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Relationship between *Helicobacter pylori* infection and osteoporosis: a systematic review and meta-analysis

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ABSTRACT

Objectives Many studies have explored the association between *Helicobacter pylori* infection and osteoporosis. However, the results remain controversial. Therefore, we performed this systematic review and meta-analysis to evaluate the association between *H. pylori* infection and osteoporosis.

Design Systematic review and meta-analysis of case–control studies.

Data sources Databases, including PubMed, Embase, Web of Science and Chinese Biomedical Literature Database, were screened from inception to 30 April 2018.

Eligibility criteria Case–control studies aimed at assessing the association between *H. pylori* infection and osteoporosis.

Data extraction and analysis Study characteristics and study quality sections were reviewed. Studies were selected, and data were extracted by two reviewers. Pooled ORs and 95% CIs were calculated using random effects model if heterogeneity existed; otherwise, fixed effects model was used. Subgroup analyses were performed to explore the source of heterogeneity. Publication bias and sensitivity analyses were also tested.

Results A total of 21 studies with 9655 participants were included in our analyses. Taking together, we found that *H. pylori* infection was associated with increased odds of osteoporosis (OR (95% CI): 1.39 (1.13 to 1.71)); there was no significant difference between osteoporosis and osteopaenia; the association between osteoporosis and *H. pylori* infection was relatively higher in men than women but did not reach significant level. However, the decrease of bone mineral density in *H. pylori*-positive patients was not significant when compared with *H. pylori* negative controls, which may due to the sample size.

Conclusions Our meta-analysis suggests an association between osteoporosis and *H. pylori* infection. The clinicians should pay more attention to the patients infected with *H. pylori*. Further studies were still needed to exploring the confounding factors among studies and to elucidate the underlying biological mechanisms.

Strengths and limitations of this study

► Twenty-one studies with conflicting results were included for testing the association between osteoporosis and *Helicobacter pylori* infection.

► This is the third and most comprehensive meta-analysis, bringing the overall results of statistical significance and increased odds.

► The results of the meta-analysis should be interpreted with caution due to the number and quality of studies included and obvious heterogeneity.

► Causality cannot be established in observational study as the chronological order between *H. pylori* infection and osteoporosis cannot be confirmed.

The prevalence of *H. pylori* infection is approximately 30% in developed countries and up to 80% in developing countries[2 3] and up to 90% in patients with dyspepsia.[4] In North Europe and North America, about one-third of adults are infected, and in South and East Europe, South America and Asia, the prevalence of *H. pylori* is often higher than 50%.[5] Moreover, infected subjects born abroad (first-generation immigrants) had a higher risk of *H. pylori* infection than second-generation immigrants in a multiethnic European city.[6] *H. pylori* has been well known to be associated with gastrointestinal diseases, such as gastritis, gastric ulcer, stomach cancer and so on.[7] Furthermore, some non-gastrointestinal diseases have also been proven to be associated with *H. pylori* by large-scale population researches or meta-analysis, such as pre-eclampsia,[8] autoimmune thyroid diseases,[9] myocardial infarction,[10] hepatic encephalopathy[11] and prostatitis.[12]

Osteoporosis is one of the most common metabolic bone diseases, characterised by decreased bone mineral density (BMD), increased bone fragility and then increased susceptibility to fracture,[13] especially in spine and hip. Osteoporosis has become a major health concern for both individuals and

INTRODUCTION

Helicobacter pylori, a Gram-negative and spiral-shaped bacterium dwelling on the gastric epithelium, has an influence on approximately 50% of the global population, especially those living in developing countries.[1]
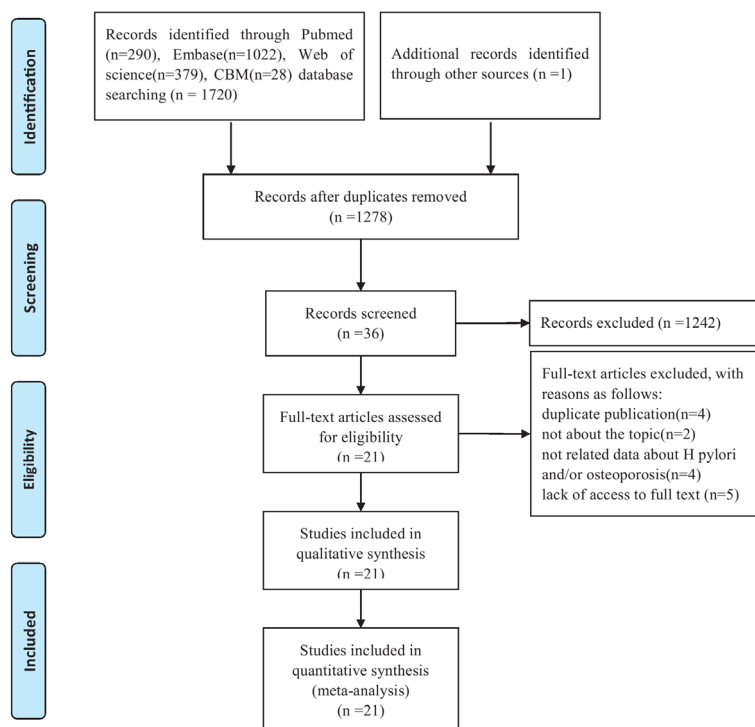
Figure 1 Flow diagram of the article selection for systematic review.

