



Association of *Helicobacter pylori* and Coronary heart disease in Iran: A meta-analysis

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Abstract

Background: Several studies in the recent decade have supported a relationship between different types of infections and CHD (Coronary Heart Disease); however, such a relationship is not definitely proven. *Helicobacter pylori* is one of the most common infections in human. The role of inflammation in the pathogens of CAD (Coronary Artery Disease) has been widely discussed; although, the mechanism is not clearly known yet.

Methods: In this systematic review and meta-analysis all case-control articles on the relationship between *Helicobacter pylori* and CHD published from 31st June 2000 to 31st June 2016 indexed in Scopus, PubMed, Google Scholar, Science Direct, and Iranian databases Magiran, Iran Medex, Irandoc, and SID were included. The articles were searched using the following keywords in Farsi and English. The extracted data was imported into Microsoft Excel and analyzed in Stata 12.

Results: Thirty case-control studies conducted in different regions of Iran (15 provinces) have been published from 2001 to 2015 included in this study. A general estimate of OR (Odds Ratio) for the association of *Helicobacter pylori* and heart diseases in Iran was 2.351 (95 CI: (1.715, 3.221)).

Conclusion: According to the observed association between *Helicobacter pylori* and heart diseases in the recent study, most of the hosts of the bacterium are afflicted with the infection in their childhood. Therefore, personal hygiene promotion and preventive programs for Iranian children may have a considerable role in reducing the risk of the infection and cardiovascular diseases, consequently.

Keywords: Coronary heart disease, *Helicobacter pylori*, Iran, Meta-analysis

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Introduction

Several studies in the recent decade have supported a relationship between different types of infections and CHD (Coronary Heart Disease); however, such a relationship is not definitely proven. Bacteria such as *Helicobacter pylori* have been found effective on the development of atherosclerosis (1, 2). Prevalence of *Helicobacter pylori* infection in Iran exceeds 80%; although, this rate has started a declining trend in the recent years (3). There is a mutual relationship between the infection and hygiene condition in the society, so that prevalence of the infection is high in

the developing countries including Iran.(4).

The role of inflammation mechanism in pathogens and progress of CAD (Coronary Artery Disease) has been widely discussed; although, the mechanism is not clearly known yet. It is believed that the chronic inflammation caused by chronic infections (e.g. *Helicobacter pylori*) may result in advanced atherosclerosis and CAD consequently (2). Rajasekhar et al. showed in their study that high levels of C-reactive protein, lipids, lipoproteins, and coronary risk factors in the patients with unstable angina

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↑What is “already known” in this topic:

Several studies have reported a relationship between *Helicobacter* infection and ischemic heart disease, while some have rejected such a relationship. Since there are no study supporting a definite relationship between *Helicobacter pylori* infection and Coronary Heart Disease (CHD) in Iran, the present study was conducted to examine this theory.

→What this article adds:

The present study showed that there was a strong association between *Helicobacter pylori* and CHD in Iranian population so that the chance of CHD in patients with *Helicobacter pylori* was twofold higher than healthy people.

and positive *Helicobacter pylori* indicated that the pathogen may affect the risk factors of coronary arteries and had a role to play as a pathogen of atherosclerosis. Tamura et al. carried out a study in Japan and reported that *Helicobacter pylori* infection led atrophic gastritis into a chronic disease, which in turn reduced vitamin B12 in the plasma and folic acid level. These changes result in an increase in homocysteine level, which is a risk factor for atherosclerosis (5-7).

Several studies have reported a relationship between *Helicobacter* infection and IHD, while some have rejected such a relationship (8-11). Mandell et al. were the first group to examine the relationship between *Helicobacter pylori* infection and development of CHD and they found a significant relationship between the infection and the disease (12). Danesh and Peto carried out a meta-analysis of 18 epidemiologic studies on 10000 patients and concluded that there was no significant relationship between *Helicobacter pylori* and CHD (13). Khodaie et al. showed in their study that MI (Myocardial Infarction) was significantly higher in populations with a higher frequency of *Helicobacter* infection (14).

