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Systematic review with meta-analysis: the effects of family history on the risk of Barrett's oesophagus and oesophageal adenocarcinoma

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Summary

Background: Current guidelines recommend different screening approaches for individuals with a family history of Barrett's oesophagus (BO) or oesophageal adenocarcinoma (OAC), varying from no screening to screening all individuals with a positive family history.

Aims: To determine evidence-based risk estimates for individuals with a family history of BO or OAC

Methods: We systematically searched Pubmed, Embase and Cochrane Library until October 2020 to identify all studies that reported on the association between family history and the risk of BO and OAC. Pooled summary estimates of adjusted relative risks and prevalence of familial BO/OAC with 95% confidence intervals (CIs) were calculated using a random effects model.

Results: Fourteen studies comprising 16 189 BO/OAC patients were analysed. Familial clustering was seen in 8.84% (95% CI: 5.54-13.82) and 4.37% (95% CI: 2.15-8.69) of patients with BO and OAC, respectively (nine studies). Screening first-degree relatives of BO patients had a diagnostic yield between 12% and 44% for BO (four studies). However, the yield for high-grade dysplasia and OAC was low (<2%). Individuals with a positive family history had a higher risk of having BO (aRR 3.26; 95% CI 1.43-7.40; $I^2 = 46\%$; three studies) and OAC (aRR 2.19; 95% CI 1.14-4.21; $I^2 = 48\%$; five studies) compared to individuals without a family history.

Conclusions: A verified family history of BO or OAC is a strong risk factor for both BO and OAC. A positive family history could be a clinically meaningful way to identify high-risk individuals who may benefit from early detection strategies.

1 | INTRODUCTION

During the past 30 years, the incidence of oesophageal adenocarcinoma (OAC) has increased up to sixfold in Western countries.[1,2] With 35 000 new cases in 2018, nearly 50% of the worldwide cases of OAC occur in Europe and North America.[3] OAC still has a poor prognosis with a 5-year survival rate of only 20%, despite improvements in multimodality therapy.[4] The vast majority of patients with OAC present with locally advanced or metastatic disease, as symptoms of early OAC and its precursor lesions are often absent or barely distinct from gastro-oesophageal reflux disease (GERD).[1]

Barrett's oesophagus (BO) is the major precursor of OAC, increasing the risk of developing OAC by a factor 10-30.[5,6] The population prevalence of BO is estimated to be approximately 1%-2%, which increases to 8%-20% in individuals with long-term GERD.[7,8] Unfortunately, in daily practice, >90% of patients with OAC never had prior endoscopy and only a minority of BO patients are currently diagnosed and under surveillance.[9] Hence, identifying patients with BO and early detection of OAC could be potentially helpful in reducing OAC-related mortality.

As the annual risk of OAC in patients with BO is low (0.1%-0.5%), the merits of population-based endoscopic screening are controversial.[5,10] It is therefore important to identify individuals at increased risk for BO and OAC. Already known risk factors for BO and OAC, including increasing age, male gender, Caucasian race, smoking, obesity and GERD, are in this regard helpful.[6]

Although the vast majority of BO and OAC cases are sporadic and caused by somatic mutations, several reports of families with multiple affected relatives suggest that there may be an underlying genetic susceptibility.[11-14] However, as the exact role of genetic factors in the development of BO and OAC has remained largely unclear, OAC is not included in familial risk management guidelines.[15] Clinical guidelines on the other hand suggest a role for endoscopic screening in individuals with a positive family history for BO or OAC.[16-19] Until now, recommendations for screening in these individuals are merely based on expert opinions and on small number of studies, and consequently recommendations vary between guidelines.[16-20]

Precise and valid evidence-based risk estimates for individuals with a family history of BO or OAC are needed to improve genetic counselling, provide rational advice, develop risk prediction models and to determine appropriate screening strategies. Understanding the association between family history and oesophageal metaplasia and related neoplasia may also improve the knowledge on the pathogenesis of BO and OAC and could be key to identify causal underlying germline mutations. The aim of this systematic review and meta-analysis was therefore to determine the prevalence of a positive family history in patients with BO and OAC. We furthermore aimed to assess the prevalence and the risk of BO and OAC in individuals with a positive family history.

2 | METHODS

2.1 | Search strategy

This systematic review and meta-analysis of studies that investigated the association between a positive family history and risk of BO and related neoplasia was conducted according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines and a predetermined protocol (Prospero: CRD42020179348).[21] We systematically searched the electronic databases of MEDLINE (Pubmed), Embase (Ovid Technologies) and the Cochrane Library from inception to the date of the search (October 2020), without any restrictions. The search terms included three main categories and comprised synonyms for 'BO' and 'OAC', 'family' and 'risk' in accordance with previous literature reviews on familial cancer.[22,23] The search strategy was performed in collaboration with an experienced medical librarian. Exact search terms are presented in Table S1. References of eligible articles and reviews on the topic were manually searched for additional articles. An additional literature search excluding the keywords related to family/genetics was performed to possibly identify studies that only reported family history as secondary outcome. We assessed the full text of a randomly selected 5% of identified articles to determine robustness of our search strategy.

2.2 | Study selection

All identified records were exported to the citation management program EndNote X8 (Clarivate Analytics) for deduplication. First, two reviewers (YP and EG) independently screened titles and abstracts. Second, the full text of all included abstracts was assessed by the same reviewers to determine eligibility of each study. Any discrepancies between reviewers in both screening phases were resolved by consensus. Remaining disagreements were resolved through discussion with a third reviewer (PS).

Studies were eligible for inclusion if they permitted quantitative assessment of the association between BO and/or OAC defined by their presence during upper endoscopy and validated by pathology review and family history for these diseases. A positive family history was defined as having any type of family history of BO or oesophageal cancer irrespective whether the family history was verified by assessing medical or pathology reports from reportedly affected relatives. Studies that did not provide the used definition of a positive family history or used another definition of family history (eg family history of gastric cancer or GERD) were excluded. Additionally, we excluded studies that did not describe how assessment of family history was performed or which relatives were assessed. Studies were included if they reported the proportion of patients with BO or OAC that had a positive family history, the proportion of BO and OAC diagnoses in individuals with a positive family history or a measure of association (relative risk [RR], odds ratio [OR] or standardised incidence ratio [SIR]), or provided data for their calculation.

Case reports, reviews, unpublished data and conference abstracts were excluded. Inclusion was not otherwise restricted by study size, language or study type. We reviewed all included studies for their independence of their study population. For studies from the same data source and investigating the same outcome measure, we included articles that best fitted the relevance to the study questions.

2.3 | Data extraction and quality assessment

After identifying relevant studies, two authors (YP and EG) independently abstracted data on study characteristics and quality, patient demographics, definitions and assessment of family history including endoscopic or histological confirmation of affected relatives, and type of outcome measure onto a standardised form. Of all included studies, differences between patients with familial BO/OAC and sporadic cases were also extracted. For each study, the prevalence of BO or OAC in first-degree relatives was calculated by dividing the cases by the total patient group at risk, while the prevalence of a positive family history was calculated by dividing the cases with a positive family history by the total patient group with BO or OAC. Also, risk estimates (RR, OR or SIR) with 95% confidence intervals (CIs) and potential confounding variables considered in the analyses were recorded for each study. Adjusted risk estimates were used if they were adjusted for relevant effect moderators. Otherwise, unadjusted estimates or raw data were collected. ORs and SIRs were considered to be equivalent to RRs, given that the prevalence of BO or OAC among asymptomatic individuals is relatively low.[24]

Risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) tool, as recommended by the Cochrane Collaboration for studies of prognostic factors.[25,26] Quality was analysed based on six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting. Studies were classified as either low, moderate or high risk of bias (Table S2). Disagreements in data extraction and quality assessment were resolved through discussion and consensus and in consultation with a third reviewer (PS).