societies. Osteoporosis has huge adverse impacts on life quality and is associated with increased morbidity rates. The in-hospital mortality rate is between 0.85% and 2.26%.[14] In Europe, about half of women and one-fifth of men aged over 50 years develop pathological fractures in hip, spine, forearm or humerus due to osteoporosis during their remaining lifetime.[15] The same situation happens in other countries or districts, such as Japan and Taiwan.[16 17]

There are well-established evidence regarding the risk factors for osteoporosis,[17] such as age, sex, body mass index, alcohol and smoking. *H. pylori* infection can induce inflammatory and immune responses, such as increasing the level of interleukin (IL)-1 and tumour necrosis factor (TNF)-α, which could trigger bone resorption and regulate bone regeneration.[18] Recently, many studies about the association between osteoporosis and *H. pylori* have been performed. However, the role of *H. pylori* in osteoporosis remains controversial. This issue has been discussed in previous meta-analysis,[19 20] but no significant association was found. As more studies evaluating the association between *H. pylori* infection and osteoporosis have been published since then,[2 21–27] we carried out this updated meta-analysis to further evaluate the association between *H. pylori* infection and osteoporosis qualitatively and the quantitative alterations of BMD in *H. pylori*-infected patients compared with those in healthy controls.

MATERIALS AND METHODS

This study was reported based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[28] Study searching and selection, quality assessment and data extraction were done by two researchers (TW and XL) independently to avoid bias, and disagreements were discussed by the two reviewers and by seeking the opinion of the third author (YZ) if necessary.

Search strategy

We searched through the databases of PubMed, Embase, Web of Science and Chinese Biomedical Literature Database (CBM). The last search for all databases was updated to 30 April 2018. We used the combined method of Medical Subject Headings (MeSH) Term and free words by applying the following terms: *Helicobacter pylori, campylobacter pylori, H. pylori, hp, helicobacter, helicobacter bill, helicobacter hepaticus, helicobacter pullorum, helicobacter species, helicobacter sp, helicobacter genus, campylobacter, campylobacter infection, campylobacteriosis, Helicobacter pylori* infection, Helicobacter infection, *pylori, enterohepatic helicobacter spp, campylobacter sp* and fragility fracture, bone density, bone mass density, osteocalcin, bone loss and osteoporosis. The search strategy is presented in the online supplementary appendix 1. Two authors evaluated potential publications by checking their titles and abstracts and then procured the most relevant publications for further examination. Bibliographies section of retrieved articles were also reviewed for additional pertinent studies that were possibly missed in the initial search.

Studies selection and data extraction

Studies were included if they met the following criteria: (1) it is an observational study; (2) its objective is to assess the

Table 1 Characteristics and quality assessment of the studies included

Author (reference)	Year	Country	Sex (M/F)	Age (mean age±SD or (range age) years)	Detection method of *H. pylori*	Detection methods of osteoporosis	Diagnosis locations	Diagnosis	Cases /controls /total	Scores of NOS	Main adjusted factors (the methods used for adjusting)
Figura et al[44]	2005	Italy	Males	65 (55–82) for patients; 64.5 (55–80) for controls.	ELISA	DEXA	Lumbar and femur bone.	Osteoporosis.	80/160/240	7	Age, socioeconomic background and smoking habits.
Kakehasi et al[43]	2007	Brazil	Postmenopausal women	61.6±7 (50–79).	Non-ELISA	DEXA	Lumbar spine.	Osteoporosis.	18/32/50	6	Mean age, body mass index, age at menarche and postmenopausal period.
Kakehasi et al[42]	2009	Brazil	Postmenopausal women	63.7±7.3for Hp(+). 62.5±7.0 for Hp(−).	Non-ELISA	DEXA	Lumbar spine and hip.	Not fitted.*	34/27/61	-	Age, postmenopausal time and BMI.
Akkaya et al[41]	2011	Turkey	Postmenopausal women	65.29±6.09 patients; 63.57±6.53 controls.	ELISA	DEXA	Lumbar and femur neck.	Osteoporosis.	58/47/105	6	Age, education level, occupation, age of menarche or menopause, duration of postmenopausal, period or daily consumption of tea, coffee, alcohol or dairy products.
Chinda et al[40]	2013	Japan	379/631	Not mentioned.	ELISA	QU	Calcaneal osteo.	Osteopaenia.	−/−/1010	7	Age, BMI, smoking, alcohol consumption, periodical exercise and latest educational level (logistic regression analysis).
Asaoka et al[39]	2014	Japan	95/105	63.1±8.8years.	Both	DEXA	Lumbar vertebrae.	Osteoporosis.	41/159/200	6	Age, gender, BMI, alcohol consumption, smoking, BAP, PUD and EGA (multivariate logistic regression analysis).
Asaoka et al[38]	2014	Japan	131/26	71.1±7.5 patients. 61.6±8.9 controls.	Not mentioned	DEXA	Lumbar.	Osteoporosis.	24/133/157	6	Age, sex, BMI, Brinkman idex (BI) and accumulated amount of alcohol (multivariate analysis).
Lin et al[37]	2014	China	Female	77 (65–97).	Non-ELISA	DEXA	Not mentioned.	Osteoporosis.	101/264/365	5	Age group, body mass index group and use of proton-pump inhibitor (multivariate logistic regression analyses).
Asaoka et al[36]	2015	Japan	130/134	69.8±6.8for patients. 61.9±8.2for controls.	Not mentioned	DEXA	Not mentioned.	Osteoporosis.	45/219/264	7	Age, sex, BMI and so on (multivariate analysis).

