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Full Length Research Paper

Association between O blood group and *Helicobacter pylori* infection: A systematic review and meta-analysis

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Helicobacter pylori* (*H. pylori*) infection is associated with several diseases including gastritis, gastric ulcer, pancreatic cancer and iron deficiency anemia. Different epidemiological studies reported controversial findings on the association between O blood group and *H. pylori* infection. This meta-analysis was conducted to verify the association between *H. pylori* infection and O blood group. Random-effects model was used to pool data on the association between *H. pylori* infection and O blood group in 18 selected studies. DerSimonian Liard statistic was used to estimate the effect size. Stability of the pooled estimates was assessed by sensitivity analysis. Publication bias was assessed by using funnel plot and Egger's test. Fourteen of the 18 included studies reported no significant association between *H. pylori* infection and O blood group. Among ten reviewed studies which were conducted among dyspeptic patients, four showed statistically significant association. However, none of six studies conducted among asymptomatic patients demonstrated statistically significant association. The pooled effect size showed no statistically significant association between O blood group and *H. pylori* infection (odds ratio (OR) = 1.18, 95% CI [0.95, 1.48]). However, the pooled effect size under stratified meta-analysis turned to be statistical significant among studies conducted in dyspeptic patients (OR = 1.44; 95% CI [1.03, 2.01]). The analysis did not show statistically significant association between *H. pylori* infection and O blood group among all study participants. However, statistically significant association between *H. pylori* infection and O blood group was observed in a subset of studies conducted among dyspeptic patients. Caution should be made while interpreting the finding as the severity of dyspepsia is not standardized and different *H. pylori* strains were not taken into account.

Key words: *Helicobacter pylori*, ABO blood group, O blood group, meta-analysis.

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative bacillus that regularly colonizes the human stomach (Passaro et al., 2002; Sasidharan et al., 2010). It is present in 20 to 50% of the population in developed countries and 80% of the population in developing countries (Wen et al., 2007). *H. pylori* causes considerable morbidity and mortality worldwide. Many recent studies have revealed that *H. pylori* infection is associated with several diseases

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including iron deficiency anemia (Wang et al., 2012), pancreatic cancer (Risch et al., 2010), gastritis, gastric ulceration and gastric cancer (Atherton et al., 1996). These different health outcomes have interested different researchers to investigate risk factors associated with *H. pylori* infection. To this end, several studies were conducted to establish a relationship between *H. pylori* infection and the ABO blood groups. However, the findings of different epidemiological studies reported on the association between O blood group and *H. pylori* infection were controversial and inconsistent.

While many authors reported statistically significant association between O blood group and *H. pylori* infection (Jaff, 2011; Mattos et al., 2010; Mattos et al., 2002), many others failed to establish such an association (Rasmi et al., 2011; Moges et al., 2006; Tadege et al., 2005; Zhub et al., 2011). Sample size, studied population and tests used to detect *H. pylori* infection were cited to be the source of variation in the findings of different studies which investigated the association between ABO blood group and *H. pylori* infection.

The aim of this meta-analysis is therefore to verify the association between O blood group and *H. pylori* infection by increasing the numbers of observations and the statistical power.

Literature search

MEDLINE, PubMed and google scholar were systematically searched without date restrictions in August, 2013. Our search was limited to articles published in English language. Medical subject heading terms (MeSH) was used as a combination of *H. pylori* and ABO blood groups. Articles cited in the retrieved articles were searched online to supplement the search. The study did not involve any contact with authors. Unpublished works were not included in this meta-analysis.

Study selection

All studies that assessed an association between ABO blood group and *H. pylori* infection were included, irrespective of the presence or absence of statistically significant association. We excluded studies which reported association between other blood groups other than ABO and *H. pylori* infection. Studies with, as well as those without a control group were included. Only full length articles were included in the analysis. Two reviewers: DS (Epidemiologist) and DD (Medical Microbiologist) independently assessed the eligibility of articles. Only studies which excluded study participants who had been receiving treatment for *H. pylori* infection were included in this meta-analysis.

