

Screening for esophageal adenocarcinoma and precancerous conditions (dysplasia and Barrett's esophagus) in patient with chronic gastroesophageal reflux disease with or without other risk factors: introduction of two systematic reviews to inform a guideline of the Canadian Task Force on Preventive Health Care (CTFPHC)

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KQ1: Benefits and Harms of screening
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Abbreviations/Glossary

ACG	American College of Gastroenterology
ACP	American College of Physicians
AGA	American Gastroenterological Association
AMSTAR	A Measurement Tool to Assess Systematic Reviews
BE	Barrett's Esophagus
BMI	Body mass index
CAG	Canadian Association of Gastroenterology
CI	Confidence interval
COMET	Core Outcome Measures in Effectiveness Trials
CTFPHC	Canadian Task Force on Preventive Health Care
EAC	Esophageal adenocarcinoma
EGD	Esophagogastroduodenoscopy
EME	Enhanced magnification-directed endoscopy
ESCC	Esophageal squamous cell carcinoma
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard ratio
ITS	Interrupted time series
NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa Scale
NR	Not reported
P-EGD	Peroral endoscopy
PCORI	Patient Centered Outcomes Research Institute
PICOS	Population, Interventions, Comparisons, Outcomes, Study design
PPI	Proton pump inhibitors
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
ROB	Risk of bias
RR	Risk ratio
SD	Standard deviation
SPOR	Strategy for Patient-Oriented Research
SR	Systematic review
TNE	Transnasal esophagoscopy
Transoral-EGD	Transoral esophagoscopy
VCE	Video capsule esophagoscopy
ZAP	Z-line appearance

Chapter 1

1 Introduction

1.1 Background

Purpose

These systematic reviews (SR) outline knowledge syntheses that will be used by the Canadian Task Force on Preventive Health Care (CTFPHC) to inform a guideline on screening adults (≥ 18 years) with chronic gastroesophageal reflux disease (GERD) with or without other risk factors for esophageal adenocarcinoma and associated precancerous lesions (Barrett's Esophagus (BE) and dysplasia). These SRs synthesize the evidence on the benefits and harms of screening in this population and the preferences and values in relation to screening.

Definition

In esophageal cancer, malignant cells form in the tissues of the esophagus, primarily in glandular cells (esophageal adenocarcinoma or EAC) or squamous cells (esophageal squamous cell carcinoma or ESCC).

Prevalence and burden of esophageal adenocarcinoma

ESCC is the most prominent form of esophageal neoplasm worldwide, with 398,000 cases of ESCC compared to 52,000 cases of EAC in 2012¹. Nearly 50% of the worldwide cases of EAC occur in Northwestern Europe and North America².

Rates in Canada provided by the Canadian Cancer Society do not separate EAC and ESCC, and report the overall rates of esophageal cancer. In 2017, projected new cases of esophageal cancer were 2,330 cases (1,800 among men and 530 among women) with 2,130 deaths from the disease (1,650 among men and 480 among women). Although esophageal cancer has a lower incidence than other cancers (ranked 13th among men and 19th among women), it has a high mortality rate and a low five-year survival rate (14%), the second lowest survival rate after pancreatic cancer³. The probability of developing esophageal cancer in the next 10 years increases with age in men, but not women (**Figure 1**)³.

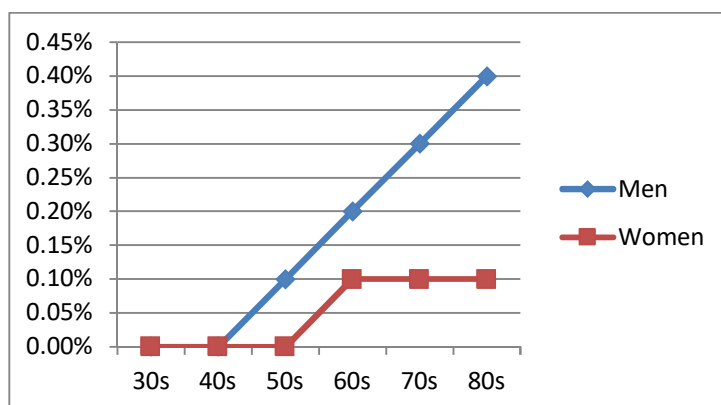


Figure 1 - Probability of developing esophageal cancer in the next 10 years

From 1986-2006, EAC incidence in Canada rose by 3.9% in males and 3.6% in females per year, while the incidence of ESSC declined by 3.3% in males and 3.2% in females per year². Given the geographic distribution and increasing incidence of EAC in Canada, the focus of the guideline will be on EAC.

Risk factors

Commonly cited risk factors for EAC are chronic GERD, BE, age ≥ 50 years, male sex, European descent, obesity, smoking, a family history of BE or EAC, and a diet low in fruits and vegetables⁴⁻⁷.

Chronic GERD and precancerous conditions

The prevalence of GERD in Western countries has increased over the past few decades and is one of the most commonly encountered conditions in primary care practice with an estimated prevalence of between 18-27% in the United States and 9-26% in Europe⁸. Extrapolating these prevalence estimates to the Canadian population, since no Canadian incidence studies exist, would mean that 3.4-6.8 million persons in Canada experience GERD⁹. GERD is a chronic disease with varying definitions⁹⁻¹². The Montreal definition has been adopted by clinicians and researchers, and defines GERD as “a condition which develops when the reflux of stomach contents causes troublesome symptoms (e.g., retrosternal burning (heartburn), regurgitation) and/or complications (e.g., esophagitis, esophageal stricture)”¹³. According to the American Society for Gastrointestinal Endoscopy, chronic, long-standing GERD is defined as frequent severe GERD symptoms for over five years and requiring regular acid suppression therapy¹⁴. However, experts differ in the definition of the duration of symptoms and whether acid suppression therapy is considered in defining chronic GERD¹⁵⁻¹⁷.

The most common complications of GERD are esophagitis, esophageal stricture, BE (a premalignant lesion, further described below), and EAC⁹. Approximately 60% of people with EAC have experienced symptoms of GERD and there is an association between the frequency and severity of symptoms and increased risk of EAC^{18,19}. In a 2008 guideline developed by the American College of Gastroenterology, BE was defined as “a change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus.”²⁰ BE is known to develop in around 6%-14% of people with GERD, and among those with BE (with or without GERD), 0.2%-0.5% develop EAC²¹. However, not all individuals with BE will experience chronic GERD symptoms, and it is still unclear why such a small percentage of people with GERD develop BE^{22,23}. Once an individual is diagnosed with BE, regular surveillance using endoscopy should be considered, as BE can progress over time from low- to high-grade dysplasia and into EAC^{24,25}. Patients who have EAC discovered as a result of endoscopic screening or as part of a surveillance program for BE are diagnosed with earlier-stage tumours, are less likely to have lymph node involvement, and have better short-term life expectancies than those who present with alarm symptoms such as dysphagia and weight loss²⁶.

With Canada’s increasing senior population and longer life expectancy, there is an expected increase in the incidence rates of GERD and EAC, and, therefore, increased demand for gastrointestinal endoscopies^{9,27}. From the Canadian Institute for Health Information National Physician Database, between 2004 and 2008 the number of upper endoscopies performed in

Canada has increased by approximately 16%²⁸. However, the reason for the endoscopy was not detailed.

Current recommendations and clinical practice in Canada

We are not aware of any primary care national recommendations on screening for EAC in Canada.

However, the BC Cancer Agency provides a guideline for primary care on prevention, screening, diagnosis, treatment, and follow-up of upper gastrointestinal diseases and cancer²⁹. They do not recommend screening asymptomatic patients for BE, and follow the American Gastroenterological Association (AGA) recommendations that screening should be considered among those with persistent reflux or with multiple EAC risk factors (e.g., chronic GERD, ≥ 50 years of age, tobacco smoking)³⁰. The province of Alberta has a guideline on the diagnostic work-up, treatment and management of patients with esophageal cancer (both EAC and ESCC)³¹. The 2004 Canadian Association of Gastroenterology (CAG) has recommendations focused on the management of GERD and BE, including a consensus statement on management of GERD, based on expert opinion³². The Compendium of Therapeutic Choices, although not a screening guideline, is used by many Canadian primary care physicians for guidance about the management of GERD, which includes suggestions on when to investigate³³.

The reference method in clinical practice to detect EAC and precancerous conditions (BE with or without low- or high-grade dysplasia) is to perform an endoscopy, which typically includes the esophagus, stomach and duodenum called (i.e. esophagogastroduodenoscopy or EGD)^{2,34}. If lesions or anomalies consistent with BE, dysplasia or possible EAC are suspected, the reference method for diagnosis is to perform targeted 4-quadrant biopsies every 1-2 cm along the length of the BE segment (Seattle Protocol) with histological examination of the biopsies^{5,35}. If BE is confirmed, proton pump inhibitor (PPI) therapy is started or continued in addition to endoscopic surveillance with biopsies at different intervals, depending on the presence and level of dysplasia.

Several adjunct techniques, such as chromoendoscopy, narrow-band imaging, confocal microscopy, spectroscopy, magnification endoscopy, and high definition endoscopy have been reported to aid in the detection of early stage cancer³⁶. Other detection technologies include barium swallow, transnasal ultrathin endoscopy, cytologic examination (brush, balloon, sponge, liquid), and capsule endoscopy, many of which are emerging and not currently used in Canadian clinical practice. New methods for detection such as flow cytometry, molecular biomarkers, and laser-induced fluorescence spectroscopy have also been proposed for use in screening.

International guidelines

The following organizations outside Canada have released guidelines on endoscopic screening for esophageal cancer, including information on screening people diagnosed with GERD: the American College of Gastroenterology (ACG)²⁰, the American College of Physicians (ACP)¹⁰, the American Gastroenterological Association (AGA)²⁶, and the UK's National Institute for Health and Care Excellence (NICE)³⁷. The ACP has also developed a guideline for best practices in individuals with BE⁷.

There is a general consensus among the CAG, ACG, ACP, and AGA against screening the general population with GERD for EAC or BE. Diagnostic testing is not seen as an appropriate first step in most patients presenting with only GERD symptoms^{10,26}. However, there is a consensus on

screening males 50 years and older who are suffering from chronic GERD symptoms (defined as symptoms for more than five years^{10,26} or ten years³²) and who have one or more additional risk factors for EAC (European descent, nocturnal reflux symptoms, hiatal hernia, high body mass index, large waist circumference (abdominal obesity), and/or tobacco use)^{10,26,32,38}.

The ACP and NICE provide information on diagnostic testing individuals with alarm symptoms (i.e., dysphagia, bleeding, anemia, weight loss, and recurrent vomiting); however, this population subgroup would be considered different from that of interest to the proposed guideline, which considers only individuals with chronic GERD and no alarm symptoms. The ACP and NICE guidelines recommend routine testing in men and women with heartburn and alarm symptoms, individuals who experience GERD symptoms after four to eight weeks of PPI therapy or who have been treated two months for a severe erosive esophagitis, or individuals who have a history of esophageal stricture with recurrent symptoms of dysphagia^{10,37}.

1.2 Objective

The CTFPHC is undertaking a systematic evaluation of the evidence to inform its recommendations for primary healthcare in Canada on screening for EAC among patients with GERD because: 1) incidence of EAC is increasing in North America and Europe; 2) EAC is usually diagnosed at an advanced stage and has high mortality; 3) there are common risk factors identifiable in primary care that could be the basis for a risk calculator for selection for testing for BE, dysplasia, and early stage EAC; 4) some estimates indicate that 2.4%-13.2% of patients with GERD who are already undergoing endoscopy for surveillance will be diagnosed with BE; 5) BE with dysplasia is one pathway to the development of EAC, although there are other possible pathways; 6) preventive behavioural interventions (e.g., tobacco cessation) can be undertaken and individuals with a high risk might have increased compliance with preventive behavioural interventions; 7) interventions are available for patients with BE that may prevent EAC; and 8) treatment of early EAC may increase survival^{18,39-44}.

This document contains two SRs. The first SR (Chapter 2) focuses on synthesizing the evidence on the effectiveness (benefits and harms) of screening for EAC and precancerous conditions (BE and dysplasia). The second review (Chapter 3) evaluates patient preferences and values about undergoing screening for EAC. The analytic framework is provided below in **Figure 2**. This review is not designed to evaluate the association between different severities of GERD (mild, moderate, and severe) and progression to EAC. Rather the specific objective is to evaluate the potential benefits and harms of screening in a defined high-risk group, individuals with chronic GERD, who can be identified with some consistency in primary care practice.

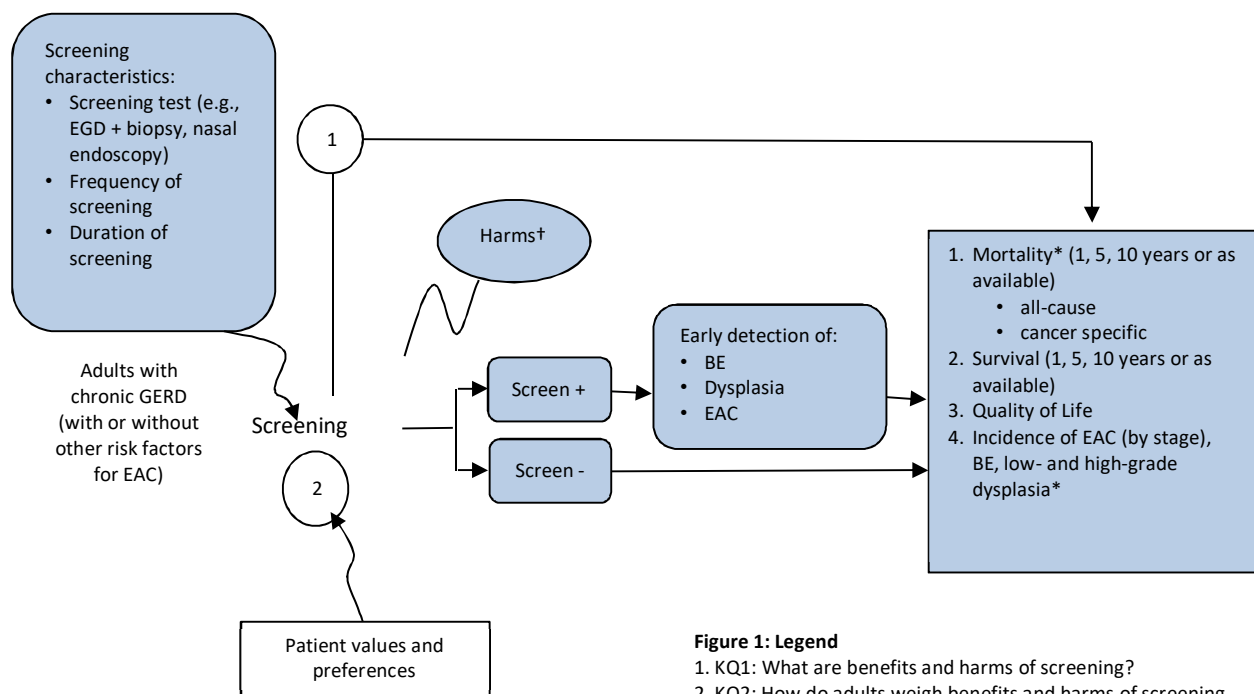


Figure 1: Legend

1. KQ1: What are benefits and harms of screening?

2. KQ2: How do adults weigh benefits and harms of screening (patient preferences)?

[†]Harms of screening

- Life threatening, severe, or medically significant consequences (such as requiring hospitalization or prolongation of hospitalization; disabling (limiting self-care or activities of daily living)
- Psychological effects (i.e., anxiety and depression)
- Major or minor medical procedures*
- Overdiagnosis[‡]

[‡] Outcomes with * will be used to calculate overdiagnosis

Figure 2 - Analytic Framework

In addition to these systematic reviews, a study on patient values and preferences is ongoing to help inform Task Force recommendations. The two groups being assessed in this study are those with GERD who can potentially be screened and those assigned or who are under surveillance with EGD. These results are not presented within this document, but will be considered in developing the guideline recommendations.

Chapter 2: Screening for esophageal adenocarcinoma and precancerous conditions (dysplasia and Barrett's esophagus) in patients with chronic gastroesophageal reflux disease with or without other risk factors: systematic review to inform a guideline of the Canadian Task Force on Preventive Health Care

Hamel C, Beck A, Thuku M, Stevens A, Skidmore B, Chatterjee A, Maziak D, Shea B, Hutton B, Little J, Moher D.

Abstract

Background: This systematic review was produced for the Canadian Task Force on Preventive Health Care to inform the development of a guideline on screening adults with chronic gastroesophageal reflux disease (GERD) with or without other risk factors for esophageal adenocarcinoma (EAC) and associated precancerous lesions (Barrett's Esophagus (BE) and dysplasia).

Objective: The goal was to systematically review the evidence on the effectiveness (benefits and harms) of screening for EAC and precancerous conditions (BE and dysplasia) among adults with chronic GERD in primary care or related settings.

Methods: We searched Ovid MEDLINE®, Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase Classic + Embase and the Cochrane Library, and unpublished literature using the CADTH Grey Matters checklist. The search was run on October 29, 2018.

The population of interest was adults (≥ 18 years old) with chronic GERD with or without other risk factors for EAC. We were interested in all screening modalities used for detecting EAC and precancerous conditions (BE and dysplasia), such as esophagogastroduodenoscopy (EGD) and transnasal endoscopy. The outcomes of interest were EAC-related and all-cause mortality; survival (at 1, 5, and 10 years or as available); life threatening, severe, or medically significant consequences; incidence of EAC, BE, low- and high-grade dysplasia; quality of life; psychological effects; major or minor medical procedures; and overdiagnosis. We included randomized controlled trials (RCTs), and as few RCTs were available, we also considered non-randomized controlled clinical trials, controlled before-after, interrupted times series, cohort studies, and case-control studies.

The liberal accelerated approach was taken for title and abstract screening and full-text screening was performed independently by two reviewers. Data extraction and risk of bias assessments were completed by one reviewer and verified by a second reviewer. Any disagreements were resolved by consensus. The rating of the certainty of the evidence was completed using the GRADE framework.

Results: After screening 7,292 studies, a total of ten studies (six RCTs, one randomized cross-over, one prospective cohort, and two retrospective cohorts) were included in this review. However, only two studies (both retrospective cohorts) compared screening (received prior EGD)

versus no screening. Authors from one study reported that there was no difference in long-term survival (approximately 6 to 12 years) between those who had received a prior EGD and those who had not (adjusted HR 0.93, 95% confidence interval (CI) 0.58-1.50), even though there may be higher odds of a stage 1 diagnosis than a more advanced diagnosis (stage 2-4) if an EGD had been performed in the previous five years (OR 2.27, 95% CI 1.00-7.67). Those who received an EGD were more likely to be diagnosed at stage 1 compared to all other stages (stage 2 through 4) ($p=0.0497$). The other study reported only one participant who received an EGD in the previous five years. Regarding studies that compared different screening modalities, there was some evidence of a significant difference between screening modalities for endoscopically suspected BE. In general, results across the outcomes were not statistically significant with the exception of psychological effects (i.e. levels of anxiety), which was lower in individuals undergoing the video capsule EGD before the procedure compared to those undergoing transnasal EGD. During the procedure, participants randomized to receive EGD experienced less anxiety than those randomized to transnasal EGD. The discomfort of the unsedated transnasal procedure may contribute to the increased anxiety. Overall, the body of evidence across available outcomes was assessed as having very low certainty.

Limitations: Only two included studies were considered low risk of bias (for histologically confirmed BE outcome). Most outcomes across comparisons were a moderate or high risk of bias. All studies performed only a one-time screening test with no follow-up and the average sample size of included trials was small ($n=172$). Due to the lack of included studies, the definition of chronic GERD was expanded to what study authors considered chronic GERD. This affected the indirectness of the evidence for the key question and was addressed with GRADE. This review only included studies in English or French language.

Conclusions: This systematic review synthesized the available evidence on the effectiveness (benefits and harms) of screening for EAC and precancerous conditions (BE and dysplasia). In summary, little evidence exists on the effectiveness of screening adults with chronic GERD for EAC and precancerous conditions, and what evidence does exist was rated as very low certainty. Further, currently no evidence exists on cancer-related or all-cause mortality, quality of life, major or minor medical procedures, or overdiagnosis. To increase the quantity and certainty of the evidence, more and better designed trials are needed that measure the missing outcomes of interest. As well, the development of a definition of chronic GERD would help identify individuals where screening can be better targeted to evaluate the effectiveness.

2 KQ1 Methods

This systematic review (SR) was developed, conducted, and prepared according to the Canadian Task Force for Preventive Health Care (CTFPHC) Procedure Manual⁴⁵ or as methods were updated by the CTFPHC. The protocol for this SR has been published with PROSPERO (CRD42017049993) and is available on the CTFPHC website.

The review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (**Appendix 1**)⁴⁶ and includes a PRISMA flow diagram. We also used AMSTAR (A Measurement Tool to Assess the Methodological Quality of Systematic Reviews) for additional quality control⁴⁷.

No work within this SR updates any previously conducted SR. Any amendment made to the protocol when conducting the review has been outlined in this manuscript.

2.1 Analytic Framework for EAC Screening

The analytic framework for this review is presented in **Figure 2** and includes both the benefits and harms of screening and patient values and preferences.

2.2 Research Key Questions

The key research questions developed were:

Key Question 1a: In adults (≥ 18 years) with chronic GERD* with or without other risk factors[†], what is the effectiveness (benefits and harms) of screening for EAC and precancerous conditions (BE and low- and high-grade dysplasia)? What are the effects in relevant subgroup populations?

* As defined by study authors

† Risk factors will be deemed so by included studies

Key Question 1b: If there is evidence of effectiveness[‡], what is the optimal time to initiate and to end screening, and what is the optimal screening interval (includes single and multiple tests and ongoing ‘surveillance’)?

‡ If there is evidence of at least moderate certainty of evidence of benefit, according to GRADE

2.3 Inclusion and Exclusion Criteria

A narrative of the inclusion and exclusion criteria is provided below and the PICOS (Population, Interventions, Comparison, Outcomes, Study design) table can be found in **Appendix 2**.

Population

The population of interest for this SR was adults (≥ 18 years old) with chronic GERD with or without other risk factors for EAC. Those experiencing alarm symptoms for EAC, including dysphagia, recurrent vomiting, anorexia, weight loss, gastrointestinal bleeding or other symptoms identified by authors as ‘alarm’ were excluded. In addition, those diagnosed with other gastro-esophageal conditions (e.g., gastric cancer, esophageal atresia, and other life threatening esophageal conditions) or pre-existing disease (BE, dysplasia, or EAC) were also excluded.

Intervention

All modalities used to screen for EAC and precancerous conditions (BE and dysplasia) were considered, including EGD (also known as upper GI endoscopy) with or without biopsy, EGD plus adjunct techniques (e.g., chromoendoscopy and narrow-band imaging), transnasal endoscopy, cytologic examination, and capsule endoscopy. We excluded any follow-up diagnostic tests, such as 24-hour esophageal pH test or any test for staging purposes, such as CT (computerized tomography) and magnetic resonance imaging.

Comparison

For key question 1a, we included studies that compared screening versus no screening, and one screening modality to another screening modality. For key question 1b, we included any study that compared one interval of screening versus another interval of screening, one timepoint at which to initiate screening versus another timepoint, and one timepoint at which to cease screening versus another timepoint.

Outcomes

To measure screening effectiveness, outcomes were selected and ranked by the CTFPHC and a patient group. The patient group comprised of a sample of 17 participants (7 women and 10 men aged 18-68 years old (mean age 37.18 years (standard deviation (SD) 13.28 years)) diagnosed with GERD (6 were diagnosed with either BE or dysplasia and three were currently undergoing screening for esophageal cancer). Patients represented urban, suburban, and rural areas from six Canadian provinces.

The outcomes of interest that are considered *critical* for decision-making are:

1. Mortality (all-cause and EAC-related) at 1, 5 and 10 years or as available, considered from the time of allocation to screening or control arm;
2. Survival at 1, 5, and 10 years or as available, considered from the time of allocation to screening or control arm; and
3. Life threatening, severe, or medically significant consequences of screening, such as requiring hospitalization or prolongation of hospitalization; disabling, limiting self-care or activities of daily living.

Outcomes considered *important* for decision-making are:

4. Incidence of EAC (by stage), BE, low- and high-grade dysplasia;
5. Quality of life (validated scales only);
6. Psychological effects (e.g., anxiety and depression);
7. Major and minor medical procedures following screening; and
8. Overdiagnosis

Overdiagnosis, defined as the diagnosis of disease which would never have become clinically apparent in a person's lifetime (i.e., causing neither symptoms nor death)⁴⁸, would be considered as judged by the study author or by the CTFPHC working group using information provided by authors, where available. In the absence of reporting of overdiagnosis by study authors, outcomes 1, 4, and 7 were used to judge the extent of overdiagnosis, if available.

Study design

Relevant study designs included randomized controlled trials (RCTs), including cluster RCTs, non-randomized controlled clinical trials, controlled before-after studies, studies of interrupted time series, cohort studies, and case-control studies. Cross-sectional studies, case series, case reports, and other publication types (editorials, commentaries, notes, letter, and opinion pieces) were excluded.

Settings

Settings were limited to primary care or settings in which a primary care physician could refer a patient for esophageal screening.

Timing

There were no limits set for publication dates.

Language

There was no language restriction in the electronic searches. However, only English and French articles were included at full-text.

2.4 Literature Search

The search strategy was developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. Using the OVID platform, we searched Ovid MEDLINE®, Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Embase Classic + Embase. We also searched the Cochrane Library on Wiley. There were no language or date restrictions in the search. The searches were run from the inception date of the databases on October 29, 2018.

Strategies utilized a combination of controlled vocabulary (e.g., “Gastroesophageal Reflux”, “Esophageal Neoplasms”, “Endoscopy”) and keywords (e.g., “GERD”, “esophageal cancer”, “esophagoscopy”), with vocabulary and syntax adjusted across databases, as required. When possible, animal-only and opinion-pieces were removed from the results.

The search strategy, which was peer-reviewed using the PRESS 2015⁴⁹, can be found in **Appendix 3**.

To search for unpublished literature (e.g., reports, theses, governmental publications) we used the CADTH Grey Matters checklist. The CADTH checklist includes national and international health technology assessment agencies, clinical practice guideline organizations, drug and device regulatory agencies, health economics resources, clinical trials registries, Canadian health prevalence and incidence databases, statistics, search engines, and databases. The clinical trial registries listed within the checklist included the Canadian Cancer Trials, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, ISRCTN, CenterWatch, and Clinical Trials Registry India.

In addition to the Grey Matters checklist, we searched the following websites suggested by our clinical experts: Canadian Association of Gastroenterology, Cancer Care Ontario, Canadian Cancer Society, Canadian Digestive Health Foundation, Ontario Association of Gastroenterology,

American Society for Gastrointestinal Endoscopy, American College of Gastroenterology, American Gastroenterological Association, British Society of Gastroenterology, American College of Physicians, American Cancer Society, US Preventive Services Task Force, Agency for Healthcare Research and Quality, and the Centers for Disease Control and Prevention.

The searches utilized the following terms “GERD”, “GORD”, “gastroesophageal”, “gastro-esophageal”, “gastro-oesophageal”, “reflux”, “endoscopy”, “esophageal”.

2.5 Study Selection

Duplicates across searches were identified and removed using Reference Manager⁵⁰. The remaining articles were uploaded into Distiller Systematic Review (DistillerSR) Software©⁵¹ for title and abstract screening and full-text screening of the remaining potential relevant articles.

A pilot testing phase among reviewers was performed prior to commencing broad screening of titles and abstracts (50 titles and abstracts) and screening of full-text potentially relevant articles (25 studies) (**Appendix 4**). Titles and abstracts were independently screened for relevance by two reviewers, using the liberal accelerated method, which requires one user to include for further assessment at full-text and two reviewers to exclude. References were reviewed in random order, with each reviewer unaware if the reference had already been assessed and excluded by the other reviewer. Subsequently, full-texts were retrieved and two reviewers independently assess the article for relevancy. Conflicts at full-text were resolved by consensus or a third team member. Articles not available for download were ordered from the library through interlibrary loans. Those that were not received within 30 days were excluded and labelled accordingly. We also scanned the bibliographies of relevant systematic reviews and clinical practice guidelines.

Where chronic GERD was not defined in a study, we attempted to contact the study authors twice over two weeks by email to obtain more information. If authors did not respond, and the lack of definition for chronic GERD was the only reason for possible exclusion, we included the study.

Reports in abstract form and protocols were coded as such, and a search was completed to see if the full-text was available. Those that were not available as full-texts were excluded and studies available only in abstract form are listed in the list of excluded studies (**Appendix 7**).

2.6 Data extraction and management

Full data extraction was completed by one reviewer and verified by a second reviewer. Any disagreements were resolved by consensus. Study characteristics were summarized narratively and are presented in the table of study characteristics (**Table 1**) (e.g., funding source, setting, GERD definition, inclusion/exclusion criteria). Where information was unclear or missing, authors were contacted by email twice over two weeks. If no response was received and the information affected the ability for quantitative analysis, the study was analyzed narratively.

2.7 Risk of Bias (ROB) Assessment

All included studies were assessed for the ROB by one reviewer, with verification completed by a second reviewer. Disagreements were resolved by consensus or third party adjudication. Assessments were considered in the Grading of Recommendations Assessment, Development and

Evaluation (GRADE) domain of study limitations. The Cochrane ROB tool⁵² (**Appendix 5**) was used to evaluate the ROB in RCTs. The Newcastle-Ottawa scale (NOS)⁵³ (**Appendix 6**) was used to evaluate the ROB in cohort studies. Outcome-specific domains were assessed at the outcome level. The overall ROB for the body of evidence involved a judgement of the relative importance of domains, guided by known empirical evidence of bias, the likely direction of bias, and the likely magnitude of bias⁵².

2.8 Analysis

Study characteristics of all included studies are presented in tables and summarized narratively.

2.8.1 Meta-Analysis

Raw data were extracted from all articles when available. Raw data were entered into Review Manager Software version 5.3⁵⁴ and Hazard Ratios (HR) were produced for the survival outcome and Risk Ratios (RR) were calculated for all other outcomes.

2.8.2 Subgroup analysis

A priori-defined subgroup analysis variables included age, sex, body mass index (BMI), smoking history, duration of chronic GERD, definition of chronic GERD, groupings of risk factors, and various ethnic groups. Reporting did not allow for these to be undertaken.

2.8.3 Sensitivity analysis

Sensitivity analyses were planned to restrict to those studies as being low risk of bias, and based on the timing of publication. Sensitivity analysis was not undertaken.

2.8.4 Small study effects

To assess for small study effects, a combination of graphical aids (e.g., funnel plot) and/or statistical tests (e.g., Egger regression test, Hedges-Olkin) were planned if at least 10 studies were available in any given analysis.

2.8.5 Rating the certainty of the evidence

For each critical and important outcome, the GRADE framework^{45,55} was used to assess the strength and certainty of the evidence. We followed the GRADE guidance for determining the extent of the risk of bias for the body of evidence⁵⁶. The online software GRADEpro GDT (<https://grade.pro.org/>) was used for the GRADE assessments. Assessment of each GRADE domain (study limitations, consistency, precision, directness, reporting bias) was presented, where possible, with the information provided in the studies. If there was missing information, a narrative description was provided.

2.9 Amendments to the protocol

A predefined definition of chronic GERD described in the protocol was: (1) symptoms for ≥ 12 months, with no specific frequency; and/or (2) PPI (or other pharmacotherapy) use for GERD for ≥ 12 months. The timing of symptoms for ≥ 12 months which was used to be over-inclusive as a scoping exercise resulted in few studies that defined chronic GERD. Using the pre-defined

definition of chronic GERD would have resulted in no included studies. The definition has been expanded to include what study authors considered chronic GERD, and indirectness to the main study question has been addressed in the GRADE assessments.

