Systematic Review and Meta-Analysis

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Association between *Helicobacter pylori* infection and nonalcoholic fatty liver

A meta-analysis

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Abstract

Background: Opinion regarding whether *Helicobacter pylori* infection can promote the occurrence and development of nonalcoholic fatty liver (NAFLD) is divided. Therefore, we aimed to assess the exact relationship between *H pylori* infection and NAFLD by integrating all available data.

Methods: The articles about *H pylori* infection and NAFLD were collected by searching the databases of PubMed, Embase, Web of Science, Scopus, China National Knowledge Infrastructure, and WanFang. The random-effects model was used for data analysis, followed by subgroup analysis and meta-regression to explore sources of heterogeneity.

Results: Twenty-one articles were included in the study. Pooled analysis showed that *H pylori* infection indeed promoted NAFLD. Subgroup analysis and regression analysis showed that case-control ratio may be one of the sources of heterogeneity.

Conclusions: *H pylori* infection is indeed one of the factors that promotes the progression of NAFLD for the Asian population. This provides new approaches for clinical prevention and treatment for NAFLD.

Abbreviations: CI = confidence interval, NAFLD = nonalcoholic fatty liver, OR = odds ratio.

Keywords: *Helicobacter pylori*, meta-analysis, nonalcoholic fatty liver

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a metabolic stress-induced liver injury characterized by diffuse hepatocyte macrovesicular fatty lesions in addition to alcohol and other defined liver injury factors.[1] With improving economic stability and lifestyle changes, the incidence of NAFLD is increasing yearly, and its incidence rate is as high as 20% to 30% on a global scale, which seriously affects people's health.[2,3] The etiology of NAFLD is complex, primarily characterized by abnormal lipid metabolism, insulin resistance, and genetic factors.[4,5] In recent years, studies have found that abnormal fat metabolism in the liver can lead to dysbacteriosis of the intestinal flora; dysregulation of the flora leads to disorders of lipid metabolism, which eventually promotes lipid deposition in liver. Moreover, there is increasing evidence that NALFD is associated with abnormalities of the intestinal flora, especially with *Helicobacter pylori*.[6–8]

H pylori is a gram-negative bacillus colonized in the deep layers of human gastric mucosa.[9] The reported infection rate of *H pylori* is as high as 50% or more worldwide.[10] Studies have shown that *H pylori* is responsible for chronic gastritis, peptic ulcer, gastrointestinal lymphoma, and gastric cancer.[11,12] In addition, new findings suggest that *H pylori* is closely related to liver tumors, obesity, diabetes, and abnormal lipid metabolism.[13,14] In recent years, studies have found that *H pylori* infection is one of the factors

Editor: Ludovico Abenavoli.

RL and QL contributed equally to this work.

The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

This work was supported by grants from the National Natural Science Foundation of China (No: 81660158, 81460092, 81400372); Natural Science Key Project of Jiangxi Province (No: 20161ACB21017); Key Research Foundation of Jiangxi Province (No: 20151BBG70223, 20181BBG70004); Youth Science Foundation of Jiangxi Province (No: 20151BAB215016, 20161BAB215198); Education Department Key Project of Jiangxi Province (No: GJJ160020); Teaching Reform of Degree and Graduate Education Research Project of Jiangxi Province (No: JXYJG-2018-013); Grassroots Health Appropriate Technology "Spark Promotion Plan" Project of Jiangxi Province (No: 20188003); Health Development Planning Commission Science Foundation of Jiangxi Province (No: 20175116); Health Development Planning Commission Science TCM Foundation of Jiangxi Province (No: 20150823).

The authors have no conflicts of interest to disclose.

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How to cite this article: Liu R, Liu Q, He Y, Shi W, Xu Q, Yuan Q, Lin Q, Li B, Ye L, Min Y, Zhu P, Shao Y. Association between Helicobacter pylori infection and nonalcoholic fatty liver. Medicine 2019;98:44(e17781).

