	51	33
Fujimori S	1996–2003	Japan	Cross-section	UBT and CLO	669	61.08 9.57	70.25	1.6	1.18–2.12	51.7	7.07	50	28
Inoue	1996–2004	Japan	Case-control	Serology	478	49.7 4.11	100	2.26	1.44–3.55	51.7	7.07	50	9
Shmuely, H	2008–2010	Israel	Cross-section	Serology	273	64.5 12.30	NA	4.07	2.26–7.35	68.9	7.1	47	31
Aydin A	1996–1997	Turkey	Cross-section	Serology	267	49.13 22.61	45.32	2.63	1.26–5.48	77.2	7.2	48	26
Breuer-Katschinski	1993–1996	Germany	Case-control	Serology	196	62.4 9.08	NA	2.1	1.1–3.9	35.3	7.2	52	32
Mizuno	2005	Japan	Cross-section	Serology	305	59.8 2.26	57.33	3.4	1.9–6.08	51.7	7.45	43	21
Group 3 (DM prevalence: 8% –10%)													
Tongtawee T	2014–2015	Thailand	Cross-section	Pathology	303	NA	38.28	7.29	2.74–19.36	43.6	8	52	40
Bae RC	2005–2008	Korea	Case-control	UBT and CLO	346	54.1 10.50	74.57	1.037	0.67–1.59	54.0	8.6	45	29
Kim TJ	2002–2010	Korea	Cross-section	Serology	8916	51.6 7.9	100.00	1.37	1.18–1.58	54.0	8.6	45	35
Nam JH	2007–2009	Korea	Case-control	CLO	4466	NA	53.63	1.28	1.11 –1.47	54.0	8.6	45	36
Lee JY	2012–2013	Korea	Cross-section	Serology	6351	51.7 8.1	52.79	1.28	1.09–1.36	54.0	8.9	45	39
Hong SN	2010	Korea	Cross-section	Serology	2195	49.23 10.34	62.00	1.36	1.1–1.68	54.0	9	47	25
Park YM	2008–2012	Korea	Cross-section	Serology	2781	44.8 2.8	58.72	2.26	1.11- 4.62	54.0	9.0	47	38
Nam KW	2004–2005	Korea	Cross-section	Serology	598	56.33 10.34	65.38	1.93	1.24–3.01	54.0	8.8	45	8
Hu KC	2006–2015	Taiwan	Cross-section	CLO	2475	52.90 8.25	66.91	1.44	1.20–1.73	53.9	9.59	19	19
Group 4 (DM prevalence: >10%)													
Yan Ye	2014–2016	China	Cross-section	UBT	1641	50.73 8.26	66.24	1.535	1.04–1.75	55.8	10.6	52	37
Brim H	2005–2009	USA	Cross-section	pathology	1256	57 9.6	34.00	1.5	1.2–2.2	35.6	10.7	44	22
Selgrad M	2008–2013	Germany	Cross-section	Serology	377	66.38 9.82	50.13	1.85	1.14–2.99	35.3	11.9	47	23
Sonnenberg	2008–2011	USA	Cross-section	pathology	22231	57.88 15.21	41.00	1.52	1.46 -1.57	35.6	12.1	44	3
Abbass K	2008–2009	USA	Cross-section	CLO	192	59.1 12.82	38.02	1.29	0.69–2.42	35.6	12.1	44	30
Patel S	2009–2011	USA	Case-control	Pathology	798	54.83 11.51	NA	1.04	0.67–1.61	35.6	12.1	44	42
Zuniga R	2010–2012	USA	Case-control	NA	943	57‖	NA	1.55	1.13–2.12	35.6	12.3	44	41

Siddheshwar RK study only included colon polyp population; Nam JH, Tongtawee T studies only demonstrated aging disturbance.

Park YM focus age 40–49 subjects; Sonnenberg only included subjects who had *H pylori* pathology report.

CI = confidence interval, CLO = Campylobacter-like organism test, DM = diabetes mellitus, *H pylori* = *Helicobacter pylori*, UBT = urea breath test, UK = the United Kingdom.

* SD (standard deviation) or (range).

† Odds ratio: for colorectal adenoma.

‡ From Ref. 57.

§ Did not specify the reported data as range or interquartile range.