We originally intended to include lower quality study designs only if there were five or fewer RCTs. Although there were six included RCTs, all relevant studies were included as there were few studies under each comparison and only two observational studies were located.

3 Results

3.1 Summary of the Literature Search

The search for key question 1 resulted in 7,292 records. After de-duplication and the addition of records identified from the grey literature search, bibliography search, and search for full-text articles based on abstracts and protocols, 4,384 unique records were evaluated at the title and abstract level. A total of 1,645 records were evaluated at full text, with a total of ten studies included; six RCTs⁵⁷⁻⁶², one randomized cross-over trial⁶³, one prospective cohort⁶⁴, and two retrospective cohort studies^{65,66}. (Figure 3)

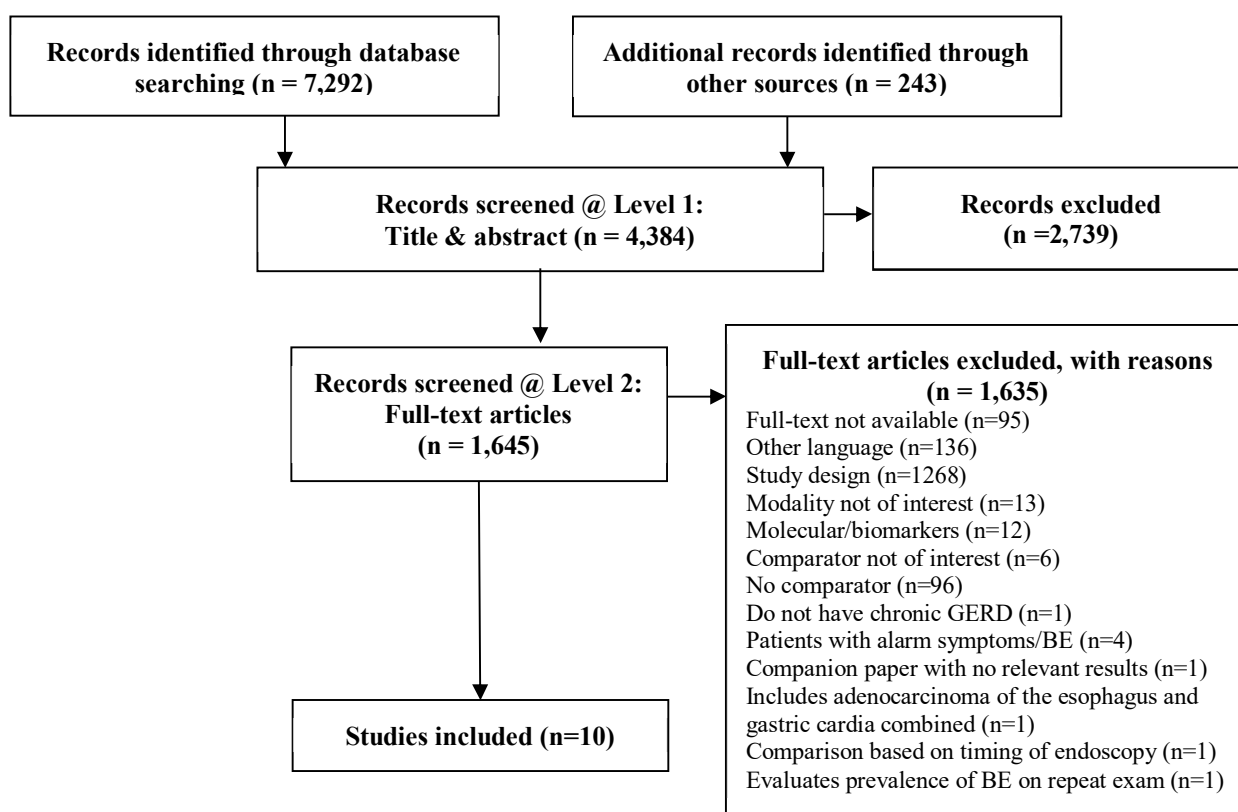


Figure 3 - KQ1 PRISMA flow diagram

Appendix 7 provides a list of excluded studies at full-text, with reasons. No studies provided adequate information to answer key question 1b. A list of ongoing studies is listed in **Appendix 8**.

3.2 Results for Key Question 1a

Key Question 1a: In adults with chronic GERD with or without other risk factors, what is the effectiveness (benefits and harms) of screening for EAC and precancerous conditions (BE and low- and high-grade dysplasia)? What are the effects in relevant subgroup populations?

3.2.1 Characteristics of Included Studies

Study characteristics of the ten included studies are shown in **Table 1**. Two retrospective cohort studies evaluated screening compared to no screening, among patients diagnosed with EAC who either had an esophagogastroduodenoscopy (EGD) in the past five years or not^{65,67}. Seven studies were randomized controlled trials, randomizing patients to different screening modalities (conventional EGD, transnasal esophagoscopy (TNE), video capsule esophagoscopy (VCE), transoral esophagoscopy (Transoral-EGD))^{57,58,60,62,63} or different biopsy methods (enhanced magnification-directed endoscopy (EME) directed-biopsies, four-quadrant random biopsy, and chromoendoscopy)^{59,61}. Lastly, one cohort study by Mori et al⁶⁴ allowed participants to select between three screening modalities (conventional EGD, transnasal or ultrathin transoral esophagoscopy).

Men represented anywhere from 42-99% of the participants in the studies, and among the five studies that reported on ethnicity, White ethnicity represented 41-99% of the participants. The mean age of the participants ranged from 48-67 years old, with wide measures of dispersion. Most studies did not report on the proportion of participants who smoked or took proton pump inhibitors (PPI) (or other medication for GERD); two studies reported that 43% and 80% were smokers and three studies reported that 17% and 48% were taking PPI and 78% were taking antisecretory medication. Only four studies reported on the mean BMI of included participants, ranging from a mean of 29.0 to 31.4.

Eight studies were conducted in the USA and one each in India and Japan. Study sizes were small, ranging from 20 participants up to 92 participants per screening modality, and a total of 60 to 378 participants for RCTs. The prospective cohort study was larger, including a total of 1580 participants, and the two retrospective cohort studies included 155 and 153 EAC patients.

Four of the included studies used questionnaires⁶⁸⁻⁷⁰ to help define GERD. Sami 2015⁶⁰ and Chang 2011⁵⁸ defined GERD using the GERQ, with Chang 2011 using two additional questionnaires.

Studies did not report on all critical and important outcomes of interest. None of the studies reported on all-cause or cause-specific mortality, quality of life, major or minor medical procedures, or overdiagnosis. Furthermore, BE is presented separately for endoscopically suspected BE (based on screening modalities evaluated in the study) and histologically confirmed BE (based on biopsy).

3.2.2 Risk of Bias

Only two studies were considered low risk of bias for the histologically confirmed BE outcome^{57,63}. Overall, most outcomes across comparisons were at a moderate or high risk of bias (**Table 2a. Cochrane ROB for RCTs**). Within the RCTs, most studies used an appropriate method of randomization; however, there was little description of allocation concealment. For performance

and detection bias, several outcomes would not have been possible to blind the participants, the personnel or the outcome assessors (e.g., suspected BE), and this could bias the results. As the majority of studies were a one-time test with no follow-up of the participants, most included all participants in the outcome data. Few studies reported on a protocol, and only two were registered in ClinicalTrials.gov. Outcomes reported in the two studies with registered protocols did not match the main objectives or outcomes that were listed in these protocols and were considered high risk for selective reporting bias. In addition, studies tended to report on an outcome that was not listed in the objectives or methods section. Regarding other potential sources of bias, most studies did not report on how it was funded, and among those that did, one was funded by the manufacturer of the screening equipment⁵⁸, and another study had authors who had received funding from the manufacturer of the screening equipment⁶⁰. Neither of these studies provided any information on if and how the manufacturer was involved in any part of the study or the decision to publish, however, one study declared that there were no conflicts of interest to disclose. Both studies were judged as unclear for this bias.

Outcomes in the three observational studies evaluated with NOS were of moderate^{65,67} or high risk⁶⁴ of bias (**Table 2b. NOS for cohort studies**). Some questions in NOS were difficult to assess or were not relevant (e.g., comparability) because of a lack of reporting by study authors. Cohorts were not truly representative of the population, as both retrospective cohort studies included patients with EAC not specific to those with chronic GERD and the other study reported on a cohort where the purpose was to diagnose GERD. For all studies, the ascertainment of exposure was completed with secure records. Demonstration that the outcome of interest was not present at the start of study was not applicable in the retrospective cohort studies^{65,67} and was not reported in Mori 2010⁶⁴. Both retrospective cohort studies received a negative assessment for the comparability of cohorts on the basis of the design or analysis as they only provided comparison based on age and comorbidities, without further description⁶⁵, while the Hammad et al. did not provide any details specific to the population of interest for this review⁶⁷. For the assessment of incidence of EAC, BE, and low- and high-grade dysplasia outcome, Rubenstein 2008⁶⁵ and Hammad 2019⁶⁷ used medical records and Mori 2010 did not provide any information on how this was collected. There was no follow-up in the cohort study by Mori 2010⁶⁴, as it was a one-time test.

3.2.3 Comparison: Screening versus no screening

3.2.3.1 Esophagogastroduodenoscopy (EGD) versus no prior EGD

Two retrospective cohort studies by Rubenstein 2008⁶⁵ and Hammad 2019⁶⁷, studied a group of individuals with EAC and evaluated their electronic medical records or the institutional cancer registry to see if they had an EGD in the five years prior to cancer diagnosis or not. In Rubenstein et al, GERD was identified in the electronic medical records on the basis of International Classification of Diseases codes. Rubenstein et al. reported on survival and EAC stage at diagnosis, while Hammad et al. reported on EAC stage at diagnosis. A table of results, forest plots, and the GRADE evidence profile and summary of findings tables can be found in **Evidence Set 1**.

Survival

Survival data was reported using a Kaplan-Meier curve, which showed no difference between survival rates at year 1 and 10. Authors report that there was no difference in long-term survival

(approximately 6 to 12 years) between those who had received a prior EGD and those who had not (adjusted HR 0.93, 95% confidence interval (CI) 0.58-1.50).

A GRADE assessment of very low certainty was given because the risk of bias, indirectness, and imprecision were deemed as serious concerns.

Incidence of EAC (stage at diagnosis)

Two studies reported information to evaluate whether an EGD in the previous five years influenced the incidence of EAC by stage of diagnosis at time of detection. It was difficult to determine a range of effects across studies for most stage-based analyses as one study only had one eligible patient with a prior EGD and the stage of diagnosis unknown (author correspondence)⁶⁷. The other study, Rubenstein et al., reported that there may be a higher odds of a stage 1 diagnosis than a more advanced diagnosis (stages 2-4) (OR 2.77, 95% CI 1.00-7.67; p=0.0497), corroborated by the data shown in Evidence Set 1 – Results table. But, there is uncertainty in this estimate due to wide confidence intervals from a small data set.

A GRADE assessment of very low certainty was given because the risk of bias, indirectness, and imprecision were deemed as serious concerns.

3.2.4 Comparison: One screening modality versus another screening modality

3.2.4.1 Esophagogastroduodenoscopy (EGD) versus transnasal esophagoscopy (TNE)

Four studies evaluated EGD compared to TNE; two RCTs by Chang 2011⁵⁸ and Sami 2015⁶⁰, one randomized crossover study by Jobe 2006⁶³, and one cohort study by Mori 2010⁶⁴. A table of results, forest plots, and the GRADE evidence profile and summary of findings tables can be found in **Evidence Set 2**.

Sami 2015⁶⁰ evaluated EGD compared to TNE in either a hospital- or mobile-based setting. Study authors did not provide raw results for each screening modality, but provided the overall p-value to measure differences between all three screening modalities (EGD, hospital-based TNE and mobile-based TNE). Chang 2011⁵⁸ was the pilot trial for Sami 2015⁶⁰, but due to the poor performance of video capsule endoscopy, TNE was evaluated, instead, for Sami 2015⁶⁰. Although the same database for recruitment was used, the population in Chang 2011⁵⁸ was selected from 1976-2006 whereas for Sami 2015⁶⁰ the sample was from 1988-2009. Mori et al⁶⁴ allowed participants to select which screening modality they were given.

Life threatening, severe, or medically significant consequences of screening

Sami 2015⁶⁰ evaluated safety, defined as serious adverse events, including pain, abdominal discomfort, bleeding, perforation, or need for hospitalization at 1 and 30 days after the procedures in all participants. No serious adverse events were reported in either group.

A GRADE assessment of very low certainty was given because the risk of bias was a very serious concern. As well, indirectness and imprecision were deemed as serious concerns.

Incidence of EAC, BE and low- and high-grade dysplasia

Incidence of EAC

For this outcome, Jobe et al⁶³ reported only on those who were receiving initial screening (i.e. excluding those who were being followed with BE). There were no cases of EAC reported between either screening modality.

A GRADE assessment of very low certainty was given because the risk of bias, indirectness, and imprecision were deemed as serious concerns.

Incidence of endoscopically suspected BE

Chang 2011⁵⁸, Sami 2015⁶⁰, and Mori 2010⁶⁴ reported on the number of participants with endoscopically suspected BE. Outcomes were defined differently across those studies. Sami 2015 reported the results using a p-value, therefore a meta-analysis was not performed and results are presented narratively.

Both RCT studies showed no significant difference between screening modalities; Chang 2011⁵⁸ (RR 1.90, 95%CI 0.19-19.27) and Sami 2015⁶⁰ (p=0.37). However, Mori 2010⁶⁴ (observational study design) did show a significant difference between screening modalities, with those being screened with TNE having a higher incidence of suspected BE (RR 2.09, 95%CI 1.30-3.36; *Forest Plot 2.1*).

For the RCTs (Chang 2011⁵⁸ and Sami 2015⁶⁰), a GRADE assessment of very low certainty was given because the risk of bias was a very serious concern. As well, indirectness and imprecision were deemed as serious concerns. For the observational study (Mori 2010)⁶⁴, a GRADE assessment of very low certainty was given because the risk of bias, indirectness, and imprecision were deemed as serious concerns.

Incidence of histologically confirmed BE

Sami 2015⁶⁰ and Jobe 2006⁶³ both defined confirmed BE as the presence of intestinal metaplasia with goblet cells in biopsies. Those with suspected BE in Sami 2015 were given EGD with a histological assessment by a gastrointestinal pathologist to confirm BE diagnosis. Jobe et al. obtained biopsies using the TNE device and a pathologist examined the results.

Both studies reported no difference in incidence of confirmed BE between screening modalities; Sami 2015 (p=0.44) and Jobe 2006 (RR 0.89, 95%CI 0.59-1.33).

A GRADE assessment of very low certainty was given because the risk of bias, indirectness, and imprecision were deemed as serious concerns.

Incidence of dysplasia

One RCT by Chang 2011⁵⁸ and one randomized crossover study by Jobe 2006⁶³ reported on incidence of dysplasia. Jobe et al reported low- and high-grade dysplasia while Chang et al reported on dysplasia which was undefined.

Chang et al⁵⁸ reported that there were no cases of dysplasia among the 40 participants, while Jobe et al⁶³ reported that five participants screened with EGD and four participants screened with TNE

had dysplasia. A meta-analysis of these results showed no difference of incidence between screening modalities (RR 1.54, 95%CI 0.44-5.44; *Forest Plot 2.2*).

A GRADE assessment of very low certainty was given because the risk of bias, indirectness, and imprecision were deemed as serious concerns.

Psychological effects

Chang 2011⁵⁸ Sami 2015⁶⁰, and Jobe 2006⁶³ used the same measurement tool to measure anxiety, however, there were differences in when the tool was utilized. Jobe 2006 reported on anxiety before the procedure, during insertion, and during procedure. Chang 2011 and Sami 2015 only reported on anxiety during the procedure.

No meta-analysis was performed and no forest plots were created for this outcome as all three studies used different methods of reporting outcomes. Chang et al⁵⁸ reported the median score (range 0-7) only among those who were screened with TNE. Sami et al⁶⁰ reported levels of anxiety using the mean (standard deviation (SD)) score (max of 10) for those given EGD, hospital TNE, and mobile TNE. Lastly, Jobe et al⁶³ reported the number of individuals whose anxiety levels were none, mild, moderate, and severe. A narrative analysis is therefore provided.

Anxiety before the procedure

Jobe 2006⁶³ reported no difference between screening modalities in the proportion of those who experienced anxiety before the procedure ($p=0.084$).

A GRADE assessment of very low certainty was given because the risk of bias was a very serious concern. As well, indirectness and imprecision were deemed as serious concerns.

Anxiety during insertion

Jobe 2006⁶³ reported that those given EGD had less anxiety overall during the insertion compared to those screened with TNE ($p=0.0001$).

A GRADE assessment of very low certainty was given because the risk of bias was a very serious concern. As well, indirectness and imprecision were deemed as serious concerns.

Anxiety during the procedure

Overall, those who were randomized to receive EGD experienced less anxiety during the procedure than those randomized to TNE. Both Sami 2015⁶⁰ and Jobe 2006⁶³ reported significantly less anxiety during the procedure for those given EGD compared to those with TNE, $p<0.001$ and $p=0.0001$, respectively. Chang et al⁵⁸ do not report if those given EGD were given the tolerability questionnaire.

A GRADE assessment of very low certainty was given because the risk of bias was a very serious concern. As well, indirectness and imprecision were deemed as serious concerns.

3.2.4.2 Esophagogastroduodenoscopy (EGD) versus Video Capsule Esophagoscopy (VCE)

One RCT by Chang (2011)⁵⁸ compared EGD to VCE to evaluate endoscopically suspected BE, dysplasia, and anxiety during the procedure. Table of results, forest plot, and GRADE evidence profile and summary of findings tables are presented in **Evidence Set 3**.

Incidence of EAC, BE and low- and high-grade dysplasia

Incidence of endoscopically suspected BE

Endoscopically suspected BE was classified as presence of 1 cm or more of columnar lined epithelium above the gastroesophageal junction for EGD and as ZAP grade 2 or 3 for VCE. There was no difference of incidence between screening modalities (RR 0.57, 95%CI 0.11-3.01; *Forest Plot 3.1*).

A GRADE assessment of very low certainty was given because the risk of bias was a very serious concern. As well, indirectness and imprecision were deemed as serious concerns.

Incidence of confirmed BE

Study authors do not describe if those initially given EGD were biopsied and confirmed. Participants with suspected BE based on VCE were offered EGD and BE was confirmed through biopsy. Of the three participants with suspected BE who received VCE, none were confirmed cases of BE.

A GRADE assessment of very low certainty was given because the risk of bias, indirectness, and imprecision were deemed as serious concerns.

Incidence of dysplasia

Author do not describe how dysplasia was defined, but do state that there were no cases of dysplasia among either group.

A GRADE assessment of very low certainty was given because the risk of bias, indirectness, and imprecision were deemed as serious concerns.

3.2.4.3 Esophagogastroduodenoscopy (EGD) versus Transoral-EGD

One cohort study by Mori 2010⁶⁴ included those who had previously been screened for upper intestinal tract disorders, and allowed participants to choose between three screening modalities. In addition to the 574 patients who initially chose transoral-EGD, 25 patients who chose transnasal endoscopy failed intubation and were assigned to transoral-EGD. There was no difference in gender and age among the participants in each screening modality group. Results comparing EGD to transoral-EGD, forest plots, and GRADE evidence and summary of findings tables are presented in **Evidence Set 4**.

Incidence of EAC, BE and low- and high-grade dysplasia

Incidence of endoscopically suspected BE

Suspected BE was defined using an older method of BE classification which measured the mucosa between the esophagogastric junction and squamocolumnar junction. Mucosa was graded as 0 (no BE) or grade 1, 2 or 3 based on length of circumferential or tongue type. Overall, the authors reported no difference in the frequency, distribution or severity of BE among EGD and transnasal-EGD modalities in those with grade 2 or 3 BE (RR 1.30, 95%CI 0.83-2.03; *Forest Plot 4.1*).

A GRADE assessment of very low certainty was given because the risk of bias was a very serious concern. As well, indirectness and imprecision were deemed as serious concerns.

3.2.4.4 Transnasal esophagoscopy (TNE) versus Video capsule esophagoscopy (VCE)

Chak 2014⁵⁷ and Chang 2011⁵⁸ compared TNE to VCE and reported on endoscopically suspected BE, histologically confirmed BE, dysplasia, and psychological effects. Chak 2014 included participants with and without GERD symptoms (approximately 50%)⁶⁸. Chang 2011 provided baseline information on those eligible and contacted, but do not provide this information for those who took part in the study. Symptoms of GERD were obtained through three questionnaires⁶⁸⁻⁷⁰. They also only report on offering EGD to confirm BE for those in the VCE group and report that the tolerability questionnaire was given only to those randomized to the TNE screening modality. Due to these limitations in reporting, it was not possible to meta-analyze the results; therefore, a narrative synthesis is provided. A results table, forest plots, and GRADE evidence profile and summary of findings tables are presented in **Evidence Set 5**.

Incidence of EAC, BE and low- and high-grade dysplasia

Incidence of endoscopically suspected BE

Both Chak 2014⁵⁷ and Chang 2011⁵⁸ used the ZAP classification of grade 2 or higher to determine the need for biopsy. Suspected BE using TNE was defined as “endoscopic presence of 1 cm of more of columnar-lined distal esophagus above the gastroesophageal junction (either circumferential or in tongues) in Chang et al⁵⁸. Overall, there was no difference in the prevalence of endoscopically suspected BE between screening modalities (RR 0.86, 95%CI 0.29-2.56; *Forest Plot 5.1*).

A GRADE assessment of very low certainty was given because the risk of bias was a very serious concern. As well, indirectness and imprecision were deemed as serious concerns.

Incidence of confirmed BE

Participants who were suspected of BE or had other abnormal findings were referred to EGD for histological confirmation. It is unclear in Chang (2011)⁵⁸ if those suspected of BE with TNE were referred to EGD. Chak 2014⁵⁷ reported no difference between TNE and VCE for those with confirmed BE (RR 0.62, 95%CI 0.15-2.52). Chang 2011 did not report on those who were screened with TNE and reported that 0 of the 3 participants suspected of BE with VCE had histologically confirmed BE.

A GRADE assessment of very low certainty was given because the risk of bias, indirectness, and imprecision were deemed as serious concerns.

Incidence of dysplasia

Chang 2011⁵⁸ does not describe how dysplasia was defined or diagnosed, but reported that there were no cases with either screening modality.

A GRADE assessment of very low certainty was given because the risk of bias, indirectness, and imprecision were deemed as serious concerns.

Psychological effects

Anxiety before the procedure

Chak 2014⁵⁷ reported a statistically significant difference in level of anxiety, nervousness, or worry before the procedure, with those in the TNE group experiencing more than those in the VCE group (RR 2.28, 95%CI 1.33-3.88; *Forest Plot 5.2*).

A GRADE assessment of very low certainty was given because the risk of bias was a very serious concern. As well, indirectness and imprecision were deemed as serious concerns.

Anxiety during the procedure

Levels of anxiety during the procedures were also significant in Chak et al⁵⁷ (RR 2.14, 95%CI 1.22-3.77; *Forest Plot 5.3*). Chang 2011⁵⁸ only reported giving the questionnaire to the participants in the TNE group and reported a median score and range, making it not possible to compare between screening modalities.

A GRADE assessment of very low certainty was given because the risk of bias was a very serious concern. As well, indirectness and imprecision were deemed as serious concerns.

3.2.4.5 Transnasal esophagoscopy (TNE) versus Transoral EGD

One RCT by Zaman 1999⁶² randomized participants, with upper gastrointestinal (GI) symptoms, who accepted to be in the study (57% of those asked) to either modality. One cohort study by Mori 2010⁶⁴ included those who had previously been screened for upper intestinal tract disorders, and allowed participants to choose between three screening modalities. In addition to the 574 patients who initially chose transoral-EGD, 25 patients who chose transnasal endoscopy failed intubation and were assigned to transoral-EGD. There was no difference in gender and age among the participants in each screening modality group. Results comparing TNE to transoral-EGD, forest plots, and GRADE evidence and summary of findings tables are presented in **Evidence Set 6**.

Life threatening, severe, or medically significant consequences

Zaman et al⁶² reported that one woman, who had received transnasal endoscopy, experienced facial swelling several hours after her discharge from the hospital. A small proximal esophageal perforation was diagnosed with an x-ray swallowing series using a water-soluble contrast. A

surgical exploration of the neck was then performed, with no perforation revealed. A full recovery was made from this complication. There were no other complications reported, and no differences between screening modalities (RR 4.04, 95% CI 0.17-95.20; *Forest Plot 6.1*).

A GRADE assessment of very low certainty was given because the risk of bias was a serious concern. As well, indirectness and imprecision were deemed as serious concerns.

Incidence of EAC, BE and low- and high-grade dysplasia

Incidence of endoscopically suspected BE

Zaman et al⁶² reported no difference between screening modalities. There were three cases of suspected BE among the 59 participants who were successfully screened, with one in the transnasal and two in the transoral group (RR 0.68, 95%CI 0.07-7.09; *Forest Plot 6.2*).

In the observational study by Mori et al⁶⁴ suspected BE was defined as the mucosa between the esophagogastric junction and squamocolumnar junction. Mucosa was graded as 0 (no BE) or grade 1, 2 or 3 based on length of circumferential or tongue type. Overall, authors reported a significant difference in the frequency of BE, with those screened with TNE less likely to have suspected BE (grade 2 or 3) compared to transoral EGD (RR 0.62, 95%CI 0.41-0.94; *Forest Plot 6.3*).

A GRADE assessment of very low certainty was given because the risk of bias was a very serious concern. As well, indirectness and imprecision were deemed as serious concerns.

Psychological effects

Zaman et al⁶² evaluated the levels of anxiety before the procedure, during insertion, and during the procedure. Anxiety was assessed on a scale of 10, with 0 representing no anxiety and 10 representing severe anxiety. Anxiety before the procedure was assessed prior to screening, while the other two measures were post-screening. Overall, there was no significant difference between levels of anxiety at any time (*Forest Plots 6.4-6.6*).

A GRADE assessment of very low certainty was given because the risk of bias was a serious concern. As well, indirectness and imprecision were deemed as serious concerns.

3.2.5 Comparison: One biopsy method versus another biopsy method

3.2.5.1 Random biopsy versus Enhanced magnification-directed endoscopy (EME) biopsies (with acetic acid)

One RCT study by Ferguson 2006⁵⁹ included patients with a threshold score on a validated GERD questionnaire⁷¹, but it is unclear what this score was and how it was determined. All patients received standard sedated EGD. Participants with any variation of >5mm between the lowest and highest point of the squamocolumnar junction from the gastroesophageal junction using the findings from the standard endoscopy was considered as suspected BE, and participants were randomized at that point to different biopsy methods. Participants allocated to conventional random biopsy had random biopsies taken every 2 cm. Patients who did not have a circumferential appearance of BE had biopsies taken in proportion to the amount of mucosa involved. Participants

allocated to EME-directed biopsy had acetic acid sprayed and EME-directed biopsies performed. As all participants were evaluated on suspected BE through EGD, only incidence of histologically confirmed BE is reported in **Evidence Set 7**.

Incidence of EAC, BE and low- and high-grade dysplasia

Incidence of histologically confirmed BE

Overall, there was no difference in yield of confirmed BE between different methods of biopsy. This was found in both those with pattern III and IV specialized intestinal metaplasia (RR 0.98, 95%CI 0.59-1.64; *Forest Plot 7.1*) and among all specialized intestinal metaplasia pattern types (RR 1.14, 95%CI 0.71-1.82; *Forest Plot 7.2*).

A GRADE assessment of very low certainty was given to both incidences of confirmed BE with SIM pattern types III/IV and all SIM pattern types because the risk of bias, indirectness, and imprecision were deemed as serious concerns.

3.2.5.2 Random biopsy versus chromoendoscopy

One RCT by Wani 2014⁶¹ compared EGD with random biopsy compared to EGD with chromoendoscopy. All participants were given conventional EGD (n=378) and those with suspected BE were randomized to either random biopsy (n=33) or chromoendoscopy (n=23). Suspected BE was defined as columnar lined epithelium that was reddish in colour and velvety texture which could be distinguished easily from normal pale and glossy esophageal squamous epithelium. This study reports only on histologically confirmed BE, defined as having specialized intestinal metaplasia with intestinal goblet cells present. Results, forest plot, and GRADE evidence profile and summary of findings tables are presented in **Evidence Set 8**.

Incidence of EAC, BE and low- and high-grade dysplasia

Incidence of confirmed BE

Wani et al⁶¹ reported no difference in the number of participants with BE between random biopsy and chromoendoscopy (RR 0.87; 95%CI 0.26-2.90; *Forest Plot 8.1*).

A GRADE assessment of very low certainty was given because the risk of bias was a very serious concern. As well, indirectness and imprecision were deemed as serious concerns.

3.3 Results for Key Question 1b

If there is evidence of effectiveness[†], what is the optimal time to initiate and to end screening, and the optimal screening interval (includes single and multiple tests and ongoing ‘surveillance’)? [†]If there is evidence of at least moderate certainty of evidence, according to GRADE

The certainty of the evidence to answer KQ1a was very low, therefore, this question was not addressed.

4 Discussion

Few studies have assessed the effectiveness of screening of individuals with chronic GERD. Only two retrospective cohort studies^{65,67} evaluated screening compared to no screening among 308 individuals with EAC. Among all seven randomized studies, none compared screening to no screening, all performed a one-time screening test with no follow-up of these individuals, and had an average sample size of 172 included participants (range 60 to 378). One cohort study⁶⁴ was substantially larger (n=1580) and allowed people to select which modality they were given, among those evaluated in the study.

The lack of screening trials was also confirmed by a 2012 Cochrane systematic review by Yang et al⁷², which set out to include only RCTs comparing screening versus no screening, and found no studies meeting their inclusion criteria. Five years later, the present systematic review found no additional randomized controlled trials comparing screening to no screening. As there were 95 articles where the full-text was not available, and 136 in a language other than English and French, it is possible that there may exist additional evidence not considered in this review.

In Rubenstein (2008)⁶⁵ there may be higher odds of stage 1 diagnosis if an EGD had been performed in the previous five years, although the study included a small number of cases, resulting in low precision. Those diagnosed at earlier stages (T1 and T2) can be treated with potentially curable therapies, primarily surgical and endoscopic therapies. In tertiary care centres, esophagectomy in patients with high-grade dysplasia and stage T1a cancer has been associated with a greater survival; 89% at 1-year, 77% at five-years, and 68% at 10-years⁷³. Comparatively, those with late stage cancer that cannot be cured by surgery receive chemotherapy/chemoradiation and have a 15% five-year survival rate¹. As only one EAC patient had received an EGD in the previous five years, and this patient was diagnosed with an unknown stage of EAC, the study by Hammad et al.⁶⁷ did not provide any additional data to that outcome.

There was some evidence that there was a significant difference between screening modalities for endoscopically suspected BE. The Mori (2010)⁶⁴ cohort study suggests less suspected BE in TNE compared to EGD. This study used an older method for defining suspected BE by measuring the mucosa between the squamocolumnar junction and the esophagogastric junction, rather than using the newer Prague Classification as used in Sami 2015⁶⁰. Results across outcomes in RCTs were mainly not statistically significant with the exception of psychological effects (i.e. levels of anxiety). The discomfort of the unsedated transnasal procedure, which ultimately fails for some patients, could contribute to increased anxiety.

