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Helicobacter pylori infection is associated with reduced risk of Barrett's esophagus: a meta-analysis and systematic review

Yan-Lin Du, Ru-Qiao Duan and Li-Ping Duan^{*}

Abstract

Background: *Helicobacter pylori (Hp)* is a class I carcinogen in gastric carcinogenesis, but its role in Barrett's esophagus (BE) is unknown. Therefore, we aimed to explore the possible relationship.

Methods: We reviewed observational studies published in English until October 2019. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for included studies.

Results: 46 studies from 1505 potential citations were eligible for inclusion. A significant inverse relationship with considerable heterogeneity was found between Hp (OR = 0.70; 95% Cl, 0.51–0.96; P = 0.03) and BE, especially the CagA-positive Hp strain (OR = 0.28; 95% Cl, 0.15–0.54; P = 0.0002). However, Hp infection prevalence was not significantly different between patients with BE and the gastroesophageal reflux disease (GERD) control (OR = 0.99; 95% Cl, 0.82–1.19; P = 0.92). Hp was negatively correlated with long-segment BE (OR = 0.47; 95% Cl, 0.25–0.90; P = 0.02) and associated with a reduced risk of dysplasia. However, Hp had no correlated with short-segment BE (OR = 1.11; 95% Cl, 0.78–1.56; P = 0.57). In the present infected subgroup, Hp infection prevalence in BE was significantly lower than that in controls (OR = 0.69; 95% Cl, 0.54–0.89; P = 0.005); however, this disappeared in the infection history subgroup (OR = 0.88; 95% Cl, 0.43–1.78; P = 0.73).

Conclusions: *Hp*, especially the CagA-positive *Hp* strain, and BE are inversely related with considerable heterogeneity, which is likely mediated by a decrease in GERD prevalence, although this is not observed in the absence of current *Hp* infection.

Keywords: Helicobacter pylori, Barrett's esophagus, Gastroesophageal reflux disease

Background

Owing to improvements in hygiene and living conditions, the prevalence of *Helicobacter pylori* (*Hp*) has continued to fall in developed countries, along with the incidence of gastric cancer and peptic ulcer, although it remains high in some developing countries, such as 70.1% in Africa [1, 2]. Interestingly, in contrast to the decline in the rate of Hp infection, the incidence of esophageal

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adenocarcinomas (EAC) has increased significantly. Current epidemiological studies present a consistent, rapidly increasing incidence of EAC in the United States and most other western countries, especially among males, with an observed or estimated start between 1960 and 1990, while the incidence of esophageal squamous cell carcinoma is stable or declining in all racial groups [3, 4]. The etiology of EAC is multifactorial, and Barrett's esophagus (BE) is a premalignant lesion that is observed in the majority of patients with EAC, and carries a risk of eventual development of EAC that is up to 30- to 125fold higher than that in patients without this condition



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[5, 6]. Previous studies have identified several risk factors for the development of BE, including male sex, older age, smoking, white race, obesity, hiatal hernia, and gastroesophageal reflux disease (GERD) [7, 8]. However, the possible role of Hp in BE is uncertain. Currently, Hp is classified by the World Health Organization as a class 1 carcinogen, since it promotes gastric cancer, and is also regarded as a commensal organism that confers some protection against asthma, allergies, and even obesity [9, 10]. Hp seems to have a protective influence on BE, however, the relationship between Hp and BE remains controversial.

Multiple studies have highlighted the relationship between Hp and BE [11-13]. Recently, Wang used individual-level data from six case-control studies to conduct analysis. Their study provided evidence that *Hp* infection was strongly inversely associated with BE, which was even stronger among individuals with cytotoxin-associated gene A (CagA) positive strain [14]. Another extensive meta-analysis also demonstrated that Hp infection was associated with a reduced risk of BE, and dysplastic, non-dysplastic, and long-segment BE (LSBE), and demonstrated that the risk reduction was not correlated with geographical location [15]. However, some researchers concluded that there was no clear association between Hp and BE, or demonstrated contrary conclusions in case-control studies and cohort studies [16, 17]. Fischbach's meta-analysis of 49 observational studies identified a protective effect of Hp on BE, and showed great heterogeneity between the majority of studies, which was potentially due to selection and information bias [18]. Consequently, it is understandable that different metaanalyses come to different conclusions.

Previous meta-analysis results are inconsistent, and the heterogeneity between them may derive from selection of the control group, the definition of BE, and the Hp detection method. To better understand this relationship, we performed meta-analysis and subgroup analysis based on the potential sources of heterogeneity. This study would contribute to the design of clinical studies and the decisions on whether to eradicate Hp.

Methods

Search strategy

PubMed, EMBASE, and COCHRANE databases were searched from inception to October 2019. We used the following MeSH terms or keywords as search terms: (("Barrett Esophagus"[Mesh]) OR (Barrett metaplasia) OR (Barrett metaplasias) OR (Barrett's Metaplasia) OR (Metaplasia, Barrett) OR (Metaplasias, Barrett) OR (Barrett's Syndrome) OR (Barrett's syndrome) OR (Barrett Syndrome) OR (Barrett's Esophagus) OR (Barrett's oesophagus) OR (Barretts Esophagus) OR (Barrett's oesophagus) OR (Esophagus, Barrett's) OR (oesophagus, Barrett's) OR (Esophagus, Barrett) OR (oesophagus, Barrett) OR (Barrett Epithelium) OR (Epithelium, Barrett) OR (Barrett's) OR (Barrett)) AND (("Helicobacter pylori"[Mesh]) OR (Helicobacter pylori) OR (H pylori) OR (H. pylori) OR (Helicobacter) OR (Campylobacter)) AND (Humans).

Inclusion and exclusion criteria

All eligible studies satisfied the following inclusion criteria:

- 1. Observational studies: Case–control, cohort, or cross-sectional studies
- 2. Providing raw data on *Hp* infection in the BE and control groups
- 3. Studies conducted in adult populations

Studies with the following exclusion criteria were eliminated:

- 1. Full-text articles in languages other than English
- 2. Studies in which the data came from a review article or other non-full-text article
- 3. Less than five points in the Newcastle–Ottawa Scale (NOS)

When the same data appeared in different articles, only the study with the most complete relevant data was included.

Data extraction

Data were extracted by two independent investigators after reading each included study. When agreement was reached by discussion or with the help of third investigators, the data were recorded in a designed Excel 2019 sheet. We collected data on author, year of publication, journal, geographical location, study type, Hp infection testing methods, definition of cases and controls, number of cases and controls, number of Hp infections in cases and controls, and whether matched in sex, age, obesity, smoking, alcohol, and race. Data on dysplasia, segment length and infection of CagA-positive Hp strain were included when present. When the subjects of multiple reports are the same. Only one, the most complete, would be included.

Statistical analysis

Our primary objective was to compare the prevalence of Hp infection between BE groups and controls. The secondary objective was to conduct subgroup analysis according to the differences in definitions of the control group, the definitions of BE, and the Hp detection methods, in order to clarify the impact of these aspects on the overall results. The correlation between Hp and BE was determined by calculating the odds ratios (ORs) and 95% confidence intervals (CIs) for risk. The results of the meta-analysis were displayed on a forest map, heterogeneity was assessed using Cochrane's Q and I² statistics, and publication biases were checked by visual assessment of funnel plots. Heterogeneity was regarded as moderate, substantial, and considerable when the I² was between 30-60%, 50-90%, and 75-100%, respectively. All calculations were conducted by Review Manager 5.3.

Results

Searches initially generated 1505 potential citations after removing 546 duplicates from 2051 citations. A large sample study (n=1445) was further excluded by screening titles, abstracts, and browsing full-text. A total of 62 studies remained for full-text review, and six studies without original data [19–24]. and seven studies with less than five points in NOS were additionally excluded [25–31]. Three studies were excluded because of repetitive research subjects [32–34]. Finally, Forty-five studies were included in this article; data from 36 of these were extracted to explore the relationship between Hp and BE, while others examined the correlation in Hp and BE dysplasia, lengths of BE, and the correlation between the CagA-positive Hp strain and BE. The study selection process is shown in Fig. 1.

Prevalence of Hp infection in BE and controls

The 36 included studies comprised a total of 90,895 BE patients and 430,846 controls [11-13, 35-67]. A summary of the characteristics of these studies is shown in Table 1. The prevalence of *Hp* infection in BE patients was significantly lower than that in controls (OR = 0.70; 95% CI, 0.51–0.96; P=0.03), with considerable heterogeneity observed between studies ($I^2 = 98\%$, P < 0.00001) (Fig. 2). Funnel plots suggested no obvious publication bias (Fig. 3). Subgroup analysis was conducted according to differences in definition of control group. Fourteen studies regarded patients with GERD as control group [37, 43, 49, 52, 54, 55, 58-606263, 6466, 67]. There was no significant difference in the prevalence of Hp infection between BE and GERD controls (OR=0.99; 95% CI, 0.82–1.20; P=0.91; $I^2=33\%$). In contrast, the negative relationship between Hp prevalence and BE was enhanced when defining subjects undergoing endoscopy in another 14 studies (OR=0.55; 95% CI, 0.31-0.95;



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Authors	Years	Journal	<i>Hp</i> testing meth od	Biopsy locati on	BE	Control	Sex match	Age m atch	BMI/obesity match	Smoking match	Alcohol match	Race match
Aghayeva et al. [36]	2019	Dis Esophagus	H*,R ⁺	Antrum	IM ⁺	Endoscopy	Yes	Yes	Not clear	Not clear	Not clear	Yes
Chen et al. [13]	2016	PLoS One	Я	Antrum	IM	Primary care	Yes	Yes	Not clear	Not clear	Not clear	Not clear
Chuang et al. [37]	2019	Kaohsiung Journal of Medical Sci- ences	H, R, U ^s	Not clear	Not clear	GERD ^{II}	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
Corley et al. [38]	2008	Gut	S ª		M	Population	Yes	Yes	Not clear	Not clear	Not clear	Not clear
Csendes et al. [39]	1997	Dis Esophagus	Т	Antrum	Gastric epithe- lium ≥ 3 cm or IM	Endoscopy, Primary care	No	No	Not clear	Not clear	Not clear	Not clear
Dore et al. [63]	2016	Scand J Gastro- enterol	H, R, 13C-UBT	Antrum, Angu- lus, Corpus	M	GERD	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
Ferrández et al. [12]	2006	BMC Gastroen- terol	S		M	Blood donor	Yes	Yes	Not clear	No	No	Not clear
Fischbach et al. [40]	2014	Am J Gastroen- terol	H, C*	Antrum, Cor- pus, Cardia	M	Endoscopy	Yes	Yes	Yes	No	Not clear	No
Hackelsberger et al. [41]	1998	Gut	H, R	Antrum, Corpus	Endoscopic diagnose	Endoscopy	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
Hirota et al. [42]	1999	Gastroenterol- ogy	т	EGJ ⁺⁺	M	Endoscopy	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
Katsinelos et al. [44]	2013	Hippokratia	ж	Antrum	M	Endoscopy	Yes	Yes	Yes	Yes	Yes	Not clear
Keyashian et al. [64]	2013	Dis Esophagus	H, S, stool antigen	Not clear	M	GERD	No	No	Yes	Yes	Not clear	Not clear
Kiltz et al. [45]	2002	Eur J Gastroen- terol Hepatol	R, S	Antrum, Corpus	MI	Endoscopy	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
Laheij et al. [46]	2002	Alimentary Pharmacology and Therapeu- tics	H, R, C	Antrum	CM [#]	Endoscopy	No	Not clear	Not clear	Not clear	Not clear	Not clear
Loffeld et al. [47]	2000	Digestion	H, R, S, C	Antrum	CM	Endoscopy	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
Loffeld et al. [48]	2004	Netherlands Journal of Medicine	H, C	Antrum	Not clear	Endoscopy	Not clear	No	Not clear	Not clear	Not clear	Not clear
Newton et al. [49]	1997	Gut	ж	A ntrum	Not clear	GERD	No	No	Not clear	Not clear	Not clear	Not clear

Table 1 (cont	tinued)											
Authors	Years	Journal	<i>Hp</i> testing meth od	Biopsy locati on	BE	Control	Sex match	Age m atch	BMI/obesity match	Smoking match	Alcohol match	Race match
Öberg et al. [43]	1999	Archives of Surgery	т	Antrum, biop- sies just below SCJ ^{§§}	M	GERD	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
Park et al. [50]	2009	J Clin Gastro- enterol	H, R, S	Not clear	M	Endoscopy	No	No	No	No	No	Yes
Paull and Yardley [51]	1988	Gastroenterol- ogy	Т	Gastric biopsy	Not clear	Endoscopy	Yes	Yes	Not clear	Not clear	Not clear	Not clear
Rajendra et al. [<mark>5</mark> 2]	2007	Helicobacter	H, R, S	Antrum, Cor- pus, Cardia	M	GERD	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
Ronkainen et al. [53]	2005	Gastroenterol- ogy	H, C	Antrum, Corpus	M	Population	Not clear	Not clear	Not clear	No	No	Not clear
Rubenstein et al. [54]	2014	Clin Gastroen- terol Hepatol	S		M	GERD	Yes	Not clear	Not clear	Not clear	Not clear	Not clear
Sharifi et al. [<mark>55</mark>]	2014	Gastroenterol Res Pract	ж	Antrum	M	GERD	Yes	No	No	Yes	Yes	Not clear
Sonnenberg et al. [56]	2010	Gastroenterol- ogy	Т	Stomach	M	Endoscopy	No	No	Not clear	Not clear	Not clear	Not clear
Sonnenberg et al. [11]	2017	Aliment Phar- macol Ther	Т	Stomach	M	Endoscopy	No	No	Not clear	Not clear	Not clear	No
Thrift et al. [57]	2012	Int J Cancer	S		M	Population	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
Usui et al. [35]	2019	J Clin Gastro- enterol	S		Endoscopic diagnose	Endoscopy	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
Vaezi et al. [58]	2000	Am J Gastroen- terol	Н,S	Antrum, Corpus	M	GERD	Not clear	Yes	Not clear	Not clear	Not clear	Not clear
Vicari et al. [59]	1998	Gastroenterol- ogy	H, S	Antrum, Fun- dus, Cardia	CM ≥ 3 cm or IM	GERD	Not clear	Yes	Not clear	Not clear	Not clear	Yes
Vieth et al. [65]	2000	Digestion	Т	Antrum, Corpus	MI	NUD	No	No	Not clear	Not clear	Not clear	Not clear
Weston et al. [60]	2000	Am J Gastroen- terol	Т	Stomach	M	GERD	Yes	Yes	Not clear	Yes	Yes	No
White et al. [61]	2008	Can J Gastro- enterol	Т	Not clear	M	Normal SCJ	No	Yes	Not clear	Not clear	Not clear	Not clear
Wu et al. [66]	2000	Alimentary Pharmacology and Therapeu- tics	H, R	Antrum, Corpus	M	GERD	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear
Zaninotto et al. [67]	2002	Dig Liver Dis	Т	Esophagus	M	GERD	No	No	Not clear	Not clear	Not clear	Not clear

Authors	Years	Journal	<i>Hp</i> testing meth od	Biopsy locati on	BE	Control	Sex match	Age m atch	BMI/obesity match	Smoking match	Alcohol match	Race match
Zhang et al. [62]	2004	World J Gastro- enterol	т	Antrum	M	GERD	Not clear	Not clear	Not clear	Not clear	Not clear	Not clear

*: Histology, 1: Rapid urease test, 4: Intestinal metaplasia, 5: Urea breath test, ||: Gastroesophageal reflux disease, ¶: Serology, **: Culture, 11: Esophagogastric junction, ‡ #: Columnar metaplasia, 55: Squamous Columnar Junction, |||: Non-ulcer dyspepsia

	BE		Con	trol		Odds Ratio	Odds Ratio
Studys	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
Aghayeva 2019	53	83	103	167	3.0%	1.10 [0.64, 1.89]	
Chen 2016	42	148	261	588	3.1%	0.50 [0.34, 0.74]	
Chuang 2019	224	369	1548	2597	3.2%	1.05 [0.84, 1.31]	+
Corley 2008	36	309	67	295	3.1%	0.45 [0.29, 0.70]	
Csendes 1997	20	100	38	190	2.9%	1.00 [0.55, 1.83]	
Dore 2016	47	108	1251	2928	3.1%	1.03 [0.70, 1.52]	
Ferrández 2006	91	104	159	213	2.9%	2.38 [1.23, 4.59]	
Fischbach 2014	35	218	146	439	3.1%	0.38 [0.25, 0.58]	
Hackelsberger 1998	43	108	156	315	3.1%	0.67 [0.43, 1.05]	
Hirota 1999	4	104	64	738	2.4%	0.42 [0.15, 1.18]	
Katsinelos 2013	14	75	414	1915	2.9%	0.83 [0.46, 1.50]	
Keyashian 2013	24	52	205	420	2.9%	0.90 [0.50, 1.60]	
Kiltz 2002	8	35	175	545	2.7%	0.63 [0.28, 1.41]	
Laheij 2002	6	23	281	528	2.5%	0.31 [0.12, 0.80]	
Loffeld 2000	14	36	248	454	2.8%	0.53 [0.26, 1.06]	
Loffeld 2004	55	179	1550	3975	3.1%	0.69 [0.50, 0.96]	
Newton 1997	4	16	15	36	2.1%	0.47 [0.13, 1.73]	
Park 2009	39	215	12173	20154	3.1%	0.15 [0.10, 0.21]	
Paull 1988	10	26	11	26	2.3%	0.85 [0.28, 2.58]	
Rajendra 2007	29	55	37	80	2.8%	1.30 [0.65, 2.58]	- <u>+</u>
Ronkainen 2005	5	16	383	984	2.4%	0.71 [0.25, 2.07]	
Rubenstein 2014	25	150	86	375	3.0%	0.67 [0.41, 1.10]	
Sharifi 2014	12	34	204	702	2.8%	1.33 [0.65, 2.74]	
Sonnenberg 2010	144	2510	9356	76475	3.2%	0.44 [0.37, 0.52]	-
Sonnenberg 2017	1972	76475	20683	284552	3.3%	0.34 [0.32, 0.35]	¥
Thrift 2012	28	296	73	390	3.0%	0.45 [0.28, 0.72]	_ .
Usui 2019	1764	7419	4596	29196	3.3%	1.67 [1.57, 1.78]	×
Vaezi 2000	28	83	36	108	2.9%	1.02 [0.56, 1.87]	
Vicari 1998	15	48	30	84	2.7%	0.82 [0.38, 1.74]	
Vieth 2000	463	1054	378	712	3.2%	0.69 [0.57, 0.84]	
Weston 2000	73	208	96	217	3.1%	0.68 [0.46, 1.01]	
White 2008	2	39	3	29	1.5%	0.47 [0.07, 3.00]	
Wu 2000	0	6	77	225	0.9%	0.15 [0.01, 2.65]	• • • • • • • • • • • • • • • • • • • •
Zaninotto 2002	6	34	7	32	2.2%	0.77 [0.23, 2.58]	•
Zhang 2004	60	120	31	93	3.0%	2.00 [1.14, 3.50]	
Oberg 1999	5	40	8	69	2.2%	1.09 [0.33, 3.59]	
Total (95% CI)		90895		430846	100.0%	0.70 [0.51, 0.96]	•
Total events	5400		54949				
Heterogeneity: Tau ² =	0.81; Chi ²	= 1855.	.34, df = 3	35 (P < 0.	00001); l ²	= 98%	
Test for overall effect:	Z = 2.18 (P = 0.03	3)	·	.,		Favours [BE] Favours [control]

