Research Article

# An Updated Systematic Review and Meta-Analysis to Determine the Association between Iron Deficiency Anemia and Helicobacter Pylori Infection in Low and Middle Income Countries

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## Abstract

**Background:** Studies focusing on the examination of the association between iron deficiency anemia (IDA) and Helicobacter Pylori (H. Pylori) infection is very important especially in developing countries. Therefore, the primary aim of the study was to assess if patients with H. Pylori infection were more prone to IDA than patients who were not suffering from H. Pylori.

**Methods:** Databases used for this purpose include but not limited to Google Scholar, PubMed, Web of Science, MEDLINE, SCOPUS, EMBASE, and the Cochrane Library. As per our detailed search from last ten years data from above sources we found seventeen observational studies and four randomized controlled trials (RCTs) satisfying our criteria for meta-analyses. By using random effects model we obtained Pooled odds ratio (OR), pooled standardized difference in means (SMD), and 95% confidence intervals (CIs). Forest plots were generated from these values.

**Results:** Meta-analysis from our above study gave very remarkable results [Pooled OR: 1.649; 95% CI: 0.883-3.082; p-value = 0.117]. Results showed decreased likelihood of iron deficiency anemia (IDA) in participants having evidence of Helicobacter Pylori (H. Pylori) as compared to uninfected ones and a remarkable variation was found too in studies ($I^2$ = 88.7%; p-value = 0.001).

A significant increase in ferritin (Pooled SMD: 0.504; 95% CI: 0.135-0.873; p-value = 0.007) and hemoglobin (Pooled SMD: 0.476; 95% CI: 0.111-0.840; p-value = 0.011) levels was observed from meta-analyses of four RCTs by giving patient anti-H. Pylori treatment along with iron supplement as compared to using only iron supplement in iron deficiency anemia.

**Conclusion:** Our study gave us conclusive results about decreased likelihood of prevalence of iron deficiency anemia as compared to *Helicobacter Pylori (H. Pylori)* infection in developing regions. Further to this effect we can say with certainty that combined H. Pylori eradication & iron supplement can be useful in improving values of ferritin and hemoglobin.

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**Key Words |** *Helicobacter Pylori*, iron deficiency anemia, systematic review, meta-analysis, randomized controlled trials.

## Introduction

Anemia, a blood condition, is a major public health problem affecting 1.62 billion people across the whole world and approximately 24.8% of the overall world population suffers from anemia. The most common cause of anemia is lack or scarcity of iron stores in the blood, anemia is highly prevalent is in preschool-age children and lowest in men. Although health care professional and policy makers across the globe have made efforts to control anemia caused by deficiency of iron but still its occurrence is alarmingly high in a number of geographic regions especially in developing regions of the world.[1]

*Helicobacter Pylori* (H. Pylori) belongs to gram-negative class of bacteria colonizing in the mucosa of stomach of about half of the people across the whole world. It is suggested that it has got a part in controlling state of equilibrium of storage of iron in the body. Infection of *H. Pylori* is found to have relation with the onset of much pathology of GI tract causing active chronic gastritis, peptic ulcers, gastric cancer, extra-gastric manifestations, thrombocytepenic purpura and anemia due to deficiency of iron stores (IDA). Many researches initiated to evaluate the causes of this blood condition, results of some have proposed that only by removing or curing *H. Pylori* infection, iron stores return to normal levels without iron supplementation.[2]

Although the process by which *H. Pylori* causes lack of iron and/ or anemia are not well known till now but few proposed possible ways are as follows: raise in pH levels inside stomach and decreased quantity of ascorbic acid in juices of stomach, disturbs absorption of iron, leads to persistent bleeding due to formation of small attritions in mucosa of stomach, synthesis of lactoferrins by neutrophil and use of iron by bacteria colonizing gastric mucosa. Iron absorption in small intestine is interfered by increased production of hepcidin, a major controller of iron breakdown. The excess synthesis of cytokines IL-6 and IL-1beta is caused by increased activity of a constituent of the lipopolysaccharide of *H. Pylori*, this in turn can enhance synthesis of hepcidin in cells of liver.[3,4]

Through several studies conducted in recent times there have been observed an association in *H. Pylori* and anemia due to iron deficiency but findings differ till date. To this effect it is recommended to examine and deal *H. Pylori* infection in patients reporting with unexplained iron deficiency anemia. In order to gather current evidence regarding this review, we assessed if patients with *H. Pylori* infection were more prone to IDA than patients who were not suffering from *H. Pylori* infection. Levels of ferritin and hemoglobin were assessed in patients taking *H pylori* treatment plus supplements of iron and patients taking supplements of iron as a sole therapy.

