Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Helicobacter pylori Infection Is Associated With Carotid Intima and Media Thickening: A Systematic Review and Meta-Analysis

Orsolya Anna Simon, MD; Anikó Görbe; Péter Hegyi, MD, PhD, DSc; Lajos Szakó, MD; Eduard Oštarijaš, MD; Fanni Dembrovszky, MD; Szabolcs Kiss, MD; László Czopf, MD, PhD; Bálint Erőss, MD, PhD; Imre Szabó, MD, PhD

BACKGROUND: *Helicobacter pylori* (*H. pylori*) infection affects ≈4.4 billion people worldwide. Several studies suggest that this pathogen impacts the digestive system, causing diverse and severe conditions, and results in extragastrointestinal disorders like vascular diseases. Our study aims to examine the association between *H. pylori* infection and carotid intima-media thickness.

METHODS AND RESULTS: Electronic databases (MEDLINE, Embase, CENTRAL, Web of Science, and Scopus) were searched for studies, comparing the thickness of the carotid intima-media in *H. pylori*–infected and noninfected individuals listed until October 20, 2020. Statistical analyses were performed using the random effects meta-analysis of model of weighted mean differences with the corresponding 95% CI using the DerSimonian and Laird method. The protocol was registered in advance in PROSPERO (International Prospective Register of Systematic Reviews; CRD42021224485). Thirteen studies were found meeting inclusion criteria for our systematic review and meta-analysis, presenting data on the thickness of the carotid intima-media considering the presence of *H. pylori* infection. Altogether, 2298 individuals' data were included (1360 *H. pylori* positive, 938 negative). The overall carotid intima-media thickness was significantly larger among infected patients compared with uninfected participants (weighted mean difference: 0.07 mm; 95% CI, 0.02–0.12; P=0.004; I^2=91.1%; P<0.001). In case of the right common carotid artery, the intima-media thickening was found to be significant as well (weighted mean difference, 0.08 mm; 95% CI, 0.02–0.13, P=0.007; I^2=85.1%; P<0.001), while it showed no significance in the left common carotid artery (weighted mean difference, 0.12 mm; 95% CI, −0.05 to 0.28, P=0.176; I^2=97.4%; P<0.001).

CONCLUSIONS: *H. pylori* infection is associated with increased carotid intima-media thickness. Therefore, the infection may indirectly contribute to the development of major vascular events.

Key Words: atherosclerosis ■ carotid intima-media thickness ■ *Helicobacter pylori* ■ infection ■ meta-analysis

Over half of the world's population is affected by *Helicobacter pylori* infection; in 2015, the estimated number of infected individuals was 4.4 billion.[1] The prevalence of *H. pylori* is around 80% in middle-aged adults in developing countries.[2] While 48.6% of the examined adults were *H. pylori* positive, only 32.6% of children (<18 years) were infected worldwide, according to a recent meta-analysis based on 183 studies mainly from Asia, Europe, Latin America, and the Caribbean.[3]

The relationship between atherosclerosis and *H. pylori* infection has been extensively studied. Karadag et al[4] examined carotid intima-media thickness (CIMT), epicardial adipose tissue thickness, and biologic markers of inflammation (high-sensitivity C-reactive protein) in patients who were *H. pylori*

Correspondence to: Imre Szabó, MD, PhD, First Department of Medicine, University of Pécs, Ifjúság útja 13., H-7624 Pécs, Hungary.
E-mail: szabo.imre@pte.hu

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022919

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Data of 13 observational studies on carotid intima-media thickness, comprising 2298 individuals (1360 *Helicobacter pylori*–positive and 938 negative cases), were included in our systematic review and meta-analysis.
- Weighted mean differences were calculated to determine significant differences in terms of carotid intima-media thickness between the *H. pylori*–positive and –negative groups.
- The analyses revealed statistically significant association of *H. pylori* infection and overall carotid intima-media thickness as well as the right but not left common carotid arteries.

What Are the Clinical Implications?

- *H. pylori* testing might be considered in individuals with a thicker carotid intima-media, especially in those with other risk factors of cerebrovascular or cardiovascular diseases.
- The screening and eradication of *H. pylori* infection in the general population should not be fully discarded as a potential intervention to contribute to the risk reduction of future cerebrovascular and cardiovascular events.
- The inequality of the cost-benefit ratio is a severe limitation of this approach.

Nonstandard Abbreviations and Acronyms

CIM	carotid intima-media
TC	total cholesterol
WMD	weighted mean difference

positive and found a relationship between the infection and CIMT.[5]

The published literature on the link between *H. pylori* infection and stroke is controversial. In 1996, a nested case-control study by Whincup et al[6] found an association between *H. pylori* infection and increased risk of stroke; however, the relationship was not significant after adjustment for major risk factors. Later, Doheim et al[7] claimed in their meta-analysis that anti–*H. pylori* IgG positivity increases the risk of stroke. In another meta-analysis, Wang et al[8] concluded that patients with chronic *H. pylori* infection are more likely to have a stroke by a noncardioembolic cause. Despite these, another meta-analysis claims no strong relationship between *H. pylori* infection and stroke.[9] Wasay et al[10] identified *H. pylori* gastritis as a nonindependent risk factor for a higher occurrence of stroke in their cohort study. A recent systematic review and meta-analysis concluded that in infected individuals the possibility of acute coronary syndrome increased.[11] Schöttker et al[12] found no association between the infection and major vascular events, cardiovascular mortality, and all-cause mortality in a population-based cohort study.

Concerning the relationship between the proliferation of the carotid arterial wall layers and the propagation of cerebrovascular and cardiovascular diseases, O'Leary et al[13] support in a cohort that CIMT is directly associated with an increased risk of major vascular events in individuals aged >65 years and no history of cardiovascular disease. Centurión[14] emphasized the importance of the noninvasive measurement of atherosclerotic burdens and also a relation of CIMT to the severity of systemic atherosclerosis.

According to Wang et al,[15] patients diagnosed with type 2 diabetes showed endothelial vascular impairment and thickening of CIM layers compared with healthy individuals. Another cross-sectional study associated time length in a range of patients with type 2 diabetes with increased CIMT.[16]

The findings mentioned above suggest a link between *H. pylori* infection and thicker carotid artery wall layers. However, clear evidence of the association is missing, and the literature is full of contradictory findings.

Our study aimed to evaluate the association of *H. pylori* infection and CIMT in a meta-analysis.

METHODS

The authors declare that all supporting data are available within the article and its online supplemental files.

A systematic review and meta-analysis of the studies was reported by the guidance of Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (Table S1).[17]

Protocol

The protocol was registered in advance in PROSPERO (International Prospective Register of Systematic Reviews) under the number CRD42021224485. Deviating from the originally planned protocol, no analyses on cytotoxin-associated gene A positivity and age distribution were performed. No hazard ratios were reported. According to the *Cochrane Handbook*, pairs were formed; if not, 2 comparable groups were published in a study.[18] Subgroup analysis was performed on the basis of geographic distribution. For dichotomous outcomes, odds ratios (ORs) with 95% CIs were calculated.

Systematic Search

The literature search of 5 electronic databases (MEDLINE, Embase, CENTRAL, Web of Science, and Scopus) from inception until October 20, 2020, was conducted. All fields/texts were searched except for Scopus ("article title, abstract, keywords"), and no filters were applied. The clinical question was based on the PECO (Population, Exposure, Comparison, Outcome) framework: In this study, *P* means the individuals whose CIMT was measured, *E* is the individuals who are *H. pylori* positive, *C* marks the comparison between participants who are *H. pylori* positive and *H. pylori* negative, and the primary *O* is the intima-media thickness in mm given separately for overall (the mean of the right and left common carotid arteries) and right and left carotid. The secondary outcomes, as part of our substantial analyses, were laboratory parameters (triglyceride, total cholesterol [TC], high-density lipoprotein [HDL], low-density lipoprotein [LDL]), the number of patients with diabetes, age, and hypertension. The following search key was used to find the relevant studies: (*Helicobacter* OR *pylori*) AND (caroti* or [Cerebrovascular Disorders] OR [Cardiovascular Diseases]). The references of the eligible articles were also reviewed to identify additional eligible studies.

Inclusion and Exclusion Criteria

Only peer-reviewed observational studies (including cohort, cross-sectional, and case-control studies) were eligible for inclusion, which reported on at least 1 CIMT in mm of adult patients who were *H. pylori* positive and adult patients who were negative. No other cardiovascular markers were needed for inclusion. Pediatric studies (<18 years) and nonhuman studies were excluded. All methods of *H. pylori* infection determination were accepted.

Selection and Data Extraction

The selection process was conducted by 2 independent authors (O.S., E.O.). All results from the databases were transferred to a reference manager program (EndNote X9.3.3., Clarivate Analytics, Philadelphia, PA). After automatic and manual removal of duplicates, the records were screened on the basis of title, abstract, and full text following predetermined principles. Disagreements were resolved by a third investigator (L.S.). Cohen's kappa coefficient was calculated to measure interrater reliability during the selection process.[19] The same independent investigators (O.S., E.O.) performed the data extraction onto a data collection sheet (Excel, Office 365, Microsoft, Redmond, WA). The following data were extracted from the eligible articles: first author, publication year, Digital Object Identifier, study design, the detection method of *H. pylori*, geographic location, age distribution, sex distribution, number of patients in each comparison group, number of patients with each event (eg, *H. pylori* positivity), laboratory parameters (triglyceride, TC, LDL, HDL), and number of patients with diabetes and hypertension in each group. The thickness of the carotid intima-media (CIM) layers is given in mm for the right side, left side, and overall. Disagreements were resolved by a third investigator (L.S.).

Measurement of CIMT

Since the method of CIMT measurement shows wild differences, any approach was accepted. Generally, the measurement of CIMT shows moderate heterogeneity. There are slight differences in the definition of CIMT and the place of measurement by ultrasound. Characteristics of the CIMT measurements in the included articles are noted in Table S2.

Inclusion of Multiple Groups From One Study

As for studies with not just 2 comparable groups, we formed pairs according to the *Cochrane Handbook*.[18] In the case of 4 articles,[20–23] not only the presence or the absence of *H. pylori* was examined but also various comorbidities. These were alcoholic liver disease,[20] diabetes,[21] at least 2 risk factors for atherosclerosis (hypertension, hyperlipidemia, obesity, diabetes, smoking, female sex, personal history of atherosclerosis, and family history of premature atherosclerosis),[22] or early-stage diabetic kidney disease.[23] We paired the *H. pylori*–positive group with the negative one, presenting the same comorbidity. In other cases, when the previously mentioned method could not be applied, we chose to compare the groups with the higher number of participants.[4,24,25]

Management of Further Sources of Inaccuracy

In the study published by El Hadidy et al,[26] CIMT results were bigger with 1 decimal than in the other articles included in this meta-analysis. Furthermore, no information was published on the definition of CIMT and the measurement area of CIM (Table S2). Influence diagnostics were performed in the case of right and left CIMT to determine this specific article's effect on the outcome. Sensitivity analysis and statistical analyses were performed with and without their data to assess the effect of their questionable results on the pooled analysis.

Substantial and Subgroup Analyses

We performed substantial analyses to see how the characteristics of the included population affect the results. Laboratory parameters of triglyceride, TC, LDL, and HDL levels were compared between the *H.*

pylori–positive and –negative groups. The pooled values were given in mmol/L. The numbers of patients with diabetes, age, and hypertension in the specific groups were also compared. We performed additional subgroup analyses based on the geographic distribution and detection method of the bacterium.

Statistical Analysis

For dichotomous outcomes (diabetes and hypertension) ORs with 95% CIs, and for continuous outcomes (CIMT, age, and laboratory parameters), weighted mean difference (WMD) with 95% CI were calculated on the basis of crude estimates. In one case,[27] the means and SDs were calculated from the median, minimum, and maximum values and the sample size according to Wan's method.[28] We used the random effect model by DerSimonian and Laird[29] with the estimate of heterogeneity in all cases. An I^2 test was performed to assess the heterogeneity. According to the *Cochrane Handbook*,[18] the interpretation of the I^2 value is the following: If it is 0% to 40%, the heterogeneity is considered as "might not be important," from 30% to 60% it is "moderate," 50% to 90% means "substantial" heterogeneity, while from 75% to 100% the heterogeneity is "considerable." Results were displayed graphically using forest plots. For our primary outcome (overall, right and left CIMT) we assessed publication bias by visually inspecting funnel plots to detect nonsymmetrical distribution of SEs around the study-level effect estimates, and the Egger's test, using a significance of $P<0.05$ to indicate significant asymmetry. These statistical analyses were performed in STATA version 16.0 (StataCorp, College Station, TX). Influence diagnostics are basic ways to detect and remove outliers in meta-analyses. Studies without particularly high or low effect sizes can still exert a very high influence on our overall results and may lead to some concerns regarding the robustness of the pooled effect.[30] In our meta-analysis, the following methods were applied: (1) Externally Standardized Residuals (rstudent), (2) DFFITS value, (3) Cook's Distance, (4) Covariance Ratio, (5) Tau^2, (6) Q values, (7) Hat value, (8) Study Weight. Influence diagnostics were performed with metafor package in R (R Foundation for Statistical Computing, Vienna, Austria).[31] As an extension to our subgroup analyses by meta-regression, the effect of continuous and categorical characteristics and the effects of multiple factors were investigated simultaneously. The minimum number of the included studies was at least 10.[18] In our meta-analysis, the groups of age difference, geographic location, and detection method met this criterion. Univariable meta-regressions were performed in R with the package meta.[32]

Risk-of-Bias Assessment

The risk of bias in the eligible studies was evaluated using the Quality in Prognosis Studies tool by 2 independent review authors (O.S., E.O.).[33] The assessment comprises 6 main domains, which were scored as low, moderate, or high risk of bias. If all domains were deemed as low risk, the overall assessment was a low risk of bias. If a study carried a domain with high risk or at least 3 domains with moderate risk, the overall assessment was a high risk of bias. All other cases were rated as moderate. Disagreements between the reviewers were resolved by consensus.

RESULTS

Selection Process

The electronic literature search identified 4725 records. After the removal of duplicates, 2824 records were left; 106 full-text articles were assessed for eligibility (Cohen's kappa coefficient, 0.83), and after the selection process (Cohen's kappa coefficient, 0.83), 13 studies were included both in qualitative and quantitative synthesis (Figure 1).[4,20–27,34–37] Table 1. presents the baseline characteristics of the enrolled studies, and Table S3 provides a further comparison of the *H. pylori*–positive and –negative groups.

Characteristics of the Included Studies

Altogether, 2298 individuals were included: 1360 *H. pylori*–positive cases and 938 negative cases. All 13 included studies were single-center, retrospective, observational studies. *H. pylori* positivity was determined by urea breath test in 377 cases, by serum ELISA in 786 cases, by histology in 127 cases, and using combined methods (stool antigen, urea breath test, histology, or cultivation) in 70 cases. In terms of the geographic distribution, 4-4 studies were performed in China and Turkey, 2-2 in Egypt and Italy, and 1 in Iran. In the way of CIMT measurement, used in included studies, no general practice was found (Table S2). Four of the included studies published data on plaques in the area of CIMT measurement,[21,24,27,34] but a standardized definition and clear inclusion/exclusion criteria are missing. Because of these, we were not able to perform any statistical analyses on plaques detected in the carotid arteries, but we would like to emphasize its importance in future studies.