Received: 8 February 2019 / Received in final form: 17 September 2019 / Accepted: 3 October 2019

http://dx.doi.org/10.1097/MD.0000000000017781

contributing to the progression of NAFLD, and elimination of *H pylori* can delay the progression of NAFLD to some extent.[15–30] However, other studies have suggested that *H pylori* infection has no clear relationship with NAFLD, and its eradication does not halt the progression of NAFLD.[31–38] Therefore, we further explored the exact relationship between *H pylori* infection and NAFLD by integrating data for meta-analysis.

2. Materials and methods

Two independent researchers searched the PubMed, Embase, Web of Science, Scopus, China National Knowledge Infrastructure, and WanFang Data. The search keywords were: (*Helicobacter pylori* or *H pylori* or Hp or *Helicobacter* spp or *H. pylori*) AND (non-alcoholic fatty liver disease or NAFLD or non-alcoholic steatohepatitis or NASH or non-alcoholic fatty liver or NAFL or fatty liver). Articles published from January 2007 to October 2018 were searched. The search method uses keywords, without any restrictions, and manually searched for references in existing literature.

2.1. Inclusion criteria

Papers were included if they:

(1) compared the risk of NAFLD in patients with *H pylori* infection and those without;
(2) provided the number of positive/negative *H pylori* infection persons in the NAFLD and control groups.

2.2. Exclusion criteria

Abstracts, conference papers, and articles detailing animal experiments were excluded, as were articles that did not provide complete data.

In this paper, 2 researchers independently conducted the literature search and extracted the first author of the articles, year of publication, country of publication, method of detection of *H pylori*, method of diagnosis of NAFLD, the number of positive/negative *H pylori* infections in the NAFLD group, and the number of positive/negative *H pylori* infections in the control group. We assessed the quality of each study according to the Newcastle–Ottawa quality assessment scale.[39] This study does not require the approval of the ethics committee.

2.3. Data analysis

All data analysis was performed using STATA version 12.0 software (Stata Corporation, College Station, TX), and heterogeneity analysis was performed using a Chi-square test or a Cochrane-Q test. Heterogeneity was assessed by I^2 statistic, wherein $I^2 < 50\%$ indicates minor heterogeneity, for which a fixed effect model was used, and $I^2 > 50$ indicates large heterogeneity, for which a random effect model was used. The subgroup analysis and regression analysis were performed to explore sources of heterogeneity. The forest plot assesses the relationship between *H pylori* infection and NAFLD. The funnel plot and Begg and Egger tests were used to investigate publication bias. $P < .05$ was considered statistically significant.

3. Results

3.1. Clinical features

By searching the aforementioned databases, we selected 1491 research articles, and further browsed the title, abstract, and full text of the literature. Next, we excluded abstracts, conference articles, animal experiment studies, and those with incomplete data. Eventually, 21 studies were included for the final analysis that researched the relationship between *H pylori* infection and NAFLD. All these articles were published between 2007 January and 2018 October. The related literatures included 2 cohort studies, 2 case-control studies, and 17 cross-sectional studies in the meta-analysis. The flow chart for the studies is shown in Figure 1. A total of 14,623 participants were included, and the sample size for each study ranged from 53 to 43,216. Fourteen articles used the breath test to confirm *H pylori* infection, 7 articles used antibodies to detect *H pylori* infection, 19 articles used ultrasound to confirm NAFLD, and 2 articles used other methods. The basic information about all included literatures is listed in Table 1.

3.2. Meta-analysis and subgroup analysis

A total of 21 articles were included, including 11 reports in English and 10 in Chinese. We conducted a meta-analysis by integrating data to find significant heterogeneity ($I^2 = 95.6\%$). Therefore, we use the random-effects model to calculate the odds ratio (OR) and 95% confidence intervals (CIs). The results indicated that *H pylori* infection is indeed one of the contributing factors to NAFLD ($P = .000$, OR [95% CI] = 1.529 [1.336, 1.750]). The forest plot results are described in Figure 2.