Given the above introduction and the diversity of the results about *Helicobacter* infection and coronary diseases, the necessity of carrying out a study to determine coronary disease prevalence in the population with *Helicobacter* infection is quite clear. Since there are no studies supporting a definite the relationship between *Helicobacter pylori* infection and CHD in Iran, the present study was conducted to confirm this theory.

Methods

Search strategy

In the systematic review and meta-analysis, all case-control articles on the relationship between *Helicobacter pylori* and CHD published from 31st June 2000 to 31st June 2016 indexed in Scopus, PubMed, Google Scholar, Science Direct, and Iranian databases including Magiran, Iran Medex, Irandoc, and SID were included. The articles were searched using the following keywords in Farsi and English. We tried to search titles and/or abstracts of articles published in all mentioned databases, simultaneously. Next, the numbers of searched articles were recorded for each database to calculate the total numbers of searched articles.

“*Helicobacter pylori*”, “H. pylori” combined with “cardiovascular disease”, “coronary heart disease”, “coronary artery disease”, “myocardial infarction”, “ischemic heart disease”, “arteriosclerotic heart disease”, “CHD”, “CVD”, or “CAD”.

Study selection and eligibility criteria

Two researchers carried out the search independently and the articles relevant to the purpose of this study were selected based on their title and/or abstract of the articles. In case of disagreement between the two researchers, a third expert assessed the quality of the article. The required data was collected based on the full text of the articles (**Error! Reference source not found.**). For the selection of the word to search, the population was

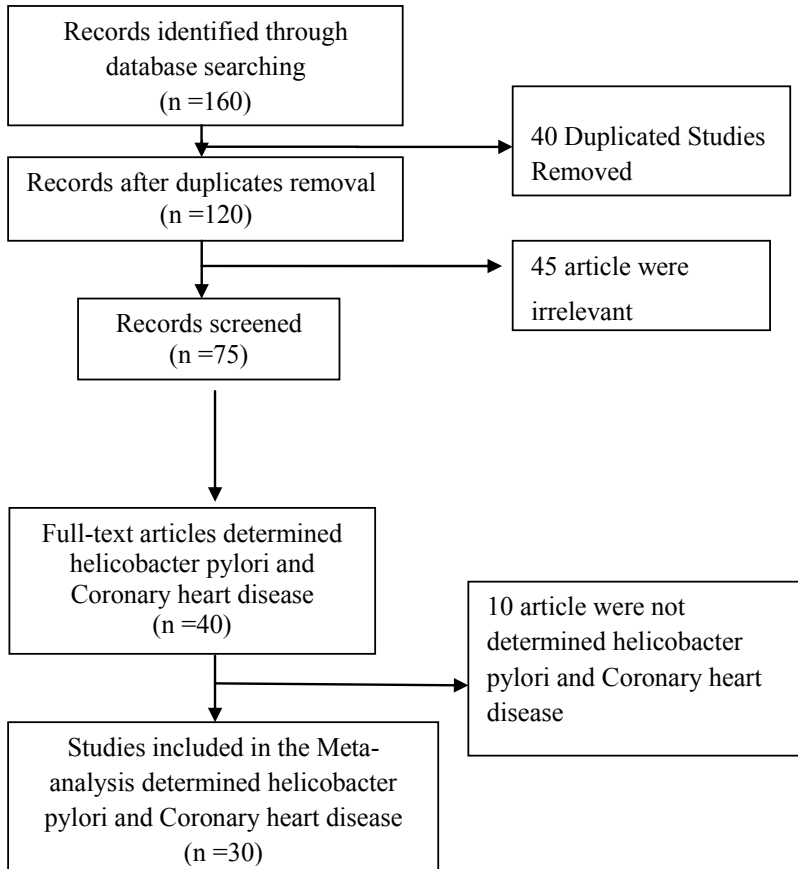


Fig.1. Flow diagram of study selection

CHD patients, comparisons are the controls do not have CHD, and the outcome was the presence of *H. pylori* antibodies in two groups.

Inclusion criteria

Case-control studies, carried out in Iranian cities or provinces, on OR (Odds Ratio) of coronary disease due to *Helicobacter pylori* infection were the inclusion criteria. In the case of articles available in two languages, the one published in a more creditable journal would be selected. Most of the papers reported IgG and IgA indices to determine *helicobacter pylori*, while only IgG index was used in this paper as the measure of infection.