2.4 | Statistical analysis

The outcomes of this study were pooled prevalences and risk estimates of both BO and OAC based on the presence or absence of a positive family history for BO or oesophageal cancer. We also assessed the proportion of patients with BO or OAC with a positive family history of these disorders. We defined familial clustering as the occurrence of two cases of BO or OAC within one family.

Proportions with 95% CIs were calculated using the method of Wilson.[27] For all outcomes, we pooled logit-transformed prevalences and risk estimates with the corresponding 95% CIs using the generic inverse variance method with a random effects model.[28,29]

This model incorporates heterogeneity by giving a weight to each study equal to the inverse of the variance of the effect estimate. Between-study variance in the random effects model was estimated by a restricted maximum-likelihood estimator (REML).[30] The between-study heterogeneity was quantified with the inconsistency index (I^2) statistic and tested for significance using Cochran's Q-test. Because this test is underpowered to detect moderate degrees of heterogeneity, P values <0.10 were defined as indicating the presence of heterogeneity.[31] I^2 values >50% indicated substantial heterogeneity.[31]

Given the observational nature of studies and variation in the effect measures used in individual studies, we anticipated heterogeneity in the analyses. To reduce heterogeneity, a stratified meta-analysis was performed according to used definitions of a positive family history. To further explore heterogeneity, we performed pre-planned sensitivity analyses on study-related variables (study design, study location, verification of a positive family history and adjustment for certain covariates). Between-study sources of heterogeneity were assessed by using sensitivity analyses by stratifying original estimates according to the study characteristics, with P values <0.05 for differences between subgroups being considered as statistically significant. To explore a GERD-independent effect of a positive family history on BO and OAC, we performed sensitivity analyses of studies that adjusted for GERD symptoms or included only patients with GERD.

We did not perform an assessment of publication bias and meta-regression because of the small number of studies (<10) for all effect estimates. Statistical calculations and transformations for proportional outcomes and risk estimates were performed using R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). For all tests (except for heterogeneity), P values of <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Study selection and included studies

Our initial search identified 3030 articles after deduplication. Of these, 2928 were excluded after screening titles and abstracts, leaving 102 articles for full-text assessment (Figure 1). Eighteen studies met our inclusion and exclusion criteria,[32-49] of which two were excluded because of overlapping patient populations.[46,47] Another two studies were excluded because the family history of gastric and oesophageal cancer was combined and no individual data could be extracted.[48,49] The sensitivity analysis on full-text search of 1050 studies on BO and OAC did not reveal additional relevant articles on family history fulfilling the eligibility criteria (Figure S1). Agreement between investigators for assessment of study eligibility was good (kappa statistic = 0.79).[50] Our final data set included 14 unique articles: 9 addressed prevalence of familial BO/OAC, 4 addressed prevalence of BO in first-degree relatives and 7 addressed risk of having/developing BO or OAC.[32-45]

FIGURE 1 Flowchart representing literature search and study selection
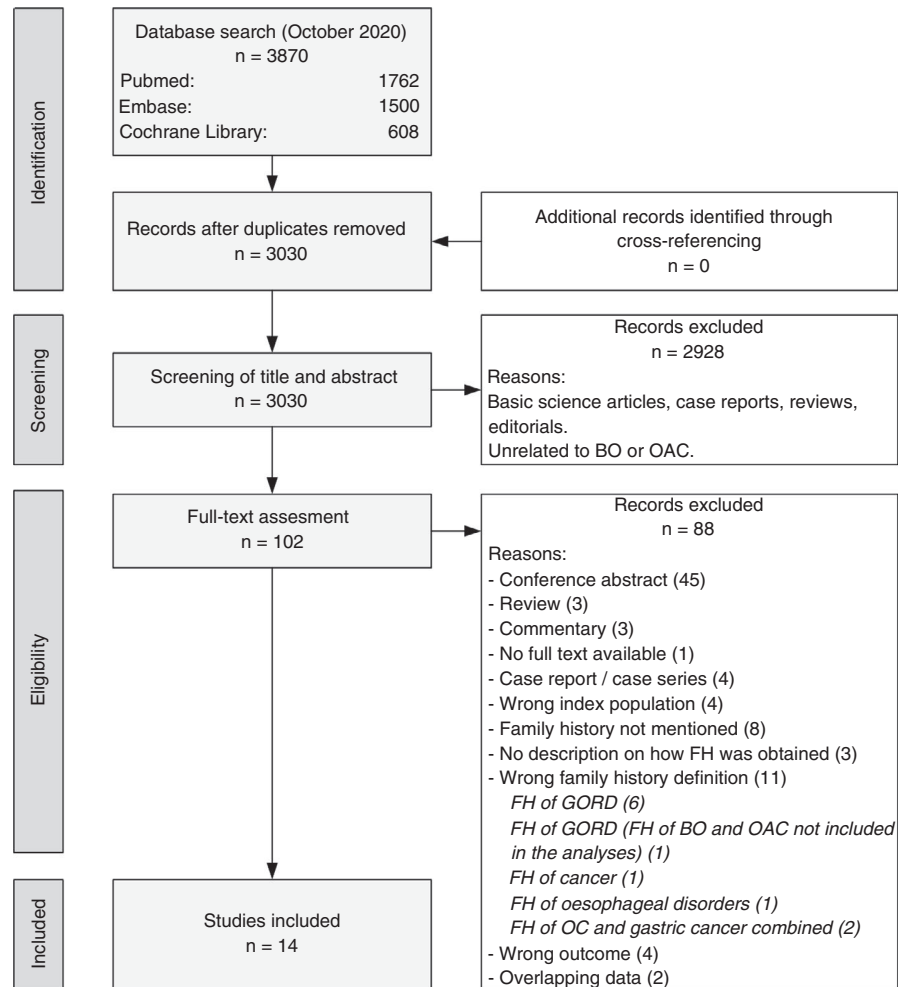
3.2 | Study characteristics and quality assessment

Study characteristics and quality of included studies are summarised in Table 1; Figures S2 and S3, and Supporting Information File A. Most of the selected studies were cohort studies (n = 8) and all were performed in Western countries. Ten studies were performed in the United States[32-38,42-44] and four in Europe.[39-41,45] The index population consisted of BO (n = 3 studies), OAC (n = 5) and BO and OAC combined (n = 6). All diagnoses of the 16 189 included index patients were confirmed using medical records and pathology reports. In all studies including BO patients, BO was defined as >1 cm segment of salmon-coloured mucosa in the oesophagus combined with the presence of intestinal metaplasia in biopsies. The most common used definition of family history was having at least one first-degree relative with BO or oesophageal cancer. A small majority of studies used confirmed family histories by assessing pathology or medical reports of relatives.[33-35,38,39,41,42,45] All other studies assessed family history using self-reports through surveys, interviews or medical reports. Of the seven studies addressing the risk of developing BO or OAC,[33,36,37,39,40,42,43] five studies controlled for age of persons at risk,[36,39,40,42,43] and three for gender of persons at risk.[39,40,42] None of the studies adjusted for family size or reported whether relatedness of study participants was addressed.