‖ No standard deviation, standard error, or range reported in the study.

Unlike *H pylori* infection disease, the prevalence of DM in the global world has persisted. The age-standardized DM prevalence increased from 4.3% in 1980 to 9.0% in 2014 in men and from 5.0% to 7.9% in women.[56] The rise in prevalence might be due to population growth and aging, as the number of adults with diabetes has increased nearly 4-fold over the past 35 years. The prevalence and number of adults with diabetes both increased and doubled in men and increased by 60% in women worldwide, shifting from an excess prevalence in women in 1980 to a higher male prevalence in 2014.[57] Persistent high blood sugar concentrations lead to damage to the blood vessels and peripheral nerves. This situation might result in an increased risk of cardiovascular diseases, such as heart attack and stroke, kidney disease, diabetic retinopathy, and foot amputations.[58] DM is also considered an increased risk factor for colon adenoma and carcinoma.[59] These DM-related complications lead to higher costs for the health care system,[60] as well as lower quality of life and reduced life expectancy.[61]

Although, a past study showed that DM prevalence was low in much of Asia and sub-Saharan Africa in the 1980s and 1990s,[62] recent reports have demonstrated an increase in China, India, Turkey, and Saudi Arabia.[63–66] Some high-income English-speaking countries, such as the USA and the United Kingdom,[44,67] also reported increased DM prevalence. On the other hand, DM prevalence did not increase in Western Europe, like Sweden, Germany, and Switzerland.[68,69] In accordance with a previous statement and based on geographical distribution, the prevalence of *H pylori* infection and DM seems to be inversely related. In our study, when the background population DM prevalence was below 6%, *H pylori* infection did not significantly increase the risk of colorectal adenoma formation (Group 1). This association became significant when the study population DM prevalence was over 6% (Groups 2–4). The odds ratio of *H pylori* infection-related colorectal formation was 2.16 (95% CI 1.61–2.91); it was the highest when the population DM prevalence was from 6% to 8% (Group 2). However, when the DM prevalence rate was elevated to 8% to 10% or more than 10% (Groups 3 and 4), the OR was mildly decreased to 1.40 (95% CI 1.24–1.57) and 1.52 (95% CI 1.46–1.57). *H pylori* infection still significantly increased colorectal adenoma but was not distinct from Group 2 (DM prevalence between 6% and 8%). However, when DM prevalence increased, *H pylori* infection might increase the risk of colorectal adenoma formation.

The cause of this condition may be related to the study period and location. Most studies in Group 2 were carried out from 1996 to 2000, and Group 3 studies were carried out from 2000 to