Exclusion criteria

Ecologic, cohort, and cross-sectional studies and those that did not report OR and CI (95%) or the data to calculate them, and studies reporting unclear data or possible errors were excluded. The author's name or journal's name had no effect on the selection of articles.

Data extraction

After final assessment of the quality of the papers, the data was extracted using a self-administrated checklist. Then the data were entered into a data extraction sheet in Excel by one person. The checklist included name and surname of the first author, year of publication, place of the study, age/mean age of the subjects, gender, sample size, number of cases and controls, OR and CI (95%) extracted using IgG in the two groups under study. We included all articles without considering the methods of laboratory testing for *H. pylori* because our aim was to

analyse the total ORs for associations regardless of the clinical methods.

Statistical analysis

The extracted data were imported and analyzed in Stata 12. Based on the heterogeneity of the study (Cochran's Q-test, Higgins and Thompson's I^2), two statistical models of fixed effect and random effect (CI = 95%) random effects and Der Simonian and Laird methods, sensitivity analysis and Meta-regression method were used for data analyses. To assess the publication bias, Begg's and Egger's tests were used. In addition, sensitivity analysis and Meta-regression method were also used.

Results

Thirty case-control studies conducted in different regions of Iran (15 provinces) have been published from 2001 to 2015 and examined in this study (Table 1). Totally, 6354 participants (3144 cases and 3210 controls) in these studies. Mean and standard deviation age of the case and control groups were 55.82 ± 4.9 and 53.58 ± 5.4 year respectively (Table 2). In addition, 1430 men and 1109 women were in the case group and 1354 men and 1216 women were in the control group (Table 2). The lowest OR was reported by Rahimi F equal to 0.479 (95% CI: (0.267, 0.86)) and the highest OR was reported by Eskandarian et al. equal to 21 (95 CI: (4.45, 99.08)).

Based on meta-analysis and the random effects model, general estimate of OR of *Helicobacter pylori* and heart diseases in Iran was 2.351 (95 CI: (1.715, 3.221)). These OR were different for three heart diseases in different papers. In general, OR of heart diseases was 2.36, and this

Table 1. Characteristics of included studies

AUTHOR	YEAR	PLACE	CASE	CONTROL	Type of CAD
F. Rahimi(15)	2001	Tehran	100	100	Coronary Heart Disease
N. Sarrafzadeh(16)	2001	Isfahan	52	55	Myocardial Infarction
B. Rahnama(17)	2001	Tabriz	104	100	Myocardial Infarction
M. AghaJani(18)	2002	Tehran	100	90	Coronary Heart Disease
F. Jalali(19)	2003	Babol	97	141	Myocardial Infarction
R. Eskandarian(20)	2004	Semnan	23	23	Cardiac Syndrome X
M.A. Bahar(21)	2004	Tehran	131	130	Coronary Heart Disease
R. Eskandarian(22)	2006	Semnan	40	40	Cardiac Syndrome X
A. Amrai(23)	2006	Tehran	82	82	Coronary Heart Disease
F. Raygan(24)	2006	Kashan	50	50	Myocardial Infarction
A.H. Faghihi(25)	2007	Tehran	131	130	Coronary Heart Disease
A. Pourya(26)	2007	Kermanshah	30	30	Coronary Heart Disease
H. Bazazi(27)	2008	Gorgan	109	85	Coronary Heart Disease
N. Sarrafzade(28)	2008	Isfahan	57	44	Coronary Heart Disease
S.M. Mohammadzadeh.(29)	2009	Urmia	54	168	Cardiac Syndrome X
Y. Nozari.(30)	2009	Tehran	70	60	Coronary Heart Disease
H. Bazazi(31)	2009	Gorgan	70	70	Myocardial Infarction
S. Davoudi(32)	2010	Tehran	69	84	Coronary Heart Disease
H. Mirzababaei(33)	2010	Tehran	288	294	Coronary Heart Disease
A. Jafarzadeh.(34)	2010	Rafsanjan	60	60	Myocardial Infarction
Z. Khodai.(14)	2010	Tehran,	500	500	Myocardial Infarction
M. H Khademiansari(35)	2009	Tabriz	100	89	Coronary Heart Disease
Z. Azarkar(36)	2011	Birjand	73	78	Myocardial Infarction
Y. Rasmi(37)	2012	Urmia	100	100	Cardiac Syndrome X
M. Rogha(38)	2012	Isfahan	62	43	Coronary Heart Disease
S. Sayyah(39)	2012	Qazvin	40	40	Coronary Heart Disease
N. Fouladi(40)	2012	Ardabil	300	300	Coronary Heart Disease
H. Honarmand(41)	2012	Rasht	100	76	Coronary Heart Disease
J. Vafaeimanesh(42)	2014	Qom	62	58	Coronary Heart Disease
N. Dehghan(43)	2015	Qazvin	90	90	Myocardial Infarction

