EPIDEMIOLOGY, RISK FACTORS, SURVEILLANCE AND DETECTION OF EARLY NEOPLASIA IN BARRETT'S OESOPHAGUS

PhD Thesis

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2020

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ABBREVIATIONS

AAC	Acetic acid chromoendoscopy
AC	Adenocarcinoma
ASGE	American Society for Gastrointestinal Endoscopy
BO	Barrett's oesophagus
C	Culture
CagA	Cytotoxin-associated gene A
CI	Confidence intervals
GI	Gastrointestinal
GOJ	Gastro-oesophageal junction
GORD	Gastro-oesophageal reflux disease
H	Histology
HP	*Helicobacter pylori*
HPI	*Helicobacter pylori* infection
IGF	Insulin-like Growth Factor
LGD	Low-grade dysplasia
LSBO	Long-segment Barrett's oesophagus
N^0	Number
NPV	Negative predictive value
OAC	Oesophageal adenocarcinoma
OGD	Esophagogastroduodenoscopy
OR	Odds ratio
PCR	Polymerase chain reaction
PIVI	Preservation and Incorporation of Valuable Endoscopic Innovations
PPV	Positive predictive value
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
R	Rapid urease test
S	Serology
SA	Stool antigen
SCC	Squamous cell carcinoma
SSBO	Short-segment Barrett's oesophagus
TNM	TNM Classification of Malignant Tumors

U	Urea breath test
USSBO	Ultrashort segment Barrett's oesophagus

INTRODUCTION

1. Barrett's oesophagus

1. 1. Definition and pathomechanism

The condition was first described in 1946 by Philip R Allison (1), but the term Barrett's oesophagus (BO) was first used in the 1950s, coined after Normann Barrett, an eminent Australian surgeon in London (2).

BO is a diagnosis based on the endoscopic and histological investigation of the distal oesophagus. Gastroscopic assessment reveals a mucosal change above the level of the cardia at the top of the gastric folds. Biopsies form this salmon coloured mucosa finds the presence of columnar epithelium in place of the non-keratotic squamous epithelium (3). It is easy to diagnose BO if the endoscopic investigator considers this pathology and obtains biopsy specimen for the histologic assessment. On the histologic evaluation, the columnar mucosa harbours intestinal metaplasia or goblet cells, which is one of the diagnostic criteria of BO (4, 5)

According to the most commonly accepted theory in the development of BO, gastro-oesophageal reflux disease (GORD) plays the most critical role. It is thought that chronic inflammation caused by the irritating gastric acid in the lower oesophagus leads to the change in the epithelium of the lower oesophagus, but the exact pathophysiology remains an essential subject of research (6).

1.2. Epidemiology

The prevalence of BO is increasing in developed countries. However, since an upper endoscopic investigation is needed to confirm the diagnosis, the increasing availability of this modality contributes to the rising trend. Current estimates suggest that the prevalence of BO is between 1-2% in the general population and around 10% in subjects with GORD (3).

The national prevalence of BO in Hungary has not been explored yet. Unpublished data of a Hungarian epidemiologic study by Rosztóczy et al. investigating GORD would have suggested that GORD is not as common in Hungary as it is in Western Europe or North America but these results are limited by the lack of representativeness of the study sample. These data may suggest that the prevalence of BO in Hungary is low, but it needs to be emphasised that reliable epidemiologic data on GORD or BO are missing.

1.3. Clinical presentation and symptoms

The diagnosis of BO is made after a diagnostic gastroscopy for upper gastrointestinal (GI) symptoms, that is dyspepsia, abdominal pain, heartburn or other signs of GORD most frequently, or after a gastroscopy for any other indication. It has to be noted that BO is often diagnosed when symptoms driven by the pathologies of the oesophagus or the cardia are investigated. A large proportion of patients diagnosed with BO does not have any BO-related symptoms (3).

1.4. Risk factors

According to current literature, the risk factors of BO are male gender, white ethnicity, older age, presence of GORD symptoms, large hiatal hernia, increased waist circumference, cigarette smoking and family history of GORD, BO or oesophageal adenocarcinoma (OAC). Body mass index, alcohol and non-steroidal anti-inflammatory drug use do not seem to modify the risk of BO (3).

The above-listed risk factors of BO are rapidly changing in the developed countries and in Hungary too. The increasing life expectancy, the obesity pandemic are all increasing the risk of BO.

The investigation of the association between BO and *Helicobacter pylori* infection (HPI) goes back to the late 1980s (7), soon after the discovery of the bacterium (8).

1.5. Association between Barrett's oesophagus and *Helicobacter pylori* infection

Results of individual studies demonstrated different associations between HPI and BO. Some studies found an increased, others a decreased risk of BO.

Four previous meta-analyses analysed the association between HP and BO, three of which concluded that HPI is associated with a lower BO prevalence (9-11). On the contrary, a fourth, Wang et al. did not find a clear relationship between HPI and BO (12). The three earlier meta-analyses used small subsets of studies; they included five, nine and 12 trials (10-12). The most recent and extensive meta-analysis of Fischbach identified 49 trials with data on the association between HPI and BO. Besides proving the protective role of HPI in general and a marked protective effect of the CagA positive strains, they described a significant heterogeneity among the studies included. The source of heterogeneity was one of the foci of discussion, concluding that both selection and information bias were potential contributors (9).

The above meta-analyses have not published analytical results of subgroup analysis for geographical regions, for the segment length of the BO and the presence of dysplasia in BO.

Hungary had a high prevalence of HPI in the past, but its prevalence in younger generations is much lower (13). It is not unexpected, as the same decreasing trend is observed in other developed countries (14).

1.6. Recognition and diagnosis

As BO has stringent endoscopic and histologic criteria, the diagnosis can be made by endoscopic assessment and confirmatory biopsies.

The columnar mucosal changes are conspicuous to the expert endoscopist, the mucosa which looks like the gastric mucosa can be seen above the top of gastric folds while the squamocolumnar junction is proximally displaced.

Endoscopists diagnosing BO must describe the length of Barrett's segment. The Prague classification should be used to give an accurate description of the macroscopic changes (**Figure 1)** (15).

There is evidence that the length of BO is directly associated with the risk of cancer conversion. Short segment BO (<3 cm) has a lower risk than long segment BO (≥3 cm), these are 0.19 and 0.33% annually, respectively (16).

Biopsies must confirm the diagnosis of BO, and current guidelines recommend the use of the so-called Seattle protocol (17)

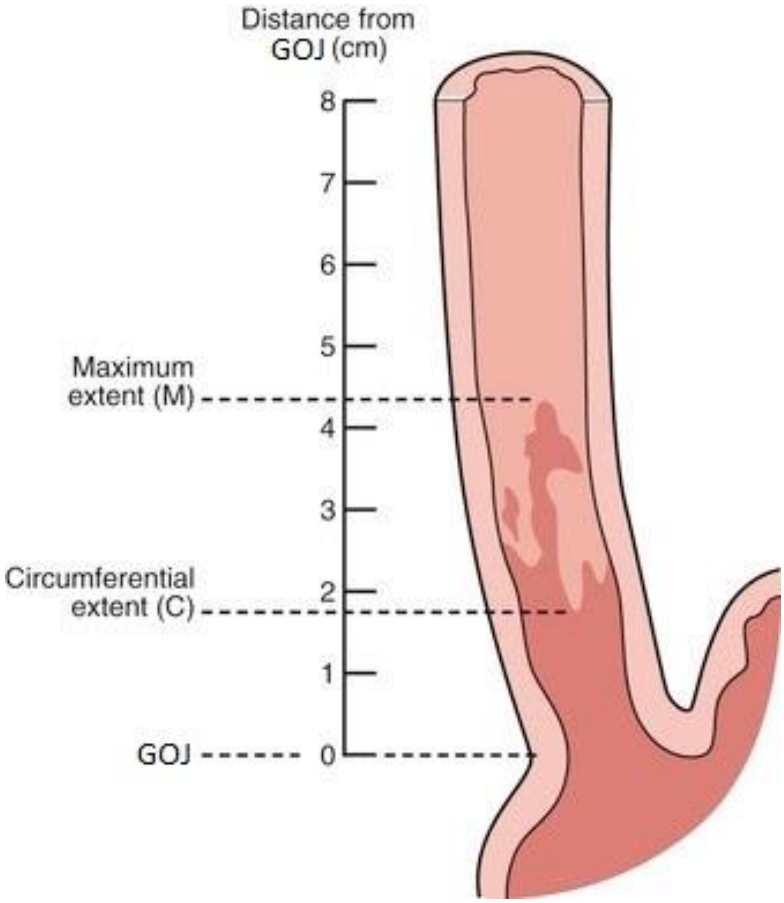

Figure 1 The concept of the Prague classification. C describes the circumferential extent (here 2 cm) and M describes the maximal extent (here 4 cm) of the columnar lined mucosa. Thus this example BO is classified as a C2M4. GOJ: gastro-oesophageal junction.

1.7. Surveillance and early neoplastic changes

The cancer progression of the columnar lined oesophagus is very similar to that of the colon. It takes long time, therefore regular endoscopic assessment, the so-called BO surveillance, ensures a window of opportunity to detect malignant transformation at an early stage. Since BO is the precursor for (OAC), improving detection at the earliest stages is a desirable goal (18).

Detection of the early neoplastic changes within the BO can prevent the development of advanced OAC as endoscopic treatment has a high success rate. Therefore, international and national guidelines give very detailed recommendations on the surveillance and treatment of early neoplasia in BO (4, 5, 19).

2. Adenocarcinoma of the oesophagus

2.1. Definition and pathomechanism

OAC is the malignant tumour most commonly in the distal third of the oesophagus. It arises from the columnar mucosa of the gastro-oesophageal junction or Barrett's segment (20). The pathomechanism of development has not fully understood yet.

2.2. Prognosis

Oesophageal cancer is currently the sixth leading cause of cancer-related mortality in the world (21). More than 85% of the patients die within 5-years following the diagnosis of oesophageal cancer (22). Poor survival is also explained by the fact that the vast majority of tumours are not suitable for surgical resection at the time of diagnosis (18). Patients with metastatic disease treated with palliative chemotherapy have a median survival of less than one year (23).

Most commonly, the diagnosis of oesophageal cancer is made after the onset of symptoms, which usually indicates a locally advanced tumour (24). The most common symptoms are dysphagia and weight loss in 74 and 57.3%, respectively (25).

The absence of well-described precancerous states and the lack of early symptoms preclude effective screening programs for all oesophageal cancers (18), except for BO (discussed above) and OAC, where endoscopic surveillance is recommended (4, 5, 26).

2.3. International and Hungarian epidemiologic trends

Oesophageal cancer is the eighth most common cancer globally. It has an estimated annual incidence above 480,000 cases, and 410.000 patients die from it each year (27).

Previously, squamous cell cancer was the more common form of oesophageal cancer, but in recent decades, the incidence of OAC significantly increased in Western Europe and the United States, and in some countries, OAC is now the leading histological type (28).

As part of our oesophageal cancer research, we collected and analysed data of 2,632 patients with primary oesophageal cancer between 1992 and 2018 in Hungary in a multicenter, longitudinal study. This study showed that the relative prevalence of OAC compared to the relative prevalence of squamous cell cancer of the oesophagus is quickly increasing, which trend attains the level of statistical significance **Figure 2**. This study is currently submitted for publication to an international journal.

This is a histological trend of primary oesophageal cancers which may or may not be related to an underlying epidemic of undiagnosed BO, which may well be the case, bearing in mind the fact that BO is often entirely asymptomatic.

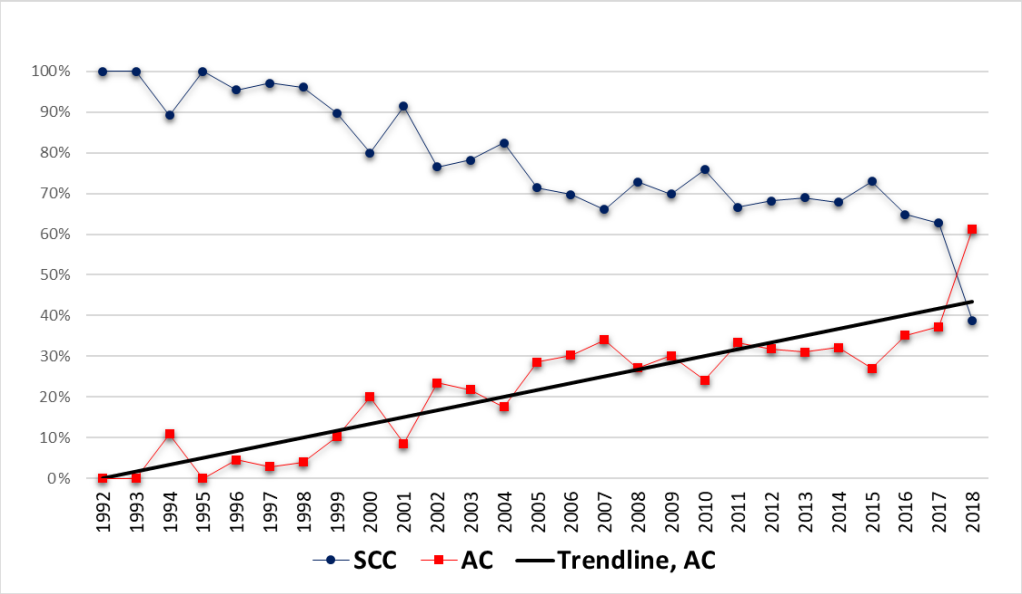

Figure 2 The relative incidence of adenocarcinoma and squamous cell cancer of the oesophagus over 26 years in Hungary. AC: adenocarcinoma; SCC: squamous cell carcinoma.