There was significant heterogeneity among the studies. To further explore the heterogeneity sources, we performed a subgroup analysis based on the study type, region, *H pylori* detection method, NAFLD detection method, sample size, and case-control ratio. The results of all subgroup analyses are shown in Table 2. Unfortunately, we did not find the cause of heterogeneity in the subgroup analysis.

3.3. Regression analysis

To find the source of heterogeneity, we also performed regression analysis (Table 2). The results showed that the heterogeneity was caused by case-control ratio ($P = .000$) instead of study type ($P = .658$), NAFLD test method ($P = .477$), *H pylori* detection method ($P = .841$), race ($P = .542$), publication year ($P = .904$), or language ($P = .620$).

3.4. Publication bias

We used a funnel plot to qualitatively detect the publication bias, and Egger and Begg tests to quantify the publication bias. The funnel plots were almost symmetric (Fig. 3). *P*-value of Egger test was.370. *P* was greater than.05, and no significant bias was observed.

4. Discussion

NAFLD is characterized by simple fatty liver in the early stage, which can evolve and progress to steatohepatitis, cirrhosis, liver cancer, and liver failure.[40,41] It is one of the most common liver diseases that affects people's life and health.[42] Currently, there are some theories to explain how *H pylori* infection causes NAFLD. *H pylori* can upregulate the expression of various inflammatory factors such as tumor necrosis factor, C-reactive protein, and interleukin to promote insulin resistance.[43,44] At the same time, *H pylori* can retrograde into the liver through the hepatic bile duct or intestinal ectopic, leading to chronic liver