Continued

Table 1 Continued

Author (reference)	Year	Country	Sex (M/F)	Age (mean age±SD or (range age) years)	Detection method of *H. pylori*	Detection methods of osteoporosis	Diagnosis locations	Diagnosis	Cases /controls /total	Scores of NOS	Main adjusted factors (the methods used for adjusting)
Asaoka et al[16]	2015	Japan	120/135	63.2±8.5.	Both	DEXA	Lumbar vertebrae.	Osteoporosis.	43/212/255	6	Age, sex, BMI, cumulative alcohol intake, BI, type 2 diabetes mellitus, calcium channel blocker, PPI, haemoglobin, calcium, gamma glutamyl transpeptidase, bone-specifi alkaline phosphatase, NTX, hiatal hernia and EGA (multivariate logistic regression analysis).
Chung et al[35*]	2015	Korea	Men	54.4±10.7 for Hp+. 51.9±12.1 for Hp–.	ELISA	DEXA	Lumbar (L1–L4).	Osteopaenia.	–/–/1126	7	Height, weight, BMI, alcohol and exercise.
Fotouk-Kiai et al[34*]	2015	Iran	575/392	68.3±6.8 for Hp+. 69.3±7.4 for Hp–.	ELISA	DEXA	Lumbar vertebra and femur.	Osteoporosis.	314/653/967	5	Age, sex, smoking, alcohol consumption and BMI.
Mizuno et al[33]	2015	Japanese	Men	62.1±5.0 for low TBD. 58.4±5.7 for normal.	ELISA	QU	Not mentioned.	Decreased BMD.	116/114/230	8	Age, BMI and smoking habit (logistic regression analysis).
Chinda et al[21]	2016	Japan	Men	50.2±15.4 years.	ELISA	QU	Not mentioned.	Osteopaenia.	–/–/295	7	Age, BMI, serum level of oestradiol, the intake of calcium per day, smoking, drinking, periodical exercise and last educational background (logistic regression).
Chinda et al[22]	2016	Japan	Females	52.2±15.2.	ELISA	QU	Not mentioned.	Osteopaenia.	–/–/473	6	Age, BMI, smoking, alcohol consumption, periodical exercise, last educational level, serum level of oestradiol and calcium intake per day (multiple logistic regression).
Kalantarhormozi et al[23*]	2016	Iran	Postmenopausal women	58.87±8.02.	ELISA	DEXA	Lumbar spine and femur.	Osteoporosis.	16/234/250	6	Age and BMI (multiple linear regression).
Zhan et al[24]	2016	China	194/126	38.32±10.64 for patients. 38.27±7.46 for controls.	Non-ELISA	DEXA	Not mentioned.	Osteoporosis.	160/160/320	5	Age, gender and gene (multiple logistic regression).
Abdolahi et al[25]	2017	Iran	Postmenopausal women	Not mentioned.	ELISA	Not mentioned	Not mentioned.	Osteoporosis.	73/34/107	8	Not mentioned.
Chinda et al[26]	2017	Japan	Females	62.5±8.6 for patients. 44.9±10.9 for controls.	ELISA	QU	Calcaneus.	Osteopaenia.	197/276/473	4	Age, smoking and drinking habit, schooling duration, estradiol levels, menopause, birth history (multiple logistic regression analysis).

