

## ORIGINAL ARTICLE

# Effect of vitamin D on *Helicobacter pylori* infection and eradication: A meta-analysis

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**Abstract**

**Background:** Various studies reported the relationship between *Helicobacter pylori* (*H pylori*) and vitamin D, but there is some controversy around that. This study aimed to conduct a meta-analysis to clarify the relationship between vitamin D and *H pylori* infection, and vitamin D and *H pylori* eradication.

**Methods:** Articles published until June 1, 2019, in the PubMed, MEDLINE, and EMBASE databases with English-language medical studies were searched. According to the inclusion criteria, relevant statistical data were extracted to Microsoft Excel and analyzed by STATA15.1.

**Results:** Ten articles were finally included. It was demonstrated that average 25(OH)D level in *H pylori*-positive patients was lower than *H pylori*-negative (SMD = -0.53 ng/mL, 95% CI = (-0.91, -0.16 ng/mL)). For *H pylori* eradication individuals, the result showed that average 25(OH)D level in *H pylori* successful eradication individuals was higher than unsuccessful (SMD = 1.31 ng/mL, 95% CI = [0.60, 2.02 ng/mL]). In addition, individuals with vitamin D deficiency had lower *H pylori* eradicate rate (OR = 0.09, 95% CI = [0.02, 0.41]). Sensitivity analysis showed that the meta-analysis results were stable and reliable.

**Conclusions:** Vitamin D was a protective factor to *H pylori* infection. Moreover, vitamin D can improve the success rate of *H pylori* eradication.

**KEYWORDS**

eradicate, *Helicobacter pylori*, vitamin D

## 1 | INTRODUCTION

*Helicobacter pylori* (*H pylori*) is the Gram-negative microaerophilic bacterium colonizing in human gastric mucosa, which caused stomach injury. Numerous studies have demonstrated that *H pylori* infection is commonly associated with gastroduodenal diseases in humans, such as chronic gastritis, peptic ulcers, gastric mucosa-associated lymphoid tissue lymphoma, and even gastric cancer.<sup>1-4</sup> *H pylori* infection has become a public health issue which has attracted the attention of many countries. *H pylori* gastritis has been defined as an infectious disease transmitted through oral-oral and fecal-oral, which can be detected in dental plaques, houseflies, human and animal feces, and natural environmental

waters.<sup>5,6</sup> *H pylori* infection has remained high in the worldwide, and it is inversely related to socioeconomic development according to the human development index (HDI).<sup>7,8</sup> Numerous factors can affect *H pylori* infection. Previous study has shown that *H pylori* infection is related to geographical latitude and average daily sunshine, and speculated that the root cause is vitamin D deficiency.<sup>9</sup> Vitamin D is an immunoregulatory agent widely known to mediate bone metabolism and plays a key role in target tissues.<sup>10</sup> Through vitamin D receptor (VDR), vitamin D plays biological activities.<sup>10</sup> Several studies have uncovered the relationship between vitamin D and *H pylori* infection, and vitamin D and *H pylori* eradication. Kawaura et al<sup>11</sup> even indicated that long-term use of vitamin D daily can significantly reduce the rate of *H pylori* infection.

In order to get a more convincing result, in this study, we aimed to conduct a meta-analysis to confirm the relationship between vitamin D and *H pylori* infection firstly. Second, we were committed to determining whether vitamin D levels would affect effective rate of *H pylori* eradication.

## 2 | METHODS

### 2.1 | Data sources and study selection

Articles published until June 1, 2019, in the PubMed, MEDLINE, and EMBASE databases with restrictions of English-language medical literature for human studies were searched. We used following terms in order to cover as many articles as possible: (*Helicobacter pylori* OR *H pylori* OR *Helicobacter infection* OR *Helicobacter\** OR *HP* OR *Helicobacter pylori* (MeSH)), AND (vitamin D OR 25-Hydroxyvitamin D OR calcitriol OR VD (MeSH)). After the primary election, the inclusion and exclusion criteria were used for the next screening. Eligible studies were included in the meta-analysis if they met all the following criteria: (a) published as full article, (b) obtained data that met the needs of the research on the association between *H pylori* and vitamin D, and (c) *H pylori* infection was confirmed by serology and/or histology and/or urea breath test (UBT) and/or rapid urea test (RUT) and/or bacterial culture. Studies that (a) did not meet the mentioned criteria above, (b) patients had a history of *H pylori* eradication, and (c) duplicate publications were excluded.