## Methods

This study was carried out according to the PRISMA guidelines. Google Scholar, PubMed, Web of Science, MEDLINE, SCOPUS, EMBASE, and the Cochrane Library databases were searched in detailed. The terms used in search comprised of “Helicobacter Pylori, *H. Pylori*, iron deficiency anemia, iron deficiency, anemia”.

Entitled studies selected for this purpose included observational and interventional studies along with clinical trials performed in low and middle income countries. To make this research more focused case reports, case series, duplicate reports, letters to editors, commentaries, authors' replies, and descriptive researches done in specified populations with having problems of unstable reserves of iron. To make it more accurate patients with Celiac disease or on regular hemodialysis were not included in study and search was confined to articles published in English from 1st January, 2010 to June 30, 2020.

To meet the set criteria of eligibility data was extracted using screening of all titles and abstracts. Full-text articles were assessed by two reviewers as per PICOS (population, intervention, comparison, and outcomes) criteria and disagreements were resolved

by discussions. Design of study, population under study, sampling frame, sample size, method of detection for *H. Pylori*, indicators for iron levels, categorization of anemia due to lack of iron, deficiency of iron & anemia, outcomes were extracted from selected articles. For each study group data was categorized in following ways: the number of patients affected by *H. Pylori*, the proportion of patients not affected by H pylori, and the number of patients suffering from IDA.

For original article data about the odds ratio (OR), 95% confidence intervals (CIs) and p-value was extracted from observational studies and for original articles these parameters were calculated using the study data. Data about the patients in the intervention & comparison groups, the means & standard deviations (SDs) of reference line and follow-up ferritin & hemoglobin levels was extracted from randomized clinical trials (RCTs). In order to make our study more precise authors of the original articles of RCTs were also contacted to recover missing statistics and where authors not replied these constraints were calculated accordingly.

The association between Helicobacter Pylori (*H. Pylori*) and IDA were examined through meta-analysis. Pooled odd ratio (OR), pooled standardized mean difference (SMD) and 95% CIs of observantional studies were acquired by use of the random effects model and a correlation of 0.5 was assumed between the reference point and follow-up ferritin & hemoglobin levels. During meta-analyses of RCTs, ferritin & hemoglobin level comparison were made between patients receiving combine therapy against *H. Pylori* & supplements of iron and those patients receiving iron supplementation only.

Further to this effect Heterogeneity $I^2$ index scale was used to test heterogeneity among the studies, forest plots were generated and Comprehensive Meta analysis Software Package was used for data analysis.

## Results

As per literature search carried out for the subject study there were fourteen hundred and forty (1440) total studies, out of which one five hundred and twenty five (525) were identical. Out of remaining nine hundred and fifteen (915) references studies on the basis of their titles or abstracts yielded one hundred and fifty (150) potentially eligible articles. Screening of full text of these sixty two (150) articles resulted in twenty one (21) relevant studies: seventeen (17) observational studies and four (04) clinical and interventional trials.

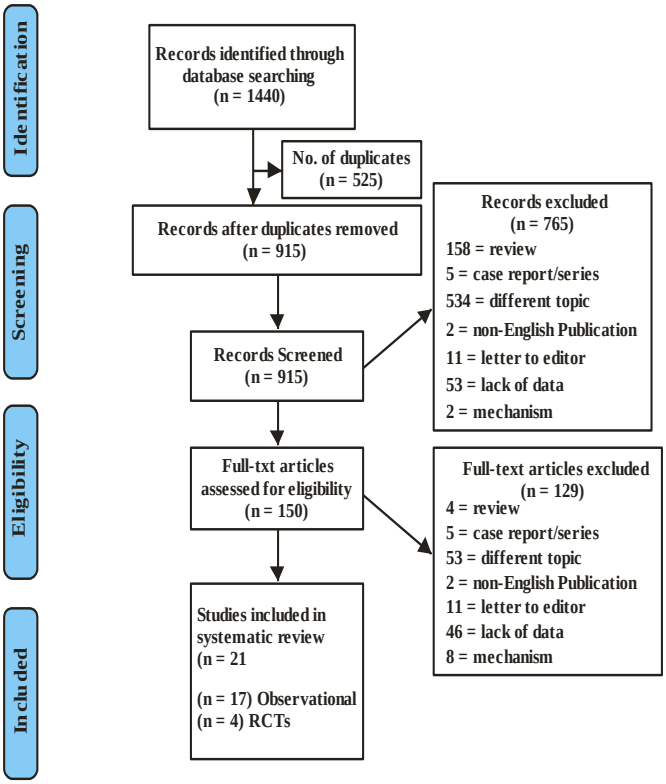


**Figure 1:** *Flow diagram of number of studies screened and included in meta-analysis*

Only seventeen (17) selected observational studies met the inclusion criteria and among these observationnal studies there were eleven (11) cross-sectional studies, 7-17 five (05) case-control studies,[18-22] and one (01) longitudinal study.[2] These studies were different based on design of study, population being studied, technique employed for identifying H. Pylori infection, categorization of anemia due to deficiency of iron, iron deficiency, and/ or anemia and outcomes.