The rapid and concerning rise of the incidence of OAC points towards the change of environmental factors and also to the increasing life expectancy. The same risk factors of BO account for the rising prevalence of OAC.

3. Early neoplastic lesions of Barrett's oesophagus

3.1. Definition of early neoplasia

BO increases the risk of OAC 30-150-fold compared to a matched population without BO (29). Both the prevalence of BO and the incidence of OAC are increasing (30), and OAC often develops in BO (3, 18). Early neoplasia of BO can be defined as OAC in very early histologic stages. Currently, low-grade dysplasia, high-grade dysplasia, intramucosal cancers are regarded as early neoplastic lesions. These are often tiny lesions, spreading superficially without invading deeper layers of the oesophageal mucosa (3, 5, 31). The annual cancer conversion rate of BO without dysplasia is very low, around 0.1% (16, 32). However, the cancer conversion rates of BO with early neoplasia are much higher around 10% and above (33, 34).

3.2. Recognition of early neoplasia

As early neoplastic lesions are very subtle, they can be missed on endoscopic assessment. Therefore it is pivotal that patients undergoing surveillance gastroscopies for BO need high-quality endoscopic evaluation (4, 5).

There are multiple key performance indicators proposed to monitor and improve the quality of the upper GI endoscopic procedures. There is an increasing body of evidence that the length of the procedure has a significant impact on lesion recognition. A recent high-quality article by Veitch et al. concluded that the procedure should last no less than 8 minutes; the interval cancer rate will be unacceptably high otherwise (35).

The guidelines on BO surveillance recommend regular endoscopies with biopsies by the Seattle protocol between 6 months and five years, based on risk stratification of cancer conversion (4, 5). However, the Seattle protocol (quadrantic biopsies every 2 cm of Barrett's segment) is poorly followed (36, 37) and can miss more than the third of endoscopically curable early cancers (38). One important reason is that dysplastic BO is often flat and challenging to discover, with only 1 in 8 lesions appearing as elevated polyps (39).

To increase the detection rate of early neoplasia, numerous strategies and technical approaches are recommended, enabling targeted biopsy, such as tri-modal imaging (40-42) chromoendoscopy with dye (43, 44). Acetic acid (AAC) is a weak acid that can highlight irregular and suspicious surface patterns in Barrett's mucosa by an aceto-whitening reaction (45). Dysplastic areas lose their white discolouration quicker than areas without dysplasia (46); these highlighted lesions should be biopsied in a targeted manner. The use of 10-30 millilitres of 2.5% AAC in the oesophagus carries no increased risk of adverse reactions, complications and does not hamper the histological assessment of the samples. The diagnostic accuracy of AAC in dysplasia detection in high-risk populations was demonstrated by two studies, showing sensitivity and specificity of 90-95% and 75-85% for dysplasia detection, respectively (47, 48). One of these studies demonstrated that the number of targeted biopsies needed to detect a case with dysplasia is 5.2 with the use of acetic acid. In comparison, this number is 228 with the conventional mapping biopsies (48). Another study result showed that the use of acetic acid in a surveillance population resulted in a 6-fold increase in neoplasia detection rate compared to the standard Seattle protocol (without acetic acid) (49).

3.3. Treatment of early neoplasia

When early neoplasia is detected by endoscopy and confirmed by pathology, endoscopic therapy performs effectively. Histologically proven low- and high-grade dysplasia, T1a intramucosal cancers, and even T1sm1 low-risk adenocarcinoma (lack of lymphovascular invasion and well-differentiated features) are all suitable for endoscopic treatment modalities **Figure 3**. The treatment involves endoscopic resection of the dysplastic lesions, followed by the ablation of the residual Barrett's segment (3-5).

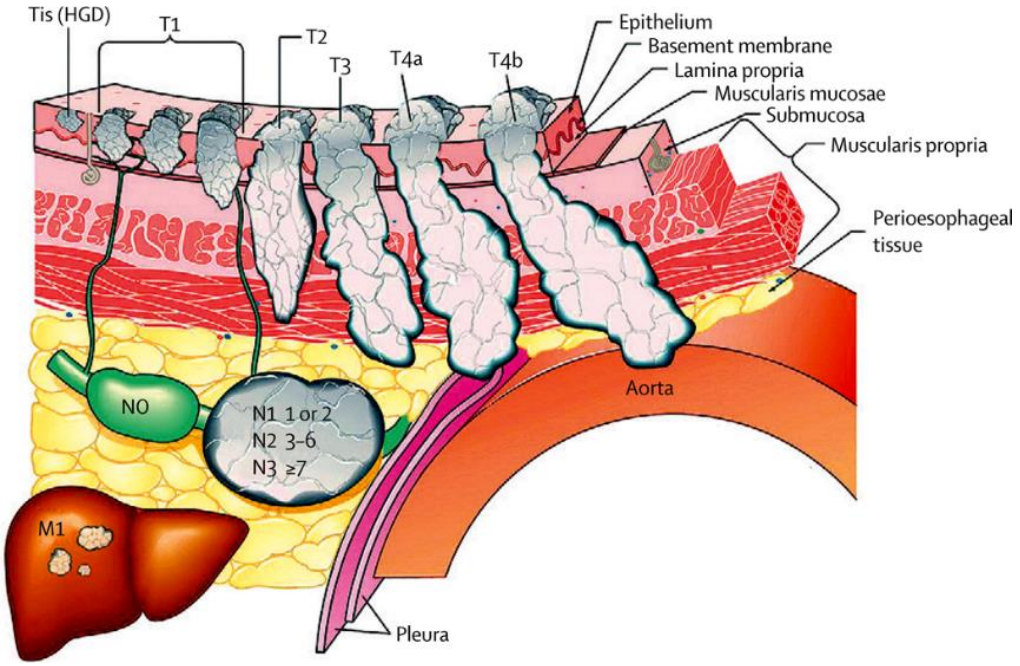

Figure 3 TNM classification of neoplastic oesophageal lesions. The figure shows the cross-section of the oesophagus with the surrounding anatomical regions (only illustrative) (20). Early neoplastic lesions include superficial dysplasia, in situ (Tis) and T1a adenocarcinomas not invading through the muscularis mucosae. In the TNM classification, T describes the extension of local tumour invasion, N describes lymphatic metastases and M describes remote metastases.

3.4. Clinical implications

In summary, we can conclude that increased detection of early neoplasia in BO is the ultimate goal of the endoscopic surveillance program, as it can lead to the discovery of early-stage adenocarcinomas and can significantly improve the outcomes of OAC by curative treatment.

OBJECTIVES

This thesis describes two research projects.

1) Inspired by the conflicting results from numerous publications about the role of HPI in the development of Barrett's oesophagus, we aimed to **perform a prognostic meta-analysis**, thereby synthesising all available evidence quantitatively.
2) Since lesion detection is often a challenge during Barrett's surveillance endoscopy while the stake of missing a neoplastic lesion is high, we aimed to **develop and test training module** to increase the efficacy of the procedure.

THE STUDIES

4. Meta-analysis

4.1. Methods

4.1.1. Summary publications: the overview of meta-analyses

The number of scientific publications is still growing: in the MEDLINE database covering most English-language records, more than 1 million new records are indexed annually. The „publication explosion" led to a challenge: keeping our knowledge up-to-date, even within a narrow field of science, requires a considerable time investment. This served as a reason for summary publications to come to live: they are to ease digestion of a large volume of information so that readers can acquire up-to-date knowledge quickly.

Considering the taxonomy of summary publications, systematic reviews and meta-analyses should be highlighted. A systematic review aims to collect and re-synthesize all evidence related to a specific question. If a systematic review performs quantitative synthesis with dedicated statistical methods, we call it a meta-analysis (50).

Meta-analyses have several advantages. The method is cheap and rapid to carry out: it yields high-quality results with practical relevance within a year if used properly. Since patients are not involved, ethical permission is not required. Accumulating already published data from multiple records (with small or large sample size) will inevitably result in a higher sample size than that of the individual studies, which helps to avoid a beta-type error. Since data are available for re-analysis, questions not raised by the individual studies may be addressed.

We have to note that meta-analyses have limitations. The aggregate of the individual studies carries all limitations of the original data including the methodological limitations of the individual publications. Some of these flaws can be avoided, but some are inevitable when pooling data. Results are particularly vulnerable to bias (systematic error) which should be thoroughly and systematically explored in meta-analyses. It is hard (or even impossible) to identify all publications because small studies with neutral („negative results") often fall out of the scope of a systematic search covering the international literature (that is, publication bias).

4.1.2. Clinical question

PECO items of the strategy were:

1. (Population) adult population,
2. (Exposure) past or current HPI,

3. (Comparator) patients without HPI,
4. (Outcome) BO.

4.1.3. Protocol

A prognostic meta-analysis and systematic review were performed using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (51). The analysis was registered in advance on PROSPERO with registration number CRD42017077509.

4.1.4. Systemic literature search

A systematic search was conducted in MEDLINE (via PubMed), EMBASE and CENTRAL databases from inception to December 2016. Records were managed by EndNote X7.4, software (Clarivate Analytics, Philadelphia, PA, USA) to exclude duplicates.

Keywords for the computer-aided search were (Barrett's OR Barrett's metaplasia OR Barrett metaplasia OR Barrett's oesophagus OR Barrett's esophagus OR Barrett oesophagus OR Barrett esophagus) AND (*Helicobacter pylori* or *H pylori or H. pylori* or *Helicobacter*). Additional articles were identified from the reference lists of eligible primary studies.

4.1.5. Inclusion and exclusion criteria

All studies with relevant information on HPI prevalence in BO patients and controls within the same population were included in our analysis. All studies with abstracts in English were included, full-text articles in languages other than English were read, appraised and data were extracted by researchers who speak and understand the respective language. Full-text articles and abstracts were both included. Different articles reporting data on the prevalence of HPI (proven by serological and/or histological studies and/or stool antigen testing and/or bacterial culture and/or rapid urease or urea breath test) and BO from the same population were thoroughly scrutinised, and only one record with the highest number of BO cases was included in the meta-analysis. Articles from identical populations, where the prevalence of HPI was more detailed for different lengths of BO were excluded from the overall analysis, but they were included in the subgroup analysis for BO segment length. All types of comparative observational studies were included, regardless of whether they were prospective or retrospective. Non-human studies and review articles were excluded.

4.1.6. Data extraction

Numeric data were extracted by two investigators and manually populated onto a purpose-designed Excel 2016 sheet (Office 365, Microsoft, Redmond, WA, USA). Data were collected on the year of publication, study type, geographical location, number of cases and controls and basic demographics (age, sex ratio) in both groups and method(s) of HPI testing. Most importantly, data were collected on the prevalence of HPI in BO cases and controls, also in dysplastic and non-dysplastic BO and in different segment lengths of BO, for further subgroup analysis. Data on the prevalence of CagA positive HPI were also collected. Other relevant findings were mentioned in an additional column as free text.

4.1.7. Statistical analysis

HPI prevalence data from individual studies were extracted, and raw data were calculated, followed by the calculation of odds ratios (ORs) and 95% confidence intervals (CIs) for BO in case of HPI. Pooled estimates were calculated with the random-effects model by using the DerSimonian–Laird method (52). Results of the meta-analysis were displayed graphically on forest plots. Heterogeneity was assessed using Cochrane's Q and the I^2 statistics, where Q exceeds the upper-tail critical value of chi-square on k–1 degrees, and I^2 represents the percentage of effect size heterogeneity that cannot be explained by random chance. As suggested by the Cochrane Handbook, I^2 values were interpreted as negligible (<30%), moderate (30–60%), substantial (50–90%), and considerable (75–100%) heterogeneity (50). Publication bias of the included studies was checked by Egger's test (53) and by visual assessment of funnel plots.

All calculations were performed by Stata 11 data analysis and statistical software (Stata Corp LLC, College Station, TX, USA).

4.1.8. Assessment of risk of bias and study quality

The evaluations of both the risk of bias and the quality were done at data extraction.