Based on the QUIPS tool, a total of three studies were classified as low risk of bias.[39,42,45]

3.3 | Prevalence of familial BO and OAC

Nine studies including 1623 BO and 998 OAC patients assessed the prevalence of having at least one first-degree relative with BO or oesophageal cancer.[32,33,35-37,40,43-45] A family history of BO or OAC was present in 1% to 10% of BO or OAC cases, except in one study,[33] in which a higher prevalence of familial BO (29%) and OAC (17%) was reported (Figure 2). The overall pooled prevalence of a positive family history in patients with BO (8.8%; 95% CI: 5.5-13.8; I^2 = 76%; six studies) was higher than in patients with OAC (4.4%; 95% CI: 2.2-8.7; I^2 = 75%; seven studies, P = 0.10). Only one study reported the prevalence of a family history of BO in patients with BO (prevalence: 17.1%; 95% CI: 8.1-32.7) and four studies reported the prevalence of a family history of oesophageal cancer in patients with OAC (pooled prevalence: 2.3%; 95% CI: 1.3-3.9; I^2 = 0%). A significant higher pooled prevalence of familial OAC was found in the three studies[33,35,45] that confirmed the positive family history (10.0%; 95% CI: 6.4-15.4; I^2 = 8%) compared with the four studies[32,36,37,40] with no confirmation of family history (2.5%; 95% CI: 1.6-3.9; I^2 = 8%,

TABLE 1 Baseline characteristics of the included studies

Author	Year	Country	Enrolment date	Study design	Index population	Age range (y)	Control group	Cases (n)	Controls (n)	FH assessment	Type of relative	Diagnoses in relatives	FH confirmed
Ash[32]	2011	United States	NS	R	BO ± dysplasia, OAC	NS	None	603	—	Medical reports Interview	FDR	BO, OC	No
Chak[33]	2002	United States	1999-2000	CC	BO ≥3 cm, OAC, OGJAC	≥18	Hospital-based GERD	58	106	Survey	FDR/SDR	BO ≥3 cm, OAC, OGJAC	Most
Chak[34]	2004	United States	NS; 3 y	P	BO ≥3 cm, OAC	NS	None	62 FDR	—	Endoscopy	FDR	BO, OAC	Yes
Chak[35]	2006	United States	NS; 1-4 y	CS	BO ≥3 cm, OAC	≥18	None	392	—	Survey	FDR/SDR	BO ≥3 cm, OAC	Yes
Dhillon[36]	2001	United States	1993-1995	CC	OAC	30-79	Population-based	293	695	Interview	FDR	OC	No
Jiang[37]	2014	United States	1992-1997	CC	OAC	30-74	Population-based	147	1297	Interview	FDR	OC	No
Juhasz[38]	2011	United States	NS	P	HGD, OAC	≥19	None	47 FDR	—	Endoscopy	FDR	BO	Yes
Kharazmi[39]	2018	Sweden	1958-2015	R	OAC	NS	Cancer database	13.325a	NS	Registry	FDR	OAC	Yes
Lagergren[40]	2000	Sweden	1995-1997	CC	OAC	<80	Population based	189	816	Interview	FDR	OC	No
Mussetto[41]	2013	Italy	2009	P	BO	≥18	None	18 FDR	—	Endoscopy	FDR	BO	Yes
Romero[42]	2002	United States	1996-1999	P	BO ± OAC	≥18	Hospital-based GERD	100 FDR	100	Endoscopy	FDR	BO ≥3 cm	Yes
Rubenstein[43]	2020	United States	2008-2011	P	CRC screenees (BO)	50-80	Screening based	70	751	Survey	Any FH	OC	No
Tofani[44]	2019	United States	2006-2016	R	Dysplastic BO	NS	None	282	—	Medical reports	FDR	OAC	No
Verbeek[45]	2014	The Netherlands	2000-2011	CS	BO ≥2 cm, OAC	All	None	603	—	Survey	FDR/SDR	BO or OAC	Yes

Abbreviations: BO, Barrett's oesophagus; CC, case-control study; CS, cross-sectional study; OAC, oesophageal adenocarcinoma; OC, oesophageal cancer; OGJAC, oesophagogastric junctional adenocarcinoma; FDR, first-degree relatives; FH, family history; GERD, gastro-oesophageal reflux disease; NS, not stated; P, prospective cohort study; R, retrospective cohort study; SDR, second-degree relatives; ±, with or without.

aOesophageal cancer patients.

$P < 0.001$). The prevalence for familial BO in the three studies that verified a positive family history[33,35,45] was also higher than in the three studies that did not verify family history[32,43,44] (10.6%; 95% CI: 3.7-26.6; I^2 = 90% vs 7.3%; 95% CI: 5.6-9.3; I^2 = 0%), but this difference was not statistically significant ($P = 0.48$).

The study by Chak et al[33] was identified as statistical outlier in the analyses on the prevalence of familial BO. Excluding this study, however, did not result in a significantly decreased pooled prevalence of having a positive family history in BO patients (6.8%; 95% CI: 5.7-8.2; $P = 0.31$), but heterogeneity decreased to 0%.

3.4 | Characteristics of familial BO and OAC

Of the 14 included articles, five studies addressed differences between patients with familial BO/OAC and sporadic cases.[32,34,35,44,45] No differences in ethnicity, smoking, alcohol consumption and obesity or body mass index were found. Nonetheless, one study including 26 OAC patients showed a significantly lower proportion of males in the familial OAC group,[44] whereas the remaining studies found no differences in gender between sporadic and familial BO/OAC. Two studies reported a lower age at BO or OAC diagnosis for patients with familial BO/OAC compared with sporadic BO (mean age: 58 vs 64 years).[32,44] This was not found in three other studies.[34,35,45] One study showed that familial BO/OAC patients were younger at onset of heartburn compared with patients without a positive family history.[45]