**Table 1:** *Observational studies assessing association between Helicobacter Pylori infection and iron deficiency anemia*

| Study/ Location | Study design | Participants | *H. Pylori* detection | Outcomes |
|---|---|---|---|---|
| 1. Rahman et al. [7] Bangladesh | Cross-sectional study | Men and women (n = 168) Age: 18-60 years | Urea breath test | Serum ferritin (µg/L) Hemoglobin (g/dL) MCV (fL) MCH (pg) **IDA** Men: Ferritin < 15 µg/L Hb < 13 g/dL Women: Ferritin < 15 µg/L Hb < 11.5 g/dL |
| 2. Mendoza et al. [2] Mexico | Longitudinal study | Children (n = 350) Age: 6-14 years | Urea breath test | Serum ferritin (µg/L) Hemoglobin (g/dL) Serum hepcidin (ng/mL) **IDA** Ferritin < 15 µg/L Hb < 11 g/dL |
| 3. Zahmatkeshan et al. [8] Iran | Cross-sectional study | Children (n = 71) Age: Less than 18 years | Histopathological examination Urea breath test | Serum ferritin (µg/L) Hemoglobin (g/dL) MCV (fL) **IDA** Ferritin < 10 µg/L Hb < 11 g/dL |

**Table 1 (cont'd):** *Observational studies assessing association between Helicobacter Pylori infection and iron deficiency anemia*

| Study/ Location | Study design | Participants | *H. Pylori* detection | Outcomes |
|---|---|---|---|---|
| 4. Kitila et al. [9] Ethiopia | Cross-sectional study | Women (n = 332) Age:16-45 years | Stool antigen detection | Hemoglobin (g/dL) **Anemia** Hb: Pregnant women < 11 g/dL Non-pregnant women < 12 g/dL |
| 5. Pita-Rodríguez et al. [10] Cuba | Cross-sectional study | Women (n = 391) Age:18-40 years | Urea breath test | Serum ferritin (µg/L) Hemoglobin (g/dL) IDA Ferritin < 15 µg/L Hb < 12 g/dL |
| 6. Xu et al. [11] China | Cross-sectional study | Men and women (n = 17,791) Age: 40-60 years | Serum IgG and IgA antibodies by ELISA | Hemoglobin (g/dL) MCV (fL) MCH (pg) **Anemia** Men: Hb < 13 g/dL Women: Hb < 12 g/dL |
| 7. Saleh and Hassan [18] Egypt | Case-control study | Men and women (n = 120) Cases: 70 Controls: 50 Age: 20-43 years | Stool antigen detection | Serum ferritin (µg/L) Hemoglobin (g/dL) MCV (fL) Hematocrit (%) **IDA** Men: Ferritin < 18 µg/L Hb < 13 g/dL Women: Ferritin < 18 µg/L Hb < 11.5 g/dL |

**Table 1 (cont'd):** *Observational studies assessing association between Helicobacter Pylori infection and iron deficiency anemia*

| Study/ Location | Study design | Participants | *H. Pylori* detection | Outcomes |
|---|---|---|---|---|
| 8. Darvishi et al. [19]<br>Iran | Case-control study | Children<br>(n = 134)<br>Cases: 64<br>Controls: 70<br>Age: 40-75 months | Serum IgG antibodies by ELISA | Serum ferritin (µg/L)<br>Hemoglobin (g/dL)<br>TIBC (µg/dL)<br>**IDA**<br>Ferritin < 20 µg/L<br>Hb < 11 g/dL<br>TIBC > 350 µg/dL |
| 9. Nashaat and Mansour [20]<br>Egypt | Case-control study | Pregnant women<br>(n = 100)<br>Cases: 50<br>Controls: 50<br>Age:18-48 years | Serum IgG and IgA antibodies by ELISA | Serum ferritin (µg/L)<br>Hemoglobin (g/dL)<br>TIBC (µg/dL)<br>**IDA**<br>Ferritin < 20 µg/L<br>Hb < 11 g/dL<br>TIBC > 350 µg/dL |
| 10. Mubarak et al. [12]<br>Sudan | Cross-sectional study | Pregnant women<br>(n = 179)<br>Mean age: 26 years | Serum IgG and IgA antibodies by ELISA | Serum ferritin (µg/L)<br>Hemoglobin (g/dL)<br>**IDA**<br>Ferritin < 15 µg/L<br>Hb < 11 g/dL |
| 11. Bazmamoun et al. [21]<br>Iran | Case-control study | Children<br>(n = 200)<br>Cases: 102<br>Controls: 98<br>Age: 2-16 years | Giemsa staining | Serum ferritin (µg/L)<br>Hemoglobin (g/dL)<br>**IDA**<br>Ferritin < 15 µg/L<br>Hb < 11 g/dL |