Fig. 2 Forest plot of the random effect analysis of the 36 studies. The weights and heterogeneities of studies are indicated too. OR: Odds ratio, CI: 95% confidence interval

P=0.03; $I^2=99\%$) or normal control (population or primary care people) in four studies (OR=0.48; 95% CI, 0.38–0.61; P<0.00001; $I^2=0\%$) as control groups (Fig. 4) [11, 13, 35, 36, 38, 40–42, 44–48, 50, 51, 53, 56, 57]. When BE was defined as intestinal metaplasia (IM) in 26 studies, we found an increased negative correlation between Hp prevalence and BE (OR=0.64; 95% CI, 0.51–0.80; P=0.0001; $I^2=90\%$) [11, 12, 13, 36, 38, 40, 42–45, 50, 52–58, 60–67]. However, the negative correlation disappeared (OR=0.76; 95% CI, 0.51–1.14; P=0.18; $I^2=92\%$) in the other subgroups, which diagnosed BE with columnar metaplasia (CM), endoscopic presentation, no clear definition, and gastric epithelium [35, 37, 39, 41, 46–49, 51, 59]. In addition, we divided the studies according to whether Hp could be confirmed as a present infection, into the present infected subgroup (Hp positive with rapid urease test, urea breath test, histology, or culture), infection history subgroup (Hp positive with serological detection, treatment history, or infection history), and not clear subgroup. In the present infected group with 24 studies, the prevalence of Hp infection in BE was significantly lower than that in controls (OR=0.69; 95% CI, 0.54–0.89; P=0.005; $I^2=92\%$) [11, 13, 36, 37, 39–44, 4648, 49, 51, 53, 55, 56, 60–63, 65–67], while the negative correlation disappeared again in the infection



history subgroup (OR = 0.88; 95% CI, 0.43–1.78; *P*=0.73; I²=95%) (Fig. 5) [12, 35, 38, 54, 57].

Correlation between Hp and length of BE

We extracted data from 11 studies to explore the correlation between Hp and LSBE, and obtained a total of 669 BE patients and 31,243 controls [35, 42, 45, 58, 62, 67, 68–72]. We found that the risk of *Hp* infection in patients with LSBE was significantly lower than that in the controls (OR = 0.47; 95% CI, 0.25–0.90; P = 0.02; $I^2 = 82\%$). In contrast, we extracted data from 12 studies to explore the correlation between Hp and short-segment BE (SSBE), and obtained a t otal of 7886 BE patients and 31,173 controls [35, 36, 42, 45, 58, 62, 67, 73, 70, 74-76]. There was no significant difference in the prevalence of *Hp* between the SSBE and controls (OR=1.11; 95% CI, 0.78-1.56; P=0.57; I²=68%). Although the same Hp infection rate was observed in the ultra-short-segment BE (USBE) and GERD groups (22%, 2/9 vs. 22% 7/32) in Zaninotto's study, such a small sample size might lead to bias [67]. Matsuzaki's research suggested that the Hp infection rate in USBE was lower than that in controls, but the difference was not significant (66.3%, 57/86 vs 72.5%, 50/69; *P*>0.05) [76].

Correlation between Hp and BE dysplasia

Only four previous studies have focused on whether *Hp* reduces the risk of BE dysplasia [11, 36, 5765]. Decades

ago, Vieth found that patients with BE neoplasia (highgrade dysplasia or EAC) had significantly lower rates of *Hp* infection than patients with non-ulcer dyspepsia (P < 0.01), which was also lower than that observed in patients with simple BE [65]. This conclusion was further confirmed by two subsequent studies. In a populationbased case-control study, Thrift determined that patients with BE had a lower likelihood of infection with Hp (OR = 0.37; 95% CI, 0.22–0.61) as was observed in many other studies. The BE group was then divided into two subgroups: BE without dysplasia and BE with dysplasia, and showed a reduced negative correlation (OR = 0.51; 95% CI, 0.30-0.86) and an increased negative correlation (OR = 0.10; 95% CI, 0.03–0. 33) when compared to population control, respectively [57]. Another case-control study with many more research objects further verifi ed this fin ding. When defining cases as BE with dysplasia or cancer, instead of simple BE, the negative correlation between *Hp* and the cases became stronger (OR = 0.31; 95% CI, 0.26–0.37 vs OR = 0.36; 95% CI, 0.34–0.38) [11]. However, a recent study in Azerbaijan, a high-prevalence area of Hp infection, directly compared BE with and without dysplasia, and found no significant difference in *Hp* infection between the two groups (OR = 0.42; 95% CI, 0.12-1.52; P>0.05) [36]. Details of these studies are shown in Table 2.