Table 2. Descriptive Statistics

Variables	N	Minimum	Maximum	Sum	Mean	Std. Deviation
Case	30	23	500	3144	-	-
Control	30	23	500	3210	-	-
Age Case	25	42	65	-	55.82	4.9
Age Control	25	41	62.4	-	53.58	5.41
Male Case	23	6	260	1430	-	-
Female Case	23	14	240	1109	-	-
Male Control	23	7	250	1354	-	-
Female Control	23	15	250	1216	-	-

Table 3. Disease and Odds Ratio

Disease	OR	95% CI	P -value	Weight%
Myocardial Infarction	2.6	(1.313 , 5.185)	0.001	30.75%
Coronary Heart Disease	1.7	(1.264 , 2.31)	0.001	58.53%
Cardiac syndrome X	8.2	(5.003, 13.56)	0.475	10.72%
Overall	2.35	(1.7, 3.2)	0.001	100.00%

Table 4. Pooled results for 30 case-control studies

Study	Year	OR	[95% Conf. Interval]		% Weight
			Lower	Upper	
Myocardial infarction					
N. Sarrafzadeh (2001)	2001	13.219	5.096	34.292	3.05
B. Rahnema (2001)	2001	3.400	1.727	6.694	3.54
F. Jalali (2003)	2003	0.951	0.567	1.595	3.80
H. Bazazi (2009)	2009	3.035	1.383	6.661	3.35
Z. Khodai (2010)	2010	7.765	5.829	10.344	4.09
Z. Azarkar (2011)	2011	1.788	0.891	3.590	3.51
H. Honarmand (2012)	2012	2.024	0.956	4.283	3.41
N .Dehghan (2015)	2012	2.579	0.944	7.049	2.96
F. Raygan (2006)	2006	0.564	0.218	1.459	3.06
Sub-total (D+L pooled OR)	-	2.609	1.313	5.185	30.75
Coronary Heart Disease					
N. Sarrafzade (2008)	2008	0.829	0.219	3.136	2.41
A. Jafarzadeh (2010)	2010	4.643	1.880	11.467	3.14
F. Rahimi (2001)	2001	0.479	0.267	0.860	3.69
M. AghaJani (2002)	2002	0.897	0.478	1.683	3.62
M.A .Bahar (2004)	2004	1.663	1.019	2.712	3.84
A .Amrai (2006)	2006	0.598	0.280	1.278	3.40
A.H .Faghihi (2007)	2007	1.692	1.036	2.764	3.84
A. Pourya (2007)	2007	2.750	0.934	8.100	2.83
H. Bazazi (2008)	2008	2.126	0.982	4.600	3.37
Y. Nozari (2009)	2009	2.316	1.055	5.085	3.35
S. Davoudi (2010)	2010	1.034	0.543	1.971	3.59
H. Mirzababai (2010)	2010	3.435	2.443	4.831	4.03
M. Rogha (2012)	2012	1.582	0.715	3.500	3.33
S. Sayyah (2012)	2012	4.889	1.809	13.211	2.98
N .Fouladi (2012)	2012	1.917	1.358	2.708	4.03
M. Khademiansari	2009	2.173	1.204	3.924	3.68
J .Vafaeimanes (2014)	2014	2.471	1.156	5.279	3.40
Sub-total (D+L pooled OR)	-	1.708	1.264	2.310	58.53
Cardiac syndrome X					
R. Eskandarian (2004)	2004	11.455	2.167	60.559	1.94
R. Eskandarian (2006)	2006	21.000	4.451	99.082	2.09
S.M. Mohammadzadeh.	2009	5.726	2.701	12.138	3.41
Y. Rasmi (2012)	2012	9.036	3.966	20.584	3.28
Sub-total (D+L pooled OR)	-	8.237	5.003	13.562	10.72
Overall (D+L pooled OR)	-	2.351	1.715	3.221	100.00

figure is mean of three OR values for three diseases of cardiac syndrome X (OR = 8.2), myocardial infarction (OR = 2.6), and Coronary Heart Disease (OR = 1.7); further details are listed in the table below (Table 3).