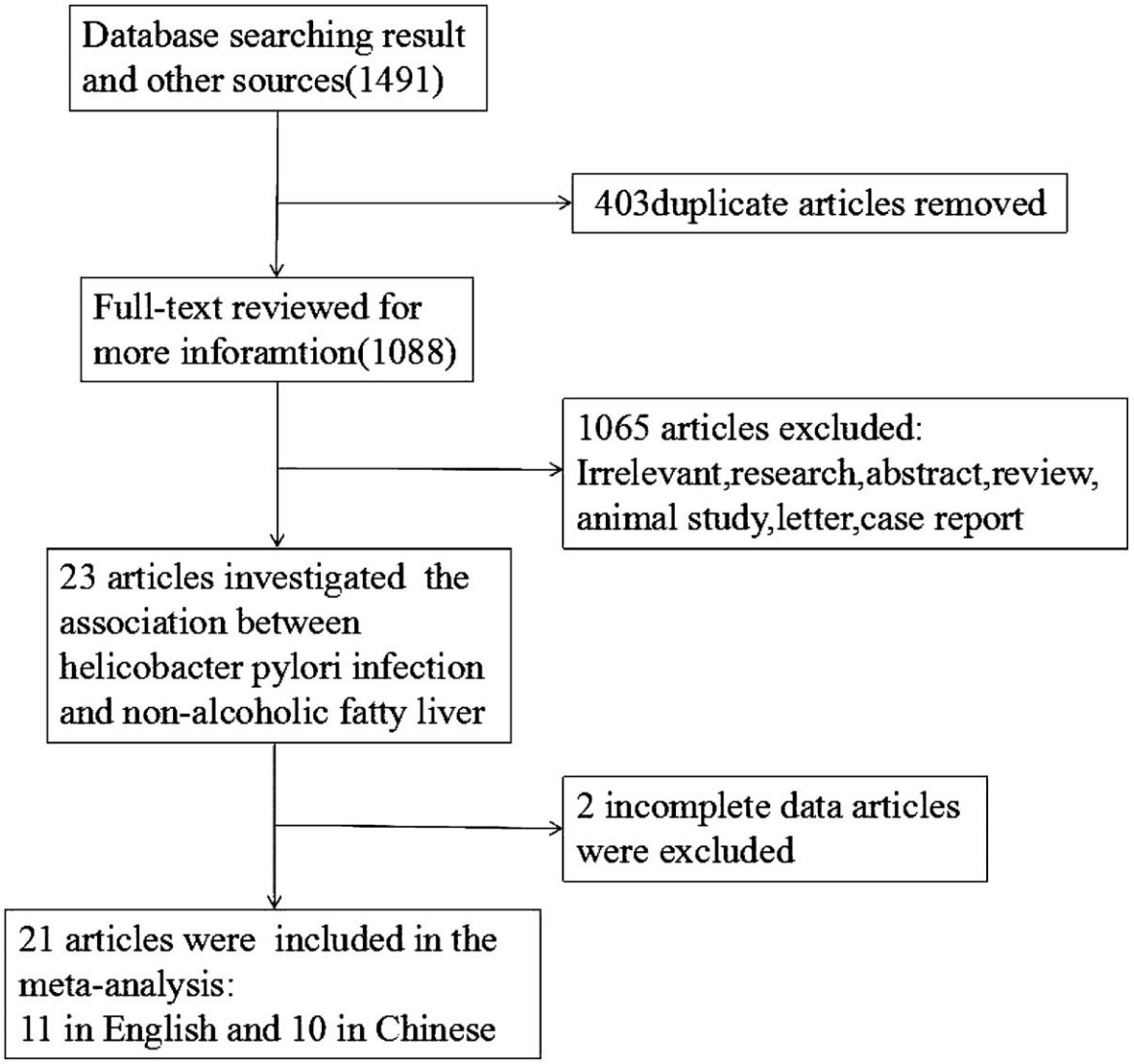

Figure 1. Flow diagram of the study screening and selection process.

inflammation, causing liver cell damage and necrosis.[45,46] The study found that human fetuin A is significantly increased in patients harboring *H pylori* infection, and human fetuin A is an important participant in insulin signaling, playing an crucial role in promoting insulin resistance and diabetes.[47–49] In addition, studies have revealed that adiponectin expression is significantly reduced in NAFLD patients infected with *H pylori*, and adiponectin inhibits fatty acid deposition in the liver and inhibits NF-KB pathway activation as an anti-inflammatory effect. When adiponectin expression is abnormal, fat accumulates more easily in the liver cells, and the liver is more susceptible to inflammatory damage.[50,51] Studies have also shown that lipids levels can change significantly in patients with *H pylori* infection; accordingly, dyslipidemia is common in patients with NAFLD.[52]

Our meta-analysis found that *H pylori* is one of the factors that promotes NAFLD progression, which is consistent with the results of a previous meta-analysis.[53] However, the previous meta-analysis only included six articles, 3 of which were conference abstracts, and 2 of these abstracts did not have their full-text released yet. In addition, numerous studies on the association between *H pylori* infection and NAFLD have emerged since that meta-analysis was published. Therefore, it is necessary to implement a new meta-analysis on this issue. We combined the data and found that the heterogeneity was very obvious, so we adopted a random-effects model. Considering the heterogeneity among the studies, subgroup analyses were performed. Unfortunately, we did not find the reason for this heterogeneity in subgroup analyses. However, the good news was that through regression analysis, we found that the case-control ratio may be a cause of heterogeneity ($P = .035$).

There are several shortcomings in our meta-analysis. First, small sample studies are more prone to generate heterogeneity, and only 8 of the 21 studies in the meta-analysis had over 5000 patients. Second, most of the included researches were cross-sectional studies, and the results of the research are not very strong, which is bound to have a certain impact on our conclusions. Third, the risk factors for NAFLD include dyslipidemia, obesity, age, environment, diet and sex, and additional biochemical features of selected articles cannot be

Table 1

Baseline characteristics of all studies investigating *Helicobacter pylori* infection and NAFLD.