Definition of control Events Total Weight M.H. Random, 59% CI M.H. Random, 59% CI 4.1 GEND	[0				Odda Datia
Deminstruction to Control Contro Control Contro	Definition of control	Evente	Total	Con	Total	Maight	Udds Ratio	Udds Ratio
A TOLTO Chung 2019 224 369 1548 2597 3.6% 105 [0.84, 131] Dore 2016 47 108 1251 2928 3.5% 10.0 [0.70, 152] Keystaina 7013 24 52 205 420 3.3% 0.90 [0.50, 160] Telescription 1997 4 16 15 35 2.4% 0.47 [0.13, 173] Rubenstein 2014 25 150 66 375 3.4% 0.67 [0.41, 110] Sharif 2014 12 24 204 702 3.1% 1.33 [0.65, 256] Tubenstein 2014 22 8 120 28 83 35 108 3.3% 10.2 [0.56, 167] Vacal 2000 28 83 35 108 3.3% 10.2 [0.56, 174] Vacal 2000 0 6 77 7225 1.0% 0.15 [0.01, 255] Zhang 2004 60 120 31 39 3.3% 0.09 [0.86, 174] Zhang 2004 60 120 31 39 3.3% 0.09 [0.86, 174] Tabl events 552 73 83 103 167 3.3% 1.10 [0.64, 1.89] Fischbach 2014 125 48 30 44 31% 0.39 [0.82, 1.19] Zhang 2004 60 120 31 39 3.3% 0.09 [0.82, 1.19] Zhang 2004 60 120 31 39 3.3% 0.09 [0.82, 1.19] Zhang 2004 60 120 31 193 3.3% 0.09 [0.82, 1.19] Zhang 2004 60 120 31 193 3.3% 0.09 [0.82, 1.19] Zhang 2004 60 120 31 193 3.3% 0.09 [0.82, 1.19] Zhang 2004 60 120 31 193 3.3% 0.10 [0.64, 1.89] Fischbach 2014 135 218 146 439 3.4% 0.38 [0.26, 0.59] Hitota 1999 43 108 156 15 3.4% 0.67 [0.41, 1.0] Hitot 1999 44 104 64 738 2.7% 0.42 [0.15, 1.16] Hitot 1999 43 108 156 15 3.4% 0.81 [0.62, 1.19] Hitot 1999 43 108 156 15 3.4% 0.81 [0.62, 0.50] Hitot 1999 54 210 12 [0.773 2068 2.650] Tabl events 4161 4995 Hitot 1995 44 104 64 738 2.7% 0.42 [0.15, 1.16] Hitot 1999 59 215 12173 20154 3.5% 0.81 [0.60, 0.56] Tabl events 4161 4995 Hitot 1995 44 104 64 738 2.7% 0.48 [0.20, 0.50] Hitot 1995 75 3.5% 0.44 [0.37, 0.52] Tabl events 4161 4995 Hitot 1995 75 3.5% 0.44 [0.37, 0.52] Tabl events 4161 4995 Hitot 1995 41 19 7.527 2.258 2.250 7 Tabl events 4161 42 2.10 [9.957 3.5% 0.44 [0.37, 0.52] Tabl events 4264 5477 1.068 3.4% 0.50 [0.34, 0.74] Tabl events 4224 5477 2.0683 2.456 3.3% 0.50 [0.34, 0.74] Tabl events 4224 5477 1.078 7.2277 1.29% 0.428 [0.28, 0.72] Tabl events 4224 5477 1.078 7.2277 1.29% 0.48 [0.28, 0.72] Tabl events 4224 5477 1.00001); F = 99% Test for overall effect 2.7 - 21.0 (P - 0.00001); F = 99% Test for overall effect 2.7 - 21.0 (P - 0.0000		Lveins	TOLAI	Lvents	TUtai	weight	M-11, Kaliuolii, 55% CI	
Chulag 2019 2.24 399 3940 2.297 3.5% 1.09 [0.64, 1.31] Done 2016 47 108 1251 2.282 3.5% 0.99 [0.50, 1.60] Kayashian 2013 2.4 52 205 4.20 3.3% 0.99 [0.50, 1.60] Kayashian 2013 2.4 52 205 4.20 3.3% 0.99 [0.50, 1.60] Markon 1997 4 16 15 36 2.4% 0.47 [0.15, 1.73] Rajendra 2007 2.9 55 37 80 3.2% 1.30 [0.65, 2.56] Weash 2014 2.5 150 66 3.7% 1.4% 0.67 [0.41, 1.10] Sharii 2014 2.5 150 66 3.7% 1.4% 0.68 [0.46, 1.01] Weash 2000 7 3 2.08 56 2.17 3.4% 0.68 [0.46, 1.01] Weash 2000 7 3 2.08 56 2.17 3.4% 0.68 [0.46, 1.01] Weash 2000 7 3 2.08 56 2.17 3.4% 0.68 [0.46, 1.01] Weash 2000 7 3 2.08 56 2.17 3.4% 0.68 [0.46, 1.01] Weash 2000 7 3 2.08 56 2.17 3.4% 0.58 [0.61, 7] Zhang 2004 60 120 31 39 3.3% 2.00 [1.14, 3.50] Doberg 1999 5 4 0 8 69 2.5% 1.90 [0.56, 617] Zhang 2004 60 120 31 49 3.3% 0.99 [0.82, 1.19] Subtool (9% Ct) 1323 8003 41.5% 0.99 [0.82, 1.19] Fact for overall effect 2.7 6.11 (P = 0.92) 4.2 Subjects undergoing endoscopy Aghayeva 2019 53 83 103 167 3.3% 1.10 [0.64, 1.89] Heterogeneity. Tau" = 0.03, Ch ² = 179, 5, df = 13 (P = 0.16); P = 28% Test for overall effect 2.7 6.11 (P = 0.92) 4.2 Subjects undergoing endoscopy Aghayeva 2019 53 83 103 167 3.3% 0.81 [0.12, 0.80] Hackelberger 1998 4 104 64 738 2.7% 0.42 [0.15, 1.8] Heterogeneity. Tau" = 0.03; Ch ² = 179, 5, df = 13 (P = 0.16); P = 99% Test for overall effect 2.7 6.17 [9 = 0.03] 4.2 Subjects undergoing endoscopy Aghayeva 2019 174 12 76475 2.0683 2.46453 2.3% 0.45 [0.20, 0.70] Hackelberger 1998 4 10 26 11 2.6 2.6% 0.65 [0.34, 0.74] Chef 2000 14 36 2.46 44 3.3.4% 0.50 [0.34, 0.74] Chef 2001 14 42 2.16 9.20 A 30 90 67 2.257 4.2.9% 0.45 [0.20, 0.70] Heterogeneity. Tau" = 1.03; Ch ² = 137.87, df = 13 (P < 0.00001); P = 99% Test for overall effect Z = 2.17 (P = 0.03) Test for overall effect Z = 2.17 (P = 0.03) Test for overall effect Z = 2.17 (P = 0.00001); P = 99% Test for overall effect Z = 2.17 (P = 0.0001); P = 90% Test for overall effect Z = 2.17 (P = 0.00001); P = 90% Test for overall effect Z = 2.17 (P = 0.00001); P = 9	4.1 GERD	224	200	45.40	2507	2.00/		L
Dote 2015 4 / 108 1231 2928 3.5% 10.0 [2.0, 1.52] Newton 1997 4 16 15 35 245 40 3.3% 0.90 [0.50, 1.50] Rubenstein 2014 25 150 66 375 3.4% 0.67 [0.41, 1.10] Sharif 2014 12 13 204 204 702 3.1% 1.33 [0.65, 2.56] Alexandro 2000 73 208 35 36 108 3.3% 10.0 [0.56, 1.67] Vacal 2000 10 6 77 225 1.0% 0.82 [0.81, 1.74] Weston 2000 73 208 96 217 3.4% 0.68 [0.46, 1.01] We 2000 0 6 77 225 1.0% 0.15 [0.01, 2.65] Zhang 2004 60 120 31 93 3.3% 0.20 [1.14, 3.50] Oberg 1998 5 40 8 69 2.5% 1.99 [0.58, 6.17] Zhang 2004 60 120 31 93 3.3% 0.39 [0.52, 1.19] Tatal events 552 715 545 3.0% 0.68 [0.26, 1.19] Heterogenety: Tat ² = 0.03, Ch ² = 17.95, df = 13 (P = 0.16); P = 28% Tast for overall effect 2 = 0.11; P = 0.92; 42 Subjects undergoing endoscopy 42 Subjects undergoing endoscopy 43 Subtola (15% Ct) 175 545 3.0% 0.68 [0.26, 1.16] 44 256 23 281 552 27% 0.42 (0.15, 1.18] 45 Cher 216 0.11; P = 0.92; 42 Subjects undergoing endoscopy 43 Park 2002 6 23 281 552 2.5% 0.31 [0.10, 0.81] 41 Ficto 1899 4 104 64 738 2.27% 0.42 (0.15, 1.18] 41 Ficto 1895 9 4 104 64 738 2.27% 0.42 (0.15, 1.18] 42 Subjects undergoing endoscopy 43 Park 2002 6 23 281 552 2.5% 0.58 [0.26, 1.06] 43 Park 2009 39 215 12173 20154 3.5% 0.51 [0.10, 0.21] 43 Park 2019 1764 7419 456 23196 3.6% 167 [1.5%, 1.78] 43 Park 2019 764 7419 456 23196 3.6% 168 [0.26, 0.56] 43 Park 2019 764 7419 456 23196 3.6% 168 [0.26, 0.72] 50 Cher 2016 42 418 261 588 3.4% 0.50 [0.34, 0.74] 50 Cher 2016 42 418 261 588 3.4% 0.50 [0.34, 0.74] 50 Cher 2016 42 418 261 588 3.4% 0.50 [0.34, 0.74] 50 Cher 2016 42 418 261 588 3.4% 0.50 [0.34, 0.74] 50 Cher 2016 42 418 261 588 3.4% 0.50 [0.34, 0.74] 50 Cher 2016 42 418 261 588 3.4% 0.50 [0.34, 0.74] 50 Cher 2016 42 418 261 588 3.4% 0.50 [0.34, 0.55] 50 Cher 2016 42 418 2257 12.9% 0.48 [0	Chuang 2019	224	369	1548	2597	3.6%	1.05 [0.84, 1.31]	
	Dore 2016	41	108	1251	2928	3.5%	1.03 [0.70, 1.52]	
Newton 1997 4 16 15 36 24% 047 [0.13, 17.3] Ruberstein 2014 25 150 86 375 3.4% 0.67 [0.41, 1.0] Vacal 1998 15 48 30 84 3.1% 0.82 [0.55, 1.8] Vacal 1998 15 48 30 84 3.1% 0.82 [0.38, 1.74] Vacal 2000 73 208 96 217 3.4% 0.88 [0.46, 1.01] Vacal 1998 15 48 30 84 3.1% 0.82 [0.38, 1.74] Vestino 2000 73 208 96 217 3.4% 0.88 [0.46, 1.01] Vacal 1999 15 40 3 69 2.5% 1.90 [0.58, 6.17] Table overall effect 2 = 0.11 ($P = 0.16$); $P = 28\%$ Test for overall effect 2 = 0.11 ($P = 0.92$) 4.2 Subtotal (5% C) 1232 8003 41.5% 0.99 [0.82, 1.19] Total events 552 3631 Heterogeneity: Tau ² = 0.03; Ch ² = 1795; df = 13; ($P = 0.16$); $P = 28\%$ Test for overall effect 2 = 0.11 ($P = 0.92$) 4.2 Subtotal (5% C) 1322 8003 41.5% 0.98 [0.62, 0.51] Hackeberger 1998 4 104 64 738 2.7% 0.42 [0.15, 1.18] Hackeberger 1998 4 104 64 738 2.7% 0.42 [0.15, 1.18] Hackebergeneity: Tau ² = 0.03; Ch ² = 1795; df = 13; ($P = 0.16$); $P = 28\%$ Test for overall effect 2 = 0.11 ($P = 0.92$) 4.2 Subtotal (250 2.68] Hackeberger 1998 4 104 64 738 2.7% 0.42 [0.15, 1.18] Hackebergeneity: Tau ² = 0.03; Ch ² = 0.16; $P = 28\%$ Test for overall effect 2 = 0.11 ($P = 0.92$) 4.3 Polyacian 2014 425 103 56 754 5.35% 0.63 [0.26, 1.61] Loffed 2004 14 36 244 844 3.2% 0.53 [0.26, 1.66] Loffed 2004 14 36 24 844 3.2% 0.53 [0.26, 1.66] Loffed 2004 14 36 24 844 3.2% 0.53 [0.28, 1.61] Loffed 2004 15 179 1550 3975 3.5% 0.42 [0.15, 1.78] Somemberg 2017 1472 76475 2068 3.84552 3.6% 0.50 [0.34, 0.74] Loffed 2004 15 179 2.16 4.35% 0.15 [0.10, 2.1] Paul 1988 10 26 11 26 2.6% 0.48 [0.28, 2.68] Somemberg 2017 1472 76475 2068 3.48452 2.36% 0.55 [0.31, 0.59] Total events 4161 49966 Heterogeneity: Tau ² = 0.3; Ch ² = 1759; J7, 1.4f = 31 ($P < 0.00001$); $P = 99\%$ Total events 4161 49966 Heterogeneity: Tau ² = 0.31; Ch ² = 1759; J7, 1.4f = 31 ($P < 0.00001$); $P = 99\%$ Total events 4161 4996 Heterogeneity: Tau ² = 0.31; Ch ² = 1759; J7, 1.4f = 31 ($P < 0.00001$); $P = 90\%$ Total events 111 74 Heterogeneity: Tau ² = 0.37; Ch ² = 378; Ch ² =	Keyashian 2013	24	52	205	420	3.3%	0.90 [0.50, 1.60]	
Rajendra 2007 29 65 37 30 32% 0.57 (0.1, 1.10) Shafi 2014 12 34 204 702 3.1% 0.56 (5.7.4) Vical 1998 15 48 30 84 3.1% 0.52 (0.51, 87) Vical 1998 15 48 30 84 3.1% 0.52 (0.51, 87) Vical 1998 15 48 30 84 3.1% 0.52 (0.51, 87) Vical 1998 15 48 30 84 3.1% 0.52 (0.58, 87) Vical 1998 15 48 30 84 3.1% 0.52 (0.58, 8.7) Zhang 2004 60 120 31 33 3.3% 2.00 (1.14, 3.50) Debrg 1999 5 40 8 69 2.5% 1.90 (0.58, 6.17) Zhang 2004 60 120 31 33 3.3% 0.99 (0.82, 1.19] Total events 552 9.631 Heterogenety. Tau ⁺ = 0.03; Ch ⁺ = 17.95, df = 13 (P = 0.16); P = 28% Test for overall effect $Z = 0.11 (P = 0.52)$ Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Adphayeva 2019 53 88 103 167 3.3% 1.10 [0.64, 1.89] Fischbach 2014 35 218 146 439 3.4% 0.37 (0.25, 0.58] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 125 12173 20154 3.5% 0.63 (0.28, 1.41] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.28, 1.50] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.28, 1.50] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.28, 1.50] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.28, 1.50] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.28, 1.50] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.28, 1.50] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.28, 2.68] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.28, 2.68] Hitosi 100 2.6 11 2.6 2.6% 0.56 (0.28, 2.68] Hitosi 11 7.7475 2.0683 2.0455 3.36% 0.44 (0.37, 0.52] Hitosi 0.42 (0.48, 2.74) 0.42 (0.48, 0.58] Hitosi 0.42 (0.48, 2.74) 0.44 (0.37, 0.52] Hitosi 0.5% (0) 65% (0) 769 2.257 1.2.9% 0.48 (0.38, 0.61] Hitosi 0.42 (0.5% (0) 769 2.257 1.2.9% 0.48 (0.38, 0.61] Hitosi 0.42 (0.5% (0) 769 2.257 1.2.9% 0.48 (0.38, 0.61] Hitosi 0.42 (0.5% (0) 769 2.257 1.2.9% 0.48 (0.38, 0.61] Hitosi 0.42 (0.5% (0) 769	Newton 1997	4	16	15	36	2.4%	0.47 [0.13, 1.73]	
Rubenselin 2014 25 150 86 375 3.4% 0.67 [0.41, 1.0] Vacai 1998 15 48 30 84 3.1% 0.82 [0.56, 1.87] Vacai 2000 28 83 36 108 3.3% 1.02 [0.56, 1.87] Vacai 1998 15 48 30 84 3.1% 0.82 [0.38, 1.74] Westno 2000 73 208 96 217 3.4% 0.82 [0.46, 1.01] Vacai 2000 6 6 77 225 1.0% 0.15 [0.01, 2.85] Zaninoto 2002 6 34 7 69 2.5% 1.90 [0.58, 6.17] Zanag 2004 60 120 31 93 3.33% 2.00 [1.4, 3.50] Chear 1999 5 40 8 69 2.5% 1.99 [0.33, 3.59] Total events 552 3631 Heterogenety: Tau ² = 0.3; Ch ² = 1.95 cft = 1.3 (P = 0.16); P = 28% Test for overall effect Z = 0.11 (P = 0.92) 4.2 Subjects undergoing endoscopy Aghaywa 2014 35 218 146 439 3.4% 0.38 [0.25, 0.58] Tast and 2.00 14 35 218 146 439 3.4% 0.38 [0.25, 0.58] Tast and 2.00 14 35 218 146 439 3.4% 0.53 [0.25, 0.58] Tast and 2.00 14 35 218 146 439 3.4% 0.53 [0.25, 0.58] Tast and 2.00 14 35 218 146 439 3.4% 0.53 [0.25, 0.58] Tast and 2.00 14 35 218 146 439 3.4% 0.53 [0.25, 0.58] Tast and 2.00 14 35 218 146 439 3.4% 0.53 [0.25, 0.58] Tast and 2.5% 0.53 [0.24, 1.10] Tast and 2.5% 0.5% 0.55 [0.31, 0.55] Tast and 2.5% 0.5% 0.55 [0.31, 0.55] Total events 4161 4996 Tast and 2.5% 0.5% 0.55 [0.31, 0.55] Total events 4161 4996 Tast and 2.5 (Ch ² = 1759 7.7, 1.2 (F475 3.5% 0.44 [0.32, 0.76] Total events 4161 4996 Tast and 2.5% 0.5% 0.5% 0.5% [0.31, 0.74] Total events 4161 4996 Total events 4161 7 495 (0.38) 0.44 [0.38, 0.71] Total events 4161 7 4976 Total events 4161 7 4976 Total events 4161 7 4976 Total events 4161 7 4976 Test for overall effect Z = 2.17 (P = 0.03) Tast for overall effect Z = 5.17 (P < 0.00001); P = 93% Test for overall effect Z = 5.17 (P < 0.00001); P = 93% Test for overall effect Z = 5.	Rajendra 2007	29	55	37	80	3.2%	1.30 [0.65, 2.58]	
Shafin 2014 12 34 204 702 3.1% 1.33 (0.55, 2.74) Vican 1996 15 48 30 84 3.3% 1.02 (0.56, 1.87) Vican 1998 15 48 30 84 3.1% 0.82 (0.38, 1.74) Wiston 2000 73 208 96 217 3.4% 0.68 (0.64, 1.01) Wiston 2000 6 34 7 69 2.5% 1.90 (0.86, 6.17) Zhang 204 60 120 31 33 3.3% 0.99 (0.82, 1.19] Oberg 1999 5 40 8 69 2.5% 1.90 (0.86, 6.17) Total events 552 9.631 Heterogeneity, Tau ⁺ = 0.03; Ch ⁺ = 17.95, df = 13 (P = 0.16); P = 28% Test for overall effect $Z = 0.11 (P = 0.52)$ Hitosi 1999 4 104 64 738 2.7% 0.028 (0.25, 0.58] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 4 104 64 738 2.7% 0.42 (0.15, 1.18] Hitosi 1999 125 12173 20154 3.5% 0.63 (0.28, 1.41) Hitosi 1999 125 1273 20154 3.5% 0.63 (0.28, 1.41) Hitosi 1999 126 127 2.28 2.28% 0.31 (0.16, 0.21) Hitosi 1999 126 127 2.28 2.48% 0.31 (0.2, 0.81) Hitosi 1999 126 127 2.28 2.48% 0.31 (0.16, 0.21) Hitosi 1999 126 127 2.02 2.46% 0.56 (0.28, 2.58] Somenberg 2010 114 2.510 9.376 5.36% 0.44 (0.37, 0.52] Test for overall effect $Z = 2.17 (P = 0.30)$ 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 (0.34, 0.74] Heterogeneity, Tau ⁺ = 0.07; Ch ⁺ = 137.67, df = 3 (P = 0.00001); P = 99% Test for overall effect; $Z = 2.57 (P < 0.00001)$ Total events 111 784 Heterogeneity, Tau ⁺ = 0.87; Ch ⁺ = 133.78, df = 31 (P < 0.00001); P = 94.36. Total events 111 764 Heterogeneity, Tau ⁺ = 0.87; Ch ⁺ = 133.78, ff = 3 (P < 0.00001); P = 94.36. Total events 111 704 Heterogeneity, Tau ⁺ = 0.87; Ch	Rubenstein 2014	25	150	86	375	3.4%	0.67 [0.41, 1.10]	
Vacai 1998 15 48 30 84 3.1% 0.22 (0.58, 1.87) Weston 2000 73 208 96 217 3.4% 0.68 (0.46, 101) Weston 2000 0 6 77 225 1.0% 0.15 [101], 265 Zaninoto 2002 6 34 7 69 2.5% 1.90 [0.58, 6.17] Zaninoto 2002 6 34 7 69 2.5% 1.90 [0.58, 6.17] Chang 2004 60 120 31 93 33.3% 2.00 (1.14, 3.50) Oberg 1999 5 40 8 69 2.5% 1.90 [0.33, 3.59] Subtatal (95% CI) 1323 8003 41.5% 0.99 [0.82, 1.19] Total events 552 3631 Heterogeneity: Tau ² = 0.0; Ch ² = 17, 95, df = 13 ($P = 0.16$); $P = 28\%$ Test for overall effect Z = 0.11 ($P = 0.16$); $P = 28\%$ Test for overall effect Z = 0.11 ($P = 0.16$); $P = 28\%$ Test for overall effect Z = 0.11 ($P = 0.16$); $P = 28\%$ Test for overall effect Z = 0.11 ($P = 0.92$) 4.2 Subjects undergoing endoscopy Aghayeva 2019 53 83 103 167 3.3% 1.10 [0.64, 1.89] Hackeberger 1998 43 108 165 315 3.4% 0.53 [0.25, 0.58] Hackeberger 1998 43 108 165 315 3.4% 0.53 [0.26, 1.05] Lofied 2000 14 35 248 454 3.2% 0.53 [0.26, 1.06] Lofied 2000 14 36 246 454 3.2% 0.53 [0.26, 1.06] Park 2009 39 215 12173 20154 3.5% 0.68 [0.00, 9.6] Park 2009 39 215 12173 20154 3.5% 0.58 [0.03, 0.63] Lofied 2004 55 179 1560 3975 3.5% 0.68 [0.00, 9.6] Park 2009 39 215 12173 20154 3.5% 0.58 [0.28, 2.68] Somenberg 2010 144 2510 9956 76475 3.6% 0.44 [0.32, 0.52] Somenberg 2010 142 2510 9956 76475 3.6% 0.44 [0.32, 0.52] Value vents 4161 49956 Heterogeneity: Tau ² = 1.03; Ch ² = 1759.71, df = 13 ($P < 0.0001$); $P = 99\%$ Test for overall effect $Z = 2.13 (P = 0.03)$ 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Conter 208 36 309 67 295 3.4% 0.45 [0.28, 0.72] Subtotal (95% C) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ² = 0.03; Ch ² = 0.77); P = 0.% Test for overall effect $Z = 2.12 (P = 0.03)$ Total events 111 784 Heterogeneity: Tau ² = 0.37; Ch ² = 37, P = 0.4001); P = 91.4%. Test for overall effect $Z = 2.12 (P = 0.03)$ Total events 4824 54373 100.0% 0.69 [0.49, 0.97] Total events 4824 54373 100.0% 0.69 [0.49, 0.97] Total events	Sharifi 2014	12	34	204	702	3.1%	1.33 [0.65, 2.74]	