However, given the very low certainty of the evidence, true effects may be substantially different or uncertain in light of limitations in the body of evidence. There were several important methodological limitations leading to a moderate or high risk of bias among all study outcomes. The few included studies, and generally small sample sizes leads to imprecise results that could not be assessed for consistency or publication bias. A trend that may continue in this area, as half of the potentially relevant trials are expecting sample populations of less than 200 participants (**Appendix 8**).

Blinding of participants to screening modality was not possible in these studies. The inability to blind patients could affect psychological outcomes, as a patient might have a preference to one screening modality over another. For example, conventional EGD is done under sedation, which may decrease levels of anxiety during the procedure. Although not supported by most results in the included studies, there is risk of bias for unblinded screening personnel who might have a

preconceived belief that one modality is less accurate than another, and may refer more patients to biopsy for histological confirmation, as personnel are not able to perform biopsies at the time of screening depending on the screening modality used (e.g., video capsule).

The lack of a definition of chronic GERD (discussed further below), or even how studies defined GERD, reflect a serious concern for the direct generalizability of the population represented in these studies to the target population of this review. The Montreal definition provides guidance for defining GERD¹³; however, there is no standardized definition for what defines “chronic” GERD. For this systematic review, a working group developed a pre-defined definition for what would be considered chronic GERD. No studies met this definition either from a lack of reporting or description provided in the studies. Due to a lack of response from study authors, this uncertainty has been reflected in grading the certainty of the evidence under the indirectness domain. Among studies that did provide a description on how GERD was defined, not all studies used a validated questionnaire to define GERD, while some defined GERD inclusion based on “typical symptoms”. Some studies did not define GERD at all. Jobe 2006⁶³ included those with heartburn, regurgitation or dysphagia, but did not state how many participants experienced each of these symptoms. This is of importance for this review as an exclusion criterion included those with dysphagia. The article was included, but results should be taken with caution.

Overall tolerability of the screening procedure was evaluated in half of the included studies, which included pain, choking, gagging, and anxiety. As EGD is done while the patient is sedated, it is to be likely that there would be less anxiety experienced during the procedure. However, there is also a chance for increased anxiety prior to the procedure as individuals may be anxious about going under sedation. These are considerations that should be considered in practice.

New methods of screening, such as transnasal and transoral esophagoscopy, are considered less invasive and can be performed without the use of sedation in a doctor’s office. However, the trade-off between a less invasive procedure and a higher level of anxiety for the patient must also be considered.

There was little difference in the incidence rates of EAC, BE, and dysplasia using alternative screening methods. The results from these studies may encourage increased usage of alternative methods of screening for BE and EAC. Conventional EGD uses sedation, which increases the cost of screening (e.g. monitoring patients post-procedure) and resources used (e.g. availability of a gastroenterologist, recovery room). Alternate methods do not require sedation, can be done in a primary care setting, and require little monitoring post-procedure.

Mori 2010⁶⁴ included participants who had experienced a previous screening, and allowed participants to select which screening modality they wanted. There was a large difference in what was selected (transnasal=721, transoral=599, and EGD=254) and 25 patients who chose transnasal failed intubation and were assigned to transoral. Further supporting patient choice of screening modality, RCTs reported higher levels of dropouts among those randomized to EGD compared to other screening modalities, although not always significant.

Histologically confirmed BE was reported in six included studies. In two studies, all participants received standard EGD, with the biopsy method as the comparison of interest. In the four other studies, regardless of what method was used for endoscopically suspected BE (e.g., TNE, VCE), confirmatory diagnosis was performed though standard sedated EGD with biopsy. Therefore, the histologically confirmed BE outcome for these studies do not actually reflect the screening modalities being evaluated in the study.

Dysplasia was reported in two studies, Chang 2011⁵⁸ and Jobe 2006⁶³. Neither study defined how dysplasia was defined or diagnosed. Additionally, the main and secondary objectives of Chang et al⁵⁸ was to determine how many people needed to be contacted to recruit 20 for each screening modality, to assess the variables for prediction of participation. This meant small group sizes and could represent a population of health seekers or those who were less healthy than the general population. Therefore, rates of dysplasia among those included would likely not be representative of the overall population, as those with symptoms may be more inclined to participate and receive screening.

Several other outcomes of interest, including mortality, quality of life, and overdiagnosis, were not reported in any of the included studies. This is mostly because the study results were cross-sectional in nature and these outcomes would require follow-up. In the absence of the outcomes of interest to calculate overdiagnosis, we were unable to address this.

Due to the poor reporting of variables, we were not able to perform our *a priori*-defined subgroup analysis (e.g., age, sex, BMI, smoking history, definition of chronic GERD, duration of chronic GERD, various ethnic groups and groupings of risk factors). We planned sensitivity analyses to restrict to those studies as being low risk of bias and based on the timing of publication. However only two studies, Chak 2014⁵⁷ and Jobe 2006⁶³, were considered low risk for the incidence of histologically confirmed BE and sensitivity analyses were not undertaken.

Potentially relevant, unpublished trials were identified from our grey literature search and may prove informative for any subsequent updates of this review (**Appendix 8**). The ongoing BEST3 cluster randomized controlled trial in the UK involves 120 primary care practices with a planned sample of 9000 participants. The aims are to assess whether the Cytosponge test for patients with reflux symptoms will be effective in increasing the detection of BE in primary care compared to usual care, and to evaluate cost-effectiveness and patient acceptability. However, only the planned outcomes of the incidence of BE and adverse events may be relevant. Results are anticipated for late 2019.

4.1 Implications for Research

As indicated above, the current literature contains several methodologic and issues around the certainty of the evidence, which limits our ability in considering the applicability of the evidence. Researchers might want to consider recent recommendations by the REWARD Alliance to reduce research waste and increase its value (<http://rewardalliance.net/about/recommendations/>). For example, although checklists have been developed and published (e.g. CONSORT, STROBE) providing authors with a checklist on what should be reported, many studies lack the methodological details necessary to accurately perform risk of bias. One REWARD recommendation states “Investigators, funders, sponsors, regulators, research ethics committees, and journals should systematically develop and adopt standards for the content of study protocols and full study reports, and for data sharing practices.” This would help with risk of bias assessments, and in determining the applicability of the evidence.

A consistent and transparent definition of “chronic GERD” should be developed, which would help update this systematic review and guide medical professionals in which patients should be screened for EAC and precancerous lesions. A consistent classification of BE (e.g. Prague Classification) should also be used to allow for comparability between studies.

Most included studies compared one screening method versus another screening method. As EAC is a rare disease, to more accurately assess screening effectiveness, good quality, large multi-centre (including community hospitals and university centres) RCTs on screening versus no screening should be performed. These studies should perform follow-up of the participants over time, with clearly defined pathways, to evaluate EAC-related mortality, survival time and other critical outcomes better reported and defined, as discussed by the Core Outcome Measures in Effectiveness Trials (COMET) initiative⁷⁴.

The low quality of reporting in this area is of concern and underscores the importance of proper reporting for trials using the CONSORT statement⁷⁵. Low quality reporting influences the true effects of interventions. Several journals have endorsed and incorporated the CONSORT statement in their instructions to authors. Specialty journals for gastroenterology should consider this approach in order to improve the quality of reporting of RCTs and help reduce bias⁷⁶.

Overdiagnosis has not been addressed in the current literature. de Gelder 2011⁷⁷ outlines seven approaches to estimating overdiagnosis, depending on choice of numerator and denominator. Individual patient data in studies to test the seven approaches would be ideal. This could provide additional information to a study by Pohl 2005 where it was concluded that overdiagnosis in EAC should be excluded as an explanation for the rise in incidence⁴⁸.

5 Conclusion

This review synthesized the evidence on the effectiveness (benefits and harms) of screening for EAC and precancerous conditions (BE and dysplasia). In summary, sparse evidence exists and is of very low certainty to conclude whether or not people with chronic GERD should be screened for EAC and precancerous lesions. More and better designed trials are needed and a definition of what is considered chronic GERD should be developed to help identify a patient group where screening can be better targeted to evaluate the effectiveness.

Chapter 3: Patient values and preferences in relation to screening for esophageal adenocarcinoma and precancerous conditions (dysplasia and Barrett's esophagus) in patients with chronic gastroesophageal reflux disease with or without other risk factors: systematic review to inform a guideline of the Canadian Task Force on Preventive Health Care

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Abstract

Background: This systematic review was produced for the Canadian Task Force on Preventive Health Care to inform the development of a guideline on screening adults with chronic gastroesophageal reflux disease (GERD) with or without other risk factors for esophageal adenocarcinoma (EAC) and associated precancerous lesions (Barrett's Esophagus (BE) and dysplasia).

Objective: To systematically review the current evidence regarding how adults with chronic GERD weigh the benefits and harms of screening, and what factors contribute to these preferences and to their decisions to undergo screening.

Methods: We searched Ovid MEDLINE®, Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations (searched 7 April 2017), Embase Classic + Embase (searched 7 April 2017), CINAHL (searched 7 April 2017), and the Cochrane Library (searched 7 April 2017) and followed the CADTH Grey Matters checklist to search for unpublished literature.

We were interested in adults (≥ 18 years old) with chronic GERD with or without other risk factors for EAC. All screening modalities used for EAC and precancerous conditions (BE and dysplasia), such as esophagogastroduodenoscopy (EGD) and transnasal endoscopy, were included. The outcomes of interest were how patients weigh the benefits and harms of screening, willingness to be screened, uptake of screening, factors considered in decision to be screened, and intrusiveness of the screening modality. We considered randomized controlled trials (RCTs), controlled clinical trials, controlled before-after, case-controls, and cohort study designs.

The liberal accelerated approach was taken for title and abstract screening, and full-text screening was performed independently by two reviewers. Data extraction and risk of bias assessments were completed by one reviewer and verified by a second reviewer. Any disagreements were resolved by consensus. Due to the small number of included studies and lack of data, a meta-analysis of outcomes was not conducted and a narrative synthesis was provided.

Results: Of the 1,443 studies screened, three studies were included (two RCTs and one cohort study). All three studies reported on reasons why participants were unwilling to be screened or participate in a study. No demographic or descriptive information was provided on the participants who contributed outcome data. For the two studies that provided details, reasons for patients'

unwillingness to be screened were due to anxiety (17% [18/105] and 19% [12/62]), fear of gagging (10% [10/105] and 5% [3/62]), not interested in the study or being a study subject (10% [10/105] and 6% [4/62]), and did not want to undergo a transnasal procedure (7% [7/105]). Only one study provided related information on the uptake of screening, although it was reported as the reasons why patients declined screening post-randomization. Five of 92 participants randomized to unsedated transnasal esophagoscopy (TNE) refused the screening modality because they wanted the unsedated video capsule esophagoscopy instead. Two of 92 participants randomized to unsedated video capsule esophagoscopy (VCE) group refused the procedure because they were worried that the capsule would become lodged after swallowing. There was no statistically significant difference in the uptake of screening between intervention groups ($p=0.25$). No other outcomes of interest were addressed in the included studies.

Limitations: Limitations of this review include limiting studies to English and French language studies; however, only one study was excluded as it was written in German. There were only three studies that were excluded because we could not retrieve access to the full text articles.

Conclusions: There is little evidence on the preferences and values of adults with chronic GERD for the willingness (or unwillingness) to be screened and the uptake of screening. Further, no evidence currently exists on how patients weigh the benefits and harms of screening, the factors considered in their decision to be screened, and the intrusiveness of the screening modality. To enhance the quality and quantity of evidence, adults need to be enrolled in screening trials and measures of patient preferences and values need to be included. There is a critical knowledge gap that requires new primary research in this area.

6 KQ2 Methods

This systematic review (SR) was developed, conducted, and prepared according to the Canadian Task Force on Preventive Health Care (CTFPHC) Procedure Manual⁴⁵ or as methods were updated by the Task Force. The protocol for this SR has been registered with PROSPERO (CRD# 42017050014) and is available on the CTFPHC website (<https://canadiantaskforce.ca/>).

The SR is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (**Appendix 9**)⁴⁶, and includes a PRISMA flow diagram. We also used AMSTAR (A Measurement Tool to Assess the Methodological Quality of Systematic Reviews) for additional quality control⁴⁷.

This SR does not update any previously conducted SR. Any amendments made to the protocol when conducting the review has been outlined in this manuscript.

6.1 Analytic Framework for EAC Screening

The analytic framework for this review is presented in **Figure 1** and includes both the benefits and harms of screening and patient values and preferences.

6.2 Research Key Questions

The key research question is:

KQ2. In adults with chronic gastroesophageal reflux disease (GERD), with or without other risk factors, who have been offered, received, or allocated to receive screening for esophageal adenocarcinoma (EAC) and precancerous conditions (Barrett's Esophagus (BE) and dysplasia), how do they weigh the benefits and harms of screening, and what factors contribute to these preferences and to their decisions to undergo screening?

6.3 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are specified below and the tabular presentation of this information can be found in **Appendix 10**.

Population

The population of interest for this SR was adults (≥ 18 years) with chronic GERD* with or without other risk factors for EAC.

* As defined by study authors

Those experiencing alarm symptoms for EAC, including dysphagia, recurrent vomiting, anorexia, weight loss, gastrointestinal bleeding or other symptoms identified by authors as 'alarming' were excluded. In addition, those diagnosed with other gastro-esophageal conditions (e.g., gastric cancer, esophageal atresia, and other life threatening esophageal conditions) or pre-existing disease (BE, dysplasia, or EAC) were excluded.

Intervention

Screening for EAC and other precancerous lesions (BE and/or dysplasia) with any screening modality. We excluded any follow-up diagnostic tests, such as 24-hour esophageal pH test or any test for staging purposes, such as CT (computerized tomography) and magnetic resonance imaging.

Comparison

Comparators of interest included: different screening modalities, different screening intervals, different lengths/duration of screening, and those offered screening compared to those not offered screening. Although, we did consider comparative studies that included a no screening group, we understand that the outcomes of interest would not apply to people who were not offered screening. For such studies, we only considered data for those who were offered screening.

Outcomes

The following outcomes were of interest:

- How patients weigh the benefits and harms of screening (e.g., ranking/rating of benefits and harms outcomes)
- Willingness to be screened
- Uptake of screening
- Factors considered in decision to be screened: what components/outcomes of screening do patients place more value on when deciding whether to be screened or not (e.g. potential complications resulting from screening)
- Intrusiveness of the screening modality

Study design

We planned to focus first on evidence from randomized controlled trials (RCTs). Given few RCTs were located, controlled clinical trials, controlled before-after, case-controls, cohort, interrupted time series (ITS), and cross-sectional (e.g., surveys) designs were sought. As insufficient data for the above study designs were located, qualitative studies and mixed-methods studies were also sought.

Settings

Settings were limited to primary care or settings in which a primary care practitioner could refer a patient for esophageal screening.

Timing

There were no limits set for publication dates.

Language

There was no language restriction in the electronic searches. However, only English and French articles were included in the review.

6.4 Literature Search

The search strategy was developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. Using the OVID platform,

we searched MEDLINE®, MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Embase Classic + Embase. We also searched CINAHL using the EBSCO platform and the Cochrane Library on Wiley. The searches were run from the inception date of the databases on October 29, 2018.

Strategies utilized a combination of controlled vocabulary (e.g., “Gastroesophageal Reflux”, “Patient Acceptance of Health Care”, “Informed Consent”) and keywords (e.g., “GERD”, “patient perspective”, “informed decision-making”). Vocabulary and syntax were translated, as needed, across databases. When possible, animal-only records and opinion publication types were removed from the results.

The search strategy was peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) 2015 tool⁴⁹, and can be found in **Appendix 11**.

To search for unpublished literature, we used the CADTH Grey Matters checklist. This CADTH checklist includes national and international health technology assessment agencies, clinical practice guideline organizations, drug and device regulatory agencies, health economics resources, clinical trials registries, Canadian health prevalence and incidence databases, statistics, search engines, and databases. The clinical trial registries listed within the checklist included the Canadian Cancer Trials, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, ISRCTN, CenterWatch, and Clinical Trials Registry India. We also searched the following websites: the Esophageal Cancer Awareness Association, the Canadian Cancer Society, the American Cancer Society, the American Association for Cancer Research, the Oesophageal Patients Association, the Esophageal Cancer Education Foundation, Canadian Association of Gastroenterology, and the Esophageal Cancer Action Network. Bibliographies of included studies were also scanned based on title.

6.5 Study Selection

Duplicate records across searches were identified and removed using Reference Manager⁵⁰. The remaining articles were uploaded into Distiller Systematic Review (DistillerSR) Software©⁵¹ for study selection.

A pilot testing phase of randomly selected titles and abstracts (n=50) and potentially relevant full-text articles (n=25) was performed among reviewers prior to commencing broad screening at each of those stages (**Appendix 12**). Titles and abstracts were independently screened for relevance by two independent reviewers using the liberal accelerated method (potentially relevant titles and abstracts were identified by one reviewer, and a second reviewer verified those potentially excluded). Subsequently, full-texts were retrieved and two reviewers independently assessed all articles for relevancy. Conflicts at full-text were resolved by consensus or a third team member. Articles not available for download were ordered from the library through interlibrary loans; those not received within 30 days were excluded and labelled accordingly. We also scanned the bibliographies of relevant systematic reviews and clinical practice guidelines identified from the search strategies and grey literature searching.

When chronic GERD had not been defined in a study, we contacted the study authors twice over a two-week period, by email to attempt to obtain more information. If there was no response by authors, and this was the only reason for possible exclusion, we included the study.

Protocols and reports in abstract form were excluded, but an internet search was undertaken to see if full-text reports were available.

6.6 Data extraction and management

Full data extraction was completed by one reviewer and 100% of these were verified by a second reviewer. Any disagreements were resolved by consensus. Study characteristics were summarized narratively and variable that were extracted are those presented in the table of study characteristics (**Table 3**) (e.g., funding source, setting, GERD definition, inclusion/exclusion criteria). Where information was unclear or missing, authors were contacted by email twice over a two-week period.

6.7 Risk of Bias (ROB) Assessment

All included studies, where relevant, were assessed for the ROB by one reviewer, with verification completed by a second reviewer. Disagreements were resolved by consensus. The Cochrane ROB tool⁵² (**Appendix 5**) was used to evaluate the ROB of the one RCT (Chak 2014⁵⁷) that reported an outcome which could be amenable to evaluation (**Table 4**). Outcome-specific domains (i.e., blinding of participants/personnel, blinding of outcome assessors, and incomplete outcome data) were assessed at the outcome level.

The remaining evidence that was located addressed the ‘willingness to participate/be screened’ outcome, which would have been collected only during the consent period of the studies. This, therefore, would have related to all potentially eligible participants in the study, but not determined separately for the groups being compared. In these cases, a formal ROB assessment was not performed, as relevant tools would apply to study conduct as of allocation onward.

6.8 Analysis

Study outcome data are presented in **Table 5**. Due to the nature of the data, a meta-analysis of outcomes was not done. A narrative synthesis was undertaken. Accordingly, *a priori* sensitivity analyses could not be undertaken.

6.9 Amendments to the protocol

A predefined definition of chronic GERD described in the protocol was: (1) symptoms for ≥ 12 months, with no specific frequency; and/or (2) proton pump inhibitors (PPI) (or other pharmacotherapy) use for GERD for ≥ 12 months. The timing of symptoms for ≥ 12 months was used to be over-inclusive as a scoping exercise resulted in few studies that defined chronic GERD. Using the pre-defined definition of chronic GERD would have resulted in no included studies. The definition has been expanded to include what study authors considered chronic GERD and reflected this uncertainty in our interpretation of the findings.

How patients weigh the benefits and harms was included in the question formulation, but the outcome was inadvertently missed in the outcomes list. This outcome has now been added.

7 Results

7.1 Summary of the Literature Search

The search resulted in 1,614 records. After de-duplication and the addition of records identified from the grey literature search, bibliography search, and search for full-text articles based on abstracts and protocols (n=117), 1,600 unique records were evaluated at the title and abstract level. Among these, 103 were evaluated at full-text and three studies were identified (**Figure 4**).

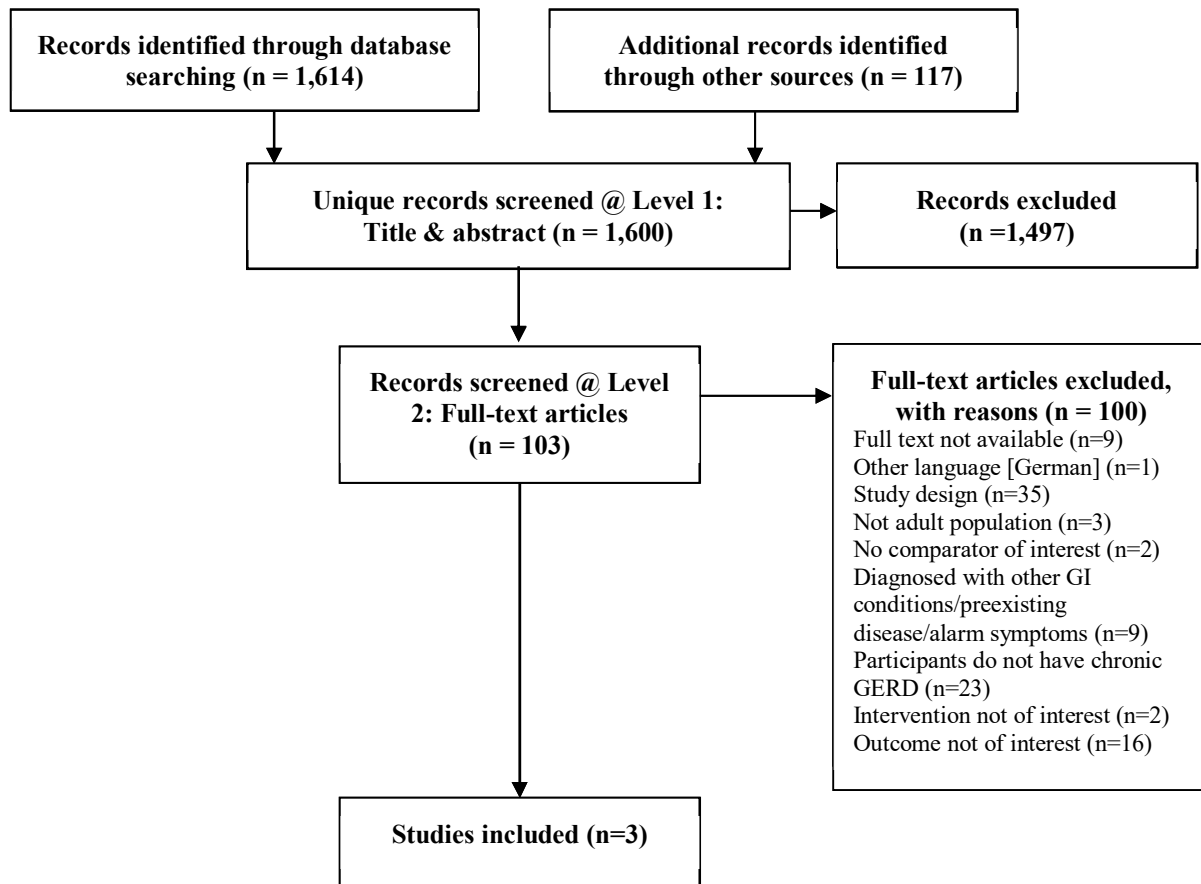


Figure 4 - PRISMA flow diagram for KQ2

Appendix 13 provides a list of studies that were excluded after full text screening, with reasons. A list of ongoing studies is provided in **Appendix 14**.

7.2 Results for Key Question 2

Three studies (Chak 2014⁵⁷, Zaman 1999⁶², and Zaman 1998⁷⁸) provided information on reasons why participants were unwilling to be part of the study or reasons for deciding against the uptake of screening once allocated⁵⁷. All studies were conducted in the USA, and consisted of two RCTs^{57,62} and one cohort⁷⁸. Objectives of the included studies were to determine the acceptance and tolerability of different screening modalities and provide data on screening results. Studies reported on those who refused participation prior to study commencement (i.e. either prior to being

screened or prior to randomization), but did not provide participant characteristics on this patient subset.

7.2.1 Characteristics of Included Studies

Table 3 provides detailed information about each of the three included studies. No demographic or descriptive information was provided on the participants who contributed outcome data. Briefly, Chak 2014⁵⁷ is a RCT which asked eligible patients to participate in a study that would randomize them to either unsedated transnasal esophagoscopy (TNE) or unsedated video capsule esophagoscopy (VCE) in an outpatient clinic. Reasons for unwillingness to participate prior to randomization were given. Allocation of those who agreed to participate was then performed, and participants were given the option of forgoing the allocated screening procedure. Zaman 1999⁶² is a RCT which asked consecutive patients with gastrointestinal (GI) symptoms to participate in a study that would randomize them to either TNE or unsedated peroral endoscopy (P-EGD). It is unclear if those invited refused to participate prior to or after randomization. Lastly, Zaman 1998⁷⁸ is a cohort which asked eligible patients, undergoing endoscopy because of upper GI symptoms, to participate in a study where they would receive P-EGD followed by sedated endoscopy. Both Zaman studies were set in the hospital gastroenterology clinic and endoscopy unit.

7.2.2 Risk of Bias

A formal ROB assessment was only performed for the uptake of screening outcome, in Chak et al⁵⁷ (**Table 4**) Overall ROB was judged to be high risk due to the inability to blind the participants, who were also the outcome assessors in this case. No studies protocols were found, therefore, selective outcome reporting could not be properly assessed. It was unclear if those randomized to each study group were similar, as the study authors did not report information about these individuals. Lastly, only one study provided information about the source of funding.

7.2.4 Results of Included Studies

A narrative summary of the results is provided herein, with detailed results in **Table 5**.

How patients weigh the benefits and harms of screening

No studies provided any data for this outcome.

Willingness to be screened

All three studies provided reasons on why those asked refused to be screened/participate in the study. A large proportion of these individuals were in one study⁵⁷ with 1,026 of the 1,210 people asked not participating, and 184 who agreed to participate. Among those who did not participate during the invitation period, 627 (52%) did not return the phone call or respond to the letter, 385 (32%) refused to participate (with no reason provided), 12 (1%) were ineligible, and two did not participate because of difficulty getting to the hospital.

The other two studies by Zaman et al invited 105 outpatients in one study and 62 in the other. Zaman 1999⁶² reported 45 of 105 (43%) patients were unwilling to participate in the study comparing transnasal to peroral EGD. Zaman 1998⁷⁸ reported 19 of 62 (31%) patients unwilling to participate in the study comparing peroral to sedated EGD.

Anxiety

The main reason unwillingness to be screened in both studies was due to anxiety, with 17% (18/105)⁶² and 19% (12/62)⁷⁸ of all those asked to participate reporting this.

Fear of gagging

Both studies also reported that a fear of gagging was the reason, with 10% (10/105)⁶² and 5% (3/62)⁷⁸ reporting this as the reason.

Other reasons

One study each reported the following reasons: not being interested in the study (10/105, 10%)⁶², not wishing to undergo a transnasal procedure (7/105, 7%)⁶², and unwillingness to be a study subject (4/62, 6%)⁷⁸.

Uptake of screening

Chak et al⁵⁷ reported seven individuals who did not receive the allocated intervention after randomization (n=184; 92 in each group). Five people randomized to the TNE group did not receive the procedure because they wanted capsule instead. Two people randomized to the VCE group did not receive the procedure because they were worried about the capsule getting stuck. There was no statistically significant difference in uptake between intervention groups (p=0.25).

Factors considered in decision to be screened

No studies provided any data for this outcome.

Intrusiveness of the screening modality

No studies provided any data for this outcome.

8 Discussion

Three studies reported on the willingness, or in this case the unwillingness, to participate and be screened in a study on screening for EAC and precancerous conditions. One study also provided outcome information on uptake of screening, more specifically reasons why they did not uptake screening after allocation. No other outcomes of interest were addressed in these studies, overall providing little evidence to answer the question. We are not aware of any other reviews that have been done in the area of upper GI screening in relation to how patients weigh the benefits and harms of screening and what factors contribute to these preferences and to their decision to undergo screening, so there is nothing to compare it to.

It was difficult to accurately assess risk of bias for these studies, as the primary purpose of the included studies was to evaluate acceptability after screening and effectiveness of the screening modality, a different lens to the context of this review. Most outcome data was collected before randomization, and as there is no formal tool to assess risk of bias prior to randomization, these outcomes were not assessed. Measurement bias may present, as studies did not clearly state how this outcome data was collected. It is not clear how the data were collected among those who refused participation during the consent period, as there is no mention of questionnaires or if and how study personnel collected this information. Only the uptake of screening outcome in one study stated that a non-completion questionnaire was given to ascertain reasons for non-completion.

The three included studies were limited to the USA. It is known that preferences for sedated or unsedated endoscopy vary among countries. For example, sedated endoscopy is more common in the USA, whereas unsedated endoscopy is routine in most European and Asian countries⁷⁹.

Two included studies stated that participating individuals had been invited to undergo endoscopy for “upper gastrointestinal symptoms”, rather than chronic GERD specifically. The indications for endoscopy for those who refused to participate were not specified. If we were to infer from those who did participate in the study, approximately 80% were undergoing upper GI for GERD (no definition was provided), dyspepsia, and other indications (e.g. abdominal pain). Therefore, the results from these studies may include participants not actually relevant to the context of this review.

It was difficult to assess the inconsistency among the included studies, mainly due to a lack of information among those contributing to outcome results. For example, the largest study invited 1210 participants, with 38% (385/1026) of those declining to participate not providing any information on why they refused. Poor reporting of patient information for those who contributed outcome data was seen in all studies. None reported on the age and sex of these participants, and indication for screening (as described above), making it difficult to understand how comparable these studies might have been.

There are several potentially relevant ongoing studies in the area of screening for EAC and precancerous lesion identified from our grey literature search that may provide additional information (**Appendix 14**). However, few actually list how patient weigh the benefits and harms of undergoing screening as a primary or secondary outcome of interest. The ongoing BEST3 cluster randomized controlled trial in the UK involves 120 primary care practices comparing the cytosponge test and usual care with usual care only. One of the possible relevant outcomes is patient acceptability. Results are anticipated for late 2019.

8.1 Implications for Research

No studies were found that focused on evaluating how adults weigh the benefits and harms of screening for EAC and pre-cancerous conditions, what factors contribute to these preferences, and to the decisions to undergo screening. The limited data on patients’ reasons for deciding against screening (e.g., preference for another modality, anxiety and fear of gagging, difficulty getting to the hospital) may help inform and stimulate future studies to consider examining the preferences of modalities and reasons why this is important to them. This identifies a need for future primary research projects on these issues.

Incorporating a systematic evaluation of patient values and preferences into the evidence considered in developing guidelines is important, and primary studies must contribute to this knowledge base. In addition, considering the gender perspective is important in recruitment strategies, should a screening program ever exist. Researchers can access national initiatives such as the Strategy for Patient-Oriented Research (SPOR) in Canada and the Patient Centered Outcomes Research Institute (PCORI) in the USA, who provide funding in research to integrate patient involvement, which is believed to lead to greater use and uptake of the research results. Additionally, INVOLVE, established in the UK in 1996, supports active public involvement in public and social care research.

Some studies provided results on those who would be screened again, if they were required to do so. These studies were not included in this review as they did not provide information on how these participants weighed the benefits and harms of screening in their decision to undergoing screening again, but rather just provided a number of those who would. Among those asked, 85% (61/72) would undergo future peroral endoscopy, and 69% (20/29) would undergo transnasal endoscopy. This information could be useful for those considering first time screening to see what other patients report.