### 2.2 | Data abstraction

Data were extracted to Microsoft Excel (2019 edition; Microsoft) for effective organization. We abstracted main study characteristics for analysis, including basic characteristics (including number of *H pylori* infection, *H pylori* eradication and control individuals, publication year, research country), serum vitamin D levels as continuous variable, and the cutoff level used to define vitamin D deficiency as dichotomous variable, strategy of *H pylori* eradication and so on. 25(OH)D was the main form of vitamin D considered in the included studies, and the cutoff level for 25(OH)D deficiency was defined as less than 20 ng/mL.<sup>12</sup> All data were double-checked by one author. Two investigators independently examined selected papers and abstract data in our analyses. If there was a disagreement, a third author would evaluate the disagreement again and form a final result after the trade. The work was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>13</sup>

### 2.3 | Statistical analysis

Standardized mean difference (SMD) was used for studies that reported mean and standard deviation (SD) values for vitamin D levels of *H pylori* infection individuals, *H pylori* eradication individuals, and controls. For provided median (interquartile range) instead of

SDs, we obtained a final SD using a reduction formula.<sup>14</sup> The odds ratio (OR, 95% confidence intervals [CIs]) was used to describe the ratio of the probability of the *H pylori* infection or *H pylori* eradication occurring in 25(OH)D deficiency individuals vs controls. Then, pooled estimates were obtained using the fixed-model (Mantel and Haenszel) method (if  $I^2 \leq 50\%$ ,  $P > .1$ ) or random-model (M-H heterogeneity) method (if  $I^2 > 50\%$ ,  $P \leq .1$ ).<sup>15</sup> Statistical heterogeneity was assessed by Cochran's Q test and the  $I^2$  statistic. In addition, sensitivity analysis was to evaluate whether the meta-analysis results were stable and reliable. Meta-regression was used to look for sources of heterogeneity (Monte Carlo permutation test). All analyses were carried out through the application of the commands metan, metaninf, and metareg in STATA 15.1 (StataCorp.).

## 3 | RESULTS

### 3.1 | Basic characteristics

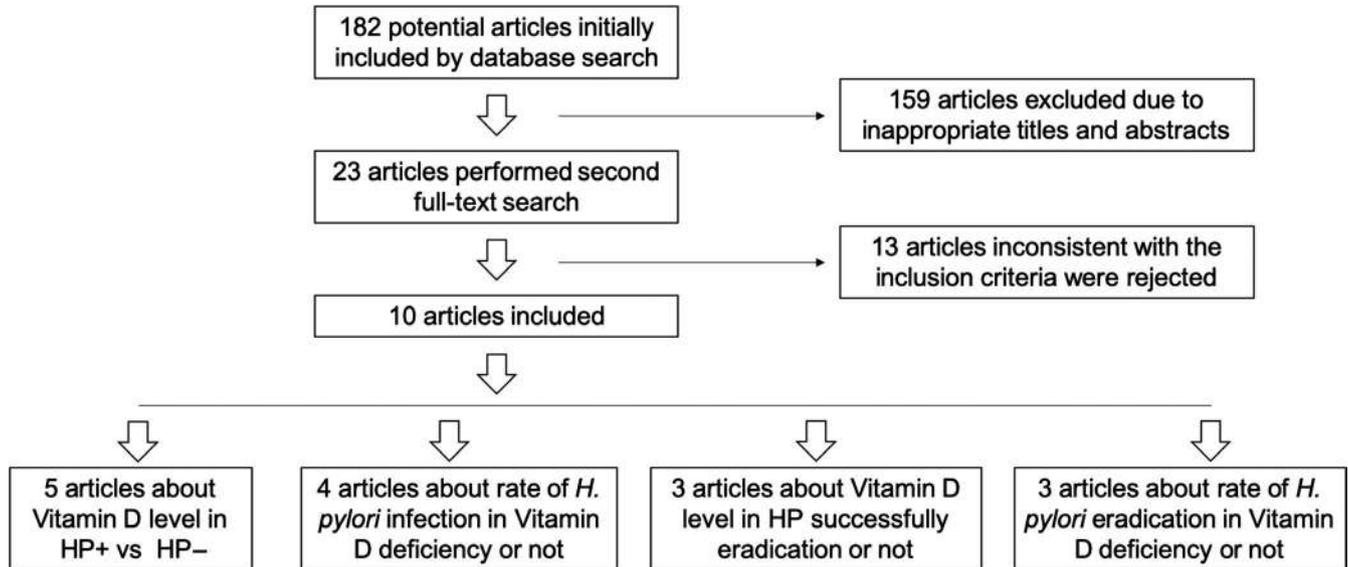
Our search identified 182 related references, of which 10 papers met our inclusion criteria.<sup>16-25</sup> The flowchart describing the process of study selection is shown in Figure 1. The 10 studies included 6 studies conducted in Asia, three in Europe, and 1 in Africa. Of the 5 studies reporting *H pylori* eradication, two studies chose 14-day triple therapy and three studies chose 14-day quadruple therapy. For data of 25(OH)D using nmol/L as the unit, we uniformly convert it to ng/mL (1 nmol/L = 2.5ng/mL). In this study, statistical heterogeneity was assessed by  $I^2$  statistic >50%. Therefore, we chose random-model (M-H heterogeneity) method to conduct the meta-analysis.