H. pylori Infection and CIMT

A significant difference was found in the case of overall CIMT, which was thicker in *H. pylori*–positive patients based on the included 11 studies (1151 patients who were *H. pylori*–positive versus 692 patients who were *H. pylori* negative; WMD, 0.07 mm; 95% CI, 0.02–0.12; $P=0.004$; $I^2=91.1\%$; $P<0.001$; Figure 2).[4,20–25,27,34,35,37] In 4 studies, the right and the left CIMT were detailed separately.[26,27,34,36] Based on these, significantly increased

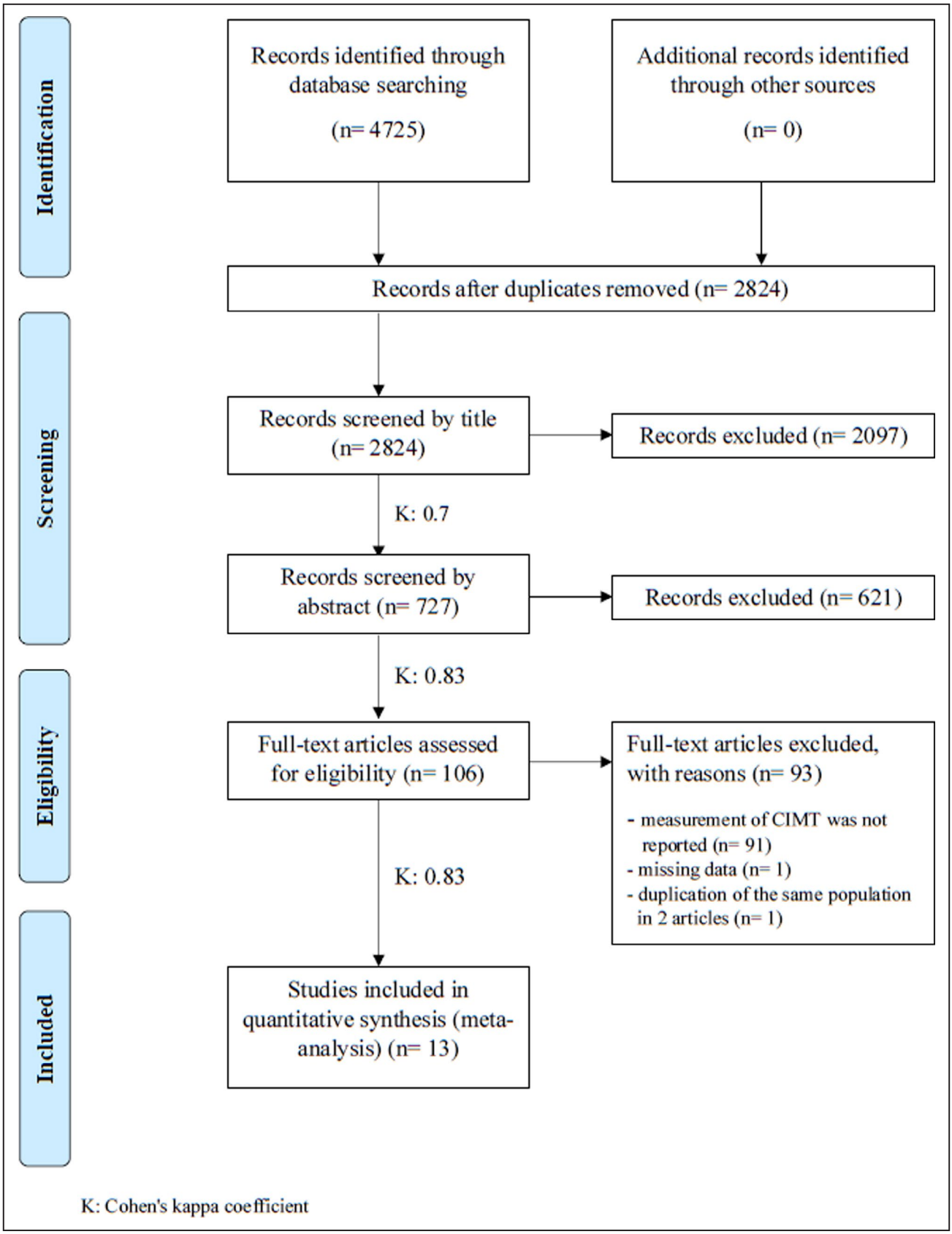


Figure 1. **Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of study selection and inclusion.**

Table. Basic Characteristics of the Included Studies

Study	HP detection method	Country	No. of patients	Age (mean±SD)		Sex (female %)	Comorbidities (considered)
				H. pylori positivity	*H. pylori* negativity		
Bao-Ge et al[20] 2017 I.	Urea breath test	China	78	46.37±7.37*	46.72±6.89*	10.26	Alcoholic liver disease
Bao-Ge et al[20] 2017 II.	Urea breath test	China	82	46.74±6.69*	46.66±6.75*	10.98	None
Başyığıt et al[34] 2012	Stool antigen, urea breath test	Turkey	61	40.9±10.3	42.3±9.4	52.45	Hypertension, diabetes
Diomedi et al[24] 2004	Serum ELISA	Italy	124	68.8±9.8	66.9±15.8	39.52	Hypertension, diabetes
El Hadidy et al[26] 2009	Serum ELISA	Egypt	60	NI	NI	73.34	Hypertension, diabetes
Hamed et al[21] 2008 I	Serum 2-step immunometric assay	Egypt	80	47.6±9.1	48.2±9.3	51.25	Diabetes
Hamed et al[21] 2008 II	Serum two-step immunometric assay	Egypt	60	46.2±9.7	50.2±6.5	40	Diabetes
Judaki et al[35] 2017	Urea breath test, histology, culture	Iran	80	45.64±8.32	46.52±5.52	48.75	Hypertension
Karadag et al[4] 2018	Histology	Turkey	45	50±8.2	52±7.9	53.34	Hypertension
Köksal et al[22] 2004 I	Serum ELISA	Turkey	84	46.7±14.7	45.1±7.1	71.43	Hypertension
Köksal et al[22] 2004 II	Serum ELISA	Turkey	50	45±11	45±10	68	Hypertension
Mayr et al[25] 2003	Serum ELISA	Italy	421	56.6†	55.7†	47.74	None
Mete et al[27] 2013	Histology	Turkey	134	49.8±8.7	50.2±9.33	58.21	Hypertension
Shan et al[36] 2018	Serum ELISA	China	395	NI	NI	57.47	Hypertension
Xu et al[37] 2016	Urea breath test	China	364	63.2±10.4	62.8±11.7	46.98	None
Feng et al[23] 2018 I	Urea breath test	China	89	46.1±0.58*	46.79±0.63*	20.22	Hypertension, diabetes, early-stage diabetic kidney disease
Feng et al[23] 2018 II	Urea breath test	China	91	46.64±0.54*	46.61±0.53*	21.98	Hypertension, diabetes, early-stage diabetic kidney disease

HP indicates, *Helicobacter pylori*; and NI, no information.
*Mean±SE.
†Mean without SD.

CIMT was also detected in the right carotid artery; among *H. pylori*–infected individuals, it was 0.08 mm thicker than in the *H. pylori*–negative group (342 *H. pylori*–positive patients versus 308 patients who were *H. pylori* negative; WMD, 0.08 mm; 95% CI, 0.02–0.13; P=0.007; I^2=85.1%; P<0.001; Figure 3), while no significant difference was found in the left carotid artery (342 patients who were *H. pylori* positive versus 308 patients who were *H. pylori* negative; WMD, 0.12 mm; 95% CI, −0.05–0.28; P=0.176; I^2=97.4%; P<0.001; Figure 4).

In case of the article by El Hadidy et al,[26] we faced several uncertainities: The values of CIMT were bigger with 1 decimal than in the other included articles regarding right and left CIMT; the definition of CIMT and the measurement area of the CIM is not reported, and it carries a high risk of bias. If such studies are detected, it is advisable to recalculate our meta-analysis without them to see if this changes the interpretation of our results.[31]

As for the influence diagnostics, based on all methods, in the case of the right carotid, the outliers, with higher values than the threshold value, are the articles by El Hadidy et al and Shan et al,[26,36] while in the case of left carotid, these are Mete et al and Shan et al.[27,36] Because of the small number of the included studies in the right and left CIMT analyses, only 1 article could be excluded at the same time. To keep it uniform and considering the above-mentioned uncertainities, we decided to choose the same publication in both cases, which is the article by El Hadidy et al.[26] By sensitivity analysis and repeating the comparison without the data published by El Hadidy et al,[26] the significant difference was still detectable in the right carotid (319 patients who were *H. pylori* positive versus 271 patients who were *H. pylori* negative; right: WMD, 0.08 mm; 95% CI, 0.02–0.13; P=0.006; I^2=89.5%; P<0.001; left: WMD, 0.13 mm; 95% CI, −0.05 to 0.30; P=0.153; I^2=98.3%; P<0.001; Figure S1 through S4).

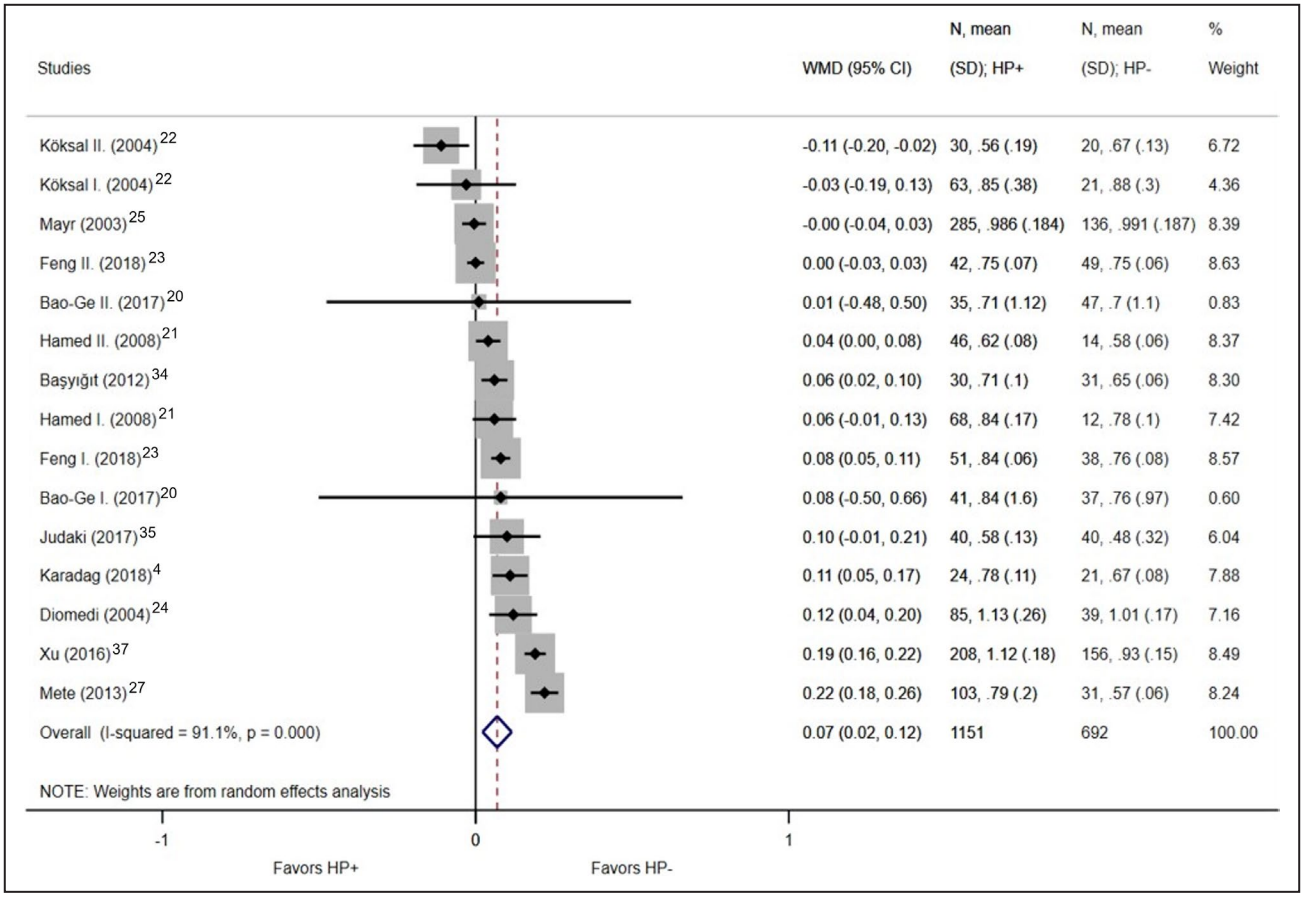


Figure 2. Forest plot of studies comparing overall carotid intima-media thickness between individuals who were *Helicobacter pylori* positive and negative.
Black diamonds represent the weighted mean difference between the 2 groups we compared, and horizontal lines show the corresponding 95% CIs. Size of the gray squares reflects the weight of a particular study. The blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs. HP indicates *Helicobacter pylori*; and WMD, weighted mean difference.

Meta-Regression to Determine the Effect of Age, Geographic Location, and Detection Method

Meta-regression could be performed if at least 10 articles were included in the specific groups. In the case of age, geographic location, and detection method, this condition is met among included individuals with published overall CIMT values. There were no significant regression of age (WMD, 0.0021; I^2=91.12%; *P*=0.9033), geographic location (WMD, −0.0248; I^2=93.84%; *P*=0.7326) and detection method (WMD, 0.0645; I^2=91.11%; *P*=0.3183; Figure S5).

Diabetes, Age, Hypertension, and Laboratory Parameters of Included Individuals

There was no significant difference in the prevalence of diabetes in the 2 compared groups (OR, 1.15; 95% CI, 0.49–2.68; *P*=0.751; I^2=0%; *P*=0.997; Figure S6A).[21,23,24,26,34] The mean age of individuals who were *H. pylori* positive did not differ from the mean age of the negative individuals (866 patients who were *H. pylori* positive versus 556 patients who were *H. pylori* negative; WMD, −0.35 years; 95% CI, −1.18 to 0.48; *P*=0.404; I^2=0%; *P*=0.961; Figure S7).[4,20–24,27,34,35,37] These results correlates with the meta-regression. There was no significant difference in the odds of patients diagnosed with hypertension in the 2 compared groups (OR, 0.91; 95% CI, 0.59–1.39; *P*=0.65; I^2=0%; *P*=1; Figure S6B).[4,22–24,26,27,34–36] Laboratory parameters of TC, triglyceride, LDL, and HDL were compared from the listed studies.[20–23,26,27,34,37] The TC level was significantly higher in the positive group (634 patients who were *H. pylori* positive versus 428 patients who were *H. pylori* negative; WMD, 0.07 mmol/L; 95% CI, 0.01–0.13; *P*=0.017; I^2=0%; *P*=0.826; Figure S8). No further significant differences were detected in case of laboratory parameters like triglyceride (664 patients who were *H. pylori* positive versus 459 patients who were *H. pylori* negative; WMD, 0.09 mmol/L; 95% CI, −0.01 to 0.19;

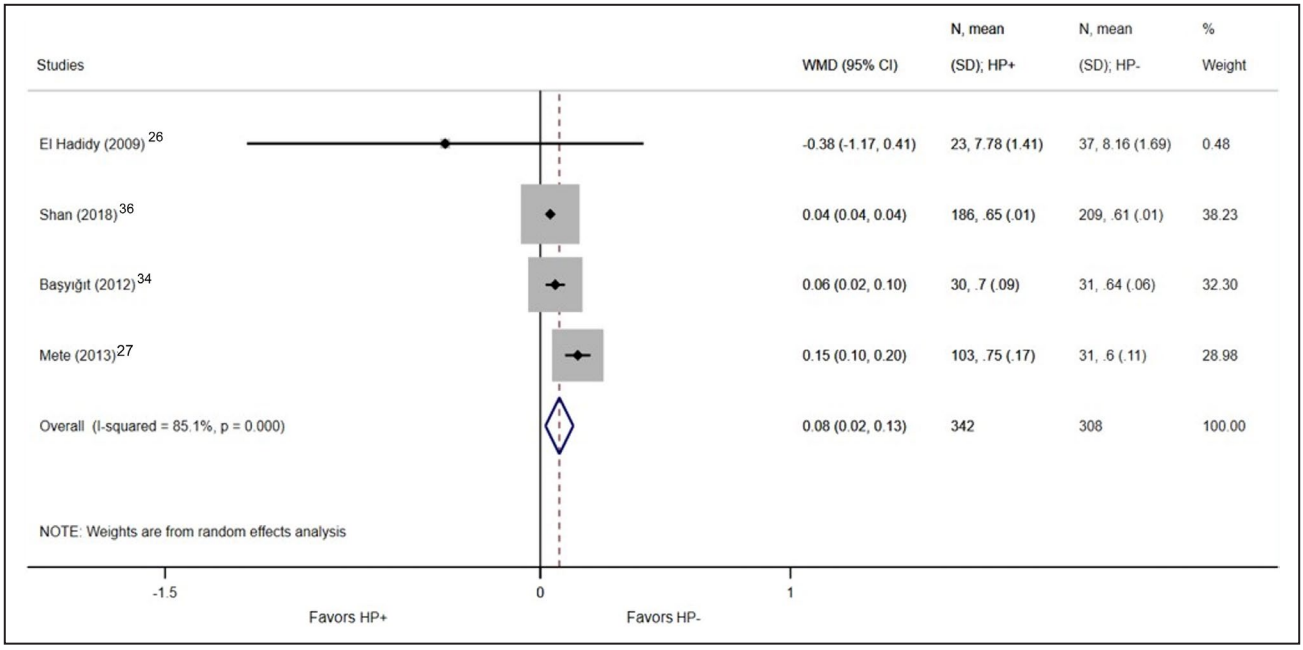


Figure 3. Forest plot of studies comparing right carotid intima-media thickness between individuals who were *Helicobacter pylori* positive and negative.
Black diamonds represent the weighted mean difference between the 2 groups we compared, and horizontal lines show the corresponding 95% CIs. Size of the gray squares reflects the weight of a particular study. The blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs. HP indicates *Helicobacter pylori*; and WMD, weighted mean difference.