A modified Newcastle-Ottawa Scale for case-control studies was used for the quality assessment of the individual studies included in our meta-analysis (for the items, see **S1 Appendix**), and the result of the assessment was graphically demonstrated in a table with color codes, green: low risk of bias; yellow: moderate or unknown risk of bias; red: high risk of bias.

4.2. Results

4.2.1. Selected studies

Our search strategy initially identified 1,705 potential studies. Removal of duplicates was followed by screening first the titles, and then the abstracts, leaving 96 studies for full-text review, including eight additional studies identified in the reference lists of the primarily eligible studies (54-61). Thirteen studies were excluded, as they did not provide sufficient data (reasons for exclusion are detailed in **S2 Appendix**) Data were extracted from 83 studies (7, 31, 54-134); however, 11 of these studies had to be excluded from the statistical analysis due to overlapping study populations (31, 63, 78, 79, 92, 96, 105, 107, 119-121). Our final statistical analysis included 72 studies. Of the 72 items, two studies provided data from populations previously reported in the 70 studies. However, these had detailed data on the different prevalence of HPI in different segment lengths of BO. Therefore these were only included in the subgroup analysis (85, 123). The study selection process is shown in **Figure 4**. The summary of the characteristics of the studies included in our review is shown in **Table 1**.

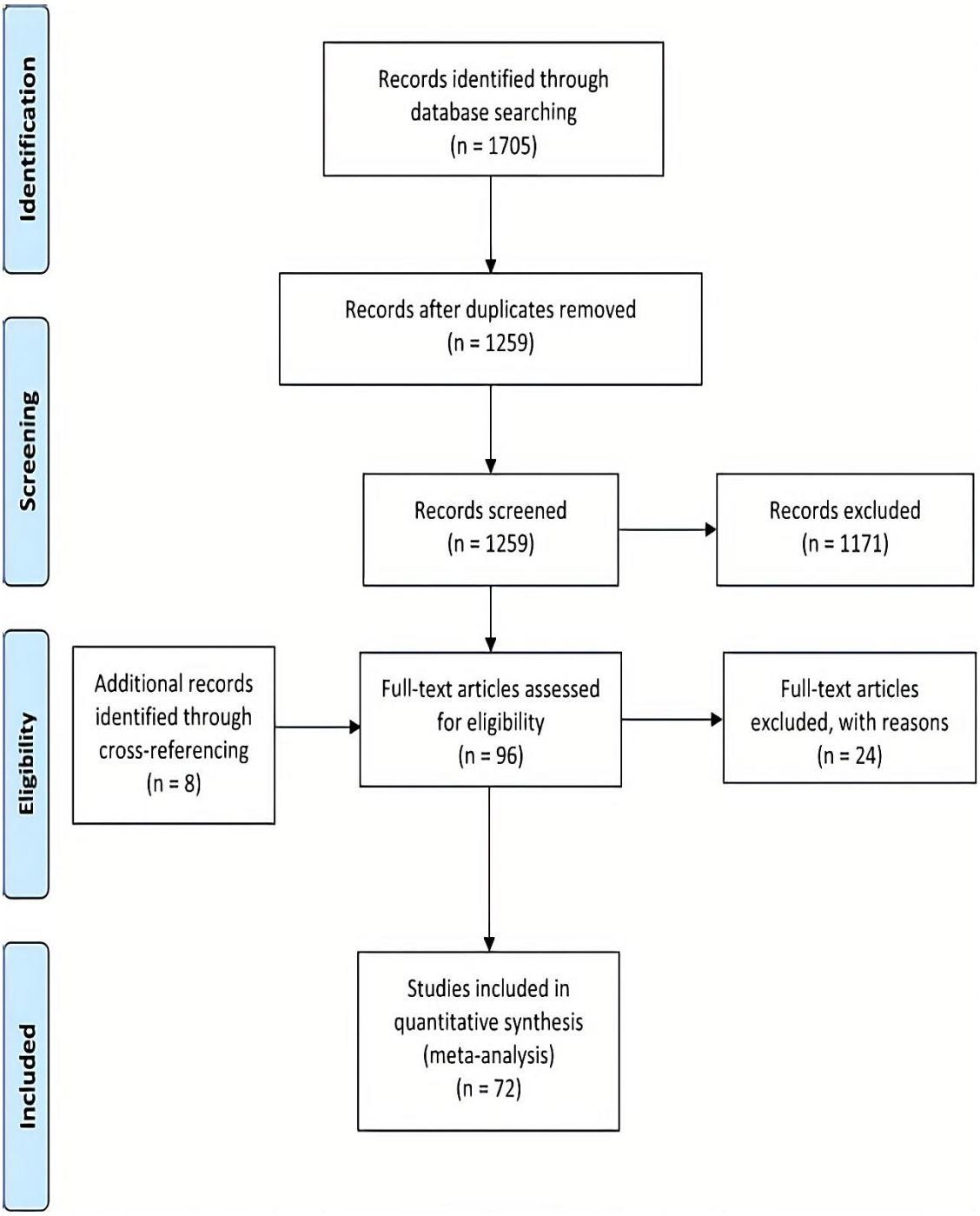

Figure 4 PRISMA flow chart of the study selection process

Table 1 Main characteristics of the studies included. C: culture, GORD: gastro-oesophageal reflux disease, H: histology, PCR: polymerase chain reaction, S: serology, SA: stool antigen, R: rapid urease test, U: urea breath test, †: studies only in the subgroup analysis for BO segment length, H oesophagus: HPI tested in esophageal or gastro-oesophagal junction biopsy samples only.

Study author and year	Country	Number of cases / controls	HPI testing method	Definition of controls	Only new BO cases
Abbas et al. 1995 (62)	Pakistan	29 / 29	H, R	GORD	No
Abe et al. 2009 (64)	Japan	36 / 108	H, R, S	Population	Yes
Abouda et al. 2003 (54)	UK	60 / 25	H, R, S	Endoscopy	No
Ackermack et al. 2003 (65)	The Netherlands	51 / 62	S	Endoscopy	Not stated
Ahmed et al. 2004 (66)	Sudan	11 / 47	R	GORD	Not stated
Anderson et al. 2008(67)	Ireland	224 / 260	S	Population	Yes
Blaser et al. 1991 (68)	The USA	58 / 41	H,S	Population	Not stated
Carmona et al.2003 (69)	Mexico	24 / 232	R	Endoscopy	Not stated
Chacaltana et al. 2009 (55)	Peru	11 / 911	H	Other	No
Chang et al. 2010 (70)	China	32 / 41	H	Endoscopy	No
Chen et al. 2016 (71)	Taiwan	161 / 644	R	Endoscopy	Not stated
Cooper et al. 1991 (72)	UK	26 / 30	H	GORD	No
Corley et al. 2008 (73)	The USA	318 / 299	S	Population	Yes
Csendes et al. 1997(74)	Chile	100 / 190	H	Endoscopy	No
Dore et al. 2016 (75)	Italy	131 / 1772	H, R, U	Endoscopy	No
El Serag et al. 1999 (56)	The USA	36 / 72	H	GORD	No
Fassan et al. 2009 (76)	Italy	210 / 210	H	Endoscopy	Not stated
Ferrandez et al. 2006 (77)	Spain	104 / 213	H, R, S, PCR	Population	No

Table 1 (continued)

Study author and year	Country	Number of cases / controls	HPI testing method	Definition of controls	Only new BO cases
Goldblum et al. 2002 (80)	The USA	70 / 60	H, S	Endoscopy	No
Hackelsberger et al. 1998 (81)	Germany	16 / 315	H, R	Endoscopy	No
Henihan et al. 1998 (82)	Ireland	82 / 40	H oesophagus	GORD	No
Hilal et al. 2016 (83)	The USA	323 / 1849	H	Endoscopy	No
Hirota et al. 1999 (84)	The USA	104 / 738	H oesophagus	Endoscopy	No
Inomata et al. 2006 † (85)	Japan	36 / 80	H, R, S	Endoscopy	Not stated
Johansson et al. 2007 (86)	Sweden	21 / 498	H oesophagus	Endoscopy	No
Jonaitis et al. 2011 (87)	Lithuania	33 / 160	H, R	GORD	Not stated
Kala et al. 2007 (57)	Czech Rep.	22 / 173	H, R	GORD	No
Katsienlos et al. 2013 (88)	Greece	75 / 1915	H, R	Endoscopy	Not stated
Keyashian et al. 2013 (89)	The USA	52 / 391	H, SA	Endoscopy	No
Kiltz et al. 1999 (90)	Germany	35 / 320	R, S	Endoscopy	No
Kim et al. 2006 (91)	South (Korea	31 / 224	H, R	Endoscopy	Not stated
Laheij et al. 2002 (93)	The Netherlands	23 / 528	H, R, C	Endoscopy	Not stated
Lam et al. 2008 (94)	The USA	56 / 280	S	Endoscopy	Yes
Lee et al. 2011 (95)	Malaysia	15 / 104	H, R	Endoscopy	Not stated
Loffeld et al. 1992 (97)	The Netherlands	71 / 200	H oesophagus , S	Population	Not stated
Loffeld et al. 2000 (98)	The Netherlands	36 / 454	H	Endoscopy	Yes

Table 1 (continued)

Study author and year	Country	Number of cases / controls	HPI testing method	Definition of controls	Only new BO cases
Loffeld et al. 2004 (99)	The Netherlands	307 / 5341	H, C	Endoscopy	No
Lord et al. 2000 (100)	Australia	91 / 214	H	Endoscopy	No
Martinek et al. 2003 (101)	Czech Rep.	31 / 259	H, R	Endoscopy	Not stated
Meng et al. 2008 (58)	The USA	28 / 104	PCR	Endoscopy	Not stated
Monkemuller et al. 2008 (102)	Germany	97 / 97	H	Endoscopy	No
Nandurkar et al. 1997 (103)	Australia	46 / 112	H oesophagus	Endoscopy	Yes
Newton et al. 1997 (104)	UK	16 / 25	H, R	Endoscopy	No
Pascareno et al. 2014 (106)	Romania	24 / 218	H	Endoscopy	Not stated
Paull et al. 1988 (7)	The USA	26 / 26	H	Endoscopy	No
Peng et al. 2009 (108)	China	27 / 110	R	GORD	Not stated
Rajendra et al. 2004 (59)	Malaysia	123 / 1741	H, R	Endoscopy	Not stated
Rajendra et al. 2007 (109)	Malaysia	55 / 53	H, S	Endoscopy	No
Rex et al. 2003 (110)	The USA	48 / 764	R	Population	Yes
Rodriguez et al. 2014 (111)	Spain	8 / 192	H	Endoscopy	Yes
Ronkainen et al. 2005 (60)	Sweden	16 / 984	H, C, S	Population	Not stated
Rubenstein et al. 2014 (112)	The USA	150 / 177	S	Endoscopy	No
Rugge et al. 2001 (113)	Italy	53 / 53	H	Endoscopy	Not stated
Schenk et al. 1999 (114)	Netherlands	49 / 88	H	GORD	No

Table 1 (continued)

Study author and year	Country	Number of cases / controls	HPI testing method	Definition of controls	Only new BO cases
Sharifi et al. 2014 (115)	Iran	34 / 702	H, R	GORD	Not stated
Sonnenberg et al. 2010 (116)	The USA	2510 / 76475	H	Endoscopy	No
Sonnenberg et al. 2016 (117)	The USA	76475 / 284552	H	Endoscopy	No
Thrift et al. 2012 (118)	Australia	0/ 398	S	Population	Yes
Toruner et al. 2004 (61)	Turkey	29 / 306	H	Endoscopy	Yes
Uno et al. 2011 (122)	Japan	126 / 100	H, S, R	Endoscopy	No
Vaezi et al. 2000 † (123)	The USA	83 / 60	H, S	GORD	Not stated
Veldhuyzen et al. 2006 (124)	Canada	25 / 1015	H	Endoscopy	Yes
Vicari et al. 1998 (125)	The USA	48/57	H,S	GORD	No
Vieth et al. 2000 (126)	Germany	1054 / 712	H	Endoscopy	No
Watari et al. 2009 (127)	Japan	88 / 52	H, C	Other	No
Werdmuller et al. 1997 (128)	Netherlands	13 / 399	H, C, R, S	Endoscopy	Not stated
Weston et al. 2000 (129)	The USA	208 / 217	H	GORD	No
White et al. 2008 (130)	Canada	39 / 29	H oesophagus	Endoscopy	No
Wong et al. 2002 (131)	China	10 / 448	H, R, U	Endoscopy	Yes
Wu et al. 2000 (132)	Hong Kong	6 / 85	H, R	GORD	Not stated
Zaninotto et al. 2002 (133)	Italy	34 / 32	H oesophagus	GORD	No
Zullo et al. 2014 (134)	Italy	17 / 1037	H	Endoscopy	Not stated

4.2.2. The association of *H. pylori* infection with Barrett's oesophagus

Our results confirmed that BO was significantly less frequent in patients with HPI compared to those without HPI: OR = 0.68 (CI: 0.58-0.79, $p < 0.001$) based on the data of the 70 studies, including a total of more than 90,000 BO cases and nearly 400,000 controls. Heterogeneity was substantial, $I^2 = 84.0\%$. A similar tendency was observed across subgroups in Asia, OR = 0.56 (CI: 0.35-0.90, $p = 0.016$), 14 studies; in Australia, OR = 0.56 (CI: 0.39-0.80, $p = 0.002$), 3 studies; in Europe, OR = 0.75 (CI: 0.58-0.96, $p = 0.022$), 31 studies, and in North-America, OR = 0.59 (CI: 0.47-0.74, $p < 0.001$) 19 studies. The low numbers of studies from South-America (55, 74) and Africa (66) mean that the meta-analytical calculations of the studies from these regions are not suitable for any conclusions, although these studies could not demonstrate a clear association between HPI and BO (**Figure 5**).