Data extraction

The two researchers completed the data extraction using a standardized spread sheet that collected information on the first author, year of publication, study design, study population (symptomatic versus asymptomatic), country (developed versus developing), frequency of infection by ABO blood group and mean age. Disagreement between reviewers occurred only on one study and was resolved through discussion to achieve consensus.

Data analysis

Extracted data from the selected studies were entered and analyzed using stata 12, College Station, TX 77 845, USA. The original studies was described using frequency and forest plot. Two measures of heterogeneity: chi-squared test of heterogeneity and I^2 were used to asses between studies heterogeneity. A chi-squared value with a p-value < 0.05 and I^2 value > 40% were used to quantify heterogeneity between studies (Crowther et al., 2010). The selected studies had substantial hetero-geneity with heterogeneity chi-squared value = 58.6, df (16) and p-value = 0.0001 and I^2 value = 64.2%. As a result, random-effects model was used. A pooled estimate of the odds ratio comparing O blood group to non O blood groups for *H. pylori* infection was calculated using random-effects model. DerSimonial Liard statistics was used to estimate the effect size. To account for the observed heterogeneity we employed stratified meta-analysis by different study characteristics such as study population (dyspeptic, asymptomatic) and source continent. Finally, sensitivity analysis was conducted to determine whether the pooled results were robust. Individual studies were removed and their effect on the overall effect size evaluated. Removal of a study by Jaff (2011) (weight: 8.9%) changed the statistically significant pooled effect size for dyspeptic study population not to attain statistical significance. However, the study was retained in the final analysis for its higher quality and larger sample size. Funnel plot and egger's test were used to assess publication bias.

RESULTS

Study selection

The literature search identified 258 studies, of which 191 were excluded after reviewing the topic and abstracts. Further 49 articles were excluded after reviewing full