P=0.088; I^2=44.5%; *P*=0.063), LDL (664 patients who were *H. pylori* positive versus 459 patients who were *H. pylori* negative; WMD, 0.06 mmol/L; 95% CI, −0.00 to 0.13; *P*=0.058; I^2=22.8%; *P*=0.233), or HDL (664 patients who were *H. pylori* positive versus 459 patients who were *H. pylori* negative; WMD, 0.09 mmol/L; 95% CI, −0.01 to 0.19; *P*=0.693; I^2=88.5%; *P*<0.001; Figure S9 through 11).

Subgroup Analyses Based on Geographic Location

We performed subgroup analyses on overall CIMT for geographic localization. Three studies published data on 704 subjects from China; 377 were *H. pylori* positive and 327 negatives.[20,23,37] Four studies were from Turkey with 374 participants,[4,22,27,34] 250 were infected and 124 were not infected. There were no significant differences between the CIMT of infected and noninfected subjects in neither Chinese (WMD, 0.09 mm; 95% CI, −0.01 to 0.19; *P*=0.094; I^2=94.5%; *P*<0.001) nor Turkish studies (WMD, 0.06 mm; 95% CI, −0.04 to 0.16; *P*=0.259; I^2=92.9%; *P*<0.001), if the individuals were compared with noninfected controls from the same country (Figure S12 and S13). These results correlate with the meta-regression.

Even in the geographically uniform subgroup analyses, there was a considerable degree of remaining heterogeneity within subgroups.

Subgroup Analyses Based on *H. pylori* Detection Method

We performed subgroup analyses among individuals involved in the analysis of overall CIMT based on the detection method of the pathogen. In 3 studies, urea breath test identified 377 positive and 327 negative individuals.[20,23,37] Serology was used in 4 studies, identifying 577 positive and 242 negative individuals.[21,22,24,25] In the case of the urea breath test (WMD, 0.09 mm; 95% CI, −0.01 to 0.19; *P*=0.094; I^2=94.5%; *P*<0.001) and serum ELISA (WMD, 0.02 mm; 95% CI, −0.03 to 0.07, *P*=0.456, I^2=73.8%, *P*=0.002), there was no significant differences in the CIMTs (Figure S14 and S15). These results correlate with the meta-regression.

Risk-of-Bias Assessment

The Quality in Prognosis Studies tool was applied for our primary outcomes, the overall, right, and left CIMT. The 6 main domains were scored as low, moderate, or high risk of bias. The overall risk of bias for overall CIMT was low in 10 studies,[4,20–24,27,34,35,37] while it was moderate in 1.[25,38] As for studies publishing data on right and left CIMT, in both cases, 3 studies carried low risk,[27,34,36] and 1 study carried a high risk of bias.[26] Details are shown in Figure 5 and Figure S16.

Publication Bias

The visual assessment of the funnel plot for overall CIMT showed relatively big study samples and small

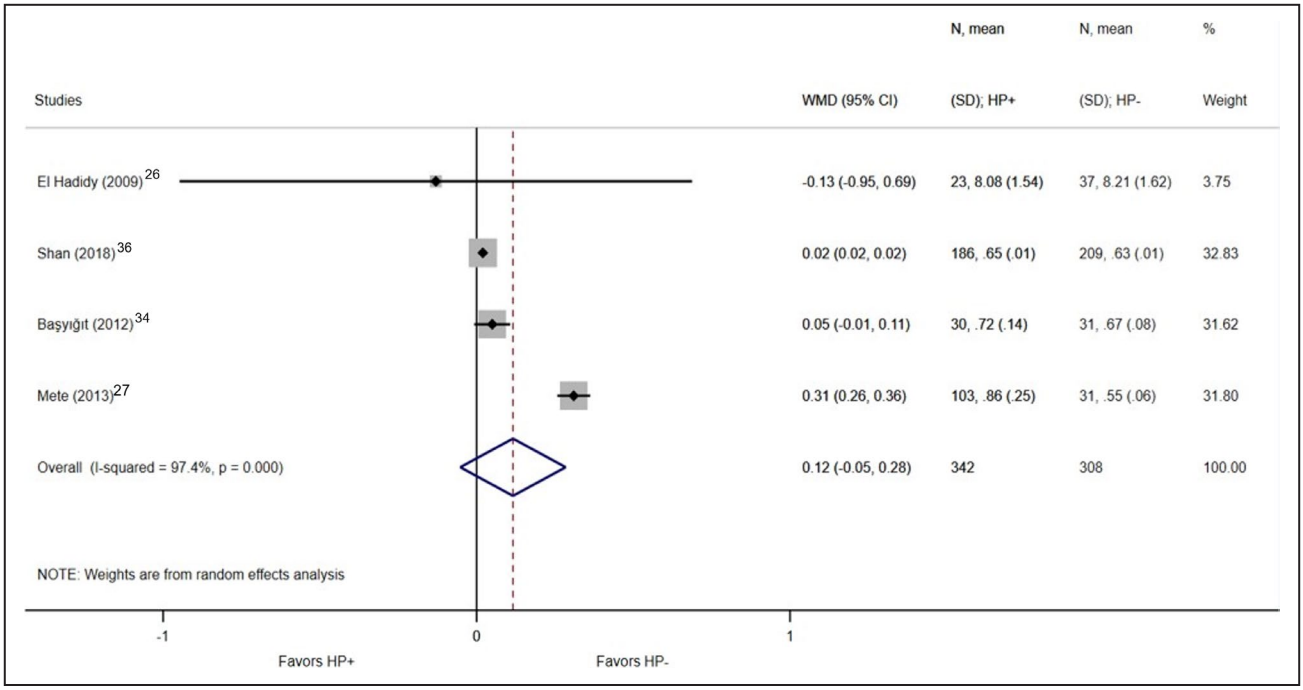


Figure 4. Forest plot of studies comparing left carotid intima-media thickness between individuals who were *Helicobacter pylori* positive and negative.

Black diamonds represent the weighted mean difference between the 2 groups we compared, and horizontal lines show the corresponding 95% CIs. Size of the gray squares reflects the weight of a particular study. The blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs. HP indicates *Helicobacter pylori*; and WMD, weighted mean difference.

SE, suggesting that publication bias is unlikely. The Egger test revealed no small-study effect (P=0.971). As for right and left CIMT, the sample numbers are low (Figure S17).

DISCUSSION

Our meta-analysis supported that *H. pylori* infection is associated with the overall CIMT. The thickening was more detectable in the right carotid artery. The substantial analyses found higher TC levels among infected patients. Still, there were no significant differences between the *H. pylori*–positive and –negative groups regarding the other investigated laboratory parameters (triglyceride, LDL, and HDL) influencing atherosclerosis.

In our analysis, the overall CIMT of the individuals who were *H. pylori* positive individuals was 0.07 mm bigger than in the negative group. According to the measurements on individuals with no cardiovascular risk factors by Jarauta et al,[39] the normal CIMT was found to be 0.59 to 0.95 mm in men, and 0.52 to 0.93 mm in women. Willeit et al[40] claim that the average of CIMT is 0.65 to 0.9 mm in adults, and the thickness is increasing by 0 to 0.04 mm/y. Intimal thickening and later atherosclerosis in areas of low and oscillatory shear stress are attributable to prolonged endothelial exposure.[41] A 3-year study by Pessin et al[42] draw attention to the importance of the detection of silent carotid artery diseases, as 50% of their patients suffered moderate to severe carotid stroke without any warning clinical symptoms such as transient ischemic attack. A clinical trial scanning both carotid and femoral arteries of asymptomatic individuals found, that a future cardiovascular event can be predicted using arterial morphology classification and ultrasound arterial score.[43] Another study claims that patients with a thicker CIM should be examined for coronary artery lesions.[44] In 2008, the American Society of Echocardiography consensus statement concluded that the measurement of carotids could specify the cardiovascular disease risk assessment only with limitations in general clinical practice.[45] In addition, a recent guideline, published in 2016 by the European Society of Cardiology, did not recommend the screening of carotid arteries to estimate cardiovascular risk.[46]

A significant difference was found when comparing the thickness of the right carotid between the *H. pylori*–positive and –negative groups. Both by inclusion and exclusion of the unclear data provided by El Hadidy,[26] CIM was 0.08 mm thicker among individuals who were *H. pylori* infected. We found no difference of CIMT between positive and negative participants in the subgroup analysis of the studies with detailed data on the left CIMT. Luo et al[47] examined the right and left

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis reporting	Overall risk of bias	Included in the overall CIMT analysis
Overall CIMT								
Bao-ge et al,[20] 2017	+	NA	+	+	+	+	+	Yes
Başyığıt et al,[34] 2012	+	NA	+	+	+	+	+	Yes
Diomedi et al,[24] 2004	+	NA	+	+	+	+	+	Yes
Feng et al,[23] 2018	+	NA	+	+	+	+	+	Yes
Hamed et al,[21] 2008	+	NA	+	+	+	+	+	Yes
Judaki et al,[35] 2017	+	NA	+	+	+	+	+	Yes
Karadag et al,[4] 2018	+	NA	+	+	+	+	+	Yes
Köksal et al,[22] 2004	+	NA	+	+	+	+	+	Yes
Mayr et al,[25] 2003	?	NA	+	+	+	?	?	Yes
Mete et al,[27] 2013	+	NA	+	+	+	+	+	Yes
Xu et al,[37] 2016	+	NA	+	+	+	+	+	Yes
Right CIMT								
Başyığıt et al,[34] 2012	+	NA	+	+	+	+	+	Yes
El Hadidy et al,[26] 2009	+	NA	+	-	?	+	-	Yes
Mete et al,[27] 2013	+	NA	+	+	+	+	+	Yes
Shan et al,[36] 2018	+	NA	+	+	+	+	+	Yes
Left CIMT								
Başyığıt et al,[34] 2012	+	NA	+	+	+	+	+	Yes
El Hadidy et al,[26] 2009	+	NA	+	-	?	+	-	Yes
Mete et al,[27] 2013	+	NA	+	+	+	+	+	Yes
Shan et al,[36] 2018	+	NA	+	+	+	+	+	Yes

Figure 5. Result of risk-of-bias assessment for primary outcomes.
If all domains were deemed as low risk, the overall assessment was a low risk of bias (green, +). When a study carried a domain with high risk or at least 3 domains with moderate risk, the overall risk was defined as high (red, -). All other cases were rated as moderate (yellow, ?). CIMT indicates carotid intima-media thickness; and NA, not applicable.

carotid arteries separately. He found that the thickness of the right carotid artery is more likely to be associated with altered hemodynamic parameters, whereas the change in the left carotid thickening rather correlates with changes in biochemical indices. The anatomic difference can be the other explanation.[48] High shear stress in the left carotid artery results in greater hemodynamic stress in the left cerebral hemisphere.[49] According to a cohort study, the plaques in the right carotid artery were found to be more stable because of pronounced calcification, while the left carotid plaques were more vulnerable, often with intraplaque hemorrhage.[50] However, the Rotterdam Study suggests that the difference in recognizability can be responsible for the higher number of reported left-sided clinical strokes and transient ischemic attacks.[51] As for cardiac relevance, both mean right and left CIMTs were significantly higher among individuals with coronary artery disease than in the control group. Furthermore, the thickness of the common carotid artery on both sides suggested a positive correlation to more severe coronary artery disease.[52]

Presumably, several factors and mechanisms influence the thickening of the carotid arteries. According to the review of the major risk factors on CIMT, age, sex, hypertension, systolic blood pressure, smoking, body mass index, diabetes, dyslipidemia, impaired TC and LDL- and HDL-cholesterol levels, and fasting glucose level seem to have the most important influence. Furthermore, biological markers were also found to be associated with CIMT.[53] Besides these, Libby et al[54] also noted alteration in the endothelium, triglyceride, and inflammation. Vijayvergiya et al,[55] going into the details of possible mechanisms in *H. pylori*–related atherosclerosis, identified the elevated level of cytokines in chronic *H. pylori* infection. Furthermore, their decrease after eradication was also observed. This suggests that *H. pylori* causing chronic inflammation might play a role in atherosclerotic plaque formation and endothelial dysfunction. Similarly, several studies found that *H. pylori* positivity was associated with dyslipidemia with higher TC, triglyceride, LDL, and apolipoprotein-B, and lower HDL and apolipoprotein-A levels, and reverse changes were observed after eradication. At the same time, other research could not show the effect on laboratory parameters.

Our meta-analysis has some limitations, including small sample size and different diagnostic methods. All the included studies were retrospective, which have their limitations, and according to our risk-of-bias assessment, the presence of moderate and high-risk domains was detected. Statistical heterogeneity could be explained by the clinical heterogeneity caused by slight differences in CIM definition and measurement, geographic distribution, and different detection methods. We performed subgroup analyses to reduce the heterogeneity and examine the causative role of the latter 2 factors on our primary outcomes. However, the heterogeneity remained high, which may limit the generalizability of the meta-analysis. Our sample size may also limit the testing of the effects of multiple covariates. Lack of standardized imaging approaches and the inclusion of common carotid artery areas with plaques may result in bias as well. The inclusion of multiple groups from one study and pair formation may also limit our results. No publication bias was found.

As for basic research, further studies might give additional evidence on molecular changes induced by chronic inflammation such as *H. pylori* infection leading to plaque formation. Studies with high sample numbers in measurements of separate right and left CIMTs are warranted. By performing future clinical studies among patients who are *H. pylori* infected, we would have a more accurate view of this arising role.

In clinical practice, *H. pylori* testing might be considered in individuals with thicker CIM, especially in those with other risk factors of cerebrovascular or cardiovascular diseases. A recent meta-analysis based on 100.667 participants' data estimated that by reducing the progression of CIM thickening by 0.01, 0.02, 0.03 or 0.04 mm/y, the relative risk of cardiovascular disease would be 0.84 (0.75–0.93), 0.76 (0.67–0.85), 0.69 (0.59–0.79), or 0.63 (0.52–0.74), respectively.[40] On the other hand, the screening and eradication of *H. pylori* infection in the general population should not be fully discarded as a potential intervention to contribute to the risk reduction of future cerebrovascular and cardiovascular events. However, the inequality of the cost-benefit ratio is a severe limitation of this approach, as the benefits are unlikely to outweigh the costs.

In conclusion, infection with *H. pylori* is associated with the thickening of the CIM, as it was found to be more prominent in individuals who were *H. pylori* positive. By understanding the molecular changes and performing large-sample-size randomized clinical trials, the pathomechanism could also be further clarified. The early screening and eradication of the bacteria in individuals with a thicker CIMT should be considered.

ARTICLE INFORMATION

Received June 16, 2021; accepted December 10, 2021.

Affiliations

Institute for Translational Medicine, Medical School, University of Pécs, Hungary (O.A.S., A.G., P.H., L.S., E.O., F.D., S.K., B.E.); János Szentágothai Research Centre, University of Pécs, Hungary (O.A.S., L.S., E.O., F.D., S.K.); First Department of Medicine (P.H.); and Doctoral School of Clinical Medicine (S.K.), University of Szeged, Hungary; Division of Cardiology, First Department of Medicine, Medical School (L.C.) and Division of Gastroenterology, First Department of Medicine, Medical School, University of PécsHungary, (O.A.S., I.S.).

Acknowledgments

All authors provided critical input and approved the final form of the manuscript. Dr Simon: conceptualization, methodology, validation, investigation, and writing (original draft); Görbe: formal analysis and writing (review and editing); Dr Hegyi: writing (review and editing); Dr Szakó: conceptualization, methodology, validation, investigation, and supervision; Dr Oštarijaš: conceptualization, methodology, validation, and investigation; Dr Dembrovszky: conceptualization, methodology, validation, and supervision; Dr Kiss: conceptualization, methodology, validation, and writing (review and editing); Dr Czopf: writing (review and editing) and supervision; Dr Erőss: conceptualization, methodology, validation, and writing (review and editing); Dr Szabó: conceptualization, methodology, validation, writing (review and editing), and supervision.

Sources of Funding

This work will be funded by the Economic Development and Innovation Operational Programme Grant (GINOP-2.3.2-15-2016-00048 - STAY ALIVE and GINOP-2.3.4-15-2020-00010 Competence Center for Health Data Analysis, Data Utilisation and Smart Device and Technology Development at the University of Pécs), the New National Excellence Program of the Ministry for Innovation and Technology from the source of the National Research, Development and Innovation Fund (ÚNKP-20-3), and Tandem Funding of University of Pécs (granted to Dr Szabó, KA-2020-32).

Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S17

REFERENCES

1. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, Malfertheiner P, Graham DY, Wong VWS, Wu JCY, et al. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. *Gastroenterology*. 2017;153:420–429. doi: 10.1053/j.gastro.2017.04.022
2. Wang F, Meng W, Wang B, Qiao L. Helicobacter pylori-induced gastric inflammation and gastric cancer. *Cancer Lett*. 2014;345:196–202. doi: 10.1016/j.canlet.2013.08.016
3. Zamani M, Ebrahimtabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J, Derakhshan MH. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. *Aliment Pharmacol Ther*. 2018;47:868–876.
4. Karadag Z, Sehitoglu T, Cure MC, Rakici H, Ayvaz MA, Bedir R, Kizilkaya B, Şahin OZ, Cure E. Helicobacter pylori can be related to carotid intima-media thickness, epicardial adipose tissue thickness and serum neutrophil gelatinase-associated lipocalin (NGAL) levels. *Bratisl Med J*. 2018;119:302–307. doi: 10.4149/BLL_2018_057
5. Qu B, Qu T. Causes of changes in carotid intima-media thickness: a literature review. *Cardiovasc Ultrasound*. 2015;13:46. doi: 10.1186/s12947-015-0041-4
6. Whincup PH, Mendall MA, Perry IJ, Strachan DP, Walker M. Prospective relations between Helicobacter pylori infection, coronary heart disease, and stroke in middle aged men. *Heart*. 1996;75:568–572. doi: 10.1136/hrt.75.6.568
7. Doheim MF, Altaweel AA, Elgendy MG, Elshanbary AA, Dibas M, Ali A, Dahy TM, Sharaf AK, Hassan AE. Association between Helicobacter pylori infection and stroke: a meta-analysis of 273,135 patients. *J Neurol*. 2020. doi: 10.1007/s00415-020-09933-x
8. Wang ZW, Li Y, Huang LY, Guan QK, Xu DW, Zhou WK, Zhang XZ. Helicobacter pylori infection contributes to high risk of ischemic stroke: evidence from a meta-analysis. *J Neurol*. 2012;259:2527–2537. doi: 10.1007/s00415-012-6558-7
9. Yu M, Zhang Y, Yang Z, Ding J, Xie C, Lu N. Association between Helicobacter pylori infection and stroke: a meta-analysis of prospective observational studies. *J Stroke Cerebrovasc Dis*. 2014;23:2233–2239. doi: 10.1016/j.jstrokecerebrovasdis.2014.04.020
10. Wasay M, Jafri W, Khealani B, Azam I, Hussaini A. Helicobacter pylori gastritis and risk of ischaemic stroke. *J Pak Med Assoc*. 2008;58:368–370.
11. Fang Y, Fan C, Xie H. Effect of Helicobacter pylori infection on the risk of acute coronary syndrome: a systematic review and meta-analysis. *Medicine*. 2019;98:e18348. doi: 10.1097/MD.0000000000018348
12. Schöttker B, Adamu MA, Weck MN, Müller H, Brenner H. Helicobacter pylori infection, chronic atrophic gastritis and major cardiovascular events: a population-based cohort study. *Atherosclerosis*. 2012;220:569–574. doi: 10.1016/j.atherosclerosis.2011.11.029
13. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular health study collaborative research group. *N Engl J Med*. 1999;340:14–22. doi: 10.1056/NEJM199901073400103
14. Centurión OA. Carotid intima-media thickness as a cardiovascular risk factor and imaging pathway of atherosclerosis. *Crit Pathw Cardiol*. 2016;15:152–160. doi: 10.1097/HPC.0000000000000087
15. Wang M, Sui J, Wang S, Wang X. Correlations of carotid intima-media thickness with endothelial function and atherosclerosis degree in patients with type 2 diabetes mellitus. *Clin Hemorheol Microcirc*. 2019;72:431–439. doi: 10.3233/CH-180486
16. Lu J, Ma X, Shen Y, Wu Q, Wang R, Zhang L, Mo Y, Lu W, Zhu W, Bao Y, et al. Time in range is associated with carotid intima-media thickness in type 2 diabetes. *Diabetes Technol Ther*. 2020;22:72–78. doi: 10.1089/dia.2019.0251
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine*. 2009;6:e1000097. doi: 10.1371/journal.pmed.1000097
18. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org
19. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med*. 2012;22:276–282. doi: 10.11613/BM.2012.031
20. Bao-Ge Q, Hui W, Yi-Guo J, Ji-Liang S, Zhong-Dong W, Ya-Fei W, Xing-Hai H, Yuan-Xun L, Jin-Dun P, Guang-Ying R. The correlation and risk factors between carotid intima-media thickening and alcoholic liver disease coupled with helicobacter pylori infection. *Sci Rep*. 2017;7:43059. doi: 10.1038/srep43059
21. Hamed SA, Amine NF, Galal GM, Helal SR, Tag El-Din LM, Shawky OA, Ahmed EA, Abdel Rahman MS. Vascular risks and complications in diabetes mellitus: the role of Helicobacter pylori infection. *J Stroke Cerebrovasc Dis*. 2008;17:86–94. doi: 10.1016/j.jstrokecerebrovasdis.2007.10.006
22. Köksal A, Ekmekçi Y, Karadeniz Y, Köklü S, Apan T, Yilmaz M, Sezikli M, Unal B, Demirel T, Yildiz A. Helicobacter pylori seropositivity and atherosclerosis risk factors. *Dig Dis*. 2004;22:386–389.
23. Feng L, Deng C, Li Y. Assessment of the relationship between carotid intima-media thickening and early-stage diabetic kidney disease coupled with Helicobacter pylori infection. *Dis Markers*. 2018;2018:3793768.
24. Diomedi M, Pietroiusti A, Silvestrini M, Rizzato B, Cupini LM, Ferrante F, Magrini A, Bergamaschi A, Galante A, Bernardi G. Caga-positive Helicobacter pylori strains may influence the natural history of atherosclerotic stroke. *Neurology*. 2004;63:800–804. doi: 10.1212/01.WNL.0000138025.82419.80
25. Mayr M, Kiechl S, Mendall MA, Willeit J, Wick G, Xu Q. Increased risk of atherosclerosis is confined to CagA-positive Helicobacter pylori strains: prospective results from the Bruneck Study. *Stroke*. 2003;34:610–615.
26. El Hadidy EHM, Abdul-Aziz MY, Mokhtar A-R, Abo El Ata MM, El Gwad SSA. Helicobacter pylori infection and vascular complications in patients with type 2 diabetes mellitus. *J Taibah Univ Med Sci*. 2009;4:62–72. doi: 10.1016/S1658-3612(09)70082-4
27. Mete R, Oran M, Alpsoy S, Gunes H, Tulubas F, Turan C, Topcu B, Aydin M, Yildirim O. Carotid intima-media thickness and serum paraoxonase-1 activity in patients with Helicobacter pylori. *Eur Rev Med Pharmacol Sci*. 2013;17:2884–2889.
28. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135. doi: 10.1186/1471-2288-14-135
29. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188. doi: 10.1016/0197-2456(86)90046-2
30. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. *Doing Meta-Analysis with R: A Hands-On Guide*. Boca Raton, FL and London: Chapmann & Hall/CRC Press; 2021: ISBN 978-0-367-61007-4.
31. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;1:2010.

32. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22:153–160. doi: 10.1136/ebmental-2019-300117
33. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med*. 2013;158:280–286. doi: 10.7326/0003-4819-158-4-201302190-00009
34. Başyığıt S, Akbaş H, Süleymanlar İ, Kemaloğlu D, Koç S, Süleymanlar G. The assessment of carotid intima-media thickness, lipid profiles and oxidative stress markers in Helicobacter pylori-positive subjects. *Turk J Gastroenterol*. 2012;23:646–651. doi: 10.4318/tjg.2012.0441
35. Judaki A, Norozi S, Ahmadi MRH, Ghavam SM, Asadollahi K, Rahmani A. Flow mediated dilation and carotid intima media thickness in patients with chronic gastritis associated with Helicobacter pylori infection. *Arq Gastroenterol*. 2017;54:300–304. doi: 10.1590/s0004-2803.201700000-39
36. Shan J, Bai X, Han L, Yuan Y, Yang J, Sun X. Association between atherosclerosis and gastric biomarkers concerning Helicobacter pylori infection in a Chinese healthy population. *Exp Gerontol*. 2018;112:97–102. doi: 10.1016/j.exger.2018.09.009
37. Xu Y, Wang Q, Liu Y, Cui R, Lu K, Zhao Y. Association between Helicobacter pylori infection and carotid atherosclerosis in patients with vascular dementia. *J Neurol Sci*. 2016;362:73–77. doi: 10.1016/j.jns.2016.01.025
38. Glurich I, Grossi S, Albini B, Ho A, Shah R, Zeid M, Baumann H, Genco RJ, De Nardin E. Systemic inflammation in cardiovascular and periodontal disease: comparative study. *Clin Diagn Lab Immunol*. 2002;9:425–432.
39. Jarauta E, Mateo-Gallego R, Bea A, Burillo E, Calmarza P, Civeira F. Carotid intima-media thickness in subjects with no cardiovascular risk factors. *Rev Esp Cardiol*. 2010;63:97–102.
40. Willeit P, Tschiderer L, Allara E, Reuber K, Seekircher L, Gao LU, Liao X, Lonn E, Gerstein HC, Yusuf S, et al. Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: meta-analysis of 119 clinical trials involving 100 667 patients. *Circulation*. 2020;142:621–642. doi: 10.1161/CIRCULATIONAHA.120.046361
41. Gokaldas R, Singh M, Lal S, Benenstein RJ, Sahni R. Carotid stenosis: from diagnosis to management, where do we stand? *Curr Atheroscler Rep*. 2015;17:480. doi: 10.1007/s11883-014-0480-7
42. Pessin MS, Hinton RC, Davis KR, Duncan GW, Roberson GH, Ackerman RH, Mohr JP. Mechanisms of acute carotid stroke. *Ann Neurol*. 1979;6:245–252. doi: 10.1002/ana.410060311
43. Belcaro G, Nicolaides AN, Laurora G, Cesarone MR, De Sanctis M, Incandela L, Barsotti A. Ultrasound morphology classification of the arterial wall and cardiovascular events in a 6-year follow-up study. *Arterioscler Thromb Vasc Biol*. 1996;16:851–856. doi: 10.1161/01.ATV.16.7.851
44. Kotsis VT, Pitiriga V, Stabouli SV, Papamichael CM, Toumanidis ST, Rokas SG, Zakopoulos NA. Carotid artery intima-media thickness could predict the presence of coronary artery lesions. *Am J Hypertens*. 2005;18:601–606. doi: 10.1016/j.amjhyper.2004.11.019
45. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography carotid intima-media thickness task force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr*. 2008;21:93–111; quiz 189–190. doi: 10.1016/j.echo.2007.11.011
46. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney M-T, Corrà U, Cosyns B, Deaton C, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315–2381. doi: 10.1093/eurheartj/ehw106
47. Luo X, Yang Y, Cao T, Li Z. Differences in left and right carotid intima-media thickness and the associated risk factors. *Clin Radiol*. 2011;66:393–398. doi: 10.1016/j.crad.2010.12.002
48. Rodríguez Hernández SA, Kroon AA, van Boxtel MP, Mess WH, Lodder J, Jolles J, de Leeuw PW. Is there a side predilection for cerebrovascular disease? *Hypertension*. 2003;42:56–60. doi: 10.1161/01.HYP.0000077983.66161.6F
49. Hedna VS, Bodhit AN, Ansari S, Falchook AD, Stead L, Heilman KM, Waters MF. Hemispheric differences in ischemic stroke: is left-hemisphere stroke more common? *J Clin Neurol*. 2013;9:97–102. doi: 10.3988/jcn.2013.9.2.97
50. Selwaness M, van den Bouwhuijsen Q, van Onkelen RS, Hofman A, Franco OH, van der Lugt A, Wentzel JJ, Vernooij M. Atherosclerotic plaque in the left carotid artery is more vulnerable than in the right. *Stroke*. 2014;45:3226–3230. doi: 10.1161/STROKEAHA.114.005202
51. Portegies ML, Selwaness M, Hofman A, Koudstaal PJ, Vernooij MW, Ikram MA. Left-sided strokes are more often recognized than right-sided strokes: the Rotterdam Study. *Stroke*. 2015;46:252–254. doi: 10.1161/STROKEAHA.114.007385
52. Azarkish K, Mahmoudi K, Mohammadifar M, Ghajarzadeh M. Mean right and left carotid intima-media thickness measures in cases with/without coronary artery disease. *Acta Med Iran*. 2014;52:884–888.
53. Nezu T, Hosomi N, Aoki S, Matsumoto M. Carotid intima-media thickness for atherosclerosis. *J Atheroscler Thromb*. 2016;23:18–31. doi: 10.5551/jat.31989
54. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, Tokgözoğlu L, Lewis EF. Atherosclerosis. *Nat Rev Dis Primers*. 2019;5:56. doi: 10.1038/s41572-019-0106-z
55. Vijayvergiya R, Vadivelu R. Role of Helicobacter pylori infection in pathogenesis of atherosclerosis. *World J Cardiol*. 2015;7:134–143.

SUPPLEMENTAL MATERIAL

Table S1. PRISMA checklist.

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they	7

Section and Topic	Item #	Checklist item	Reported on page #
		worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6-9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6-9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	10
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8-9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results	9

Section and Topic	Item #	Checklist item	Reported on page #
		of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	10
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	10-11
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	14-17
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	19-20
Results of	19	For all outcomes, present, for each study: (a) summary statistics	14-19

Section and Topic	Item #	Checklist item	Reported on page #
individual studies		for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	19-20
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	14-19
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	14-19
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	14-15
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	19-21
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	21-23
	23b	Discuss any limitations of the evidence included in the review.	23
	23c	Discuss any limitations of the review processes used.	23
	23d	Discuss implications of the results for practice, policy, and future research.	24
OTHER INFORMATION			

Section and Topic	Item #	Checklist item	Reported on page #
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	25
Competing interests	26	Declare any competing interests of review authors.	25
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

NA: not applicable

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Table S2. Characteristics of the CIMT measurement.

Study	Definition of CIMT	Area of CIM measurement	Calculation of the overall CIMT	Machine
Bao-Ge *et al.*[20] 2017	inner surface of the inner membrane - external surface of the tunica media	1 cm proximal to the CCA bifurcation in the left and right CCAs	mean of three separate values	3.5–5 MHz convex probe and a high-resolution B-mode ultrasound scanner
Başyığıt *et al.*[34] 2012	leading edge of the lumen intimal interface -leading edge of the media adventitia interface of the far wall	NI	mean of right and left values	high-resolution grey-scale Doppler ultrasonography
Diomedi *et al.*[24] 2004	NI	1.5 cm proximal to the CCA flow divider	mean of the maximum wall thickness for the near and far wall on the left and right side	continuous-wave Doppler and color flow B-mode Doppler ultrasound (Esaote Biomedica, Genova, Italy) with a high-resolution 7.5-MHz linear array-imaging probe
El Hadidy *et al.*[26] 2009	NI	NI	NI	B mode grey scale ultrasound
Hamed *et al.*[21] 2008	NI	1 cm before carotid bifurcation	mean of the two sides	5-MHz linear transducer of a color duplex flow imaging system (128 XP, Acuson Corp, Mountain View, Calif), modes: real-time B, color, and spectral Doppler

Judaki *et al.*[35] 2017	NI	NI	average of the measurements of left and right common CIMT	B-mode ultrasonography (Esaote, MylabTM 70 Co., Italy) using a high-resolution, 18-MHz linear array transducer
Karadag *et al.*[4] 2018	distance between the lumen and the intima and the distance between the media and adventitia	1 cm proximal to the carotid bifurcation	average value of the eight measurements on four with 1 mm distant adjacent localizations of the right and left carotid arteries	NI
Köksal *et al.*[22] 2004	distance between the echoes arising from the intima-media interface and media-adventitia interface	1 cm before the carotid bifurcation at the far wall of the CCA	At least 6 longitudinal and cross-sectional measurements of both CCAs were summarized and a mean CIMT was calculated	linear-array real-time ultrasound equipment with a 7.5-MHz transducer (GE LOGIQ MD 400, Milwaukee, Wisc., USA)
Mayr *et al.*[25] 2003	lumen-intima interface - leading edge of the media-adventitia interface on the far wall	CCA proximal and distal segments on either side	NI	10-MHz imaging probe and 5-MHz Doppler
Mete *et al.*[27] 2013	viewable distance between the lumen-intima interface and the mediaadventitia interface	distal 1 cm of CCAs on both sides	CIMT measurements taken from both sides were averaged	grey scale high-resolution color Doppler ultrasound Esaote MyLab 50 (Genoa, Italy) equipped with a 5-12-MHz linear transducer
Shan *et al.*[36] 2018	mean of the maximal intimamedia thickness of the near and far walls	1 cm proximal to the flow divider on the distal wall of the CCA	The average of the left and right CIMT values	M-mode examinations, Philips iE33 Ultrasound System, Holland)