Continued

Table 1 Continued

Author (reference)	Year	Country	Sex (M/F)	Age (mean age±SD or (range age) years)	Detection method of *H. pylori*	Detection methods of osteoporosis	Diagnosis locations	Diagnosis	Cases /controls /total	Scores of NOS	Main adjusted factors (the methods used for adjusting)
Lu et al[2]	2018	China	1474/393	54.0±9.6.	Non-ELISA	QU	Calcaneus.	Osteoporosis.	900/967/1867	6	Gender and age.
Pan et al[27]	2018	China	568/299	55.9±11.3.	Non-ELISA	DEXA	Not mentioned.	Decreased BMD.	311/556/867	5	Sex, age, BMI, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and peptic ulcer disease (multiple stepwise logistic regression analyses).

Not fitted*: this study only explored the alteration of BMD in patients with *H. pylori* infection.

*This study also reported the BMD in patients with *H. pylori* infection.

BAP, bone-specific alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; DEXA, dual-energy X-ray absorptiometry scan; EGA, endoscopic gastric mucosal atrophy; *H. pylori*, *Helicobacter pylori*; NOS, Newcastle-Ottawa S scale; NTX, collagen type I cross-linked N telopeptide; PPI, proton pump inhibitor; PUD, peptic ulcer disease; TBD, trabecular bone density; QU, quantitative ultrasound.

association between *H. pylori* infection and osteoporosis or compare the alteration of BMD between *H. pylori*-positive and *H. pylori*-negative participants; (3) they either provided ORs and 95% CIs, or sufficient information was available to calculate the ORs and 95%CIs, or BMD in both *H. pylori*-positive and *H. pylori*-negative participants. Articles were excluded if they were duplicate publications, reviews, animal studies, editorials or case reports. The papers were also excluded if no effect estimate was reported or not enough raw data for ORs and 95% CIs calculation was available. In the case of multiple studies with the same or overlapping data published by the same researchers, we selected the most recent study with the largest number of participants. All papers meeting the criteria defined above were included for further analysis.

The literatures included were carefully reviewed for information about the first author, publication year, country, population, sample size, sex, age, detection methods of *H. pylori* and osteoporosis, diagnosis location, diagnosis and adjusted covariates.

If data could be acquired from the tabulated literature search results, they would be extracted carefully into 2×2 tables from all eligible publications by two independent reviewers. If data were not directly available, they would be calculated from published positive predictive values and/ or negative predictive values if appropriate. The adjusted OR (95% CI), if existed, was adopted instead of rude OR (95% CI).[29] In addition, for the studies comparing the BMD of participants with and without *H. pylori* infection, the data on BMD were also extracted.

Quality assessment

Quality assessment was performed using the Newcastle-Ottawa Quality Assessment Scale (NOS).[30] Two researchers conducted blinded quality assessment of the included literatures. The NOS assigns a maximum of 9 points to studies of highest quality according to three quality parameters: selection, comparability and outcome.

Statistical analyses

The primary measures were ORs and 95% CIs for the association between *H. pylori* infection and osteoporosis, and standardised mean difference (SMD) for BMD alterations between *H. pylori*-positive and *H. pylori*-negative participants. To assess heterogeneity among the studies, we calculated the Cochran's χ^2 test (with $p<0.10$ indicating statistically significant heterogeneity) and the statistic I^2 (the heterogeneity might not be important with I^2 of 0%–40%, while moderate heterogeneity with I^2 of 30%–60%, substantial heterogeneity with I^2 of 50%–90% and considerable heterogeneity with I^2 of 75%–100%).[31] The pooled results were calculated using fixed effects model (inverse variance) if no obvious heterogeneity existed; otherwise, random effects model (I–V heterogeneity) was used ($p<0.10$ was considered indicative of obvious heterogeneity). The cumulative meta-analysis was conducted for the extracted data using a pooled random effects model with the publication year to confirm
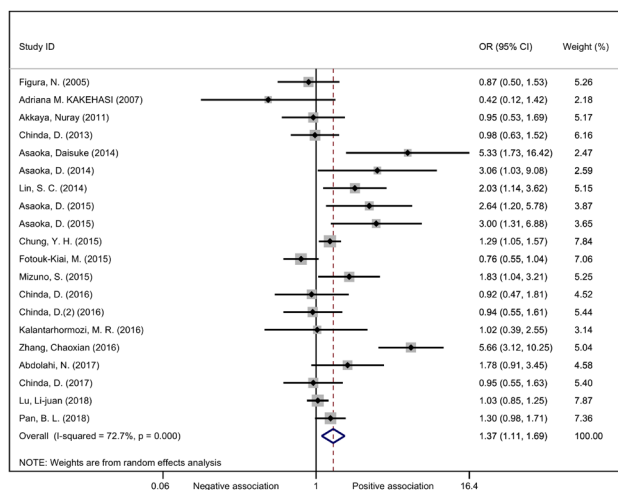
Figure 2 Forest plot of the included studies assessing the association between *Helicobacter pylori* and osteoporosis (random effects models).

whether the effect size was affected by sample size or not. In the event of obvious heterogeneity, subgroup analysis was performed according to sex, postmenopausal or not, country, Asian or not, detection methods of *H. pylori*, detection methods of osteoporosis and detection location of dual-energy X-ray absorptiometry (DEXA). Meta regression (using ReML methods) was also performed to explore the potential heterogeneity. Publication bias was assessed by funnel plot and Egger's test.[32] A sensitivity analysis was completed by converting the pooled results from random effects model into fixed effects model or from fixed effects model into random effects model. All statistical analyses were performed using Stata V.12.0.