8.2 Limitations of the review

This review was developed using rigorous methodological standards, as detailed *a priori* in a registered protocol. There may however be some limitations. There is a risk of missing studies, although we feel this risk is low as we searched multiple databases, and used several techniques to search for grey literature. We included only English and French language studies; however, only one study was excluded due to language of publication. Also, there were nine studies that were excluded because we could not get access to the full text, although many were abstracts and not full-text publications.

9 Conclusion

There is currently insufficient evidence to make firm conclusions on how adults with chronic GERD weight the benefits and harms of screening, and what factors contribute to these preferences and to their decisions to undergo screening. As the importance of this area is well documented, there is a critical information gap that requires new primary research.

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Tables

Table 1 KQ1 Study Characteristics

Table 2 KQ1 Risk of Bias results

Table 3 KQ2 Study Characteristics

Table 4 KQ2 Risk of Bias results

Table 5 KQ2 Results

Table 1. KQ1 Study Characteristics

Study year Country	Study design (total sample)	Data collection	Intervention & Comparator(s) (n allocated) Setting	Population			Outcome(s)
				GERD ¹ definition	Inclusion/Exclusion criteria	Patient characteristics	
Chak 2014 ⁵⁷ USA	Randomized Controlled Trial (n=184)	Not reported Follow-up: one time test	Transnasal esophagoscopy (TNE) ² (n=92) Video capsule esophagoscopy (VCE) ³ (n=92) Outpatient clinic	Symptoms of GERD (from questionnaire ⁴) or use of acid suppression medicine (within 7 days of screening)	Inclusion: Veterans aged 45-85 years, without a prior EGD in the past 10 years and with no contraindications to VCE or TNE (history of recurrent epistaxis), with or without GERD. Exclusion: Altered nasopharyngeal anatomy, allergy to lidocaine derivatives, bleeding diathesis, prolonged prothrombin time, known swallowing disorders, having a cardiac pacemaker or other eletromechanical implants, suspected gastrointestinal obstruction, strictures, or fistulas based on clinical picture.	Mean (SD) age: 59 (8) years Males: 96% White ethnicity: 41% PPI therapy: 46% Smokers: 80% Mean (SD) BMI: TNE: 31.25 (7.66) ECE: 31.38 (6.98)	Endoscopically suspected BE Histologically confirmed BE Anxiety, nervousness, or worry <u>before</u> and <u>during</u> the procedure
Chang 2011 ⁵⁸ USA	Randomized Controlled Trial (n=60)	Feb 2009 - May 2010 Follow-up: one-time test	Transnasal esophagoscopy T(NE) ⁵ (n=20) Video capsule esophagoscopy (VCE) ² (n=20)	Symptoms obtained through three validated questionnaires ^{4,8,9}	Inclusion: Patients over 50 years old from the Olmsted Country cohort, who had not undergone sedated EGD in the past 5 years Exclusion: History of known BE, upper endoscopy within past 5 years, history of dysphagia, Zenker	Age: NR Males: 55% White ethnicity: NR PPI therapy: NR Smokers: NR Mean (SD) BMI: NR	Endoscopically suspected BE Histologically confirmed BE Dysplasia

¹ Gastro-esophageal Reflux Disease

² Performed with Vision Sciences disposable sheath TNE-5000 digital esophagoscope

³ Performed with the Given Imaging PillCam ESO 2 capsule endoscopy

⁴ Locke GR, Talley NJ, Weaver AL, et al. A new questionnaire for gastroesophageal reflux disease. Mayo Clin Proc. 1994; 69:539–47

⁵ Performed with Fujinon EG-530N endoscope

⁸ Talley NJ, Phillips SF, Melton J III, Wiltgen C, Zinsmeister AR. A patient questionnaire to identify bowel disease. Ann Intern Med 1989; 111 :671-674.

⁹ Talley NJ, Phillips SF, Wiltgen CM, Zinsmeister AR, Melton LJ III. Assessment of functional gastrointestinal disease: the bowel disease questionnaire. Mayo Clin Proc 1990; 65: 1456-1479.

Study year Country	Study design (total sample)	Data collection	Intervention & Comparator(s) (n allocated) Setting	Population			Outcome(s)
				GERD ¹ definition	Inclusion/Exclusion criteria	Patient characteristics	
			EGD ^{6,7} (n=20) Clinical research centre		diverticulum, epiphrenic diverticulum, known or suspected intestinal obstruction, cardiac pacemaker, any implanted electromedical device, pregnancy, any MRI anticipated within 7 days, any abdominal surgery within previous 6 months (except cholecystectomy), history of recurrent epistaxis, no longer an Olmsted County, Minnesota resident, deceased, any serious illness that may impair ability to complete a questionnaire, any contraindication to esophageal biopsy		
Ferguson 2006 ⁵⁹ USA	Randomized Controlled Trial (n=137)	Not reported Follow-up: one time test	EGD + biopsy ¹⁰ (n=69) Enhanced magnification-directed endoscopy ¹¹ biopsies (with acetic acid) (n=68) Outpatient clinic	Validated questionnaire, ¹² GERD score	Inclusion: Patients presenting for EGD with a history of GERD Exclusion: Patients with a known history of esophageal cancer, BE with dysplasia, esophagectomy, previous endoscopic ablation therapy, contraindication to procurement of biopsies, or those with an allergy to acetic acid	Age: EGD: 62.8 y (15.0) EME: 62.2 y (15.6) Male: 42% White ethnicity: NR PPI therapy: NR Smokers: NR Mean (SD) BMI: NR	Specialized Intestinal Metaplasia

⁶ Esophagogastroduodenoscopy

⁷ Performed with PENTAX Medical video endoscope

¹⁰ Conventional four-quadrant random biopsies taken every 2 cm

¹¹ Performed with the Olympus GIF-Q160-Z endoscope

¹² Ofman J, Shaw M, Sadik K, et al. Identifying patients with gastroesophageal reflux disease: Validation of a practical screening tool. Dig Dis Sci 2002; 47: 1863-9.

Study year Country	Study design (total sample)	Data collection	Intervention & Comparator(s) (n allocated) Setting	Population			Outcome(s)
				GERD ¹ definition	Inclusion/Exclusion criteria	Patient characteristics	
Sami 2015 ⁶⁰ USA	Randomized Controlled Trial (n=209)	Apr 2011 - Oct 2013 Follow-up: one time test	EGD ¹³ (n=61) Hospital-based transnasal esophagoscopy ¹ (n=72) Hospital outpatient endoscopy suite Mobile-based transnasal esophagoscopy ¹ (n=76) Mobile research vehicle	GERQ questionnaire ⁴ and defined as “heartburn or acid regurgitation ≥1 week, <1 week, or none”	Inclusion: Subjects ≥50 years of age from the Olmsted County cohort, who previously completed validated gastrointestinal symptom questionnaires from 1988 to 2009 Exclusion: History of progressive dysphagia or recurrent epistaxis, known Zenker’s or epiphrenic diverticulum, moved out of Olmsted County or deceased, significant illness that may impair ability to complete questionnaires, and coagulopathy.	Mean (SD) age: 65 y (9) Males: 46% White ethnicity: 99% PPI therapy: 17% Smokers: NR BMI mean (SD): EGD: 28.8 (5.8) hTNE: 30.5 (13.9) mTNE: 29.0 (5.6)	Endoscopically suspected BE Histologically confirmed BE Anxiety experienced during the procedure Serious adverse events
Wani 2014 ⁶¹ India	Randomized Controlled Trial (n=378)	Jan 2010-Feb 2012 Follow-up: one time test	EGD ¹⁴ + biopsy ¹⁰ (n=33) EGD ⁹ + chromo-endoscopy ¹⁵ (n=23) Setting not reported	Described as “characteristics symptoms of GERD”.	Inclusion: Patients with GERD from five northern states of India Exclusion: Not reported	Mean (SD) age: 48.15 y (10.9) Males: 66.7% White ethnicity: NR PPI therapy: NR Smokers: NR Mean (SD) BMI: NR	Histologically confirmed BE (Specialized Intestinal Metaplasia)
Zaman 1999 ⁶² USA	Randomized Controlled Trial (n=105)	Not reported	Unsedated transnasal endoscopy (T-EGD) ¹⁶	not defined	Inclusion: Upper gastrointestinal symptoms. Exclusion: Acute gastrointestinal hemorrhage, history of sinus surgery	Mean age (range): 46 y (21-84) Males: 58% White ethnicity: NR PPI therapy: NR	Life threatening, severe, or medically

¹³ Performed with the Olympus GIF-180 high definition endoscope

¹⁴ Performed with Olympus GIF-Q180 video endoscope

¹⁵ Done with methylene blue directed biopsies

¹⁶ Olympus N200 and N230 ultrathin endoscopes

Study year Country	Study design (total sample)	Data collection	Intervention & Comparator(s) (n allocated) Setting	Population			Outcome(s)
				GERD ¹ definition	Inclusion/Exclusion criteria	Patient characteristics	
		Follow-up: one time test	(n=29) ¹⁷ Unsedated peroral endoscopy (P-EGD) ¹⁶ (n=31) ¹⁷ Hospital gastroenterology clinics and endoscopy unit		or recurrent sinusitis, any current anticoagulation therapy, dysphagia possibly requiring esophageal dilation, a need for sclerotherapy or band ligation of varices, or surveillance for Barrett's esophagus.	Smokers: NR Mean (SD) BMI: NR	significant consequence Endoscopically suspected BE <u>Anxiety before procedure, during insertion, and during procedure</u>
Jobe 2006 ⁶³ USA	Randomized crossover study (n=134)	Mar 2004-Mar 2005 Follow-up: one time test for each modality	EGD + biopsy ¹⁰ then transnasal esophagoscopy ¹⁸ (n=62) Transnasal esophagoscopy then EGD + biopsy (n=72) Office-based screening performed in randomized order 1 week to 1 month later in all patients.	Heartburn, regurgitation or dysphagia	Inclusion: Outpatients ≥18 years who were scheduled for endoscopic screening for symptoms of chronic GERD and all patients ≥18 years of age with histologically proven BE who were enrolled in endoscopic surveillance Exclusion: Patients with a history of prior antireflux surgery, endoscopic antireflux procedure, Zenker's diverticulum, epiphrenic diverticulum, pregnancy, anticoagulation therapy, esophageal varices, history of recurrent epistaxis, or head or neck malignancy	Median age (IQR): 59 y (51-71) Males: 80% White ethnicity: 95% Antisecretory medication: 78% Smokers: 73% Mean (SD) BMI: 30.1 (5.9)	Histologically confirmed BE Dysplasia (low- and high-grade) Esophageal adenocarcinoma <u>Anxiety before procedure, during insertion, and during procedure</u>

¹⁷ 4 patients randomized to transnasal required crossover to the peroral group. One crossover also could not complete the peroral screening and received endoscopy under general anesthesia.

¹⁸ Transnasal esophagoscopy performed with Olympus 5.1 mm diameter flexible endoscope. Sedated EGD performed with Olympus 9.8 mm diameter flexible endoscope

Study year Country	Study design (total sample)	Data collection	Intervention & Comparator(s) (n allocated) Setting	Population			Outcome(s)
				GERD ¹ definition	Inclusion/Exclusion criteria	Patient characteristics	
Mori 2010 ⁶⁴ Japan	Prospective cohort (n=1580)	Not reported Follow-up: one time test	EGD ¹⁹ (n=254) Ultrathin nasal EGD ⁵ (n=727) ²⁰ Ultrathin oral EGD ⁵ (n=599) Hospital setting	Not defined	Inclusion: Consecutive outpatients who underwent EGD for screening upper intestinal tract disorders in Inuyama Chuo Hospital and Ichinomiya Nishi Hospital Exclusion: Patients with esophagogastric cancers, gastroduodenal ulcers, and histories of esophagogastrintestinal surgery as well as those taking proton-pump-inhibitors or histamine-2 receptor antagonists.	Mean (SD) age: 60 y (16) Males: 50% White ethnicity: NR PPI therapy: NR Smokers: NR Mean (SD) BMI: NR	Endoscopically suspected BE
Rubenstein 2008 ⁶⁵ USA	Retrospective controlled cohort study (n=155)	1995-2003 Follow-up: none or prior EGD in the past 5 years, depending on patient	EGD (n=25) no prior EGD (n=130)	GER identified by International Classification of Diseases codes 530.10-530.12, 530.81, or 787.1	Inclusion: Veterans diagnosed with adenocarcinoma of the distal third of the esophagus or of the gastric cardia from 1995 through 2003, and who had gastroesophageal reflux diagnosed before the diagnosis of cancer Exclusion: Subjects who did not have at least one admission or outpatient encounter in each of the 5 years before the cancer diagnosis, those with dysplasia but with no evidence of EAC, and subjects without EAC (such as gastric cardia adenocarcinoma, which shares the same ICD code as EAC) (based on the review of the electronic medical records).	Age: NR Males: 99% White ethnicity: 84% PPI therapy: NR Smokers: NR Mean (SD) BMI: NR	Esophageal adenocarcinoma stage at diagnosis Long-term survival

¹⁹ Performed with Olympus GIF-XQ240 or XQ260. Appears to be unsedated.

²⁰ 25 patients chose N-EGD but had failed transnasal intubation and were converted to transoral EGD

Study year Country	Study design (total sample)	Data collection	Intervention & Comparator(s) (n allocated) Setting	Population			Outcome(s)
				GERD ¹ definition	Inclusion/Exclusion criteria	Patient characteristics	
Hammad 2018 ⁶⁷ USA	Retrospective cohort study (n=153*) *excludes 29 patients under surveillance for BE	Feb 2005-Sept 2017 Follow-up: none or prior EGD in the past 5 years, depending on patient	No EGD (n=152) EGD <5 years ago (n=1)	Not defined	Inclusion: Patients diagnosed with EAC between February 2005 to September 2017. Exclusion: Not reported	Mean age: 67.5 y (SD 9.3) Males: 99.3% White ethnicity: 84.3% PPI therapy: 47.7% Any anti-acid: 58.8% Active smokers: 43.1% Ex-smoker: 41.2% Mean (SD) BMI: 30 (6.5)	Esophageal adenocarcinoma stage at diagnosis

Table 2. KQ1 Risk of Bias (ROB)

Table 2a. Cochrane ROB for RCTs

Author/Year	Sequence generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other	Overall ROB
Critical Outcome 1: Mortality								
<i>All-cause mortality</i>								
Not reported								
<i>Cancer-related mortality</i>								
Not reported								
Critical Outcome 2 Survival								
Not reported								
Critical Outcome 3: Life threatening, severe, or medically significant consequences								
Sami 2015 ⁶⁰	+	-	-	-	+	-	?	High
Zaman 1999 ⁶²	-	-	+	?	+	?	?	Moderate
Important Outcome 4: Incidence of EAC, BE, and low- and high-grade dysplasia								
<i>Incidence of EAC</i>								
Jobe 2006 ⁶³	+	+	+	?	+	?	+	Moderate
<i>Incidence of endoscopically suspected BE</i>								
Chak 2014 ⁵⁷	+	+	-	-	+	?	+	High
Chang 2011 ⁵⁸	?	?	-	-	-	-	?	High
Sami 2015 ⁶⁰	+	-	-	-	+	-	?	High
Zaman 1999 ⁶²	?	?	-	-	+	?	?	High
<i>Incidence of histologically confirmed BE</i>								
Chak 2014 ⁵⁷	+	+	+	+	+	?	+	Low
Chang 2011 ⁵⁸	?	?	+	-	-	-	?	High
Ferguson 2006 ⁵⁹	+	?	+	+	+	?	?	Moderate
Sami 2015 ⁶⁰	+	-	+	+	+	-	?	High
Wani 2014 ⁶¹	?	?	+	+	+	?	?	Moderate
Jobe 2006 ⁶³	+	+	+	+	+	?	+	Low
<i>Incidence of low- and high-grade dysplasia</i>								
Chang 2011 ⁵⁸	?	?	?	?	?	-	?	Moderate
Jobe 2006 ⁶³	+	+	?	?	+	?	+	Moderate
Important Outcome 5: Quality of Life								
Not reported								
Important Outcome 6: Psychological effects								
Chak 2014 ⁵⁷	+	+	-	-	+	?	+	High
Sami 2015 ⁶⁰	+	-	-	-	+	-	?	High
Jobe 2006 ⁶³	+	+	-	-	+	?	+	High
Zaman 1999 ⁶²	?	?	-	-	+	?	?	High
Important Outcome 7: Major or minor medical procedures								
Not reported								
Important Outcome 8: Overdiagnosis								
Not reported								

(+) low risk; (?) unclear risk; (-) high risk

Table 2b. Newcastle-Ottawa Scale (NOS) for Cohort studies

Author/Year	SELECTION				COMPARABILITY	OUTCOME			Overall ROB
	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow Up of Cohorts	
CRITICAL OUTCOME 1: Mortality									
All-cause mortality									
Not reported									
Cancer-related mortality									
Not reported									
CRITICAL OUTCOME 2: Survival									
Rubenstein 2008 ⁶⁵	-	*	*	n/a	-	*	*	*	Moderate
CRITICAL OUTCOME 3: Life threatening, severe, or medically significant consequences									
Not reported									
IMPORTANT OUTCOME 4: Incidence of EAC (by stage), BE, and low- and high-grade dysplasia									
Incidence of EAC									
Rubenstein 2008 ⁶⁵	-	*	*	n/a	-	*	*	*	Moderate
Hammad 2019 ⁶⁷	-	*	*	n/a	-	*	*	*	Moderate
Incidence of endoscopically suspected BE									
Mori 2010 ⁶⁴	-	*	*	-	*	-	n/a	n/a	High
Incidence of histologically confirmed BE									
Not reported									
Incidence of dysplasia									
Not reported									
IMPORTANT OUTCOME 5: Quality of Life									
Not reported									
IMPORTANT OUTCOME 6: Psychological effects									
Not reported									
IMPORTANT OUTCOME 7: Major or minor medical procedures									
Not reported									
IMPORTANT OUTCOME 8: Overdiagnosis									
Not reported									

(*) low risk; (-) high risk; (n/a) not applicable

Table 3. KQ2 Study Characteristics

Study year Country Funding	Setting	Patient flow and timing of outcome data collection	Population			Intervention & Comparator(s)
			GERD ¹ definition	Inclusion/Exclusion criteria	Patient characteristics providing outcome data ²	
Chak 2014 ⁵⁷ USA U.S. Public Health Service	Outpatient clinic	1210 patients were asked to participate in a RCT. 1026 patients did not participate prior to randomization. The 184 who agreed to participate were given the option to withdraw after randomization. Seven patients withdrew - these patients were asked to fill out a non-completion questionnaire to ascertain reasons for non-completion.	Symptoms of GERD (from questionnaire ³) or use of acid suppression medicine (within 7 days of screening)	Inclusion: Veterans aged 45-85 years, without a prior EGD in the past 10 years and with no contraindications to VCE or transnasal esophagoscopy (history of recurrent epistaxis), with or without GERD. Exclusion: Altered nasopharyngeal anatomy, allergy to lidocaine derivatives, bleeding diathesis, prolonged prothrombin time, known swallowing disorders, having a cardiac pacemaker or other eletromechanical implants, suspected gastrointestinal obstruction, strictures, or fistulas based on clinical picture.	Not reported	Transnasal esophagoscopy ⁴ Video capsule esophagoscopy ⁵
Zaman 1999 ⁶² USA NR	Hospital gastroenterology clinics and endoscopy unit over a 12- month period	105 consecutive patients were asked to participate in a RCT. 45 patients refused participation and provided reasons why.	Not defined	Inclusion: Upper gastrointestinal symptoms. Exclusion: Acute gastrointestinal hemorrhage, history of sinus surgery or recurrent sinusitis, any current anticoagulation therapy, dysphagia possibly requiring esophageal dilation, a need for sclerotherapy or band ligation of varices, or surveillance for Barrett's esophagus.	Not reported	Unsedated transnasal endoscopy ⁶ Unsedated peroral endoscopy ⁷
Zaman 1998 ⁷⁸ USA NR	Hospital gastroenterology clinics and endoscopy units over a 6-month period	62 patients were asked to participate in a study where they would receive peroral endoscopy followed by standard sedated EGD. Those who refused participation were asked to provide their reasons.	Not defined	Inclusion: Patients being evaluated for upper gastrointestinal symptoms Exclusion: Evidence of acute gastrointestinal hemorrhage	Not reported	Unsedated peroral endoscopy ⁷ Standard sedated EGD ⁸

1 Gastro-esophageal Reflux Disease

2 We only collected data on the population that is providing relevant outcome information (e.g., reasons for not participating in screening)

3 Locke GR, Talley NJ, Weaver AL, et al. A new questionnaire for gastroesophageal reflux disease. Mayo Clin Proc. 1994; 69:539–47

4 Performed with Vision Sciences disposable sheath TNE-5000 digital esophagoscope

5 Performed with the Given Imaging PillCam ESO 2 capsule endoscopy

6 Performed with the Olympus N200 or N230 ultrathin endoscopes (N200 is the original name, and the later model is N230). A 6-mm diameter upper endoscope

7 Performed with the Olympus XGIF-N200H. A 6-mm ultrathin (UT) video endoscope

8 Performed with the Olympus GIF-100. A 9.5 mm diameter upper endoscope

Table 4. KQ2 Risk of Bias (ROB)

Table 4a. Cochrane Risk of Bias for RCTs

Author/Year	Sequence generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other	Overall ROB
Chak 2014 ⁵⁷	Low	Low	High	High	Low	Unclear	Unclear	High

Table 5. KQ2 Results

Author Year Study design	Intervention & Comparator(s)	Results
Chak 2014 ⁵⁷ RCT	Transnasal esophagoscopy vs. Video capsule esophagoscopy	<p>1210 eligible participants were invited, and 184 agreed.</p> <p>Unwillingness to participate 1026 invited participants did not participate for the following reasons:</p> <ul style="list-style-type: none"> - Did not return phone call/did not respond to letter (n=627) - <i>Declined to participate (n=385) [with no reasons provided]</i> - EGD in past 10 years (n=2) - Did not meet inclusion criteria (n=10) - <i>Difficulty getting to the hospital (n=2)</i> <p>Uptake of screening 7 individuals declined post-randomization. In the TNE group, 5 wanted capsule instead. In the ECE group, 2 were worried about capsule getting stuck (p=0.25).</p>
Zaman 1999 ⁶² RCT	T-EGD vs. P-EGD	<p>105 consecutive outpatients undergoing upper endoscopy because of GI symptoms were asked to participate and 45 patients refused participation (43%).</p> <p>Unwillingness to participate Reasons given included anxiety (18/105, 17%), a fear of gagging (10/105, 10%), not being interested in the study (10/105, 10%), or not wishing to undergo a transnasal procedure (7/45, 7%).</p> <p>Many of these patients were expecting sedation when initially approached about the study.</p>
Zaman 1998 ⁷⁸ Cohort	P-EGD and sedated EGD	<p>62 patients undergoing outpatient endoscopy for gastrointestinal symptoms were asked to participate, of whom 19 refused participation (31%).</p> <p>Unwillingness to participate Reasons for nonparticipation included anxiety (12/62, 19%), fear of gagging (3/62, 5%), and unwillingness to be study subjects (4/62, 6%).</p>

KQ1 Evidence Sets

The table below presents the outcomes of interest, the comparisons in the included studies, and which studies report on these comparisons and outcomes. If the cell is blank, no study reported this outcome for that comparator, and there are no results presented in the results tables or any results in the GRADE tables.

	Evidence Set 1	Evidence Set 2	Evidence Set 3	Evidence Set 4	Evidence Set 5	Evidence Set 6	Evidence Set 7	Evidence Set 8
	EGD vs no prior EGD	EGD vs Transnasal esophagoscopy	EGD vs Video capsule esophagoscopy	EGD vs Transoral esophagoscopy	Transnasal esophagoscopy vs Video capsule esophagoscopy	Transnasal esophagoscopy vs Transoral esophagoscopy	Random biopsy vs Enhanced magnification-directed endoscopy	Random biopsy vs chromoendoscopy
Mortality								
Survival	Rubenstein 2008							
Serious adverse events*		Sami 2015†				Zaman 1999		
Esophageal adenocarcinoma	Rubenstein 2008 Hammad 2019	Jobe 2006						
Suspected Barrett's Esophagus		Chang 2011; Sami 2015†; Mori 2010	Chang 2011	Mori 2010	Chak 2014; Chang 2011	Zaman 1999 Mori 2010		
Confirmed Barrett's Esophagus		Sami 2015†; Jobe 2006	Chang 2011		Chak 2014; Chang 2011		Ferguson 2006	Wani 2014
Dysplasia		Chang 2011; Jobe 2006	Chang 2011		Chang 2011			
QoL								
Psychological effects		Chang 2011; Sami 2015†; Jobe 2006			Chak 2014	Zaman 1999		
Medical procedures								
Overdiagnosis								

EGD: esophagogastroduodenoscopy

* Life threatening, severe or medically significant consequences

† Evaluates transnasal esophagoscopy in the hospital and in a mobile van.

Evidence Set 1: Esophagogastroduodenoscopy (EGD) versus no prior EGD

Evidence Set 1 - Results table

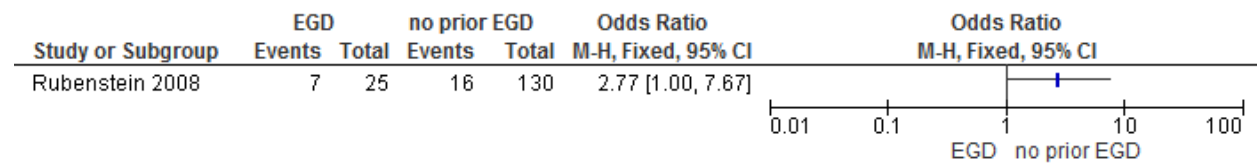
Author Year Study design	Outcome(s) description	Results		ROB assessment	Notes
		EGD	no prior EGD		
CRITICAL OUTCOME 2: Long-term survival					
Rubenstein 2008 ⁶⁵ Retrospective cohort	Long-term survival ²¹ : 1 year after diagnosis of cancer 5 years after diagnosis of cancer 10 years after diagnosis of cancer	51.6%	50.2%	Moderate	Study authors report that there was no difference in long-term survival between those who had received a prior EGD and those who had not (HR 0.82 [95%CI 0.52-1.29]). Adjusting for age, comorbidities, and year of diagnosis yielded similar results (HR 0.93 [95% CI, 0.58-1.50]).
		21.9%	10.3%		
		6.1%	6.1%		
IMPORTANT OUTCOME 4: Incidence of EAC (by stage), BE, and low- and high-grade dysplasia					
EAC					
Rubenstein 2008 ⁶⁵ Retrospective cohort	EAC stage at diagnosis ²² :			Moderate	It was difficult to determine a range of effects across studies due to very low sample size in the EGD group of the Hammad 2019 study. Of the 155 participants with EAC, 25 had previous EGD in the past 1-5 years, and 130 had not (Rubenstein).
	Stage 1	7/25 (28%)	16/130 (12%)		
	Stage 2	11/25 (44%)	47/130 (36%)		
	Stage 3	3/25 (12%)	31/130 (24%)		
	Stage 4	4/25 (16%)	36/130 (28%)		
Hammad 2019 ⁶⁷ Retrospective cohort	EAC stage at diagnosis:			Moderate	Among the 153 EAC patients with no previously known BE, 1 had a previous EGD in the last 5 years and 152 had not (Hammad).
	Stage 0	0/1 (0%)	2/152 (1%)		
	Stage 1	0/1 (0%)	8/152 (5%)		
	Stage 2	0/1 (0%)	37/152 (24%)		
	Stage 3	0/1 (0%)	31/152 (20%)		
	Stage 4	0/1 (0%)	70/152 (46%)		
	Unknown	1/1 (100%)	4/152 (3%)		

²¹ numbers estimated from Kaplan-Meier curve

²² numbers estimated from figure 2

Evidence Set 1 - Forest Plots

Forest Plot 1.1: EAC Stage 1 at diagnosis



Evidence Set 1 - GRADE evidence profile table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EGD	no EGD	Relative (95% CI)	Absolute (95% CI)		
Survival												
1	observational studies	serious ^a	not serious	serious ^b	serious ^c	none	Study authors report that there was no difference in long-term survival between those who had received a prior EGD and those who had not (HR 0.82 [95%CI 0.52-1.29]). Adjusting for age, comorbidities, and year of diagnosis yielded similar results (HR 0.93 [95% CI, 0.58-1.50]).				⊕○○○ VERY LOW	CRITICAL
EAC stage 1 at diagnosis												
1	observational studies	serious ^a	not serious	serious ^b	serious ^c	none	7/25 (28.0%)	16/130 (12.3%)	RR 2.27 (1.04 to 4.95)	156 more per 1,000 (from 5 more to 486 more)	⊕○○○ VERY LOW	IMPORTANT
EAC stage at diagnosis												
1	observational studies	serious ^d	not serious	serious ^e	serious ^c	none	One out of 153 patients, not under surveillance for BE, had received an EGD in the previous five years. An additional 15 had received an EGD more than five years ago, with no additional details on timing. For the purposes of this review, these patients were grouped with those with no prior EGD. This one patient was diagnosed with "unknown stage" of EAC.				⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; EGD: Esophagogastroduodenoscopy; RR: Risk ratio

Explanations

a. The study consisted of a group of veterans, and there was a significant difference between groups on comorbidities.

b. GER identified by ICDs codes 530.10-530.12, 530.81, or 787.1

c. Too few participants.

d. This study consists of patients diagnosed with EAC at the VA Medical Centre. The authors do not provide a comparison for the participants of interest for this review, as their larger population included 29 patients undergoing surveillance for BE. These participants were excluded from our results. This left one patient not under surveillance for BE who received an EGD in the previous five years.

e. GERD was not defined and only two-thirds of the participants included in this review had GERD diagnosis.

Evidence Set 1 - Summary of Findings Table

EGD compared to no prior EGD for screening for EAC and precancerous conditions (BE and dysplasia)

Setting: Hospital-based
Intervention: EGD
Comparison: no prior EGD

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no prior EGD	Risk with EGD				
Survival	Study authors report that there was no difference in long-term survival between those who had received a prior EGD and those who had not (HR 0.82 [95% CI 0.52-1.29]). Adjusting for age, comorbidities, and year of diagnosis yielded similar results (HR 0.93 [95% CI, 0.58-1.50]).			(1 observational study)	⊕○○○ VERY LOW ^{a,b,c}	
EAC stage 1 at diagnosis	123 per 1,000	279 per 1,000 (128 to 609)	RR 2.27 (1.04 to 4.95)	155 (1 observational study)	⊕○○○ VERY LOW ^{a,b,c}	
EAC stage at diagnosis	One out of 153 patients, not under surveillance for BE, had received an EGD in the previous five years. An additional 15 had received an EGD more than five years ago, with no additional details on timing. For the purposes of this review, these patients were grouped with those with no prior EGD. This one patient was diagnosed with "unknown stage" of EAC.			153 (1 observational study)	⊕○○○ VERY LOW ^{c,d,e}	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; EGD: Esophagogastroduodenoscopy RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. The study consisted of a group of veterans, and there was a significant difference between groups on comorbidities.

b. GER identified by ICDs codes 530.10-530.12, 530.81, or 787.1

c. Too few participants.

d. This study consists of patients diagnosed with EAC at the VA Medical Centre. The authors do not provide a comparison for the participants of interest for this review, as their larger population included 29 patients undergoing surveillance for BE. These participants were excluded from our results. This left one patient not under surveillance for BE who received an EGD in the previous five years.

e. GERD was not defined and only two-thirds of the participants included in this review had GERD diagnosis.