**Table 1 (cont'd):** *Observational studies assessing association between Helicobacter Pylori infection and iron deficiency anemia*

| Study/ Location | Study design | Participants | *H. Pylori* detection | Outcomes |
|---|---|---|---|---|
| 12. Queiroz et al. [13]<br>Multicenter study<br>Latin America | Cross-sectional study | Children<br>(n = 311)<br>Age: 3-16 years | Culture<br>Urea breath test | Serum ferritin (µg/L)<br>Hemoglobin (g/dL)<br>Transferrin saturation (%)<br>Hematocrit (%)<br>MCV (fL)<br>MCH (pg)<br>IDA<br>Ferritin: Children (3-5 years) < 12 µg/L<br>Children (6-16 years) < 15 µg/L<br>Hb: Children (3-5 years) < 11 g/dL<br>Children (6-11 years) < 11.5 g/dL<br>Children (12-16 years) < 12 g/dL |
| 13. Shak et al. [14]<br>Haiti | Cross-sectional study | Children<br>(N = 336)<br>Age: 6-59 months | Serum IgG antibodies by ELISA | Hemoglobin (g/dL)<br>Anemia<br>Hb < 11 g/dL |
| 14. Jasem et al. [22]<br>Baghdad | Case-control study | Men and women<br>(n = 100)<br>Cases: 78<br>Controls: 22<br>Age: 18-45 years | Serum IgG antibodies by ELISA | Serum ferritin (µg/L)<br>Hemoglobin (g/dL)<br>IDA<br>Men: Ferritin < 15 µg/L<br>Hb < 13 g/dL<br>Women: Ferritin < 15 µg/L<br>Hb < 11.5 g/dL |

**Table 1 (cont'd):** *Observational studies assessing association between Helicobacter Pylori infection and iron deficiency anemia*

| Study/ Location | Study design | Participants | *H. Pylori* detection | Outcomes |
|---|---|---|---|---|
| 15. UmaKiran et al. [15] India | Cross-sectional study | Children (n = 484) Age: 5-12 years | Urea breath test | Serum ferritin (µg/L) Hemoglobin (g/dL) **IDA** Ferritin < 12 µg/L Hb < 11 g/dL |
| 16. Araf et al. [16] Brazil | Cross-sectional study | Children (n = 194) Age: 10-16 years | Urea breath test | Serum ferritin (µg/L) Hemoglobin (g/dL) **IDA** Ferritin < 15 µg/L Hb: Males < 13 g/d Females < 12 g/dL |
| 17. Hoseinzadeh et al. [17] Iran | Cross-sectional study | Children (n = 100) Age: 7-12 years | Serum IgG antibodies by ELISA | Serum ferritin (µg/L) Hemoglobin (g/dL) TIBC (µg/dL) **IDA** Ferritin < 10 µg/L Hb < 11 g/dL |

Nine studies (09) enrolled children,[2,8,13-17,19,21] four studies (04) included both men and women,[7,11,18,22] two studies (02) only enrolled women, [9-10]and remaining two studies (02) included pregnant women.[12,20]

Results of meta-analysis of these observational studies showed decreased risk of anemia due to iron deficiency in patients having *H. Pylori* infection than patients not suffering from this infection (Pooled OR: 1.649; 95% CI: 0.883-3.082; p-value = 0.117) and remarkable difference regarding different characteristics was also observed in these researches found among the studies.