Vican 1998 15 48 30 84 3.1% 0.82 [0.38, 174] Weston 2000 73 208 96 217 3.4% 0.68 (0.46, 101) Wu 2000 0 6 77 225 1.0% 0.15 [0.01, 265] Zhang 2004 60 120 31 93 3.3% 2.00 [1.14, 3.50] Oberg 1999 5 40 8 69 2.5% 1.09 [0.33, 3.59] Subtotal (95% CI) 1223 8003 41.5% 0.99 [0.32, 1.19] Total events 552 3631 Heterogeneity: Tat" = 0.03, Chi ² = 17.95, df = 13 (P = 0.16); P = 28% Test for overall effect $Z = 0.11$ (P = 0.92) 4.2 Subjects undergoing endoscopy Aghayeva 2014 63 83 103 167 3.3% 1.10 [0.64, 1.89] Fischbach 2014 35 218 146 439 3.4% 0.38 [0.25, 0.58] Hickebaspergr 199 43 108 156 315 3.4% 0.67 (0.43, 105) Hickebaspergr 199 44 104 64 738 2.7% 0.42 [0.15, 118] Katsindes 2013 14 75 414 1975 3.3% 0.30 [0.46, 1.50] Hickebaspergr 199 43 108 156 315 3.4% 0.67 (0.43, 105) Hickebaspergr 199 44 104 64 738 2.7% 0.42 [0.15, 1.18] Lafiel 2000 14 36 248 454 3.2% 0.53 [0.26, 1.61] Lafiel 2000 14 36 248 454 3.2% 0.53 [0.26, 1.61] Lafiel 2000 14 251 9275 3.5% 0.59 [0.50, 0.56] Park 2009 39 215 12173 20154 3.5% 0.15 [0.10, 0.21] Paul 1988 10 26 11 26 2.6% 0.85 [0.28, 2.88] Somenberg 2017 1972 76475 20683 284552 3.6% 0.34 [0.37, 0.52] Total events 4161 4956 Heterogeneiby: Tat" = 1.03; Chi ² = 1759.71, df = 13 (P < 0.0001); P = 99% Test for overall effect $Z = 213$ (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 568 3.4% 0.50 [0.34, 0.74] Total events 111 784 Heterogeneiby: Tat" = 1.03; Chi ² = 159.71, df = 13 (P < 0.0001); P = 99% Test for overall effect $Z = 213$ (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 568 3.4% 0.50 [0.34, 0.74] Total events 111 784 Heterogeneiby: Tat" = 1.03; Chi ² = 1.07; P = 0.67); P = 0.67); P = 0.67; P = 0.570; P = 0.57	Vaezi 2000	28	83	36	108	3.3%	1.02 [0.56, 1.87]	- +
Weston 2000 73 208 96 217 3.4% 0.88 [0.46, 101] Wu 2000 0 6 77 225 1.0% 0.15 [0.01, 2.65] Zaninoto 2002 6 34 7 69 2.5% 1.90 [0.58, 6.17] Deer 1999 5 40 8 69 2.5% 1.90 [0.58, 6.17] Deer 1999 5 40 8 69 2.5% 1.90 [0.33, 3.69] Total events 552 3631 Heterogeneity: Tat ² = 0.03; Chi ² = 17.95, df = 13 ($P = 0.16$); $P = 28$ % Test for overall effect $Z = 0.11 (P = 0.2)$ 4.2 Subjects undergoing endoscopy Aghayeva 2019 53 83 103 167 3.3% 1.10 [0.64, 1.89] Test for overall effect $Z = 0.11 (P = 0.2)$ 4.2 Subjects undergoing endoscopy Aghayeva 2019 53 83 103 167 3.3% 0.81 [0.45, 1.58] Hackeberger 1998 43 108 156 315 3.4% 0.83 [0.25, 0.58] Hackeberger 1998 43 108 156 315 3.4% 0.83 [0.25, 0.58] Hackeberger 1998 43 108 156 315 3.4% 0.38 [0.25, 0.58] Loffed 2000 14 35 248 424 3.2% 0.53 [0.28, 1.41] Loffed 2000 14 36 248 454 3.2% 0.53 [0.28, 1.41] Loffed 2000 14 36 246 443 3.2% 0.53 [0.26, 1.06] Park 2009 39 215 1217 20154 3.5% 0.68 [0.50, 0.96] Park 2009 39 215 1217 20154 3.5% 0.44 [0.32, 0.52] Sonnenberg 2010 144 2510 9365 76475 3.6% 0.44 [0.32, 0.52] Valuto 14 9956 Heterogeneity: Tat ² = 1.03; Ch ² = 1759; 71, df = 13 ($P < 0.0001$); $P = 99\%$ Total events 4161 49956 Heterogeneity: Tat ² = 1.03; Ch ² = 1759; 71, df = 13 ($P < 0.0001$); $P = 99\%$ Total events 4161 49956 Heterogeneity: Tat ² = 0.03; Ch ² = 0.77; $P = 0.87$; $P = 0.77$; $P = 0.87$; $P = 0.$	Vicari 1998	15	48	30	84	3.1%	0.82 [0.38, 1.74]	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Weston 2000	73	208	96	217	3.4%	0.68 [0.46, 1.01]	
Zanincito 2002 6 34 7 69 2.5% 1.90 [0.58, 6.17] Zhang 2004 60 120 31 93 33% 2.00 [1.14, 3.50] Oberg 1999 5 40 8 69 2.5% 1.09 [0.33, 3.59] Subtatal (95% CI) 1323 3631 41.5% 0.99 [0.32, 1.19] Total events $= 0.52$ 3631 Heterogeneity: Tau ² = 0.03; Ch ² = 17.5; df = 13 (P = 0.16); l ² = 28% Test for overall effect $Z = 0.11 (P = 0.32)$ 4.2 Subjects undergoing endoscopy Aghayeva 2019 53 83 103 167 3.3% 1.10 [0.64, 1.89] Hackelsbarger 1998 43 108 156 315 3.4% 0.38 [0.25, 0.58] Hickatinelos 2013 14 75 414 1915 3.3% 0.42 [0.15, 1.18] Hickatinelos 2013 14 75 414 1915 3.3% 0.63 [0.26, 1.60] Loffed 2000 14 36 2.248 454 3.2% 0.63 [0.26, 1.60] Loffed 2000 14 36 2.248 2.8% 0.31 [0.12, 0.40] Hackelsbarger 2010 144 2510 3936 76475 3.6% 0.44 [0.37, 0.52] Park 2009 39 2.15 12173 20154 3.5% 0.059 [0.50, 0.56] Park 2009 39 2.15 12173 20154 3.5% 0.59 [0.50, 0.56] Park 2009 39 2.15 12173 20154 3.5% 0.59 [0.50, 0.56] Park 2009 39 2.15 12173 20154 3.5% 0.59 [0.50, 0.56] Park 2009 39 2.15 12173 20154 3.5% 0.54 [0.28, 2.58] Somenberg 2010 144 2.510 3956 76475 3.6% 0.44 [0.37, 0.52] Park 2009 39 2.15 12173 20154 3.5% 0.55 [0.31, 0.55] Somenberg 2010 147 719 4766 2.2968 3.6% 1.57 [1.57, 1.78] Subtal [95% CI) 87506 419479 45.5% 0.55 [0.31, 0.55] Total events 4161 499966 Heterogoneity: Tau ² = 1.03; Ch ² = 1759 71, df = 13 (P < 0.00001); l ² = 99% Test for overall effect Z = 2.13 (P = 0.31) Total events 4161 49966 Heterogeneity: Tau ² = 0.07; Ch ² = 31 (P < 0.00001); l ² = 99% Test for overall effect Z = 2.13 (P = 0.31) Total events 4161 49966 Heterogeneity: Tau ² = 0.07; Ch ² = 31 (P < 0.00001); l ² = 98% Test for overall effect Z = 2.13 (P = 0.31) Total events 4162 424 54371 Heterogeneity: Tau ² = 0.07; Ch ² = 31 (P < 0.00001); l ² = 98% Test for overall effect Z = 2.12 (P = 0.33) Test for overall effect Z = 2.12 (P = 0.33) Test for overall effect Z = 2.12 (P = 0.33) Test for overall effect Z = 2.12 (P = 0.33) Test for overall effect Z = 2.13 (P < 0.00001); l ² = 98% Test for o	Wu 2000	0	6	77	225	1.0%	0.15 [0.01, 2.65]	
Zhang 2004 60 120 31 93 3.3% 2.00 [1:4, 3.60] Oberg 1999 5 40 8 69 2.5% 109 0.33, 359] Subtotal (95% CI) 1323 8003 41.5% 0.99 [0.32, 1.19] Total events 552 3631 Heterogeneity: Tau ² = 0.03; Ch ² = 17.95, df = 13 (P = 0.16); P = 28% Test for overall effect $Z = 0.11 (P = 0.92)$ 4.2 Subjects undergoing endoscopy Aghayeva 2019 53 83 103 167 3.3% 1.10 [0.64, 1.89] Hackebserger 1998 43 108 156 315 3.4% 0.38 [0.25, 0.58] Hackebserger 1998 43 108 156 315 3.4% 0.38 [0.25, 0.58] Hackebserger 1998 43 108 156 315 3.4% 0.03 [0.28, 1.10] Katsinelos 2013 14 75 414 1915 3.3% 0.33 [0.46, 1.50] Loffed 2000 14 36 248 454 3.2% 0.53 [0.28, 1.06] Loffed 2000 14 36 248 454 3.2% 0.53 [0.26, 1.06] Loffed 2004 55 179 1550 3975 3.5% 0.69 [0.50, 0.56] Park 2009 39 215 12173 20154 3.5% 0.59 [0.31, 0.52] Somenberg 2010 144 2510 9356 76475 3.6% 0.44 [0.37, 0.52] * Somenberg 2010 144 2510 9356 76475 3.6% 0.44 [0.37, 0.52] * Somenberg 2010 144 2510 9356 76475 3.6% 0.44 [0.37, 0.52] * Somenberg 2010 144 2510 9356 76475 3.6% 0.44 [0.37, 0.52] * Somenberg 2010 144 2510 9356 76475 3.6% 0.44 [0.37, 0.52] * Somenberg 2010 144 2510 9356 76475 3.6% 0.44 [0.37, 0.52] * Subtotal (95% CI) 87506 419479 45.6% 0.55 [0.31, 0.55] * Subtotal (95% CI) 87506 419479 45.6% 0.55 [0.31, 0.55] * Subtotal (95% CI) 769 2257 7.2% 0.48 [0.28, 0.72] * Subtotal (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.71] Total events 111 764 Heterogeneity: Tau ² = 0.3; Ch ² = 13.78, 7.18 = 31.(P < 0.0001); P = 98% Test for overall effect: $Z = 2.12$ (P = 0.3) * Total events 111 764 Heterogeneity: Tau ² = 0.37; Ch ² = 13.19 (P < 0.0001); P = 98% Test for overall effect: $Z = 2.12$ (P = 0.3) * Total events 4424 54371 Heterogeneity: Tau ² = 0.37; Ch ² = 13.178 - 0.0001); P = 98% Test for overall effect: $Z = 2.12$ (P = 0.3) * Heterogeneity: Tau ² = 0.37; Ch ² = 13.178 - 0.0001); P = 98% Test for overall effect: $Z = 2.12$ (P = 0.3) * Heterogeneity: Tau ² = 0.37; Ch ² = 23.36; df = 2 (P < 0.0001); P = 98% Test for overall effe	Zaninotto 2002	6	34	7	69	2.5%	1.90 [0.58, 6.17]	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Zhang 2004	60	120	31	93	3.3%	2.00 [1.14, 3.50]	
Subtoral (95% CI) 1323 8003 41.5% 0.99 [0.82, 1.19] Total events 552 3631 Heterogeneily: Tau ² = 0.03; Ch ² = 17.95, df = 13 (P = 0.16); P = 28% Test for overall effect $Z = 0.11$ (P = 0.92) 4.2 Subjects undergoing endoscopy Aphayeva 2019 53 83 103 167 3.3% 1.10 [0.64, 1.89] Hackelsberger 1998 43 108 156 315 3.4% 0.67 [0.43, 1.05] Hackelsberger 1998 43 108 156 315 3.4% 0.67 [0.43, 1.05] Hackelsberger 1998 43 108 156 315 3.4% 0.67 [0.43, 1.05] Hackelsberger 1998 43 108 156 315 3.4% 0.67 [0.43, 1.05] Hackelsberger 1998 43 108 156 315 3.4% 0.63 [0.28, 1.41] Lafhei 2002 6 23 281 528 2.8% 0.31 [0.12, 0.80] Laffiel 2004 55 179 1550 3975 3.5% 0.69 [0.50, 0.96] Park 2009 39 215 12173 20154 3.5% 0.59 [0.50, 0.96] Park 2009 39 215 12173 20154 3.5% 0.59 [0.31, 0.52] Somenberg 2010 144 2510 9366 76475 3.6% 0.44 [0.37, 0.52] Somenberg 2010 144 2510 9366 76475 3.6% 0.43 [0.37, 0.52] Somenberg 2017 1972 76475 20683 284552 3.65% 0.43 [0.37, 0.52] Total events 4161 49956 Heterogeneity: Tau ² = 1.03; Ch ² = 178,71, df = 13 (P < 0.0001); P = 99% Test for overall effect: Z = 2.13 (P = 0.87); P = 0% Heterogeneity: Tau ² = 0.13; Ch ² = 133; P = 0.87; P = 0.87; P = 0% Test for overall effect: Z = 5.97 (P < 0.0001); P = 91% Total events 412 A 24 54371 Heterogeneity: Tau ² = 0.7; P = 0.73; P = 0% Test for overall effect: Z = 2.13 (P = 0.87); P = 0% Test for overall effect: Z = 2.13 (P = 0.87); P = 0% Test for overall effect: Z = 2.13 (P = 0.87); P = 0% Test for overall effect: Z = 2.13 (P = 0.87); P = 0% Test for overall effect: Z = 2.13 (P = 0.87); P = 0% Test for overall effect: Z = 2.13 (P = 0.87); P = 0% Test for overall effect: Z = 2.13 (P = 0.87); P = 0% Test for overall effect: Z = 2.13 (P = 0.87); P = 0% Test for overall effect: Z = 2.13 (P = 0.83) Heterogeneity: Tau ² = 0.7; Ch ² = 133; C = 0.0001; P = 914%. Heterogeneity: Tau ² = 0.7; C = 131; C = 0.0001; P = 914%. Heterogeneity: Tau ² = 0.7; C = 131; C = 0.0001; P = 914%. Heterogeneity: Tau ² = 0.7; C = 131; C = 0.0001; P = 9	Öberg 1999	5	40	8	69	2.5%	1.09 [0.33, 3.59]	— <u>+</u>
Total events 552 3631 Heterogeneity: Tar ² = 0.03; Ch ² = 17.95, df = 13 (P = 0.16); P = 28% Test for overall effect $Z = 0.11$ (P = 0.92) 4.2 Subjects undergoing endoscopy Aghayeva 2019 53 83 103 167 3.3% 1.10 [0.64, 1.89] Fischbach 2014 35 218 146 439 3.4% 0.38 [0.25, 0.58] Hirota 1999 4 104 64 738 2.7% 0.42 [0.15, 1.18] Hirota 1999 4 104 64 738 2.7% 0.42 [0.15, 1.18] Hirota 1999 4 104 64 738 2.7% 0.42 [0.15, 1.18] Hirota 1999 4 104 64 738 2.7% 0.42 [0.15, 1.18] Labeig 2002 6 23 281 528 2.8% 0.53 [0.26, 1.06] Hirota 1999 215 12173 20154 3.5% 0.163 [0.28, 1.41] Labeig 2002 6 23 281 528 2.8% 0.53 [0.26, 1.06] Hirota 1999 215 12173 20154 3.5% 0.156 [0.10, 0.21] Paul 1988 10 26 11 26 2.6% 0.85 [0.28, 2.58] Sonnenberg 2017 1972 76475 20683 284552 3.6% 0.34 [0.32, 0.35] Usu 2019 174 7419 4596 29196 3.6% 1.67 [1.57, 1.78] Subtotal [9% CI) 87506 419479 4.56% 0.55 [0.34, 0.74] Heterogeneity: Tau ² = 0.3; Ch ² = 1759, 71, df = 13 (P < 0.0001); P = 99% Test for overall effect: Z = 2.13 (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Colle yeards 4824 54371 Heterogeneity: Tau ² = 0.07; H ² = 73, 99 0.0%, 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.0; Ch ² = 0.87); P = 0.% Test for overall effect: Z = 2.19 (P = 0.00) Total events 4824 54371 Heterogeneity: Tau ² = 0.07; H ² = 131 (P < 0.00001); P = 98% Test for overall effect: Z = 2.19 (P = 0.03) Test for subgroup differences: Ch ² = 233 6, df = 2 (P < 0.0001); P = 98% Test for overall effect: Z = 2.12 (P = 0.03) Test for subgroup differences: Ch ² = 2.36, df = 2 (P < 0.0001); P = 98% Test for overall effect: Z = 2.12 (P = 0.03) Test for subgroup differences: Ch ² = 2.36, df = 2 (P < 0.0001); P = 98% Test for overall effect: Z = 2.12 (P = 0.03) Test for subgroup differences: Ch ² = 2.36, df = 2 (P < 0.0001); P = 98% Test for overall effect: Z = 2.12 (P = 0.03) Test for subgroup differences: Ch ² = 2.36, df = 2 (P < 0.00001); P = 98% Test for ov	Subtotal (95% CI)		1323		8003	41.5%	0.99 [0.82, 1.19]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Total events	552		3631				
Test for overall effect: $Z = 0.11 (P = 0.92)$ 4.2 Subjects undergoing endoscopy Aghayeva 2019 53 83 103 167 3.3% 1.10 [0.64, 1.89] Fischeach 2014 35 218 146 439 3.4% 0.38 [0.25, 0.58] Hackelsberger 1998 43 108 156 315 3.4% 0.67 [0.43, 1.06] Hirota 1999 4 104 64 738 2.7% 0.42 [0.15, 1.18] Kiliz 2002 8 35 175 545 3.0% 0.63 [0.28, 1.41] Laheij 2002 6 23 281 528 2.8% 0.31 [0.12, 0.80] Loffeld 2000 14 36 248 454 3.2% 0.53 [0.26, 1.60] Loffeld 2000 14 250 13975 3.5% 0.69 [0.50, 0.96] Park 2009 39 215 12173 20154 3.5% 0.69 [0.50, 0.96] Park 2009 39 215 12173 20154 3.5% 0.69 [0.50, 0.52] Favours 2010 144 2510 3956 76477 5.6% 0.44 [0.37, 0.52] Total events 4161 49956 Heterogeneity. Tau' = 10.3, Chi = 1759 71, df = 13 (P < 0.0001); P = 99% Test for overall effect: $Z = 2.13$ (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.45 [0.28, 0.70] 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.45 [0.29, 0.70] Heterogeneity. Tau' = 0.13, Chi = 0.71, r = 13 (P < 0.00001); P = 99% Test for overall effect: $Z = 2.13$ (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.45 [0.28, 0.72] Total events 111 784 Heterogeneity. Tau' = 0.07, He = 175, 71, F = 0% Test for overall effect: $Z = 2.59$; (P < 0.00001) Total (9% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4624 54371 Heterogeneity. Tau' = 0.03, Chi = 137, P < 0.00001); P = 98% Test for overall effect: $Z = 2.12$ (P = 0.03) Test for subgroup differences: Chi = 233.6, df = 2 (P < 0.00001); P = 98% Test for overall effect: $Z = 2.12$ (P = 0.03) Test for subgroup differences: Chi = 2.33.6, df = 2 (P < 0.00001); P = 98% Test for overall effect: $Z = 2.12$ (P = 0.03) Test for subgroup differences: Chi = 2.33.6, df = 2 (P < 0.00001); P = 98% Test for overall effect: $Z = 2.12$ (P = 0.03) Test for subgroup differences: Chi = 2.33.6, df = 2 (P < 0.00001); P = 98%	Heterogeneity: Tau ² = 0	03 [.] Chi ² =	= 17 95 d	f = 13 (P)	$= 0.16)$ · l^{2}	= 28%		