Xu *et al.*[37] 2016	leading edge of the media adventitia interface of the far wall - the leading edge of the lumen intimal interface	1 and 2 cm away from the bifurcation, and the average of the two measurements	mean value between the right and left CCAs	Toshiba 790A color Doppler system (Toshiba Medical Systems Corporation, Ottawa, Tochigi, Japan) with a 10 MHz transducer
Feng *et al.*[23] 2018	vertical distance from the edge of the first to the second echogenic line	1.5 cm proximal to the carotid bifurcation	The average CIMT was obtained from three independent measurements in the bilateral CCAs	Doppler ultrasound machine (Siemens G50, Germany) with a 7.5MHz transducer

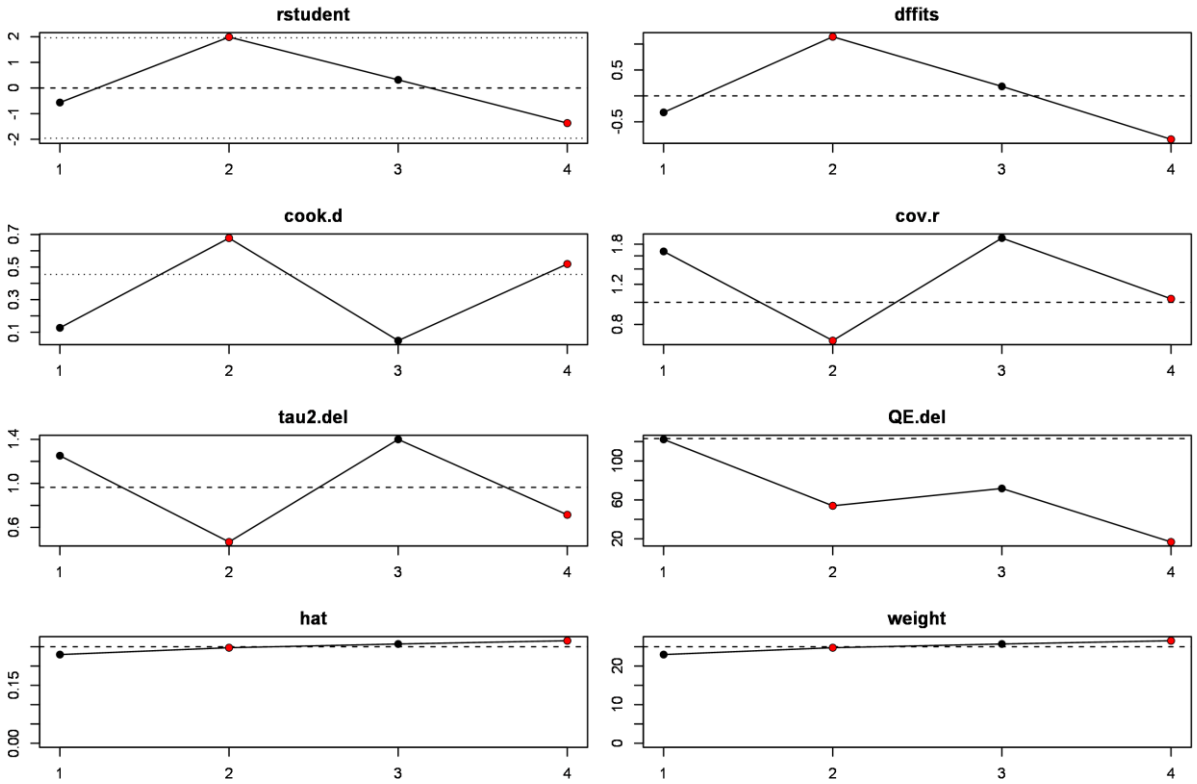
CIM: carotid intima-media, CIMT: carotid intima-media thickness, cm: centimeter, CCA: common carotid artery, NI: no information

Table S3. Comparison between *H. pylori* positive and negative participants.

Study	N⁰ of patients	*H. pylori* positivity				*H. pylori* negativity			
		N⁰ of patients	Sex (female%)	Age (mean±SD)	Overall CIMT (mean±SD)	N⁰ of patients	Sex (female%)	Age (mean±SD)	Overall CIMT (mean±SD)
Bao-Ge *et al.*[20] 2017 I.	78	41	12.2	46.37±7.37*	0.84±0.25*	37	8.11	46.72±6.89*	0.76±0.16*
Bao-Ge *et al.*[20] 2017 II.	82	35	8.57	46.74±6.69*	0.71±0.19*	47	12.77	46.66±6.75*	0.7±0.16*
Başyığıt *et al.*[34] 2012	61	30	53.33	40.9±10.3	O: 0.71±0.1 L: 0.72±0.14 R: 0.7±0.09	31	51.61	42.3±9.4	O: 0.65±0.06 L: 0.67±0.08 R: 0.64±0.06
Diomedi *et al.*[24] 2004	124	85	36.47	68.8±9.8	1.13±0.26	39	46.15	66.9±15.8	1.01±0.17
El Hadidy *et al.*[26] 2009	60	23	82.61	NI	L: 8.08±1.54 R: 7.78±1.41	37	67.57	NI	L: 8.21±1.62 R: 8.16±1.69
Hamed *et al.*[21] 2008 I.	80	68	48.53	47.6±9.1	0.84±0,17	12	66.67	48.2±9.3	0.78±0.1
Hamed *et al.*[21] 2008 II.	60	46	39.13	46.2±9.7	0.62±0.08	14	42.86	50.2±6.5	0.58±0.1
Judaki *et al.*[35] 2017	80	40	55	45.64±8.32	0.58±0.13	40	42.5	46.52±5.52	0.48±0.32
Karadag *et al.*[4] 2018	45	24	50	50±8.2	0.78±0.11	21	57.14	52±7.9	0.67±0.08
Köksal *et al.*[22] 2004 I.	84	63	73.02	46.7±14.7	0.85±0.38	21	66.67	45.1±7.1	0.88±0.3
Köksal *et al.*[22] 2004 II.	50	30	66.67	45±11	0.56±0.19	20	70	45±10	0.67±0.13
Mayr *et al.*[25] 2003	421	285	47	56.6†	0.986±0.184	136	49	55.7†	0.991±0.189
Mete *et al.*[27] 2013	134	103	57.29	49.8±8.7	O: 0.73 (0.34-1.35)‡ L: 0.74 (34-1.6)‡ R: 0.72 (34-1.2)‡	31	61.29	50.2±9.33	O: 0.57 (0.44-0.70)‡ L: 0.55 (0.44-0.67)‡ R: 0.57 (0.4-0.85)‡
Shan *et al.*[36] 2018	395	186	NI	NI	L: 0.65±0.01 R: 0.65±0.01	209	NI	NI	L: 0.63±0.01 R: 0.61±0.01
Xu *et al.*[37] 2016	364	208	46.15	63.2±10.4	1.12±0.18	156	48.1	62.8±11.7	0.93±0.15
Feng *et al.*[23] 2018 I.	89	51	19.61	46.1±0.58*	0.84±0.009*	38	21.05	46.79±0.63*	0.76±0.013*
Feng *et al.*[23] 2018 II.	91	42	21.43	46.64±0.54*	0.75±0.011*	49	22.45	46.61±0.53*	0.75±0.009*

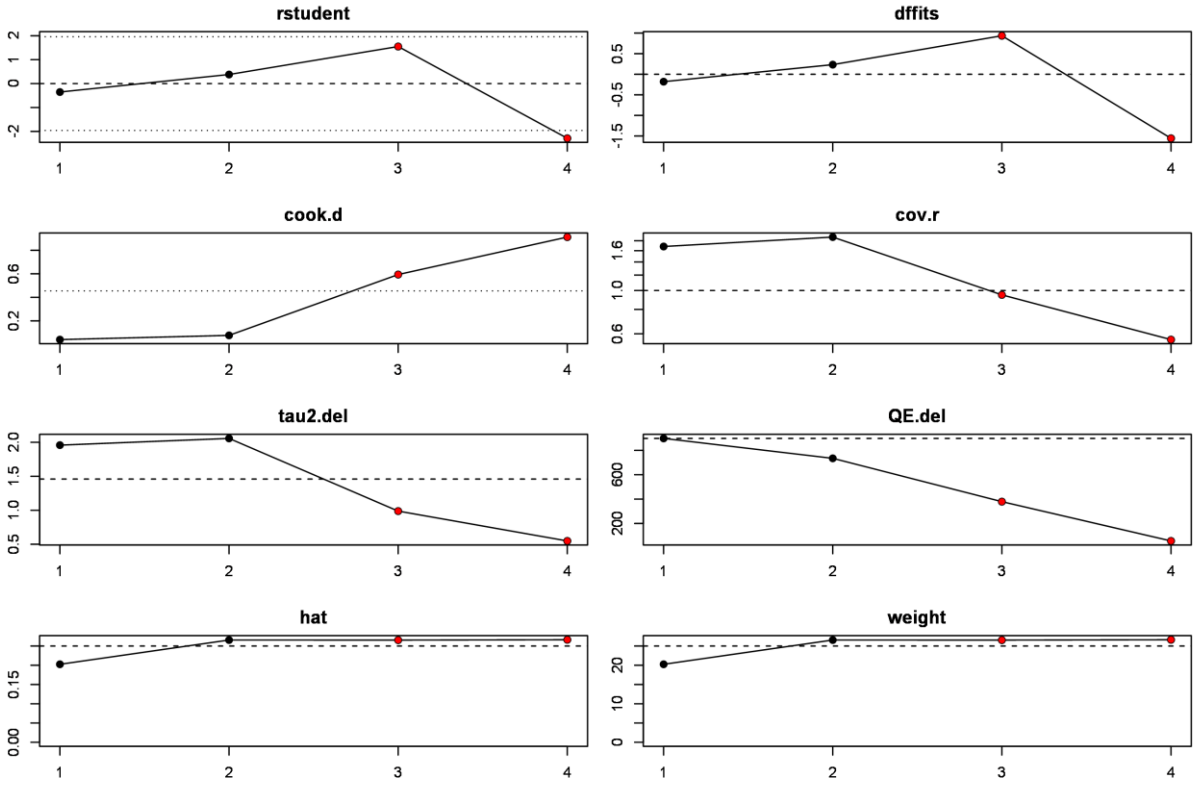
*mean±SE, † mean without SD, ‡ median (min-max), HP: *H. pylori*, SD: standard deviation, SE: standard error, NI: no information, CIMT: carotid intima-media thickness, O: overall, L: left, R: right

Figure S1. Influence diagnostics of the four included studies in the right carotid intima-media thickness analyses with various methods (Externally Standardized Residuals (rstudent), DFFITS value, Cook's Distance, Covariance Ratio, tau2, Qvalues, Hat & Weight).



1: Başyığıt *et al.* [23] (2012), 2: El Hadidy *et al.* [26] (2009), 3: Mete *et al.* [27] (2013), 4: Shan *et al.* [36] (2018).

Figure S2. Influence diagnostics of the four included studies in the left carotid intima-media thickness analyses with various methods (Externally Standardized Residuals (rstudent), DFFITS value, Cook's Distance, Covariance Ratio, tau2, Qvalues, Hat & Weight).



1: Başyığıt *et al.* [23] (2012), 2: El Hadidy *et al.* [26] (2009), 3: Mete *et al.* [27] (2013), 4: Shan *et al.* [36] (2018).

Figure S3. Sensitivity analyses of the four included studies in the right and in the left carotid intima-media thickness analyses.

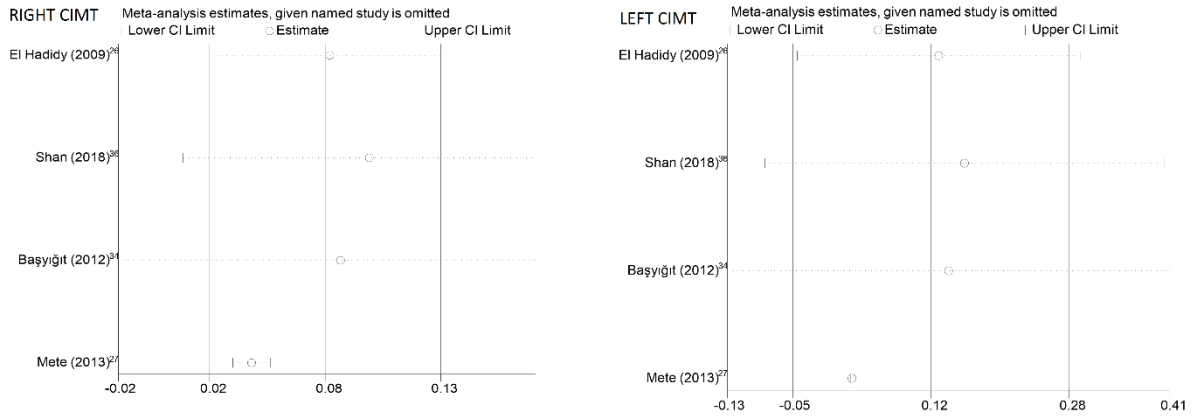
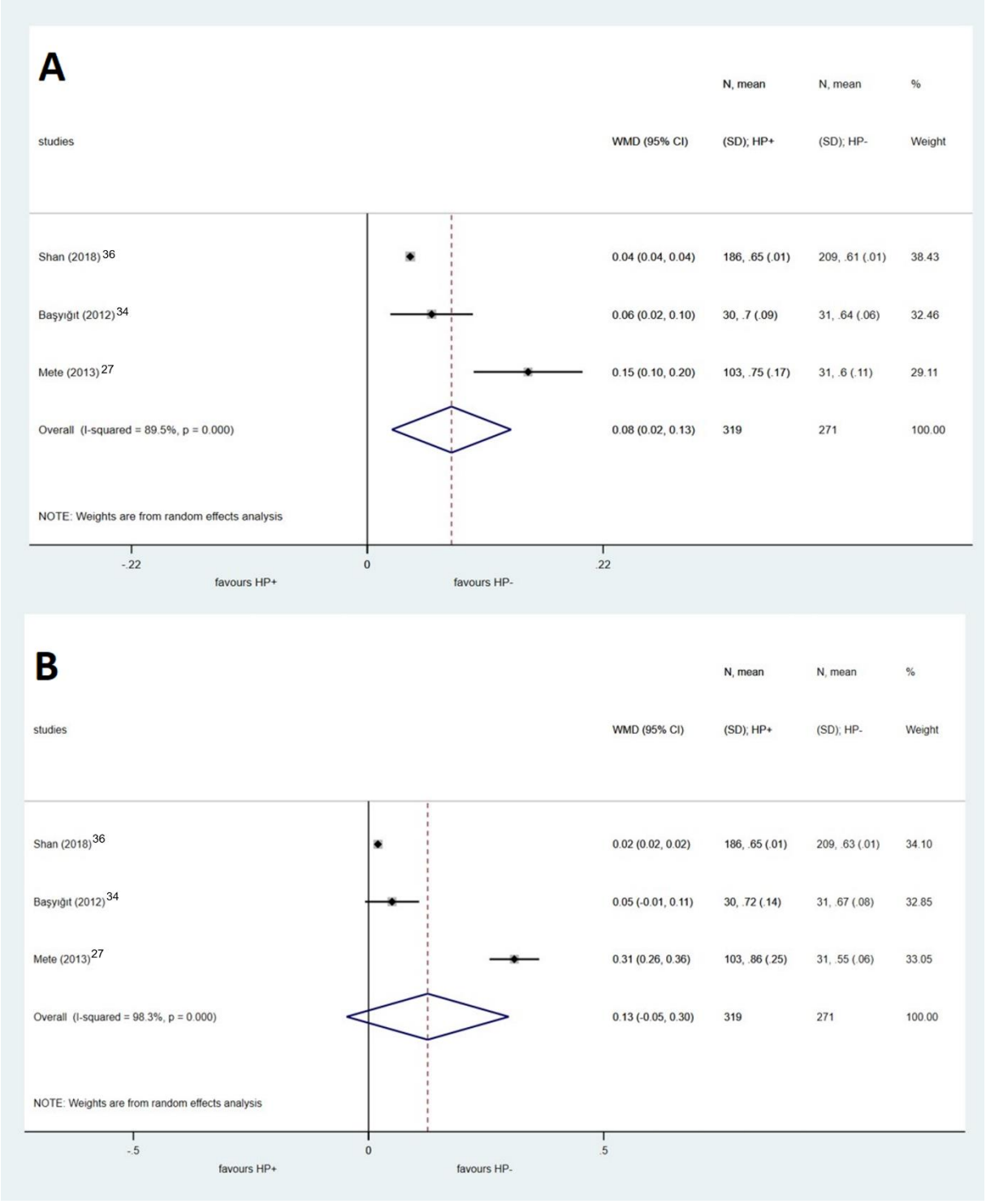