### 3.2 | Relationship between *H pylori* infection and vitamin D

Five studies reported vitamin D levels in *H pylori* -positive and *H pylori* -negative individuals. The basic characteristics are shown in Table 1. It showed that the average 25(OH)D level in *H pylori*-positive patients was 0.53 ng/mL less than that in *H pylori* -negative patients (SMD = -0.53 ng/mL, 95% CI = (-0.91, -0.16 ng/mL),  $I^2 = 91.8\%$ ,  $P < .01$ ; Figure 2A). Next, we aimed to determine whether patients with vitamin D deficiency were more susceptible to *H pylori* infection. Four articles provided the data we needed. The result was not consistent with our assumption (OR = 3.54, 95% CI = (0.70, 17.94),  $I^2 = 96.2\%$ ,  $P < .01$ ; Figure 3A).

### 3.3 | Relationship between *H pylori* eradication and vitamin D

In this part, three studies telling us vitamin D levels in *H pylori* successful eradication individuals and unsuccessful eradication individuals were presented in Table 2. The result showed that average 25(OH)D level in *H pylori* successful eradication individuals was 1.31 ng/mL more than that in *H pylori* unsuccessful eradication individuals (SMD = 1.31 ng/mL, 95% CI = (0.60, 2.02 ng/mL),  $I^2 = 88.3\%$ ,  $P < .01$ ; Figure 2B). Moreover, we found that individuals



**FIGURE 1** The flowchart describing the process of study selection

with vitamin D deficiency were 0.09 times more likely to eradicate *H pylori* successfully (OR = 0.09, 95% CI = (0.02, 0.41),  $I^2 = 90.6\%$ ,  $P < .01$ ; Figure 3B).

### 3.4 | Meta-regression and sensitivity analysis

Meta-analysis results show significant heterogeneity. Sensitivity analysis results showed that the results of dichotomous variable were fluctuant, but it was still stable and reliable (Figure 4). Heterogeneity of *H pylori* infection and vitamin D did not come from *H pylori* test ( $P = .524$ ), vitamin D test ( $P = .339$ ), or study region ( $P = .478$ ) through meta-regression. In addition, meta-regression demonstrated that *H pylori* test ( $P = .648$ ), vitamin D test ( $P = .648$ ), or study region ( $P = .366$ ) was not the source of heterogeneity in *H pylori* eradication and vitamin D.

## 4 | DISCUSSION

In clinical studies, the relationship between vitamins D and *H pylori* infection is still controversial, especially the effect of vitamins D on *H pylori* eradication. In this study, we collected studies published about vitamins D and *H pylori* in order to provide sufficient