Odd ratios were obtained based on the number of instances in the case and control groups using the random effects and fixed models. Heterogeneity was determined using I^2 and Cochran's Q; in addition, heterogeneity test was used to evaluate H_0 so that all the papers were examined as to the same effect. Heterogeneity effect was obtained using I^2 , which is a measure of inconsistency between the studies and determines if total percentage of changes between the studies is random or due to heterogeneity;

a value of I^2 bigger than 50% indicates heterogeneity among the studies. Here, I^2 was equal to 85.6%, $p < 0.001$; therefore, random effects and Der Simonian and Laird methods were used in addition to the sensitivity analysis and Meta regression method.

Combined OR value was 2.35, which indicates that the OR (of exposure) in the case group was 1.35% higher than that of the control group ($p = 0.001$) (Table 4).

Significant publication bias among the included studies (all $p > 0.05$), (Figs. 3, 4).

The random effect model was used to decrease the rate of heterogeneity. We also applied the sensitivity analysis to evaluate the reasons of heterogeneity but the sensitivity

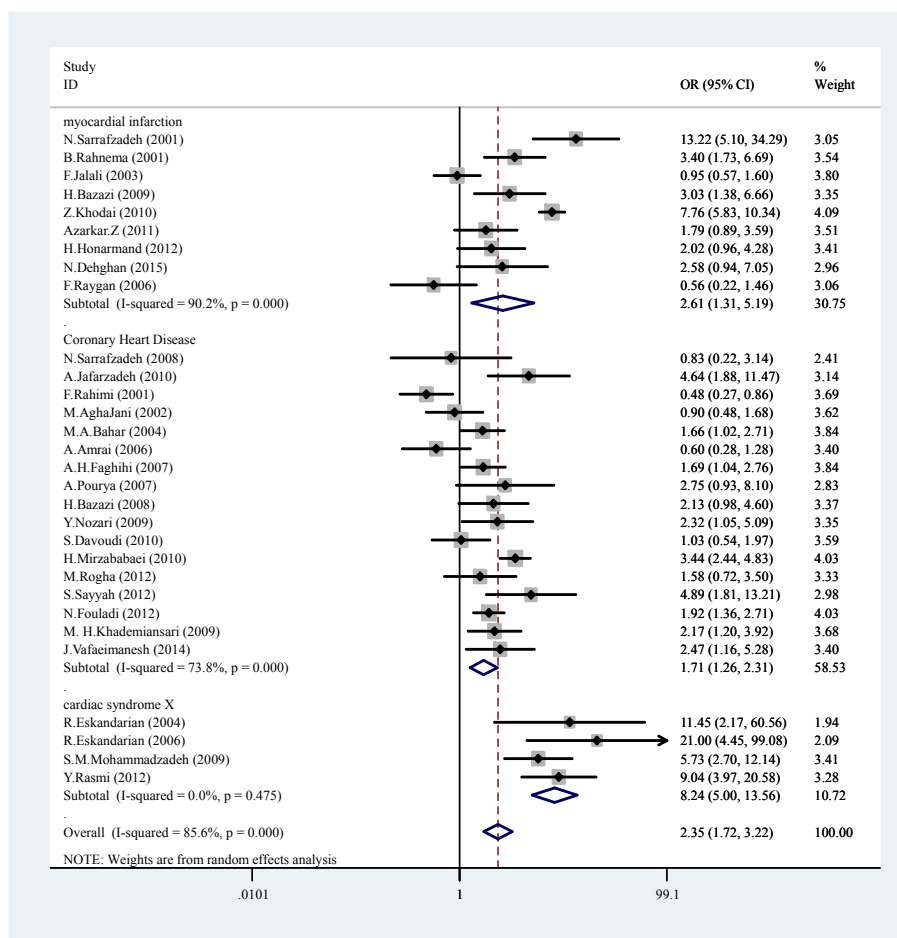


Fig. 2. A forest plot of the association between helicobacter pylori infection and CHD