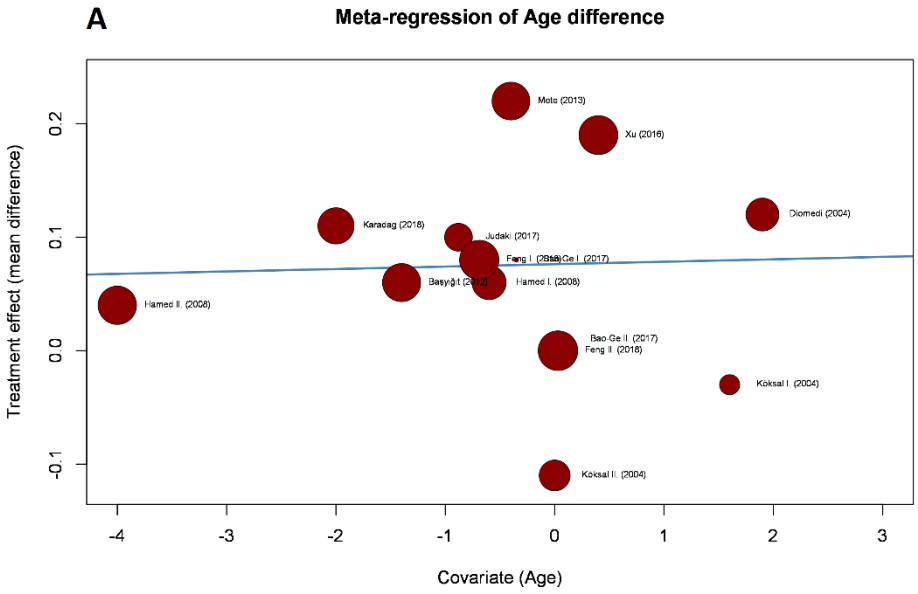
Figure S4. Forest plot of studies comparing right (A) and left (B) carotid intima-media thickness between *Helicobacter pylori* positive and negative individuals without the study published by El Hadidy *et al.*

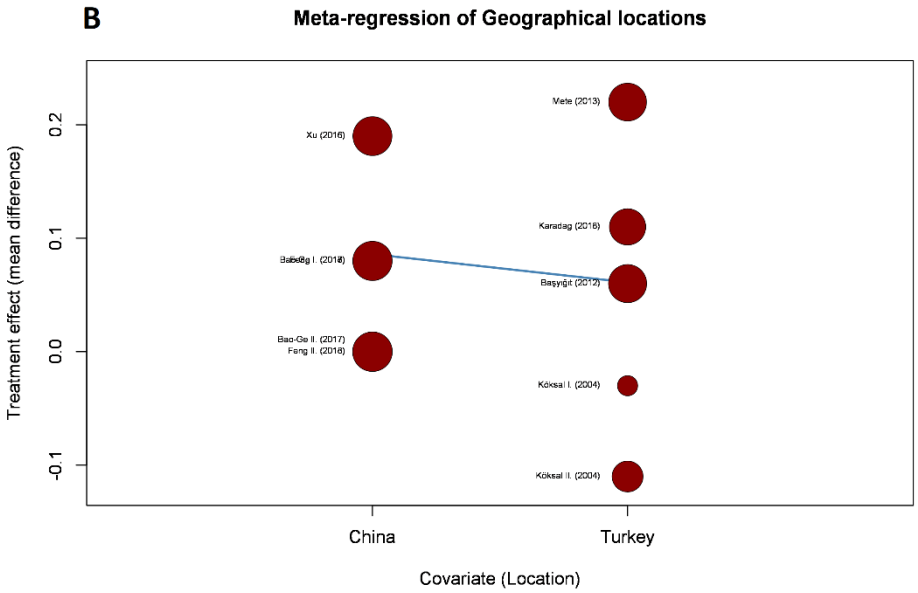


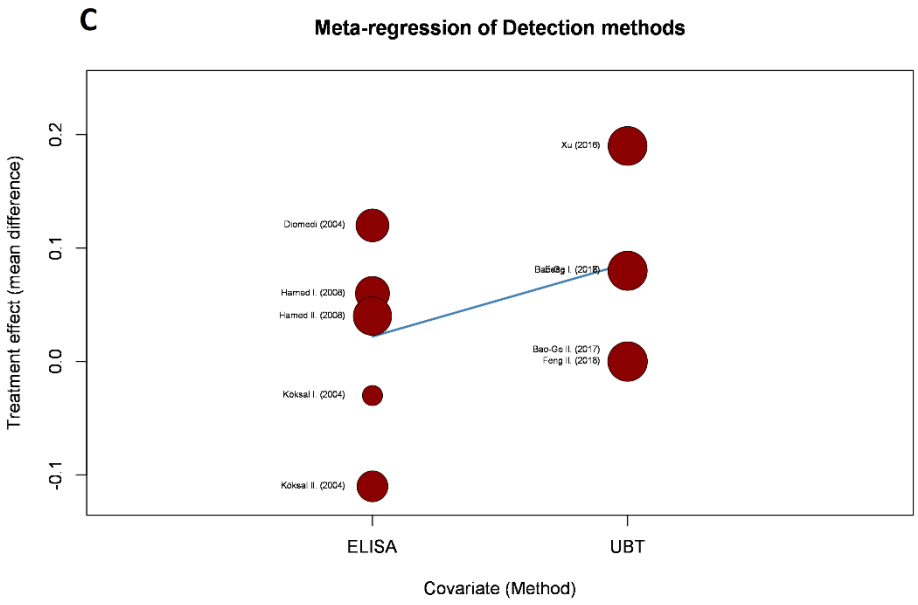
Black diamonds represent the weighted mean difference between the two groups we compared and horizontal lines show the corresponding 95% confidence intervals (CI). Size of the grey

squares reflect the weight of a particular study. The blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs.

Figure S5. A, Meta-regression of age difference. X-axis represents age. The estimate predicts the increase of the effect size, if one was added to the predictor (age, continuous variable) B, Meta-regression of geographical location. X-axis represents the geographical locations, China and Turkey. The estimate predicts the decrease of the effect size, if Turkey was compared to China. C, Meta-regression of detection method. X-axis represents the detection methods, enzyme-linked immunosorbent assay and urea breath test. The estimate predicts the increase of the effect size, if urea breath test was compared to enzyme-linked immunosorbent assay.

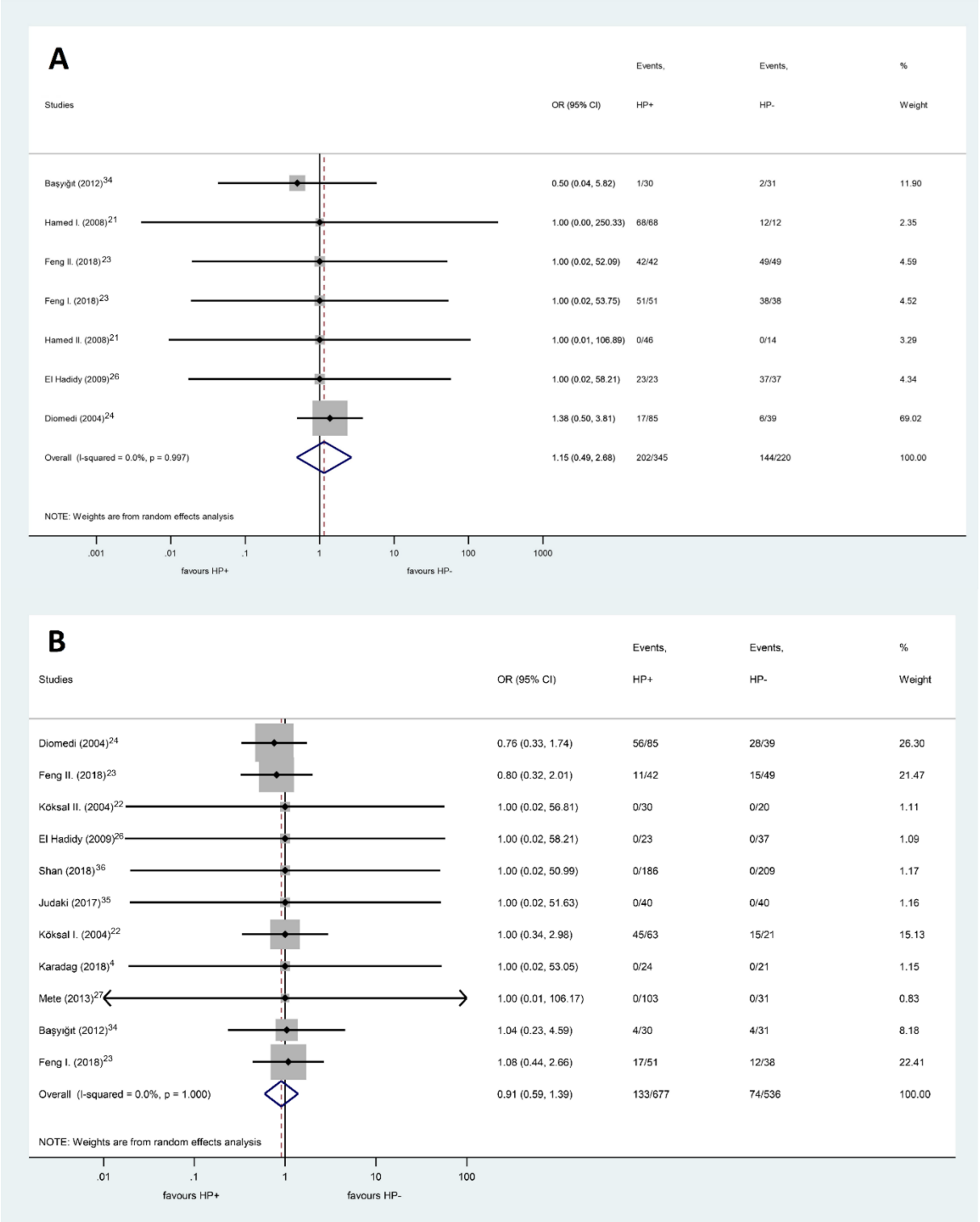

A
Meta-regression of Age difference
Mete (2013)
Xu (2016)
Diomedi (2004)
Karadag (2016)
Judaki (2017)
Hamed I. (2008)
Hamed II. (2008)
Bao-Ge II. (2017)
Feng II. (2016)
Köksal I. (2004)
Köksal II. (2004)
Treatment effect (mean difference)
Covariate (Age)


B
Meta-regression of Geographical locations
Mete (2013)
Xu (2016)
Karadag (2016)
Başyiğit (2012)
Bao-Ge II. (2017)
Feng II. (2016)
Köksal I. (2004)
Köksal II. (2004)
China
Turkey
Treatment effect (mean difference)
Covariate (Location)


C
Meta-regression of Detection methods
Xu (2016)
Diomedi (2004)
Hamed I. (2008)
Hamed II. (2008)
Bao-Ge II. (2017)
Feng II. (2016)
Köksal I. (2004)
Köksal II. (2004)
ELISA
UBT
Treatment effect (mean difference)
Covariate (Method)

In all cases, Y-axis represents the weighted mean differences of overall carotid intima-media thickness in articles reporting these results. Each red dot represents one of these articles.

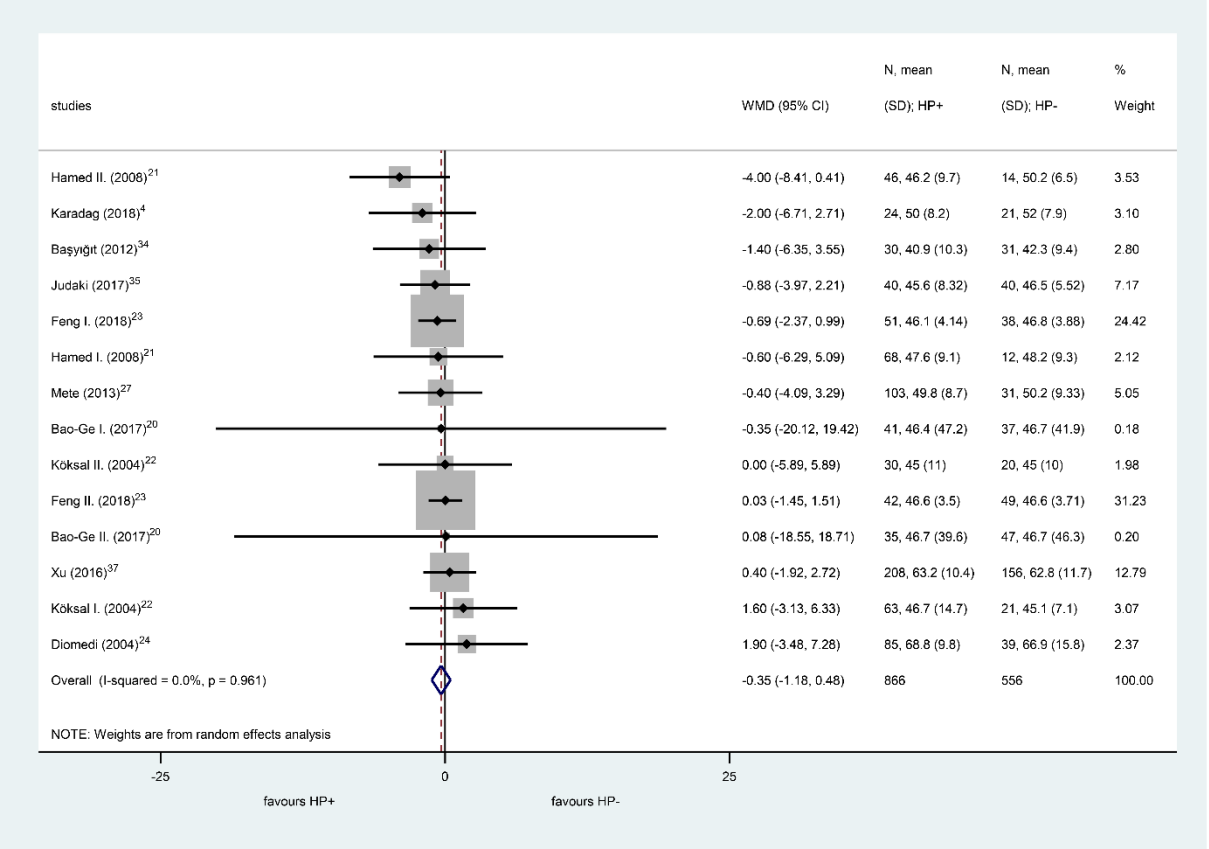
Figure S6. Forest plot of studies comparing the prevalence of diabetes mellitus (A) and hypertension (B) between *Helicobacter pylori* positive and negative individuals.



Black diamonds represent the odds ratios and horizontal lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflect the weight of a particular study. The

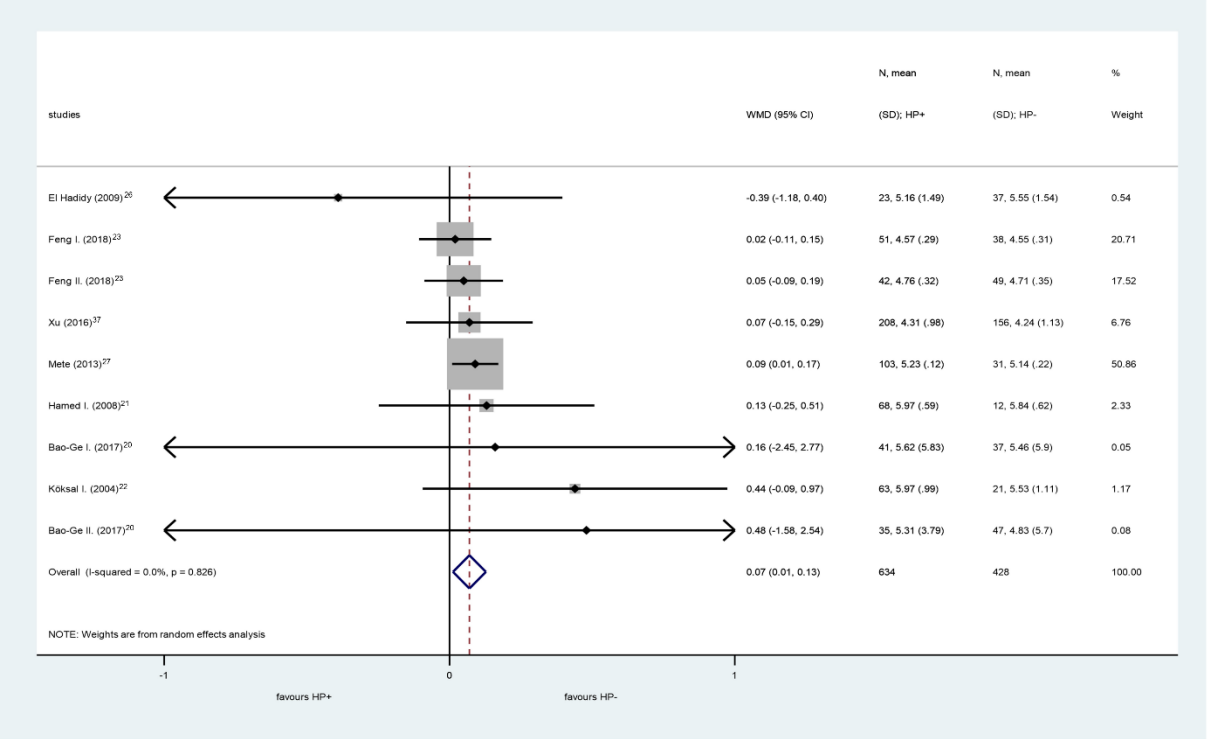
blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs.