Evidence Set 2: Esophagogastroduodenoscopy (EGD) versus Transnasal esophagoscopy (TNE)

Evidence Set 2 - Results table

Author Year Study design	Outcome(s) description		Results		ROB assessment	Notes
			EGD	TNE		
CRITICAL OUTCOME 3: Life threatening, severe, or medically significant consequences						
Sami 2015 ⁶⁰ RCT	Serious adverse events (e.g., bleeding, perforation, hospitalization)		0/61	hospital TNE 0/72 mobile TNE 0/76	High	Assessed 1 and 30 days after the procedure.
IMPORTANT OUTCOME 4: Incidence of EAC (by stage), BE, and low- and high-grade dysplasia						
EAC						
Jobe 2006 ⁶³ Randomized crossover	EAC		0/43	0/54	Moderate	Excludes those undergoing surveillance endoscopy (analysis).
Suspected BE (endoscopically)						
Chang 2011 ⁵⁸ RCT	Classified as endoscopic presence of 1 cm or more of columnar-lined distal esophagus above the gastroesophageal junction (z-line appearance (ZAP) classification).		2/20 (10%)	1/19 (5%)	High	
Sami 2015 ⁶⁰ RCT	Defined as the presence of columnar mucosa at least 1 cm length in the tubular esophagus (Prague Classification)		There was no difference in procedure yield between the study arms with regards to suspected (p=0.37) BE.		High	
Mori 2010 ⁶⁴ Cohort study	Measurement of the mucosa between the esophagogastric junction and squamocolumnar junction.	Grade 1 ²³	61/254 (24%)	188/727 (25.9%)	High	Patients were asked to select between screening options. There was no significant difference in the frequency distribution of the severity of BE.
		Grade 2 ²⁴	26/254 (10.2%)	31/727 (4.3%)		
		Grade 3 ²⁵	1/254 (0.39%)	6/727 (0.8%)		
Confirmed BE (histologically)						
Sami 2015 ⁶⁰ RCT	Defined as the presence of intestinal metaplasia with goblet cells in biopsies.		There was no difference in procedure yield between the study arms with regards to confirmed (p=0.44) BE.		High	Participants in the TNE groups were offered “confirmatory” EGD with histology in 2 weeks’ time.
Jobe 2006 ⁶³ Randomized crossover	Intestinal metaplasia required the unequivocal presence of goblet cells within columnar epithelium.		32/121 (26%)	36/121 (30%)	Moderate	Investigators performing TNE were unaware of whether the subject was undergoing a screening or surveillance procedure (28% (37/134)).
			p-value=0.503			

²³ BE grade 1 (circumferential (C) or tongue (T) type, longest BE <1cm)

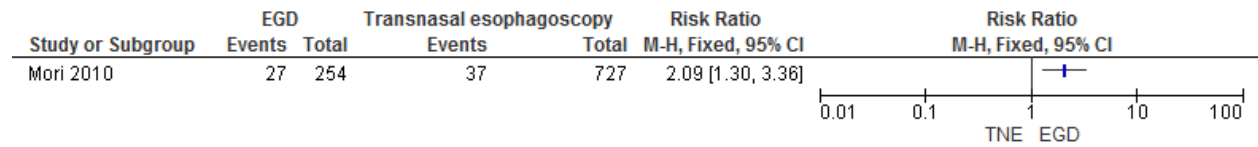
²⁴ BE grade 2 (C type, 3cm > longest BE ≥1cm or T type, longest BE ≥1cm)

²⁵ BE grade 3 (C type, shortest BE ≥3cm)

Author Year Study design	Outcome(s) description	Results		ROB assessment	Notes	
		EGD	TNE			
Dysplasia						
Chang 2011 ⁵⁸ RCT	Dysplasia (not defined)	0/20	0/20	Moderate		
Jobe 2006 ⁶³ Randomized crossover	Dysplasia			Moderate	Each modality detected 4 cases of low-grade dysplasia with concordance on only one case.	
	Low-grade	4 /52	4/64			
	High-grade	1/52	0/64			
IMPORTANT OUTCOME 6: Psychological effects						
Chang 2011 ⁵⁸ RCT	Anxiety during the procedure (median score (range))	Not reported	1.5 (0-7)	High	Study only gave those in the TNE group the tolerability questionnaire.	
Sami 2015 ⁶⁰ RCT	Anxiety during the procedure (Mean (SD)) (scale of 0-10, where 10 is severe)	0.8 (1.5)	hospital TNE 2.3 (2.2) mobile TNE 2.8 (2.8)	High	p<0.001 between modalities	
Jobe 2006 ⁶³ Randomized crossover	Anxiety during procedure			High	The largest differences in comfort level between procedure type occurred primarily within the “none” to “mild” range; the “moderate” to “severe” categories were statistically similar between endoscopic approaches in all questions.	
	None	87/116	62/116			
Mild	11/116	38/116				
Moderate	11/116	12/116				
Severe	7/116	4/116				
		p=0.0001				
Jobe 2006 ⁶³ Randomized crossover	Anxiety before procedure					
	None	64/116	59/116			
	Mild	26/116	39/116			
	Moderate	16/116	13/116			
	Severe	10/116	5/116			
			p=0.084			
	Anxiety during insertion					
	None	83/116	45/116			
	Mild	15/116	43/116			
	Moderate	7/116	19/116			
Severe	11/116	9/116				
		p=0.0001				

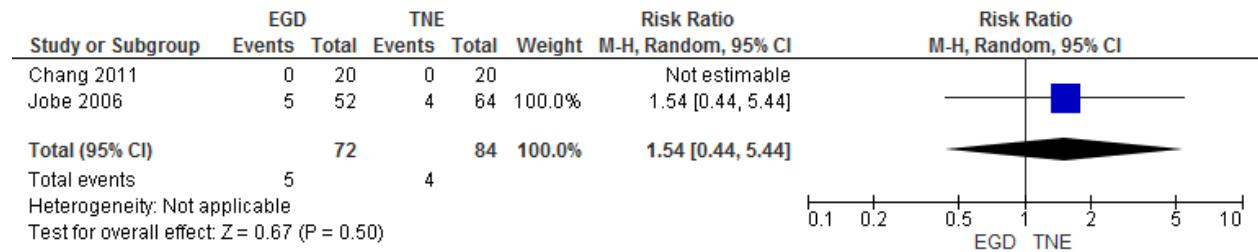
Evidence Set 2 - Forest Plots

Forest Plot 2.1: Incidence of endoscopically suspected BE (Grade 2 and 3) [observational]



Includes those with Barrett's Esophagus grade 2 and 3

Forest Plot 2.2: Incidence of dysplasia



Evidence Set 2 - GRADE evidence profile table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EGD	TNE	Relative (95% CI)	Absolute (95% CI)		
Life threatening, severe, or medically significant consequences												
1 ^a	randomized trials	very serious ^b	not serious	serious ^c	serious ^d	none	Serious adverse events were assessed 1 and 30 days after the procedure. No serious adverse events were reported in any of the study arms. Hospital-based TNE and mobile-based TNE were combined for this outcome under TNE.				⊕○○○ VERY LOW	CRITICAL
Incidence of EAC												
1 ^e	randomized trials	serious ^f	not serious	serious ^g	serious ^d	none	Among the participants who were receiving their initial screening (i.e., not those undergoing surveillance endoscopy), 0/43 and 0/54 were found to have EAC when randomized to be screened first with EGD or TNE, respectively.				⊕○○○ VERY LOW	IMPORTANT
Incidence of suspected BE												
2	randomized trials	very serious ^h	not serious	serious ⁱ	serious ^d	none	Sami 2015 reported that there was no difference in procedure yield between study arms with regards to suspected BE (p=0.37) [this considers all three study arms]. Chang 2011 reported 2/20 participants in the EGD and 1/19 participants in the TNE group having suspected BE.				⊕○○○ VERY LOW	IMPORTANT
Incidence of suspected BE												
1	observational studies	serious ^j	not serious	serious ^k	serious ^d	none	27/254 (10.6%)	37/727 (5.1%)	RR 2.09 (1.30 to 3.36)	55 more per 1,000 (from 15 fewer to 120 more)	⊕○○○ VERY LOW	IMPORTANT
Incidence of confirmed BE												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EGD	TNE	Relative (95% CI)	Absolute (95% CI)		
2 ^e	randomized trials	serious ^l	not serious	serious ^{c,g}	serious ^d	none	Sami 2015 reported no difference in procedure yield between study arms (p=0.44) [this considers all three study arms]. Jobe 2006 reported 32/121 (26%) of those randomized first to EGD had confirmed BE and 36/121 (30%) randomized to TNE first had confirmed BE (p=0.503).				⊕○○○ VERY LOW	IMPORTANT
Incidence of dysplasia												
2 ^e	randomized trials	serious ^f	not serious	serious ^{g,i}	serious ^d	none	5/72 (6.9%)	4/84 (4.8%)	RR 1.54 (0.44 to 5.44)	26 more per 1,000 (from 27 fewer to 211 more)	⊕○○○ VERY LOW	IMPORTANT
Psychological effects (anxiety before the procedure)												
1 ^e	randomized trials	very serious ^m	not serious	serious ^g	serious ^d	none	Authors report those who experienced no anxiety, and mild, moderate and severe anxiety. There was no difference between screening modalities (p=0.084)				⊕○○○ VERY LOW	IMPORTANT
Psychological effects (anxiety during insertion)												
1 ^e	randomized trials	very serious ^m	not serious	serious ^g	serious ^d	none	Authors report those who experienced no anxiety, and mild, moderate and severe anxiety. There was a statistically significant difference between modalities (p=0.0001), with those randomized to TNE experiencing more anxiety during insertion.				⊕○○○ VERY LOW	IMPORTANT
Psychological effects (anxiety during procedure)												
3 ^e	randomized trials	very serious ^m	not serious	serious ^{c,g,i}	serious ^d	none	Chang 2011 appears to only have given the questionnaire to the TNE group and reports the results using median score and the range, Sami 2015 reports the results using mean (SD) on a scale of 0-10, and Jobe 2006 reports the results using the number of participants who selected the level of anxiety as "none", "mild", "moderate", and "severe". Both Sami and Jobe report a statistically significant differences between modalities with those randomized to TNE experiencing more anxiety during the procedure, p<0.001 and p=0.0001, respectively.				⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; **EGD:** Esophagogastroduodenoscopy; **RR:** Risk ratio; **TNE:** Transnasal esophagoscopy

Explanations

- a. Defined in Sami 2015 as safety (adverse events including pain, abdominal discomfort, bleeding, perforation, or need for hospitalization)
- b. Many domains were judged as high risk of bias (e.g., allocation concealment, blinding of participants, personnel and outcome assessors)
- c. Defined as "heartburn or acid regurgitation >1 week, <1 week, or none" using a GERQ questionnaire
- d. Too few participants.
- e. One study is a randomized crossover design (Jobe 2006)
- f. Many domains were judged as unclear (e.g., sequence generation, allocation concealment, blinding of participants and personnel, etc); as such the overall ROB was considered moderate risk.
- g. GERD defined as "heartburn, regurgitation or dysphagia"
- h. Many domains were judged as high risk of bias (e.g., blinding of participants, personnel and outcome assessors, etc).
- i. Symptoms obtained through questionnaires and were not clearly defined
- j. GERD was not defined in the cohort.
- k. GERD was not defined and the assessment of the outcome could be influenced by the personnel's knowledge and possible bias to the screening modality.
- l. No description of allocation concealment in Sami 2015, and some selective outcome reporting.
- m. Participants were aware of what screening modality they were being given and this could influence the level of anxiety.

Evidence Set 2 - Summary of Findings Table

EGD compared to transnasal esophagoscopy (TNE) for screening for EAC and precancerous conditions (BE and dysplasia)						
Setting: Hospital- and office-based (depending on modality) Intervention: EGD Comparison: TNE						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TNE	Risk with EGD				
Life threatening, severe, or medically significant consequences	Serious adverse events were assessed 1 and 30 days after the procedure. No serious adverse events were reported in any of the study arms. Hospital-based TNE and mobile-based TNE were combined for this outcome under TNE.			209 (1 RCT) ^a	⊕○○○ VERY LOW ^{b,c,d}	
Incidence of EAC	Among the participants who were receiving their initial screening (i.e., not those undergoing surveillance endoscopy), 0/43 and 0/54 were found to have EAC when randomized to be screened first with EGD or TNE, respectively.			97 (1 RCT) ^e	⊕○○○ VERY LOW ^{d,f,g}	
Incidence of suspected BE	Sami 2015 reported that there was no difference in procedure yield between study arms with regards to suspected BE (p=0.37) [this considers all three study arms]. Chang 2011 reported 2/20 participants in the EGD and 1/19 participants in the TNE group having suspected BE.			(2 RCTs)	⊕○○○ VERY LOW ^{d,h,i}	
Incidence of suspected BE	51 per 1,000	106 per 1,000 (66 to 171)	RR 2.09 (1.30 to 3.36)	981 (1 observational study)	⊕○○○ VERY LOW ^{d,j,k}	Includes those with Grade 2 and 3, as those with Grade 1 would not have been considered as BE in Chang 2011 and Sami 2015.
Incidence of confirmed BE	Sami 2015 reported no difference in procedure yield between study arms (p=0.44) [this considers all three study arms]. Jobe 2006 reported 32/121 (26%) of those randomized first to EGD had confirmed BE and 36/121 (30%) randomized to TNE first had confirmed BE (p=0.503).			(2 RCTs) ^e	⊕○○○ VERY LOW ^{c,d,g,l}	
Incidence of dysplasia	48 per 1,000	73 per 1,000 (21 to 259)	RR 1.54 (0.44 to 5.44)	156 (2 RCTs) ^e	⊕○○○ VERY LOW ^{d,f,g,i}	
Psychological effects (anxiety before the procedure)	Authors report those who experienced no anxiety, and mild, moderate and severe anxiety. There was no difference between screening modalities (p=0.084)			(1 RCT) ^e	⊕○○○ VERY LOW ^{d,g,m}	
Psychological effects (anxiety during insertion)	Authors report those who experienced no anxiety, and mild, moderate and severe anxiety. There was a statistically significant difference between modalities (p=0.0001), with those randomized to TNE experiencing more anxiety during insertion.			(1 RCT) ^e	⊕○○○ VERY LOW ^{d,g,m}	

EGD compared to transnasal esophagoscopy (TNE) for screening for EAC and precancerous conditions (BE and dysplasia)

Setting: Hospital- and office-based (depending on modality)

Intervention: EGD

Comparison: TNE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TNE	Risk with EGD				
Psychological effects (anxiety during procedure)	Chang 2011 appears to only have given the questionnaire to the TNE group and reports the results using median score and the range, Sami 2015 reports the results using mean (Standard Deviation) on a scale of 0-10, and Jobe 2006 reports the results using the number of participants who selected the level of anxiety as "none", "mild", "moderate", and "severe". Both Sami and Jobe report a statistically significant differences between modalities with those randomized to TNE experiencing more anxiety during the procedure, $p < 0.001$ and $p = 0.0001$, respectively.			(3 RCTs) ^e	⊕○○○ VERY LOW c,d,g,i,m	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Defined in Sami 2015 as safety (adverse events including pain, abdominal discomfort, bleeding, perforation, or need for hospitalization)

b. Many domains were judged as high risk of bias (e.g., allocation concealment, blinding of participants, personnel and outcome assessors)

c. Defined as "heartburn or acid regurgitation >1 week, <1 week, or none" using a GERQ questionnaire

d. Too few participants.

e. One study is a randomized crossover design (Jobe 2006)

f. Many domains were judged as unclear (e.g., sequence generation, allocation concealment, blinding of participants and personnel, etc); as such the overall ROB was considered moderate risk.

g. GERD defined as "heartburn, regurgitation or dysphagia"

h. Many domains were judged as high risk of bias (e.g., blinding of participants, personnel and outcome assessors, etc).

i. Symptoms obtained through questionnaires and were not clearly defined

j. GERD was not defined in the cohort.

k. GERD was not defined and the assessment of the outcome could be influenced by the personnel's knowledge and possible bias to the screening modality.

l. No description of allocation concealment in Sami 2015, and some selective outcome reporting.

m. Participants were aware of what screening modality they were being given and this could influence the level of anxiety.

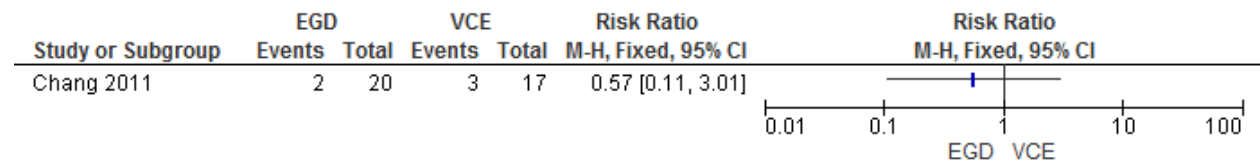
Evidence Set 3: Esophagogastroduodenoscopy (EGD) versus Video capsule esophagoscopy (VCE)

Evidence Set 3 - Results table

Author Year Study design	Outcome(s) description	Results		ROB assessment	Notes
		EGD	VCE		
IMPORTANT OUTCOME 4: Incidence of EAC (by stage), BE, and low- and high-grade dysplasia					
Suspected BE (endoscopically)					
Chang 2011 ⁵⁸ RCT	Endoscopically suspected BE, classified as endoscopic presence of 1 cm or more of columnar-lined distal esophagus above the gastroesophageal junction (with EGD) and as ZAP grade 2 or 3 (with VCE).	2/20 (10%)	3/17 (18%)	High	Three VCE patients had suspected BE and were offered EGD.
Confirmed BE (histologically)					
Chang 2011 ⁵⁸ RCT	Confirmed BE. Patients suspected of BE on VCE were offered EGD and BE was confirmed through biopsy.	Not reported	0/3 (0%)	High	The three patients in the were those who were identified as having suspected BE based on VCE. BE was histologically confirmed with EGD. All cases of BE were short-segment.
Dysplasia					
Chang 2011 ⁵⁸ RCT	Dysplasia (not defined)	0/20 (0%)	0/20 (0%)	Moderate	

Evidence Set 3 - Forest Plot

Forest Plot 3.1: Incidence of endoscopically suspected BE



Evidence Set 3 - GRADE evidence profile table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EGD	VCE	Relative (95% CI)	Absolute (95% CI)		
Incidence of suspected BE												
1	randomized trials	very serious ^a	not serious	serious ^b	serious ^c	none	2/20 (10.0%)	3/17 (17.6%)	RR 0.57 (0.11 to 3.01)	76 fewer per 1,000 (from 157 fewer to 355 more)	⊕○○○ VERY LOW	IMPORTANT
Incidence of confirmed BE												
1	randomized trials	serious ^d	not serious	serious ^b	serious ^c	none	Authors do not report on the incidence of confirmed BE in the EGD group and 0 of 3 had confirmed BE in the VCE group.				⊕○○○ VERY LOW	IMPORTANT
Incidence of dysplasia												
1	randomized trials	serious ^d	not serious	serious ^b	serious ^c	none	There were no cases of dysplasia in either group.				⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; EGD: Esophagogastroduodenoscopy; RR: Risk ratio; VCE: video capsule esophagoscopy

Explanations

a. The lack of blinding of the study personnel could influence this outcome. There were also many other domains that were judged as unclear risk (e.g., sequence randomization, allocation concealment, blinding of outcome assessors, etc).

b. Chronic GERD was not defined. Symptoms were obtained through validated questionnaires.

c. Too few participants.

d. There were many domains that were unclear risk of bias, due to lack of reporting (e.g., sequence generation, allocation concealment, blinding of outcome assessors, etc); as such, it has been judged as moderate risk of bias.

Evidence Set 3 - Summary of Findings Table

Sedated EGD compared to esophageal video capsule esophagoscopy (VCE) for screening for EAC and precancerous conditions (BE and dysplasia)

Setting: Clinical Research Centre

Intervention: EGD

Comparison: Video capsule esophagoscopy (VCE)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Ne of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with VCE	Risk with EGD				
Incidence of suspected BE	176 per 1,000	101 per 1,000 (19 to 531)	RR 0.57 (0.11 to 3.01)	37 (1 RCT)	⊕○○○ VERY LOW ^{a,b,c}	
Incidence of confirmed BE	Authors do not report on the incidence of confirmed BE in the EGD group and 0 of 3 had confirmed BE in the VCE group.			17 (1 RCT)	⊕○○○ VERY LOW ^{b,c,d}	
Incidence of dysplasia	There were no cases of dysplasia in either group.			40 (1 RCT)	⊕○○○ VERY LOW ^{b,c,d}	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **EGD:** Esophagogastroduodenoscopy; **RR:** Risk ratio; **VCE:** video capsule esophagoscopy

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. The lack of blinding of the study personnel could influence this outcome. There were also many other domains that were judged as unclear risk (e.g., sequence randomization, allocation concealment, blinding of outcome assessors, etc).

b. Chronic GERD was not defined. Symptoms were obtained through validated questionnaires.

c. Too few participants.

d. There were many domains that were unclear risk of bias, due to lack of reporting (e.g., sequence generation, allocation concealment, blinding of outcome assessors, etc); as such, it has been judged as moderate risk of bias.

Evidence Set 4: Esophagogastroduodenoscopy (EGD) versus Transoral-EGD

Evidence Set 4 - Results table

Author Year Study design	Outcome(s) description	Results		ROB assessment	Notes
		EGD	Transoral-EGD		
IMPORTANT OUTCOME 4: Incidence of EAC (by stage), BE, and low- and high-grade dysplasia					
Suspected BE (endoscopically)					
Mori 2010 ⁶⁴ Cohort study	Measurment of the mucosa between the esophagogastric junction and squamocolumnar junction			High	Patients were asked to select between screening options. There was no significant difference in the frequency distribution of the severity of BE among EGDs.
	Grade 1 ²³	61/254 (24%)	150/599 (25%)		
	Grade 2 ²⁴	26/254 (10.2%)	46/599 (7.7%)		
	Grade 3 ²⁵	1/254 (0.39%)	3/599 (0.5%)		

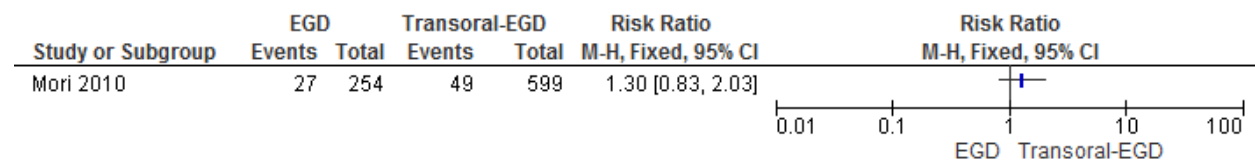
²³ BE grade 1 (circumferential (C) or tongue (T) type, longest BE <1cm)

²⁴ BE grade 2 (C type, 3cm > longest BE ≥1cm or T type, longest BE ≥1cm)

²⁵ BE grade 3 (C type, shortest BE ≥3cm)

Evidence Set 4 - Forest Plot

Forest Plot 4.1: Incidence of suspected BE (grade 2 and 3)



Evidence Set 4 - GRADE evidence profile table: EGD compared to Transoral EGD for screening for EAC and precancerous conditions (BE and dysplasia)


Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EGD	Transoral EGD	Relative (95% CI)	Absolute (95% CI)		
Incidence of suspected BE												
1	observational studies	very serious ^a	not serious	serious ^b	serious ^c	none	27/254 (10.6%)	49/599 (8.2%)	RR 1.30 (0.83 to 2.03)	25 more per 1,000 (from 14 fewer to 84 more)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

- a. A cohort who had received prior EGD who were allowed to select which screening modality they were exposed to. There is no description on how the outcome was assessed.
b. One of the main objectives of the study was to diagnose GERD. Patients who had previous EGD for screening upper intestinal tract disorders were enrolled in the present study.
c. Too few participants.

Evidence Set 4 - Summary of Findings Table

EGD compared to transoral EGD for screening for EAC and precancerous conditions (BE and dysplasia)						
Setting: Hospital						
Intervention: EGD						
Comparison: Transoral EGD						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with transoral EGD	Risk with EGD				
Incidence of suspected BE	82 per 1,000	106 per 1,000 (68 to 166)	RR 1.30 (0.83 to 2.03)	853 (1 observational study)	 VERY LOW a+b+c	Includes those with Grade 2 and 3, as those with Grade 1 would not normally be considered as having BE based on other included studies (Chang 2011 and Sami 2015).
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).						
CI: Confidence interval; RR: Risk ratio						
GRADE Working Group grades of evidence						
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect						
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different						
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect						
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect						

Explanations

- A cohort who had received prior EGD who were allowed to select which screening modality they were exposed to. There is no description on how the outcome was assessed.
- One of the main objectives of the study was to diagnose GERD. Patients who had previous EGD for screening upper intestinal tract disorders were enrolled in the present study.
- Too few participants.

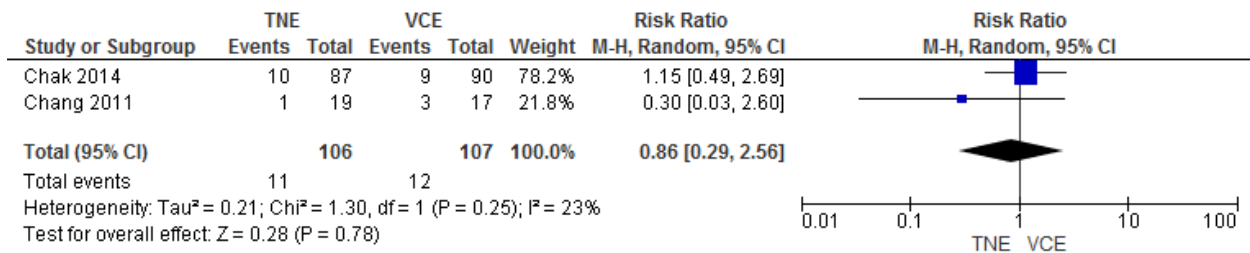
Evidence Set 5: Transnasal esophagoscopy (TNE) versus Video capsule esophagoscopy (VCE)

Evidence Set 5 - Results table

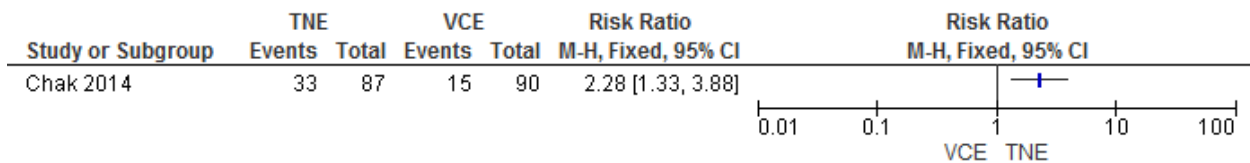
Author Year Study design	Outcome(s) description	Results		ROB assessment	Notes
		TNE	VCE		
IMPORTANT OUTCOME 4: Incidence of EAC (by stage), BE, and low- and high-grade dysplasia					
Suspected BE (endoscopically)					
Chak 2014 ⁵⁷ RCT	Suspected BE (ZAP classification) determined the need for biopsy.	10/87	9/90	High	Subjects with suspected BE (ZAP grade 2 or higher) or other findings (e.g., mass) were referred for EGD.
Chang 2011 ⁵⁸ RCT	Suspected BE, classified as endoscopic presence of 1 cm or more of columnar-lined distal esophagus above the gastroesophageal junction (for TNE) or as ZAP grade 2 or 3, and patients were offered EGD for confirmation (for VCE).	1/19 (5%)	3/17 (18%)	High	All cases of BE were short-segment. Three VCE patients had suspected BE and were offered EGD. Results of exam and biopsy were normal.
Confirmed BE (histologically)					
Chak 2014 ⁵⁷ RCT	BE (Prague classification) confirmed through sedated EGD and histologic examination of biopsy.	3/87	5/90	Low	Subjects with suspected BE (ZAP grade 2 or higher) or other findings (e.g., mass) were referred for EGD.
		p-value=0.49			
Chang 2011 ⁵⁸ RCT	Confirmed BE by sedated EGD exam and biopsy	Not reported	0/3 (0%)	High	
Dysplasia					
Chang 2011 ⁵⁸ RCT	Dysplasia (not defined)	0/20	0/20	Moderate	
IMPORTANT OUTCOME 6: Psychological effects					
Chak 2014 ⁵⁷ RCT	Anxiety, nervousness, or worry <u>before</u> the procedure	33/87 (38%)	15/90 (17%)	High	
		p-value=0.001			
Chak 2014 ⁵⁷ RCT	Anxiety, nervousness, or worry <u>during</u> the procedure	29/87 (33%)	14/90 (16%)		
		p-value=0.006			

Evidence Set 5 - Forest Plots

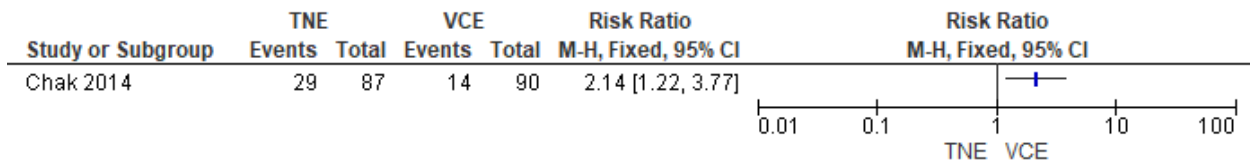
Forest Plot 5.1: Incidence of endoscopically suspected BE



Forest Plot 5.2: Anxiety before the procedure



Forest Plot 5.3: Anxiety during the procedure



Evidence Set 5 - GRADE evidence profile table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNE	VCE	Relative (95% CI)	Absolute (95% CI)		
Incidence of suspected BE												
2	randomized trials	very serious ^a	not serious	serious ^{b,c}	serious ^d	none	11/106 (10.4%)	12/107 (11.2%)	RR 0.86 (0.29 to 2.56)	16 fewer per 1,000 (from 80 fewer to 175 more)	⊕○○○ VERY LOW	IMPORTANT
Incidence of confirmed BE												
2	randomized trials	serious ^e	not serious	serious ^{b,c}	serious ^d	none	Chak 2014 reports 3/87 and 5/90 (p=0.49) cases of confirmed BE from TNE and VCE, respectively. Chang 2011 does not report how many cases of confirmed BE were in the TNE group, and reports that 0/3 of those with suspected BE were confirmed.				⊕○○○ VERY LOW	IMPORTANT
Incidence of dysplasia												
1	randomized trials	serious ^f	not serious	serious ^c	serious ^d	none	There were no cases of dysplasia in either group.				⊕○○○ VERY LOW	IMPORTANT
Psychological effects (anxiety, nervousness, or worry before the procedure)												
1	randomized trials	very serious ^g	not serious	serious ^b	serious ^d	none	33/87 (37.9%)	15/90 (16.7%)	RR 2.28 (1.33 to 3.88)	213 more per 1,000 (from 55 more to 480 more)	⊕○○○ VERY LOW	IMPORTANT
Psychological effects (anxiety during the procedure)												
1	randomized trials	very serious ^g	not serious	serious ^{b,c}	serious ^d	none	29/87	14/90	RR 2.14 (1.22 to 3.77)	177 more per 1,000 (from 34 more to 431 more)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio; TNE: Transnasal esophagoscopy; VCE: video capsule esophagoscopy

Explanations

- a. Personnel and outcome assessors were aware of screening modality and could be influenced by this knowledge.
- b. Chak 2014 defined GERD based on symptoms of GERD (from questionnaire) or use of acid suppression medicine (within 7 days of screening).
- c. Chang 2011 defined GERD based on symptoms obtained through validated questionnaires.
- d. Too few participants.
- e. Chak 2014 was considered low risk but contributed a greater amount of data to the outcome. Chang 2011 was considered high risk, but only contributed 20 participants to each comparison.
- f. Many ROB domains were unclear due to lack of reporting for this study.
- g. Participants were aware of screening modality and could be influenced by this knowledge. Personnel could also influence the level of anxiety by knowledge of the screening modality.