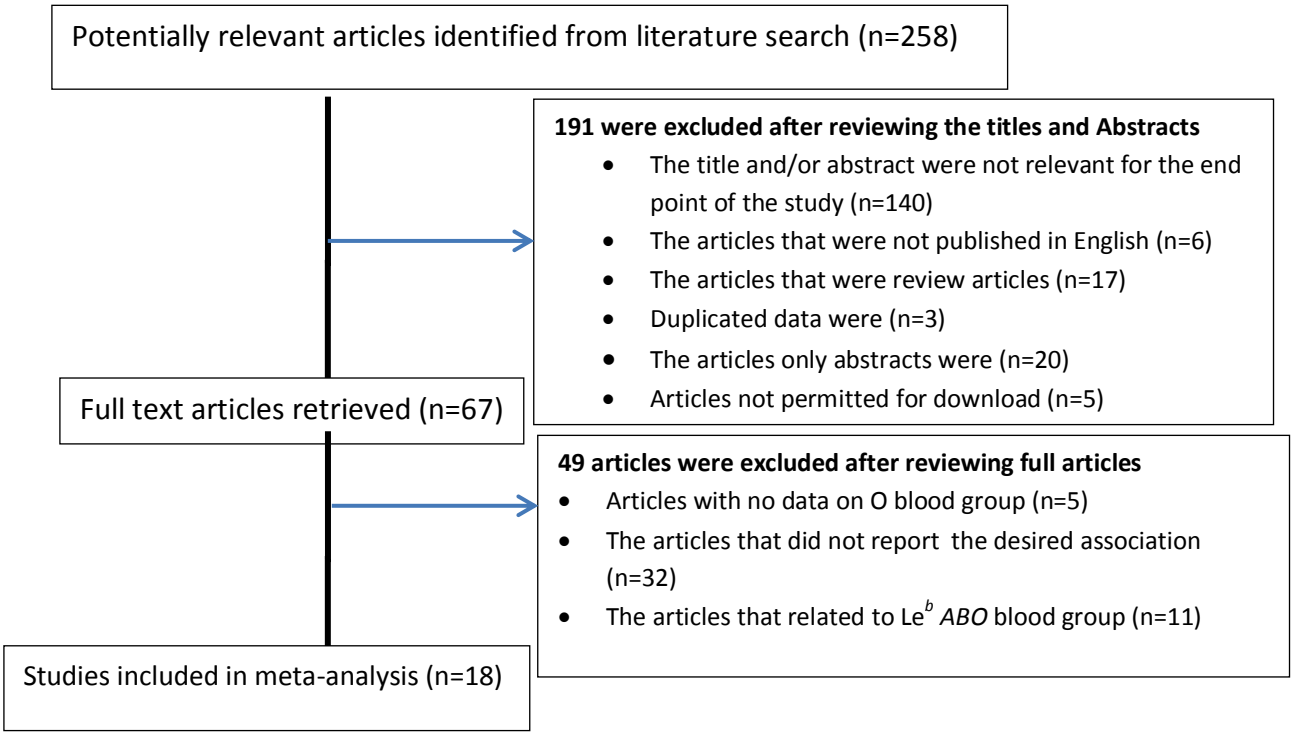

Figure 1. Schematic presentation of study selection process.

length articles. Hence, complete information could be extracted from a total of 18 eligible studies (Figure 1).

Description of original studies

Of the 18 observational studies included in the analysis, three were from Africa (Nwodo et al., 2009; Moges et al., 2006; Tadege et al., 2005), eight were from Asia (Rasmi et al., 2011; Wu et al., 2003; Romshoo et al., 1997; Valliani et al., 2013; Aryana et al., 2013; Jafarzadeh et al., 2007; Jaff, 2011), five were from Europe (Loffeld and Stobberingh, 1991; Petrovic et al., 2011; Zhub et al., 2011; Heneghan et al., 1998; Lopes et al., 2013) and two were from Latin America (Mattos et al., 2002; Mattos et al., 2010). This meta-analysis is computed on a total sample of 5,036 study participants from the selected 18 studies. The sample size ranged from 80 in Kashmir, India (Romshoo et al., 1997) to 1108 in Iraq, Asia (Jaff, 2011). The studies included in the analysis were cross-sectional in design (Tables 1 and 2).

Ten of the included studies were conducted among dyspeptic patients and six studies among asymptomatic study participants (Table 1). In 11 of the included studies, *H. pylori* infection was diagnosed by an ELISA test. The sample size and particularly the number of study participants with O blood group in each included studies is generally low (Table 1).

Pooled effect-size

The estimates of the specific studies showed positive association between O blood group and *H. pylori* infection in four of the included studies. However, in the rest majority of the included studies, 14 (77.7%), no statistically significant association was demonstrated between O blood group and *H. pylori* infection (Figure 2). Among ten reviewed studies which were conducted among dyspeptic patients, four showed statistically significant association. However, none of six studies conducted among asymptomatic patients demonstrated statistically significant association.The selected studies had substantial heterogeneity with heterogeneity chi-squared value = 58.6, df (16) and p-value = 0.0001 and I^2 value = 64.2%. As a result, random-effects model was used. Based on the random effects model, the overall pooled estimate failed to show statistically significant association between O blood group and *H. pylori* infection, DerSimonian Liard pooled OR = 1.18, 95% CI [0.95, 1.48]. The specific and pooled estimates are presented in the forest plot (Figure 2).

Table 1. Description of studies included in the analysis, 2013.