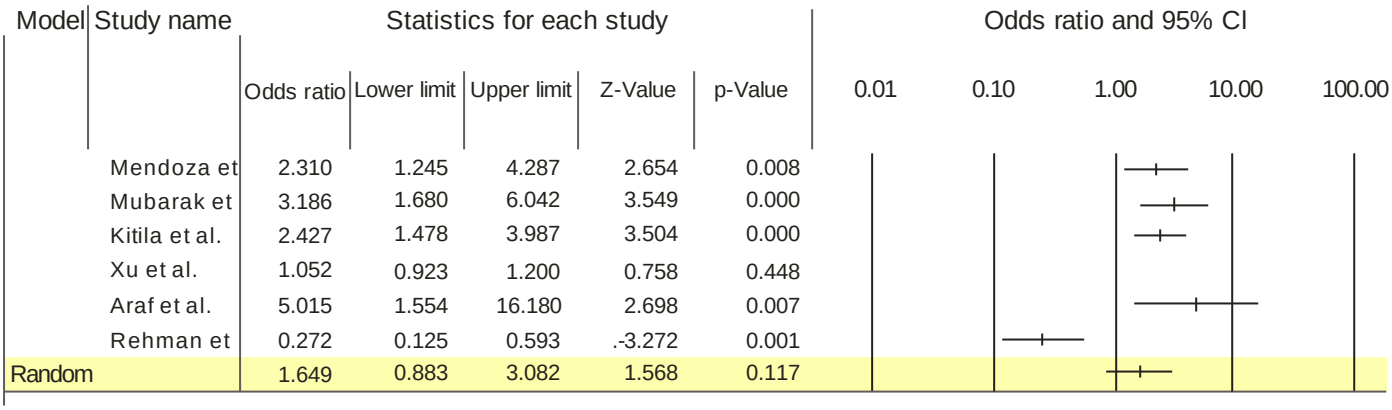


**Figure 2:** *Forest plot of meta-analysis on association between Helicobacter Pylori infection and iron deficiency anemia. OR, Odds ratio; CI, Confidence interval*

During randomized controlled trials (RCT) four (04) studies[23-26] were identified that evaluated the role of *H. Pylori* cure on anemia of iron deficiency in the last ten years in which three. Out of these four (04) RCTs the target population consisted of children in three (03) studies[23-24,26] and pregnant women in remaining one.[25]

**Table 2:** *Randomized controlled trials assessing the impact of anti-Helicobacter Pylori therapy on hemoglobin and iron biomarkers*

| Study/ Location | Study design | Participants | H. Pylori detection | Intervention | Control | Outcomes |
|---|---|---|---|---|---|---|
| 1. Habib *et al*. [23] India | RCT | Children (n = 18) Randomization (n = 18) Intervention group (n = 9) Control group (n = 9) Age: 12-15 years | Serum IgG antibodies by ELISA Urea breath test | Sequential *H. Pylori* eradication therapy for 5 days, followed by standard *H. Pylori* eradication therapy for another 5 days | Standard *H. Pylori* eradication therapy for 10 days | Serum ferritin (µg/L) Hemoglobin (g/dL) **IDA** Ferritin < 24 µg/L Hb < 12 g/dL |

**Table 2 (cont'd):** *Randomized controlled trials assessing the impact of anti-Helicobacter Pylori therapy on hemoglobin and iron biomarkers*

| Study/ Location | Study design | Participants | H. Pylori detection | Intervention | Control | Outcomes |
|---|---|---|---|---|---|---|
| 2. Xia *et al*. [24] China | RCT | Girls (n = 1037) Randomization (n = 80) Intervention group (n = 37) Control group (n = 43) Age: 12-18 years | Serum IgG antibodies by ELISA Stool antigen detection | First 12 weeks oral iron supplementation and next 2 weeks *H. Pylori* eradication triple therapy | Oral iron supplementation alone for 14 weeks | Serum ferritin (µg/L) Hemoglobin (g/dL) sTfR (µmol/L) **IDA** Ferritin < 24 µg/L Hb < 12 g/dL sTfR > 24.5 µmol/L |

**Table 2 (cont'd):** *Randomized controlled trials assessing the impact of anti-Helicobacter Pylori therapy on hemoglobin and iron biomarkers*

| Study/ Location | Study design | Participants | H. Pylori detection | Intervention | Control | Outcomes |
|---|---|---|---|---|---|---|
| 3. Malik et al. [25] India | RCT | Pregnant women (n = 201) Randomization (n = 40) Intervention group (n = 20) Control group (n = 20) Age: 20-45 years | Stool antigen detection | First 2 weeks H. Pylori eradication triple therapy and next 4 weeks oral iron supplementation therapy | First 2 weeks placebo and oral iron supplementation therapy and next 4 weeks oral iron supplementation therapy and folic acid | Serum ferritin (µg/L) Hemoglobin (g/dL) Serum iron (µg/dl) TIBC (µg/dL) Transferrin saturation (%) **IDA** Ferritin < 24 µg/L Hb < 11 g/dL Serum iron < 60 µg/dl TIBC > 350 µg/dL Transferrin saturation < 16 % |
| 4. Duque et al. [26] Mexico | RCT | Children (n = 700) Randomization (n = 72) Intervention group (n = 38) Control group (n = 34) Age: 6-13 years | Serum IgG antibodies by ELISA Urea breath test | First 12 weeks oral iron supplementation and next 2 week H. Pylori eradication triple therapy | Oral iron supplementation alone for 14 weeks | Serum ferritin (µg/L) Hemoglobin (g/dL) **IDA** Ferritin < 24 µg/L Hb < 12 g/dL |

All studies enrolled patients with deficient reserves of iron and the results of *H pylori* treatment in intervention group were different in different researches. In all four RCTs, we assessed differences in ferritin and hemoglobin values in patients receiving anti-*H. Pylori* treatment along with iron and in patients receiving iron alone.

