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The Association Between Obesity and Malignant Progression of Barrett's Esophagus: A Systematic Review and Dose-Response Meta-Analysis

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BACKGROUND AND AIMS: **Obesity is a risk factor for both Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC). However, it is unclear whether obesity drives the malignant progression of BE. We aimed to assess whether obesity is associated with high-grade dysplasia (HGD) or cancer in patients with BE.**

METHODS: **We searched MEDLINE and EMBASE from inception through April 2024 for studies reporting the effect of body mass index (BMI) on the progression of nondysplastic BE or low-grade dysplasia (LGD) to HGD or EAC. A 2-stage dose-response meta-analysis was performed to estimate the dose-response relationship between BMI with malignant progression. Study quality was appraised using a modified Newcastle-Ottawa scale.**

RESULTS: **Twenty studies reported data on 38,565 patients (74.4% male) in total, of whom 1684 patients were diagnosed with HGD/cancer. Nineteen studies were considered moderate to high quality. Eight cohort studies reported data on 6647 male patients with baseline nondysplastic BE/LGD, of whom 555 progressed to HGD/EAC (pooled annual rate of progression, 0.02%; 95% confidence interval [CI], 0.01%–0.03%), and 1992 female patients with baseline nondysplastic BE/LGD, with 110 progressors (pooled annual rate of progression, 0.01%; 95% CI, 0.01%–0.02%). There was no significant difference in pooled annual rate of progression between males and females ($P = .15$). Each 5-kg/m^2 increase in BMI was associated with a 6% increase in the risk of malignant progression (adjusted odds ratio, 1.06; 95% CI, 1.02–1.10; $P < .001$; $I^2 = 0\%$).**

CONCLUSION: **Our meta-analysis provides some evidence that obesity as measured by BMI is associated with malignant progression of BE with a dose-response relationship. This finding requires confirmation in future high-quality cohort studies. Future risk prediction models could incorporate measures of obesity to potentially improve risk stratification in patients with BE. PROSPERO, Number: CRD42017051046.**

Keywords: Barrett's Esophagus; EAC; Risk Factor; Obesity.

Esophageal adenocarcinoma (EAC) is an aggressive cancer with a poor prognosis.[1] The 5-year overall survival rate of patients with EAC is below 20%.[2] Barrett's esophagus (BE), the only recognized precursor lesion to EAC, is associated with a 30-fold increase in the incidence of EAC.[3] Patients with BE are at a 4.5-fold relative increase in death from esophageal cancer compared with the general population.[4] Malignant progression of BE is characterized by a metaplasia-dysplasia-adenocarcinoma sequence, whereby nondysplastic BE epithelium progresses through dysplasia (low-grade dysplasia [LGD] then high-grade dysplasia [HGD]) to invasive adenocarcinoma.[5–7] Current guidelines advocate endoscopic surveillance to aid prevention

Abbreviations used in this paper: AO, abdominal obesity; BE, Barrett's esophagus; BMI, body mass index; CI, confidence interval; EAC, esophageal adenocarcinoma; EC, esophageal carcinoma; GERD, gastroesophageal reflux disease; HGD, high-grade dysplasia; IL, interleukin; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus; OR, odds ratio; PPI, proton pump inhibitor; WHR, waist-to-hip ratio.

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and the early detection of adenocarcinoma in patients with BE.[8–10] However, it is well established the majority of patients do not progress to cancer.[11,12] There may be a marked rise in the population prevalence of BE in the future with the emergence of effective screening measures, such as the Cytosponge-trefoil factor 3 test.[13] It is therefore important to establish the relevant clinical risk factors for malignant progression in this cohort to enable risk stratification and facilitate a personalized approach to the long-term management of patients with BE.

Obesity has been implicated in the pathogenesis of many reflux-related esophageal disorders such as gastroesophageal reflux disease (GERD), BE, and EAC.[14–18] Guidelines advocate obesity as a criterion for targeted screening for BE in patients with chronic reflux symptoms.[8,10] While obesity is a recognized risk factor for both BE and EAC,[19–22] it is unclear whether obesity per se is a risk factor for progression to HGD or EAC in patients with BE. This systematic review and meta-analysis aimed to assess whether anthropometric measures of obesity are associated with risk of HGD or EAC in patients with BE.