Author, Publication year	Country	Study population	Diagnosis	Population	Sample Size	*H. pylori* Infected	O Blood group
Tadege et al. (2005)	Ethiopia	Both**	ELISA	Child	200	124	86
Romshoo et al. (1997)	Kashmir	Both**	Biopsy	Adult	80	48	37
Loffeld et al. (1991)	Netherland	Asymptomatic	ELISA	Adult	402	143	176
Jaff et al. (2011)	Iraq	Dyspeptic	ELISA	Adult	1108	718	423
Mattos et al. (2010)	Brazil	Dyspeptic	PCR	Adult	110	73	63
Rasmi et al. (2011)	Iran	Asymptomatic	ELISA	Adult	151	98	8
Aryana et al. (2013)	Iran	Dyspeptic	UBT	Adult	135	68	51
Lopes et al. (2013)	Coimbra	Dyspeptic	*	Adult	114	76	55
Petrovic et al. (2011)	Serbia	Dyspeptic	UBT	Adult	227	93	69
Heneghan et al. (1998)	Ireland	Dyspeptic	ELISA	Adult	198	90	110
Zuhubi et al. (2011)	Kosovo	Asymptomatic	ELISA	Adult	671	382	298
Jafarzadeh et al. (2007)	Iran	Asymptomatic	ELISA	Child	386	180	166
Valliani et al. (2013)	Pakistan	Dyspeptic	Biopsy	Adult	93	36	41
Keramati et al. (2012)	Iran	Asymptomatic	ELISA	Adult	171	131	63
Moges et al. (2006)	Ethiopia	Dyspeptic	ELISA	Adult	215	184	90
Nwodo et al. (2009)	Nigeria	Dyspeptic	ELISA	Adult	225	181	109
deMattos et al. (2002)	Brazil	Dyspeptic	PCR	Adult	125	74	53
Wu et al. (2003)	China	Asymptomatic	ELISA	Adult	425	124	206

*Chemiluminscent, UBT: urea breath test, ** asymptomatic and symptomatic

Table 2. Sample size of included studies by continent, 2013.

Continent	Sample size	Percent (%)
Africa	640	12.7
Asia	2549	50.6
Europe	1612	32
Latin America	235	4.7
Total	5036	100

Stratum-specific effect size

Because there was substantial heterogeneity between included studies, we employed stratified meta-analysis taking study population (symptomatic, asymptomatic or both), continent and type of country (developing versus developed) as stratifying variables. Across all the strata, the heterogeneity statistic (I^2) varied substantially. Accordingly, we used fixed-effects model when I^2 for a given stratum is less than 40% and *p*-value greater than 0.05 and random-effects model otherwise (Table 3). The pooled estimate under the stratified analysis showed statistically significant association between O blood group and *H. pylori* infection when the study subjects were symptomatic (dyspeptic), OR = 1.44; 95% CI (1.03, 2.01) (Figure 3 and Table 3) and in studies conducted in Latin America, 3.45; 95% CI (1.94, 6.12). There was no statistically significant association between O blood group and *H. pylori* infection among asymptomatic patients. Similarly, subgroup analysis by continent showed no statistically significant association between O blood group and *H. pylori* in studies conducted in Africa, Asia and Europe (Table 3). Publication bias was assessed using funnel plot and Egger's test. The findings from an Egger's test (Coef. 0.69, standard error = 0.95 and p-value = 0.45) revealed no significant asymmetry, suggesting no publication bias.

DISCUSSION

This meta-analysis was performed primarily to reconcile the inconsistencies observed between many previous investigations. Unlike many observational studies (Valliani et al., 2013; Jaff, 2011; Mattos et al., 2010; Mattos et al., 2002), this meta-analysis demonstrated lack of significant association between *H. pylori* infection and O blood group among study participants. On the contrary, results of the stratified analysis showed statistically significant association between O blood group and *H. pylori* positivity among dyspeptic study participants, p = 0.002 (Table 3). The significant association between O blood group and *H. pylori* infection was reported in many observational studies conducted among dyspeptic patients (Mattos et al., 2010;