3.5 | Prevalence of BO in first-degree relatives

The prevalence of BO in patients with a family history of BO or OAC was assessed in four studies in which relatives of familial BO probands underwent (endoscopic) screening to identify new BO cases.[34,38,41,42] As these studies all used different study populations and screening methods, we judged that the risk estimates were too heterogeneous to provide a pooled estimate for the prevalence of BO and related neoplasia in those with a family history of BO
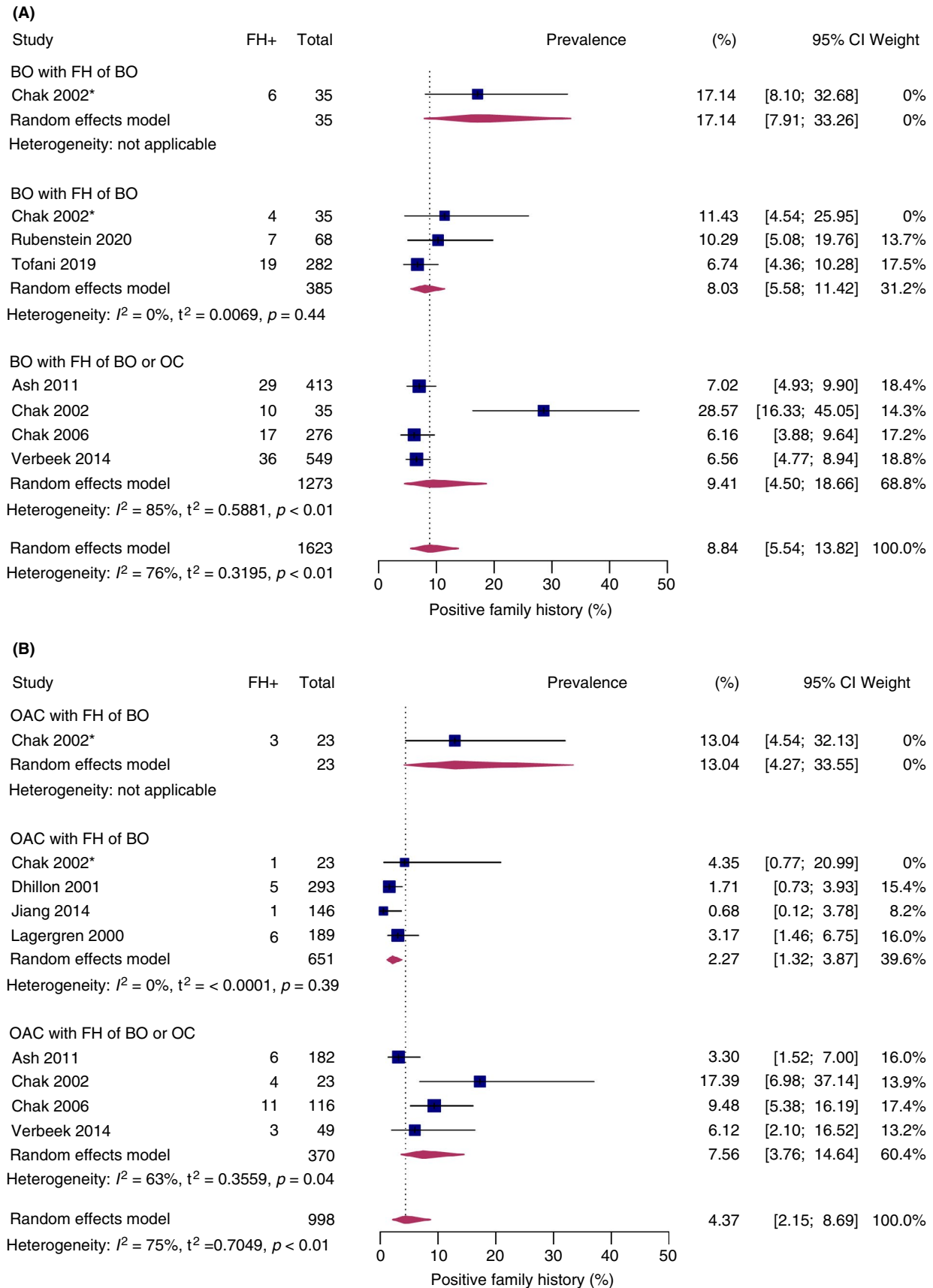
(A)

Study	FH+	Total	Prevalence	(%)	95% CI	Weight
BO with FH of BO						
Chak 2002*	6	35		17.14	[8.10; 32.68]	0%
Random effects model		35		17.14	[7.91; 33.26]	0%
Heterogeneity: not applicable						
BO with FH of BO						
Chak 2002*	4	35		11.43	[4.54; 25.95]	0%
Rubenstein 2020	7	68		10.29	[5.08; 19.76]	13.7%
Tofani 2019	19	282		6.74	[4.36; 10.28]	17.5%
Random effects model		385		8.03	[5.58; 11.42]	31.2%
Heterogeneity: $I^2 = 0\%$, $t^2 = 0.0069$, $p = 0.44$						
BO with FH of BO or OC						
Ash 2011	29	413		7.02	[4.93; 9.90]	18.4%
Chak 2002	10	35		28.57	[16.33; 45.05]	14.3%
Chak 2006	17	276		6.16	[3.88; 9.64]	17.2%
Verbeek 2014	36	549		6.56	[4.77; 8.94]	18.8%
Random effects model		1273		9.41	[4.50; 18.66]	68.8%
Heterogeneity: $I^2 = 85\%$, $t^2 = 0.5881$, $p < 0.01$						
Random effects model		1623		8.84	[5.54; 13.82]	100.0%
Heterogeneity: $I^2 = 76\%$, $t^2 = 0.3195$, $p < 0.01$						

0   10   20   30   40   50
Positive family history (%)

(B)

Study	FH+	Total	Prevalence	(%)	95% CI	Weight
OAC with FH of BO						
Chak 2002*	3	23		13.04	[4.54; 32.13]	0%
Random effects model		23		13.04	[4.27; 33.55]	0%
Heterogeneity: not applicable						
OAC with FH of BO						
Chak 2002*	1	23		4.35	[0.77; 20.99]	0%
Dhillon 2001	5	293		1.71	[0.73; 3.93]	15.4%
Jiang 2014	1	146		0.68	[0.12; 3.78]	8.2%
Lagergren 2000	6	189		3.17	[1.46; 6.75]	16.0%
Random effects model		651		2.27	[1.32; 3.87]	39.6%
Heterogeneity: $I^2 = 0\%$, $t^2 = < 0.0001$, $p = 0.39$						
OAC with FH of BO or OC						
Ash 2011	6	182		3.30	[1.52; 7.00]	16.0%
Chak 2002	4	23		17.39	[6.98; 37.14]	13.9%
Chak 2006	11	116		9.48	[5.38; 16.19]	17.4%
Verbeek 2014	3	49		6.12	[2.10; 16.52]	13.2%
Random effects model		370		7.56	[3.76; 14.64]	60.4%
Heterogeneity: $I^2 = 63\%$, $t^2 = 0.3559$, $p = 0.04$						
Random effects model		998		4.37	[2.15; 8.69]	100.0%
Heterogeneity: $I^2 = 75\%$, $t^2 = 0.7049$, $p < 0.01$						

0   10   20   30   40   50
Positive family history (%)

FIGURE 2 Forest plot: proportion of patients with (A) Barrett's oesophagus (BO) or (B) oesophageal adenocarcinoma (OAC) having a family history (FH) of BO or oesophageal cancer (EC). *Not included in the pooled analyses of the total group

(Table 2). Two studies only screened relatives with GERD symptoms using standard upper endoscopy or capsule endoscopy followed by standard endoscopy.[41,42] Of the 100 relatives screened in one study, 12 relatives were diagnosed with BO, of which one (1.0%; 95% CI: 0.2-5.5) also had OAC.[42] The other study did not report on the prevalence of high-grade dysplasia (HGD) and OAC in 18 symptomatic relatives of BO patients.[41] The remaining two studies screened all first-degree relatives of patients with BO and OAC with ultrathin endoscopy or standard upper endoscopy.[34,38] In a study including 23 index patients with HGD or OAC and 47 first-degree relatives, 13 relatives (27.7%; 95% CI: 16.9-41.8) were diagnosed with BO, but none of the relatives had neoplastic BO.[38] The prevalence of BO seemed higher in symptomatic relatives compared with asymptomatic relatives (34.3% vs 8.3%; $P = 0.09$). In the last study, BO was identified in 13 (21.0%; 95% CI: 12.6-32.8) of the 62 relatives of BO/OAC patients and one relative (1.6%; 95% CI: 0.3-8.6) was diagnosed with OAC.[34] The prevalence of BO was considerably higher in screened individuals with ≥2 relatives with known BO or OAC than in individuals with only one affected relative (40.7% vs 5.7%; $P < 0.001$).

3.6 | Risk of BO and OAC associated with a positive family history

Subjects with a family history of BO or oesophageal cancer were three (RR 3.26; 95% CI: 1.43-7.40; $I^2 = 46\%$; $P = 0.005$; three studies) and two (RR 2.19; 95% CI: 1.14-4.21; $I^2 = 48\%$; $P = 0.02$; five studies) times more likely to develop BO and OAC compared with individuals without a positive family history respectively (Figure 3).[33,36,37,39,40,42,43] The risk of OAC in individuals with a positive family history increased in studies that used a confirmed family history definition (RR 3.64; 95%CI: 2.57-5.14; $I^2 = 14\%$; $P < 0.001$).[33,39,42] Sensitivity analyses were performed to investigate potential sources of heterogeneity (Table 3). Restricting analyses to studies that accounted for GERD and body mass index,[42,43] we still observed a positive association between positive family history and risk of BO. No significant association was found between family history of oesophageal cancer and risk of OAC (RR 1.87; 95% CI: 0.86-4.08; $I^2 = 60\%$; $P = 0.12$). There was insufficient information to perform a pooled analysis on the effect of family history on the risk of developing dysplasia in BO compared with the general population.