Figure S7. Forest plot of studies comparing the mean age between *Helicobacter pylori* positive and negative individuals.



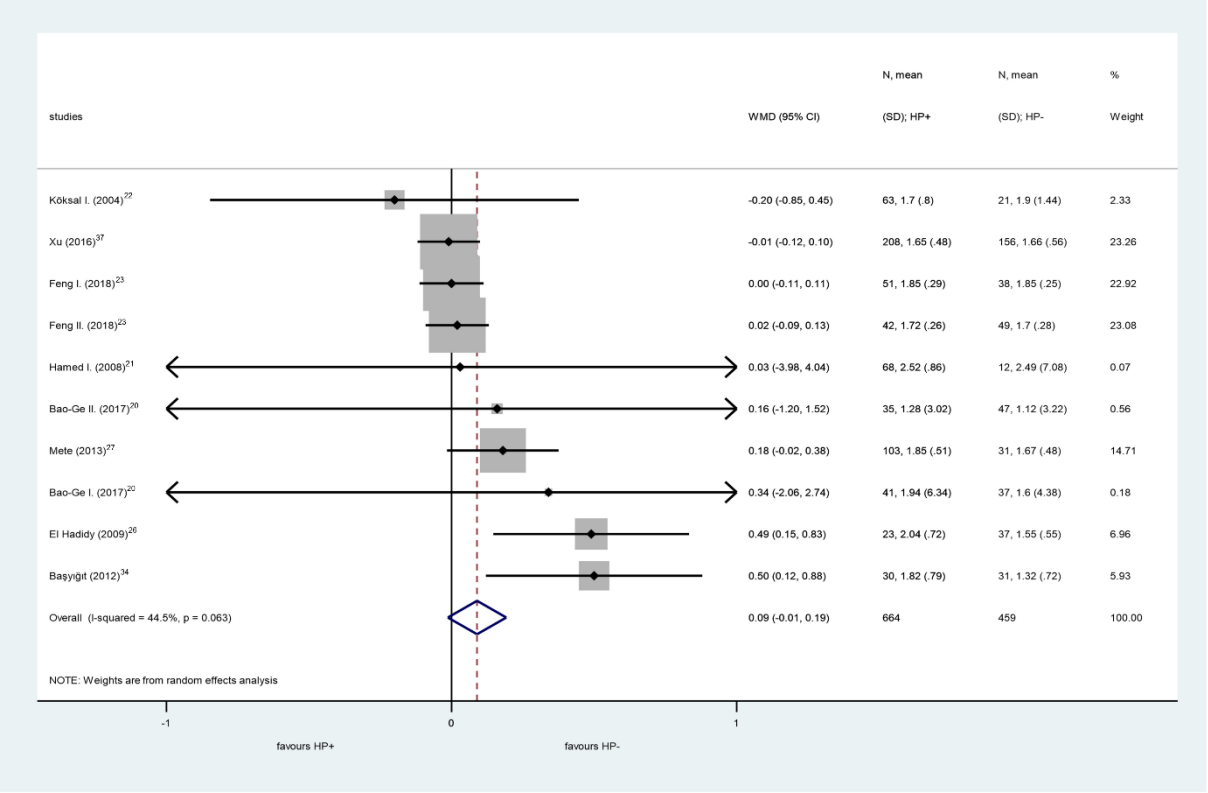
Black diamonds represent the weighted mean difference between the two groups we compared and horizontal lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflect the weight of a particular study. The blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs.

Figure S8. Forest plot of studies comparing total cholesterol levels between *Helicobacter pylori* positive and negative individuals.



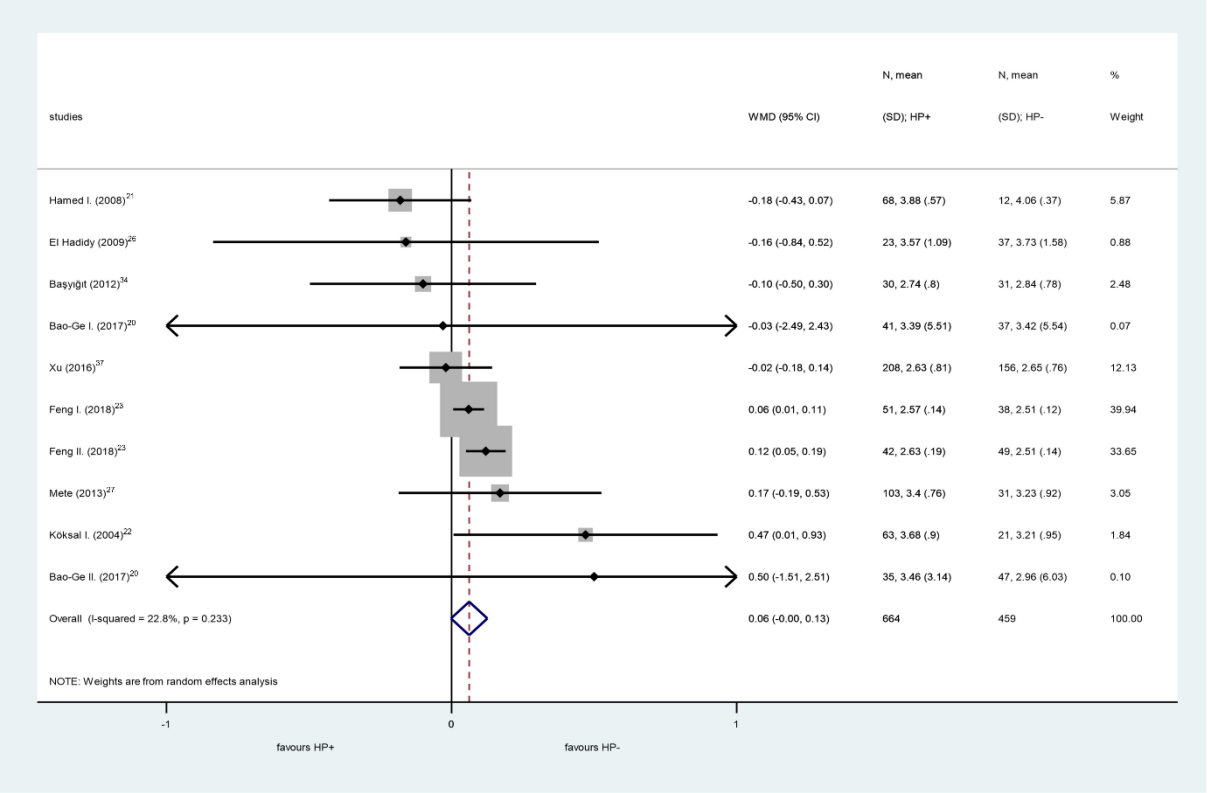
Black diamonds represent the weighted mean difference between the two groups we compared and horizontal lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflect the weight of a particular study. The blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs.

Figure S9. Forest plot of studies comparing triglyceride levels between *Helicobacter pylori* positive and negative individuals.



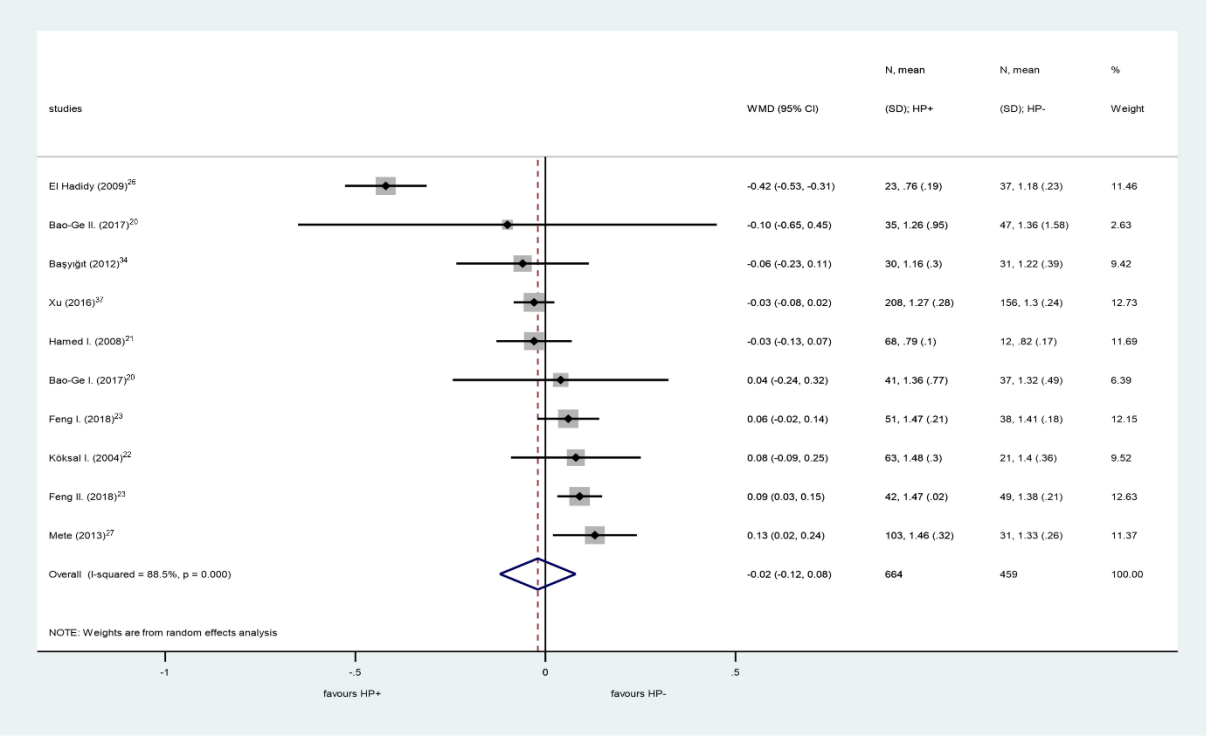
Black diamonds represent the weighted mean difference between the two groups we compared and horizontal lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflect the weight of a particular study. The blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs.

Figure S10. Forest plot of studies comparing low-density lipoprotein levels between *Helicobacter pylori* positive and negative individuals.



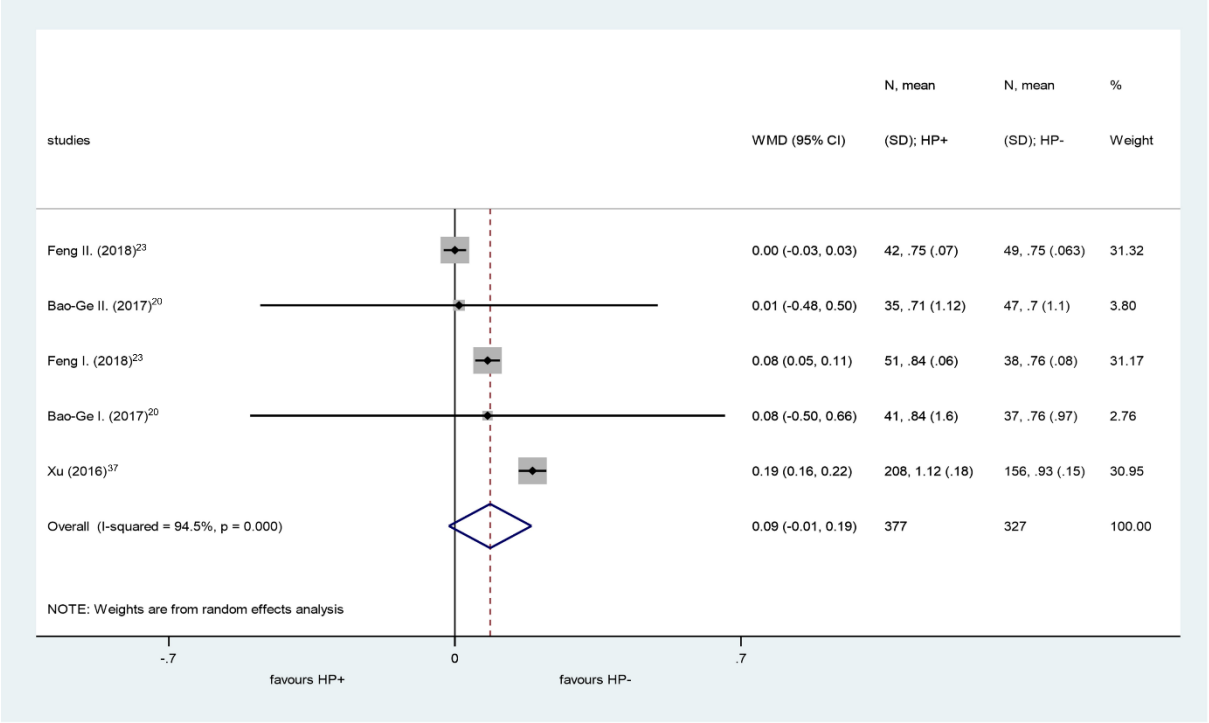
Black diamonds represent the weighted mean difference between the two groups we compared and horizontal lines show the corresponding 95% confidence intervals. Size of the grey squares reflect the weight of a particular study. The blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs.

Figure S11. Forest plot of studies comparing high-density lipoprotein levels between *Helicobacter pylori* positive and negative individuals.



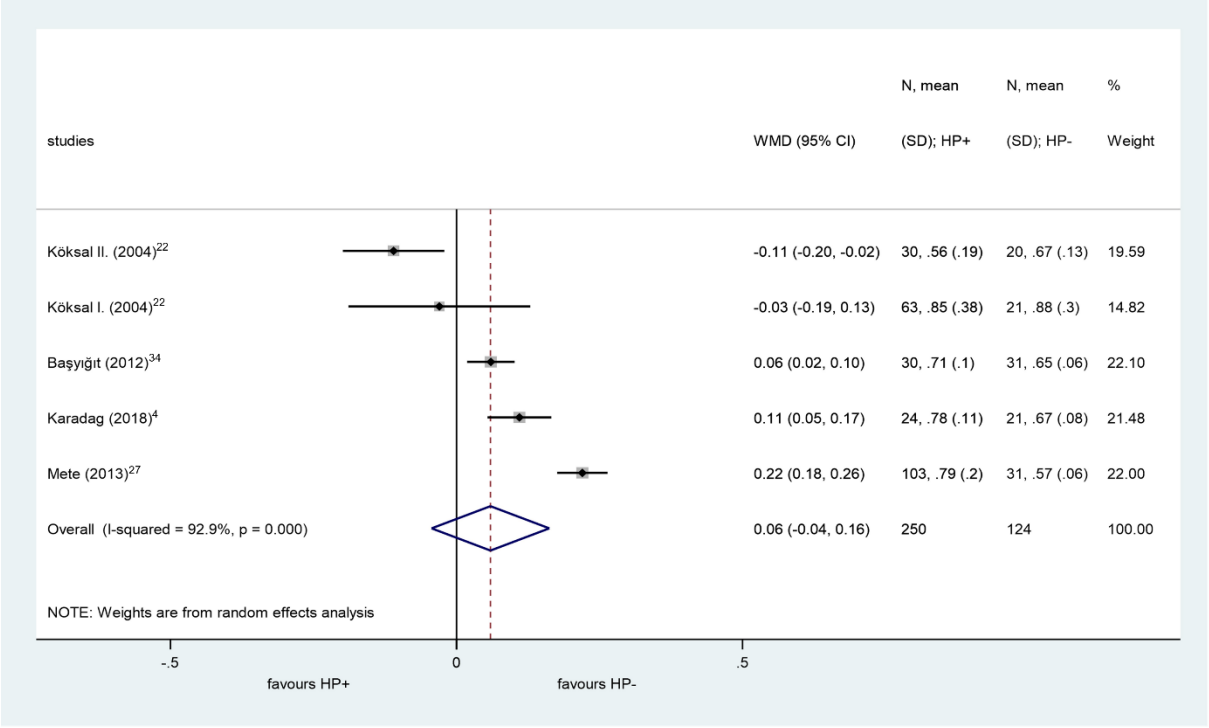
Black diamonds represent the weighted mean difference between the two groups we compared and horizontal lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflect the weight of a particular study. The blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs.

Figure S12. Forest plot of studies comparing overall carotid intima-media thickness between *Helicobacter pylori* positive and negative Chinese individuals.