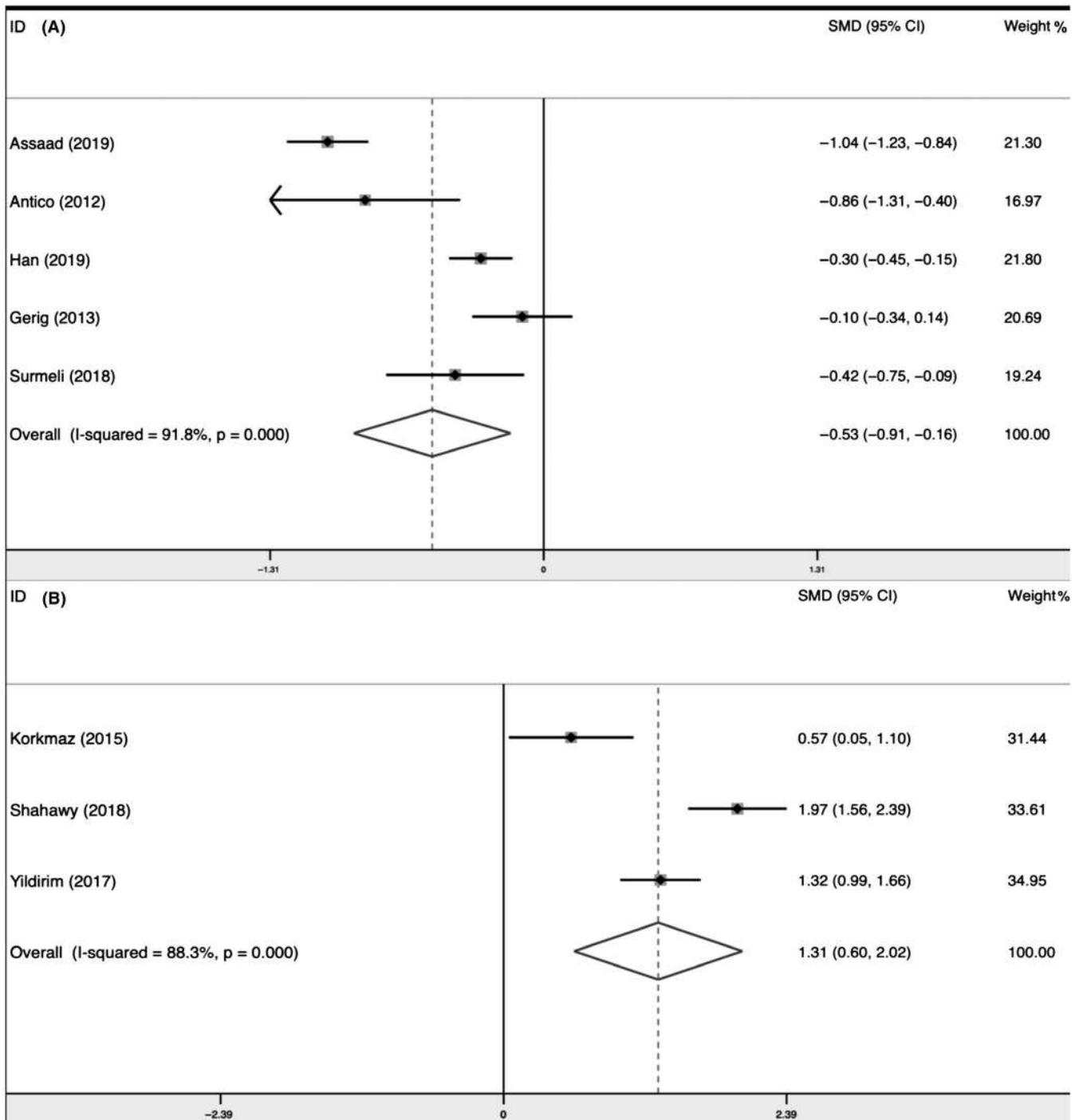
evidence between vitamins D and *H pylori* infection, and vitamins D and *H pylori* eradication. The results demonstrated that *H pylori*-positive individuals had lower vitamin D levels. In addition, *H pylori* successful eradication individuals had higher vitamin D levels, and individuals with vitamin D deficiency had higher unsuccess rate of *H pylori* eradication. It can be seen that vitamin D was an important protective factor in *H pylori* infection.

Vitamin D plays its biological role via combining with VDR, which expresses in almost all target tissues, such as the kidney, thyroid, intestine, skin, immune cells, nonparenchymal hepatocytes, and biliary epithelial cells.<sup>26</sup> Therefore, VDR is considered to be involved in a variety of biological reactions. Which mechanism does VDR participate to affect hp *H pylori* infection? The most important reason may be its antibacterial action against *H pylori*. Previous study reported that infected macrophages upregulate the production of  $\beta$ -defensin to kill *H pylori* strains by VDR.<sup>27</sup>  $\beta$ -defensins are secreted in the gastric mucosa, playing a pivotal role in the immune response of the gastrointestinal epithelium to *H pylori* infection.<sup>28</sup> In addition, cathelicidin antimicrobial protein (CAMP) is also an important antibacterial factor. *H pylori* infection leads to upregulation of the production of CAMP, which is directly regulated by binding of the VDR.<sup>29</sup> Guo et al<sup>30</sup> revealed that the expression of VDR and CAMP in the gastric epithelium is upregulated in the case of *H pylori* infection. Hosoda et