3.7 | Malignant progression in BO associated with a positive family history

Two studies reported on the effect of family history on the risk of early neoplasia (including HGD) in patients with BO.[32,44] None of the studies adjusted for other known risk factors for development of neoplasia in BO. Pooled OR for malignant progression was 1.96 (95% CI: 0.30-12.82; $I^2 = 84\%$; $P = 0.48$).

3.8 | Subgroup analyses

None of the studies considered the effect of demographic characteristics (such as gender and age at diagnosis) on the prevalence of a positive family history or on the risk of BO and OAC. We could not perform subgroup analyses according to the number and age of affected relatives, and the degree of relatedness, as not enough studies provided data on BO or OAC risks in non-first-degree relatives. Three studies assessed the number of affected relatives in

TABLE 2 Prevalence of Barrett's oesophagus (BO) and oesophageal adenocarcinoma (OAC) in individuals with a first-degree relative with confirmed BO or OAC

| Author | Screening population | Characteristics of first-degree relatives | | | | FDRs screened | Diagnoses | BO length (cm) | Prevalence of BO/OAC in FDRs |
		Age (y)	Gender	Reflux	Obesity[a]				
Chak 2004[34]	Only 1 affected FDR	Mean: 44.6	Male: 43%	77%	43%	35	BO: 2|OAC: 0	LSBO: n = 0	5.7% (95% CI: 1.6-18.6)
	≥2 affected FDRs	Mean: 45.3	Male: 55%	78%	30%	27	BO: 10|OAC: 1	LSBO: n = 5	40.7% (95% CI: 24.5-59.3)
Juhasz 2011[38]	Asymptomatic FDRs	Mean: 44.4	Male: 61%	0%	Not reported	12	BO: 1|OAC: 0	LSBO: n = 4	8.3% (95% CI: 1.5-35.4)
	Symptomatic FDRs			100%		35	BO: 12|OAC: 0		34.3% (95% CI: 20.8-50.9)
Mussetto 2013[41]	FDRs with reflux	Mean: 52	Male: 44%	100%	Not reported	18	BO: 8|OAC: 0	Mean: 1.3	44.4% (95% CI: 24.0-67.0)
Romero 2002[42]	FDRs with reflux	36% >50 years	Male: 67%	100%	65%	100	BO: 12|OAC: 1	LSBO: n = 8	12.0% (95% CI: 6.9-20.0)

Abbreviations: BO, Barrett's oesophagus; OAC, oesophageal adenocarcinoma; FDR, first-degree relative; LSBO, long-segment Barrett's oesophagus (BO segment >3 cm).

[a]Obesity was defined as a body mass index ≥27.8 kg/m^2 in males and ≥27.3 kg/m^2 in females.
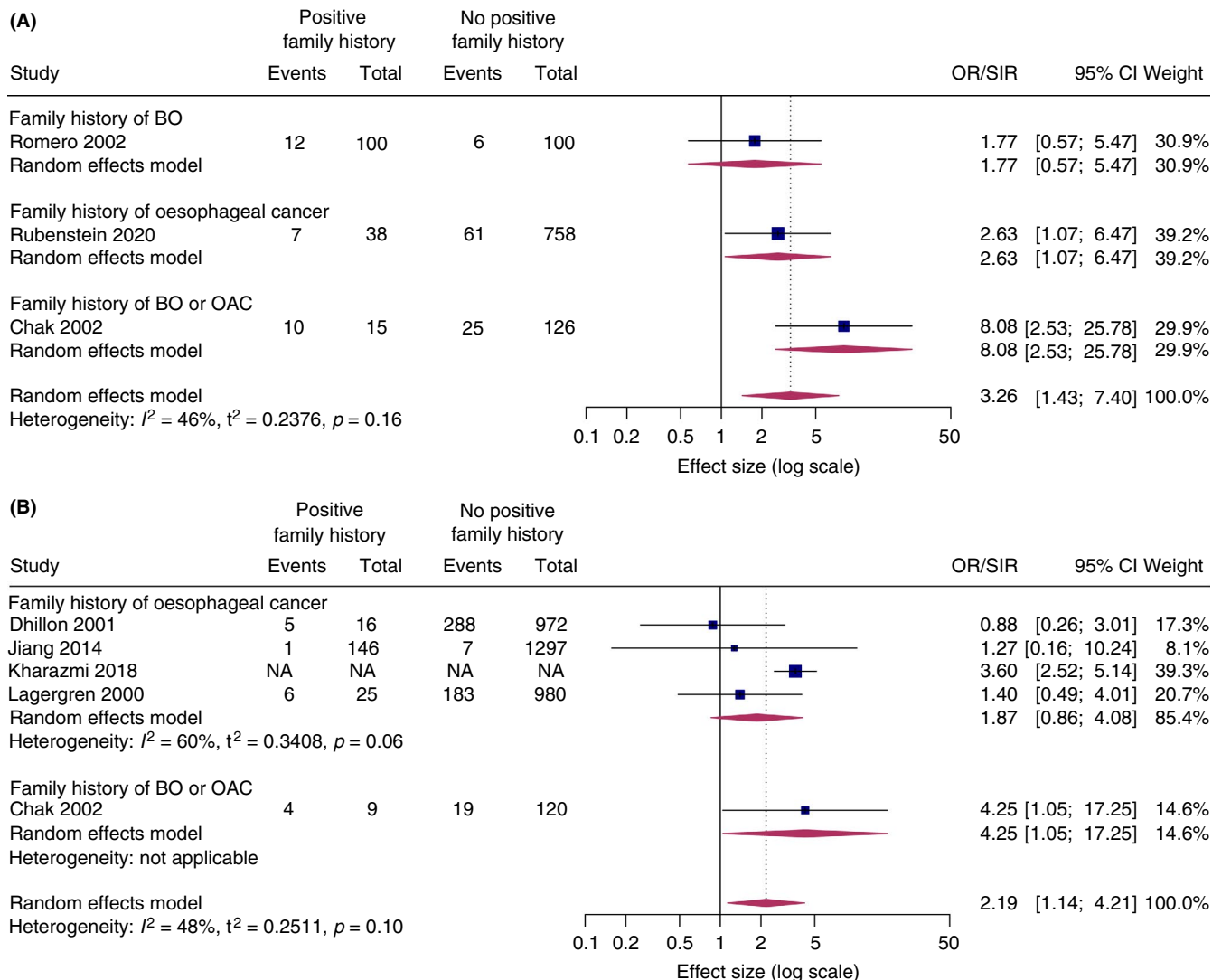
(A)

(B)

FIGURE 3 Forest plot of the association between (A) Barrett's oesophagus (BO) and (B) oesophageal adenocarcinoma (OAC) and a family history of the disease using a random effects model stratified by family history definition

familial BO/OAC families.[32,34,45] In familial BO/OAC, 10%[45], 19%[32] and 48%[34] of first-degree relatives were reported to be affected.