Patient and public involvement
There was no patient and public involvement as this was a database research study.

RESULTS
Search results
Using our search strategy, a total of 1720 articles were identified through PubMed, Web of Science, Embase and CBM, and one additional record was identified through other sources. Then, 443 duplicate papers were removed first, and 1242 papers were excluded after scanning their titles and abstracts. After screening the full texts of the included articles, 15 studies were excluded for the following reasons: duplicate publication (n=4), not about the topic (n=2), no related data about *H. pylori* and/or osteoporosis (n=4) and lack of access to full text (n=5). A total of 21 studies[2 16 21–27 33–44] were included for further analysis (figure 1).

Study characteristics
A total of 21 articles were included in this study. Of the 21 articles included, 20 provided data for association
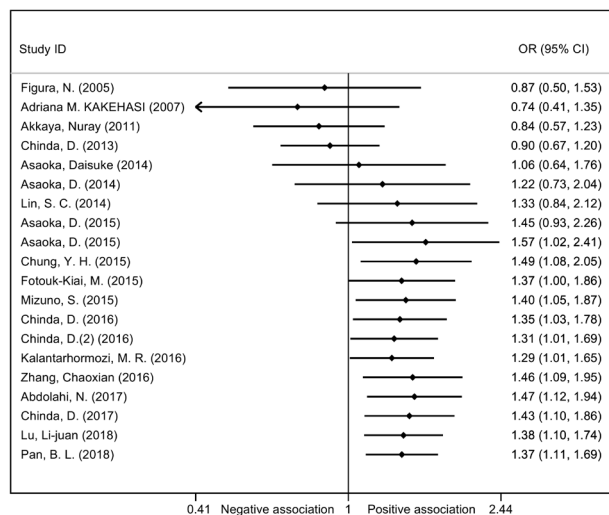

Figure 3 Forest plot of cumulative meta-analysis.

between *H. pylori* and osteoporosis,[2 16 21–27 33–41 43 44] 4 for the BMD alterations in *H. pylori* positive participants compared with negative controls[23 34 35 42] and 3 provided both.[23 34 35] All these studies were published from 2005 to 2018. Four studies were conducted in China, three in Iran, one in Italy, nine in Japan, two in Brazil, one in Korea and one in Turkey. As to the sex of participants, four were postmenopausal women, four were women, four were men, nine involved both men and women. The detection methods of *H. pylori* were mainly ELISA and ^{13}C-urea breath test, while the detection methods of osteoporosis were DEXA and quantitative ultrasound. As to the diagnosis, 5 were osteopaenia, 13 were osteoporosis and 2 provided decreased BMD (treated as osteopaenia for analysis) (table 1). In addition, 12 studies showed no significant associations of *H. pylori* infection and
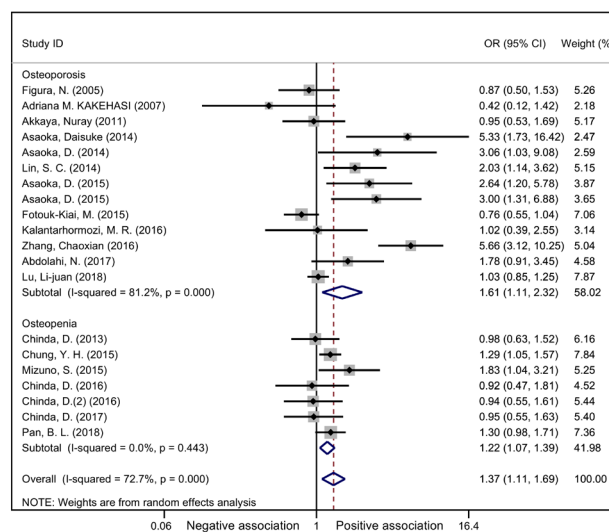

Figure 4 Forest plot of subgroup meta-analysis according to diagnosis (random effects models).

osteoporosis (or osteopaenia), while 8 showed significant associations.