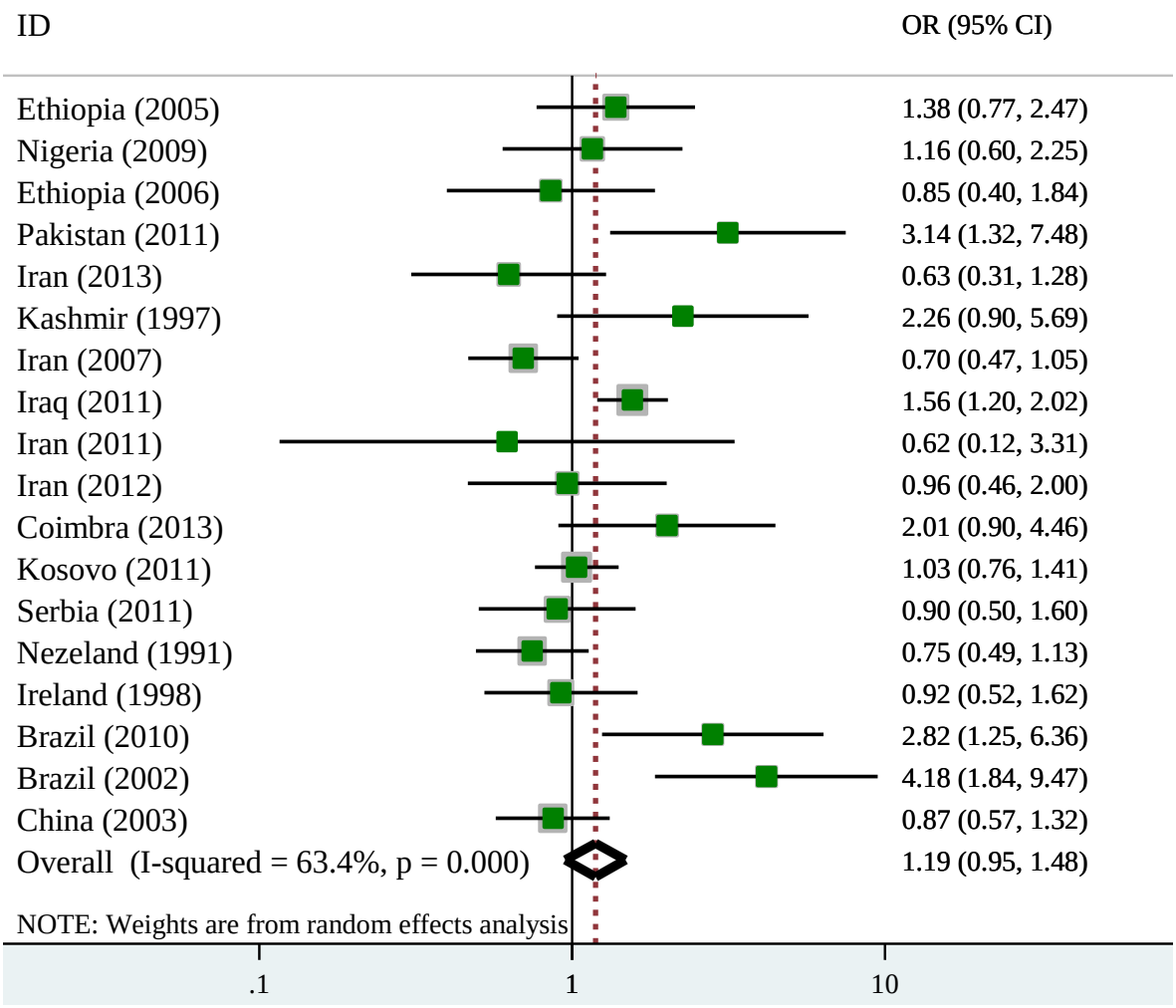

Figure 2. Forest plot of association between O blood group and *H. pylori* infection. 2013.

Table 3. Stratified meta-analysis.