What You Need to Know

Background

Obesity is a well-recognized risk factor of both Barrett's esophagus (BE) and esophageal adenocarcinoma. The role of obesity in the malignant progression of BE is yet to be established.

Findings

There is a dose-response relationship between body mass index and malignant progression of BE.

Information for patient care

Body mass index should be considered as a variable in future risk prediction models of malignant progression of BE.

Materials and Methods

This systematic review was conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines.[23] The protocol was registered on PROSPERO (CRD42017051046).

Information Sources and Search Strategy

We identified relevant articles and abstracts by searching MEDLINE and EMBASE databases from inception to March 2024 by using the OVID interface (the search strategy is detailed in Supplementary Table 1). We used the following search terms (including related terms) to construct the search strategy: "Barrett's esophagus," "dysplasia," "cancer," "esophageal adenocarcinoma," "progression," "overweight," "obese," "body mass index," and "risk factor." No language restrictions were applied on the searches. Following this, reference lists of retrieved articles were reviewed to identify any additional studies for inclusion.

Eligibility Criteria

Observational studies (case-control and cohort studies) meeting the following eligibility criteria were included: (1) adults (≥18 years of age); (2) either documented nondysplastic BE at entry for cohort studies or as a control group (who did not progress to HGD or EAC) in case-control studies or documented BE (a mixture of nondysplastic BE, either indefinite for dysplasia or LGD or unknown dysplasia status) at entry for cohort studies or as a control group (who did not progress to HGD/EAC) in case-control studies; (3) reported outcome of HGD, EAC, or esophageal cancer (EC); or (4) measure of obesity presented (body mass index [BMI] or waist-to-hip ratio [WHR]) with effect size data (or sufficient data provided for its estimation) for each category of exposure or on a continuous scale. Studies were ineligible if they (1) included the baseline population with HGD, or pure LGD or indefinite for dysplasia; or (2) did not report the effect size or values necessary for its calculation. In the event that multiple publications arose from the same population, we included the study with the most relevant and contemporaneous cohort. Two reviewers (L.A. and M.T.K.) independently screened abstracts and selected full-text articles for inclusion based on the eligibility and exclusion criteria. Discrepancies were resolved through discussion between reviewers.

Data Extraction and Quality Assessment

Two reviewers (M.T.K. and E.H.) independently extracted data from each selected article for study characteristics (study design, location, setting, recruitment period, definition of BE used, number of patients with nondysplastic BE or LGD at baseline, percentage of patients with LGD at baseline, number of patients that progressed to HGD or EAC, definition of progression, measure of obesity, time period measured for BMI, follow-up duration, method of ascertainment for BMI and the variables adjusted in multivariable analyses) and patient characteristics (age, sex, ethnicity, smoking status, use of statins, proton pump inhibitor [PPI], and aspirin at baseline).

The methodological quality of included studies was assessed by 2 independent reviewers (M.T.K. and E.H.) using a modified Newcastle-Ottawa scale for quality assessment of case-control and cohort studies[24] adapted for the purpose of this systematic review (Supplementary Tables 2 and 3). Using this scale, studies

were scored across 3 domains: selection (4 questions), comparability (3 questions), exposure for case-control studies (3 questions), and outcome for cohort studies (3 questions). Therefore, for each individual study, the highest possible score was 10 points. We categorized the quality of the studies based on their total score: low (0–4), moderate (5–7), and high (8–10). Discrepancies were resolved through consensus between reviewers.

Statistical Analysis

Characteristics of eligible studies were tabulated and coded according to BMI categories, outcomes, and comparators to determine the studies eligible for each synthesis. We performed all statistical analyses using STATA version 18 (StataCorp LP).