Study and year	Country	Age	Study type	NAFLD group		Control group		Case-control ratio	Diagnosis of *Helicobacter pylori* infection	Diagnosis of NAFLD
				HP+	HP−	HP+	HP−			
Lu 2018[17]	China	54	Cross-sectional	199	397	390	881	0.46	Breath test	Ultrasound
Polyzos 2013[18]	Greece	54.5	Cross-sectional	26	2	14	11	1.12	Antibody	Histology
Kim 2017[19]	Korea	49	Cohort study	2080	1301	7838	5809	0.25	Antibody	Ultrasound
Abdel-Razik 2018[20]	Egypt	49.5	Cohort study	23	148	0	198	0.87	Antibody	Ultrasound
Kang 2018[21]	American	44	Case-control	658	1065	390	881	0.46	Antibody	Ultrasound
Chen 2016[22]	China	NA	Cross-sectional	313	290	723	937	0.36	Breath test	Ultrasound
Zhang 2016[23]	China	NA	Case-control	300	300	144	456	1	Breath test	Ultrasound
Guo 2016[24]	China	47.5	Cross-sectional	809	1115	1649	3164	0.25	Breath test	Ultrasound
Zhang 2017[25]	China	52.5	Cross-sectional	224	132	192	164	1	Breath test	Ultrasound
Wang 2018[26]	China	38	Cross-sectional	126	74	37	163	1	Breath test	Ultrasound
Peng 2014[27]	China	53.	Cross-sectional	103	47	41	59	1.5	Breath test	Ultrasound
Xu 2011[28]	China	NA	Cross-sectional	40	22	14	36	1.24	Antibody	Ultrasound
Hou 2018[29]	China	NA	Cross-sectional	3982	9414	5519	24301	0.45	Breath test	Ultrasound
Liu 2014[30]	China	50	Cross-sectional	1657	3724	2686	6306	0.60	Breath test	Ultrasound
Baeg 2016[32]	Korea	53	Cross-sectional	505	440	1131	1587	0.34	Breath test	Histology
Cai 2018[33]	China	38	Cross-sectional	145	288	500	1118	0.26	Breath test	Ultrasound
Okushin 2015[34]	Japan	50	Cross-sectional	523	1279	926	2561	0.52	Antibody	Ultrasound
Fan 2018[35]	China	48	Cross-sectional	3905	5769	6943	11554	0.52	Breath test	Ultrasound
Guo 2013[36]	China	49	Cross-sectional	809	115	1649	3164	0.39	Antibody	Ultrasound
Wang 2016[37]	China	45.5	Cross-sectional	713	641	992	1101	1	Breath test	Ultrasound
Chen 2016[38]	China	60	Cross-sectional	767	663	1841	1888	0.38	Breath test	Ultrasound

NAFLD = nonalcoholic fatty liver.