Evidence Set 5 - Summary of Findings Table

Transnasal esophagoscopy (TNE) compared to esophageal video capsule esophagoscopy (VCE) for screening for EAC and precancerous conditions (BE and dysplasia)

Setting: Outpatient clinic and Clinical Research Centre (depending on study)

Intervention: TNE

Comparison: VCE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with VCE	Risk with TNE				
Incidence of suspected BE	112 per 1,000	96 per 1,000 (33 to 287)	RR 0.86 (0.29 to 2.56)	213 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c,d}	
Incidence of confirmed BE	Chak 2014 reports 3/87 and 5/90 (p=0.49) cases of confirmed BE from TNE and VCE, respectively. Chang 2011 does not report how many cases of confirmed BE were in the TNE group, and reports that 0/3 of those with suspected BE were confirmed.			93 (2 RCTs)	⊕○○○ VERY LOW ^{b,c,d,e}	
Incidence of dysplasia	There were no cases of dysplasia in either group.			40 (1 RCT)	⊕○○○ VERY LOW ^{c,d,f}	
Psychological effects (anxiety, nervousness, or worry before the procedure)	167 per 1,000	380 per 1,000 (222 to 647)	RR 2.28 (1.33 to 3.88)	177 (1 RCT)	⊕○○○ VERY LOW ^{b,d,g}	
Psychological effects (anxiety during the procedure)	156 per 1,000	333 per 1,000 (190 to 586)	RR 2.14 (1.22 to 3.77)	177 (1 RCTs)	⊕○○○ VERY LOW ^{b,c,d,g}	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; TNE: Transnasal esophagoscopy; VCE: video capsule esophagoscopy

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

- a. Personnel and outcome assessors were aware of screening modality and could be influenced by this knowledge.
- b. Chak 2014 defined GERD based on symptoms of GERD (from questionnaire) or use of acid suppression medicine (within 7 days of screening).
- c. Chang 2011 defined GERD based on symptoms obtained through validated questionnaires.
- d. Too few participants.
- e. Chak 2014 was considered low risk but contributed a greater amount of data to the outcome. Chang 2011 was considered high risk, but only contributed 20 participants to each comparison.
- f. Many ROB domains were unclear due to lack of reporting for this study.
- g. Participants were aware of screening modality and could be influenced by this knowledge. Personnel could also influence the level of anxiety by knowledge of the screening modality.

Evidence Set 6: Transnasal esophagoscopy (TNE) versus Transoral EGD

Evidence Set 6 - Results table

Author Year Study design	Outcome(s) description	Results		ROB assessment	Notes
		TNE	Transoral-EGD		
CRITICAL OUTCOME 3: Life threatening, severe, or medically significant consequences					
Zaman 1999 ⁶² RCT	Several hours after discharge, facial swelling developed, and eventually a small proximal esophageal perforation was diagnosed by means of an x-ray swallowing series using water-soluable contrast. Surgical exploration of the neck did not reveal a perforation.	1/25	0/34	Moderate	A woman undergoing endoscopy for abdominal pain and early satiety.
IMPORTANT OUTCOME 4: Incidence of EAC (by stage), BE, and low- and high-grade dysplasia					
Suspected BE (endoscopically)					
Zaman 1999 ⁶² RCT	Not defined	1/25	2/34	High	Patients were self-selected, as 43% of those approached declined to participate.
Mori 2010 ⁶⁴ Cohort study	Measurement of the mucosa between the esophagogastric junction and squamocolumnar junction Grade 1 ²³ Grade 2 ²⁴ Grade 3 ²⁵	188/727 (25.9%)	150/599 (25%)	High	Patients were asked to select between screening options. There was no significant difference in the frequency distribution of the severity of BE among EGDs.
		31/727 (4.3%)	46/599 (7.7%)		
		6/727 (0.8%)	3/599 (0.5%)		
		IMPORTANT OUTCOME 6: Psychological effects			
Zaman 1999 ⁶² RCT	Anxiety before the procedure (mean ± SE)	3.0 ± 0.6	3.6 ± 0.5	High	
		p=0.39			
Zaman 1999 ⁶² RCT	Anxiety during insertion (mean ± SE)	4.4 ± 0.6	4.7 ± 0.5		
		p=0.63			
Zaman 1999 ⁶² RCT	Anxiety during the procedure (mean ± SE)	3.3 ± 0.7	3.3 ± 0.5		
		p=0.99			

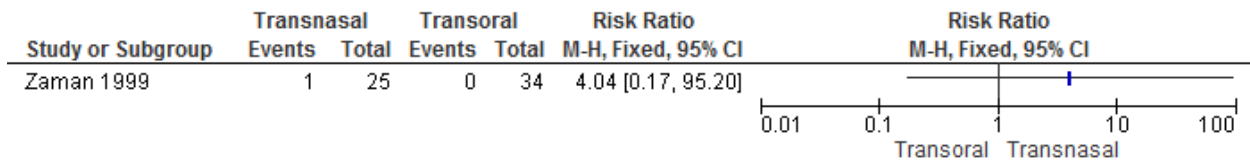
²³ BE grade 1 (circumferential (C) or tongue (T) type, longest BE <1cm)

²⁴ BE grade 2 (C type, 3cm > longest BE ≥1cm or T type, longest BE ≥1cm)

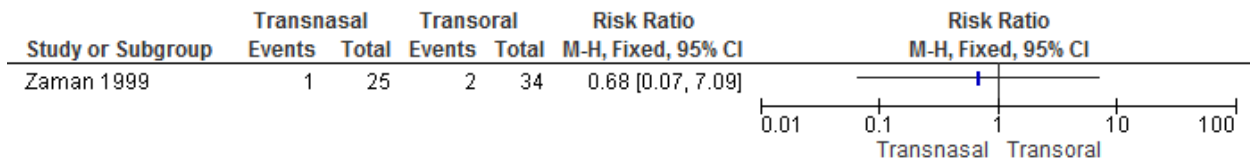
²⁵ BE grade 3 (C type, shortest BE ≥3cm)

Evidence Set 6 - Forest Plots

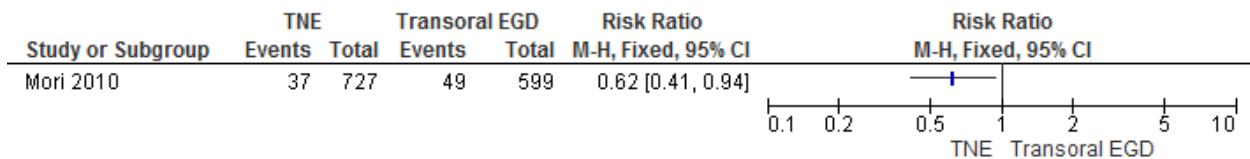
Forest Plot 6.1: Life threatening, severe, or medically significant consequences



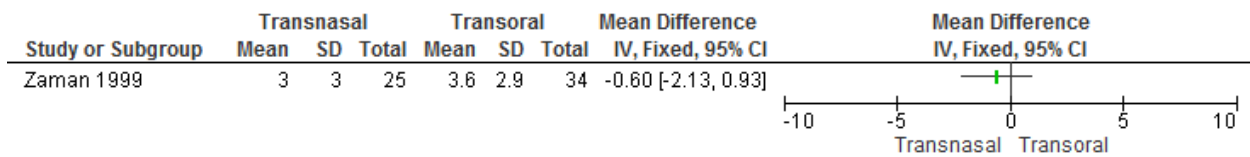
Forest Plot 6.2: Incidence of suspected BE (RCT)



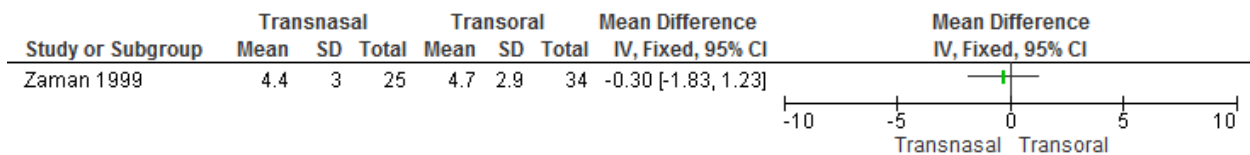
Forest Plot 6.3: Incidence of suspected BE (grade 2 and 3) (observational)



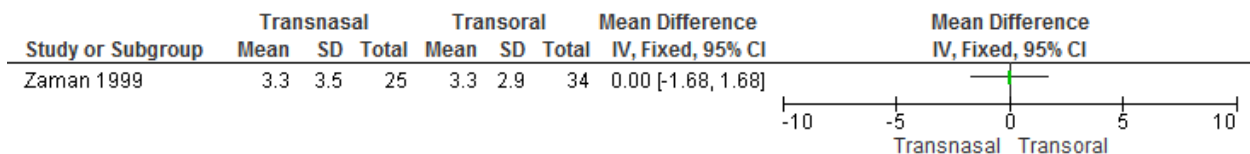
Forest Plot 6.4: Anxiety before the procedure



Forest Plot 6.5: Anxiety during insertion



Forest Plot 6.6: Anxiety during the procedure



Evidence Set 6 - GRADE evidence profile table

Setting: Hospital

Bibliography: Zaman A, Hahn M, Hapke R, Knigge K, Fennerty MB, Katon RM. A randomized trial of peroral versus transnasal unsedated endoscopy using an ultrathin videoendoscope.

Gastrointestinal Endoscopy 1999; 49(3):279-284. Mori A, Ohashi N, Yoshida A, Nozaki M, Tatcbe H, Okuno M, Hoshihara Y, Hongo M. Unsedated transnasal ultrathin esophagogastroduodenoscopy may provide better diagnostic performance in gastroesophageal reflux disease. *Disease of the Esophagus* 2011; 24:92-98.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNE	Transoral EGD	Relative (95% CI)	Absolute (95% CI)		
Life threatening, severe, or medically significant consequences												
1	randomised trials	serious ^a	not serious	serious ^b	serious ^c	none	1/25 (4.0%)	0/34 (0.0%)	not estimable		⊕○○○ VERY LOW	IMPORTANT
Incidence of suspected BE (RCT)												
1	randomised trials	very serious ^a	not serious	serious ^b	serious ^c	none	1/25 (4.0%)	2/34 (5.9%)	RR 0.68 (0.07 to 7.09)	19 fewer per 1,000 (from 55 fewer to 358 more)	⊕○○○ VERY LOW	IMPORTANT
Incidence of suspected BE (grade 2 and 3) (obs)												
1	observational studies	very serious ^d	not serious	serious ^e	serious ^c	none	37/727 (5.1%)	49/599 (8.2%)	RR 0.62 (0.41 to 0.94)	31 fewer per 1,000 (from 5 fewer to 48 fewer)	⊕○○○ VERY LOW	IMPORTANT
Anxiety prior to screening (Scale from: 0 to 10)												
1	randomised trials	very serious ^{a,f}	not serious	serious ^b	serious ^c	none	25	34	-	MD 0.6 lower (2.13 lower to 0.93 higher)	⊕○○○ VERY LOW	IMPORTANT
Anxiety during insertion (Scale from: 0 to 10)												
1	randomised trials	very serious ^{a,f}	not serious	serious ^b	serious ^c	none	25	34	-	MD 0.3 lower (1.83 lower to 1.23 higher)	⊕○○○ VERY LOW	IMPORTANT
Anxiety during the procedure (Scale from: 0 to 10)												

1	randomised trials	very serious ^{a,f}	not serious	serious ^b	serious ^c	none	25	34	-	MD 0 (1.68 lower to 1.68 higher)	⊕○○○ VERY LOW	IMPORTANT
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CI: Confidence interval; **EGD**: Esophagogastroduodenoscopy; **MD**: Mean Difference; **RR**: Risk ratio; **TNE**: Transnasal esophagoscopy

Explanations

- a. There is no information provided on the method of randomization or allocation concealment. No protocol was found to determine if all outcomes were reported. There was no information provided on how the study was funded.
- b. Participants were selected among those with upper GI symptoms, of which GERD was one reason. Other reasons included dyspepsia, abdominal pain, nausea/vomiting, anemia.
- c. Too few participants.
- d. A cohort who had received prior EGD who were allowed to select which screening modality they were exposed to. There is no description on how the outcome was assessed.
- e. One of the main objectives of the study was to diagnose GERD. Patients who had previous EGD for screening upper intestinal tract disorders were enrolled in the present study.
- f. Randomization to a particular method could cause different levels of anxiety prior to the procedure and during the procedure.

Evidence Set 6 - Summary of Findings table

TNE compared to Transoral EGD for screening for EAC and precancerous conditions (BE and dysplasia)

Setting: Hospital-based

Intervention: TNE

Comparison: Transoral EGD

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Transoral EGD	Risk with TNE				
Life threatening, severe, or medically significant consequences	0 per 1,000	Not estimable due to zero count in comparison group	not estimable	59 (1 RCT)	⊕○○○ VERY LOW ^{a,b,c}	
Incidence of suspected BE (RCT)	59 per 1,000	40 per 1,000 (4 to 417)	RR 0.68 (0.07 to 7.09)	59 (1 RCT)	⊕○○○ VERY LOW ^{a,b,c}	
Incidence of suspected BE(grade 2 and 3) (obs)	82 per 1,000	51 per 1,000 (34 to 77)	RR 0.62 (0.41 to 0.94)	1326 (1 observational study)	⊕○○○ VERY LOW ^{c,d,e}	
Anxiety prior to screening Scale from: 0 to 10		The mean anxiety prior to screening in the intervention group was 0.6 lower (2.13 lower to 0.93 higher)	-	59 (1 RCT)	⊕○○○ VERY LOW ^{a,b,c,f}	
Anxiety during insertion Scale from: 0 to 10		The mean anxiety during insertion in the intervention group was 0.3 lower (1.83 lower to 1.23 higher)	-	59 (1 RCT)	⊕○○○ VERY LOW ^{a,b,c,f}	
Anxiety during the procedure Scale from: 0 to 10		The mean anxiety during the procedure in the intervention group was 0 (1.68 lower to 1.68 higher)	-	59 (1 RCT)	⊕○○○ VERY LOW ^{a,b,c,f}	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; EGD: Esophagogastroduodenoscopy; RR: Risk ratio; TNE: Transnasal esophagoscopy

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

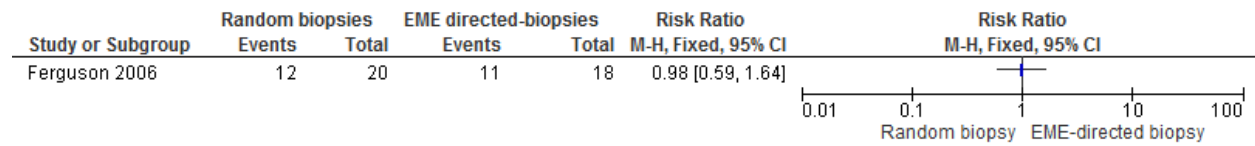
Evidence Set 7: EGD with random biopsy versus Enhanced magnification-directed endoscopy (EME) biopsies

Evidence Set 7 - Results table

Author Year Study design	Outcome(s) description	Results		ROB assessment	Notes
		EGD with random biopsy	EME directed endoscopy biopsies		
IMPORTANT OUTCOME 4: Incidence of EAC (by stage), BE, and low- and high-grade dysplasia					
Confirmed BE (histologically)					
Ferguson 2006 ⁵⁹ RCT	Specialized intestinal metaplasia (SIM) among those with endoscopically apparent BE, which was defined as any variation of >5mm between the lowest and highest point of the squamocolumnar junction from the gastroesophageal junction using only the findings on standard (or non-magnified) endoscopy. The first result includes only those with SIM patterns III/IV, while the second results include all SIM pattern types.	12/20 (60%)	11/18 (61%)	Moderate	EME tissue was classified using four pattern types [I round pits, II recticular, III villous, and IV ridged].
		p-value: 1.00			
		12/20 (60%)	19/36 (53%)		
		p-value: 0.78			

Evidence Set 7 - Forest Plots

Forest Plot 7.1: Incidence of confirmed BE (specialized intestinal metaplasia pattern III and IV)



Forest Plot 7.2: Incidence of confirmed BE (specialized intestinal metaplasia all patterns)



Evidence Set 7 - GRADE evidence profile table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EGD with random biopsy	EME-directed endoscopy biopsies	Relative (95% CI)	Absolute (95% CI)		
Incidence of confirmed BE (SIM pattern types III/IV)												
1	randomized trials	serious ^a	not serious	serious ^b	serious ^c	none	12/20 (60.0%)	11/18 (61.1%)	RR 0.98 (0.59 to 1.64)	12 fewer per 1,000 (from 251 fewer to 391 more)	⊕○○○ VERY LOW	IMPORTANT
Incidence of confirmed BE (all SIM pattern types)												
1	randomized trials	serious ^a	not serious	serious ^b	serious ^c	none	12/20 (60.0%)	19/36 (52.8%)	RR 1.14 (0.71 to 1.82)	74 more per 1,000 (from 153 fewer to 433 more)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

a. No details on allocation concealment, no protocol found, and no details on funding.

b. GERD score determined with a validated questionnaire (Ofman J, et al. Identifying patients with gastroesophageal reflux disease: Validation of a practical screening tool. Dig Dis Sci 2002; 47:1863-9), with no other information provided

c. Too few participants in the study

Evidence Set 7 - Summary of Findings Table

EGD with random biopsy compared to EME-directed endoscopy biopsies for screening for EAC and precancerous conditions (BE and dysplasia)

Setting: Outpatient clinic

Intervention: EGD random biopsy

Comparison: EME-directed endoscopy biopsies

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with EME-directed endoscopy biopsies	Risk with EGD with random biopsy				
Incidence of confirmed BE (SIM pattern types III/IV)	611 per 1,000	599 per 1,000 (361 to 1,000)	RR 0.98 (0.59 to 1.64)	38 (1 RCT)	⊕○○○ VERY LOW ^{a+b+c}	
Incidence of confirmed BE (all SIM pattern types)	528 per 1,000	602 per 1,000 (375 to 961)	RR 1.14 (0.71 to 1.82)	56 (1 RCT)	⊕○○○ VERY LOW ^{a+b+c}	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. No details on allocation concealment, no protocol found, and no details on funding.

b. GERD score determined with a validated questionnaire (Ofman J, et al. Identifying patients with gastroesophageal reflux disease: Validation of a practical screening tool. Dig Dis Sci 2002; 47:1863-9), with no other information provided

c. Too few participants in the study

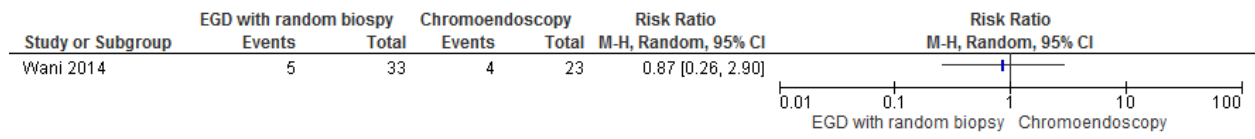
Evidence Set 8: EGD with random biopsy versus chromoendoscopy

Evidence Set 8 - Results table

Author Year Study design	Outcome(s) description	Results		ROB assessment	Notes
		EGD with random biopsy	Chromo- endoscopy		
IMPORTANT OUTCOME 4: Incidence of EAC (by stage), BE, and low- and high-grade dysplasia					
Confirmed BE (histologically)					
Wani 2014 ⁶¹ RCT	Patients were suspected of having BE if they had columnar lined epithelium that was reddish in color and velvety texture which could be distinguished easily from normal pale and glossy esophageal squamous epithelium. Specialized intestinal metaplasia was diagnosed if the intestinal goblet cells were present.	5/33 (15.2%)	4/23 (17.4%)	Moderate	All patients (n=378) received EGD. Those with columnar lined epithelium were randomized to different biopsy methods (n=56).
		p=0.55			

Evidence Set 8 - Forest Plot

Forest Plot 8.1: Incidence of confirmed BE



Evidence Set 8 - GRADE evidence profile table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EGD with random biopsy	chromoendoscopy (methylene blue-directed biopsy)	Relative (95% CI)	Absolute (95% CI)		
Incidence of confirmed BE												
1 ^a	randomised trials	serious ^b	not serious	serious ^c	serious ^d	none	5/33 (15.2%)	4/23 (17.4%)	RR 0.87 (0.26 to 2.90)	23 fewer per 1,000 (from 129 fewer to 330 more)	⊕○○○ VERY LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

a. All participants were given EGD. If BE was suspected, patients were randomized to random biopsy or chromoendoscopy.

b. Method of allocation, and allocation concealment was not discussed. No protocol was found, there is no mention on how the study was funded, and there was no description of the baseline characteristics between the two study groups.

c. GERD was described as having "characteristic symptoms of GERD".

d. Too few participants included.


Evidence Set 8 - Summary of Findings Table

EGD with random biopsy compared to chromoendoscopy (methylene blue-directed biopsy) for screening for EAC and precancerous conditions (BE and dysplasia)

Setting: Not reported

Intervention: EGD with random biopsy

Comparison: Chromoendoscopy (methylene blue-directed biopsy)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chromoendoscopy (methylene blue-directed biopsy)	Risk with EGD with random biopsy				
Incidence of confirmed BE	174 per 1,000	151 per 1,000 (45 to 504)	RR 0.87 (0.26 to 2.90)	56 (1 RCT) ^a	 VERY LOW ^{b,c,d}	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. All participants were given EGD. If BE was suspected, patients were randomized to random biopsy or chromoendoscopy.

b. Method of allocation, and allocation concealment was not discussed. No protocol was found, there is no mention on how the study was funded, and there was no description of the baseline characteristics between the two study groups.

c. GERD was described as having "characteristics symptoms of GERD".

d. Too few participants included.

Appendices

Appendix 1 KQ1 PRISMA checklist

Appendix 2 KQ1 PICOS table

Appendix 3 KQ1 Search strategy

Appendix 4 KQ1 Screening forms

Appendix 5 Cochrane risk of bias tool

Appendix 6 NOS risk of bias tool

Appendix 7 KQ1 List of excluded studies at full text

Appendix 8 KQ1 List of potentially relevant ongoing studies

Appendix 9 KQ2 PRISMA checklist

Appendix 10 KQ2 PICOS table

Appendix 11 KQ2 Search strategy

Appendix 12 KQ2 Screening forms

Appendix 13 KQ2 List of excluded studies at full text

Appendix 14 KQ2 List of potentially relevant ongoing studies

Appendix 1. KQ1 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix 2: KQ1 PICOS table

	Inclusion	Exclusion
Population	<p>Adults (≥18 years old) with chronic GERD with or without other risk factors† for EAC</p> <p>Studies addressing both adults and children, if data provided for adults are reported separately.</p> <p>Chronic GERD, as defined by study authors</p> <p>† Risk factors will be as deemed so by included studies</p>	<p>Experiencing alarm symptoms for EAC: dysphagia, recurrent vomiting, anorexia, weight loss, gastrointestinal bleeding or other symptoms identified by authors as 'alarm'</p> <p>Diagnosed with other gastro-esophageal conditions (e.g., gastric cancer, esophageal atresia, other life threatening esophageal conditions) or pre-existing disease (BE, dysplasia, or EAC)</p>
Intervention and comparator – KQ1a	<ul style="list-style-type: none"> - Screening versus no screening - One screening modality versus another screening modality <p>All screening modalities will be included, such as esophagogastroduodenoscopy (EGD)*†, EGD† plus adjunct techniques‡, transnasal endoscopy, cytologic examination</p> <p>*Also known as panendoscopy and upper GI endoscopy</p> <p>† with or without biopsy protocol</p> <p>‡For example, chromendoscopy and narrow-band imaging</p> <p>Screening for BE, dysplasia, or EAC</p>	<p>Any follow-up diagnostic tests, such 24 hour esophageal pH test or any test for staging purposes, such as CT and MRI</p>
Intervention and comparator – KQ1b	<ul style="list-style-type: none"> - One screening modality versus. another screening modality - One interval of screening versus. another interval of screening - Timepoint at which to initiate screening versus. another timepoint - Timepoint at which to cease screening versus. another timepoint 	
Outcomes/Outcome domains	<p>Critical for decision-making</p> <ol style="list-style-type: none"> 1. Mortality - all-cause and EAC-related (1, 5 and 10 year or as available)†* 2. Survival (1, 5 and 10 year or as available)† 3. Life threatening, severe, or medically significant consequences (such as requiring hospitalization or prolongation of hospitalization; disabling (limiting self-care or activities of daily living) <p>Important for decision-making</p>	

	Inclusion	Exclusion
	<p>4. Incidence of EAC (by stage), BE, low- and high-grade dysplasia*</p> <p>5. Quality of life (validated scales only; e.g. SF-36, WHOQOL)</p> <p>6. Psychological effects (e.g., anxiety and depression)</p> <p>7. Major or minor medical procedures*</p> <p>8. Overdiagnosis†</p> <p>†from the time of allocation to screening or control arm</p> <p>*These outcomes will be used to judge the extent of overdiagnosis, which is defined as the diagnosis of disease which would never have become clinically apparent in a person's lifetime (i.e., causing neither symptoms nor death).</p> <p>‡As judged by the study author or will be judged by the CTFPHC working group using information provided by authors, where available.</p>	
Timing	No limits	
Settings	Primary care	
Study designs	<p>Randomized controlled trials (RCTs), including cluster RCTs.</p> <p>If no or few randomized controlled trials (i.e. less than 5 trials) are available: Non-randomized controlled clinical trials, controlled before-after, interrupted times series, cohort studies, case-control studies, limiting to higher levels of evidence depending on the nature and volume of specific study designs.</p> <p>If no or few randomized controlled trials are available for the overdiagnosis outcome, ecological and cohort studies will be considered for all outcomes used for the judgment of overdiagnosis.</p>	Cross-sectional studies, case series, case reports, and other publication types (editorials, commentaries, notes, letter, opinions).
Language	No language restrictions in the search, however only English and French articles will be included at full-text.	
Databases	Medline, Embase, Cochrane	

Appendix 3. KQ1 Search strategy

Date Ran: 2018 Oct 29

Database: Embase Classic+Embase <1947 to 2018 October 26>, Ovid MEDLINE(R) ALL <1946 to October 25, 2018>

Search Strategy:

-
- 1 exp Gastroesophageal Reflux/ (84749)
 - 2 ((esophageal or gastric* or gastro-esophageal or gastro-oesophageal or gastroesophageal or gastrooesophageal or supraesophageal or supra-esophageal or supraoesophageal or supra-oesophageal) adj2 reflux*).tw,kw. (60380)
 - 3 GERD.tw,kw. (23254)
 - 4 GORD.tw,kw. (2189)
 - 5 SEGR.tw,kw. (14)
 - 6 (gastric adj2 regurgitat*).tw,kw. (524)
 - 7 or/1-6 (101149)
 - 8 Esophageal Neoplasms/ (54194)
 - 9 exp Esophagus/ and exp Neoplasms/ (37262)
 - 10 ((esophag* or oesophag* or pharynx-esophag*) adj3 (neoplas* or cancer* or tumour* or tumor* or carcinoma* or malignan* or metasta* or oncolog* or adenoma* or adenocarcinoma* or adeno-carcinoma* or carcinosarcoma* or carcino-sarcoma*)).tw,kw. (115398)
 - 11 Barrett Esophagus/ (23026)
 - 12 (Barrett* adj1 (esophag* or oesophag* or epitheli* or metaplasia* or syndrome?)).tw,kw. (22711)
 - 13 (dysplasia* or dysplastic* or precancer* or pre-cancer* or premalignan* or pre-malignan*).tw,kw. (237615)
 - 14 or/8-13 (381903)
 - 15 7 and 14 [GERD AND ESOPHAGEAL CANCER] (14039)
 - 16 exp Infant/ not (exp Adult/ and exp Infant/) (1653036)
 - 17 exp Child/ not (exp Adult/ and exp Child/) (3188154)
 - 18 15 not (16 or 17) [CHILD-ONLY REMOVED] (13587)
 - 19 exp Animals/ not (exp Animals/ and Humans/) (16928885)
 - 20 18 not 19 [ANIMAL-ONLY REMOVED] (9917)
 - 21 (comment or editorial or interview or news).pt. (1857143)
 - 22 (letter not (letter and randomized controlled trial)).pt. (2039050)
 - 23 20 not (21 or 22) [OPINION PIECES REMOVED] (9328)
 - 24 limit 23 to systematic reviews [Limit not valid in Embase; records were retained] (5438)
 - 25 meta analysis.pt. (93528)
 - 26 exp meta-analysis as topic/ (55716)
 - 27 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (320935)
 - 28 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (380695)
 - 29 exp Technology assessment, biomedical/ (23572)
 - 30 (cochrane or health technology assessment or evidence report).jw. (38344)
 - 31 or/25-30 (663092)

32 23 and 31 (237)
 33 24 or 32 [REVIEWS] (5478)
 34 exp Guidelines as Topic/ (618496)
 35 exp Clinical Protocols/ (244747)
 36 Guideline.pt. (16000)
 37 Practice Guideline.pt. (24370)
 38 standards.fs. (661949)
 39 Consensus Development Conference.pt. (10837)
 40 (guidance* or guideline* or standards or recommendation*).ti. (311034)
 41 (expert consensus or consensus statement* or consensus conference* or practice parameter* or
 position statement* or policy statement* or CPG or CPGs).tw. (111573)
 42 or/34-41 (1639102)
 43 23 and 42 [GUIDELINES] (344)
 44 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (558557)
 45 clinical trials as topic.sh. (185080)
 46 (randomi#ed or randomly or RCT\$1 or placebo*).tw. (2078317)
 47 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (382260)
 48 trial.ti. (451524)
 49 or/44-48 (2552566)
 50 23 and 49 [RCTS] (446)
 51 controlled clinical trial.pt. (92722)
 52 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (564652)
 53 (control* adj2 trial*).tw. (536268)
 54 Non-Randomized Controlled Trials as Topic/ (10101)
 55 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (110148)
 56 (nRCT or nRCTs or non-RCT\$1).tw. (1682)
 57 Controlled Before-After Studies/ (212209)
 58 (control* adj3 ("before and after" or "before after")).tw. (8951)
 59 Interrupted Time Series Analysis/ (204342)
 60 (time series adj3 interrupt*).tw. (5071)
 61 (pre- adj3 post-).tw. (194013)
 62 (pretest adj3 posttest).tw. (10024)
 63 Historically Controlled Study/ (222590)
 64 (control* adj2 stud\$3).tw. (488554)
 65 Control Groups/ (123900)
 66 (control\$ adj2 group\$1).tw. (1094939)
 67 trial.ti. (451524)
 68 or/51-67 (3041588)
 69 23 and 68 [NON-RCTS] (859)
 70 exp Cohort Studies/ (2201726)
 71 cohort\$1.tw. (1281888)
 72 Retrospective Studies/ (1057885)
 73 (longitudinal or prospective or retrospective).tw. (2746922)
 74 ((followup or follow-up) adj (study or studies)).tw. (111610)
 75 Observational study.pt. (53767)
 76 (observation\$2 adj (study or studies)).tw. (221881)
 77 ((population or population-based) adj (study or studies or analys#s)).tw. (36252)
 78 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (245)