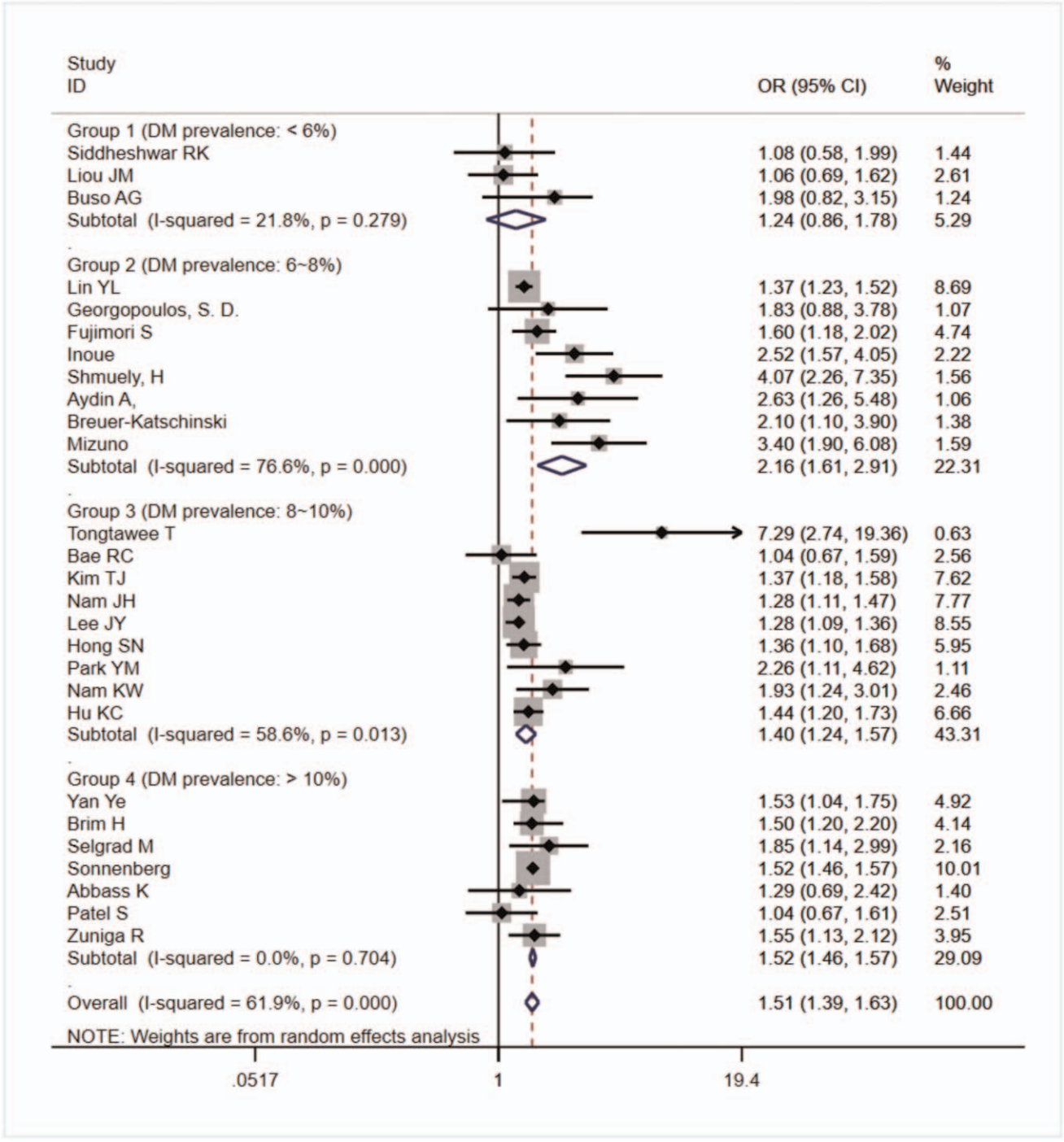

Figure 2. Forest plot showing individual and pooled odds ratio (95% CIs) of all studies included with subgroups of the prevalence of DM. Each study is labeled with the authors' name. CIs = confidence intervals, DM = diabetes mellitus.

2010. The study's location may also affect this result. Most of the Group 3 studies were from Korea, and Group 4 studies were from the USA. The Group 2 studies were more heterogeneous in location, including Japan, Taiwan, Turkey, Israel, and Germany. The *H pylori* infection rate of the study population was also collected and is shown in Table 1. There was no significant difference in the ORs of *H pylori* infection-associated colorectal adenoma between the lower infection rate area (USA or Germany, 35.3%–35.6%) and the middle infection rate area (Japan, Korea, China, Taiwan; approximately 51.7%–55.8%). Further evaluation for the other reason that Group 2 studies revealed higher ORs in *H pylori* infection-associated colorectal adenoma is necessary. In addition, our study might partially answer Plummer query "How to explain that some areas had a high prevalence of *H pylori* infection but low CRC risk?"[10] According to our study, we could see that Brazil et al. had a