The Stata command glst was used to estimate trends across different categories of exposure. Considering that malignant progression of BE is a relatively rare outcome, effect sizes from odds ratios (ORs), relative risks, or hazard ratios would be expected to approximate one another. A 2-stage dose-response random-effects meta-analysis was performed to estimate the dose-response relationship between the anthropometric measure of interest (BMI) on a continuous scale with malignant progression.[25,26] In the first stage, the generalized least-squares method was used to estimate the linear trend for each included study that provides category-specific effect sizes. In the second stage, the linear trends derived from the first stage were combined and studies reporting associations on a continuous scale were also included, using a random-effects dose-response meta-regression model. A 2-sided *P* value of .05 or less was considered statistically significant. For studies that reported BMI in a categorical range, the midpoint of the cutpoints of that category was assigned as the dose value. For open-ended categories (eg, BMI >35 kg/m^2), we assigned the estimated median BMI from previous observational studies as the dose value, according to whether the studies were population-based or primarily hospital-based.[27,28] For studies that do not provide the distribution of cases and controls (or progressors and nonprogressors), pseudocounts were calculated from the estimated covariance of the published effect sizes.[29] The possible nonlinear relationship was modeled using restricted cubic splines (with 3 knots).

Heterogeneity between studies was assessed using the inconsistency index (I^2) statistic. I^2 values of <30%, 30%–59%, 60%–75%, and ≥75% were considered to represent low, moderate, substantial, and considerable heterogeneity, respectively.[30,31] We also conducted subgroup analyses to explore the potential between-study sources of heterogeneity for the following characteristics: study design, study setting, baseline dysplasia, study outcome, exposure ascertainment, concurrent medication use, definition of BE, follow-up duration, period excluded until the diagnosis of HGD/EAC, and study quality. The results of subgroup analyses were considered statistically significant if *P* value for subgroup differences was <0.1.[32] It was not possible to stratify the effect of obesity on malignant progression of BE according to sex. Therefore, a post hoc analysis was undertaken to assess the influence of study level proportion of men (%) on the association between BMI and malignant progression using meta-regression. Small study effects were assessed visually using a funnel plot and Egger's regression for comparisons with at least 10 estimates.[33]

Results

Search and Selection of Studies

Among 1187 articles identified from the literature search, 65 full-text articles were assessed for eligibility, with 20 ultimately selected for inclusion (Figure 1).[28,34–53] Forty-five articles were rejected because the baseline population did not have established BE or included patients with HGD (n = 4), the reported outcome was not HGD/EAC or EC (n = 2), measures of obesity were not presented with effect sizes or there was insufficient data for their estimation (n = 38), and 1 study included overlapping data from a study with a larger cohort (Supplementary Table 4).

Study Characteristics

Twenty studies reported data on 38,565 patients in total, of whom 1684 patients were diagnosed with HGD/EAC/EC. Study characteristics are shown in Table 1. These studies were published between 2005 and 2022, and the enrollment period ranged from 1976 to 2019. Thirteen were from Europe,[28,34–38,41,42,46,47,49,50,52,53] 5 were from the United States,[39,40,44,45,51] and 2 involved cohorts from multiple countries.[43,48] Five were population based,[35,38,39,43,44] 9 were multicenter,[28,36,41,42,46,48–50,52,53] and 6 were single-center studies.[34,37,40,45,47,51] Twelve were cohort studies,[38–42,45–48,50–52] 4 were case-control studies,[34,36,37,49] and 4 were nested case-control studies.[28,35,43,44,53] BE was defined as the presence of endoscopic appearance of columnar lined esophagus confirmed by the presence of intestinal metaplasia on histology in 16 studies.[28,34,36,37,39–42,45–53] In the remaining 4 studies, the definition of BE was based on clinical codes (Read code, International Classification of Diseases–Ninth Revision code, etc.).[35,38,43,44] Progression was defined as development of HGD in 1 study,[37] EC in 1 study,[38] EAC in 4 studies,[34–36,44] and HGD/EAC in 14 studies.[28,39–43,45–53] The majority of the patients had nondysplastic BE as baseline (78.8% in cohort studies). Baseline dysplasia status was not reported in 4 database studies due to the absence of detailed histopathology data in these studies.[35,38,43,44] Twelve cohort studies reported data on 19,223 patients with baseline nondysplastic BE