Strata	Sample size	Pooled OR (95% CI)	I^2 in % (P-value)	Model used
Study population				
Dyspeptic	2550	1.44 (1.03, 2.01)	64.8 (0.002)	Random
Asymptomatic	2206	0.86 (0.72, 1.03)	0.0 (0.68)	Fixed
Both	280	1.59 (0.97, 2.60)	0.0 (0.38)	Fixed
Continents				
Africa	640	1.16 (0.79, 1.70)	0 (0.62)	Fixed
Asia	2549	1.12 (0.77, 1.63)	70.2 (0.001)	Random
Europe	1612	0.97 (0.79, 1.18)	20 (0.29)	Fixed
Latin America	235	3.45 (1.94, 6.12)	0 (0.5)	Fixed
Type of country				
Developing	3424	1.302 (0.96, 1.77)	68 (<0.001)	Random
Developed	1612	0.97 (0.79, 1.18)	20 (0.29)	Fixed

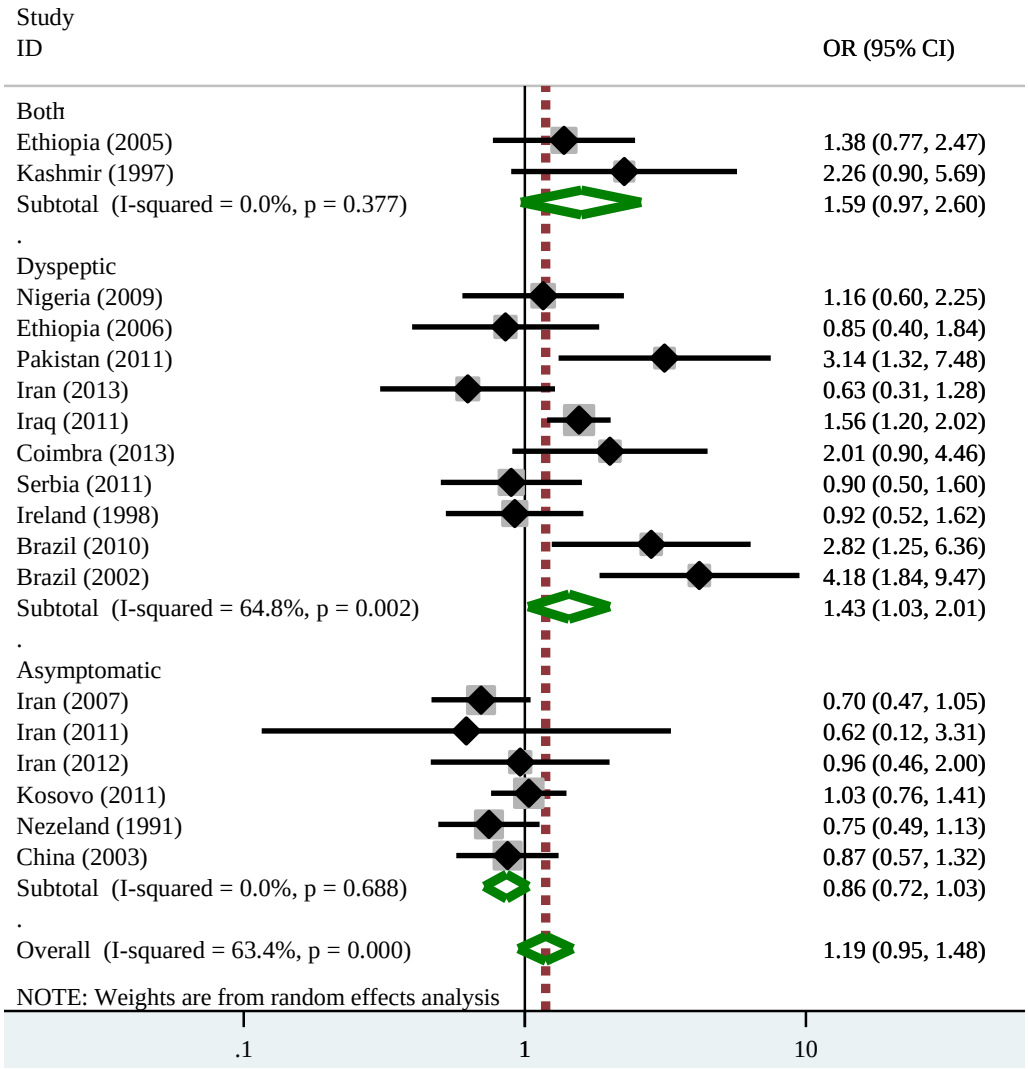

Figure 3. Forest plot of the association between O blood group and *H. pylori* infection by symptom status of the study participants.