$\begin{array}{c} 4.2 \text{ Subjects undergoing endoscopy} \\ 4.2 \text{ Subjects undergoing endoscopy} \\ \text{Fischbach 2019} & 53 & 83 & 103 & 167 & 3.3\% & 1.01 [0.64, 1.89] \\ \text{Fischbach 2014} & 35 & 218 & 146 & 439 & 3.4\% & 0.38 [0.25, 0.58] \\ \text{Hackelsberger 1998} & 43 & 108 & 156 & 315 & 3.4\% & 0.67 [0.43, 1.05] \\ \text{Hackelsberger 1998} & 43 & 108 & 156 & 315 & 3.4\% & 0.67 [0.43, 1.05] \\ \text{Hackelsberger 1998} & 43 & 108 & 156 & 315 & 3.4\% & 0.63 [0.28, 1.41] \\ \text{Laheij 2002} & 6 & 23 & 281 & 528 & 2.8\% & 0.31 [0.12, 0.80] \\ \text{Loffiel 2004} & 55 & 179 & 1550 & 3975 & 3.5\% & 0.69 [0.50, 0.96] \\ \text{Park 2009} & 39 & 215 & 12173 & 20154 & 3.5\% & 0.45 [0.28, 2.58] \\ \text{Sonnenberg 2010} & 144 & 2510 & 9356 & 76475 & 3.6\% & 0.34 [0.32, 0.35] \\ \text{Usui 2019} & 1764 & 7419 & 4565 & 36\% & 0.34 [0.32, 0.35] \\ \text{Usui 2019} & 1764 & 7419 & 4565 & 36\% & 0.55 [0.31, 0.95] \\ \text{Total events} & 4161 & 49956 \\ \text{Heterogeneity: Tau" = 1.03, Chi" = 1759.71, df = 13 (P < 0.00001); P = 99\% \\ \text{Test for overall effect: Z = 2.13 (P = 0.03) \\ \textbf{4.3 Population or primary care people \\ \text{Chen 2016} & 42 & 148 & 261 & 588 & 3.4\% & 0.50 [0.34, 0.74] \\ \text{Total events} & 111 & 784 \\ \text{Heterogeneity: Tau" = 0.00; fint = 0.77; P = 0\% \\ \text{Total events} & 111 & 784 \\ \text{Heterogeneity: Tau" = 0.10; fint = 0.71, fi = 3 (P < 0.00001); P = 99\% \\ \text{Total events} & 111 & 784 \\ \text{Heterogeneity: Tau" = 0.07, P = 0.037; P = 0\% \\ \text{Total events} & 4824 & 54371 \\ \text{Heterogeneity: Tau" = 0.00; Hint = 0.77, P = 0\% \\ \text{Total events} & 4824 & 54371 \\ \text{Heterogeneity: Tau" = 0.03, P = 0.37; P = 0\% \\ \text{Total events} & 4824 & 54371 \\ \text{Heterogeneity: Tau" = 0.03, P = 0.37; P = 0\% \\ \text{Test for overall effect: Z = 2.12 (P = 0.03) \\ \text{Total events} & 4824 & 54371 \\ \text{Heterogeneity: Tau" = 0.03; P = 0.37; P = 0\% \\ \text{Test for overall effect: Z = 2.12 (P = 0.03) \\ \text{Test for subgroup differences: Chi" = 2.376, df = 2 (P < 0.00001); P = 98\% \\ \text{Test for overall effect: Z = 2.12 (P = 0.03) \\ \text{Test for subgroup differences: Chi" = 2.336, df = 2 (P < 0.00001); P = 914\% \\ \end{array}$	Test for overall effect: 7	= 0 11 (P	= 0.92		0.10), 1	20/0		
4.2 Subjects undergoing endoscopy Aghayeva 2019 53 83 103 167 3.3% 1.10 [0.64, 1.89] Fischeach 2014 35 218 146 439 3.4% 0.38 [0.25, 0.58] Hackelsberger 1998 43 108 156 315 3.4% 0.67 [0.43, 1.05] Hirota 1999 4 104 64 738 2.7% 0.42 [0.15, 1.18] Kitz 2002 8 35 175 545 3.0% 0.63 [0.28, 1.41] Laheij 2002 6 23 281 528 2.8% 0.31 [0.12, 0.80] Loffeld 2004 14 36 248 454 3.2% 0.53 [0.26, 1.06] Loffeld 2004 55 179 1550 3975 3.5% 0.69 [0.50, 0.96] Park 2009 39 215 1273 20154 3.5% 0.65 [0.50, 0.21] Paull 1988 10 26 11 26 2.6% 0.85 [0.28, 2.58] Somenberg 2010 144 2510 9365 76475 3.6% 0.44 [0.37, 0.52] Somenberg 2017 1972 76475 2068 248455 3.6% 0.55 [0.28, 0.35] \cdot Usu 2019 1764 7419 4596 29196 3.6% 1.67 [157, 1.78] Subtotal (95% CI) 87506 419479 45.6% 0.55 [0.31, 0.95] Total events 1611 49956 Heterogeneity: Tau ² = 1.03; Chi ² = 1759 71, df = 13 (P < 0.00001); P = 99% Test for overall effect: Z = 2.13 (P = 0.03) 4.3 Population or primary care people Cohen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Codey 2008 36 309 67 295 3.4% 0.45 [0.29, 0.70] Ronkainen 2005 5 16 383 984 2.27% 0.71 [0.25, 2.07] Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71; J ² = 0.9% Test for overall effect: Z = 5.97 (P < 0.00001); I ² = 98% Test for overall effect: Z = 5.97 (P < 0.00001) Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71; J ² = 0.9% Test for overall effect: Z = 2.12 (P = 0.03) Heterogeneity: Tau ² = 0.00; Chi ² = 0.73; J ³ = 0.000 (J; J ² = 98%) Test for overall effect: Z = 2.97 (P < 0.00001) Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71; J ² = 0.9% Test for overall effect: Z = 2.97 (P < 0.00001); J ² = 98% Test for overall effect: Z = 2.97 (P < 0.00001); J ² = 98% Test for overall effect: Z = 2.97 (P < 0.00001); J ² = 98% Test for overall effect: Z = 2.03) Heterogeneity: Tau ² = 0.03; Chi ² = 0.37; J ⁴ = 31 (P < 0.00001); J ² = 98% Test for overall effect: Z = 2.12 (P = 0.03) Heterogeneity: Tau ² = 0.67 (D ² = 2.276, df = 2 (P		0.11(1	0.02)					
$ \begin{array}{c} \text{Ad by over 2019} & \text{53} & \text{63} & 103 & 167 & 3.3\% & 1.10 [0.64, 1.89] \\ \text{Fischbach 2014} & 35 & 218 & 146 & 439 & 3.4\% & 0.38 [0.25, 0.58] \\ \text{Fischbach 2014} & 35 & 218 & 146 & 439 & 3.4\% & 0.38 [0.25, 0.58] \\ \text{Hackelsberger 1998} & 4 & 104 & 64 & 738 & 2.7\% & 0.42 [0.15, 1.18] \\ \text{Hirota 1999} & 4 & 104 & 64 & 738 & 2.7\% & 0.42 [0.15, 1.18] \\ \text{Hirota 1999} & 4 & 104 & 64 & 738 & 2.7\% & 0.42 [0.15, 1.18] \\ \text{Hirota 1999} & 4 & 104 & 64 & 738 & 2.7\% & 0.42 [0.15, 1.18] \\ \text{Hirota 1999} & 4 & 104 & 64 & 738 & 2.7\% & 0.42 [0.15, 1.18] \\ \text{Label 2002} & 6 & 23 & 281 & 528 & 2.8\% & 0.31 [0.12, 0.80] \\ \text{Lofield 2000} & 14 & 36 & 248 & 454 & 3.2\% & 0.55 [0.61, 0.61] \\ \text{Lofield 2004} & 55 & 179 & 1550 & 3975 & 3.5\% & 0.69 [0.50, 0.96] \\ \text{Park 2009} & 39 & 215 & 12173 & 20154 & 3.5\% & 0.15 [0.10, 0.21] \\ \text{Paul: 1988} & 10 & 26 & 11 & 26 & 2.6\% & 0.48 [0.28, 2.58] \\ \text{Sonnenberg 2010} & 144 & 2510 & 9386 & 76475 & 3.6\% & 0.44 [0.37, 0.52] \\ \text{Sonnenberg 2017} & 1972 & 76475 & 20683 & 284552 & 3.6\% & 0.43 [0.32, 0.35] \\ \text{Usui 2019} & 1764 & 7419 & 4566 & 29196 & 3.6\% & 1.67 [1.57, 1.78] \\ \text{Subtotal [95\% CI)} & 87506 & 419479 & 45.6\% & 0.55 [0.31, 0.95] \\ \text{Test for overall effect: Z = 2.13 (P = 0.03) \\ \text{4.3 Population or primary care people} \\ \text{Chen 2016} & 42 & 148 & 261 & 588 & 3.4\% & 0.50 [0.34, 0.74] \\ \text{Total events} & 4161 & 49966 \\ \text{Heterogeneity: Tau" = 0.00; Ch" = 0.71, df = 3 (P = 0.87); P = 9\% \\ \text{Total events} & 111 & 784 \\ \text{Heterogeneity: Tau" = 0.00; Ch" = 0.71, df = 3 (P = 0.87); P = 0\% \\ \text{Test for overall effect: Z = 5.57 (P < 0.00001) \\ \text{Total events} & 4824 & 54371 \\ \text{Heterogeneity: Tau" = 0.00; Ch" = 0.71, df = 31 (P < 0.00001); P = 98\% \\ \text{Test for overall effect: Z = 5.57 (P < 0.00001) \\ \text{Total events} & 4824 & 54371 \\ \text{Heterogeneity: Tau" = 0.87; Ch" = 13378, df = 31 (P < 0.00001); P = 98\% \\ \text{Total events} & 4824 & 54371 \\ \text{Heterogeneity: Tau" = 0.87; Ch" = 13378, df = 2 (P < 0.00001); P = 98\% \\ \text{Total events} & 4824 & 54371 \\ Heterogeneity: Tau" = 0.87; Ch" = 1337$	4.2 Subjects undergoin	na endoso	CODV					
$ \begin{array}{c} \label{eq:constraints} \begin{array}{c} \label{eq:constraints} \end{tabular} \\ \label{eq:constraints} \end{tabular} \end{tabular} \\ $	Achavova 2010	g 0	2019J 02	102	167	2 20/	1 10 [0 64 1 90]	_ _
$ \begin{array}{c} \text{Is solutiout 2014} & 53 & 210 & 140 & 433 & 5476 & 0.50 & [0.2, 3, 0.5] \\ \text{Hirota 1999} & 4 & 104 & 64 & 738 & 2.7\% & 0.42 & [0.15, 1.18] \\ \text{Hackelsberger 1998} & 4 & 104 & 64 & 738 & 2.7\% & 0.42 & [0.15, 1.18] \\ \text{Katsinelos 2013} & 14 & 75 & 414 & 1915 & 3.3\% & 0.83 & [0.46, 1.50] \\ \text{Katsinelos 2013} & 14 & 75 & 414 & 1915 & 3.3\% & 0.83 & [0.46, 1.50] \\ \text{Lofield 2000} & 14 & 36 & 248 & 44 & 3.2\% & 0.53 & [0.28, 1.41] \\ \text{Lofield 2000} & 14 & 36 & 248 & 443 & 3.2\% & 0.53 & [0.26, 1.06] \\ \text{Lofield 2004} & 55 & 179 & 1550 & 3975 & 3.5\% & 0.69 & [0.50, 0.96] \\ \text{Park 2009} & 39 & 215 & 12173 & 20154 & 3.5\% & 0.48 & [0.50, 2.8, 2.58] \\ \text{Sonnenberg 2010} & 144 & 2510 & 9356 & 76475 & 3.6\% & 0.44 & [0.37, 0.52] \\ \text{Sonnenberg 2010} & 144 & 2510 & 9356 & 76475 & 3.6\% & 0.44 & [0.37, 0.52] \\ \text{Sonnenberg 2010} & 144 & 2510 & 9356 & 76475 & 3.6\% & 0.44 & [0.32, 0.35] \\ \text{Usu 2019} & 1764 & 7419 & 4596 & 29169 & 3.6\% & 1.67 & [1.77, 1.78] \\ \text{Subtotal (95\% CI)} & 87506 & 419479 & 45.6\% & 0.55 & [0.34, 0.74] \\ \text{Carley 2008} & 36 & 309 & 67 & 295 & 3.4\% & 0.50 & [0.34, 0.74] \\ \text{Carley 2008} & 36 & 309 & 67 & 295 & 3.4\% & 0.45 & [0.28, 0.72] \\ \text{Subtotal (95\% CI)} & 769 & 2257 & 12.9\% & 0.48 & [0.38, 0.61] \\ \text{Contey 2008} & 36 & 309 & 67 & 295 & 3.4\% & 0.45 & [0.28, 0.72] \\ \text{Subtotal (95\% CI)} & 769 & 2257 & 12.9\% & 0.48 & [0.38, 0.61] \\ \text{Total events} & 111 & 784 \\ \text{Heterogeneity: Tau" = 0.00; Chi" = 0.77, 1f = 31 (P < 0.00001); I^{P} = 98\% \\ \text{Test for overall effect: } Z = 5.97 (P < 0.00001) \\ \hline \text{Total events} & 4824 & 54371 \\ \text{Heterogeneity: Tau" = 0.87; Chi" = 1837.87, df = 31 (P < 0.00001); I^{P} = 98\% \\ \text{Test for overall effect: } Z = 5.97 (P < 0.00001) \\ \hline \text{Test for subgroup analysis according to definition of control group \\ \hline \textbf{Favours [BE] Favours [control]} \\ \hline Favours [Chi] = 0.33, chi = 2 & (0.0$	Ficebbach 2014	35	219	105	107	3.3%	0.38 (0.35, 0.58)	- - -
Trackessberger 1950 43 100 150 315 34% 0.07 [0.43, 1.03] Hirota 1999 4 104 64 738 2.7% 0.42 [0.15, 1.18] Katsinelos 2013 14 75 414 1915 3.3% 0.83 [0.46, 1.50] Kiltz 2002 8 35 175 545 3.0% 0.63 [0.28, 1.41] Laheij 2002 6 23 281 528 2.8% 0.31 [0.12, 0.80] Loffeld 2000 14 36 248 454 3.2% 0.53 [0.26, 1.06] Loffeld 2000 14 36 248 454 3.2% 0.53 [0.26, 1.06] Loffeld 2000 14 251 12173 20154 3.5% 0.15 [0.10, 0.21] Paull 1988 10 26 11 26 2.6% 0.85 [0.28, 2.58] Sonnenberg 2010 144 2510 9356 76475 3.6% 0.44 [0.32, 0.35] Sonnenberg 2017 1792 76475 20683 28452 3.6% 0.34 [0.32, 0.35] Usui 2019 1764 7419 4596 29196 3.6% 1.67 [1.57, 1.78] Subtotal (95% CI) 87506 419479 45.6% 0.55 [0.31, 0.95] Total events 4161 49956 Heterogeneity: Tau ^a = 1.03; Chi ^a = 1759.71, df = 13 (P < 0.0001); P = 99% Test for overall effect: Z = 2.13 (P = 0.03) 4.3 Population or primary care people Chen 2016 42 1148 261 588 3.4% 0.50 [0.34, 0.74] Corley 2008 36 309 67 295 3.4% 0.45 [0.29, 0.70] Ronkainen 2005 5 16 383 984 2.7% 0.71 [0.25, 2.07] Thrift 2012 28 296 73 390 3.4% 0.45 [0.28, 0.72] Subtotal (95% CI) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ^a = 0.00; Chi ^a = 0.71, df = 3 (P < 0.0001); P = 98% Test for overall effect: Z = 2.12 (P = 0.03) Total events 4824 54371 Heterogeneity: Tau ^a = 0.87; Chi ^a = 1837.87, df = 31 (P < 0.00001); P = 98% Test for overall effect: Z = 2.12 (P = 0.03) Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ^a = 0.87; Chi ^a = 1837.87, df = 31 (P < 0.00001); P = 98% Test for overall effect: Z = 2.12 (P = 0.03) Favours [BE] Favours [Control] Total events 4824 54371 Heterogeneity: Tau ^a = 0.87; Chi ^a = 3136, df = 2 (P < 0.00001); P = 914 %. Favours [BE] Favours [Control] Favours [BE] Favours [Control] Favours [BE] Favours [Control]	Fischbach 2014	35	210	140	439	3.4% 2.4%	0.30 [0.25, 0.56]	
$ \begin{array}{c} \text{Introta 1999} & 4 & 104 & 64 & 736 & 2.7\% & 0.42 [21.5, 1.6] \\ \text{Katisnelos 2013} & 14 & 75 & 414 & 1915 & 3.3\% & 0.83 [0.46, 1.50] \\ \text{Katisnelos 2012} & 6 & 23 & 281 & 528 & 2.8\% & 0.31 [0.12, 0.80] \\ \text{Loffeld 2000} & 14 & 36 & 248 & 454 & 3.2\% & 0.53 [0.26, 1.06] \\ \text{Loffeld 2004} & 55 & 179 & 1550 & 3975 & 3.5\% & 0.69 [0.50, 0.96] \\ \text{Park 2009} & 39 & 215 & 12173 & 20154 & 3.5\% & 0.15 [0.10, 0.21] \\ \text{Paull 1988} & 10 & 26 & 11 & 26 & 2.6\% & 0.88 [0.28, 2.58] \\ \text{Sonnenberg 2017} & 1972 & 76475 & 20683 & 284552 & 3.6\% & 0.44 [0.37, 0.52] \\ \text{Sonnenberg 2017} & 1972 & 76475 & 20683 & 284552 & 3.6\% & 0.34 [0.32, 0.35] \\ \text{Usu' 2019} & 1764 & 7419 & 4596 & 29196 & 3.6\% & 1.67 [1.57, 1.78] \\ \text{Subtotal (95\% CI)} & 87506 & 419479 & 45.6\% & 0.55 [0.31, 0.95] \\ \text{Total events} & 4161 & 49956 \\ \text{Heterogeneity: Tau2 = 1.03; Ch2 = 1759.71, df = 13 (P < 0.00001); l2 = 99\% \\ \text{Test for overall effect: Z = 2.13 (P = 0.03) \\ \textbf{4.3 Population or primary care people \\ \text{Chen 2016} & 42 & 148 & 261 & 588 & 3.4\% & 0.50 [0.34, 0.74] \\ \text{Corley 2008} & 36 & 309 & 67 & 295 & 3.4\% & 0.45 [0.28, 0.72] \\ \text{Subtotal (95\% CI)} & 769 & 2257 & 12.9\% & 0.48 [0.38, 0.61] \\ \text{Total events} & 111 & 784 \\ \text{Heterogeneity: Tau2 = 0.07; Ch2 = 0.77, df = 3 (P < 0.00001); l2 = 98\% \\ \text{Test for overall effect: Z = 5.97 (P < 0.00001)} \\ \text{Total events} & 4824 & 54371 \\ \text{Heterogeneity: Tau2 = 0.07; Ch2 = 1837.87, df = 31 (P < 0.00001); l2 = 98\% \\ \text{Test for overall effect: Z = 2.12 (P < 0.00001)} \\ \text{Total events} & 4824 & 54371 \\ \text{Heterogeneity: Tau2 = 0.87; Ch2 = 2336, df = 2 (P < 0.00001); l2 = 98\% \\ \text{Test for overall effect: Z = 2.12 (P < 0.00001)} \\ \text{Total events} & 4824 & 54371 \\ \text{Heterogeneity: Tau2 = 0.87; Ch2 = 2336, df = 2 (P < 0.00001), l2 = 98\% \\ \text{Test for overall effect: Z = 2.12 (P < 0.00001)} \\ \text{Total events} & 4824 & 54371 \\ Heterogeneity: Tau2 = 0.87; Ch2 = 2336, df = 2 (P < 0.00001), l2 = 98\% \\ \text{Test for overall effect: Z = 2.12 (P < 0.00001), l2 = 98\% \\ \text{Test for ove$	Hackelsberger 1996	43	100	150	315	3.4%	0.67 [0.45, 1.05]	
Katisnelos 2013 14 15 16 17 16 16 17 16 16 17 16 16 17 16 16 17 16 16 17 16 16 17 16 16 17 16 16 17 16 16 17 16 16 17 16 16 16 17 16 16 16 17 17 17 17 17 17 17 17 17 17	Hirota 1999	4	104	64	138	2.1%	0.42 [0.15, 1.18]	-
Kilt 2002 8 35 175 545 3.0% 0.65 [0.28, 1.41] Laheij 2002 6 23 281 528 2.8% 0.31 [0.12, 0.80] Loffeld 2000 14 36 248 454 3.2% 0.53 [0.26, 1.06] Loffeld 2004 55 179 1550 3975 3.5% 0.68 [0.50, 0.96] Park 2009 39 215 12173 20154 3.5% 0.15 [0.10, 0.21] Paul 1988 10 26 11 26 2.6% 0.88 [0.28, 2.58] Sonnenberg 2010 144 2510 9356 76475 3.6% 0.44 [0.37, 0.52] Sonnenberg 2017 1972 76475 20683 284552 3.6% 0.34 [0.32, 0.35] Sonnenberg 2017 1972 76475 20683 284552 3.6% 0.34 [0.32, 0.35] Total events 4161 49956 Heterogeneity: Tau ² = 1.03; Chi ² = 1759.71, df = 13 (P < 0.0001); l ² = 99% Test for overall effect: Z = 2.13 (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Cortey 2008 36 309 67 295 3.4% 0.45 [0.28, 0.72] Whothai (95% Cl) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ² = 0.67; Chi ² = 0.87); l ² = 0% Test for overall effect: Z = 5.97 (P < 0.00001) Total (95% Cl) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: Z = 5.97 (P < 0.00001) Total (95% Cl) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: Z = 5.37, (f = 2 (P < 0.0001); l ² = 98% Test for overall effect: Z = 5.37, (f = 2 (P < 0.0001); l ² = 98% Test for overall effect: Z = 5.37, (f = 2 (P < 0.0001); l ² = 98% Test for overall effect: Z = 5.37, (f = 31 (P < 0.0001); l ² = 98% Test for overall effect: Z = 5.37, (f = 2 (P < 0.0001); l ² = 98% Test for overall effect: Z = 5.37, (f = 2 (P < 0.0001); l ² = 914.4%. Fig. 4 Forest plot of subgroup analysis according to definition of control group	Katsinelos 2013	14	15	414	1915	3.3%	0.83 [0.46, 1.50]	