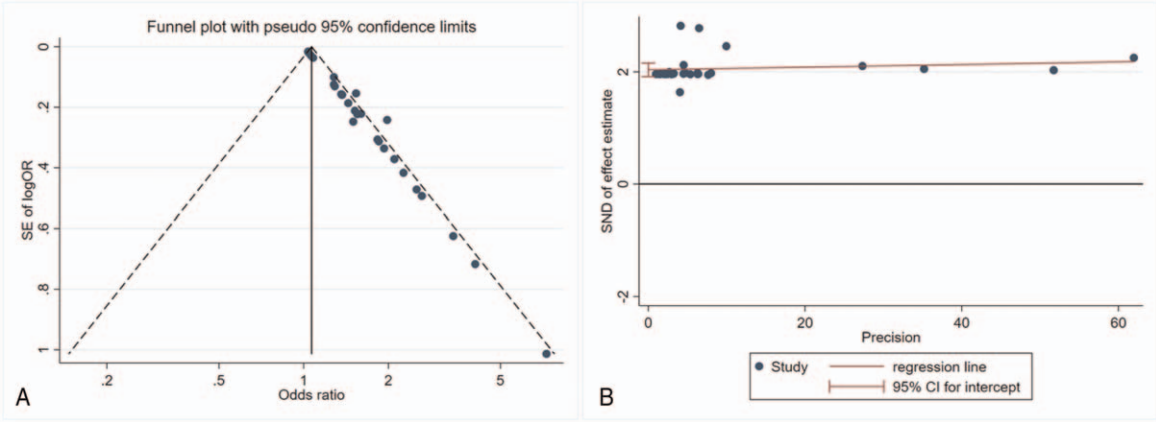

Figure 3. (A) Funnel plot of all studies included examining the relation between *Helicobacter pylori* infection and colon adenoma. (B) Egger regression test of all studies including the relation between *Helicobacter pylori* infection and colon adenoma.

higher *H pylori* infection prevalence (71.2%) but a lower DM prevalence rate (5.8%). (Table 1) Buso study demonstrated that the *H pylori* infection proportion did not significantly increase colorectal adenoma risk (OR: 1.98, 95% CI 0.82–3.15).[34] However, when the DM prevalence was higher (>10%), even when the *H pylori* infection rate was lower (35.6%), the OR of colorectal adenoma with *H pylori* infection was significantly increased (Group 4: OR: 1.52, 95% CI 1.46–1.57). This means that the DM prevalence rate might be the key factor of increased colorectal adenoma risk with *H pylori* infection.

Our previous study demonstrated the interaction of hyperglycemia and *H pylori* infection in colon adenoma formation. We found that the OR for adenoma was 1.437 (95% CI 1.197–1.726) if *H pylori* was present or 1.629 (95% CI 1.239–2.14) if HbA_{1c} ≥6.5. When combining these 2 factors, the OR was elevated to 4.712 (95% CI 3.189–6.963), suggesting that these 2 factors may have a synergistic effect in colorectal adenoma.[19] The likely reason for the synergistic effect may involve several processes. First, hyperglycemia status affected gastrointestinal morphology and function and resulted in gut barrier loss and changes in intestinal mucosa permeability. Second, high-fat and high-caloric diets also increase gut permeability, and this situation was more significant in DM patients.[70] Third, some intestinal microorganism-related products, such as lipopolysaccharides, would more efficiently pass through the gut barrier and stimulate the Toll-like receptors in the mucosa. This would trigger a serious inflammatory process, and finally, IL(interleukin)-17 and IL-6 will increase. IL-17 activates the signal transducer and activator of the transcription 3 pathway, promoting cell proliferation and survival and finally inducing tumorigenesis.[71]

These animal models and individualized study results support this study finding that states that an elevated DM prevalence rate enhances the risk of colorectal adenoma in *H pylori*-infected populations. Our study still had several limitations. First, in our subgroup analysis, we found that the Group 2 studies had more heterogeneity. The reason for this condition may be related to population studies with differences in study location, population, aging, and gender. Despite this heterogeneity, *H pylori* infection also increased the risk of colorectal adenoma. Second, the asymmetry of the results of Egger test and funnel plots suggested the possibility of publication bias. However, because most of our included studies[3,6,8,9,19,21–42] had statistically significant results, Egger test and funnel plots would show asymmetry. Third, the population DM prevalence rate might not completely represent our included studies participant's diabetes condition. Only Lin et al.[24] and Hu et al.[19] included the DM prevalence rate in their studies. To the best of our knowledge, we tried to estimate the diabetes rate of each study as accurately as possible.

5. Conclusion

In conclusion, our study demonstrated that population DM prevalence affects the risk of colorectal adenoma with *H pylori* infection. Since diabetes prevalence was over 6% in the background study population, *H pylori* infection became a more significant factor in inducing colorectal adenoma formation. Given the increasing prevalence of diabetes in the world, *H pylori* eradication and hyperglycemia control might have an impact on the prevention of colorectal neoplasm formation.

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Author contributions

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