Jaff, 2011; Mattos et al., 2002). Like in many studies elsewhere (Loffeld and Stobberingh, 1991; Rasmi et al., 2011; Zhub et al., 2011; Jafarzadeh et al., 2007; Keramati et al., 2012), such an association is not evident among asymptomatic study participants in this analysis (Table 3). Among ten reviewed studies which were conducted among dyspeptic patients, four showed statistically significant association. However, none of six studies conducted among asymptomatic patients demonstrated statistically significant association. It is noteworthy that the study participants with dyspepsia in the included studies might not be homogenous with regard to the dyspepsia severity.

Though the exact biologic mechanism of the association of blood group O and *H. pylori* infection among dyspeptic patients remains not well understood, according to some authors it is related with the expression of carbohydrates (glycoproteins, glycolipds and free oligosaccharides) rich in fucose molecules which act as receptors of *H. pylori* into gastric tissues in greater quantities in individuals with O blood group as a result of interactions with different microorganisms (Dematttos, 2012; Mattos et al., 2002). Also, individuals with O blood group were reported to have an increased density of colonization of epithelial cells and higher inflammatory responses to *H. pylori* infection than individuals with other blood groups (Alkout et al., 2000). According to the same report, the increased inflammatory response is believed to contribute to the increased susceptibility of O blood group individuals to peptic ulceration.

Owing to an enhanced inflammatory response to *H. pylori* infection and increased density of colonization, it is likely that *H. pylori* infection might be detected easily in individuals with O blood group than individuals with other blood groups. Conversely, the likelihood of serological detection of *H. pylori* infection in individuals with blood groups other than O would be lower compared to O blood group individuals. This might have artificially contributed to the observed association. According to the current analysis, the finding that none of the six studies conducted among asymptomatic study participants failed to show statistically significant association may mean that there is no real association between O blood group and *H. pylori* infection. Should real association exist between O blood group and *H. pylori* infection, the association should be evident across all strata (symptomatic and asymptomatic). However, in the role of different confounders, study methods and study participants used should not be ignored.

Close investigation of the methods used in each of the included studies showed that significant numbers of studies were conducted with few number of study participants, lacking the desired statistical power to detect the difference if it really exists. For instance, 33.3 and 56% of studies included in this meta-analysis had less than 150 and 200 study participants, respectively. More worrying problem is that 61.1% of the included studies had less than 100 study participants (as low as 8 and as high as 90) with O blood group (Table 1). The inconsistent associations reported by different authors might have occurred as a result of compromised study power in such comparative studies. None of the 18 studies have reported sample size determination.

The inconclusive findings of different epidemiological studies can also be viewed in relation with the tests used. Though serological methods used as diagnostic tool of *H. pylori* are generally simple, reproducible and inexpensive, the performance of these serological methods is reported to vary considerably depending on the methods, antigen used and type of population studied (Tadege et al., 2005). Misdiagnosis of the organism cannot be ruled out partly because it is not totally possible to exclude people in whom the bacilli were eliminated as a result of unreported antibiotics taken for illnesses other than *H. pylori.* Another limitation of the current analysis is that though different strains of the organism were reported to be accompanied by different severity of disease and distribution, the differences in the strains were not taken into account while pooling the data.

Conclusion

The study did not show statistically significant association between *H. pylori* infection and O blood group among all study participants. However, statistically significant association between *H. pylori* infection and O blood group was observed in a subset of studies conducted among dyspeptic patients. The observed association may not mean the association is a cause-effect one. Caution should be made while interpreting the finding as the dyspeptic study participants might not be homogenous with regard to the dyspepsia severity; the sample sizes in individual included studies is generally low and different *H. pylori* strains were not taken into account.

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