**Table 3:** *Findings from randomized controlled trials that assessed effect of combined anti-Helicobacter Pylori and iron therapy on ferritin level compared to iron therapy alone*

| Study | Anti-H. Pylori therapy plus iron therapy Mean (SD) Baseline | Anti-H. Pylori therapy plus iron therapy Mean (SD) Follow-up | Iron therapy alone Mean (SD) Baseline | Iron therapy alone Mean (SD) Follow-up | Follow-up time |
|---|---|---|---|---|---|
| 1. Habib et al. [23] India | 26.6 (16.9) | 29.6 (22.1) | 53.6 (30.8) | 39 (21.3) | 6 weeks after therapy |
| 2. Xia et al. [24] China | 10.2 (0.7) | 15.2 (2.1) | 10.1 (0.6) | 11.1 (1) | 3 months after therapy |
| 3. Malik et al. [25] India | 5 (0.4) | 7.6 (0.6) | 4.9 (0.3) | 5.5 (0.4) | 6 weeks after therapy |
| 4. Duque et al. [26] Mexico | 7.9 (0.7) | 11.3 (0.8) | 11 (0.7) | 11.2 (1) | 3 months after therapy |

**Table 4:** *Findings from randomized controlled trials that assessed effect of combined anti-Helicobacter Pylori and iron therapy on hemoglobin level compared to iron therapy alone*

| Study | Anti-H. Pylori therapy plus iron therapy Mean (SD) Baseline | Anti-H. Pylori therapy plus iron therapy Mean (SD) Follow-up | Iron therapy alone, Mean (SD) Baseline | Iron therapy alone Mean (SD) Follow-up | Follow-up time |
|---|---|---|---|---|---|
| 1. Habib et al. [23] India | 10 (0.5) | 11.1 (0.3) | 9.8 (0.6) | 10.5 (0.4) | 6 weeks after therapy |
| 2. Xia et al. [24] China | 11.2 (0.8) | 12.2 (5.6) | 11.2 (0.4) | 11.4 (0.5) | 3 months after therapy |
| 3. Malik et al. [25] India | 9.5 (0.9) | 11.6 (0.9) | 9 (0.9) | 11 (0.9) | 6 weeks after therapy |
| 4. Duque et al. [26] Mexico | 11.6 (0.7) | 12.3 (0.9) | 10.9 (0.8) | 11 (1) | 3 months after therapy |

Meta-analyses showed significant rise in the levels of ferritin with anti-*H. Pylori* treatment along with iron supplementation compared to those who took iron supplement alone (Pooled SMD: 0.504; 95% CI: 0.135–0.873; p-value = 0.007) and no remarkable heterogeneity in the different researches was noted ($I^2$=39.6%; p-value = 0.174).

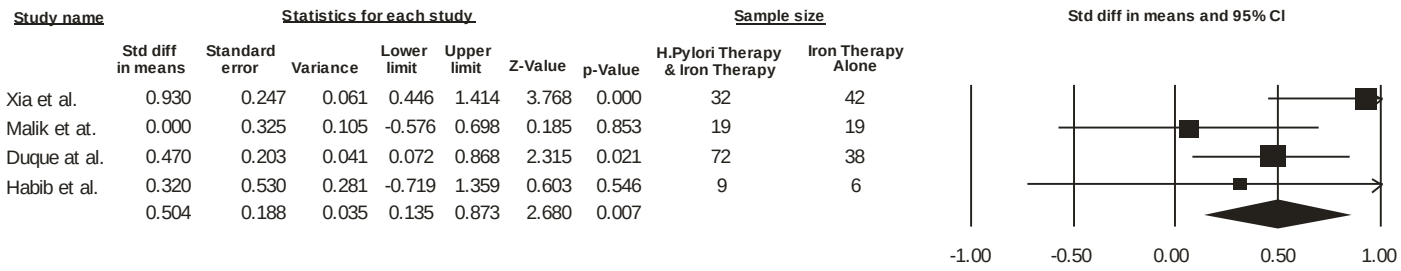


**Figure 3:** *Effect of anti-Helicobacter Pylori therapy plus iron supplementation compared to iron supplementation alone on serum ferritin levels, meta-analysis of randomized controlled trials. SMD, standardized difference in means; CI, confidence interval*

Meta-analyses further showed significant raise in hemoglobin levels after taking anti-*H. Pylori* treatment with supplements of iron contrasted with those taking iron supplements only (Pooled SMD: 0.476; 95% CI: 0.111-0.840; p-value=0.011) and similarly as above remarkable heterogeneity was absent in the related searches. ($I^2$ = 38.6%; p-value = 0.180).