Lahei 2002 6 23 281 528 2.8% 0.31 [0.12, 0.80] Loffeld 2000 14 36 248 454 3.2% 0.53 [0.26, 1.06] Loffeld 2004 55 179 1550 3975 3.5% 0.69 [0.50, 0.96] Park 2009 39 215 12173 20154 3.5% 0.15 [0.10, 0.21] Paull 1988 10 26 11 26 2.6% 0.85 [0.28, 2.58] Sonnenberg 2010 144 2510 9366 76475 3.6% 0.34 [0.32, 0.35] Usui 2019 1764 7419 4596 29196 3.6% 1.67 [1.57, 1.78] Subtotal (95% CI) 87506 419479 45.6% 0.55 [0.31, 0.95] Total events 4161 49956 Heterogeneity: Tau ² = 1.03; Chi ² = 1759.71, df = 13 (P < 0.00001); l ² = 99% Test for overall effect: Z = 2.13 (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Corley 2008 36 309 67 295 3.4% 0.45 [0.29, 0.70] Total events 111 784 Heterogeneity: Tau ² = 0.67; Chi ² = 1837.87, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: Z = 5.97 (P < 0.00001) Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: Z = 2.12 (P = 0.03) Favours [BE] Favours [BE] Favours [BE] Favours [Control]	Kiltz 2002	8	35	1/5	545	3.0%	0.63 [0.28, 1.41]	
Loffeld 2000 14 36 248 454 3.2% 0.53 [0.26, 1.66] Loffeld 2004 55 179 1550 3975 3.5% 0.69 [0.50, 0.96] Park 2009 39 215 12173 20154 3.5% 0.15 [0.10, 0.21] Paull 1988 10 26 11 26 2.6% 0.85 [0.28, 2.58] Sonnenberg 2010 144 2510 9356 76475 3.6% 0.44 [0.37, 0.52] Sonnenberg 2017 1972 76475 20683 284552 3.6% 0.34 [0.32, 0.35] Usui 2019 1764 7419 4596 29196 3.6% 1.67 [1.57, 1.78] Subtoal (95% CI) 87506 419479 45.6% 0.55 [0.31, 0.95] Total events 4161 49956 Heterogeneity: Tau ² = 1.03; Chi ² = 1759.71, df = 13 (P < 0.00001); l ² = 99% Test for overall effect: Z = 2.13 (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Corley 2008 36 309 67 295 3.4% 0.45 [0.28, 0.72] Subtoal (95% CI) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 4111 784 Heterogeneity: Tau ² = 0.01; Chi ² = 0.71, df = 3 (P = 0.87); l ² = 0% Test for overall effect: Z = 5.97 (P < 0.00001) Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 123.787, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: Z = 5.97 (P < 0.00001) Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 123.787, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: Z = 5.97 (P < 0.00001) Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 12(P < 0.03) Test for subgroup analysis according to definition of control group	Laheij 2002	6	23	281	528	2.8%	0.31 [0.12, 0.80]	
Loffeld 2004 55 179 1550 3975 3.5% 0.69 [0.50,0.96] Park 2009 39 215 12173 20154 3.5% 0.15 [0.10, 0.21] Paull 1988 10 26 11 26 2.6% 0.85 [0.28, 2.58] Sonnenberg 2010 144 2510 9356 76475 3.6% 0.44 [0.37, 0.52] Sonnenberg 2017 1972 7647 20683 284552 3.6% 0.34 [0.32, 0.35] Usui 2019 1764 7419 4596 29196 3.6% 1.67 [1.57, 1.78] Subtotal (95% CI) 87506 419479 45.6% 0.55 [0.31, 0.95] Total events 4161 49956 Heterogeneity: Tau ² = 1.03; Chi ² = 1759.71, df = 13 (P < 0.00001); l ² = 99% Test for overall effect: Z = 2.13 (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.45 [0.29, 0.70] Ronkainen 2005 5 16 383 984 2.7% 0.71 [0.25, 2.07] Thrift 2012 28 296 73 390 3.4% 0.45 [0.28, 0.72] Subtotal (95% CI) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71, df = 3 (P = 0.87); l ² = 0% Test for overall effect: Z = 5.97 (P < 0.00001) Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 137.87, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: Z = 2.12 (P = 0.03) Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 137.87, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: Z = 2.12 (P = 0.03) Test for overall effect: Z = 2.12 (P = 0.03) Test for subgroup differences: Chi ² = 2.(P < 0.00001); l ² = 98% Test for overall effect: Z = 2.12 (P = 0.03) Test for subgroup analysis according to definition of control group	Loffeld 2000	14	36	248	454	3.2%	0.53 [0.26, 1.06]	
Park 2009 39 215 12173 20154 3.5% 0.15 [0.10, 0.21] Paull 1988 10 26 11 26 2.6% 0.85 [0.28, 2.58] Sonnenberg 2010 144 2510 9356 76475 3.6% 0.44 [0.37, 0.52] Sonnenberg 2017 1972 76475 20683 284552 3.6% 0.34 [0.32, 0.35] Usui 2019 1764 7419 4596 29196 3.6% 1.67 [1.57, 1.78] Subtotal (95% CI) 87506 419479 45.6% 0.55 [0.31, 0.95] Total events 4161 49956 Heterogeneity: Tau ² = 1.03; Chi ² = 1759.71, df = 13 ($P < 0.00001$); $P = 99\%$ Test for overall effect: Z = 2.13 ($P = 0.03$) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Corley 2008 36 309 67 295 3.4% 0.45 [0.29, 0.70] Thrift 2012 28 296 73 390 3.4% 0.45 [0.28, 0.72] Subtotal (95% CI) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71, df = 3 ($P = 0.87$); $P = 0\%$ Test for overall effect: Z = 5.97 ($P < 0.00001$) Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 ($P < 0.00001$); $P = 98\%$ Test for overall effect: Z = 5.97 ($P < 0.00001$) Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 ($P < 0.00001$); $P = 98\%$ Test for overall effect: Z = 2.12 ($P = 0.03$) Test for overall effect: Z = 2.13 ($P = 0.87$); $P = 0\%$ Test for overall effect: Z = 2.12 ($P = 0.03$) Test for overall effect: Z = 2.12 ($P = 0.03$) Test for overall effect: Z = 2.12 ($P = 0.03$) Test for overall effect: Z = 2.12 ($P = 0.03$) Test for overall effect: Z = 2.12 ($P = 0.03$) Test for overall effect: Z = 2.12 ($P = 0.03$) Test for overall effect: Z = 2.12 ($P = 0.03$) Test for overall effect: Z = 2.12 ($P = 0.03$) Test for overall effect: Z = 2.12 ($P = 0.03$) Test for overall effect: Z = 2.12 ($P = 0.03$) Test for subgroup differences: Chi ² = 2.35, df = 2 ($P < 0.00001$); $P = 91.4\%$. Test for overall effect: Z = 2.12 ($P = 0.03$) Test for subgroup differences: Chi ² = 2.35, df = 2 ($P < 0.00001$); $P = 91.4\%$. Test for subgroup differences: Chi ² = 2.35, df = 2 ($P < 0.00001$); $P = 91.4\%$. Test for	Loffeld 2004	55	179	1550	3975	3.5%	0.69 [0.50, 0.96]	
Pauli 1988 10 26 11 26 2.6% 0.85 [0.28, 2.58] Sonnenberg 2010 144 2510 9356 76475 3.6% 0.44 [0.37, 0.52] Sonnenberg 2017 1972 76475 20683 284552 3.6% 0.34 [0.32, 0.35] Usui 2019 1764 7419 4596 29196 3.6% 1.67 [1.57, 1.78] Subtotal (95% CI) 87506 419479 45.6% 0.55 [0.31, 0.95] Total events 4161 49956 Heterogeneity: Tau ² = 1.03; Chi ² = 1759.71, df = 13 (P < 0.00001); l ² = 99% Test for overall effect: Z = 2.13 (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Corley 2008 36 309 67 295 3.4% 0.45 [0.29, 0.70] Ronkainen 2005 5 16 383 984 2.7% 0.71 [0.25, 2.07] Thrift 2012 28 296 73 390 3.4% 0.45 [0.28, 0.72] Subtotal (95% CI) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71, df = 3 (P = 0.87); l ² = 0% Test for overall effect: Z = 5.97 (P < 0.00001) Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 137.87, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: Z = 2.12 (P = 0.03) Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 137.87, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: Z = 2.12 (P = 0.03) Test for overall effect: Z = 2.12 (P = 0.03) Test for subgroup differences: Chi ² = 23 36, df = 2 (P < 0.00001); l ² = 94 4%. Feg. 4 Forest plot of subgroup analysis according to definition of control group	Park 2009	39	215	12173	20154	3.5%	0.15 [0.10, 0.21]	
Sonnenberg 2010 144 2510 9356 76475 3.6% 0.44 [0.37, 0.52] Sonnenberg 2017 1972 76475 20683 284552 3.6% 0.34 [0.32, 0.35] Usui 2019 1764 7419 4596 29196 3.6% 1.67 [1.57, 1.78] Subtotal (95% Cl) 87506 419479 45.6% 0.55 [0.31, 0.95] Total events 4161 49956 Heterogeneity: Tau ² = 1.03; Chi ² = 1759.71, df = 13 (P < 0.00001); l ² = 99% Test for overall effect: Z = 2.13 (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Corley 2008 36 309 67 295 3.4% 0.45 [0.29, 0.70] Ronkainen 2005 5 16 383 984 2.7% 0.71 [0.25, 2.07] Thrift 2012 28 296 73 390 3.4% 0.45 [0.28, 0.72] Subtotal (95% Cl) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71, df = 3 (P = 0.87); l ² = 0% Test for overall effect: Z = 5.97 (P < 0.00001) Total (95% Cl) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 554371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: Z = 2.12 (P = 0.03) Test for overall effect: Z = 2.12 (P = 0.03) Test for subgroup differences: Chi ² = 2.36, df = 2 (P < 0.00001); l ² = 91 4%. Favours [BE] Favours [Control] Test for subgroup analysis according to definition of control group	Paull 1988	10	26	11	26	2.6%	0.85 [0.28, 2.58]	
Sonneberg 2017 1972 76475 20683 284552 3.6% 0.34 [0.32, 0.35] Usi 2019 1764 7419 4596 29196 3.6% 1.67 [1.57, 1.78] Subtotal (95% CI) 87506 419479 45.6% 0.55 [0.31, 0.95] Total events 4161 49956 Heterogeneity: Tau ² = 1.03; Chi ² = 1759.71, df = 13 ($P < 0.00001$); $I^2 = 99\%$ Test for overall effect: $Z = 2.13$ ($P = 0.03$) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Corley 2008 36 309 67 295 3.4% 0.45 [0.29, 0.70] Ronkainen 2005 5 16 383 984 2.7% 0.71 [0.25, 2.07] Thrift 2012 28 296 73 390 3.4% 0.45 [0.28, 0.72] Subtotal (95% CI) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71, df = 3 ($P = 0.87$); $I^2 = 0\%$ Test for overall effect: $Z = 5.97$ ($P < 0.00001$) Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 ($P < 0.00001$); $I^2 = 98\%$ Test for overall effect: $Z = 2.12$ ($P = 0.03$) Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 ($P < 0.00001$); $I^2 = 98\%$ Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P = 0.03$) Test for overall effect: $Z = 2.12$ ($P $	Sonnenberg 2010	144	2510	9356	76475	3.6%	0.44 [0.37, 0.52]	+
Usui 2019 1764 7419 4596 29196 3.6% 1.67 [1.57, 1.78] Subtotal (95% CI) 87506 419479 45.6% 0.55 [0.31, 0.95] Total events 4161 49956 Heterogeneity: Tau ² = 1.03; Ch ² = 1759.71, df = 13 ($P < 0.00001$); $P = 99\%$ Test for overall effect: $Z = 2.13 (P = 0.03)$ 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Corley 2008 36 309 67 295 3.4% 0.45 [0.29, 0.70] Thirft 2012 28 296 73 390 3.4% 0.45 [0.28, 0.72] Subtotal (95% CI) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71, df = 3 ($P = 0.87$); $P = 0\%$ Test for overall effect: $Z = 5.97 (P < 0.00001)$ Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 ($P < 0.00001$); $P = 98\%$ Test for overall effect: $Z = 2.12 (P = 0.03)$ Test for overall effect: $Z = 2.12 (P = 0.03)$ Test for overall effect: $Z = 2.36$, df = 2 ($P < 0.00001$); $P = 914\%$ Fig. 4 Forest plot of subgroup analysis according to definition of control group	Sonnenberg 2017	1972	76475	20683	284552	3.6%	0.34 [0.32, 0.35]	•
Subtotal (95% CI) 87506 419479 45.6% 0.55 [0.31, 0.95] Total events 4161 49956 Heterogeneity: Tau ² = 1.03; Chi ² = 1759.71, df = 13 (P < 0.00001); l ² = 99% Test for overall effect: $Z = 2.13$ (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Corley 2008 36 309 67 295 3.4% 0.45 [0.29, 0.70] Thrift 2012 28 296 73 390 3.4% 0.45 [0.28, 0.72] Subtotal (95% CI) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71, df = 3 (P = 0.87); l ² = 0% Test for overall effect: $Z = 5.97$ (P < 0.00001) Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: $Z = 2.12$ (P = 0.03) Test for overall effect: $Z = 2.12$	Usui 2019	1764	7419	4596	29196	3.6%	1.67 [1.57, 1.78]	•
Total events 4161 49956 Heterogeneity: Tau ² = 1.03; Chi ² = 1759.71, df = 13 (P < 0.00001); l ² = 99% Test for overall effect: $Z = 2.13$ (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Corley 2008 36 309 67 295 3.4% 0.45 [0.29, 0.70] Ronkainen 2005 5 16 383 984 2.7% 0.71 [0.25, 2.07] Thift 2012 28 296 73 390 3.4% 0.45 [0.28, 0.72] Subtotal (95% CI) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71, df = 3 (P = 0.87); l ² = 0% Test for overall effect: $Z = 5.97$ (P < 0.00001) Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: $Z = 2.12$ (P = 0.03) Test for overall effect: $Z = 2.12$ (P = 0.03) Test for subgroup differences: Chi ² = 23 36, df = 2 (P < 0.00001); l ² = 91.4% Favours [BE] Favours [Control]	Subtotal (95% CI)		87506		419479	45.6%	0.55 [0.31, 0.95]	\bullet
Heterogeneity: Tau ² = 1.03; Chi ² = 1759.71, df = 13 (P < 0.00001); l ² = 99% Test for overall effect: $Z = 2.13$ (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Corley 2008 36 309 67 295 3.4% 0.45 [0.29, 0.70] Ronkainen 2005 5 16 383 984 2.7% 0.71 [0.25, 2.07] Thrift 2012 28 296 73 390 3.4% 0.45 [0.28, 0.72] Subtotal (95% CI) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71, df = 3 (P = 0.87); l ² = 0% Test for overall effect: $Z = 5.97$ (P < 0.00001) Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 (P < 0.00001); l ² = 98% Test for overall effect: $Z = 2.12$ (P = 0.03) Test for overall effect: $Z = 2.12$ (P = 0.03) Test for subgroup differences: Chi ² = 23.36, df = 2 (P < 0.00001), l ² = 91.4% Favours [BE] Favours [Control]	Total events	4161		49956				
Test for overall effect: $Z = 2.13$ (P = 0.03) 4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Corley 2008 36 309 67 295 3.4% 0.45 [0.29, 0.70] Ronkainen 2005 5 16 383 984 2.7% 0.71 [0.25, 2.07] Thrift 2012 28 296 73 390 3.4% 0.45 [0.28, 0.72] Subtotal (95% CI) 769 2257 12.9% 0.48 [0.38, 0.61] • Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71, df = 3 (P = 0.87); l ² = 0% • • Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 • • • Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 (P < 0.00001); l ² = 98% • • • • Test for overal	Heterogeneity: Tau ² = 1	.03; Chi ² =	= 1759.71	1, df = 13	(P < 0.000))01); ² = 99	%	
4.3 Population or primary care people Chen 2016 42 148 261 588 3.4% 0.50 [0.34, 0.74] Corley 2008 36 309 67 295 3.4% 0.45 [0.29, 0.70] Ronkainen 2005 5 16 383 984 2.7% 0.71 [0.25, 2.07] Thrift 2012 28 296 73 390 3.4% 0.45 [0.28, 0.72] Subtotal (95% CI) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71, df = 3 (P = 0.87); I ² = 0% Test for overall effect: $Z = 5.97$ (P < 0.00001) Total (95% CI) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 (P < 0.00001); I ² = 98% Test for overall effect: $Z = 2.12$ (P = 0.03) Test for overall effect: $Z = 2.12$ (P = 0.03) Test for subgroup differences: Chi ² = 23 36, df = 2 (P < 0.00001), I ² = 91 4% Fig. 4 Forest plot of subgroup analysis according to definition of control group	Test for overall effect: Z	= 2.13 (P	= 0.03)	-				
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Ronkainen 2005 5 16 383 984 2.7% 0.71 [0.25, 2.07] Thrift 2012 28 296 73 390 3.4% 0.45 [0.28, 0.72] Subtotal (95% Cl) 769 2257 12.9% 0.48 [0.38, 0.61] Total events 111 784 Heterogeneity: Tau ² = 0.00; Chi ² = 0.71, df = 3 (P = 0.87); l ² = 0% Test for overall effect: Z = 5.97 (P < 0.00001)	Corley 2008	36	309	67	295	3.4%	0.45 [0.29 0.70]	
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Total (95% Cl) 89598 429739 100.0% 0.69 [0.49, 0.97] Total events 4824 54371 Heterogeneity: Tau ² = 0.87; Chi ² = 1837.87, df = 31 (P < 0.00001); l ² = 98% 0.005 0.1 1 10 200 Test for overall effect: Z = 2.12 (P = 0.03) Favours [BE] Favours [Control] Favours [Control] Favours [Control]	Test for overall effect. Z	= 5.97 (P	< 0.0000)))				
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Test for subgroup differences: Chi ² = 23.36, df = 2 ($P < 0.00001$), $P = 91.4\%$ Fig. 4 Forest plot of subgroup analysis according to definition of control group	l est for overall effect: Z	= 2.12 (P	= 0.03)					Favours [BE] Favours [control]
ig. 4 Forest plot of subgroup analysis according to definition of control group	Test for subgroup difference	ences [.] Ch	$r^2 = 23.36$	$f_{, df} = 2 (F_{, df})$	P < 0 0000	11), 1² = 91 4	%	
	Fig. 4 Forest plot of sub	group an	alysis ac	cording t	o definitio	on of contro	ol group	