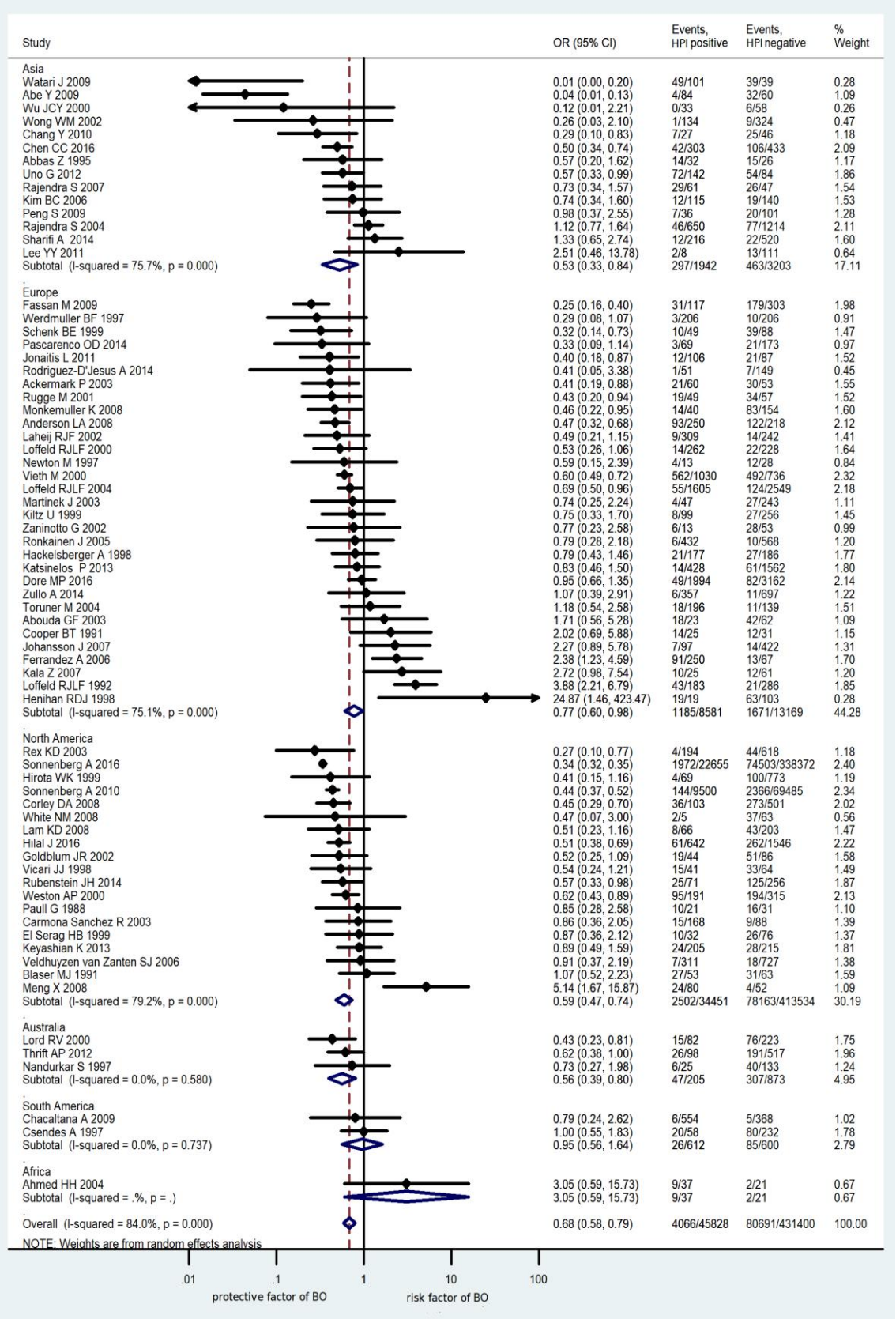

Figure 5 Odds ratios from 70 studies included in the overall analysis and subgroups for continents. BO: Barrett's oesophagus, CI: confidence interval, OR: odds ratio, HPI: HPI.

4.2.3. The association of CagA positive *H. pylori* infection with Barrett's oesophagus

There were four additional studies reporting prevalence of CagA positive HPI in relation to BO, in addition to the studies identified by Fischbach et al. which included results from 7 studies (9). In total 11 studies were included in the subgroup analysis (58, 65, 67, 73, 77, 98, 109, 112, 113, 123, 125). A further study from Abouda et al in 2003 reported data on *H. pylori* strain positive for both CagA and VacA and not CagA strains only. As their data reported on more specific *H. pylori* strain their results were not included in our subgroup analysis (54). BO was significantly less frequent with HPI than without it, OR = 0.50 (CI: 0.29-0.87, p = 0.014). Our results confirm the findings of Fischbach et al. calculating an OR = 0.38 (CI: 0.189-0.781). The forest plot of this subgroup analysis is shown in **Figure 6**.

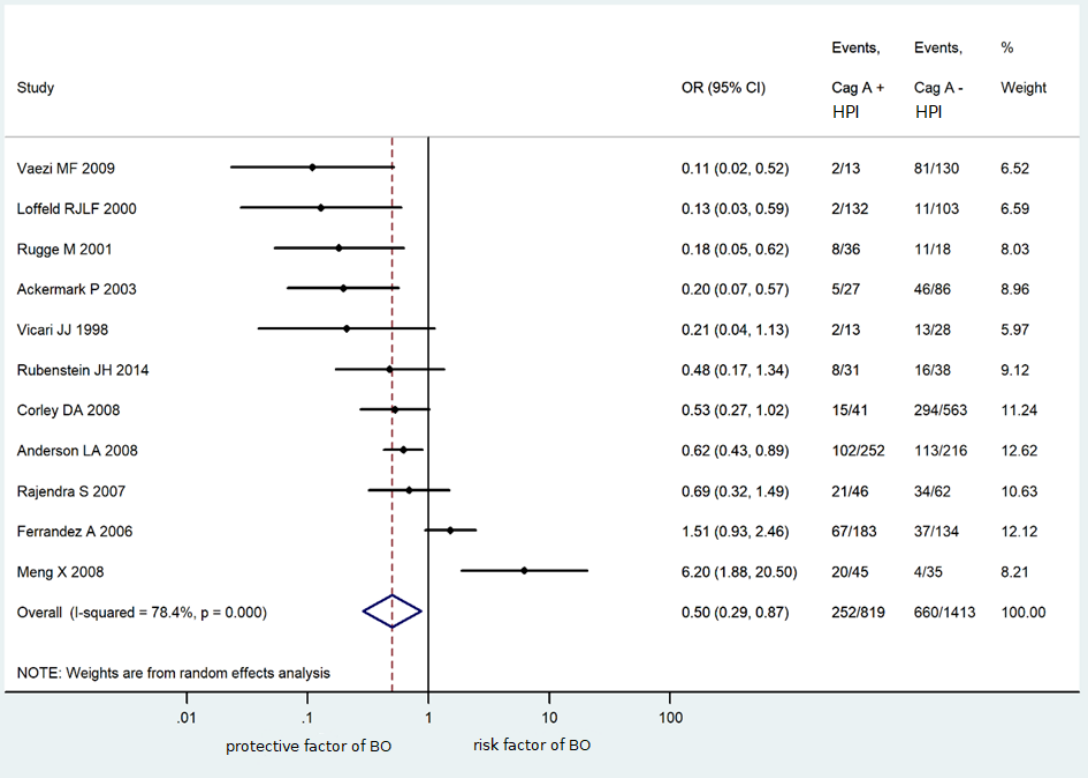

Figure 6 Odds ratios from the 11 studies included in the subgroup analysis for the association of CagA status H.pylori and Barrett's oesophagus. BO: Barrett's oesophagus, CI: confidence interval, HPI: H. pylori, OR: odds ratio.

4.2.4. The association of *H. pylori* infection the length of Barrett's segment

Prevalence of HPI for different segment lengths of BO was detailed in 9 studies (84, 85, 87, 106, 109, 110, 122, 123, 133). Two articles detailed data on ultrashort segment BO (USSBO, <1cm) (106, 133) and they were not included in the short segment BO (SSBO) subgroup. We note that the new guideline of the British Society of

Gastroenterology defines BO by at least 1cm of metaplastic columnar lining, which questions the justification of the diagnosis of USSBO (4). However, the meta-analytical calculation was performed for this subgroup as well.

Long segment BO (LSBO) was significantly less common with HPI, OR = 0.25 (CI: 0.11-0.59, p = 0.001). Although the point estimate showed a reduced odds ratio for SSBO, the results did not attain a level a statistical significance OR = 0.63 (CI: 0.32-1.26, p = 0.191). The results on USSBO or intestinal metaplasia at the cardia are not suitable for any conclusion (**Figure 7)**.

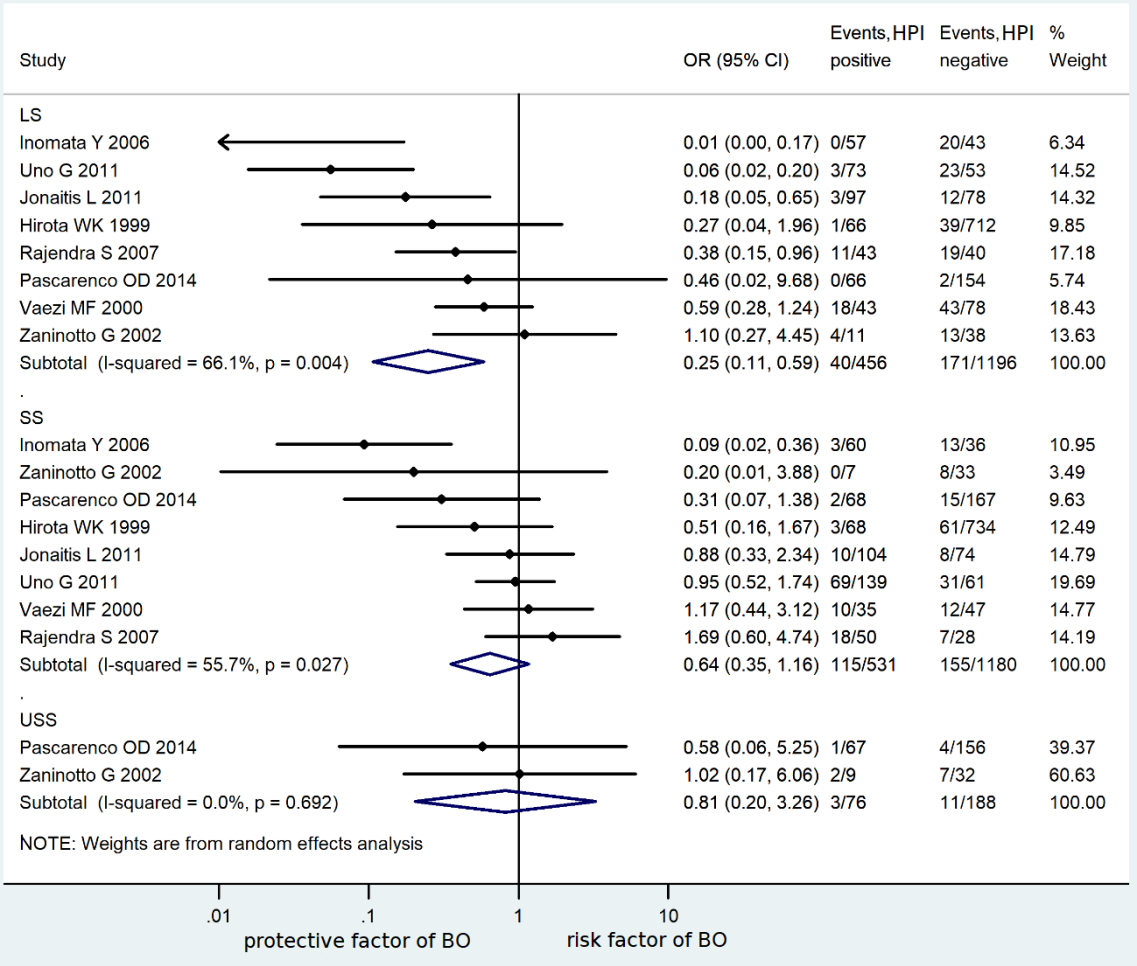

Figure 7 Odds ratios from the nine studies included in the subgroup analysis for different segment lengths of Barrett's oesophagus. BO: Barrett's oesophagus, CI: confidence interval, HPI: H. pylori, LS: long-segment Barrett's oesophagus, OR: odds ratio SS: short-segment Barrett's oesophagus, USS: ultrashort-segment Barrett's oesophagus.