**TABLE 1** Basic characteristics of *Helicobacter pylori* infection and vitamin D

Author	Year	Country	Hp+ (n)	Vitamin D <sup>a</sup> in Hp+	Hp- (n)	Vitamin D <sup>a</sup> in Hp-
Assaad	2019	Lebanon	225	18.04 ± 7.16	235	30.74 ± 15.66
Antico	2012	Italy	21	11.10 ± 8.40	212	21.30 ± 12.20
Han	2019	China	496	17.00 ± 6.90	257	19.20 ± 8.00
Gerig	2013	Switzerland	85	19.60 ± 12.00	315	20.80 ± 11.60
Surmeli	2018	Switzerland	43	9.00 ± 8.37	211	13.60 ± 11.26

<sup>a</sup>The unit of vitamin D was ng/mL.

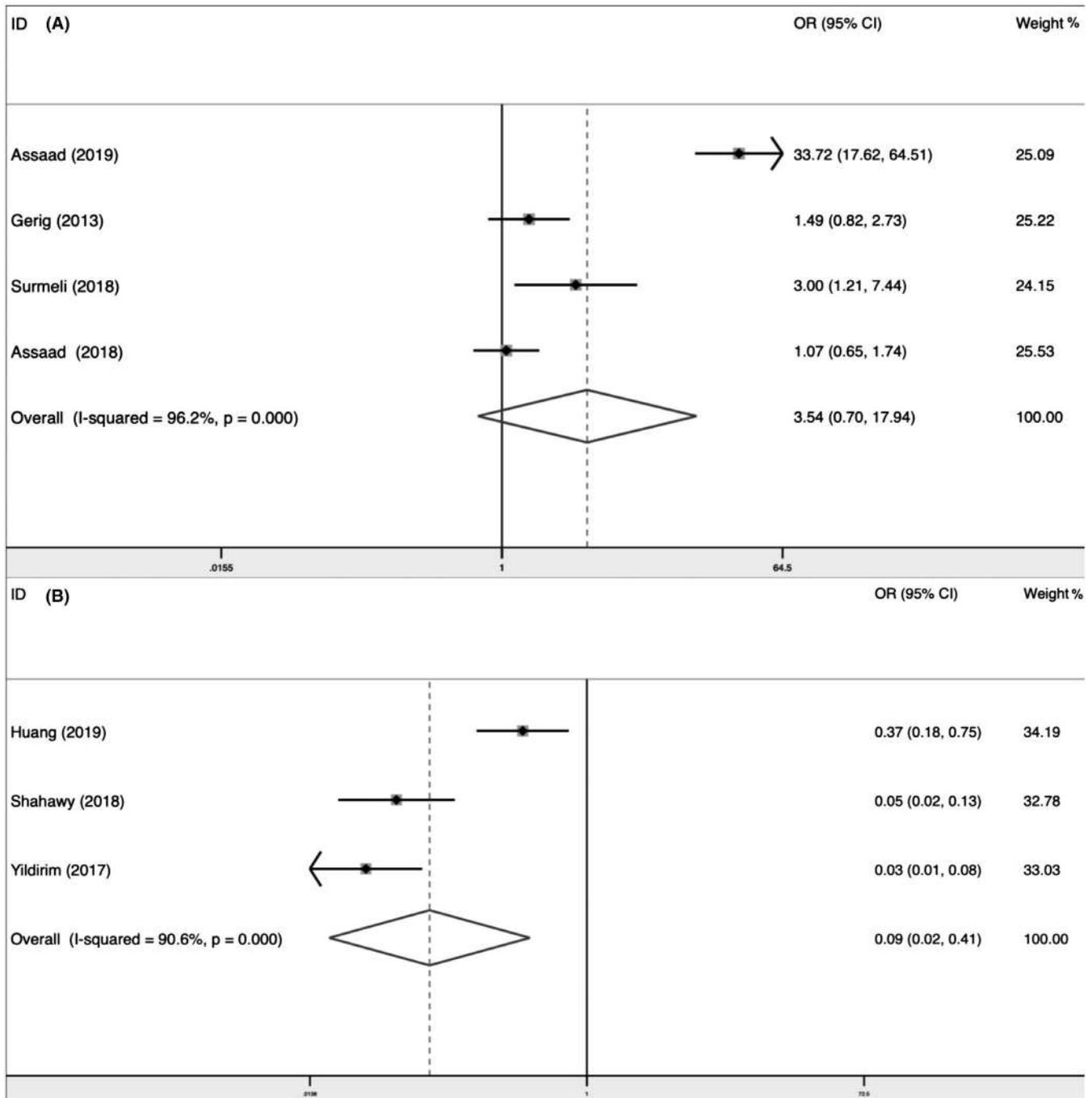


**FIGURE 2** A, Average 25(OH)D level in *Helicobacter pylori* -positive patients was 0.53 ng/mL less than that in *H pylori*-negative patients (SMD = -0.53 ng/mL, 95% CI = (-0.91, -0.16 ng/mL),  $I^2 = 91.8\%$ ,  $P < .01$ ); B, vitamin D deficiency was not more susceptible to *H pylori* infection (OR = 3.54, 95% CI = (0.70, 17.94),  $I^2 = 96.2\%$ ,  $P < .01$ )

al<sup>31</sup> demonstrated another mechanism that the vitamin D3 decomposition product (VDP1) exerts an antibacterial action against *H pylori* but not against other bacteria. Treatment with VDP1 induced a collapse of cell membrane structures of *H pylori*.<sup>31</sup>

Another major factor may be the immune response. Previous study demonstrated that the CagA of *H pylori* activated various intracellular signaling pathways, including the NF- $\kappa$ B pathway and MAP kinases via EGFR activation.<sup>32</sup> In vitro, Sierra et al<sup>33</sup> showed

that a specific EGFR inhibitor was able to decrease the epithelial DNA damage induced by *H pylori* infection. It can be seen that EGFR plays a key role in the process of *H pylori* infection. Zhang et al found that in lung cancer, EGFR mutations may remain responsive to and are likely to benefit from 1,25(OH)<sub>2</sub>D<sub>3</sub> administration.<sup>34</sup> It was inferred that in *H pylori* infection, vitamin D may also affect *H pylori* by adjusting EGFR. Recently, Hu et al<sup>35</sup> demonstrated that vitamin D activates the autolysosomal degradation function against