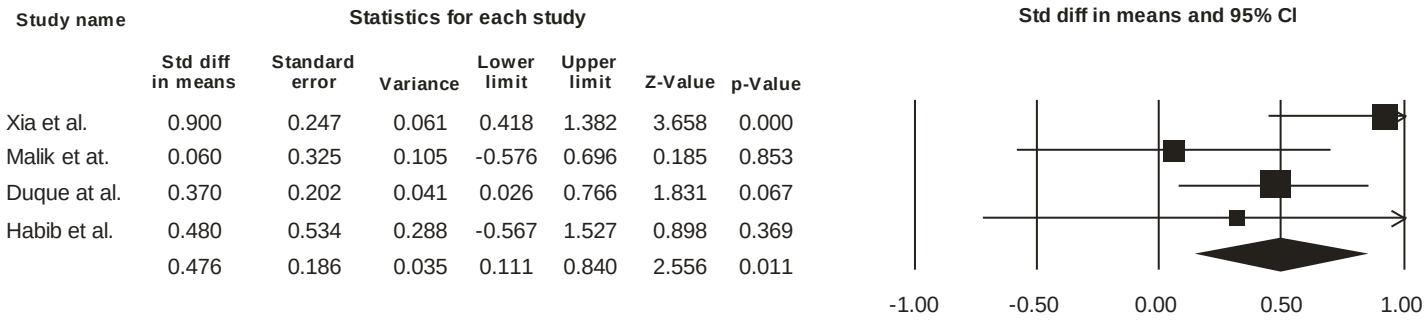


**Figure 4:** *Effect of anti-Helicobacter Pylori therapy plus iron supplementation compared to iron supplementation alone on hemoglobin levels, meta-analysis of randomized controlled trials. SMD, standardized difference in means; CI, confidence interval*

## Discussion:

Anemia, caused by iron deficiency, is a common disorder in developing countries.[7] In our society its increased prevalence is associated with many causes; some of them are renowned and explored whereas a few are novel and need time and experimentation to prove their relation with H pylori infection. Association of *H. Pylori* with iron deficiency anemia have been proved in few cases of peptic ulcers and gastric malignancies but most patients with H pylori infection do not suffer from ulcer of stomach or carcinoma of stomach instead of it many of them have persistent inflammation of stomach that is not related to anemia. Studies being conducted in recent years stress more on diseases outside GI tract caused by H pylori and this includes anemia of iron deficiency also.[11,27] Systematic review and meta-analysis of one research showed a relation in study *H. Pylori* infection and an raised risk of reduced stores of ir-on.[27] A current large cohort retrospective study has stated that when possible confounders are adjusted, patients having *H. Pylori* infection were at increased risk of normocytic anemia.[11] There has been a robust relation in *H. Pyl-ori* infection and anemia of iron deficiency is evident in kids, adults, and pregnant women.[28]

In contrast to above observations in developing countries, *H. Pylori* seropositivity relation to iron deficiency anemia was not found in Estonian children with age ranging from 7-18 years.[29] Similar studies conducted in other developed and developing countries didn't show prevalence of any association of H. Pylori with iron deficiency anemia (IDA).[30] This variation in study results could be due to different conditions prevailing in poor and developed countries as a result of different environmental and racial dissemination of patient's age, criteria for inclusion in study, sample size, sampling procedures, techniques for detecting anemia and *H. Pylori* infection.

Despite large scale studies conducted to discover relationship of *H. Pylori* infection in causing iron deficiency anemia (IDA) there have been no clear findings on this subject. Our present meta-analysis too has showed decreased possibility of IDA among patients having confirmation of *H. Pylori* infection than patients without this infection (Pooled OR: 1.649; 95% CI: 0.883-3.082; p-value = 0.117) in developing regions. Furthermore remarkable heterogeneity was present in these studies ($I^2$ = 88.7%; p-value = 0.001).

Basis our study we are of the opinion that hap-pening of iron deficiency anemia (IDA) and *H. Pyl-ori* infection together can be by chance as both these illnesses are extremely predominant in developing regions. Besides a number of causes can initiate iron deficiency anemia (IDA) including but not limited to malnutrition, vitamin deficiencies, chronic disorders, infections, and certain chronic blood loss conditions. Large number of studies reflecting *H. Pylori*

infection to be an independent risk factor for IDA was conducted in school-aged children, adolescents, and pre-menopausal & pregnant women as in these cases there is a comparatively increased demand of iron for fulfillment of burdens of growth and menstruation.[27]

There has been an established opinion that variation in results of various studies might also be due to various types of *H. Pylori* bacteria involved. *e.g.* Cag -PAL positive organisms usually cause symptoms of peptic ulcer and GI tract signs and symptoms, whereas a few species of *H. Pylori* are connected to ulcer of stomach and anemia due to deficiency of iron (IDA). Besides level of serum ferritin, an acute phase protein, employed for detection of the iron deficiency anemia (IDA) has also been found being affected by some additional features apart from scarcity of iron.[30]