Prevalen ce of CagA- positive Hp in BE and controls

In the ten studies that examined patients with BE, the prevalence of the CagA-positive H p strain was significantly lower than that in controls (208/1080 [20.5%]

vs 605/2070 [29.1%]) (OR=0.28; 95% CI, 0.15–0.54, P=0.0002; I²=83%) (Fig. 6) [12, 38, 45, 47, 54, 58, 59, 69, 71, 72]. In a case–control study in 2008, Corley confirmed that the inverse association between *Hp* and BE

[DE		Com			Odda Datia		Odda Datia
Status of Hn infection	BE Events	Total	Events	Total	Weight	M-H Pandom 95%	21	Odds Ratio M-H Bandom 95% Cl
5 1 Present infected s	ubarou	n	Lvents	Total	weight	W-11, Random, 30%	<u>.</u>	
Aghaveva 2019	53	P 83	103	167	3.0%	1 10 [0 64 1 89	1	_ <u>_</u>
Chen 2016	42	148	261	588	3.1%	0.50 [0.34, 0.74]]	
Chuang 2019	224	369	1548	2597	3.2%	1 05 [0.84, 1.31	ן ו	+
Csendes 1997	20	100	38	190	2.9%	1 00 [0.55, 1.83	1	— —
Dore 2016	47	108	1251	2928	3.1%	1 03 [0 70 1 52	1	
Fischbach 2014	35	218	146	439	3.1%	0.38 [0.25, 0.58	1	
Hackelsberger 1998	43	108	156	315	3.1%	0 67 [0 43 1 05	1	
Hirota 1999	4	104	64	738	2.4%	0.42 [0.15, 1.18	i	— +
Katsinelos 2013	14	75	414	1915	2.9%	0.83 [0.46, 1.50	í	- _
Laheij 2002	6	23	281	528	2.5%	0.31 [0.12, 0.80	i	
Loffeld 2004	55	179	1550	3975	3.1%	0.69 0.50, 0.96	i	
Newton 1997	4	16	15	36	2.1%	0.47 [0.13, 1.73	j	
Paull 1988	10	26	11	26	2.3%	0.85 [0.28, 2.58	1	
Ronkainen 2005	5	16	383	984	2.4%	0.71 [0.25, 2.07]	
Sharifi 2014	12	34	204	702	2.8%	1.33 [0.65, 2.74]	
Sonnenberg 2010	144	2510	9356	76475	3.2%	0.44 [0.37, 0.52]	+
Sonnenberg 2017	1972	76475	20683	284552	3.2%	0.34 [0.32, 0.35]	-
Vieth 2000	463	1054	378	712	3.2%	0.69 [0.57, 0.84]	
Weston 2000	73	208	96	217	3.1%	0.68 [0.46, 1.01]	
White 2008	2	39	3	29	1.5%	0.47 [0.07, 3.00]	
Wu 2000	0	6	77	225	0.9%	0.15 [0.01, 2.65] 4	
Zaninotto 2002	6	34	7	32	2.2%	0.77 [0.23, 2.58]	
Zhang 2004	60	120	31	93	3.0%	2.00 [1.14, 3.50]	
Öberg 1999	5	40	8	69	2.2%	1.09 [0.33, 3.59]	
Subtotal (95% CI)		82093		378532	64.6%	0.69 [0.54, 0.89]		◆
Total events	3299		37064					
Heterogeneity: Tau ² = 0 Test for overall effect: 2	0.27; Ch Z = 2.83	i² = 282 (P = 0.0	30, df = 005)	23 (P <)	0.00001);	l² = 92%		
5.2 Infection history s	ubgrou	р						
Corley 2008	36	309	67	295	3.1%	0.45 [0.29, 0.70	1	- - -
Ferrández 2006	91	104	159	213	2.9%	2.38 1.23, 4.59	i	
Rubenstein 2014	25	150	86	375	3.0%	0.67 [0.41, 1.10]	
Thrift 2012	28	296	73	390	3.0%	0.45 [0.28, 0.72]	
Usui 2019	1764	7419	4596	29196	3.2%	1.67 [1.57, 1.78]	
Subtotal (95% CI)		8278		30469	15.2%	0.88 [0.43, 1.78]		
Total events	1944		4981					
Heterogeneity: Tau ² = 0	0.59; Ch	i² = 75.	10, df = 4	↓ (P < 0.0	00001); l²	= 95%		
Test for overall effect: 2	Z = 0.35	(P = 0.)	73)					
5.3 Not clear subgrou	ip			. = .				
Keyashian 2013	24	52	205	420	2.9%	0.90 [0.50, 1.60]	
Kiltz 2002	8	35	175	545	2.7%	0.63 [0.28, 1.41]	
Loffeld 2000	14	36	248	454	2.8%	0.53 [0.26, 1.06]	
Park 2009	39	215	12173	20154	3.1%	0.15 [0.10, 0.21	J	
	29	55	3/	80	2.8%	1.30 [0.65, 2.58]	⁻
Vaezi 2000	41	230	151	434	3.1%	0.41 [0.27, 0.60]	
VICARI 1998	15	48 674	30	84 22474	2.1%	0.82 [0.38, 1.74	J	
Subtotal (95% CI)	470	671	40040	22171	20.2%	0.55 [0.29, 1.05]		\bullet
Hotorogonoity: Tou? = (2 - EG	13019		00011.12	- 90%		
Test for overall effect: 2	Z = 1.81	(P = 0.0)	92, ui = 6 07)	ס (ד < ט.נ	000 I), I ²	- 03%		
Total (95% CI)		91042		431172	100.0%	0.68 [0.50, 0.94]	I	◆
Total events	5413		55064					
Heterogeneity: Tau ² = 0	0.80: Ch	i² = 185	5.85. df	= 35 (P <	0.00001); ² = 98%		
Test for overall effect: 2	Z = 2.36	(P = 0.0)	02)	v		*	0.01	
Test for subgroup differ	rences: ($Chi^2 = 0$.93, df =	2(P = 0)	63), l² = ()%		
Fig. 5 Forest plot of subg	roup ana	alysis aco	cording to	o status o	f Hp infect	ion. 5.1: <i>Hp</i> positive with	n rapid ur	ease test, urea breath test, histology or

Fig. 5 Forest plot of subgroup analysis according to status of *Hp* infection. 5.1: *Hp* positive with rapid urease test, urea breath t culture; 5.2: *Hp* positive with serological detection, treatment history, or infection history; 5.3: not sure to status of *Hp* infection

Authors	Years	Journal	<i>Hp</i> testing method	Biopsy location	BE	Cases	+dH	Total	Controls	+ d H	Total
Aghayeva et al. [36]	2019	Dis Esophagus	H [*] , R [†]	Antrum	± ₩	BE with dysplasia	5	11	BE without dysplasia	48	72
Sonnenberg et al. [11]	2017	Aliment Pharmacol Ther	Т	Stomach	₹	BE without dysplasia or cancer	1972	76,475	Endoscopy	20,683	284,552
						BE with dysplasia or cancer	138	6167	Endoscopy	20,683	284,552
Thrift et al. [57]	2012	Int J Cancer	S [§]		₹	BE	28	296	Population	73	390
						BE without dysplasia	25	208	Population	73	390
						BE with dysplasia	e	88	Population	73	390
Vieth et al. [65]	2000	Digestion	н	Antrum, Corpus	≧	BE	463	1054	NUD	378	712
						Barrett's neoplasia (HGD or adenocarcinoma)	54	138	DUD	378	712
*: Histoloav. †: Rapid ureas e t e	st. ±: Intest	tinal metaplasia. §: Seroloav. :	Hiah dvsplasia								

 Table 2
 Characteristics of the four studies about the correlation between Hp and BE dysplasia

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Fig. 6 Forest plot of the correlation between the CagA-positive *Hp* strain and BE. The weights and heterogeneities of studies are also indicated. OR: Odds ratio, CI: 95% confidence interval

was stronger in subjects with the CagA-positive strain, weaker but still p resent in those with CagA-negative stra in [38]. Meanwhile, there were no substantial differences in the pattern of BE and the CagA-positive *Hp* stra in after adjustment for GERD symptom severity or GERD symptom frequency, which w as similar to Anderson's conclusion [38, 69]. However, Anderson found a somewhat weaker pattern between the CagA-positive *Hp* strain and BE when analyzing for the CagA antig en only [69].

Description of publication bias, heterogeneity, and sensitivity analysis

A visual inspection of the funnel plot was used to assess publication bias in the studies. There was no asymmetry in the funnel plots of the respective analyses and subgroup analyses. Considerable heterogeneity was noted in meta -analyses concerning the correlation between Hp prevalence and BE. Substantial heterogeneity was also noted when analyzing the relationship between Hp and lengths of BE, and th at between the CagA-positive Hp strain and BE. Through sensitivity analyses, we found that the significant heterogeneity could be attributed to factors other than a single study. We sometimes discovered decreased heterogeneity in the following subgroup metaanalyses. In the subgroup analysis of GERD, population and primary care people, the heterogeneity decreased considerably to 33% and 0%, respectively. This finding suggests that regarding subjects undergoing endoscopy as control might be the most potential sources of heterogeneity. There was also a significant decrease in heterogeneity when subgroup analysis was performed based on whether or not a match was made for sex and age. There were many factors closely related to Hp and BE, including sex, age, smoking, alcohol consumption, race, geographic location, definition of BE and control group, methods of Hp testing. It was hard to analyze and discuss each factor due to the limited number of publications and the heterogeneity of the description.

Discussion

In accordance with recent studies, our meta-analysis showed an inverse relationship between the prevalence of *Hp*, especially the CagA-positive *Hp* strain, with BE. The conclusions of most of the previous studies are consistent with those of the current study [14, 15, 77], in that Hp is a protective factor for BE. It is generally recognized that Hp causes corpus-predominant gastritis with decreased acid secretion, which is associated with a decreased risk of GERD and BE [78, 79]. Meanwhile, *Hp* infection reduces the chance of regurgitation by promoting gastric emptying and reducing the incidence of ob esity [79]. In subgroup analyses, Hp infection and BE were inversely related when compared with subjects undergoing endoscopy and normal control (population or primary care people), but not GERD control. Furthermore, the prevalence of *Hp* was not significantly different between patients with BE and those with GERD. Combined to previous studies, this protective effect of *Hp* is likely mediated by a decrease in prevalence of GERD in Hp-infected patients, since it disappears in patients with GERD [14]. However, there were no substantial differences in the relationship between BE and CagA-positive *Hp* strains after adjustment for GERD symptom seve rity or frequency [38, 71]. It suggested that CagA-positive *Hp* might reduce the risk of BE in some other ways.

Although Hp has been classified as a class 1 carcinogen, the majority of infected people had no symptoms associated with Hp infection actually [1]. Nowadays, the negative associations between Hp and asthma, allergies, GERD and inflammatory bowel disease are increasingly recognized [80]. The present study also revealed the protective effect of Hp on BE. Meanwhile, long-term use of proton pump inhibitors has been shown to increase the risk of gastric cancer after confounding factors, the HRs increased with cumulative duration, cumulative omeprazole equivalents and time since treatment initiation [81, 82]. Therefore, it would be important to explore new treatment options to alleviate BE symptoms and personalize Hp eradication.

The most likely protective mechanism of Hp to BE is the effect on gastric reflux by its influence on gastric acid secretion. Usually, antral-predominant gastritis is associated with increased acid secretion, whereas corpus-predominant gastritis, often accompanied by gastric atrophy, is associated with decreased acid secretion [83]. Ten previous studies only detected Hp infection with tissue from the antrum [13, 35, 36, 39, 44, 46-49, 55]; The meta-analysis of these arti c les showed Hp no protective impact to BE (OR=0.80; 95% CI, 0.58–1.10; P=0.17; $I^2=66\%$) although with decreased heterogeneity. In contrast, studies that defined *Hp* exclusively from esophageal biopsies tended to find a positive association between Hp and BE [18]. Hp directly damages the esophageal mucosa with bacterial products, increases the production of prostaglandin, sensitizes the afferent nerve, reduces the pressure of the lower esophageal sphincter, and increases acidity via Gastrin, an oncogenic growth factor that contributes to esophageal carcinogenesis [84-88]. Due to the lack of classified discussion on the severity of gastric mucosal lesions after *Hp* infection in those included publications, our study is not able to prove the potential protective effect of *Hp* on BE might be explained by decreased acid secretion due to corpus-predominant gastritis. There are limited studies on the relationship between the duration, site, and severity of *Hp* infection and BE, and further disc ussions on classification are yet to be conducted.

In subgroup analyses based on different definitions of control and BE, we found that the inverse relationship disappeared when comparing BE with GERD control, and when BE was defined as a change other than IM. Conversely, the OR values of the other subgroups decreased to some extent. In particular, the prevalence of Hp infection in the normal control (population or primary care people) was much lower than that in patients with BE compared to the endoscopy subgroup. We also found that Hp was negatively correlated with LSBE, and that Hp infection could reduce BE dysplasia; however, there was no apparent correlation between Hp and SSBE. When it came to different detection methods for Hp, we found that the inverse relationship disappeared in the Hp infection history subgroup. Serological detection, treatment history, or infection history of Hp cannot reflect the current infection status of the study subjects, which will increase the uncertainty of information. In the present infected subgroup, our meta-analysis discovered a protective association between Hp and BE that was not present in the Hpinfection history subgroup.

A few studies without obvious selection and information bias have reported a reduced risk of BE in people infected with Hp [18, 38, 53, 71]. The relationship between Hp infection and BE is controversial due to the considerable heterogeneity observed in most studies; indeed, significant heterogeneity was also noted in the current meta-analysis. A study by Fischbach et al. identified selection and information bias as potential sources of heterogeneity [71].

Subgroup analyses of the GERD and normal control (population or primary care people) showed a decrease of heterogeneity to 33% and 0%, respectively. The endoscopy subgroup might be one of the greatest sources of heterogeneity, since endoscopy might be associated with multiple gastrointestinal diseases. Applying subjects undergoing endoscopy, who were more likely to be colonized with Hp than the general population, as control, would lead to selection bias [38]; however, it also represents the most common and easiest control group. In the same way, blood donors cannot represent the population because they are likely to be healthier and younger [15]. Subject from the same geographical area as the BE patient would be the best choice of control.

A final, but no less important finding was that a significant decrease in overall heterogeneity was also observed when performing subgroup analyses based on whether or not a match was made for sex and age. Males and aging have been shown to be risk factors for Hp infection and BE, and in the current study, the protective effect of Hp infection wasn't presented when matching both sex and/or age (OR=0.72; 95% CI, $0.50-1.05; P=0.09; I^2=76\%$ [12, 13, 36, 38, 40, 44, 51, 60]. This result might be influenced by heterogeneity in definition of control group, definition of BE, Hp detection method, age, sex and so on. We collected information about whether or not the BE and control subjects were matched in sex, age, obesity, smoking, alcohol consumption, and race. However, it is unfortunate that, due to too many interfering factors, there were too few studies in single factor subgroups to perform additional subgroup analyses. The heterogeneity of existing studies is great, and a large number of rigorous and precise design studies are still needed to obtain more convincing conclusions.

Conclusions

In conclusion, the results showed a statistically significant inverse relationship between the prevalence of Hp, especially CagA-positive Hp strain, with BE. The prevalence of *Hp* was not significantly different between patients with BE and GERD controls, suggesting that this protective effect of *Hp* is probably mediated by a de crease in the prevalence of GERD. In addition, Hp was negatively correlated with LSBE, and *Hp* infection could reduce the BE dysplasia; however, there was no clear correlation between Hp and SSBE. In addition, the inverse relationship between Hp and BE disappeared in the *Hp* infection history subgroup. The heterogeneity of existing studies is great. To understand the extent to which *Hp* reduces the risk of BE, further well-designed studies are needed. Researchers should pay attention to, but not only to, the definition of the control group, the definition of BE, status of Hp infection, sampling site, gastritis type, sex, age, obesity, smoking, alcohol, and race.

Abbreviations

Hp: Helicobacter pylori; BE: Barrett's esophagus; OR: Odds ratio; CI: Confidence interval; GERD: Gastroesophageal reflux disease; LSBE: Long-segment BE; SSBE: Short-segment BE; USBE: Ultra-short-segment BE; EAC: Esophageal adenocarcinomas; CagA: Cytotoxin-associated gene A; NOS: Newcastle–Ottawa Scale; IM: Intestinal metaplasia; CM: Columnar metaplasia; S: Serology; R: Rapid urease test; U: Urea breath test; H: Histology; T: Treatment history; C: Culture; NUD: Non-ulcer dyspepsia; HGD: High grade dysplasia; SCJ: Squamous Columnar Junction; EGJ: Esophagogastric junction.

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Authors' contributions

Y-LD carried out the study selection and drafted the manuscript; Y-LD and R-QD contributed to extraction and analysis of the data. L-PD designed and supervised the study. All authors commented on drafts of the paper and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

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Competing interests

The authors declare that they have no competing interests.

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References

- 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(2):420–9.
- Graham DY. History of *Helicobacter pylori*, duodenal ulcer, gastric ulcer and gastric cancer. World J Gastroenterol. 2014;20(18):5191–204.
- Edgren G, Adami HO, Weiderpass E, Nyren O. A global assessment of the oesophageal adenocarcinoma epidemic. Gut. 2013;62(10):1406–14.
- Cook MB, Chow WH, Devesa SS. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977–2005. Br J Cancer. 2009;101(5):855–9.
- 5. Sharma P. Clinical practice. Barrett's esophagus. N Engl J Med. 2009;361(26):2548–56.
- Perez N, Taylor W. Epidemiology of Barrett's oesophagus and oesophageal adenocarcinoma. Med Stud. 2019;35(1):61–8.
- Qumseya BJ, Bukannan A, Gendy S, Ahemd Y, Sultan S, Bain P, Gross SA, lyer P, Wani S. Systematic review and meta-analysis of prevalence and risk factors for Barrett's esophagus. Gastrointest Endosc. 2019;90(5):707-717. e701.
- Arora Z, Garber A, Thota PN. Risk factors for Barrett's esophagus. J Dig Dis. 2016;17(4):215–21.
- Møller H, Heseltine E, Vainio H. Schistosomes, liver flukes and *Helicobacter* pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7–14 June 1994. IARC Monogr Eval Carcinog Risks Hum. 1994;61:1–241.
- Blaser MJ. Helicobacter pylori and esophageal disease: wake-up call? Gastroenterology. 2010;139(6):1819–22.
- 11. Sonnenberg A, Turner KO, Spechler SJ, Genta RM. The influence of *Helicobacter pylori* on the ethnic distribution of Barrett's metaplasia. Aliment Pharmacol Ther. 2017;45(2):283–90.
- Ferrández A, Benito R, Arenas J, García-González MA, Sopeña F, Alcedo J, Ortego J, Sainz R, Lanas A. CagA-positive *Helicobacter pylori* infection is not associated with decreased risk of Barrett's esophagus in a population with high *H. pylori* infection rate. BMC Gastroenterol. 2006;6:1–10.
- Chen CC, Hsu YC, Lee CT, Hsu CC, Tai CM, Wang WL, Tseng CH, Hsu CT, Lin JT, Chang CY. Central obesity and *H. pylori* infection influence risk of Barrett's esophagus in an Asian population. PLoS ONE. 2016;11(12):e0167815.
- Wang Z, Shaheen NJ, Whiteman DC, Anderson LA, Vaughan TL, Corley DA, El-Serag HB, Rubenstein JH, Thrift AP. *Helicobacter pylori* infection is associated with reduced risk of Barrett's esophagus: an analysis of the barrett's and esophageal adenocarcinoma consortium. Am J Gastroenterol. 2018;113(8):1148–55.
- Erőss B, Farkas N, Vincze Á, Tinusz B, Szapáry L, Garami A, Balaskó M, Sarlós P, Czopf L, Alizadeh H, et al. *Helicobacter pylori* infection reduces the risk of Barrett's esophagus: a meta-analysis and systematic review. Helicobacter. 2018;23(4):e12504.
- Liu FX, Wang WH, Shuai XW. Prevalence of *Helicobacter pylori* in patients with Barrett's esophagus: a meta-analysis. Chin J Evid Based Med. 2008;8(12):1086–93.
- Wang C, Yuan Y, Hunt RH. *Helicobacter pylori* infection and Barrett's esophagus: a systematic review and meta-analysis. Am J Gastroenterol. 2009;104(2):492–500 (quiz 491, 501).
- Fischbach LA, Nordenstedt H, Kramer JR, Gandhi S, Dick-Onuoha S, Lewis A, El-Serag HB. The association between Barrett's esophagus and *Helicobacter pylori* infection: a meta-analysis. Helicobacter. 2012;17(3):163–75.
- Blaser MJ, Perez-Perez GI, Lindenbaum J, Schneidman D, Van Deventer G, Marin-Sorensen M, Weinstein WM. Association of infection due to *Helicobacter pylori* with specific upper gastrointestinal pathology. Rev Infect Dis. 1991;13(Suppl 8):S704-708.
- Johansson J, Håkansson HO, Mellblom L, Kempas A, Johansson KE, Granath F, Nyrén O. Risk factors for Barrett's oesophagus: a population-based approach. Scand J Gastroenterol. 2007;42(2):148–56.
- 21. Goldblum JR, Richter JE, Vaezi M, Falk GW, Rice TW, Peek RM. *Helicobac*ter pylori infection, not gastroesophageal reflux, is the major cause of

inflammation and intestinal metaplasia of gastric cardiac mucosa. Am J Gastroenterol. 2002;97(2):302–11.