Quality evaluation

The NOS was adopted to evaluate the quality of these case–control studies. Among the selection items, the evaluation results ranged from 4 to 8, with the median NOS score was 6, indicating a medium quality of the studies included. The most common source of bias came from selection and comparability (table 1)

Synthesis of the results

As shown in figure 2, the overall OR was obtained based on the 20 studies involving the *H. pylori* and osteoporosis (including osteopaenia) (a total of 8788 patients and healthy controls). As the existence of obvious heterogeneity (χ^2=69.60, I^2=72.7%, p<0.01), random effect model was used and the pooled results of OR and its 95% CI were 1.37 (1.11 to 1.69), indicating *H. pylori* infection was significantly associated with increased odds of osteoporosis/osteopaenia. A cumulative meta-analysis was conducted with publication year in ascending order, and the results indicated that the pooled OR (95% CI) started to show statistical significance at 1.57 (95% CI 1.02 to 2.41) from the ninth analysed study, with gradually stabilising results afterwards (figure 3).

Subgroup analyses

Given that obvious heterogeneity existed, subgroup analyses were performed based on the potential confounding factors. All 20 studies were involved in these subgroup analyses. Figure 4 showed that both osteoporosis and osteopaenia were significantly associated with *H. pylori* infection with OR (95% CI) of 1.61 (1.11 to 2.32) and 1.22 (1.07 to 1.39), respectively. Although the OR was a little higher in osteoporosis group, the meta regression analysis showed no significant difference between these two groups (t=1.18, p=0.26). Therefore, we pooled osteoporosis and osteopaenia together to analyse other confounding factors.

Results of subgroup analyses by other factors were shown in table 2. We found that the association between *H. pylori* infection and osteoporosis was significant in men and both sexes, but not in women. However, meta-regression analysis showed no significant difference between these two groups. Moreover, no significant associations between *H. pylori* infection and osteoporosis were observed in either the postmenopausal women or non-postmenopausal women subgroup. When stratified by countries, we found significant associations between *H. pylori* infection and osteoporosis in China, Japan and Korea (three East Asian countries). Other factors that may affect the results were presented in table 2.

Publication bias and sensitivity analyses

Funnel plot was used to examine the publication bias of this meta-analysis. As shown in figure 5, the funnel plot indicated no publication bias, which was also confirmed by Egger's test, with t of 1.57 and p of 0.13 in figure 6.

Sensitivity analysis was also performed by converting the pooled model from the random effects model to the fixed effects model. The result of fixed effects model was 1.21 (1.10–1.33), which showed no obvious differences compared with the result of random effects model, indicating the pooled results was relatively stable.

Alterations of BMD in *H. pylori*-infected population

Four studies were involved in this meta-analysis.[23 34 35 42] As each study included for this analysis has two different DEXA detection locations, we carried out the subgroup analysis based on detection locations, and the patients are not being counted twice in each subgroup. In addition, we chose SMD as pooled outcome for the detection methods varied with studies. As shown in online supplementary appendix 2, the BMD (g/cm^2) alterations between *H. pylori*-positive and *H. pylori*-negative participants were −0.01 (−0.45 to 0.42) for hip, −0.94 (−3.15 to 1.28) for lumber and −0.04 (-0.40 to 0.31) for femur using random effects model as obvious heterogeneity existed. No significant associations were observed so far.

DISCUSSION

Although osteoporosis is not a deadly disease, it causes huge burden to individuals and society owing to its high morbidity. Here, we got a comprehensive result by meta-analysis, indicating that *H. pylori* infection may be a risk factor for osteoporosis. However, the mechanism is still unclear. Several possible mechanisms may explain this result. First, *H. pylori* infection may lead to systemic inflammation, and release of cytokines, such as TNF-α, IL-1 and IL-6,[45] which may cause bone turnover indirectly. Second, many studies have shown that low vitamin B12 may be associated with *H. pylori* infection.[46] If the serum vitamin B12 levels are decreased, the folate becomes trapped as methyltetrahydrofolate and interrupts for folate-related DNA synthesis, which is an important factor for bone remodelling. Therefore, the decrease of vitamin B12 may lead to decreased BMD and osteoporosis.[47] Third, *H. pylori* infection may decrease the calcium absorption by causing the gastric mucosal atrophy and decreasing acid secretion. Thus, eradication of *H. pylori* may increase calcium absorption and stop the process of osteoporosis through decreasing the levels of inflammatory cytokines and improving gastric mucosal atrophy.

The present meta-analysis of 20 studies indicated that patients with *H. pylori* infection were associated with an estimated 1.37 times higher ORs of developing osteoporosis as compared with those without *H. pylori* infection, while no associations were found in previous meta-analysis[19 20] (one had five studies involving 1321 participants, and one had four studies involving 520 participants). As the previous meta-analysis studies had no quality assessment and our analysis included more studies and participants, the results in our study might be more reliable than the previous meta-analysis studies.