4.2.5. The association of *H. pylori* infection and early neoplasia in Barrett's oesophagus

Prevalence of HPI in association with the presence of dysplasia in BO was detailed in 7 studies (76, 82, 117, 118, 125, 126, 129). We defined the subgroup of dysplastic BO by the presence of low or high-grade dysplasia or adenocarcinoma in the BO.

Dysplastic BO was less common with HPI than without it, OR = 0.37 (CI: 0.26-0.51, p < 0.001). We note that the study by Henihan et al. did not report any dysplastic BO with HPI; therefore, the result of their study could not be interpreted by the random effect model in this subgroup and had to be excluded (82). Findings were consistent with non-dysplastic BO **Figure 8**.

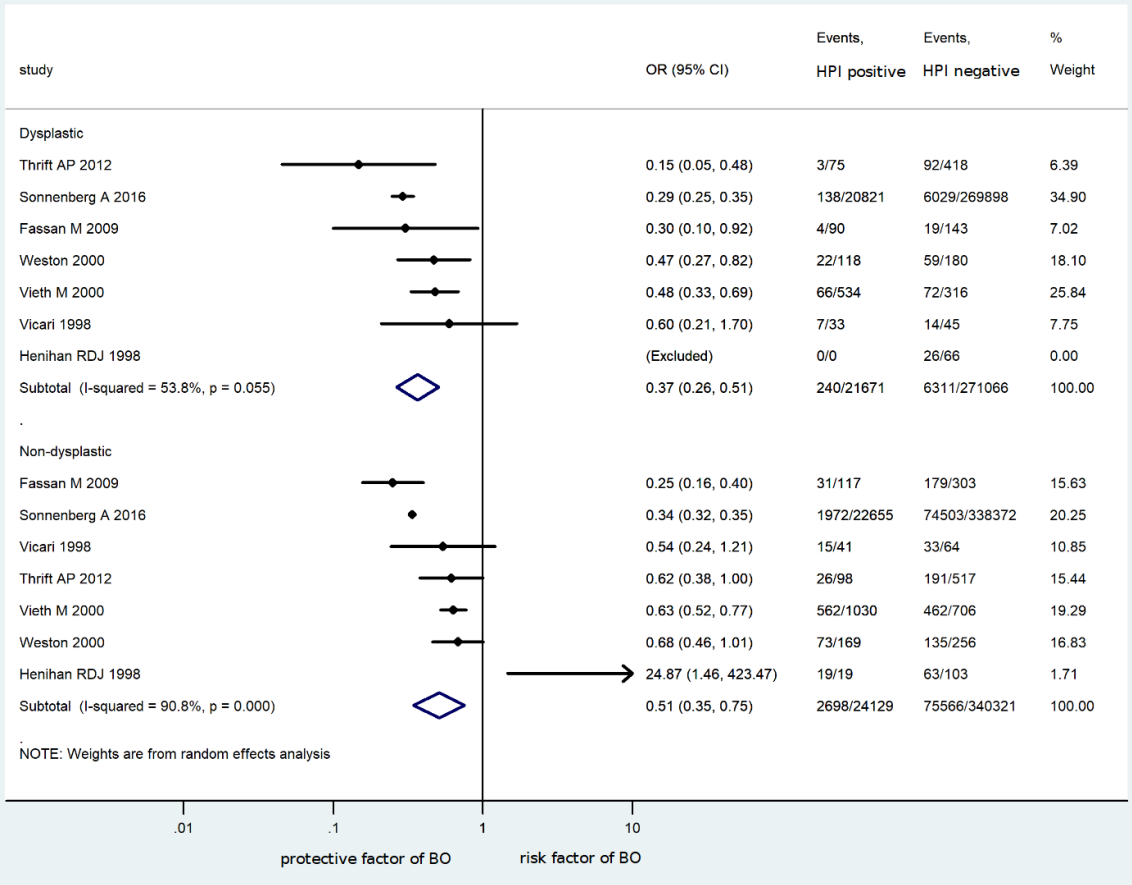

Figure 8 Odds ratios from the seven studies included in the subgroup analysis for the presence of dysplasia in Barrett's oesophagus. BO: Barrett's oesophagus, CI: confidence interval, HPI: H. pylori, OR: odds ratio.

4.2.6. Attempt to look for causes of heterogeneity among the studies

To understand the association between the risk of BO and the prevalence of HPI further subgroup analyses were performed, and the results are detailed in **Table 2**.

Table 2 Exploration of heterogeneity with subgroup analyses. BO: Barrett's oesophagus, CI: confidence interval, GORD: gastro-oesophageal reflux disease, HPI: H. pylori infection, PCR: polymerase-chain-reaction.

Subgroups	Odds ratio, 95% confidence interval	N0 of studies	Residual heterogeneity in the subgroup
Types of the control group			
Population	0.65, 0.33-1.27	9	I2 = 90.7%, p < 0.001
GORD	0.86, 0.58-1.27	14	I2 = 58.5%, p = 0.003
Endoscopy	0.64, 0.54-0.76	45	I2 = 81.9%, p < 0.001
Types of HPI detection			
Multiple methods	0.77, 0.59-1.01	30	I2 = 72.4%, p < 0.001
Histology (gastric)	0.54, 0.44-0.66	22	I2 = 79.5%, p < 0.001
Rapid urease test	0.67, 0.38-1.19	5	I2 = 52.9%, p = 0.075
Serology	0.50, 0.41-0.61	6	I2 = 0.0%, p = 0.906
Histology (oesophagus)	1.00, 0.44-2.27	6	I2 = 58.8%, p = 0.033
PCR	5.14, 1.67-15.87	1	I2 = 84.0%, p < 0.001
Only new diagnoses of BO			
New BO	0.48, 0.34-0.68	12	I2 = 60.6%, p = 0.003

4.2.6.1. Subgroups for different controls

Stratification by the different control groups was possible for four subgroups of studies with population GORD, endoscopy and other controls as indicated in. In subgroups of studies with population and GORD controls, the associations between HPI and BO were not significant. Only the studies with endoscopy controls showed a significant difference between groups, OR = 0.48 (CI: 0.31-0.74, p = 0.001). There remained substantial and considerable heterogeneity across studies in all subgroups (**Table 2).**

4.2.6.2. Subgroups for different testing methods

Stratification by the HPI testing method was possible for four subgroups of studies with histology from the stomach, histology from the oesophagus, serology and rapid urease test as indicated in **Table 1**. One study used polymerase chain reaction and in 30

studies multiple modalities were used for the detection of HPI. In case of rapid urease test and histology from the oesophagus, the ORs from the studies cover a wide range and the pooled ORs for these methods are not significant. A significant difference was seen in the pooled ORs for HPI testing by histology from the stomach and serology. Heterogeneities in all subgroups are substantial, save for serology where the studies showed no significant heterogeneity (I^2 = 0.0%, p = 0.060) (**Table 2).**

4.2.6.3. Subgroups for new diagnoses of Barrett's cases

We identified 12 studies, which clearly stated that only new BO cases were included or previously diagnosed BO cases were excluded (61, 64, 67, 73, 94, 98, 103, 110, 111, 118, 124, 131). The subgroup analysis showed an OR = 0.48 (CI: 0.34-0.68, p < 0.001) with substantial heterogeneity (I^2 = 60.6%, p = 0.003) (**Table 2).**

4.2.7. Publication bias

The Egger's tests calculated significant publication bias in the meta-analysis of all 70 studies, p < 0.001 and in the subgroup of the segment length of BO (p = 0.051), but not in the subgroup analyses on the CagA status (p = 0.188), the presence of dysplasia (p = 0.160) and the newly diagnosed BOs (p = 0.465). The visual inspection of the funnel plot of the overall assessment from the 70 studies revealed asymmetry (**S3 Appendix)**. There was no asymmetry on the funnel plots of the subgroup analyses.

4.2.8. Risk of bias in the studies included

The results of our quality and risk assessment by the modified Newcastle-Ottawa scale for case-control studies are shown in **Table 3.**

It is important to note that our meta-analysis includes 78 studies of the meta-analysis by Fischer and our quality and risk assessment revealed both selection and information bias, which had been reported by Fischbach et al. (9). In-depth scrutiny for causes of the bias in the additional 25 studies, showed a similar pattern of flaws in study design.

Table 3 Quality and risk of bias assessment. Items in columns 1: Clear definition of BO cases, 2: Representativeness of BO cases, 3: Selection of controls, 4: Clear definition of controls, 5: Comparable BO cases and controls, 6: Investigator blinded for the asce

Study author and year	1	2	3	4	5	6	7
Abbas Z 1995	●	●	●	●	●	●	●
Abe Y 2009	●	●	●	●	●	●	●
Abouda GF 2003	●	●	●	●	●	●	●
Ackermack P 2003	●	●	●	●	●	●	●
Ahmed HH 2004	●	●	●	●	●	●	●
Anderson LA 2008	●	●	●	●	●	●	●
Blaser MJ 1991	●	●	●	●	●	●	●
Carmona S. R 2003	●	●	●	●	●	●	●
Chacaltana A 2009	●	●	●	●	●	●	●
Chang Y 2010	●	●	●	●	●	●	●
Chen CC 2016	●	●	●	●	●	●	●
Cooper BT 1991	●	●	●	●	●	●	●
Corley DA 2008	●	●	●	●	●	●	●
Csendes A 1997	●	●	●	●	●	●	●
Dore MP 2016	●	●	●	●	●	●	●
El Serag HB 1999	●	●	●	●	●	●	●
Fassan M 2009	●	●	●	●	●	●	●
Ferrandez A 2006	●	●	●	●	●	●	●
Goldblum JR 2002	●	●	●	●	●	●	●
Hackelsberger A 1998	●	●	●	●	●	●	●
Henihan RDJ 1998 ‡	●	●	●	●	●	●	●
Hilal J 2016	●	●	●	●	●	●	●
Hirota WK 1999 ‡	●	●	●	●	●	●	●
Inomata 2006 †	●	●	●	●	●	●	●
Johansson J 2007 ‡	●	●	●	●	●	●	●
Jonaitis L 2011	●	●	●	●	●	●	●
Kala Z 2007	●	●	●	●	●	●	●
Katsinelos P 2013	●	●	●	●	●	●	●
Keyashian K 2013	●	●	●	●	●	●	●
Kiltz U 1999	●	●	●	●	●	●	●
Kim BC 2006	●	●	●	●	●	●	●
Laheij RJF 2002	●	●	●	●	●	●	●
Lam KD 2008	●	●	●	●	●	●	●
Lee YY 2011	●	●	●	●	●	●	●
Loffeld RJLF 1992 ‡	●	●	●	●	●	●	●
Loffeld RJLF 2000	●	●	●	●	●	●	●

Table 3. Quality and risk of bias assessment (continued).

Study author and year	1	2	3	4	5	6	7
Loffeld RJLF 2004	●	●	●	●	●	●	●
Lord RV 2000	●	●	●	●	●	●	●
Martinek J 2003	●	●	●	●	●	●	●
Meng X 2008	●	●	●	●	●	●	●
Monkemuller K 2008	●	●	●	●	●	●	●
Nandurkar S 1997 ‡	●	●	●	●	●	●	●
Newton M 1997	●	●	●	●	●	●	●
Pascareno OD 2014	●	●	●	●	●	●	●
Paull G 1988	●	●	●	●	●	●	●
Peng S 2009	●	●	●	●	●	●	●
Rajendra S 2004	●	●	●	●	●	●	●
Rajendra S 2007	●	●	●	●	●	●	●
Rex KD 2003	●	●	●	●	●	●	●
Rodriguez-D. A 2014	●	●	●	●	●	●	●
Ronkainen J 2005	●	●	●	●	●	●	●
Rubenstein JH 2014	●	●	●	●	●	●	●
Rugge M 2001	●	●	●	●	●	●	●
Sharifi A 2014	●	●	●	●	●	●	●
Schenk BO 1999	●	●	●	●	●	●	●
Sonnenberg A 2010	●	●	●	●	●	●	●
Sonnenberg A 2016	●	●	●	●	●	●	●
Thrift AP 2012	●	●	●	●	●	●	●
Toruner M 2004	●	●	●	●	●	●	●
Uno G 2011	●	●	●	●	●	●	●
Vaezi MF 2000 †	●	●	●	●	●	●	●
Veldhuyzen v Z SJO 2006	●	●	●	●	●	●	●
Vicari JJ 1998	●	●	●	●	●	●	●
Vieth M 2000	●	●	●	●	●	●	●
Watari J 2009	●	●	●	●	●	●	●
Werdmuller BFM 1997	●	●	●	●	●	●	●
Weston AP 2000	●	●	●	●	●	●	●
White NM 2008 ‡	●	●	●	●	●	●	●
Wong WM 2002	●	●	●	●	●	●	●
Wu JCY 2000	●	●	●	●	●	●	●
Zaninotto G 2002 ‡	●	●	●	●	●	●	●
Zullo A 2014	●	●	●	●	●	●	●

4.3. Strengths and limitations

To date, this is the largest and most comprehensive meta-analysis in this topic and includes data from 5 continents and 72 individual studies which suggest that imprecision is unlikely. To our best knowledge, this is the first meta-analysis on the effect of HPI on the length of BO and the presence of dysplasia in BO.