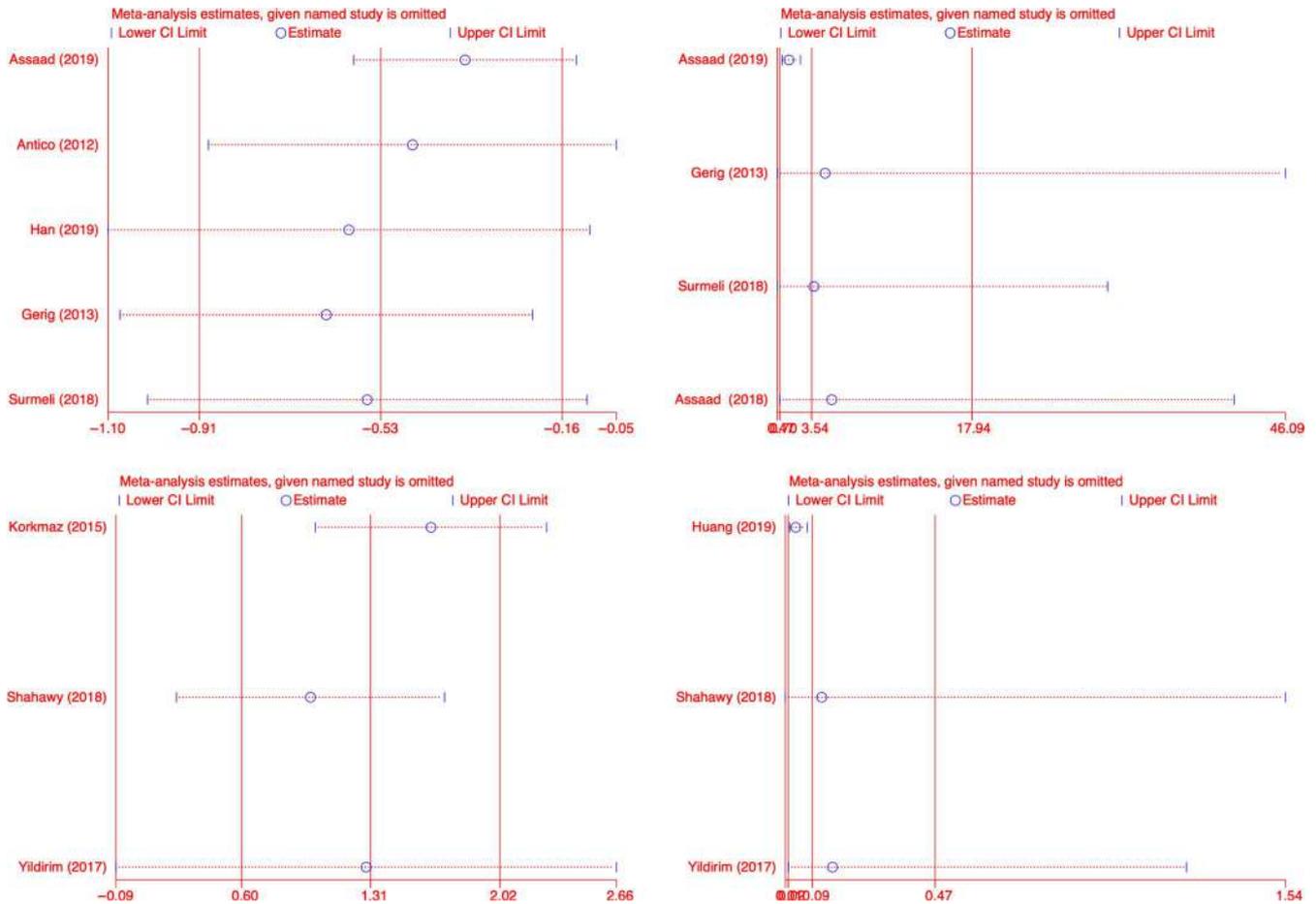


**FIGURE 3** A, Average 25(OH)D level in *H pylori* successful eradication individuals was 1.31 ng/mL more than that in *H pylori* unsuccessful eradication individuals (SMD = 1.31 ng/mL, 95% CI = (0.60, 2.02 ng/mL),  $I^2 = 88.3%$ ,  $P < .01$ ); B, individuals with vitamin D deficiency were 0.09 times more likely to eradicate *H pylori* successfully (OR = 0.09, 95% CI = (0.02, 0.41),  $I^2 = 90.6%$ ,  $P < .01$ )

**TABLE 2** Basic characteristics of vitamin D levels in *Helicobacter pylori* eradication individuals

Author	Year	Country	Hp+ eradication successful (n)	Vitamin D <sup>a</sup>	Hp- eradication unsuccessful (n)	Vitamin D <sup>a</sup>
Korkmaz	2015	Turkey	29	20.50 ± 10.00	29	15.10 ± 8.90
Shahawy	2018	Egypt	105	27.41 ± 7.10	45	14.70 ± 4.50
Yildirim	2017	Turkey	170	19.00 ± 8.10	50	9.10 ± 4.70

<sup>a</sup>The unit of vitamin D was ng/mL.



**FIGURE 4** Sensitivity analysis results showed that the results of dichotomous variable were fluctuant, but it was still stable and reliable

*Helicobacter pylori* through the PDIA3 receptor in gastric epithelial cells, which provided a novel pathogenic mechanism.

This study was the first comprehensive analysis of the relationship between *H pylori* infection and vitamin D, and *H pylori* eradication and vitamin D, but there were still some shortcomings. The first and most important issue was heterogeneity of the selected articles. Although the sensitivity analysis showed that the research is still stable, some reasons still led to the emergence of heterogeneity. Differences in vitamin D detection methods may be one of the factors. The difference in the number of patients enrolled in each study was also another factor. The emergence of heterogeneity reduced the credibility of the conclusion, but it can still provide sufficient evidence. Second, there were not enough articles or prospective studies selected for this meta-analysis. The more articles can provide more data and research evidence. In addition, the choice of different eradication programs may also affect different research results.

In conclusion, this meta-analysis firstly demonstrated that vitamin D levels in *H pylori*-positive patients were lower than *H pylori*-negative patients. *H pylori* successful eradication individuals had higher vitamin D levels than unsuccessful eradication individuals. In addition, individuals with vitamin D deficiency had lower success rate of *H pylori* eradication. In the future, more prospective studies are needed to validate the results of this study.

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## CONFLICT OF INTEREST

The authors declare there is no conflict of interest regarding the publication of this paper.

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