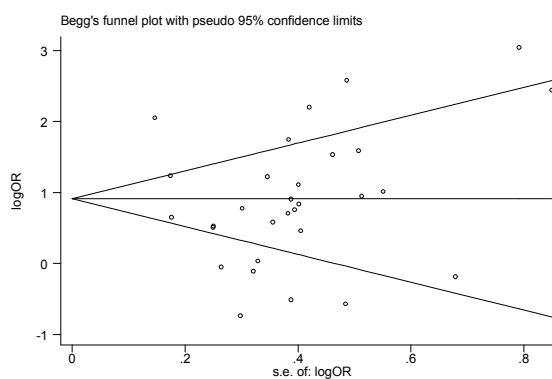


Fig. 3. Begg's Funnel plot with pseudo 95% confidence limit

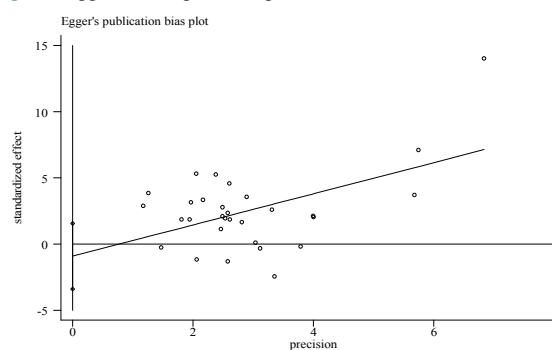


Fig. 4. Eggers publication bias plot

analysis was not so useful to detect the reason of hetero-

geneity. Therefore, we used the Meta-regression method. Variables such as coronary heart disease type, sample size and age of patients were included. Using the Meta-regression we evaluated the simultaneous effect of three mentioned variables. Our analysis showed that the rate of variation due to the heterogeneity was decreased up to 53.88%. At the significant level of 0.05, only the sample size was significant while the variables of sample size, disease 3 and age were significant at 0.1 level of significance (Tables 5-9 & Figs. 5, 6).

The Meta-regression analysis showed that the OR of having *H. pylori* had a negative correlation with the age of participants ($p=0.005$), (Table 7, Fig. 5).

Discussion

The results about the relationship between *Helicobacter pylori* infection and heart diseases were inconsistent, and despite several studies in this field, one cannot be sure about such relationship. The present study is the only systematic review study in Iran on this topic.

The findings showed that OR of heart diseases in case groups with *Helicobacter pylori* infection was higher than that of the control group without the infection. Total OR of heart diseases in the case group was 2.35 times higher than that of the control group.

Mendel et al. conducted one of earliest studies on the re-

Table 5. Test(s) of heterogeneity

	Heterogeneity statistic	Degrees of freedom	P -value	I-squared**	Tau-squared
myocardial infarction	81.56	8	0.001	90.2%	0.957
Coronary Heart Disease	61.15	16	0.001	73.8%	0.271
cardiac syndrome X	2.50	3	0.475	0.0%	0.000
Overall	201.68	29	0.001	85.6%	0.610

** I-squared: the variation in OR attributable to heterogeneity), Note: between group heterogeneity not calculated; only valid with inverse variance method
Significance test(s) of OR=1

Myocardial infarction	z= 2.74	p = 0.006
Coronary Heart Disease	z= 3.48	p = 0.000
cardiac syndrome X	z= 8.29	p = 0.000
Overall	z= 5.32	p = 0.000

Table 6. Meta-regression1

Parameters	Coefficient	Standard errors	t	P> t	[95% Conf. Interval]
Disease 2	-0.42	0.25	-1.66	0.112	[-0.94, 0.1]
Disease 3	0.9	0.43	2.06	0.053	[-0.01, 1.82]
Sample size	0.002	0.001	2.16	0.043	[0.001, 0.002]
Age	-0.05	0.03	-1.77	0.092	[-0.115, 0.009]
Constant	3.77	1.69	2.23	0.037	[0.24, 7.29]