Limitations of the evidence include:

1. Lack of clear definition of BO. Although most of the studies defined it by endoscopy and histology findings at the same time, these diagnostic criteria show variability in time and place.
2. Many exclusion criteria often limited the BO cases included in the studies.
3. We found only one study in which the controls truly represented the population (118); most of the other studies used endoscopy controls. A smaller proportion of studies used blood donors as controls, who are often healthier and younger than the normal population.
4. Selection of controls in endoscopy is necessary for the exclusion of asymptomatic BO patients from the controls, but it means that these controls go through a gastroscopy with the purpose of investigating GI symptoms, which most likely influences their prevalence of HPI even if there is no gastritis or ulcer disease. Patients with GORD formed the control group in several studies. This also results in bias, as there is convincing evidence that HPI is a reduces the risk of GORD (10).
5. Comparability was poor in most of the studies, as only 23 of the studies had age- and sex-matched cases and controls and an additional 7 of them had either sex or age-matched cases and controls. Some of the studies described the significantly different proportion of races in the cases and controls and there is ample evidence that ethnicity influences the prevalence of both HPI and BO (89, 94, 105).
6. Only 3 studies stated clearly that the investigators were blinded to BO when testing HPI or vice versa (7, 64, 81). In some of the articles, the study design suggested that the single pathologist involved was aware of the BO and the HPI status when assessing the histology slides for BO and HPI, while in other studies the endoscopist was aware of the BO diagnosis at the time when the rapid urease test was performed. However, the vast majority of the studies did

not describe the process of HPI ascertainment; this is also a potential source of bias.

7. Testing of HPI in the studies was performed by the same method in both groups in nearly all studies. However, some articles described alternative methods of HPI testing (i.e. positive result of rapid urease test and/or histology and/or culture and/or serology and/or stool antigen test) and it is not clear what proportion of these tests were used in the cases and controls.

4.4. Discussion of the meta-analysis

The role of HPI in the pathogenesis of BO is often described as controversial (135). As mentioned before, our meta-analysis showed an inverse association between HPI and BO. However, there are several previous studies with altogether different conclusions: reporting that HPI has no correlation with BO (74, 108) or even a positive association (82, 97) (describing HPI as a risk factor). Most papers (especially the ones with higher patient numbers) are in parallel with our findings (73, 76, 116).

If we accept that HPI leads to risk reduction, the following question arises: what could be the cause or mechanism behind this inverse association? This question is not only important from a theoretical, but also from a clinical standpoint: understanding the mechanism is crucial for evaluating the risks and benefits of *H. pylori* eradication therapy, in addition to bringing us closer to explaining the increasing incidence of BO.

HPI is a proven risk factor for gastric non-cardia adenocarcinoma and other cancers, including lymphoma; however, not too much is known about its relationship with gastric cardia and oesophagal adenocarcinoma (136). Epidemiological data shows a simultaneous decline of HPI and the increase of the aforementioned two tumor types. Along with the decrease of *H. pylori* positivity, the incidence of non-cardia adenocarcinomas is also falling (137).

As to why and how exactly could HPI reduce the risk of BO development, several theories exist, but none of them is considered proven. Multiple articles attribute this fact to the effect of HPI on the gastric mucosa: the microorganism causes corpus-predominant gastritis, which leads to a decreased gastric output. In this case, the oesophagus is less exposed to the harmful effect of gastric acid; thus, it has a reduced risk for developing BO and OAC (9, 11, 135, 138).

Several studies that did not find a negative correlation between HPI and BO only did so when looking at patients that were infected with a CagA positive subgroup *of H. pylori* (136). Other articles that found an inverse association between HPI and BO reported an even stronger correlation when comparing only the CagA positive subgroup instead of all *H. pylori*-positive patients (9, 11, 123).

Chow et al. and Vaezi et al. hypothesize that this phenomenon might be caused by the CagA positive sting's increased virulence towards gastric mucosa and results in a multifocal atrophic gastritis that also involves the destruction of gastric parietal cells, which further impairs acid secretion (more severely as compared to the CagA negative subgroup). Consequently, the reduced acidity of the reflux's convent reduces the risk of complications of GORD, such as BO and OAC (123, 136).

Contrary to this theory, based on a population-based Swedish case-control study, Ye et al. speculate that it is unlikely that HPI lowers the risk of BO through the reduction of gastric acidity. They drew this conclusion because no correlation was found between gastric atrophy and oesophagal adenocarcinoma in their study; however, they did find a significant association between gastric atrophy and cardia adenocarcinoma (139).

In a meta-analysis on the subject, Fischbach et al. describe another theory that aims to explain the inverse relationship between HPI and BO. They speculate that HPI is associated with reduced risk for obesity, thus not only reducing the likeliness for acidic reflux but also the insulin level in the blood. This leads to the decreased production of insulin-like growth factor (IGF), which normally acts as an agent that potentiates the proliferation of Barrett's epithelium (9). With the reduced amount of circulating IGF due to HPI, BO is less likely to develop (33).

In contrast to these theories, Kountouras et al. highlighted the conflicting nature of data available on this topic via editorial letters written in response to some previously cited articles. He mentions that in the Malay population, HPI incidence is traditionally low; however, contrary to expectations, the incidence of BO and distal oesophagal tumours are also below average (140).

He not only points to the fact that according to several studies, HPI might be a risk factor for BO, but also describes potential mechanisms to explain this positive connection. He states that the HPI induced overproduction of gastrin contributes to the neoplastic

progression in BO through pathway signalling. Furthermore, HPI also has a pro-inflammatory effect that might also potentiate said progression (141).

According to our results and the majority of conclusions available in the literature, a persistent HPI would be desirable for the prevention of BO. However, it is exactly the aforementioned atrophic gastritis that acts as the leading risk factor for gastric non-cardia adenocarcinoma. This two-sided effect of HPI is what causes clinicians to pose the question that is penitently described as Hamletic by Zullo et al.: to eradicate or not to eradicate (138)? However, we have to emphasise that no evidence should prevent us from eradicating *H. pylori*, regardless of coexisting reflux esophagitis or BO. HPI needs treatment, when it is identified.

An editorial in a highly-ranked journal, Gastroenterology, elaborates on the possibility that the decline in HPI incidence might have other consequences, not necessarily limited to the field of gastroenterology. For example, *H. pylori* might have an effect in regulating ghrelin and leptin, two hormones produced (partly in case of leptin) by the stomach and related to metabolism-regulation. The article suggests that with the continuous fall of HPI incidence, we might see an increase in diabetes and obesity due to the dysregulation of these hormones (137).

Our results confirm the conclusion of previous meta-analyses (9-11) and we calculated a similar magnitude of risk reduction. Gisbert et al. in 2002 calculated an OR = 0.60 (CI: 0.48-0.76) (10), Rokkas et al. in 2007 found an OR = 0.64 (CI: 0.43-0.94, p = 0.025) (11), Fischbach et al. in 2012 reported a RR = 0.73 (CI: 0.66-0.80) (9).

5. Development of a training module in endoscopy

5.1. Methods

5.1.1. Objectives

We aimed to develop and test a training program for the use of AAC in BO endoscopic surveillance for experts and novices. To do so, we organised a prospective, educational evaluation study at the Queen Alexandra Hospital (Portsmouth, United Kingdom) – an expert centre for BO – between March and April 2015.

5.1.2. Ethical approval

The study was approved by the National Health Service Research Ethics Committee (reference number REC 15/SC/0085).

5.1.3. Study design

The study had two phases: an online training module and a live interactive session (**Figure 9**). Diagnostic performance of participants was measured at three cross-sections in time at study entry, after the completion of the online module and after the live session with a diagnostic assessment test to determine the learning curves.

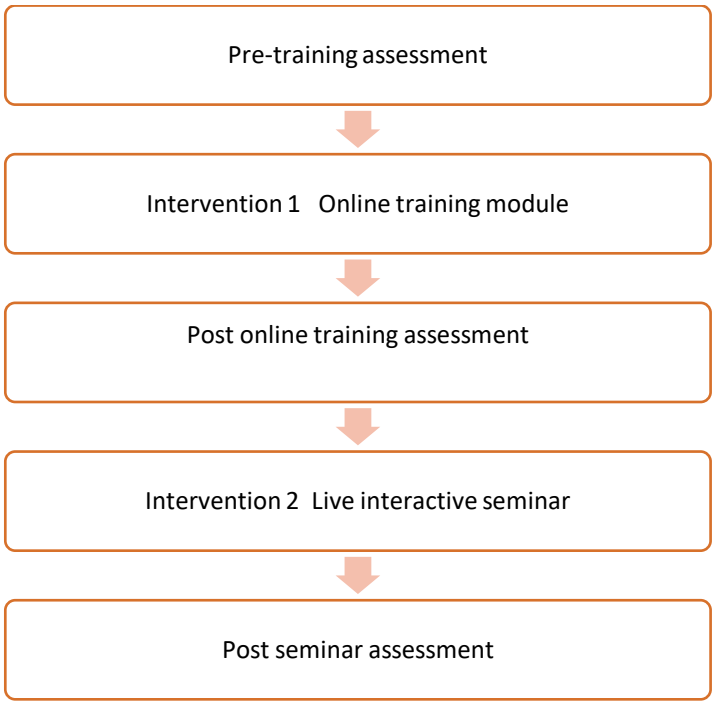

Figure 9 Flow of the study

5.1.4. Online training module

5.1.4.1. Platform development

First, we performed a comprehensive search and a review to determine the critical features of the use of AAC in BO surveillance. As a result, a new classification of AAC was developed and validated (142), and learning objectives for the training module were defined. To ease access to the training, an online training module (with embedded images and videos) was developed using the Moodle platform (Moodle Pty. Ltd., Perth, Australia), hosted by the University of Portsmouth. The online platform had seven domains (**S4 Appendix**).

5.1.4.2. Selection of images and videos

High-definition still images and videos of BO surveillance with 2.5% AAC and corresponding biopsy results were selected from a repository of more than 500 such procedure, which were recorded in Queen Alexandra Hospital Endoscopy Unit before the development of the module. Images and videos were reviewed for quality and visibility of the critical features of AAC. High-definition videos were edited (MP4 format) to demonstrate BO in white light, and following the use of AAC, the videos intentionally did not focus on areas of early neoplasia. Videos were blinded to histology to avoid bias. Snapshots were captured from videos and stored in portable network graphic format.

Altogether 40 still images (21 non-dysplastic, 19 early neoplasia) and 20 videos (ten non-dysplastic, ten early neoplasia) were selected from 60 individuals. A heterogeneous mix of non-dysplastic and dysplastic cases was created to obtain unbiased accuracy rates. Examples of invasive cancer were not used in the training module as the endoscopic appearance is conspicuous.

5.1.4.3. Structure and operation

The training module consisted of eight images (four non-dysplastic and four dysplastic) and nine videos (three benign and six neoplastic), explaining the critical features of AAC-assisted lesion recognition. Included within the training module was a sample quiz of eight questions that provided immediate feedback, with a clear explanation of the diagnosis, surface pattern, loss of acetowhitening reaction, and morphology. Endoscopists could not access the training module without completing the baseline assessment. Participants could repeat the training module as many times as they wished. Participants could complete the online training module and assessments in separate

sessions. On completion of the training module, the test of baseline assessment was immediately repeated without feedback on prior performance.

5.1.5. Live interactive seminar

The seminar was held in Queen Alexandra Hospital on 24th April 2015. A state-of-the-art lecture reiterated the key features of AAC-assisted lesion recognition. Five live cases were performed with endoscopists observing via interactive video link. Cases were carefully pre-selected to include two cases of non-dysplastic BO, two cases of dysplastic BO, and one case of intramucosal cancer. At the end of the interactive seminar, endoscopists immediately repeated the same assessment exercise without feedback on performance.