4 | DISCUSSION

This systematic review and meta-analysis provides evidence that confirmed familial clustering is seen in 10% of individuals with BO and OAC. Individuals with a first-degree relative with BO or oesophageal cancer were three and two times more likely to have BO and OAC compared with individuals without a positive family history respectively. Interestingly, OAC risk almost doubled in individuals with a verified family history of BO and OAC. We showed that offering screening to first-degree relatives of patients with BO or OAC had a diagnostic yield between 12% and 44% for BO, which is higher than in the general population (~2%).[7] However, the yield was low for HGD and OAC. The number of BO diagnoses increased in relatives

with GERD symptoms and in individuals with ≥2 affected relatives according to two individual studies.

Hitherto, one systematic review assessed the association between BO risk and family history as well as other risk factors. However, this review devoted a short paragraph on family history and included only four studies on screening first-degree relatives of BO patients.[51] The authors showed a pooled prevalence of BO in individuals with a positive family history of 24%. However, descriptive data on the study populations were not reported, although necessary when applying the results to a specific patient population and informing relatives about their risk. Furthermore, this prevalence is probably an overestimation, as studies were confounded by the inclusion of particularly motivated individuals, relatives with additional risk factors and multiple individuals from multiplex families.

Familial clustering of BO and OAC could imply a genetic predisposition to BO or OAC, but may equally be caused by a common

TABLE 3 Subgroup analysis: risk of Barrett's oesophagus (BO) and oesophageal adenocarcinoma (OAC) in individuals with a positive family history

Category	Studies (n)	RR (95% CI)	P value	I^2 (%)	References
Barrett's oesophagus					
All studies	3	3.26 (1.43-7.40)	0.005	46	33,42,43
Study design					
Case-control	1	8.08 (2.53-25.78)	<0.001	NA	33
Cohort	2	2.26 (1.12-4.56)	0.02	0	42,43
Study location					
United States	3	3.26 (1.43-7.40)	0.005	46	33,42,43
Europe	0	NA	NA	NA	
Verification of BO and OAC in relatives					
Confirmed family history	2	3.76 (0.85-16.64)	0.08	70	33,42
Verbal family history (no confirmation)	1	2.63 (1.07-6.47)	0.04	NA	43
Adjusted for age	2	2.26 (1.12-4.56)	0.02	0	42,43
Adjusted for gender	1	1.77 (0.57-5.47)	0.32	NA	42
Adjusted for GERD	2	2.26 (1.12-4.56)	0.02	0	42,43
Adjusted for obesity	2	2.26 (1.12-4.56)	0.02	0	42,43
Oesophageal adenocarcinoma					
All studies	5	2.19 (1.14-4.21)	0.02	48	33,36,37,39,40
Study design					
Case-control	4	1.55 (0.80-3.00)	0.19	0	33,36,37,40
Cohort	1	3.60 (2.52-5.14)	<0.001	NA	39
Study location					
United States	3	1.69 (0.57-4.97)	0.34	29	33,36,37
Europe	2	2.57 (1.06-6.24)	0.04	64	39,40
Verification of BO and OAC in relatives					
Confirmed family history	2	3.64 (2.57-5.14)	<0.001	14	33,39
Verbal family history (no confirmation)	3	1.17 (0.55-2.46)	0.69	0	35,36,39
Adjusted for age	3	1.92 (0.80-4.63)	0.15	71	36,39,40
Adjusted for gender	2	2.57 (1.06-6.24)	0.04	64	39,40
Adjusted for GERD	1	1.40 (0.49-4.01)	0.53	NA	40
Adjusted for obesity	2	1.15 (0.52-2.56)	0.73	0	36,40

Abbreviations: BO, Barrett's oesophagus; GERD, gastro-oesophageal reflux disease; OAC, oesophageal adenocarcinoma; RR, relative risk.

environmental exposure in family members or a genetic susceptibility to recognised risk factors such as GERD and obesity.[52,53] In the current meta-analysis, adjustment for GERD symptoms attenuated the risk of BO and OAC associated with a positive family history. This GERD-dependent effect of family history on BO and OAC was supported by two case-control studies, which suggested a familial predisposition for GERD in relatives of BO patients.[54,55] No differences in other lifestyle factors between familial and non-familial cases were found. On the other hand, the reported early age of disease diagnosis in familial BO/OAC cases compared with sporadic cases might indicate that relatives share one or more inherited genetic mutations.[11,13,46] This is further supported by multiple case reports and a study of inheritance patterns in 70 families, which suggested an autosomal dominant inheritance pattern in familial BO/OAC.[11,12,56]

Although the exact pathogenesis of BO and OAC still needs to be unravelled, current evidence is in favour of a genetic susceptibility underlying the observed familial clustering at least in families with multiple affected relatives.[57,58] In patients with a less extensive family history, shared environmental factors (in particular GERD symptoms) may potentially play a more important role.

The current meta-analysis showed that the risk estimate of a positive family history was lower for OAC than for BO. Although most studies included in our systematic review considered familial BO and OAC to be part of the same genetic trait,[59] familial OAC may at least to some extent be distinct from familial BO, as a previous study speculated about the existence of a non-BO pathway to OAC.[60] It is also plausible that individuals with a family history of OAC may undergo upper endoscopy more often, leading to enhanced detection and

eradication of early neoplasia. Hence, a positive family history may have a stronger effect on OAC risk than shown in our meta-analysis.

The future of OAC prevention relies on early detection of BO or early-stage OAC in high-risk individuals, followed by surveillance and endoscopic treatment for (dysplastic) BO.[61] Current guidelines recommend different screening approaches for individuals with a family history of BO or OAC, varying from no screening,[20] considering screening in relatives who also have other risk factors,[16-18] to screening all individuals with a positive family history.[19] Our findings confirm that a verified positive family history is a strong risk factor for BO and OAC. However, the observed pooled risk estimate is lower than the assumed risk of 12 reported by Chak et al,[33] which has become the key reference in most screening guidelines.[16,17,19] In our meta-analysis, this study was actually identified as an outlier. Although verification of family history was performed, the study by Chak et al was assessed as moderate risk of bias as it was limited by a small sample size, including only patients from tertiary hospitals, and combining BO, OAC and gastro-oesophageal junction adenocarcinoma for study outcomes. Additionally, another study showed that the number of new BO cases identified in a screening program of asymptomatic individuals with one first-degree affected relative was comparable to the prevalence in the general population.[7,34] Taken together, the results of this meta-analysis do, in our opinion, not support a strong recommendation to endoscopically screen all first-degree relatives of patients with confirmed BO or OAC, given the number of first-degree relatives involved, the relatively low risk of BO and OAC in these individuals, associated direct and indirect costs, and invasiveness and potential complications of upper endoscopy.[62]

However, this review emphasises the need for gastroenterologists to be aware of familial clustering and highlights the importance of obtaining a careful family history in all patients with BO or OAC. Although this systematic review could not conclusively quantify the higher risk of BO and OAC for individuals with ≥2 affected first-degree relatives, individual studies and multiple case reports have shown an increased risk of BO and OAC in families with multiple affected relatives, suggesting an underlying genetic aetiology.[11,13,34] We believe that endoscopic screening of first-degree relatives should particularly be considered in families with ≥2 affected individuals. For individuals with a less extensive family history, endoscopic screening could be considered in first-degree relatives with multiple risk factors, such as age >50 years, male gender, obesity and GERD symptoms. For these individuals, minimally invasive screening options could also be considered.[61,63,64]

The strengths of this analysis include a thorough systematic literature search according to a standardised protocol with well-defined inclusion criteria. We included all available studies without restricting analyses based on study design or language. All index patients had an endoscopic and histological confirmed BO or OAC diagnosis. Furthermore, a rigorous evaluation of study quality was performed, and two authors independently completed study selection and data extraction. Adjusted risk estimates were used to account for the effect of potential confounders. Finally, sensitivity analysis

of between-study variation provided insight into data stability of pooled estimates and heterogeneity.