Meta-regression	Number of obs= 25
REML estimate of between-study variance	Tau ² = 0.155
% residual variation due to heterogeneity	I-squared _{res} = 53.88%
Proportion of between-study variance explained	Adj R-squared = 66.71%
Joint test for all covariates	Model F(4,20) = 6.57
Prob> F	0.0015

relationship between *Helicobacter pylori* and OR of heart diseases. They studied 111 patients and 74 healthy participants in case and control groups respectively and compared them in terms of *Helicobacter* infection and risk of heart diseases. They reported that OR of heart diseases in the presence of the infection was two times more than that without the infection (12). Their results are consistent with our results. Their study raised the worries about the probable relationship between *Helicobacter* infection and heart diseases and followed by several studies conducted in this area in the following years. Inconsistent results have been reported by different studies so that some have found a positive relationship and some have reported no significant relationship between the variables (44). The results of the present review study showed that studies with small sample group reported higher OR of heart diseases in presence of *Helicobacter pylori* infection. On the other hand, studies with large sample group on controlling the main risk factors of heart diseases found no such relationship (45). To reach a conclusion, all studies conducted in Iran on the relationship between *Helicobacter pylori* and heart diseases were included regardless of their sample size.

A study based on polymerase chain reaction (PCR) to diagnose *Helicobacter pylori* infection coronary arteries plaque in patients under coronary artery bypass grafting (CABG) showed that 29.5% of the surgery patients had positive *Helicobacter pylori* infection culture. Serology evidences of infection were observed in 53.3% of 105 patients. Therefore, *Helicobacter pylori* infection was effective on ruptured plaque and development of the coronary ischemic disease. It is believed that chronic inflammation caused by chronic infections may lead to the development of advanced atherosclerosis and CAD consequently (46, 47).

The results showed that OR of MI in people with *Helicobacter* infection was 2.5 times more than individuals without the infection (48, 49). Results of one of the few studies conducted as a systematic review work at international level to examine the relationship between *Helicobacter pylori* infection and MI indicated that OR of MI in patients with this type of infection was 1.73 times

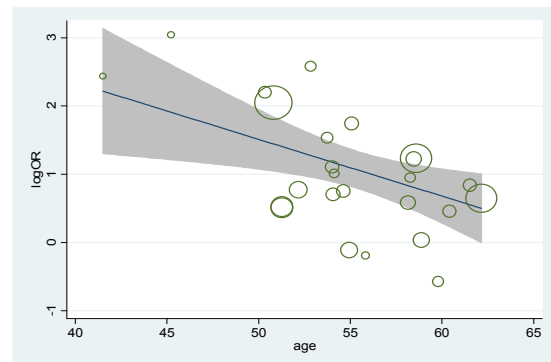


Fig. 5. Diagram of OR of having H. pylori and age

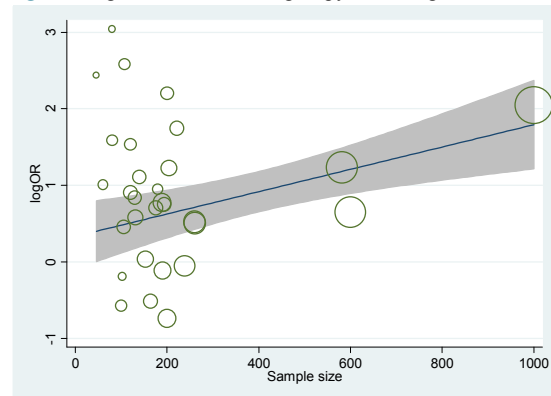


Fig. 6. Diagram of OR of having H. pylori and Sample size

Table 7. Meta-regression 2

Parameters	Coefficient	Standard errors	t	P> t	[95% Conf. Interval]
Constant	6.64	1.82	3.63	0.001	[2.86, 10.42]
Age	-0.10	0.03	-3.11	0.005	[-0.17, -0.03]
Meta-regression					Number of obs= 25
REML estimate of between-study variance					Tau ² = 0.3415
% residual variation due to heterogeneity					I-squared_res = 77.67%
Proportion of between-study variance explained					Adj R-squared = 26.67%