5.1.6. Inquiry about confidence and preferences

Before the pre-training assessment, participants were asked to complete a questionnaire regarding their confidence in the use of AAC; the same questionnaire was completed after all training. Along with confidence, participants were asked about their views with regard to their preference of BO surveillance assessments by the Seattle protocol biopsies to an AAC targeted technique.

5.1.7. Study participants

A total of 13 endoscopists took part in the study. The endoscopists were independent endoscopists with experience in BO endoscopy but without formal training in AAC- assisted lesion recognition. The group consisted of five consultant gastroenterologists, two consultant upper GI surgeons, and six non-medical endoscopists (**Table 4**).

Table 4 Characteristics of the study participants. GI, gastrointestinal; OGD, oesophagogastroduodenoscopy; AAC, acetic acid chromoendoscopy.

Job title	Years' experience	No. of OGDs	No. of Barrett's cases	No. of AAC cases
1. Consultant GI Physician	33	10000	1500	200
2. Consultant GI Physician	13	6500	1000	225
3. Consultant GI Physician	15	10000	1250	300
4. Consultant GI Physician	15	8000	700	100
5. Consultant GI Physician	17	5000	880	60
6. Consultant GI Physician	45	17000	4000	0
7. Consultant GI Physician	18	7000	2000	0
8. Nurse Endoscopist	12	8000	3000	0
9. Nurse Endoscopist	7	8400	1680	288
10. Nurse Endoscopist	4	2496	381	1
11. Nurse Endoscopist	2	695	76	4
12. Nurse Endoscopist	9	9000	1000	1
13. Nurse Endoscopist	12	15000	1500	1

5.1.8. Construct validity of the diagnostic performance test

To estimate a baseline difference by experience, the test was completed by experts and novices in AAC-assisted lesion recognition. Two experts in the use of AAC who were not involved in the selection, editing and preparation of the training images and videos for the test module completed the test to benchmark expert performance. To assess the performance of the test for novices in the AAC, three independent endoscopists (one senior trainee in endoscopy, two established gastroenterologists) completed the same test module. The above experts and novices were not involved in the subsequent training.

Overall, there was a significant difference in the performance of experts and novices in both image- and video-based assessments. The agreement was extremely high between experts and fair between learners (**Table 5**).

Table 5 Validation of the test module showing a significant difference in performance between experts and novices when assessed with still images and video clips. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Group	Accuracy, % (95%CI)	Sensitivity, % (95%CI)	Specificity, % (95%CI)	PPV, % (95%CI)	NPV, % (95%CI)	Kappa
Images						
• **Experts n = 2**	96 (0.88-0.96)	100 (0.92-1.0)	93 (0.85-0.93)	93 (0.85-0.93)	100 (0.91-1.0)	0.80
• **Novices n = 3**	73 (0.63-0.80)	72 (0.62-0.80)	73 (0.64-0.81)	71 (0.61-0.79)	74 (0.65-0.82)	0.30
• ***p* value**	0.009	0.096	0.313	0.111	0.019	
Videos						
• **Experts n = 2**	97.5 (0.84-0.98)	95 (0.81-0.95)	100 (0.86-1.0)	100 (0.85-1.0)	95 (0.82-0.95)	0.9
• **Novices n = 3**	77 (0.63-0.87)	77 (0.63-0.87)	77 (0.63-0.87)	77 (0.63-0.87)	77 (0.63-0.87)	0.40
• ***p* value**	0.021	0.408	0.133	0.018	0.382	

Based on these data in sample size calculation for a chi^2 test using a 5% significance level, 80% power and detecting a difference of 20%, 59 independent observations would have been needed to differentiate by expertise (that is, construct validity). However, because the data are not truly independent (same images and videos shown to different observers), we doubled this number.

5.1.9. Statistical analysis

To examine the content validity of the training module, a 10% improvement in sensitivity between pre- (70%) and post-training (80%) performance was deemed to be clinically relevant. For a chi^2 test with a 5% significance level and 80% power, and again assuming the data are not truly independent, at least 291 observations would be required. Yet, because the data are not truly independent, we assumed 780 observations for each stage of assessment, from 13 observers, would more than satisfy the power calculation.

Sensitivity, specificity, accuracy, positive predictive value (PPV), and NPV were calculated for each observer (n = 13) at each time point, using histopathological diagnosis as the reference standard. All analyses were performed using these summary values.

Confidence intervals were calculated to illustrate the uncertainty in the estimated values, and the two-sided paired t-test was used to compare between time points.

Interobserver agreement for images and videos was assessed using the multirater Fleiss kappa (κ) statistic. A κ value of <0.2 was regarded as poor agreement, 0.21-0.40 as fair agreement, 0.41-0.60 as moderate agreement, 0.61-0.80 as substantial agreement, and 0.81-1.00 as almost perfect agreement.

Analyses were performed using the SPSS statistical package, version 22 for Macintosh (IBM Corp., Armonk, New York, USA).

5.2. Results

5.2.1. Online and live interactive training

A total of 13 endoscopists (experts and learners) participated in online training. Assessment images and videos were completed before and repeated after the online training module, and demonstrated a significant improvement in sensitivity and negative predictive value (NPV) following the online training module (**Table 6**).

Table 6 Baseline vs post-online training assessment.. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

	Accuracy, % (95%CI)	Sensitivity, % (95%CI)	Specificity, % (95%CI)	PPV, % (95%CI)	NPV, % (95%CI)	Kappa
Images						
• **Baseline**	79 (0.75-0.83)	83 (0.79-0.86)	76 (0.73-0.79)	76 (0.72-0.79)	83 (0.79-0.86)	0.48
• **Post online training**	86 (0.83-0.88)	95 (0.92-0.97)	79 (0.76-0.81)	80 (0.78-0.82)	94 (0.91-0.98)	0.67
• ***p* value**	<0.01	<0.01	0.522	0.459	<0.01	
Videos						
• **Baseline**	78 (0.72-0.83)	73 (0.67-0.78)	83 (0.77-0.88)	81 (0.75-0.87)	76 (0.70-0.80)	0.41
• **Post online training**	82 (0.77-0.86)	91 (0.86-0.95)	74 (0.69-0.78)	78 (0.73-0.81)	89 (0.83-0.94)	0.51
• ***p* value**	0.281	0.011	0.194	0.505	0.041	

Following the completion of the interactive training, the assessment tool was repeated and showed a significant improvement in sensitivity and NPV for videos and a trend for improvement for images (**Table 7**).

Table 7 Post-online training vs post-interactive training assessment. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

	Accuracy, % (95%CI)	Sensitivity, % (95%CI)	Specificity, % (95%CI)	PPV, % (95%CI)	NPV, % (95%CI)	Kappa
Images						
• **Post online training**	86 (0.83-0.88)	95 (0.92-0.97)	79 (0.76-0.81)	80 (0.78-0.82)	94 (0.91-0.98)	0.67
• **Post interactive seminar**	82 (0.80-0.84)	98 (0.95-0.99)	68 (0.66-0.69)	74 (0.72-0.75)	97 (0.94-0.99)	0.75
• ***p* value**	0.028	0.084	0.007	0.002	0.131	
Videos						
• **Post online training**	82 (0.77-0.86)	91 (0.86-0.95)	74 (0.69-0.78)	78 (0.73-0.81)	89 (0.83-0.94)	0.51
• **Post interactive seminar**	79 (0.75-0.81)	99 (0.95-1.0)	60 (0.56-0.61)	71 (0.68-0.72)	98 (0.91-1.0)	0.63
• ***p* value**	0.322	0.003	0.005	0.035	0.004	

There was no difference between assessment by still images and assessment by videos (**Table 8**). It suggests that still images serve as a reliable surrogate for videos. The performance after each intervention improved given the results, most prominently following online training (**Table 8).**

Table 8 Comparison of images and videos for each stage of training. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value. [1] *p <0.05.*

	Accuracy, % (95%CI)	Sensitivity, % (95%CI)	Specificity, % (95%CI)	PPV, % (95%CI)	NPV, % (95%CI)
Pre-training					
• **Images**	79 (0.75-0.83)	83 (0.79-0.86)	76 (0.73-0.79)	76 (0.72-0.79)	83 (0.79-0.86)
• **Videos**	78 (0.72-0.83)	73 (0.67-0.78)	83 (0.77-0.88)	81 (0.75-0.87)	76 (0.70-0.80) [1]
Post online training					
• **Images**	86 (0.83-0.88)	95 (0.92-0.97)	79 (0.76-0.81)	80 (0.78-0.82)	94 (0.91-0.98)
• **Videos**	82 (0.77-0.86)	91 (0.86-0.95)	74 (0.69-0.78)	78 (0.73-0.81)	89 (0.83-0.94)
Post interactive seminar training					
• **Images**	82 (0.80-0.84)	98 (0.95-0.99)	68 (0.66-0.69)	74 (0.72-0.75)	97 (0.94-0.99)
• **Videos**	79 (0.75-0.81)[1]	99 (0.95-1.0)	60 (0.56-0.61) [1]	71 (0.68-0.72)	98 (0.91-1.0)

5.2.2. Effect of preexisting expertise in the use of acetic acid

Table 9 shows a subgroup analysis comparing six AAC users (with more than 50 AAC procedures before participation in the study) compared with seven AAC naïve participants (with less than 10 AAC procedures). All users experienced an improvement in sensitivity for each stage of training with significant increases in accuracy following the online training module.

Table 9 Subgroup analysis of performance for acetic acid naïve vs acetic acid users for images and video clips. PPV, positive predictive value; NPV, negative predictive value. [1] p <0.05 compared with the preceding training stage

	Accuracy, %		Sensitivity, %		Specificity, %		PPV, %		NPV, %	
	Naïve	User	Naïve	User	Naïve	User	Naïve	User	Naïve	User
Images										
• **Pre-training**	78	81	71	95	83	68	81	74	77	94
• **Post online**	85[1]	88[1]	92[1]	97	78	79[1]	80	81[1]	93[1]	97
• **Post interactive seminar**	83	82	97	99	70	66	75	72	97	99
Videos										
• **Pre-training**	71	83	59	84	84	81	83	82	67	87
• **Post online**	82	83	90[1]	92	74	76	80	80	89[1]	89
• **Post interactive seminar**	81	78	99[1]	98[1]	63	57	73	71	98	98[1]

5.2.3. Confidence of the endoscopist in the use of acetic acid

Endoscopist confidence in the use of the AAC for BO increased during the training, with a mean confidence level of 2.5 (5-point scale) before and a confidence level of 3.9 ($p < 0.001$) after the training. The training by the module increased the willingness of endoscopists to switch from a 2-cm quadrantic biopsy protocol to an AAC targeted technique, with a mean willingness of 2.6 (5-point scale) before the training, rising to 3.8 after the training ($p < 0.001$). Confidence in the diagnosis for images also improved during training, with 41% of diagnoses made with high confidence pre-training, rising to 63% after the online training module ($p < 0.001$). The same was true for videos, with 47% of diagnoses made with high confidence before the training, rising to 67% following the online training ($p < 0.001$). Following the interactive training day, high-confidence responses increased from 63 to 72% for images ($p = 0.045$) and did not change at 67% for videos.

5.3. Discussion of results

This study involved the development of a new training module for AAC-assisted in vivo diagnosis of BO early neoplasia. The well-validated training module proved to be feasible for training in AAC BO surveillance and lesion recognition. The advantage of online training is that learners can complete it at their convenience. The online module took a median of 3 hours to complete. The interactive training day had an additional clinical benefit, which is integral to achieving competence in AAC-assisted lesion recognition in BO.

Endoscopists of various backgrounds and expertise participated, and all of them demonstrated clinically relevant improvements in the detection of early neoplasia in BO with AAC. The results showed the validity, effectiveness, and widespread applicability of this tool. The technique of AAC is simple and can be performed by any endoscopist. However, our results showed that recognition of early neoplasia after AAC is not easy and necessitates training. Baseline assessment data showed poor performance (before training) from both expert and non-expert BO endoscopists, thus justifying the need for our training tool.

The interobserver agreement significantly improved after training, with substantial agreement by the end of training. It is essential, as previous studies (143) have demonstrated poor interobserver agreement of endoscopists naïve to AAC technique without training.

Our study showed that the technique of in vivo diagnosis for early neoplasia IN BO using AAC could be taught using images and videos. But it appears that endoscopists find it more challenging to identify neoplasia from videos compared with still images. It may be explained by the fact that still images have been pre-selected and edited to focus on neoplasia, whereas videos focus on the entire BO, requiring more complex assessment. Video performance improved following training. Sensitivity and NPV improved following the interactive seminar, but accuracy and specificity worsened. It can be explained by a higher number of false-positive results, making AAC safer by reducing the risk of missed early neoplasia. At the end of the study, participant's sensitivity was 98% for images and 99% for videos, which is confidently above the ≥90% required by the American Society for Gastrointestinal Endoscopy (ASGE) Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) criteria (144).