Some limitations of our study need, however, to be mentioned as well. First, although we performed the search strategy in accordance with previous meta-analyses on familial cancer risk,[22,23] we did not assess the full text of all studies on BO and OAC, making it possible that studies that only reported the influence of a family history on BO or OAC as secondary outcome in the full text may have been missed. However, our sensitivity analysis and references of eligible articles and literature reviews did not reveal any additional articles. Second, results were derived from a combination of cohort and case-control studies with different study populations and heterogeneous nature of family history definitions, resulting in substantial heterogeneity in analyses. Most importantly, only eight studies verified the accuracy of self-reported data or used objective measures to confirm a positive family history. Furthermore, five studies only assessed family history of oesophageal cancer and did not distinguish between adenocarcinoma and squamous cell carcinoma of the oesophagus in relatives.[32,36,37,40,43] Third, not all studies were adjusted for potential confounders, especially the effect of obesity, GERD and family size. Additionally, some studies combined BO and OAC for study outcomes and multivariable analyses could therefore not be included. Fourth, although reported family history is thought to be fairly accurate, controls may have been more likely to underreport their family history than BO or OAC patients (recall bias).[65,66] Fifth, literature shows that the higher the number of affected relatives with cancer and the lower the age at cancer diagnosis in relatives, the greater the risks for an individual to develop cancer.[22,23,67] Unfortunately, few studies reported on age at diagnosis of index patients or on the affected relatives or adjusted for number of family members. Also, data on BO and OAC risks for individuals with at least two affected first-degree relatives or second-degree relatives were limited and no study reported on the length of the BO segment in relatives. Hence, we were not able to assess BO or OAC risks according to the age of the individual at risk, age at diagnosis of the relative(s), degree of familial relation between the individual and relatives and number of affected relatives.

This review draws attention to the limited number of well-designed studies assessing a positive family history as a predictor of BO and OAC. Future longitudinal studies with well-defined family history criteria determining the risk of BO and OAC according to the number and age of affected relatives are needed to provide additional insight into the impact of family history on BO and neoplastic progression. Additionally, future research should focus on the underlying mechanisms of familial BO and identifying genetic risk factors. This could lead to more individualised screening, surveillance, prevention and treatment strategies for the clinical management of BO and OAC.

In conclusion, this systematic review and meta-analysis shows that familial aggregation is observed in a small but important subgroup of patients with BO and OAC. The currently available evidence identified a verified positive family history as a strong risk factor for BO and OAC. The review emphasises the importance of

obtaining a careful family history in all patients with BO or OAC. A confirmed family history of having at least two affected first-degree relatives and/or family history combined with other risk factors for BO and OAC can be used to identify individuals in which (endoscopic) screening might be considered to prevent OAC-related mortality.

AUTHORSHIP

Guarantor of the article: Yonne Peters.

Author contributions: Yonne Peters was involved in study concept and design, data acquisition, quality control of data, data analysis and interpretation, statistical analysis, manuscript preparation, editing and review. Evi van Grinsven was involved in data acquisition, quality control of data, data analysis and critical revision of the manuscript. Peter D. Siersema was involved in study concept and design, data interpretation, critical revision of the manuscript and study supervision.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

1. Smyth EC, Lagergren J, Fitzgerald RC, et al. Oesophageal cancer. *Nature Rev Dis Primers*. 2017;3:17048.
2. Arnold M, Laversanne M, Brown LM, et al. Predicting the future burden of esophageal cancer by histological subtype: international trends in incidence up to 2030. *Am J Gastroenterol*. 2017;112:1247-1255.
3. Arnold M, Ferlay J, van Berge Henegouwen MI, et al. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. *Gut*. 2020;69:1564.
4. van Putten M, de Vos-Geelen J, Nieuwenhuijzen GAP, et al. Long-term survival improvement in oesophageal cancer in the Netherlands. *Eur J Cancer*. 2018;94:138-147.
5. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med*. 2011;365:1375-1383.
6. Peters Y, Al-Kaabi A, Shaheen NJ, et al. Barrett oesophagus. *Nat Rev Dis Primers*. 2019;5:35.
7. Ronkainen J, Aro P, Storskrubb T, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology*. 2005;129:1825-1831.
8. Rex DK, Cummings OW, Shaw M, et al. Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. *Gastroenterology*. 2003;125:1670-1677.

9. Tan MC, Mansour N, White DL, et al. Systematic review with meta-analysis: prevalence of prior and concurrent Barrett's oesophagus in oesophageal adenocarcinoma patients. *Aliment Pharmacol Ther*. 2020;52:20-36.
10. Peters Y, Honing J, Kievit W, et al. Incidence of progression of persistent nondysplastic Barrett's esophagus to malignancy. *Clin Gastroenterol Hepatol*. 2019;17:869-877.e5.
11. Sappati Biyyani RS, Chessler L, McCain E, et al. Familial trends of inheritance in gastro esophageal reflux disease, Barrett's esophagus and Barrett's adenocarcinoma: 20 families. *Dis Esophagus*. 2007;20:53-57.
12. Jochem VJ, Fuerst PA, Fromkes JJ. Familial Barrett's esophagus associated with adenocarcinoma. *Gastroenterology*. 1992;102:1400-1402.
13. Drovdlic CM, Goddard KAB, Chak A, et al. Demographic and phenotypic features of 70 families segregating Barrett's oesophagus and oesophageal adenocarcinoma. *J Med Genet*. 2003;40:651.
14. Martincorena I, Fowler JC, Wabik A, et al. Somatic mutant clones colonize the human esophagus with age. *Science*. 2018;362:911-917.
15. Robson ME, Bradbury AR, Arun B, et al. American society of clinical oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol*. 2015;33:3660-3667.
16. Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: diagnosis and management of Barrett's esophagus. *Am J Gastroenterol*. 2016;111:30-50; quiz 1.
17. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut*. 2014;63:7-42.
18. Weusten B, Bisschops R, Coron E, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. *Endoscopy*. 2017;49:191-198.
19. Qumseya B, Sultan S, Bain P, et al. ASGE guideline on screening and surveillance of Barrett's esophagus. *Gastrointest Endosc*. 2019;90:335-59.e2.
20. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology*. 2011;140:1084-1091.
21. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008-2012.
22. Roos VH, Mangas-Sanjuan C, Rodriguez-Girondo M, et al. Effects of family history on relative and absolute risks for colorectal cancer: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2019;17:2657-67.e9.
23. Wong MCS, Chan CH, Lin J, et al. Lower relative contribution of positive family history to colorectal cancer risk with increasing age: a systematic review and meta-analysis of 9.28 million individuals. *Am J Gastroenterol*. 2018;113:1819-1827.
24. Greenland S, Thomas DC. On the need for the rare disease assumption in case-control studies. *Am J Epidemiol*. 1982;116:547-553.
25. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. *Ann Intern Med*. 2013;158:280-286.
26. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods*. 2020;12:55–61. http://dx.doi.org/10.1002/jrsm.1411.
27. Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc*. 1927;22:209-212.
28. Berkson J. Application of the logistic function to bio-assay. *J Am Stat Assoc*. 1944;39:357-365.
29. Lipsey MW, Wilson DB. *Practical meta-analysis*. SAGE Publications Inc.; 2001.
30. Viechtbauer W. Bias and efficiency of meta-analytic variance estimators in the random-effects model. *J Educ Behav Stat*. 2005;30:261-293.

31. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.

32. Ash S, Vaccaro BJ, Dabney MK, et al. Comparison of endoscopic and clinical characteristics of patients with familial and sporadic Barrett's esophagus. *Dig Dis Sci*. 2011;56:1702-1706.

33. Chak A, Lee T, Kinnard MF, et al. Familial aggregation of Barrett's oesophagus, oesophageal adenocarcinoma, and oesophagogastric junctional adenocarcinoma in Caucasian adults. *Gut*. 2002;51:323-328.

34. Chak A, Faulx A, Kinnard M, et al. Identification of Barrett's esophagus in relatives by endoscopic screening. *Am J Gastroenterol*. 2004;99:2107-2114.

35. Chak A, Ochs-Balcom H, Falk G, et al. Familiality in Barrett's esophagus, adenocarcinoma of the esophagus, and adenocarcinoma of the gastroesophageal junction. *Cancer Epidemiol Biomarkers Prev*. 2006;15:1668-1673.

36. Dhillon PK, Farrow DC, Vaughan TL, et al. Family history of cancer and risk of esophageal and gastric cancers in the United States. *Int J Cancer*. 2001;93:148-152.

37. Jiang X, Tseng CC, Bernstein L, et al. Family history of cancer and gastroesophageal disorders and risk of esophageal and gastric adenocarcinomas: a case-control study. *BMC Cancer*. 2014;14:60.

38. Juhasz A, Mittal SK, Lee TH, et al. Prevalence of Barrett esophagus in first-degree relatives of patients with esophageal adenocarcinoma. *J Clin Gastroenterol*. 2011;45:867-871.

39. Kharazmi E, Babaei M, Fallah M, et al. Importance of tumor location and histology in familial risk of upper gastrointestinal cancers: a nationwide cohort study. *Clin Epidemiol*. 2018;10:1169-1179.

40. Lagergren J, Ye W, Lindgren A, et al. Heredity and risk of cancer of the esophagus and gastric cardia. *Cancer Epidemiol Biomarkers Prev*. 2000;9:757-760.

41. Mussetto A, Manno M, Fuccio L, et al. Screening for Barrett's oesophagus with oesophageal capsule endoscopy in first-degree relatives of patients affected by Barrett's oesophagus: results of a pilot study. *Arab J Gastroenterol*. 2013;14:51-54.

42. Romero Y, Cameron AJ, Schaid DJ, et al. Barrett's esophagus: prevalence in symptomatic relatives. *Am J Gastroenterol*. 2002;97:1127-1132.

43. Rubenstein JH, Tavakkoli A, Koeppe E, et al. Family history of colorectal or esophageal cancer in Barrett's esophagus and potentially explanatory genetic variants. *Clin Transl Gastroenterol*. 2020;11:e00151.

44. Tofani CJ, Gandhi K, Spataro J, et al. Esophageal adenocarcinoma in a first-degree relative increases risk for esophageal adenocarcinoma in patients with Barrett's esophagus. *United Eur Gastroenterol J*. 2019;7:225-229.

45. Verbeek RE, Spittuler LF, Peute A, et al. Familial clustering of Barrett's esophagus and esophageal adenocarcinoma in a European cohort. *Clin Gastroenterol Hepatol*. 2014;12:1656-63.e1.

46. Chak A, Chen Y, Vengoechea J, et al. Variation in age at cancer diagnosis in familial versus nonfamilial Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev*. 2012;21:376-383.

47. Ji J, Hemminki K. Familial risk for esophageal cancer: an updated epidemiologic study from Sweden. *Clinical Gastroenterol Hepatol*. 2006;4:840-845.

48. Baldwin-Hunter BL, Knotts RM, Leeds SD, et al. Use of the electronic health record to target patients for non-endoscopic Barrett's esophagus screening. *Dig Dis Sci*. 2019;64:3463-3470.

49. De Ceglie A, Filiberti R, Blanchi S, et al. History of cancer in first degree relatives of Barrett's esophagus patients: a case-control study. *Clin Res Hepatol Gastroenterol*. 2011;35:831-838.

50. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33:159-174.

51. Qumseya BJ, Bukannan A, Gendy S, et al. Systematic review and meta-analysis of prevalence and risk factors for Barrett's esophagus. *Gastrointest Endosc*. 2019;90:707-17.e1.

52. Mohammed I, Cherkas LF, Riley SA, et al. Genetic influences in gastro-oesophageal reflux disease: a twin study. *Gut*. 2003;52:1085-1089.

53. Stunkard AJ, Foch TT, Hrubec Z. A twin study of human obesity. *JAMA*. 1986;256:51-54.

54. Trudgill NJ, Kapur KC, Riley SA. Familial clustering of reflux symptoms. *Am J Gastroenterol*. 1999;94:1172-1178.

55. Romero Y, Cameron AJ, Locke GR 3rd, et al. Familial aggregation of gastroesophageal reflux in patients with Barrett's esophagus and esophageal adenocarcinoma. *Gastroenterology*. 1997;113:1449-1456.

56. Groves C, Jankowski J, Barker F, et al. A family history of Barrett's oesophagus: another risk factor? *Scand J Gastroenterol*. 2005;40:1127-1128.

57. Gharahkhani P, Fitzgerald RC, Vaughan TL, et al. Genome-wide association studies in oesophageal adenocarcinoma and Barrett's oesophagus: a large-scale meta-analysis. *Lancet Oncol*. 2016;17:1363-1373.

58. Sun X, Elston R, Barnholtz-Sloan J, et al. A segregation analysis of Barrett's esophagus and associated adenocarcinomas. *Cancer Epidemiol Biomarkers Prev*. 2010;19:666-674.

59. Ek WE, Levine DM, D'Amato M, et al. Germline genetic contributions to risk for esophageal adenocarcinoma, Barrett's esophagus, and gastroesophageal reflux. *J Natl Cancer Inst*. 2013;105:1711-1718.

60. Sawas T, Killcoyne S, Iyer PG, et al. Identification of prognostic phenotypes of esophageal adenocarcinoma in two independent cohorts. *Gastroenterology*. 2018;155:1720–1728.e4. http://dx.doi.org/10.1053/j.gastro.2018.08.036.

61. Fitzgerald RC, di Pietro M, O'Donovan M, et al. Cytosponge-trefoil factor 3 versus usual care to identify Barrett's oesophagus in a primary care setting: a multicentre, pragmatic, randomised controlled trial. *Lancet (London, England)*. 2020;396:333-344.

62. Ben-Menachem T, Decker GA, Early DS, et al. Adverse events of upper GI endoscopy. *Gastrointest Endosc*. 2012;76:707-718.

63. Peters Y, Schrauwen RWM, Tan AC, et al. Detection of Barrett's oesophagus through exhaled breath using an electronic nose device. *Gut*. 2020:gutjnl-2019-320273.

64. Sami SS, Dunagan KT, Johnson ML, et al. A randomized comparative effectiveness trial of novel endoscopic techniques and approaches for Barrett's esophagus screening in the community. *Am J Gastroenterol*. 2015;110:148-158.

65. Aitken J, Bain C, Ward M, et al. How accurate is self-reported family history of colorectal cancer? *Am J Epidemiol*. 1995;141:863-871.

66. Khoury MJ, Flanders WD. Bias in using family history as a risk factor in case-control studies of disease. *Epidemiology*. 1995;6:511-519.

67. Lowery JT, Ahnen DJ, Schroy PC 3rd, et al. Understanding the contribution of family history to colorectal cancer risk and its clinical implications: a state-of-the-science review. *Cancer*. 2016;122:2633-2645.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.