Table 8. Meta-regression 3

Parameters	Coefficient	Standard errors	t	P> t	[95% Conf. Interval]
Sample size	0.001	< 0.01	0.93	0.35	[- 0.001, 0.002]
Constant	0.68	0.24	2.76	0.01	[0.17, 1.18]
Meta-regression					Number of obs30
REML estimate of between-study variance					Tau ² = 0.5865
% residual variation due to heterogeneity					I-squared_res = 79.99%
Proportion of between-study variance explained					Adj R-squared = 2.24%

Table 9. Meta-regression 4

Parameters	Coefficient	Standard errors	t	P> t	[95% Conf. Interval]
Disease1	-1.27	0.49	-2.55	0.017	[-2.3, -0.24]
Disease2	-1.7	0.46	-3.63	0.001	[-2.66, -0.74]
Constant	2.23	0.43	5.18	< 0.001	[1.35, 3.12]
Meta-regression					Number of obs30
REML estimate of between-study variance					Tau ² = 0.4102
% residual variation due to heterogeneity					I-squared_res = 81.40%
The proportion of between-study variance explained					Adj R-squared = 31.63%
Joint test for all covariates					Model F (2,27) = 6.79
Prob> F					= 0.0041

more than those without the infection and after removing the lower quality articles, the OR was increased to 2.1 that was consistent with results of the present study. It is notable, however, that the OR of MI in Asian populations with *Helicobacter* infection was 1.75 times more than that of the control group. This shows that OR of *Helicobacter* infection in Iranian population is higher than that of other Asian countries (49). Consistently, a study in India reported that risk of MI in individuals with *Helicobacter* infection was 2.5 times more than that of those without the infection (29). In addition, several other studies have shown a relationship between *Helicobacter* infection and MI so that the group with the infection had higher OR of MI. Prevalence of *Helicobacter* infection was relatively high in both control and case groups (50-52).

Some authors have argued that *Helicobacter pylori* infection increases the risk of cardiovascular diseases. There are several mechanisms to explain how the infection increases the risk of heart diseases. It is believed that chronic inflammation caused by chronic infections may lead to advanced atherosclerosis, which in turn results in CAD. Chronic infection increases inflammatory metabolites such as cytokines, which in turn influences arteries motions, disrupts endothelium functions, and causes excessive contraction of small arteries. Increase in cytokines concentration has been reported in many patients with *Helicobacter pylori* infection. Higher concentration of cytokines increases leukocytes, which in turn increases the risk of inflammatory reaction in the patients with the infection. These inflammatory reactions may explain the correlation between *Helicobacter pylori* infection and heart diseases. Different bacterial and viral infections may have cross-reaction with classic risk factors of heart diseases such as smoking, hypertension, diabetes, lipid disor-

ders, and other pre-inflammatory stimulators (e.g. homocysteine, free radicals, cytokines, and chemokines) so that the outcome would be local and systemic intra-artery inflammation, which in turn results in atherosclerosis and thrombosis(22). Taking into account that the bacteria can prevent blood supply to walls of the heart, *Helicobacter pylori* infection may directly act as a pathogen on the wall of arteries and cause coronary diseases or indirectly cause inflammation(53,54). If the relationship between *Helicobacter pylori* infection and cardiovascular diseases is proven, one may conclude that treating the infection reduces OR of the diseases and the pertinent events.

Conclusion

Following a comprehensive research approach, the relationship between *Helicobacter pylori* infection and risk of heart diseases was examined. Thirty articles were surveyed, and the result showed that OR of heart diseases in the subjects with *helicobacter pylori* was two times more than that in the subjects without the infection. Since most of the hosts of the bacterium are afflicted with the infection in their childhood, personal hygiene promotion and preventive programs for children may have a considerable role in reducing the risk of the infection and cardiovascular diseases consequently.

Limitations

Although the results indicated that *Helicobacter* infection doubles OR of cardiovascular diseases, interpreting the data of the infections is not easy due to some disturbing variables such as childhood poverty and/or other similar factors. Future works need to take the socioeconomic condition of the participants into account in examining the relationship between the infection and

cardiovascular diseases

Conflict of Interests

The authors declare that they have no competing interests.

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