Table 2   Overall effect estimates for *Helicobacter pylori* infection and osteoporosis according to study characteristics

Factors	Categories	No. of studies	OR (95% CI)	Model used	Heterogeneity I^2	P value	Meta-regression t	P value
Sex*								
	Women	8	1.09 (0.87 to 1.35)	Fixed	33.0%	0.17	–	–
	Men	5	1.27 (1.07 to 1.50)	Fixed	14.6%	0.32	0.47	0.64
	Both	9	1.21 (1.07 to 1.37)	Random	85.6%	0.00	1.78	0.09
Postmenopausal or not								
	Non-postmenopausal women	4	1.08 (0.83 to 1.41)	Fixed	48.0%	0.12	–	–
	Postmenopausal women	4	1.09 (0.75 to 1.58)	Fixed	35.8%	0.20	−0.13	0.90
Country								
	China	4	1.86 (1.06 to 3.28)	Random	90.4%	0.00	–	–
	Japan	9	1.57 (1.08 to 2.28)	Random	63.7%	0.005	−0.39	0.70
	Italy	1	0.87 (0.50 to 1.53)		≈	–	−1.11	0.29
	Brazil	1	0.42 (0.12 to 1.42)		–	–	−1.69	0.11
	Korea	1	1.29 (1.05 to 1.57)		–	–	−0.59	0.57
	Iran	3	1.06 (0.60 to 1.86)	Random	61.3%	0.075	−1.16	0.27
	Turkey	1	0.95 (0.53 to 1.69)		–	–	−0.98	0.34
Asian country or not								
	Non-Asian country	2	0.77 (0.46 to 1.28)	Fixed	12.8%	0.28	–	–
	Asian country	18	1.44 (1.16 to 1.79)	Random	73.9%	0.00	1.60	0.13
Detection methods of *H. pylori*								
	ELISA	11	1.09 (0.96 to 1.24)	Fixed	32.1%	0.14	–	–
	Non-ELISA	5	1.62 (0.96 to 2.72)	Random	88.4%	0.00	1.52	0.15
	Both	2	3.67 (1.88 to 7.16)	Fixed	0%	0.42	2.65	0.02
Detection methods of osteoporosis								
	DEXA	13	1.58 (1.14 to 2.18)	Random	79.5%	0.00	–	–

Continued

Table 2 Continued

Factors	Categories	No. of studies	OR (95% CI)	Model used	Heterogeneity I²	Heterogeneity P value	Meta-regression t	Meta-regression P value
	QU	6	1.05 (0.90 to 1.22)	Fixed	0%	0.51	−1.33	0.20
Detection location of DEXA								
	Lumbar	6	1.75 (0.99 to 3.07)	Random	65.4%	0.013	–	–
	Femur	3	1.56 (1.17 to 2.08)	Fixed	0%	0.90	−0.17	0.87

* One study reported males, females and overall results, therefore this study was used in all subgroups analysis (males, females and both).
DEXA, dual-energy X-ray absorptiometry scan; QU, quantitative ultrasound

Despite the significant association between *H. pylori* infection and osteoporosis, obvious heterogeneity existed between the included studies. We found that sex of participates may affect the results. As known to all, women and postmenopausal women are independent risk factors of osteoporosis. Here, we explored the relationship between osteoporosis and *H. pylori* infection and found that the relationship was significant in men, but not in women (whether postmenopausal or not), which was not paradoxical with the fact that women with postmenopausal should have a higher risk of osteoporosis than men. In the group of both sexes, the results showed statistic difference and obvious heterogeneity, which may be due to the ratio of M/F and other confounding factors. Therefore, we might suggest that more attention should be paid to men than women in *H. pylori*-positive patients. However, only seven studies (four were about postmenopausal women and three were about non-postmenopausal women) were conducted in women, the results may be not that reliable due to the small sample size. Another reason may also be possible that the different degree of osteoporosis may affect the diagnosis, and some early patients may be regarded as healthy controls. Further studies

with dose–response relationship of different severity of osteoporosis and prevalence may help to confirm this hypothesis. In the subgroup analysis by criteria (osteoporosis and osteopaenia), the OR in osteoporosis was a little higher than that in osteopaenia, which may also help to prove our hypothesis. In the subgroup analysis based on countries, significant association was evidenced in three East-Asian countries (China, Japan and Korea are from East Asia), indicating many other factors associated with geography may affect the results. As only two studies were non-Asian countries, the reason of this phenomenon may be due to the sample size, the same situations also happened in other Asian countries with only one study included. In addition, as most studies included in our studies were Asian countries, especially East Asia, whether our findings can be applied to other populations around the world needs further exploring.