Interventional trials considered for this review comes as the most consistent evidence for this interaction. Joint analyses of combine anti- H. Pylori eradicateion & iron therapy showed significant increase in ferritin levels as compared to taking iron supplementation alone (Pooled SMD: 0.504; 95% CI: 0.135–0.873; p-value = 0.007). More to this point, meta-analyses showed note-worthy increase in hemoglobin levels resulting from combine anti-*H. Pylori* eradication & therapy of iron as compared to iron therapy only (Pooled SMD: 0.476; 95% CI: 0.111-0.840; p-value = 0.011).

Putting an end to *H. Pylori* connected with/without iron supplement has showed improvement in mean hemoglobin and ferritin levels as per most identified studies. A study carried out in Far East country of China using random control trial (RCT) there has been a positive role of *H. Pylori* therapy on the resolution of iron deficiency anemia (IDA) not responding to other drugs.[24]

Another research conducted for this purpose on kids affected by H. Pylori showed complete recovery from iron deficiency anemia (IDA) through removal or cure of *H. Pylori* with/without iron therapy.[26] In an uncontrolled research trial there no significant relationship was observed in serum ferritin and *H. Pylori* eradication therapy.[23] Many similar studies carried out for same purpose examined relationship of *H. Pylori* infection treatment for curing anemia and in 80% of men and 71% of postmenopausal women results were successful while only 23% of premenopausal women showed negative results.[31] Another study based on systematic review and meta -analysis showed remarkable increase in ferritin levels as a result of combine anti-*H. Pylori* eradication therapy & iron in contrast to using supplements of iron as sole therapy. In whatever way during follow up stage results showed no difference in iron deficiency anemia (IDA) among patients cured for H pylori and patients not cured for H pylori. (24.3% vs 26.5%, p-value=0.71).[27,32]

This inconsistency in above trial results may be due to age and sex distribution of the cases by virtue of their variation in physiologic iron loss & iron requirements, variation in the duration of post-treatment follow-up, and other trial design limitations like small sample sizes.

Findings from few related meta-analyses trials were mirror image of these conflicting results that examined the effect of *H. Pylori* elimination therapy for refractory anemia due to iron deficiency in children. Observational studies based on meta-analysis conducted by Qu *et al*., showed an connection between *H. Pylori* and iron deficiency anemia (IDA) among children, whereas random control trials (RCTs) analyses did not show significant betterment in hemoglobin or ferritin levels as a result of *H. Pylori* eradication among iron deficiency anemia (IDA) children.[33]

Huang *et al*. on the basis of his eight (08) random control trials (RCTs), four of such trials were conducted in children age groups, performed on *H. Pylori* elimination and iron supplementation in areas of Asia with high occurrence of iron deficiency anemia & *H. Pylori* concluded that combine *H. Pylori* eradication & iron supplementation therapy was more effective for treatment of iron deficiency anemia (IDA) not responding to drug therapy than sole iron administration for this purpose.[34]

Our current research has many strengths, some of which are as follows: This review includes both observational studies and random control trials (RCTs) from developing regions for assessment of relationship between *H. Pylori* infection and anemia due to

iron deficiency (IDA). It provides a considerable update on previously conducted systematic reviews, as those reviews were carried out with different aims and objectives. To minimize the bias for this review we adopted the data extraction procedure by using pre-determined tools and on the basis of three independent reviewers.

Our study too has certain limitations, few of which are mentioned below: Studies published in English literature only were made part of this research. As per our small sample size limitation was involved to conduct meta-regression in order to identify statistical deference between different regions of low and middle income countries. By applying sensitive search strategy and leaving unpublished data in grey list we only used published data from various databases and bibliographical lists so we may have left certain valuable information unattended from unpublished data sources. As focus of our study was limited to low and middle income countries therefore we cannot apply our findings to other regions of the world.

## Conclusion

In summary, present evidence shows decreased possibility of iron deficiency anemia (IDA) related to H. *Pylori* infection in developing regions. Additionally, *H. Pylori* eradication treatment can be useful for raising ferritin and hemoglobin levels, by giving it in addition to iron supplementation. High-quality random control trials (RCTs) are the need of the hour for detailed evaluation of *H. Pylori* treatment on reserves of iron, its long-standing affects on iron stores and associated adverse affects. Relationship of *H. Pylori* infection with iron deficiency anemia (IDA) varies in numerous populations and this warrant improved understanding and representation.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Availability of data and materials

The datasets used and/or analyzed during the current systematic review and meta-analysis are avail-able from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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