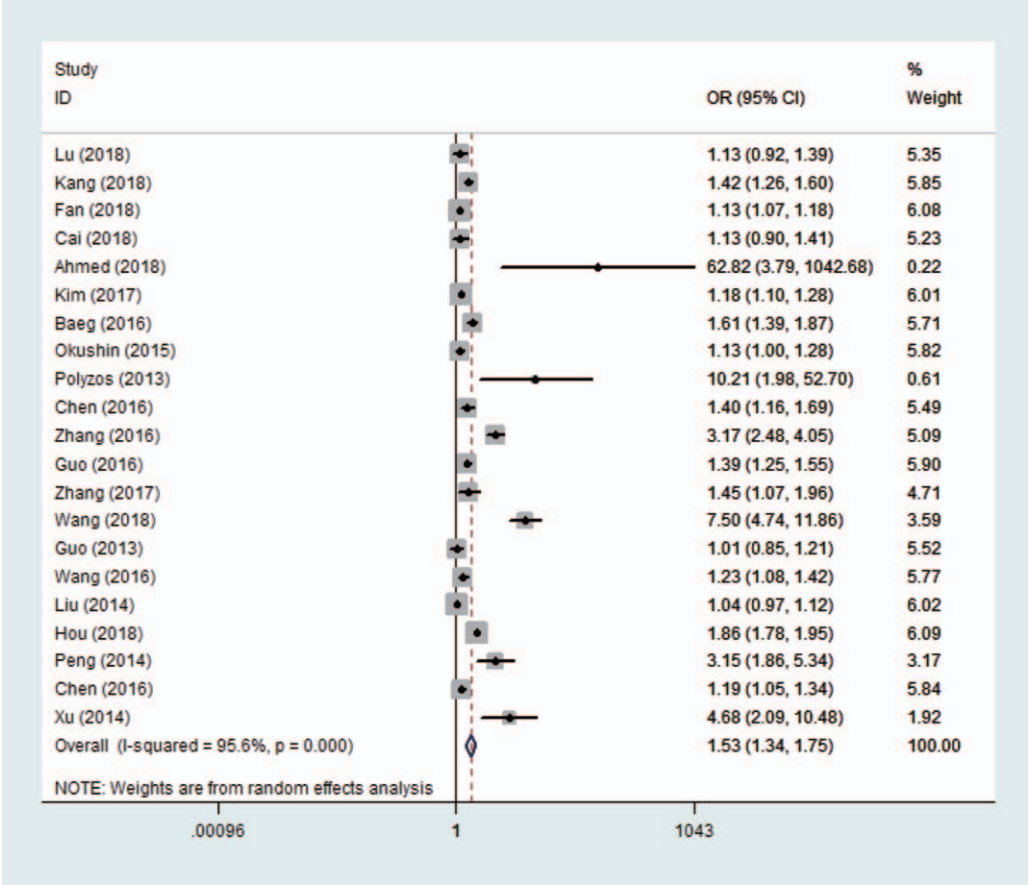

Figure 2. Forest plot of the association between *Helicobacter pylori* infection and NAFLD. NAFLD = nonalcoholic fatty liver disease.

Table 2

Meta-regression and subgroup analysis of all studies evaluating the association between *Helicobacter pylori* infection and nonalcoholic fatty liver.

Stratified study	No. of studies	Pooled OR (95%CI)		Heterogeneity		Meta-regression		
		Fixed-model	Random-model	I^2 (%)	*P*-value	Tau^2	Adj R^2 (%)	*P*-value
Year						0.2741	−9%	.904
>2016	9	1.416 (1.375, 1.458)	1.564 (1.250, 1.957)	97.3%	.000			
≤2016	12	1.242 (1.192, 1.295)	1.498 (1.27, 1.768)	91.6%	.000			
Study type						0.2772	−10.25%	.658
Cross-sectional	17	1.356 (1.321, 1.392)	1.487 (1.278, 1.732)	95.9%	.000			
Cohort study	2	1.205 (1.116, 1.302)	6.692 (0.137, 327.949)	87.2%	.338			
Case-control	2	1.667 (1.499, 1.855)	2.106 (0.961, 4.616)	97%	.063			
Diagnosis of *Helicobacter pylori* infection						0.2795	−11.12%	.841
Antibody	7	1.225 (1.160, 1.294)	1.322 (1.091, 1.602)	83.8%	.004			
Breath test	14	1.388 (1.351, 1.425)	1.579 (1.333, 1.870)	96.7%	.000			
Diagnosis of NAFLD						0.2715	−7.99%	.477
Ultrasound	19	1.347 (1.315, 1.381)	1.507 (1.310, 1.733)	95.9%	.000			
Histology	2	1.644 (1.418,1.906)	3.361 (0.571,19.798)	79.3%	.180			
Sample size						0.2287	9.06%	.101
>5000	8	1.3359 (1.301, 1.370)	1.274 (1.065, 1.523)	97.7%	.008			
<5000	13	1.475 (1.384, 1.572)	1.951 (1.501, 2.537)	92%	.000			
Race						0.2592	−9.58%	.542
Yellow	18	1.348 (1.316, 1.382)	1.506 (1.307, 1.735)	96.2%	.000			
White	3	1.499 (1.332, 1.687)	6.952 (0.819, 59.028)	84.4%	.231			
Language						0.2622	−4.28%	.620
English	11	1.225 (1.183, 1.268)	1.403 (1.215, 1.620)	90.6%	.000			
Chinese	10	1.489 (1.440, 1.540)	1.688 (1.341, 2.125)	96.8%	.000			
Case-control ratio						0.6607	73.73%	.000
≥1	6	2.902 (2.474, 3.404)	3.663 (2.122, 6.322)	87.9%	.000			
<1	15	1.330 (1.298, 1.362)	1.272 (1.116, 1.449)	95.7%	.000			

CI = confidence interval, NAFLD = nonalcoholic fatty liver, OR = odds ratio.