In our research, we also explored the heterogeneity from diagnosis methods factors. We found that the detection methods of osteoporosis (DEXA and quantitative ultrasound) affected the pooled results, and the detection locations of DEXA also contributed to the heterogeneity. From our results, we thought that DEXA might be a better tool to diagnose osteoporosis in assessing the
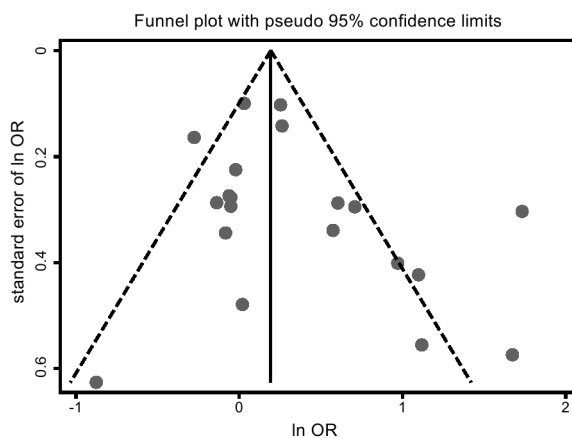

Figure 5 Funnel plot of publication bias for the association between *Helicobacter pylori* and osteoporosis.
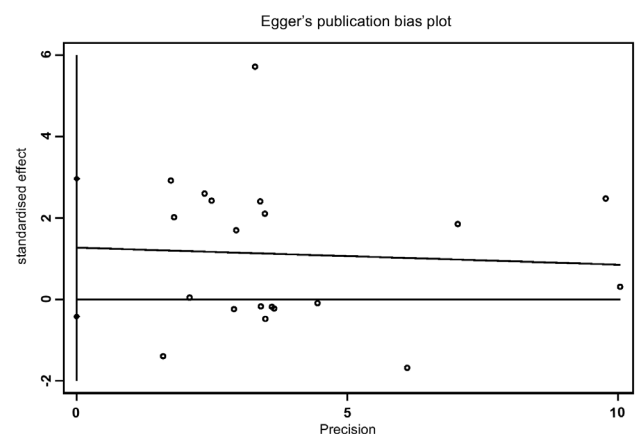

Figure 6 The Egger's test for publication bias.

association between *H. pylori* and osteoporosis. The same situation also happened in the detection methods of *H. pylori*. We found ELISA and multimethod strategy may provide more homogeneous results. In total, in despite of the significant association between *H. pylori* and osteoporosis, as the heterogeneity still existed obviously, further studies were still needed to address its potential confounding factors.

In a previous meta-analysis study, Wijarnpreecha *et al*[48] found increased odds of non-alcoholic fatty liver disease (NAFLD) among patients infected with *H. pylori*. However, Upala *et al*[49] found that no significant difference in BMD between patients with fatty liver disease and controls.[49] Combine the two meta-analysis and our results, we may guess that *H. pylori* may be an independent risk factor of NAFLD and osteoporosis, and/or *H. pylori* infection may be an important confounding factor in exploring the relationship between NAFLD and osteoporosis, or no actual relationship between NAFLD and osteoporosis exists. However, as the authors stated,[49] the review was a preliminary result because of limited amount of literature, it might be too early to have definite conclusion.

We also compared the quantitative alterations of BMD in *H. pylori* infected subjects. However, no significant difference was found. The reason may be that: (1) the sample size was relatively small, (2) the severities of *H. pylori* infection were not serious, or the infection of *H. pylori* did not last long enough to cause alterations, (3) though the basic characteristics of included studies were comparable, many other confounding factors that might affect BMD have not been adjusted. Therefore, more studies with large sample size were still needed to verify the alterations of BMD in *H. pylori* infection.

The strength of the present meta-analysis lies in inclusion of 21 observational studies reporting data on *H. pylori* infection and osteoporosis and the alterations of BMD by *H. pylori*. However, our meta-analysis has several limitations that should be recognised when interpreting the results. First, most of the included studies were hospital based or health centre based, which were not affected by detection bias but might be subjected to selection bias. However, the prevalence of *H. pylori* infection in most studies that we selected was consistent with the incidence rate in the general population. Second, our analysis had an ascertainment bias that might be present because progression of osteoporosis is continuous, and some patients may be classified as controls. However, this may lead to a more conservative result, which may help to indicate that our overall result is reliable. Third, the heterogeneity is still obvious. However, we performed subgroup analyses based on study characteristics and found that some factors may affect the association. In addition, when available, adjusted estimates were used in preference to unadjusted estimates. Even though the adjusted estimates may be closer to the true effect for adjusted results could control confounding factors,[50 51] the different adjusted factors in different studies may also contribute to the heterogeneity. Four, the qualities of included studies were medium, and some studies were published informally. We also included all these studies based on inclusion and exclusion criteria to avoid publication bias. Nevertheless, our study is still the most comprehensive about the association between *H. pylori* infection and osteoporosis.

In summary, our results suggest significant increased odds of osteoporosis in patients with *H. pylori* infection. The clinicians should pay more attentions to the patients infected with *H. pylori* by using DEXA scan, especially those patients with chronic gastritis. However, the results should be cautiously interpreted considering the heterogeneity and the fact that all studies are non-randomised and retrospective. Further studies are needed to explore the mechanism and confounding factors between *H. pylori* and osteoporosis.

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