- 22. Peitz U, Hackelsberger A, Günther T, Clara L, Malfertheiner P. The prevalence of *Helicobacter pylori* infection and the pattern of gastritis in Barrett's esophagus. Dig Dis. 2001;19(2):164–9.
- Ormsby AH, Vaezi MF, Richter JE, Goldblum JR, Rice TW, Falk GW, Gramlich TL. Cytokeratin immunoreactivity patterns in the diagnosis of shortsegment Barrett's esophagus. Gastroenterology. 2000;119(3):683–90.
- O'Connor HJ, Cunnane K. *Helicobacter pylori* and gastro-oesophageal reflux disease–a prospective study. Ir J Med Sci. 1994;163(8):369–73.
- Jonaitis L, Kriukas D, Kiudelis G, Kupčinskas L. Risk factors for erosive esophagitis and Barrett's esophagus in a high *Helicobacter pylori* prevalence area. Medicina. 2011;47(8):434–9.
- Gashi Z, Sherifi F, Shabani R. The prevalence of *Helicobacter pylori* infection in patients with reflux esophagitis—our experience. Med Arch (Sarajevo, Bosnia and Herzegovina). 2013;67(6):402–4.
- Peng S, Xiong LS, Xiao YL, Lin JK, Wang AJ, Zhang N, Hu PJ, Chen MH. Prompt upper endoscopy is an appropriate initial management in uninvestigated chinese patients with typical reflux symptoms. Am J Gastroenterol. 2010;105(9):1947–52.
- Guenther T, Hackelsberger A, Kuester D, Malfertheiner P, Roessner A. Reflux esophagitis or *Helicobacter* infection? - diagnostic value of the inflammatory pattern in metaplastic mucosa at the squamocolumnar junction. Pathol Res Pract. 2007;203(12):831–7.
- Voutilainen M, Färkkilä M, Mecklin JP, Juhola M, Sipponen P. Classical Barrett esophagus contrasted with Barrett-type epithelium at normalappearing esophagogastric junction: comparison of demographic, endoscopic, and histologic features. Scand J Gastroenterol. 2000;35(1):2–9.
- Werdmuller BFM, Loffeld RJLF. *Helicobacter pylori* infection has no role in the pathogenesis of reflux esophagitis. Dig Dis Sci. 1997;42(1):103–5.
- Lapertosa G. Helicobacter pylori in Barrett's oesophagus. Histopathology. 1991;18(6):568–70.
- 32. Garcia JM, Splenser AE, Kramer J, Alsarraj A, Fitzgerald S, Ramsey D, El-Serag HB. Circulating inflammatory cytokines and adipokines are associated with increased risk of Barrett's esophagus: a case-control study. Clin Gastroenterol Hepatol. 2014;12(2):229-238.e223.
- Hilal J, Kramer JR, Richardson P, Ramsey DJ, Alsarraj A, El-Serag H. Physical activity and the risk of Barrett's esophagus. Gastroenterology. 2014;146(5):S307–8.
- Thrift AP, Kramer JR, Qureshi Z, Richardson PA, El-Serag HB. Age at onset of GERD symptoms predicts risk of Barrett's esophagus. Am J Gastroenterol. 2013;108(6):915–22.
- Usui G, Sato H, Shinozaki T, Jinno T, Fujibayashi K, Ishii K, Horiuchi H, Morikawa T, Gunji T, Matsuhashi N. Association between *Helicobacter pylori* infection and short-segment/long-segment Barrett's esophagus in a Japanese population: a large cross-sectional study. J Clin Gastroenterol. 2019;54:439–44.
- Aghayeva S, Mara KC, Katzka DA. The impact of *Helicobacter pylori* on the presence of Barrett's esophagus in Azerbaijan, a high-prevalence area of infection. Dis Esophagus. 2019. https://doi.org/10.1093/dote/doz053.
- Chuang YS, Wu MC, Wang YK, Chen YH, Kuo CH, Wu DC, Wu MT, Wu IC. Risks of substance uses, alcohol flush response, *Helicobacter pylori* infection and upper digestive tract diseases—an endoscopy cross-sectional study. Kaohsiung J Med Sci. 2019. https://doi.org/10.1002/kjm2.12071.
- Corley DA, Kubo A, Levin TR, Block G, Habel L, Zhao W, Leighton P, Rumore G, Quesenberry C, Buffler P, et al. *Helicobacter pylori* infection and the risk of Barrett's oesophagus: a community-based study. Gut. 2008;57(6):727–33.
- Csendes A, Smok G, Cerda G, Burdiles P, Mazza D, Csendes P. Prevalence of *Helicobacter pylori* infection in 190 control subjects and in 236 patients with gastroesophageal reflux, erosive esophagitis or Barrett's esophagus. Dis Esophagus. 1997;10(1):38–42.
- Fischbach LA, Graham DY, Kramer JR, Rugge M, Verstovsek G, Parente P, Alsarraj A, Fitzgerald S, Shaib Y, Abraham NS, et al. Association between *Helicobacter pylori* and Barrett's esophagus: a case-control study. Am J Gastroenterol. 2014;109(3):357–68.
- Hackelsberger A, Gunther T, Schultze V, Manes G, Dominguez-Munoz JE, Roessner A, Malfertheiner P. Intestinal metaplasia at the gastro-oesophageal junction: *Helicobacter pylori* gastritis or gastro-oesophageal reflux disease? Gut. 1998;43(1):17–21.

- 42. Hirota WK, Loughney TM, Lazas DJ, Maydonovitch CL, Rholl V, Wong RKH. Specialized intestinal metaplasia, dysplasia, and cancer of the esophagus and esophagogastric junction: prevalence and clinical data. Gastroenterology. 1999;116(2):277–85.
- Öberg S, Peters JH, Nigro JJ, Theisen J, Hagen JA, DeMeester SR, Bremner CG, DeMeester TR. *Helicobacter pylori* is not associated with the manifestations of gastroesophageal reflux disease. Arch Surg. 1999;134(7):722–6.
- 44. Katsinelos P, Lazaraki G, Kountouras J, Chatzimavroudis G, Zavos C, Terzoudis S, Tsiaousi E, Gkagkalis S, Trakatelli C, Bellou A, et al. Prevalence of Barrett's esophagus in Northern Greece: a Prospective study (Barrett's esophagus). Hippokratia. 2013;17(1):27–33.
- Kiltz U, Pfaffenbach B, Schmidt WE, Adamek RJ. The lack of influence of CagA positive *Helicobacter pylori* strains on gastro-oesophageal reflux disease. Eur J Gastroenterol Hepatol. 2002;14(9):979–84.
- Laheij RJF, Van Rossum LGM, De Boer WA, Jansen JBMJ. Corpus gastritis in patients with endoscopic diagnosis of reflux oesophagitis and Barrett's oesophagus. Aliment Pharmacol Ther. 2002;16(5):887–91.
- Loffeld RJLF, Werdmuller BFM, Kuster JG, Pérez-Pérez GI, Blaser MJ, Kuipers EJ. Colonization with cagA-positive *Helicobacter pylori* strains inversely associated with reflux esophagitis and Barrett's esophagus. Digestion. 2000;62(2–3):95–9.
- Loffeld RJLF, van der Putten ABMM. Helicobacter pylori and gastrooesophageal reflux disease: a cross-sectional epidemiological study. Neth J Med. 2004;62(6):188–91.
- Newton M, Bryan R, Burnham WR, Kamm MA. Evaluation of *Helico-bacter pylori* in reflux oesophagitis and Barrett's oesophagus. Gut. 1997;40(1):9–13.
- Park JJ, Kim JW, Kim HJ, Chung MG, Park SM, Baik GH, Nah BK, Nam SY, Seo KS, Ko BS, et al. The prevalence of and risk factors for Barrett's esophagus in a Korean population: a nationwide multicenter prospective study. J Clin Gastroenterol. 2009;43(10):907–14.
- Paull G, Yardley JH. Gastric and esophageal Campylobacter pylori in patients with Barrett's esophagus. Gastroenterology. 1988;95(1):216–8.
- Rajendra S, Ackroyd R, Robertson IK, Ho JJ, Karim N, Kutty KM. *Helicobac-ter pylori*, ethnicity, and the gastroesophageal reflux disease spectrum: a study from the East. Helicobacter. 2007;12(2):177–83.
- Ronkainen J, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E, Vieth M, Stolte M, Talley NJ, Agreus L. Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterology. 2005;129(6):1825–31.
- Rubenstein JH, Inadomi JM, Scheiman J, Schoenfeld P, Appelman H, Zhang M, Metko V, Kao JY. Association between *Helicobacter pylori* and Barrett's esophagus, erosive esophagitis, and gastroesophageal reflux symptoms. Clin Gastroenterol Hepatol. 2014;12(2):239–45.
- 55. Sharifi A, Dowlatshahi S, Moradi Tabriz H, Salamat F, Sanaei O. The prevalence, risk factors, and clinical correlates of erosive esophagitis and Barrett's esophagus in iranian patients with reflux symptoms. Gastroenterol Res Pract. 2014. https://doi.org/10.1155/2014/696294.
- Sonnenberg A, Lash RH, Genta RM. A national study of *Helicobac-tor pylori* infection in gastric biopsy specimens. Gastroenterology. 2010;139(6):1894-1901.e1892 (quiz e1812).
- Thrift AP, Pandeya N, Smith KJ, Green AC, Hayward NK, Webb PM, Whiteman DC. *Helicobacter pylori* infection and the risks of Barrett's oesophagus: a population-based case-control study. Int J Cancer. 2012;130(10):2407–16.
- Vaezi MF, Falk GW, Peek RM, Vicari JJ, Goldblum JR, Perez-Perez GI, Rice TW, Blaser MJ, Richter JE. CagA-positive strains of *Helicobacter pylori* may protect against Barrett's esophagus. Am J Gastroenterol. 2000;95(9):2206–11.
- Vicari JJ, Peek RM, Falk GW, Goldblum JR, Easley KA, Schnell J, Perez-Perez GI, Halter SA, Rice TW, Blaser MJ, et al. The seroprevalence of cagA-positive *Helicobacter pylori* strains in the spectrum of gastroesophageal reflux disease. Gastroenterology. 1998;115(1):50–7.
- Weston AP, Badr AS, Topalovski M, Cherian R, Dixon A, Hassanein RS. Prospective evaluation of the prevalence of gastric *Helicobacter pylori* infection in patients with GERD, Barrett's esophagus, Barrett's dysplasia, and Barrett's adenocarcinoma. Am J Gastroenterol. 2000;95(2):387–94.
- White NM, Gabril M, Ejeckam G, Mathews M, Fardy J, Kamel F, Dore J, Yousef GM. Barrett's esophagus and cardiac intestinal metaplasia: two conditions within the same spectrum. Can J Gastroenterol. 2008;22(4):369–75.

- Zhang J, Chen XL, Wang KM, Guo XD, Zuo AL, Gong J. Relationship of gastric *Helicobacter pylori* infection to Barrett's esophagus and gastro-esophageal reflux disease in Chinese. World J Gastroenterol. 2004;10(5):672–5.
- Dore MP, Pes GM, Bassotti G, Farina MA, Marras G, Graham DY. Risk factors for erosive and non-erosive gastroesophageal reflux disease and Barrett's esophagus in Nothern Sardinia. Scand J Gastroenterol. 2016;51(11):1281–7.
- Keyashian K, Hua V, Narsinh K, Kline M, Chandrasoma PT, Kim JJ. Barrett's esophagus in Latinos undergoing endoscopy for gastroesophageal reflux disease symptoms. Dis Esophagus. 2013;26(1):44–9.
- Vieth M, Masoud B, Meining A, Stolte M. *Helicobacter pylori* infection: protection against Barrett's mucosa and neoplasia? Digestion. 2000;62(4):225–31.
- Wu JC, Sung JJ, Chan FK, Ching JY, Ng AC, Go MY, Wong SK, Ng EK, Chung SC. *Helicobacter pylori* infection is associated with milder gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2000;14(4):427–32.
- 67. Zaninotto G, Portale G, Parenti A, Lanza C, Costantini M, Molena D, Ruol A, Battaglia G, Costantino M, Epifani M, et al. Role of acid and bile reflux in development of specialised intestinal metaplasia in distal oesophagus. Dig Liver Dis. 2002;34(4):251–7.
- Abe Y, lijima K, Koike T, Asanuma K, Imatani A, Ohara S, Shimosegawa T. Barrett's esophagus is characterized by the absence of *Helicobacter pylori* infection and high levels of serum pepsinogen I concentration in Japan. J Gastroenterol Hepatol. 2009;24(1):129–34.
- 69. Anderson LA, Murphy SJ, Johnston BT, Watson RGP, Ferguson HR, Bamford KB, Ghazy A, McCarron P, McGuigan J, Reynolds JV, et al. Relationship between *Helicobacter pylori* infection and gastric atrophy and the stages of the oesophageal inflammation, metaplasia, adenocarcinoma sequence: results from the FINBAR case-control study. Gut. 2008;57(6):734–9.
- Csendes A, Smok G, Burdiles P, Sagastume H, Rojas J, Puente G, Quezada F, Korn O. "Carditis": an objective histological marker for pathologic gastroesophageal reflux disease. Dis Esophagus. 1998;11(2):101–5.
- Kudo M, Gutierrez O, El-Zimaity HMT, Cardona H, Nurgalieva ZZ, Wu J, Graham DY. CagA in Barrett's oesophagus in Colombia, a country with a high prevalence of gastric cancer. J Clin Pathol. 2005;58(3):259–62.
- Rugge M, Russo V, Busatto G, Genta RM, Di Mario F, Farinati F, Graham DY. The phenotype of gastric mucosa coexisting with Barrett's oesophagus. J Clin Pathol. 2001;54(6):456–60.
- Dietz J, Chaves-e-Silva S, Meurer L, Sekine S, De Souza AR, Meine GC. Short segment Barrett's esophagus and distal gastric intestinal metaplasia. Arquivos de gastroenterologia 2006;43(2):117–20.
- Chang Y, Liu B, Liu GS, Wang T, Gong J. Short-segment Barrett's esophagus and cardia intestinal metaplasia: a comparative analysis. World J Gastroenterol. 2010;16(48):6151–4.
- Dietz J, Meurer L, Maffazzoni DR, Furtado AD, Prolla JC. Intestinal metaplasia in the distal esophagus and correlation with symptoms of gastroesphageal reflux disease. Dis Esophagus. 2003;16(1):29–32.
- Matsuzaki J, Suzuki H, Asakura K, Saito Y, Hirata K, Takebayashi T, Hibi T. Etiological difference between ultrashort- and short-segment Barrett's esophagus. J Gastroenterol. 2011;46(3):332–8.
- Rokkas T, Pistiolas D, Sechopoulos P, Robotis I, Margantinis G. Relationship between *Helicobacter pylori* infection and esophageal neoplasia: a meta-analysis. Clin Gastroenterol Hepatol. 2007;5(12):1413–7 (1417. e1411-1412).
- Buttar NS, Falk GW. Pathogenesis of gastroesophageal reflux and Barrett esophagus. Mayo Clin Proc. 2001;76(2):226–34.
- 79. Abe Y, Ohara S, Koike T, Sekine H, lijima K, Kawamura M, Imatani A, Kato K, Shimosegawa T. The prevalence of *Helicobacter pylori* infection and the status of gastric acid secretion in patients with Barrett's esophagus in Japan. Am J Gastroenterol. 2004;99(7):1213–21.
- Reshetnyak VI, Burmistrov AI, Maev IV. *Helicobacter pylori*: commensal, symbiont or pathogen? World J Gastroenterol. 2021;27(7):545–60.
- Abrahami D, McDonald EG, Schnitzer ME, Barkun AN, Suissa S, Azoulay L. Proton pump inhibitors and risk of gastric cancer: population-based cohort study. Gut. 2021. https://doi.org/10.1136/gutjnl-2021-325097.
- Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Longterm proton pump inhibitors and risk of gastric cancer development after treatment for *Helicobacter pylori*: a population-based study. Gut. 2018;67(1):28–35.

- Falk GW. Evaluating the association of *Helicobacter pylori* to GERD. Gastroenterol Hepatol. 2008;4(9):631–2.
- Kountouras J, Zavos C, Chatzopoulos D, Katsinelos P. *Helicobacter pylori* and gastro-oesophageal reflux disease. Lancet (London, England). 2006;368(9540):986 (author reply 986-987).
- Abdel-Latif MM, Windle H, Terres A, Eidhin DN, Kelleher D, Reynolds JV. *Helicobacter pylori* extract induces nuclear factor-kappa B, activator protein-1, and cyclooxygenase-2 in esophageal epithelial cells. J Gastrointest Surg. 2006;10(4):551–62.
- 86. Kountouras J, Chatzopoulos D, Zavos C. Eradication of *Helicobacter pylori* might halt the progress to oesophageal adenocarcinoma in patients with gastro-oesophageal reflux disease and Barrett's oesophagus. Med Hypotheses. 2007;68(5):1174–5.
- Chu YX, Wang WH, Dai Y, Teng GG, Wang SJ. Esophageal *Helicobacter* pylori colonization aggravates esophageal injury caused by reflux. World J Gastroenterol. 2014;20(42):15715–26.
- Liu FX, Wang WH, Wang J, Li J, Gao PP. Effect of *Helicobacter pylori* infection on Barrett's esophagus and esophageal adenocarcinoma formation in a rat model of chronic gastroesophageal reflux. Helicobacter. 2011;16(1):66–77.

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