The same is true for NPV, with mean scores of 97% for images and 98% for videos, reaching the ASGE PIVI criteria of ≥98%. We believe that the high NPV is the most important parameter, as it suggests that the early neoplasia miss rate is minimal, making the technique safe. The most recent ASGE Technology Committee review endorses AAC targeted-biopsy in expert hands (145), but our data show that training by our module can ensure that participants achieve the same thresholds as experts.

Training modules on endoscopic lesion recognition and in vivo diagnosis previously relied on still images. In real life, assessments are made on live endoscopic images. Therefore, evaluation and training of endoscopists in AAC BO surveillance would be better performed using videos that more closely reflect real-time practice. However, the results of our study showed no significant difference in performance when endoscopists were assessed using images or videos.

Our construct validity data showed that experts in this field had high sensitivity (95-100%) and high NPV (95-100%). At the end of the training, even nonexpert, AAC-naïve endoscopists were able to achieve sensitivity and specificity within the expert range. This finding demonstrates the strength of our training pathway. We are unable to clarify whether performance deteriorates with time, as there were only two weeks between completion of the online training and the interactive seminar. Another limitation is that the images and videos selected did not include low-grade dysplasia (LGD). Endoscopic recognition of LGD is difficult but important given the evidence for treatment of LGD (146).

The study had a robust design with a well-validated library of images and videos, and the performance of the library was validated prior to its use. The study proved the effectiveness of an online training module for AAC and demonstrated the added clinical value of an interactive training day incorporating expert endoscopists and live cases.

SUMMARY OF THE RESULTS AND CONCLUSIONS

- The results of the meta-analysis confirmed that HPI is associated with a lower prevalence of BO; therefore, it can be considered as a protective factor.

- The results of the meta-analysis confirmed that HPI is associated with a lower prevalence of dysplastic BO as well.

- The findings from the study about the development of our training module support the usefulness of the tool in improving lesion recognition during Barrett's surveillance endoscopy.

- The learning curves from this study suggest that both experts and trainees may benefit from using this cheap and easily accessible training module.

OWN WORK IN WIDER CLINICAL CONTEXT

My goal was to simultaneously develop clinical research expertise and advance the clinical services for BO and oesophageal cancer.

I have been involved in these research projects while I developed outstanding expertise in the management of these pathologies. I have learned the multidisciplinary clinical approach to oesophageal cancers and developed the upper GI services in one of the large tertiary referral centres of the United Kingdom since 2011. I contributed to the advancement of the BO surveillance program and was involved in the revision of important guidelines on BO and oesophageal stenosis guidelines of the UK.

Since my move back to Hungary in 2017, I have been focusing my efforts on building an upper GI clinical research team. With the help and support of the clinical staff and the team of the Institute for Translational Medicine, University of Pécs, we have built a multidisciplinary team, involving senior clinicians, trainees, under- and postgraduate students and have started registries on oesophageal cancer and GI bleeding. We completed many other successful meta-analytical research projects and a significant and relevant epidemiologic study on oesophageal cancer in Hungary.

I have also significantly contributed to other research projects in different fields of gastroenterology, such as pancreatology, inflammatory bowel disease and coeliac disease.

While completing my research, I have continued to work as a clinician in gastroenterology, contributing to the service developments in gastroenterology.

In the future, I plan to continue the ongoing work in both registries and would like to contribute to the continued development of an upper GI clinical and research team, mentoring young talents.

Through this work, I believe I can significantly contribute to better care for patients with upper GI pathologies.

ACKNOWLEDGEMENT

I want to express my deepest gratitude to my supervisors Péter Hegyi and Áron Vincze for their ever-enduring optimism, encouragement, guidance, patience and help during the past two years. Without them, this work would not have been possible, and I would not have completed my PhD.

I want to thank Charles Gordon who trained me and helped me to develop the set of advanced clinical skills in upper GI diseases. Also, a special thank goes to Fergus Chedgy and Pradeep Bhandari for my involvement in their exciting study.

I want to thank Nelli Farkas for her help with the statistical analysis of my meta-analysis, and I am very grateful to Zsolt Szakacs for his methodological expert help and critical review of my projects.

I would also like to extend my thanks to all my colleagues in the Institute for Translational Medicine and the Division of Gastroenterology in the 1st Department of Internal Medicine at the University of Pécs.

I owe an exceptional thank to Judit Bajor, without whom I wouldn't have found my way back to Hungary and the fantastic team I work with now.

Finally, I would like to thank my family, especially my wife and my parents, who always encouraged and supported me during my study.

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PUBLICATIONS AND PRESENTATIONS (20.01.2020.)

Scientific metrics

The number of publications: 70

All citations: 71

Independent citations: 65

Sum of all impact factors: 100.529

Hirsch index: 5

Publications related to the topic of the PhD thesis (IF:9.981)

1. Chedgy FJQ, Kandiah K, Barr H, De Caestecker J, Dwerryhouse S, **Eross B**, Gordon C, Green S, Li A, Brown J, Longcroft-Wheaton G, Bhandari P. Development and validation of a training module on the use of acetic acid for the detection of Barrett's neoplasia. Endoscopy. 2017;49(2):121-9. **IF:6.629 (Q1), citations: 4**
2. **Eross B**, Farkas N, Vincze A, Tinusz B, Szapary L, Garami A, Balasko M, Sarlos P, Czopf L, Alizadeh H, Rakonczay Z, Jr., Habon T, Hegyi P. Helicobacter pylori infection reduces the risk of Barrett's esophagus: A meta-analysis and systematic review. Helicobacter. 2018;23(4):e12504. **IF:3.352 (Q1) citaions: 17**
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2. Clisby C, Gordon C, **Eross B**. Efficacy and complications in palliative oesophageal stenting, experinces of a tertiary referral center in the UK. United European Gastroenterology Journal. 2017;5(5):A707-A8.
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2. Berczi B, Gerencser G, Farkas N, Hegyi P, Veres G, Bajor J, Czopf L, Alizadeh H, Rakonczay Z, Vigh E, **Eross B**, Szemes K, Gyongyi Z. Association between AIRE gene polymorphism and rheumatoid arthritis: a systematic review and meta-analysis of case-control studies. Sci Rep. 2017;7(1):14096. **IF: 4.122 (D1)**
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APPENDIX

Appendix S1. Topic-tailored items of the Newcastle-Ottawa Scale

The questions for the risk assessment were as follows:

1. Was the case definition clear?

a) Yes, with positive endoscopic features of BE and supporting histology (green).

b) Yes, without a history of BE (yellow).

c) No clear description of the diagnosis of BE (red).

2. Were the BE cases representative?

a) Yes, consecutive BE cases, without significant exclusion criteria (green).

b) No, significant exclusion criteria or no description (red).

3. Was the selection of controls without selection bias?

a) Yes, community controls (green).

b) Hospital controls (endoscopy, blood donors etc.) (yellow).

c) No clear definition of controls (red).

4. Was the definition of controls clear?

a) Yes, with an endoscopy excluding BE (green).

b) No or no endoscopic exclusion of BE (red).

5. Were the BE cases and controls comparable?

a) Yes, with both age and sex matched (green).

b) Yes, with age or sex (yellow).

c) No (red).

6. Was the investigator blind to the presence of BE, when reading the result of *H. Pylori* test result, or vice versa?

a) Yes, the study description clearly states it.

b) No or no clear description.

7. Was the same method used to test HPI in BE and controls?

a) Yes (green).

No or no description (red).

Appendix S2. Reasons for exclusion of studies from the meta-analysis

Agreus et al. from Sweden reported prevalence of HPI only in reflux patients, but not in BE.[1]

Gashi et al. from Kosovo conclude that the prevalence of HPI is lower in long-segment BE than in short-segment BE, but there is no control group.[2]

Irvanloo et al. from Iran reported the prevalence of HPI only in BE, but not in controls.[3]

Láng et al. from Hungary suggested that HPI is a risk factor for oesophagal adenocarcinoma in BO, but it was not supported by detailed data.[4]

Langner et al. from Austria and Germany did not report accurate enough data on HPI prevalence in BE or in controls to be eligible for inclusion.[5]

Lee et al. from Korea reported 0% prevalence of HPI in BE, but there was no data on HPI prevalence in controls.[6]

O'Connor et al. from Ireland reported an HPI prevalence of 62.5% in BE, but there is no control group.[7]

Peitz et al. from Germany used the definition of columnar epithelia lined lower oesophagus, which included cases without histological evidence of Barrett's and H. pylori density was reported instead of prevalence.[8]

Piqué et al. from Spain reported data from a large nationwide cross-sectional study, but only 16% of patients had HPI tested.[9]

Rosaida et al. from Malaysia reported results from a large cohort of reflux patients, but there was no detailed data on the prevalence of HPI in BE and controls.[10]

Salem et al. from the USA did not report any data on BE.[11]

Smith et al. from the USA showed that the prevalence of HPI in BE is low, only 1 in 9, but the prevalence of HPI in controls was not reported.[12]

Peng et al. in 2010 reported risk of clinically significant endoscopic findings in Barrett's patients with vs without HPI infection. Raw data on HPI prevalence could not be extracted.

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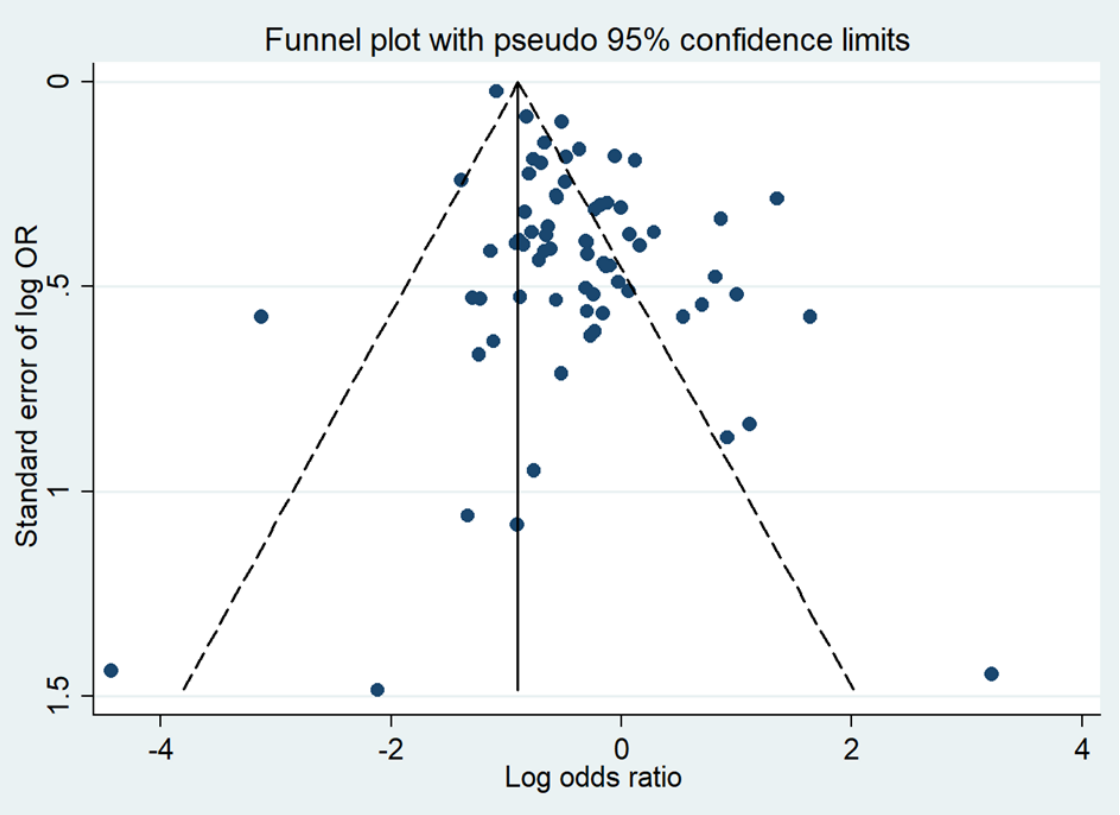
Appendix S3. Funnel plot from the 70 studies included in the meta-analysis.



The symmetry of the funnel plot is skewed, which was confirmed by the Egger's test ($p < 0.001$), revealing potential publication bias.

Appendix S4. Domains of the online platform.

1. Background and rationale of AAC use
2. Validated AAC classification
    a) Focal early loss of acetowhitening: Yes/No
    b) Surface pattern:
    – Large uniformly distributed pits (normal pit density)
    or
    – Compactly packed pits, smaller than surrounding mucosa (increased pit density)
    or
    – Focal irregularity or disorganised pits
    – Absent surface pattern
3. Lesion morphology: nodular/flat/depressed
4. Benign BO examples: images and videos
5. Dysplastic BO examples: images and videos
6. Intramucosal cancer examples: images and videos
7. In-training quiz using both images and videos with direct feedback on answers.