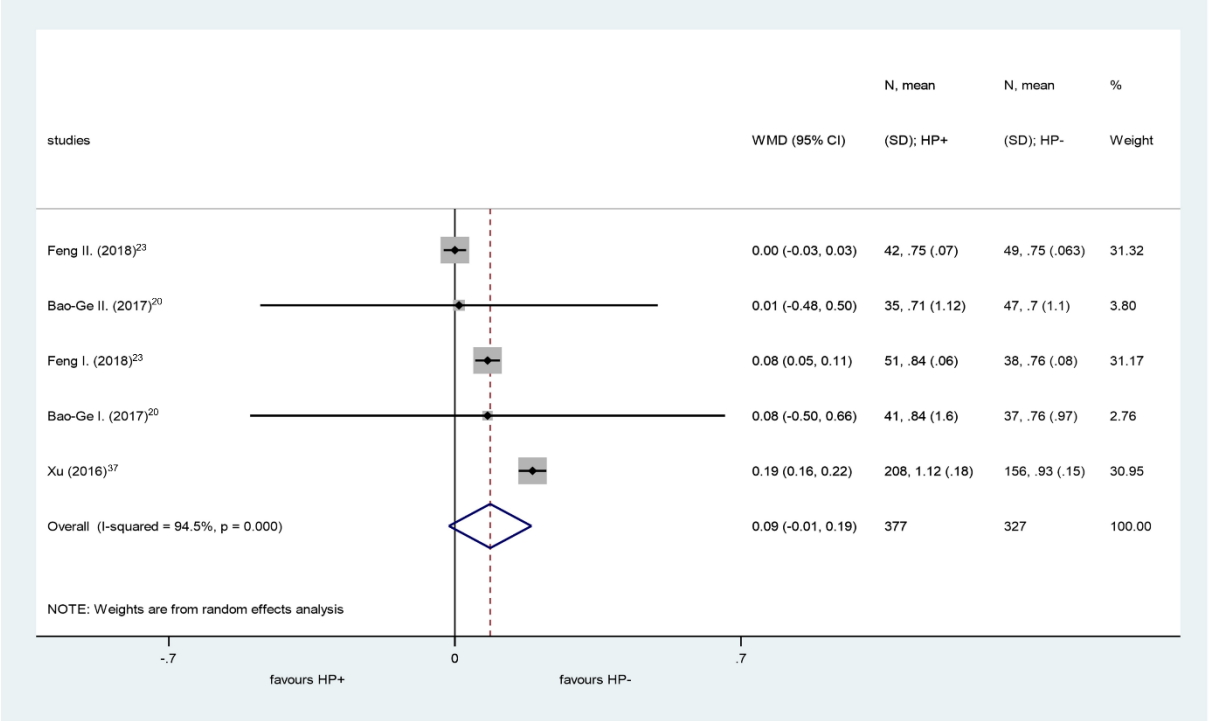
Black diamonds represent the weighted mean difference between the two groups we compared and horizontal lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflect the weight of a particular study. The blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs.

Figure S13. Forest plot of studies comparing overall carotid intima-media thickness between *Helicobacter pylori* positive and negative Turkish individuals.



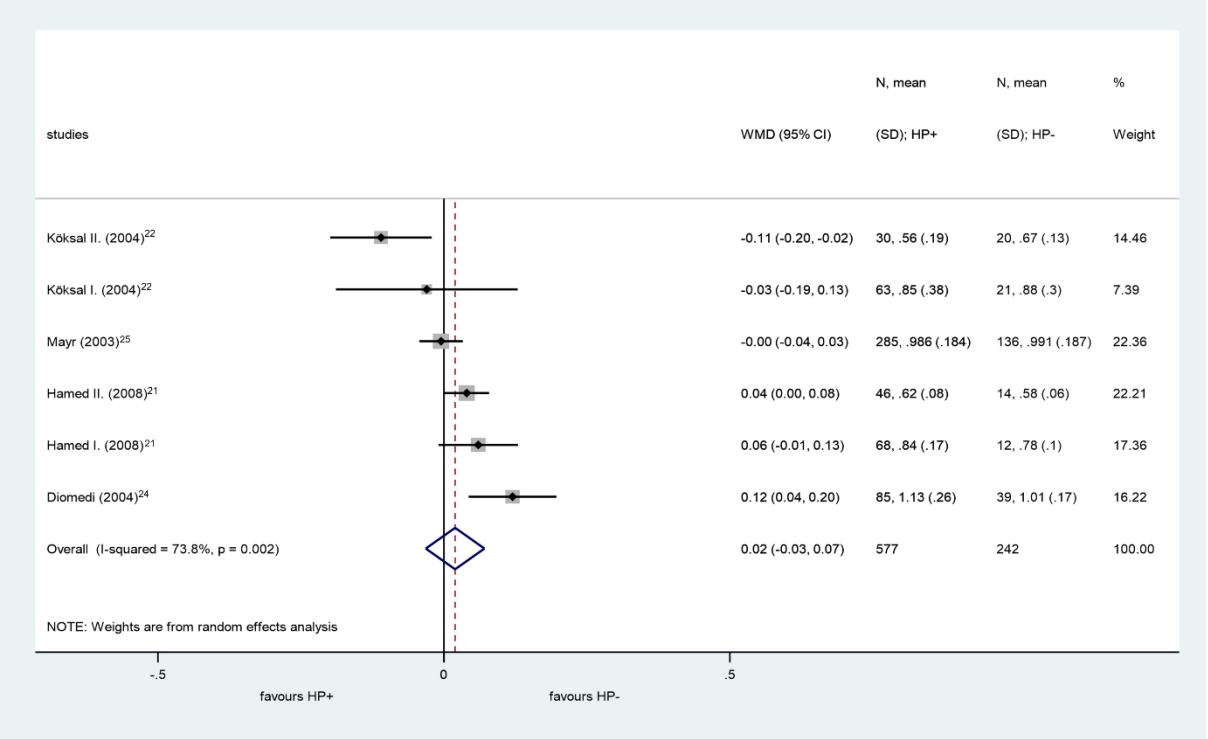
Black diamonds represent the weighted mean difference between the two groups we compared and horizontal lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflect the weight of a particular study. The blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs.

Figure S14. Forest plot of studies comparing overall carotid intima-media thickness between *Helicobacter pylori* positive and negative individuals if the pathogen was detected by urea breath test.



Black diamonds represent the weighted mean difference between the two groups we compared and horizontal lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflect the weight of a particular study. The blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs.

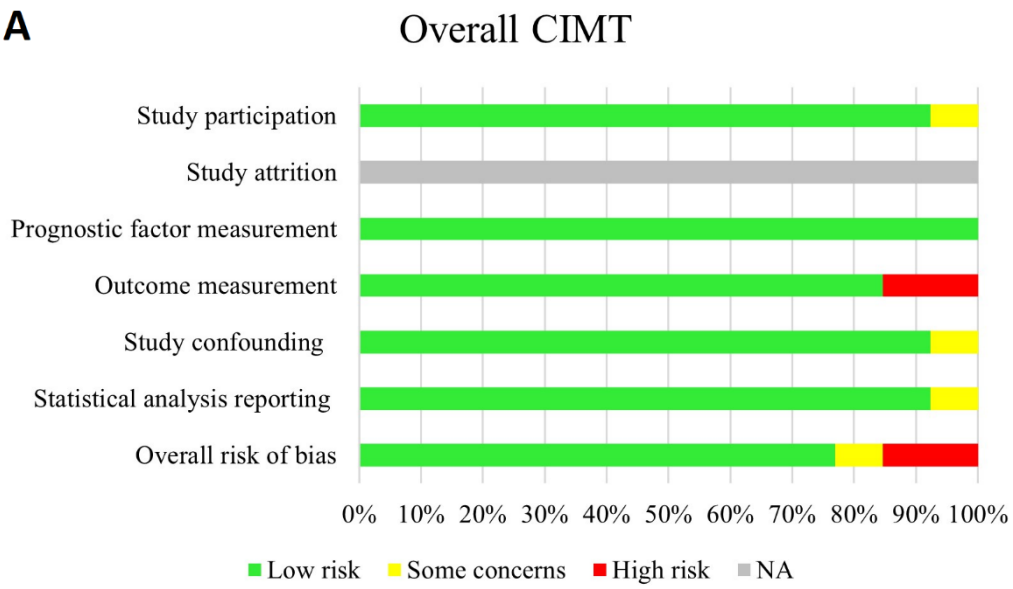
Figure S15. Forest plot of studies comparing overall carotid intima-media thickness between *Helicobacter pylori* positive and negative individuals if the pathogen was detected by enzyme-linked immunosorbent assay.



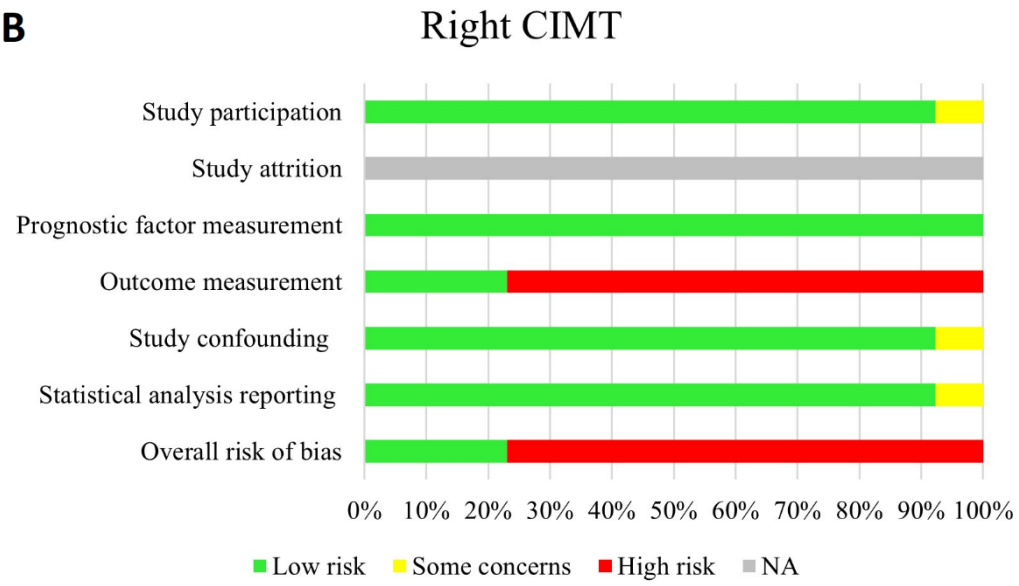
Black diamonds represent the weighted mean difference between the two groups we compared and horizontal lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflect the weight of a particular study. The blue diamond is the overall or summary effect. The outer edges of the diamonds represent the CIs.

Figure S16. Bar charts for all domains separately included in risk of bias assessment of overall (A), right (B) and left (C) carotid intima-media thickness.

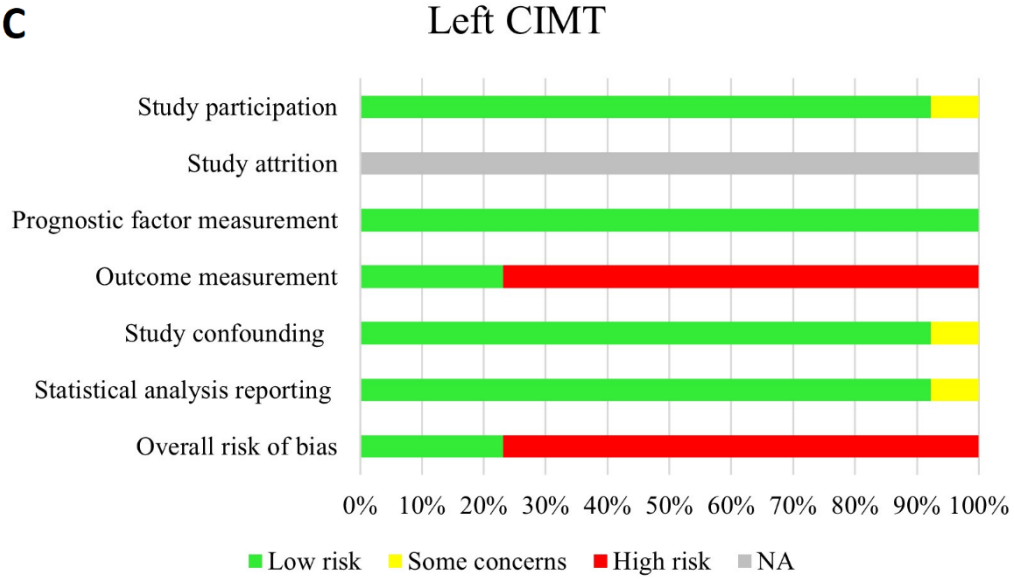
A


Overall CIMT
Study participation
Study attrition
Prognostic factor measurement
Outcome measurement
Study confounding
Statistical analysis reporting
Overall risk of bias
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Low risk
Some concerns
High risk
NA

B

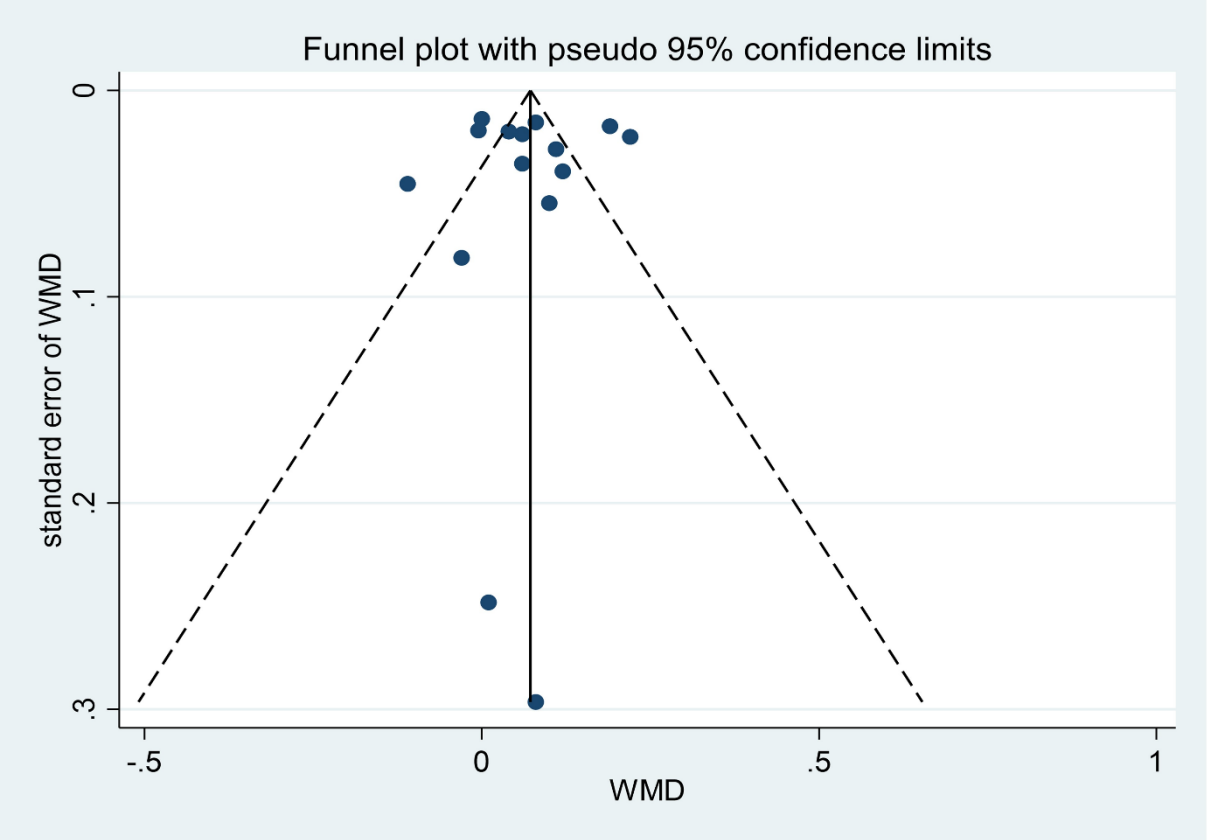

Right CIMT
Study participation
Study attrition
Prognostic factor measurement
Outcome measurement
Study confounding
Statistical analysis reporting
Overall risk of bias
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Low risk
Some concerns
High risk
NA

C


Left CIMT
Study participation
Study attrition
Prognostic factor measurement
Outcome measurement
Study confounding
Statistical analysis reporting
Overall risk of bias
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Low risk
Some concerns
High risk
NA

Green represents low risk of bias, yellow represents moderate and red represents high risk of bias. Grey represents non-applicability of the subdomain for the study. X-axis represents the percentage of each risk and the domains are represented on Y-axis.

Figure S17. Funnel plot of studies comparing overall carotid intima-media thickness between *Helicobacter pylori* positive and negative individuals.



X-axis represents the weighted mean difference between the two groups we compared. Y-axis represents the standard error of weighted mean difference. The vertical is for overall effect. The dashed lines represent the 95% confidence intervals. Each spot represents an included study of the specific analysis.