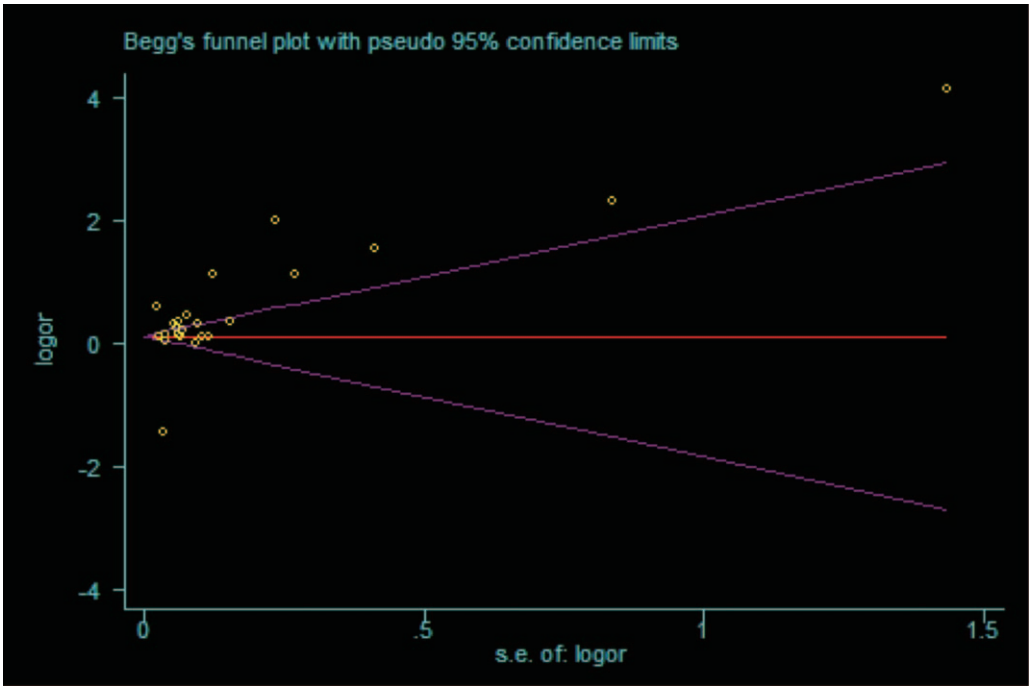

Figure 3. Begg funnel plot of publication bias.

extracted, so our data integration for the meta-analysis has not been able to control these factors. Fourth, most of the meta-analysis done is taken from studies done in the Asian region, and the results may be more suitable for the Asian population. In addition, there is no uniform standard for detection of *H pylori* infection and diagnosis of NAFLD in these studies, and it is likely that there will be some bias in the results owing to different methodologies. Furthermore, different genotypes of *H pylori* have different effects on NAFLD as mentioned in the study; hence, the effects of different genotypes of *H pylori* in the articles cannot be excluded. Finally, if it can be proved that eradication of *H pylori* can effectively prevent NAFLD progression, it can be confirmed from the sidelines that *H pylori* infection does indeed promote NAFLD.

In conclusion, our meta-analysis by integrating data further confirmed that *H pylori* infection in the gastrointestinal tract is indeed one of the factors that promotes the progression of NAFLD for the Asian population. However, given that most of the included studies are small-sample, local geographical area and cross-sectional studies, multicenter, wide geographical area and large-sample prospective studies are needed to further explore the relationship between *H pylori* infection and NAFLD.

Author contributions

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Methodology: Yi Shao.
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Writing – original draft: Rongqiang Liu, Qiuli Liu.
Writing – review and editing: Yi Shao.

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