79 Comparative Study.pt. (1812404)
 80 ((comparative or comparison) adj (study or studies)).tw. (234286)
 81 exp Case-Control Studies/ (1099012)
 82 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (214189)
 83 Cross-Sectional Studies/ (423299)
 84 ((cross-sectional or frequency or prevalence) adj (analys#s or study or studies or survey\$1)).tw.
 (426217)
 85 or/70-84 (7259652)
 86 23 and 85 [OBSERVATIONAL STUDIES] (2373)
 87 33 or 43 or 50 or 69 or 86 [ALL STUDY DESIGNS] (7084)
 88 87 use medall [MEDLINE RECORDS] (1803)
 89 gastroesophageal reflux/ (76189)
 90 ((esophageal or gastric* or gastro-esophageal or gastro-oesophageal or gastroesophageal or
 gastrooesophageal or supraesophageal or supra-esophageal or supraoesophageal or supra-
 oesophageal) adj2 reflux*).tw,kw. (60380)
 91 GERD.tw,kw. (23254)
 92 GORD.tw,kw. (2189)
 93 SEGR.tw,kw. (14)
 94 (gastric adj2 regurgitat*).tw,kw. (524)
 95 or/89-94 (94213)
 96 exp esophagus tumor/ (77710)
 97 exp esophagus/ and exp neoplasm/ (37262)
 98 ((esophag* or oesophag* or pharynx-esophag*) adj3 (neoplas* or cancer* or tumour* or tumor*
 or carcinoma* or malignan* or metasta* or oncolog* or adenoma* or adenocarcinoma* or adeno-
 carcinoma* or carcinosarcoma* or carcino-sarcoma*)).tw,kw. (115398)
 99 Barrett Esophagus/ (23026)
 100 (Barrett* adj1 (esophag* or oesophag* or epitheli* or metaplasi* or syndrome?)).tw,kw. (22711)
 101 (dysplasia* or dysplastic* or precancer* or pre-cancer* or premalignan* or pre-malignan*).tw,kw.
 (237615)
 102 or/96-101 (388236)
 103 95 and 102 [GERD AND ESOPHAGEAL CANCER] (13204)
 104 exp juvenile/ not (exp juvenile/ and exp adult/) (2337309)
 105 exp Infant/ not (exp Adult/ and exp Infant/) (1653036)
 106 exp Child/ not (exp Adult/ and exp Child/) (3188154)
 107 or/104-106 (3908908)
 108 103 not 107 [CHILD, 17 AND UNDER, REMOVED] (12752)
 109 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or
 exp vertebrate/ (47785712)
 110 exp human/ or exp human experimentation/ or exp human experiment/ (37610583)
 111 109 not 110 (10176834)
 112 108 not 111 [ANIMAL-ONLY REMOVED] (12412)
 113 editorial.pt. (1053946)
 114 letter.pt. not (letter.pt. and randomized controlled trial/) (2034134)
 115 112 not (113 or 114) [OPINION PIECES REMOVED] (11719)
 116 meta-analysis/ (244188)
 117 "systematic review"/ (181694)
 118 "meta analysis (topic)"/ (38725)

119 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (320935)
 120 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (380695)
 121 biomedical technology assessment/ (22465)
 122 (cochrane or health technology assessment or evidence report).jw. (38344)
 123 or/116-122 (719814)
 124 115 and 123 [REVIEWS] (466)
 125 exp practice guideline/ (496379)
 126 (guidance* or guideline* or standards or recommendation*).ti. (311034)
 127 (expert consensus or consensus statement* or consensus conference* or practice parameter* or position statement* or policy statement* or CPG or CPGs).tw. (111573)
 128 or/125-127 (807229)
 129 115 and 128 [GUIDELINES] (406)
 130 randomized controlled trial/ or controlled clinical trial/ (1261895)
 131 exp "clinical trial (topic)"/ (278077)
 132 (randomi#ed or randomly or RCT\$1 or placebo*).tw. (2078317)
 133 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (382260)
 134 trial.ti. (451524)
 135 or/130-134 (2842728)
 136 115 and 135 [RCTS] (792)
 137 controlled clinical trial/ (551272)
 138 "controlled clinical trial (topic)"/ (9690)
 139 (control* adj2 trial*).tw. (536268)
 140 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (110148)
 141 (nRCT or nRCTs or non-RCT\$1).tw. (1682)
 142 (control* adj3 ("before and after" or "before after")).tw. (8951)
 143 time series analysis/ (21591)
 144 (time series adj3 interrupt*).tw. (5071)
 145 pretest posttest control group design/ (353)
 146 (pre- adj3 post-).tw. (194013)
 147 (pretest adj3 posttest).tw. (10024)
 148 controlled study/ (6234502)
 149 (control* adj2 stud\$3).tw. (488554)
 150 control group/ (123900)
 151 (control* adj2 group\$1).tw. (1094939)
 152 trial.ti. (451524)
 153 or/137-152 (8064899)
 154 115 and 153 [NON-RCTS] (2112)
 155 cohort analysis/ (640633)
 156 cohort\$1.tw. (1281888)
 157 retrospective study/ (1418098)
 158 longitudinal study/ (236664)
 159 prospective study/ (965640)
 160 (longitudinal or prospective or retrospective).tw. (2746922)
 161 follow up/ (1364204)

162 ((followup or follow-up) adj (study or studies)).tw. (111610)
 163 observational study/ (205270)
 164 (observation\$2 adj (study or studies)).tw. (221881)
 165 population research/ (95192)
 166 ((population or population-based) adj (study or studies or analys#s)).tw. (36252)
 167 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (245)
 168 exp comparative study/ (3125774)
 169 ((comparative or comparison) adj (study or studies)).tw. (234286)
 170 exp case control study/ (1099012)
 171 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (214189)
 172 cross-sectional study/ (550186)
 173 ((cross-sectional or frequency or prevalence) adj (analys#s or study or studies or survey\$1)).tw.
 (426217)
 174 or/155-173 (9122540)
 175 115 and 174 [OBSERVATIONAL STUDIES] (3847)
 176 124 or 129 or 136 or 154 or 175 [ALL STUDY DESIGNS] (5431)
 177 176 use emczd [EMBASE RECORDS] (3828)
 178 88 or 177 [BOTH DATABASES] (5631)
 179 (2016 11* or 2016 12* or 2017* or 2018*).dt. (2466286)
 180 88 and 179 [MEDLINE UPDATE RECORDS] (140)
 181 (201611* or 201612* or 2017* or 2018*).dc. (3493794)
 182 177 and 181 [EMBASE UPDATE RECORDS] (545)
 183 180 or 182 [BOTH DATABASES - UPDATE PERIOD] (685)
 184 remove duplicates from 183 (573)
 185 184 use medall [UNIQUE MEDLINE UPDATE RECORDS] (140)
 186 184 use emczd [UNIQUE EMBASE UPDATE RECORDS] (433)

Cochrane

<https://www.cochranelibrary.com/advanced-search/search-manager?search=2220030>

Search Name: CTFPHC - Esophageal Cancer - GERD - No Screening Filters - Update

Date Run: 30/10/2018 03:16:43

Comment: CTFPHC (OHRI) - 2018 Oct 29 - Post-PRESS, Post-CTFPHC - updated from 2016 Nov 22

ID	Search	Hits
#1	MeSH descriptor: ["Gastroesophageal Reflux"] explode all trees	1740
#2	((esophageal or gastric* or (gastro next esophageal) or (gastro next oesophageal) or supraesophageal or (supra next esophageal) or supraoesophageal or (supra next oesophageal)) near/2 reflux*):ti,ab,kw	1064
#3	GERD:ti,ab,kw	1185
#4	GORD:ti,ab,kw	148
#5	SEGR:ti,ab,kw	1
#6	(gastric near/2 regurgitat*):ti,ab,kw	67
#7	{or #1-#6}	2862
#8	MeSH descriptor: ["Esophageal Neoplasms"] explode all trees	1308
#9	MeSH descriptor: [Esophagus] explode all trees	267

- #10 ((esophag* or oesophag* or (pharynx next esophag*)) near/3 (neoplas* or cancer* or tumour* or tumor* or carcinoma* or malignan* or metastas* or oncolog* or adenoma* or adenocarcinoma* or (adeno next carcinoma*) or carcinosarcoma* or (carcino next sarcoma*))) :ti,ab,kw 3387
- #11 MeSH descriptor: ["Barrett Esophagus"] explode all trees 207
- #12 (Barrett* near/1 (esophag* or oesophag* or epitheli* or metaplasia* or syndrome*)) :ti,ab,kw 471
- #13 (dysplasia* or dysplastic* or precancer* or (pre next cancer*) or premalignan* or (pre next malignan*)) :ti,ab,kw 3694
- #14 {or #8-#13} 7045
- #15 #7 and #14 133
- #16 MeSH descriptor: [Infant] explode all trees 14928
- #17 MeSH descriptor: [Child] explode all trees 1356
- #18 #15 not (#16 or #17) with Cochrane Library publication date Between Oct 2016 and Oct 2018 35

DSR – 1

CENTRAL - 34

Appendix 4: KQ1 Screening forms

Title and Abstract screening form

1. Does this article discuss screening adults (without other gastroesophageal condition [e.g. gastric cancer] or pre-existing disease [e.g. BE*, dysplasia or EAC]) for esophageal adenocarcinoma, Barrett's Esophagus, and/or dysplasia? (exclude case studies)

* BE may also be referred to as intestinal metaplasia, specialized intestinal metaplasia, gastric metaplasia, columnar-lined esophagus

☐ Yes/unclear

☐ No

2. Comment:

Full-text screening form

1. Full text not available:

☐ Yes

2. Language:

☐ English/French

☐ Other

3. What is the study design?

4. Does this study evaluate a screening modality/technique of interest?

(EGD, EGD plus biopsy with/without adjunct techniques, capsule endoscopy, transnasal/transoral ultrathin endoscopy, barium swallow/barium radiology, cytologic examination (e.g., brush, balloon, sponge, liquid, flow cytometry), endoscopic ultrasonography (EUS), computed tomography (CT) scan, laser-induced fluorescence spectroscopy)

☐ Yes

☐ No

☐ Unclear

☐ Molecular (e.g., cells, genes) and other biomarkers (e.g., blood, stool, urine)

5. Does this study evaluate a comparator of interest?

☐ Yes (e.g., no screening, different test, different number of tests, different intervals)

☐ No (not of interest)

- ☐ No comparator (e.g., all participants received the same test/number/interval)
- ☐ Unclear

6. Do the participants have chronic GERD?

(defined as symptoms for ≥ 12 months, with no specific frequency, and/or proton pump inhibitor (PPI) (or other pharmacotherapy) use for GERD for ≥ 12 months)

- ☐ Yes (meets our def'n)
- ☐ Yes (does not meet our def'n)
- ☐ No
- ☐ Unclear

7. How does the study define chronic GERD?

Copy and paste from article. This will help us when we contact authors for those that are unclear. It will also help us know why we said yes/no/unclear while we do conflict resolution.

8. Do participants have alarm symptoms of EAC or are diagnosed with other gastroesophageal conditions or pre-existing disease?

Alarm symptoms: dysphagia, recurrent vomiting, anorexia, weight loss, gastrointestinal bleeding or other symptoms identified by authors as 'alarm'

Other gastroesophageal conditions: for example gastric cancer, other life threatening esophageal conditions)

Pre-existing disease: Barrett's esophagus, dysplasia, or esophageal cancer

- ☐ Yes
- ☐ No
- ☐ Unclear
- ☐ Case-control (case have disease, controls do not)

9. How old are the participants?

- ☐ Adults (18 yrs +)
- ☐ Children (<18 yrs)
- ☐ Adults and children (data separated)
- ☐ Adults and children (data not separated)
- ☐ Unclear

10. Comments:

Appendix 5: Cochrane risk of bias tool

1. **Selection bias domain:** Random sequence generation

- ☐ Low risk
- ☐ Unclear risk
- ☐ High risk

Support for judgement:

2. **Selection bias domain:** Allocation concealment

- ☐ Low risk
- ☐ Unclear risk
- ☐ High risk

Support for judgement:

3. **Performance bias domain:** Blinding of participants and personnel (for each outcome)

- ☐ Low risk
- ☐ Unclear risk
- ☐ High risk

Support for judgement:

4. **Detection bias domain:** Blinding of outcome assessment (for each outcome)

- ☐ Low risk
- ☐ Unclear risk
- ☐ High risk

Support for judgement:

5. **Attrition bias domain:** Incomplete outcome data (for each outcome)

- ☐ Low risk
- ☐ Unclear risk
- ☐ High risk

Support for judgement:

6. **Reporting bias domain:** Selective reporting

- ☐ Low risk
- ☐ Unclear risk
- ☐ High risk

Support for judgement:

7. **Other sources of bias**

- ☐ Low risk
- ☐ Unclear risk
- ☐ High risk

Support for judgement:

Appendix 6: NOS risk of bias tool

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

- a) truly representative of the average _____ (describe) in the community ★
- b) somewhat representative of the average _____ in the community ★
- c) selected group of users eg nurses, volunteers
- d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

- a) drawn from the same community as the exposed cohort ★
- b) drawn from a different source
- c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

- a) secure record (eg surgical records) ★
- b) structured interview ★
- c) written self-report
- d) no description

4) Demonstration that outcome of interest was not present at start of study

- a) yes ★
- b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

- a) study controls for _____ (select the most important factor) ★
- b) study controls for any additional factor ★ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

- a) independent blind assessment ★
- b) record linkage ★
- c) self report
- d) no description

2) Was follow-up long enough for outcomes to occur

- a) yes (select an adequate follow up period for outcome of interest) ★
- b) no

3) Adequacy of follow up of cohorts

- a) complete follow up - all subjects accounted for ★
- b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ★
- c) follow up rate < ____ % (select an adequate %) and no description of those lost
- d) no statement

Appendix 7: KQ1 List of excluded studies at full text

Full text not available (n=95)

1. Pace, F., Manes, G., Conio, M., and Bianchi, Porro G. Pretreatment edoscopy - Pro & contra: Endoscopy is needed before treatment in all patients with gastroesophageal reflux disease. *Endoscopy* 2006; 38 (3): 271-275.
2. Beck, I. T., Champion, M. C., Lemire, S., Thomson, A. B., Anvari, M., Armstrong, D., Bailey, R. J., Barkun, A. N., Boivin, M., Bursey, R. F., Chaun, H., Chiba, N., Cockeram, A. W., Connon, J. J., Da Costa, L. R., Faloon, T. R., Fedorak, R. N., Gillies, R. R., Goeree, R., Hunt, R. H., Inculet, R. I., Klein, A., Leddin, D. J., Love, J. R., and Worobetz, L. J. The Second Canadian Consensus Conference on the Management of Patients with Gastroesophageal Reflux Disease. *Canadian journal of gastroenterology* 1997; 11 Suppl B: 7B-20B.
3. Lam, C., Liu, W. F., Bel, R. D., Chan, K., Miller, L., Brown, M. C., Chen, Z., Cheng, D., Patel, D., Xu, W., Darling, G. E., and Liu, G. Polymorphisms of the FOXF1 and MHC locus genes in individuals undergoing esophageal acid reflux assessments. *Diseases of the Esophagus* 2017 Feb; 30(2):1-7.
4. Piche, T. Dietary intake and risk of gastroesophageal reflux disease: A cross study of volunteers. *Hepato-Gastro* 2005; 12 (3): 229-230.
5. Garrido, Serrano A., Guerrero Igea, F. J., Lepe Jimenez, J. A., and Perianes, Hernandez C. Clinical features and endoscopic progression of gastroesophageal reflux disease. *Revista Espanola de Enfermedades Digestivas* 2003; 95 (10): 712-716.
6. Dias, Moretzsohn L., Diniz De Miranda, C. H., Barbosa, A. J. A., and Gonzaga Vaz, Coelho L. The presence of serum anti-Cag A antibodies of *Helicobacter pylori* may not represent a protective factor in the severe esophageal forms of GERD. *Gastreterologia Endoscopia Digestiva* 2003; 22 (5): 175-180.
7. Tutuian, R. and Castell, D. O. Barrett's esophagus prevalence and epidemiology. *Gastrointestinal Endoscopy Clinics of North America* 2003; 13 (2): 227-232.
8. Dincer, D., Besisik, F., Sahin, E., Demir, K., Tuncer, I., Cevikbas, U., Mungan, Z., Kaymakoglu, S., Boztas, G., Ozdil, S., Cakaloglu, Y., and Okten, A. Intestinal metaplasia of the gastric cardia: A study from Turkey. *Hepato-gastroenterology* 2002; 49 (46): 1153-1156.
9. Andrews, J. Hiatus hernia: What the GP needs to know. *Medicine Today* 2002; 3 (1): 39-43.
10. Csendes, A., Smok, G., Cerda, G., Burdiles, P., Mazza, D., and Csendes, P. Prevalence of *Helicobacter pylori* infection in 190 control subjects and in 236 patients with gastroesophageal reflux, erosive esophagitis or Barrett's esophagus. *Diseases of the Esophagus* 1997; 10 (1): 38-42.
11. D'Onofrio, V., Bovero, E., and Iaquinto, G. Characterization of acid and alkaline reflux in patients with Barrett's esophagus. *Diseases of the Esophagus* 1997; 10 (1): 16-23.
12. Lunedei, V., Bazzoli, F., Pozzato, P., De Luca, L., Zagari, R. M., Fossi, S., Ricciardiello, L., Maltoni, S., and Roda, E. Endoscopic surveillance in Barrett's esophagus. *Minerva Gastroenterologica e Dietologica* 2002; 48 (2): 63-71.
13. De Backer, A. I., De Schepper, A. M., and Pelckmans, P. The value of medical imaging in uncomplicated and complicated Barrett's esophagus. *Acta Gastro-Enterologica Belgica* 2000; 63 (1): 22-28.
14. Peng, S., Cui, Y., Xiao, Y. L., Xiong, L. S., Hu, P. J., Li, C. J., and Chen, M. H. Prevalence of erosive esophagitis and Barrett's esophagus in the adult Chinese population. *Endoscopy* 2009; 41 (12): 1011-1017.
15. Elhak, N. Gad, Mostafa, M., Salah, T., and Haleem, M. Duodenogastroesophageal reflux: results of medical treatment and antireflux surgery. *Hepato-gastroenterology* 2008; 55 (81): 120-126.
16. Koslowsky, B., Jacob, H., Eliakim, R., and Adler, S. N. PillCam ESO in esophageal studies: improved diagnostic yield of 14 frames per second (fps) compared with 4 fps. *Endoscopy* 2006; 38 (1): 27-30.
17. Sharma, Prateek Barrett esophagus: will effective treatment prevent the risk of progression to esophageal adenocarcinoma? *The American journal of medicine* 2004; 117 Suppl 5A: 79S-85S.

18. Ofman, Joshua J. Decision making in gastroesophageal reflux disease. What are the critical issues? *Gastroenterology Clinics of North America* 2002; 31 (4 Suppl): S67-S76.
19. Isolauri, J., Luostarinen, M., Isolauri, E., Reinikainen, P., Viljakka, M., and Keyrilainen, O. Natural course of gastroesophageal reflux disease: 17-22 year follow-up of 60 patients. *The American journal of gastroenterology* 1997; 92 (1): 37-41.
20. Kalsbeek, H. L. and van der Wouden, A. Barrett-oesophagus with papillomatous tumour. *Archivum chirurgicum Neerlandicum* 1971; 23 (4): 287-296.
21. Waheed, T. and Hurwitz, A. L. Elective upper gastrointestinal endoscopy in an outpatient endoscopy center: Impact on patient management. *Practical Gastroenterology* 2013; 37 (4): 38-46.
22. Lisovsky, M. and Srivastava, A. Barrett esophagus: Evolving concepts in diagnosis and neoplastic progression. *Surgical Pathology Clinics* 2013; 6 (3): 475-496.
23. Smoking Is an Independent Risk Factor for Barrett Esophagus. *Clinical Advances in Hematology and Oncology* 2012; 10 (10): 10.
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Study design: Systematic review/Meta-analysis (n=13)

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Study design: Narrative review/report (n=349)

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Study design: Cross-sectional (including diagnostic test studies) (n=316)

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Study design: Case-series/case report (n=9)

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Study design: Other (e.g., editorial, commentary, notes, letters, opinions) (n=102)

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Does not evaluate a screening modality/technique of interest (n=13)

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Evaluates molecular (e.g., cells, genes) and other biomarkers (e.g., blood, stool, urine) (n=12)

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No comparator (e.g., all participants received the same test/number/interval) (n=96)

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Participants did not have chronic GERD (n=1)

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Participants had alarm symptoms of EAC or are diagnosed with other gastroesophageal conditions or pre-existing disease (n=4)

1. Sami SS, Dunagan KT, Johnson ML, Schleck CD, Shah ND, Zinsmeister AR, Wongkeesong LM, Wang KK, Katzka DA, Rangunath K, Iyer PG. A randomized comparative effectiveness trial of novel endoscopic techniques and approaches for Barrett's esophagus screening in the community. *The American journal of gastroenterology*. 2015 Jan;110(1):148.
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3. Rangunath, K., Krasner, N., Raman, V. S., Haqqani, M. T., and Cheung, W. Y. A randomized, prospective cross-over trial comparing methylene blue-directed biopsy and conventional random biopsy for detecting intestinal metaplasia and dysplasia in Barrett's esophagus. *Endoscopy* 2003; 35 (12): 998-1003.
4. Sharriff MK, Varghese S, O'Donovan M, Abdullahi Z, Liu X, Fitzgerald RC, Di Pietro M. Pilot randomized crossover study comparing the efficacy of transnasal disposable endosheath with standard endoscopy to detect Barrett's esophagus. *Endoscopy* 2016; 48:110-116.

Companion paper with no relevant results (n=1)

1. Crews NR, Johnson ML, Schleck CD, Enders FT, Wongkeesong L-M, Wang KK, Katzka DA, Iyer PG. Prevalence and Predictors of Gastroesophageal Reflux Complications in Community Subjects. *Dig Dis Sci* 2016; 61:3221-3228.

Includes adenocarcinoma of the esophagus or gastric cardia combined (n=1)

1. Kearney DJ, Crump C, Maynard C, Boyko EJ. A case-control study of endoscopy and mortality from adenocarcinoma of the esophagus or gastric cardia in persons with GERD. *Gastrointestinal Endoscopy* 2003; 57(7):823-829.

Comparison based on timing (intervals) of endoscopy (n=1)

1. van Soest EM, Dieleman JP, Sturkenboom MCJM, Siersema PD, Kuipers EJ. Gastro-oesophageal reflux, medical resource utilization and upper gastrointestinal endoscopy in patients at risk of oesophageal adenocarcinoma. *Aliment Pharmacol Ther* 2008; 28:137-143.

Evaluates prevalence of BE on repeat exam (n=1)

1. Rodriguez S, Mattek N, Lieberman D, Fennerty B, Eisen G. Barrett's Esophagus on Repeat Endoscopy: Should We Look More Than Once? *Am J Gastroenterol* 2008; 103:1892-1897.

Appendix 8: KQ1 List of potentially relevant ongoing studies

Trial Identifier	Title	Estimated Study Completion Date
NCT02883621	Comparison Between Standard Endoscopy and Cap Assisted Endoscopy for Diagnostic Yield in Esophagus	May 2017
NCT02729948	Use of a Tethered Capsule Endoscope in Screening for Barrett's Esophagus	August 2017
NCT02852161	The Accuracy and Acceptability of Magnet Assisted Capsule Endoscopy in the Diagnosis of Esophageal Pathology: a Pilot Study	October 2017
NCT03009383	A Bedside Portable Endoscopy for the Esophageal Foreign Body	December 2017
NCT01438385	Endoscopic Retrograde Cholangiopancreatography, Endoscopic Ultrasound and Interventional Endoscopy in Pancreatico-biliary, Gastrointestinal and Esophageal Disorders	December 2017
NCT02395471	Assessment of a Minimally Invasive Esophageal Cytology Collection System in Patients With Barrett's Esophagus or GERD Symptoms	June 2018
NCT02685150	The Role of Endoscopic Tri-Modal Imaging in Distinguishing Functional Dyspepsia From Reflux Disease	June 2018
NCT02445014	Pilot Study for Imaging of Barrett's Esophagus Using an Spectrally Encoded Confocal Microscopy Tethered Endoscopic Capsule	December 2018
NCT01585103	Cytosponge Protocol	September 2019
ISRCTN68382401	Barrett's ESophagus Trial 3 (BEST3): Cluster randomised controlled trial comparing the Cytosponge-TFF3 test with usual care to facilitate the diagnosis of oesophageal pre-cancer in primary care.	September 2019
ISRCTN76017289	Quality of life measures in Barrett's Oesophagus care pathways	October 2019
NCT02560623	Minimally-Invasive Detection of Barrett's Esophagus and Barrett's Esophagus Related Dysplasia/Carcinoma by a Sponge on String Device	December 2019
ISRCTN54190466	Randomised controlled trial of surveillance and no surveillance for patients with Barrett's oesophagus: BOSS (Barrett's Oesophagus Surveillance Study)	June 2022
NCT00987857	Endoscopy Every 2 Years or Only as Needed in Monitoring Patients With Barrett Esophagus	May 2022
NCT03596476	Diagnostic Yield of Post PRandial Esophageal High Resolution Impedance Manometry in Patients With Gastro-Esophageal Reflux Disease Symptoms Resistant to Proton Pump Inhibitor Therapy (PRIMER)	January 2022
NCT03596411	The Detection of Barrett's Esophagus by Gastrointestinal Endoscopy Prevents Esophageal Carcinoma in Morbid Obese After Sleeve Gastrectomy (Refleeve)	November 2023
NCT01688908	Efficacy of Endoscopy Screening on Esophageal Cancer in a High Risk Region of Rural China: a Randomized Controlled Trial	December 2027
NCT00903136	Tethered Capsule Endoscope in Screening Participants for Barrett Esophagus	Unknown
NCT00341523	Early Detection of Esophageal Cancer	Unknown

Appendix 9. KQ2 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix 10: KQ2 PICOS table

	Inclusion	Exclusion
Population	<p>Adults (≥18 years old) with chronic GERD with or without other risk factors† for EAC who have been offered, received, or allocated to receive screening, depending on the design of the study</p> <p>Studies addressing both adults and children, if data provided for adults are reported separately</p> <p>† Risk factors will be as deemed so by included studies.</p>	<p>Experiencing alarm symptoms for EAC: dysphagia, recurrent vomiting, anorexia, weight loss, gastrointestinal bleeding or other symptoms identified by authors as ‘alarm’</p> <p>Diagnosed with other gastro-esophageal conditions (e.g., gastric cancer, esophageal atresia, other life threatening esophageal conditions) or pre-existing disease (BE, dysplasia, or EAC)</p>
Interventions	Screening for EAC and other precancerous lesions with any screening modality	Any follow-up diagnostic tests, such as 24 hour esophageal pH test or any test for staging purposes, such as CT and MRI
Comparators	<p>Depending on study design, comparators may be:</p> <ul style="list-style-type: none"> - No screening* - Different screening modality - Different screening intervals - Different lengths/duration of screening - Offered screening but did not receive screening - No comparison <p>*Although we will consider comparative studies that include a no screening arm, we understand that the outcomes of interest do not apply to people who do not receive or have not been offered screening. For such studies, we will only consider data for those who receive or are offered screening.</p>	
Outcomes	<ul style="list-style-type: none"> - How patients weigh the benefits and harms of screening (e.g., ranking/rating of benefits and harms outcomes) - Willingness to be screened - Uptake of screening - Factors considered in decision to be screened: what components/outcomes of screening do patients place more value on when deciding whether to be screened or not (e.g. potential complications resulting from screening) - Intrusiveness of the screening modality 	

	Inclusion	Exclusion
Timing	No limits	
Settings	Primary care or other settings generalizable to primary care	
Study designs	<p>Randomized controlled trials</p> <p>If insufficient data exists: Controlled clinical trials, controlled before-after, case-controls, cohort, interrupted time series (ITS), and cross-sectional (e.g., surveys)</p> <p>If insufficient data exists for the above: Qualitative studies and mixed-methods studies</p>	Commentaries, opinion, editorials, and reviews
Language	No language restrictions in the search. English and French articles will be included at full-text.	
Databases	Medline, Embase, CINAHL, Cochrane	

Appendix 11. KQ2 Search strategy

Database: Embase Classic+Embase <1947 to 2018 October 26>, Ovid MEDLINE(R) ALL <1946 to October 25, 2018>

Search Strategy:

-
- 1 exp Gastroesophageal Reflux/ (84749)
 - 2 ((esophageal or gastric* or gastro-esophageal or gastro-oesophageal or gastroesophageal or gastrooesophageal or supraesophageal or supra-esophageal or supraoesophageal or supra-oesophageal) adj2 reflux*).tw,kw. (60380)
 - 3 GERD.tw,kw. (23254)
 - 4 GORD.tw,kw. (2189)
 - 5 SEGR.tw,kw. (14)
 - 6 (gastric adj2 regurgitat*).tw,kw. (524)
 - 7 or/1-6 [GERD] (101149)
 - 8 Esophageal Neoplasms/ (54194)
 - 9 exp Esophagus/ and exp Neoplasms/ (37262)
 - 10 ((esophag* or oesophag* or pharynx-esophag*) adj3 (neoplas* or cancer* or tumour* or tumor* or carcinoma* or malignan* or metasta* or oncolog* or adenoma* or adenocarcinoma* or adeno-carcinoma* or carcinosarcoma* or carcino-sarcoma*)).tw,kw. (115398)
 - 11 Barrett Esophagus/ (23026)
 - 12 (Barrett* adj1 (esophag* or oesophag* or epitheli* or metaplasia* or syndrome?)).tw,kw. (22711)
 - 13 (dysplasia* or dysplastic* or precancer* or pre-cancer* or premalignan* or pre-malignan*).tw,kw. (237615)
 - 14 or/8-13 [ESOPHAGEAL CANCER] (381903)
 - 15 7 and 14 [GERD AND ESOPHAGEAL CANCER] (14039)
 - 16 exp Infant/ not (exp Adult/ and exp Infant/) (1653036)
 - 17 exp Child/ not (exp Adult/ and exp Child/) (3188154)
 - 18 15 not (16 or 17) [CHILD-ONLY REMOVED] (13587)
 - 19 exp Animals/ not (exp Animals/ and Humans/) (16928885)
 - 20 18 not 19 [ANIMAL-ONLY REMOVED] (9917)
 - 21 (comment or editorial or news).pt. (1829540)
 - 22 (letter not (letter and randomized controlled trial)).pt. (2039050)
 - 23 20 not (21 or 22) [OPINION PIECES REMOVED] (9328)
 - 24 exp Gastroesophageal Reflux/px (414)
 - 25 Esophageal Neoplasms/px (212)
 - 26 Barrett Esophagus/px (30)
 - 27 Mass Screening/px (2080)
 - 28 Early Detection of Cancer/px (915)
 - 29 Diagnostic Tests, Routine/px (87)
 - 30 Endoscopy/px (71)
 - 31 Endoscopy, Gastrointestinal/px (80)
 - 32 Esophagoscopy/px (17)
 - 33 Gastroscopy/px (66)
 - 34 or/24-33 [PSYCHOLOGICAL ASPECTS RE: DISEASE AND SCREENING TECHNIQUES] (3775)
 - 35 exp Adaptation, Psychological/ (175170)
 - 36 Attitude/ (105292)
 - 37 Attitude to Death/ (25924)

38 exp Attitude to Health/ (482770)
 39 Choice Behavior/ (207942)
 40 Consumer Advocacy/ (6368)
 41 *Consumer Behavior/ (10238)
 42 exp Consumer Participation/ (85545)
 43 Cooperative Behavior/ (75296)
 44 Decision Making/ (290020)
 45 Focus Groups/ (209410)
 46 Health Care Surveys/ (39038)
 47 Health Services Accessibility/ (198940)
 48 Interviews as Topic/ (183260)
 49 Life Change Events/ (46828)
 50 Narration/ (20684)
 51 Patient Acceptance of Health Care/ (93677)
 52 Patient Advocacy/ (44216)
 53 exp Patient-Centered Care/ (748675)
 54 exp Patient Education as Topic/ (186333)
 55 Patient Participation/ (47277)
 56 Patient Preference/ (21341)
 57 Patient Satisfaction/ (197656)
 58 exp Patients/px (15527)
 59 Personal Autonomy/ (28669)
 60 *"Power (Psychology)"/ (66398)
 61 Questionnaires/ (882190)
 62 Quality of Life/px (22058)
 63 exp Self Concept/ (289574)
 64 Self Efficacy/ (66626)
 65 exp Self-Help Groups/ (23022)
 66 Social Values/ (96087)
 67 ((accept* or anxiet* or anxious* or attitud* or consider* or choice? or choos* or chose? or concern* or decid* or decis* or dissatisf* or expect* or experienc* or fear* or feel* or felt or input* or opinion* or participat* or perceiv* or percepti* or perspective? or prefer* or respons* or satisf* or unsatisf* or value? or valuing or view* or worrie? or worry*) adj3 (citizen? or client? or consumer? or female? or male? or men or patient? or public or stake?holder* or user? or wom#n)).tw,kf. (1783010)
 68 (advoca* adj3 (client? or consumer? or patient?)).tw,kf. (12512)
 69 ((analys#s or valuation? or value? or valuing) adj3 (conjoint or contingent)).tw,kf. (3208)
 70 (autonom* adj3 (personal* or self)).tw,kf. (4900)
 71 (choice? adj1 (discrete or experiment*)).tw,kf. (6157)
 72 ((client? or consumer? or patient?) adj (centered or centred or focus*)).tw,kf. (52284)
 73 ((client? or consumer? or patient? or personal) adj narrati*).tw,kf. (2210)
 74 empower*.tw,kf. (49166)
 75 (focus group? or interview* or questionnaire? or survey*).tw,kf. (2689332)
 76 (freedom? or libert*).tw,kf. (100795)
 77 gambl*.tw,kf. (19958)
 78 ((health or death) adj3 (anxiet* or anxious* or attitud* or concern* or fear* or feel? or feeling* or felt or perception* or perspective? or prefer* or view* or worrie? or worry*)).tw,kf. (161154)
 79 health utilit*.tw,kf. (4626)
 80 informed choice?.tw,kf. (5052)

81 (life adj3 (event? or experience?)).tw,kf. (63360)
 82 (multi?attribute or multi?criteria).tw,kf. (2095)
 83 (preference? adj1 (elicit* or scor* or stated)).tw,kf. (3368)
 84 prospect theor*.tw,kf. (513)
 85 (self adj2 (conceiv* or concept* or percepti* or perceiv*)).tw,kf. (45854)
 86 (self adj (determin* or efficac* or help or manag* or support*)).tw,kf. (110203)
 87 (social* adj1 valu*).tw,kf. (4014)
 88 trade?off?.tw,kf. (11989)
 89 (willing* adj2 pay*).tw,kf. (13209)
 90 or/35-89 [COMBINED MeSH & TEXT WORDS FOR PATIENT PREFERENCES & VALUES] (6578882)
 91 exp Communication/ (870722)
 92 ((time\$2 or timeliness) adj2 (communica* or info*)).tw,kf. (16287)
 93 (miscommunicat* or mis-communicat*).tw,kf. (1807)
 94 (misunderstand* or mis-understand*).tw,kf. (11841)
 95 (misinform* or mis-inform*).tw,kf. (5330)
 96 ((involv* or participat*) adj3 (client? or consumer? or patient?)).tw,kf. (212048)
 97 exp Informed Consent/ (135722)
 98 (informed adj (choice* or choos* or consent* or decision*)).tw,kf. (120770)
 99 (choice? adj2 behavior*r*).tw,kf. (5292)
 100 ((client? or consumer? or patient? or personal) adj3 consent*).tw,kf. (38447)
 101 ((make or making or makes or made or shar* or support*) adj2 (choice? or choos* or decision*)).tw,kf. (364434)
 102 Patient Reported Outcome Measures/ (11401)
 103 patient reported outcome?.tw,kf. (34484)
 104 (PROM or PROMs or ePREM or ePREMs).tw,kf. (8161)
 105 or/91-104 [PATIENT COMMUNICATION / MISCOMMUNICATION / CONSENT / SUPPORT]
 (1646152)
 106 90 or 105 (7475595)
 107 34 or 106 [ALL PATIENT PREFERENCES & VALUES SETS] (7476065)
 108 23 and 107 [GERD/ESOPHAGEAL CANCER - PATIENT PREFERENCES & VALUES] (1577)
 109 108 use medall [MEDLINE RECORDS] (636)
 110 gastroesophageal reflux/ (76189)
 111 ((esophageal or gastric* or gastro-esophageal or gastro-oesophageal or gastroesophageal or gastrooesophageal or supraesophageal or supra-esophageal or supraoesophageal or supra-oesophageal) adj2 reflux*).tw,kw. (60380)
 112 GERD.tw,kw. (23254)
 113 GORD.tw,kw. (2189)
 114 SEGR.tw,kw. (14)
 115 (gastric adj2 regurgitat*).tw,kw. (524)
 116 or/110-115 (94213)
 117 exp esophagus tumor/ (77710)
 118 exp esophagus/ and exp neoplasm/ (37262)
 119 ((esophag* or oesophag* or pharynx-esophag*) adj3 (neoplas* or cancer* or tumour* or tumor* or carcinoma* or malignan* or metasta* or oncolog* or adenoma* or adenocarcinoma* or adeno-carcinoma* or carcinosarcoma* or carcino-sarcoma*)).tw,kw. (115398)
 120 Barrett Esophagus/ (23026)
 121 (Barrett* adj1 (esophag* or oesophag* or epitheli* or metaplasia* or syndrome?)).tw,kw. (22711)

122 (dysplasia* or dysplastic* or precancer* or pre-cancer* or premalignan* or pre-malignan*).tw,kw.
 (237615)
 123 or/117-122 (388236)
 124 116 and 123 [GERD AND ESOPHAGEAL CANCER] (13204)
 125 exp juvenile/ not (exp juvenile/ and exp adult/) (2337309)
 126 exp Infant/ not (exp Adult/ and exp Infant/) (1653036)
 127 exp Child/ not (exp Adult/ and exp Child/) (3188154)
 128 or/125-127 (3908908)
 129 124 not 128 [CHILD, 17 AND UNDER, REMOVED] (12752)
 130 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or
 exp vertebrate/ (47785712)
 131 exp human/ or exp human experimentation/ or exp human experiment/ (37610583)
 132 130 not 131 (10176834)
 133 129 not 132 [ANIMAL-ONLY REMOVED] (12412)
 134 editorial.pt. (1053946)
 135 letter.pt. not (letter.pt. and randomized controlled trial/) (2034134)
 136 133 not (134 or 135) [OPINION PIECES REMOVED] (11719)
 137 adaptive behavior/ (142109)
 138 attitude/ (105292)
 139 attitude to death/ (25924)
 140 attitude to disability/ (316)
 141 attitude to health/ (184789)
 142 attitude to illness/ (4863)
 143 attitude to life/ (642)
 144 consumer advocacy/ (6368)
 145 consumer attitude/ (3823)
 146 cooperation/ (40714)
 147 decision making/ (290020)
 148 health care survey/ (44378)
 149 exp interview/ (267434)
 150 life event/ (27394)
 151 patient advocacy/ (44216)
 152 exp patient attitude/ (358813)
 153 patient decision making/ (8997)
 154 exp patient education/ (186333)
 155 personal autonomy/ (28669)
 156 psychological aspect/ (478485)
 157 exp questionnaire/ (1538806)
 158 exp self concept/ (289574)
 159 self help/ (13262)
 160 exp social psychology/ (924332)
 161 ((accept* or anxiet* or anxious* or attitud* or consider* or choice? or choos* or chose? or
 concern* or decid* or decis* or dissatisf* or expect* or experienc* or fear* or feel* or felt or input* or
 opinion* or participat* or perceiv* or percepti* or perspective? or prefer* or respons* or satisf* or
 unsatisf* or value? or valuing or view* or worrie? or worry*) adj3 (citizen? or client? or consumer? or
 female? or male? or men or patient? or public or stake?holder* or user? or wom#n)).tw,kf. (1783010)
 162 (advoca* adj3 (client? or consumer? or patient?)).tw,kf. (12512)
 163 ((analys#s or valuation? or value? or valuing) adj3 (conjoint or contingent)).tw,kf. (3208)

164 (autonom* adj3 (personal* or self)).tw,kf. (4900)
165 (choice? adj1 (discrete or experiment*)).tw,kf. (6157)
166 ((client? or consumer? or patient?) adj (centered or centred or focus*)).tw,kf. (52284)
167 ((client? or consumer? or patient? or personal) adj narrati*).tw,kf. (2210)
168 empower*.tw,kf. (49166)
169 (focus group? or interview* or questionnaire? or survey*).tw,kf. (2689332)
170 (freedom? or libert*).tw,kf. (100795)
171 gambi*.tw,kf. (19958)
172 ((health or death) adj3 (anxiet* or anxious* or attitud* or concern* or fear* or feel? or feeling* or felt or perception* or perspective? or prefer* or view* or worrie? or worry*)).tw,kf. (161154)
173 health utilit*.tw,kf. (4626)
174 informed choice?.tw,kf. (5052)
175 (life adj3 (event? or experience?)).tw,kf. (63360)
176 (multi?attribute or multi?criteria).tw,kf. (2095)
177 (preference? adj1 (elicit* or scor* or stated)).tw,kf. (3368)
178 prospect theor*.tw,kf. (513)
179 (self adj2 (conceiv* or concept* or percepti* or perceiv*)).tw,kf. (45854)
180 (self adj (determin* or efficac* or help or manag* or support*)).tw,kf. (110203)
181 (social* adj1 valu*).tw,kf. (4014)
182 trade?off?.tw,kf. (11989)
183 (willing* adj2 pay*).tw,kf. (13209)
184 or/137-183 [Combined MeSH & text words for patient preferences & values] (6727797)
185 communication/ (197407)
186 exp verbal communication/ (291543)
187 ((time\$2 or timeliness) adj2 (communica* or info*)).tw,kf. (16287)
188 (miscommunicat* or mis-communicat*).tw,kf. (1807)
189 (misunderstand* or mis-understand*).tw,kf. (11841)
190 (misinform* or mis-inform*).tw,kf. (5330)
191 ((involv* or participat*) adj3 (client? or consumer? or patient?)).tw,kf. (212048)
192 informed consent/ (131281)
193 (informed adj (choice* or choos* or consent* or decision*)).tw,kf. (120770)
194 (choice? adj2 behavio?r*).tw,kf. (5292)
195 ((client? or consumer? or patient? or personal) adj3 consent*).tw,kf. (38447)
196 ((make or making or makes or made or shar* or support*) adj2 (choice? or choos* or decision*)).tw,kf. (364434)
197 patient reported outcome?.tw,kf. (34484)
198 (PROM or PROMs or ePREM or ePREMs).tw,kf. (8161)
199 or/185-198 [Additional patient preference terms] (1271333)
200 184 or 199 [ALL PATIENT PREFERENCES & VALUES SETS] (7412212)
201 136 and 200 [GERD/ESOPHAGEAL CANCER - PATIENT PREFERENCES & VALUES] (2198)
202 201 use emczd [EMBASE RECORDS] (1377)
203 109 or 202 [BOTH DATABASES] (2013)
204 (2017 04* or 2017 05* or 2017 06* or 2017 07* or 2017 08* or 2017 09* or 2017 10* or 2017 11* or 2017 12* or 2018*).dt. (1988203)
205 109 and 204 [MEDLINE UPDATE RECORDS] (34)
206 (201704* or 201705* or 201706* or 201707* or 201708* or 201709* or 201710* or 201711* or 201712* or 2018*).dc. (2921967)
207 202 and 206 [EMBASE UPDATE RECORDS] (150)

208 205 or 207 [BOTH DATABASES - UPDATE PERIOD] (184)
 209 remove duplicates from 208 (158)
 210 209 use medall [MEDLINE UNIQUE UPDATE RECORDS] (33)
 211 209 use emczd [EMBASE UNIQUE UPDATE RECORDS] (125)

Cochrane

<https://www.cochranelibrary.com/advanced-search/search-manager?search=2220026>

Search Name: CTFPHC - Esophageal Cancer - GERD - Patient Preferences - No Screening Filters - Update
 Date Run: 30/10/2018 02:50:02
 Comment: CTFPHC (OHRI) - 2018 Oct 29 - Update from April 2017

ID	Search	Hits
#1	MeSH descriptor: ["Gastroesophageal Reflux"] explode all trees	1740
#2	((esophageal or gastric* or (gastro next esophageal) or (gastro next oesophageal) or supraesophageal or (supra next esophageal) or supraesophageal or (supra next oesophageal)) near/2 reflux*):ti,ab,kw	1064
#3	GERD:ti,ab,kw	1185
#4	GORD:ti,ab,kw	148
#5	SEGR:ti,ab,kw	1
#6	(gastric near/2 regurgitat*):ti,ab,kw	67
#7	{or #1-#6}	2862
#8	MeSH descriptor: ["Esophageal Neoplasms"] explode all trees	1308
#9	MeSH descriptor: [Esophagus] explode all trees	267
#10	((esophag* or oesophag* or (pharynx next esophag*)) near/3 (neoplas* or cancer* or tumour* or tumor* or carcinoma* or malignan* or metasta* or oncolog* or adenoma* or adenocarcinoma* or (adeno next carcinoma*) or carcinosarcoma* or (carcino next sarcoma*)):ti,ab,kw	3387
#11	MeSH descriptor: ["Barrett Esophagus"] explode all trees	207
#12	(Barrett* near/1 (esophag* or oesophag* or epitheli* or metaplasia* or syndrome*)):ti,ab,kw	471
#13	(dysplasia* or dysplastic* or precancer* or (pre next cancer*) or premalignan* or (pre next malignan*)):ti,ab,kw	3694
#14	{or #8-#13}	7045
#15	#7 and #14	133
#16	MeSH descriptor: [Infant] explode all trees	14928
#17	MeSH descriptor: [Child] explode all trees	1356
#18	MeSH descriptor: [Juvenile] explode all trees	0
#19	#15 not (#16 or #17 or #18)	131
#20	MeSH descriptor: ["Gastroesophageal Reflux"] explode all trees and with qualifier(s): [PX - PX]	37
#21	MeSH descriptor: ["Esophageal Neoplasms"] explode all trees and with qualifier(s): [PX - PX]	18
#22	MeSH descriptor: ["Barrett Esophagus"] explode all trees and with qualifier(s): [PX - PX]	1
#23	MeSH descriptor: ["Mass Screening"] explode all trees and with qualifier(s): [PX - PX]	178
#24	MeSH descriptor: ["Early Detection of Cancer"] explode all trees and with qualifier(s): [PX - PX]	95

#25 MeSH descriptor: ["Diagnostic Tests, Routine"] explode all trees and with qualifier(s): [PX - PX] 2

#26 MeSH descriptor: [Endoscopy] explode all trees and with qualifier(s): [PX - PX] 190

#27 MeSH descriptor: ["Endoscopy, Gastrointestinal"] explode all trees and with qualifier(s): [PX - PX] 97

#28 MeSH descriptor: [Esophagoscopy] explode all trees and with qualifier(s): [PX - PX] 0

#29 MeSH descriptor: [Gastrosocopy] explode all trees and with qualifier(s): [PX - PX] 10

#30 {or #20-#29} 478

#31 MeSH descriptor: ["Adaptation, Psychological"] explode all trees 4942

#32 MeSH descriptor: [Attitude] explode all trees 1009

#33 MeSH descriptor: ["Attitude to Death"] explode all trees 148

#34 MeSH descriptor: ["Attitude to Health"] explode all trees 32342

#35 MeSH descriptor: ["Choice Behavior"] explode all trees 1335

#36 MeSH descriptor: ["Consumer Advocacy"] explode all trees 14

#37 MeSH descriptor: ["Consumer Behavior"] explode all trees 56

#38 MeSH descriptor: ["Consumer Participation"] explode all trees 1402

#39 MeSH descriptor: ["Cooperative Behavior"] explode all trees 929

#40 MeSH descriptor: ["Decision Making"] explode all trees 2001

#41 MeSH descriptor: ["Focus Groups"] explode all trees 522

#42 MeSH descriptor: ["Health Care Surveys"] explode all trees 547

#43 MeSH descriptor: ["Health Services Accessibility"] explode all trees 606

#44 MeSH descriptor: ["Interviews as Topic"] explode all trees 1733

#45 MeSH descriptor: ["Life Change Events"] explode all trees 449

#46 MeSH descriptor: [Narration] explode all trees 171

#47 MeSH descriptor: ["Patient Acceptance of Health Care"] explode all trees 2601

#48 MeSH descriptor: ["Patient Advocacy"] explode all trees 72

#49 MeSH descriptor: ["Patient-Centered Care"] explode all trees 557

#50 MeSH descriptor: ["Patient Education as Topic"] explode all trees 8048

#51 MeSH descriptor: ["Patient Participation"] explode all trees 1156

#52 MeSH descriptor: ["Patient Preference"] explode all trees 637

#53 MeSH descriptor: ["Patient Satisfaction"] explode all trees 11067

#54 MeSH descriptor: [Patients] explode all trees and with qualifier(s): [PX - PX] 540

#55 MeSH descriptor: ["Personal Autonomy"] explode all trees 196

#56 MeSH descriptor: ["Power (Psychology)"] explode all trees 21

#57 Any MeSH descriptor 49716

#58 MeSH descriptor: ["Quality of Life"] explode all trees and with qualifier(s): [PX - PX] 1852

#59 MeSH descriptor: ["Self Concept"] explode all trees 6343

#60 MeSH descriptor: ["Self Efficacy"] explode all trees 2661

#61 MeSH descriptor: ["Self-Help Groups"] explode all trees 725

#62 MeSH descriptor: ["Social Values"] explode all trees 154

#63 ((accept* or anxiet* or anxious* or attitud* or consider* or choice* or choos* or chose* or concern* or decid* or decis* or dissatisf* or expect* or experienc* or fear* or feel* or felt or input* or opinion* or participat* or perceiv* or percepti* or perspective* or prefer* or respons* or satisf* or unsatisf* or value* or valuing or view* or worrie* or worry*) near/3 (citizen* or client* or consumer* or female* or male* or men or patient* or public or stake*holder* or user* or woman or women)):ti,ab,kw 116467

#64 (advoca* near/3 (client* or consumer* or patient*)):ti,ab,kw 339

#65 ((analys* or valuation* or value* or valuing) near/3 (conjoint or contingent)):ti,ab,kw 90

#66 (autonom* near/3 (personal* or self)):ti,ab,kw 358
 #67 (choice* near/1 (discrete or experiment*)):ti,ab,kw 165
 #68 ((client* or consumer* or patient*) next (centered or centred or focus*)):ti,ab,kw 2741
 #69 ((client* or consumer* or patient* or personal) next narrati*):ti,ab,kw 55
 #70 empower*:ti,ab,kw 1960
 #71 ("focus group" or "focus groups" or interview* or questionnaire* or survey*):ti,ab,kw 109696
 #72 (freedom* or libert*):ti,ab,kw 3073
 #73 gamb*:ti,ab,kw 672
 #74 ((health or death) near/3 (anxiet* or anxious* or attitud* or concern* or fear* or feel or feels or feeling* or felt or perception* or perspective* or prefer* or view* or worrie* or worry*)):ti,ab,kw 14714
 #75 (health next utilit*):ti,ab,kw 431
 #76 (informed next choice*):ti,ab,kw 248
 #77 (life near/3 (event* or experience*)):ti,ab,kw 2140
 #78 (multi*attribute or multi*criteria):ti,ab,kw 87
 #79 (preference* near/1 (elicit* or scor* or stated)):ti,ab,kw 165
 #80 (prospect next theor*):ti,ab,kw 27
 #81 (self near/2 (conceiv* or concept* or percepti* or perceiv*)):ti,ab,kw 6382
 #82 (self next (determin* or efficac* or help or manag* or support*)):ti,ab,kw 14580
 #83 (social* near/1 valu*):ti,ab,kw 195
 #84 trade*off*:ti,ab,kw 636
 #85 (willing* near/2 pay*):ti,ab,kw 960
 #86 MeSH descriptor: [Communication] explode all trees 8033
 #87 (time* near/2 (communica* or info*)):ti,ab,kw 516
 #88 mis*communicat*:ti,ab,kw 41
 #89 mis*understand*:ti,ab,kw 129
 #90 mis*inform*:ti,ab,kw 76
 #91 ((involv* or participat*) near/3 (client* or consumer* or patient*)):ti,ab,kw 16155
 #92 MeSH descriptor: ["Informed Consent"] explode all trees 657
 #93 (informed next (choice* or choos* or consent* or decision*)):ti,ab,kw 13770
 #94 (choice* near/2 behavio*):ti,ab,kw 1334
 #95 ((client* or consumer* or patient* or personal) near/3 consent*):ti,ab,kw 5869
 #96 ((make or making or makes or made or shar* or support*) near/2 (choice* or choos* or decision*)):ti,ab,kw 12710
 #97 MeSH descriptor: ["Patient Reported Outcome Measures"] explode all trees 210
 #98 ("patient reported" next outcome*):ti,ab,kw 4219
 #99 (PROM or PROMS or ePREM or ePREMs):ti,ab,kw 565
 #100 {or #31-#99} 275595
 #101 #30 or #100 275631
 #102 #19 and #101 with Cochrane Library publication date Between Apr 2017 and Oct 2018 9

Appendix 12: KQ2 Screening forms

Title and Abstract screening form

1. Does this study discuss any of the following:
 - patients choosing to/choosing not to undergo screening for EAC (or BE, dysplasia); OR
 - how they weighted the benefits and harms of screening; OR
 - what factors contributed to these preferences and to their decision to undergo/not undergo screening

☐ Yes/unclear
☐ No

Full-text screening form

1. **Full text not available:**
☐ Yes
2. **Language:**
☐ English/French
☐ Other
3. **Is the study design a commentary, opinion, editorial or review?**
☐ Yes
☐ No
☐ Abstract or protocol
4. **Are included participants adults (≥ 18 years old)?**
☐ Yes
☐ No
☐ Unclear
5. **Have participants been diagnosed with other gastro-esophageal conditions (e.g., gastric cancer, esophageal atresia, other life threatening esophageal conditions) or pre-existing disease (BE, dysplasia, or EAC) or did they have alarm symptoms (e.g., vomiting, dysphagia)?**
☐ Yes
☐ No
☐ Unclear (enter why it is unclear)
6. **Do participants have "chronic GERD"?**
defined as: (1) symptoms for ≥ 12 months, with no specific frequency; and/or (2) proton pump inhibitor (PPI) (or other pharmacotherapy) use for GERD for ≥ 12 months)

- ☐ Yes
- ☐ No
- ☐ Unclear (enter GERD definition)

7. Does this article include an intervention of interest (any screening modality for EAC and other precancerous lesions)

- ☐ Yes
- ☐ No
- ☐ Unclear (describe)

8. Does this article have a comparator of interest?

- no screening - among those offered
- different screening modality
- different screening intervals
- different lengths
- duration of screening
- offered screening but did not receive screening
- no comparison

- ☐ Yes
- ☐ No
- ☐ Unclear

Comments:

Appendix 13: KQ2 List of excluded studies at full text

Full text not available (n=9)

1. Craig A, Shoeman M, Dent J. A comparison of narrow bore transnasal and transoral endoscopy in unsedated patients [abstract]. *Gastrointest Endosc* 1998;47:AB28.
2. Mulcahy HE, Alstead EM, McKenzie C, Riches A, Kiely M, Farthing MJG, Fairclough PD. A randomized trial of a 5.5 mm vs 9.5 mm diameter videogastroscope in unsedated upper GI endoscopy [abstract]. *Gastrointest Endosc* 1997;45:AB54
3. Mulcahy HE, Kelly P, Banks M, Farthing MJG, Fairclough PD, Kumar P. Factors associated with tolerance to unsedated upper gastrointestinal endoscopy [abstract]. *Gastrointest Endosc* 1998;47:AB56.
4. Lewis, Liane, Marcu, Afrodita, Whitaker, Katriina, and Maguire, Roma. Patient factors influencing symptom appraisal and subsequent adjustment to oesophageal cancer: A qualitative interview study. *European journal of cancer care* 2018; 27 (1).
5. Stasyshyn, Andriy. Diagnosis and treatment of gastroesophageal reflux disease complicated by Barrett's esophagus. *Polski przegląd chirurgiczny* 2017; 89 (4) 29-32.
6. Gehlot, V., Mahant, S., Das, K., and Das, R. Risk or lifestyle factors associated with Gastroesophageal Reflux Disease (GERD) in north India. *Helicobacter* 2016; 21 (Supplement 1) 164.
7. Sakin, Y. S., Vardar, R., Sezgin, B., Cetin, Z. E., Alev, Y., Yildirim, E., Kirazli, T., and Bor, S. The diagnostic value of 24-hour ambulatory intraesophageal PH-impedance in patients with laryngopharyngeal reflux symptoms compared to those with typical symptoms. *United European Gastroenterology Journal* 2016; 4 (5 Supplement 1) A684-A685.
8. Jovani, M., Cao, Y., Feskanich, D., Hur, C., Jacobson, B. C., and Chan, A. T. Aspirin use is associated with lower risk of Barrett's esophagus in women. *Gastroenterology* 2017; 152 (5 Supplement 1) S105.
9. Ward, M. A., Dunst, C. M., Robinson, B., Teitelbaum, E. N., Sharata, A. M., DeMeester, S. R., Reavis, K. M., and Swanstrom, L. L. 20 Year outcomes: Laparoscopic heller myotomy stands the test of time. *Surgical Endoscopy and Other Interventional Techniques* 2017; 31 (Supplement 1) S234.

Other language (n=1)

1. Dohmen W, Fuchs W. Rapidity of pain relief, medication requirement and patient satisfaction with reflux treatment in the physician's office. *MMW-Fortschritte der Medizin* 2005; 147(9): 39-. [German]

Study design (i.e., commentary, opinion, editorial, review, abstract or protocol) (n=35)

1. Munoz-Largacha JA, Fernando HC, Litle VR. Optimizing the diagnosis and therapy of Barrett's esophagus. *Journal of Thoracic Disease* 2017; 9: S146-S153.
2. Parker CE, Spada C, Mcalindon M, Davison C, Panter S. Capsule endoscopy-not just for the small bowel: A review. *Expert Review of Gastroenterology and Hepatology* 2014; 9(1): 79-89.
3. Estores D, Velanovich V. Barrett esophagus: Epidemiology, pathogenesis, diagnosis, and management. *Current Problems in Surgery* 2013; 50(5): 192-226.
4. Farnbacher MJ, Keles M, Meier M, Hagel A, Schneider T. Capsule endoscopy in a network cooperation: Assessment of the experience in 822 patients. *Scandinavian Journal of Gastroenterology* 2013; 48(9): 1088-1094.
5. Shaheen N. Barrett esophagus: Disease management and patient perceptions. *Gastroenterology and Hepatology* 2006; 2(7): 468-470.
6. Barr H. Endoscopic surveillance of patients with Barrett's oesophagus. *Gut* 2002; 51(3): 313-314.
7. Kamolz T, Velanovich V. Psychological and emotional aspects of gastroesophageal reflux disease. *Diseases of the Esophagus* 2002; 15(3): 199-203.

8. Tierney M, Bevan R, Rees CJ, Trebble TM. What do patients want from their endoscopy experience? The importance of measuring and understanding patient attitudes to their care. *Frontline Gastroenterol* 2016; 7(3): 191-198.
9. Ofman JJ, Rabeneck L. The effectiveness of endoscopy in the management of dyspepsia: a qualitative systematic review. *American Journal of Medicine* 1999; 106(3): 335-346.
10. Hinojosa-Lindsey M, Arney J, Heberlig S, Kramer JR, Street RL Jr, El-Serag HB, Naik AD. Patients' intuitive judgments about surveillance endoscopy in Barrett's esophagus: a review and application to models of decision-making. *Dis Esophagus* 2013; 26(7): 682-689.
11. Sorbi D, Chak A. Unsedated EGD. *Gastrointest Endosc* 2003; 58:102-110.
12. Atkinson M, Chak A. Unsedated small-caliber endoscopy: a new screening and surveillance tool for Barrett's esophagus. *Gastroenterology & Hepatology* 2017 Aug; 4(8):426-427.
13. Eisen GM, Baron TH, Dominitz JA, Faigel DO, Goldstein JL, Johanson JF, Mallery JS, Raddawi HM, Vargo JJ II, Waring JP, Fanelli RD, Wheeler-Harbaugh J. Complications of upper GI endoscopy. *Gastrointest Endosc* 2002; 55: 784-793.
14. Ross WA. Premedication for upper gastrointestinal endoscopy. *Gastrointest Endosc* 1989; 35(2):120-126.
15. Saeian K. Unsedated transnasal endoscopy: a safe and less costly alternative. *Curr Gastroenterol Rep* 2002; 4:213-7.
16. Waterman M, Gralnek IM. Capsule endoscopy of the esophagus. *J Clin Gastroenterol* 2009; 43:605-12.
17. Waye JD. Worldwide use of sedation and analgesia for upper intestinal endoscopy. *Gastrointest Endosc* 1999; 50:888-91.
18. Kramer JR, Arney J, Chen J, Richardson P, Duan Z, Street RLJ, Hinojosa-Lindsey M, Naik AD, El-Serag HB. Patient-centered, comparative effectiveness of esophageal cancer screening: protocol for a comparative effectiveness research study to inform guidelines for evidence-based approach to screening and surveillance endoscopy. *BMC Health Services Research* 2012; 12: 288-.
19. Tan G, Gandhi M. Outcomes of open access endoscopy in dyspepsia/GERD patients without alarm features in a community medical center. *American Journal of Gastroenterology* 2015; 110: S641-S642.
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Not adult population (n=3)

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No comparator of interest (n=2)

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Diagnosed with other GI conditions (e.g., gastric cancer, esophageal atresia, other life threatening esophageal conditions) or pre-existing disease (BE, dysplasia, or EAC) or did they have alarm symptoms (e.g., vomiting, dysphagia) (n=9)

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Participants do not have chronic GERD (n=23)

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Intervention not of interest (n=2)

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Outcome not of interest (n=16)

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Appendix 14: KQ2 List of potentially relevant ongoing studies

Trial Identifier	Title	Estimated Study Completion Date
ISRCTN35624133	Walk in nasal endoscopy (WINES) study: a pilot evaluation of the safety and feasibility, and cost savings of introducing a radically new approach to upper gastrointestinal (GI) endoscopy	December 2004
NCT02852161	The Accuracy and Acceptability of Magnet Assisted Capsule Endoscopy in the Diagnosis of Esophageal Pathology: a Pilot Study (MACE)	October 2017
NCT02729948	Use of a Tethered Capsule Endoscope in Screening for Barrett's Esophagus	August 2017
NCT02395471	Assessment of a Minimally Invasive Esophageal Cytology Collection System in Patients With Barrett's Esophagus or GERD Symptoms	June 2018
ISRCTN68382401	Barrett's Esophagus Trial 3 (BEST3): Cluster randomised controlled trial comparing the Cytosponge-TFF3 test with usual care to facilitate the diagnosis of oesophageal pre-cancer in primary care.	September 2019
NCT02445014	Pilot Study for Imaging of Barrett's Esophagus Using an Spectrally Encoded Confocal Microscopy Tethered Endoscopic Capsule	December 2018