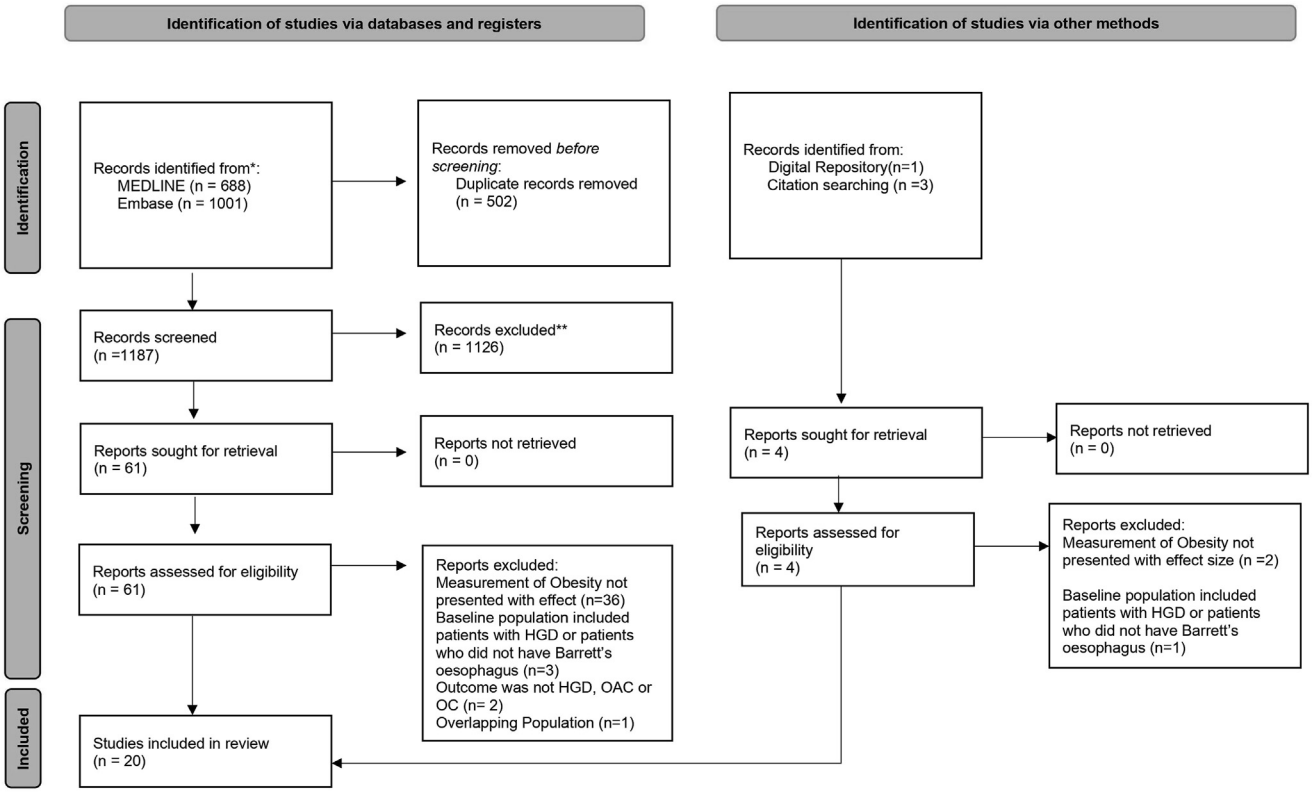

Figure 1. PRISMA flow chart.

(NDBE)/LGD, of whom 816 progressed to HGD/EAC/EC (with a pooled annual rate of progression of 0.03%; 95% confidence interval [CI], 0.02%–0.03%).[38–42,45–48,50–52]

BMI was used as a measure of obesity in all studies. Although there is a slight variation in the cutoff points for BMI between studies, the World Health Organization international classification of obesity was used in the majority of studies (ie, below 18.5 kg/m^2 is considered underweight, 18.5–24.99 kg/m^2 normal weight, 25–29.99 kg/m^2 overweight, and 30 kg/m^2 or higher obese).[28,34,37,40,41,43–45,49,53] Three studies categorized BMI using a single threshold (BMI <25 kg/m^2 vs >25 kg/m^2; BMI >30 kg/m^2).[36,46,48] Six studies reported BMI on a continuous scale.[35,39,42,47,50,52] BMI was measured at baseline or closest to the index endoscopy in 14 studies.[35–42,44–46,50–52] The time point at which BMI was measured in relation to baseline was not specified in 4 studies.[28,43,47,48,53] BMI data were extracted directly from medical records or population datasets in 13 studies[24,28,35,37–40,43–47,51,53] and they were self-reported in 6 studies.[34,36,41,42,49,50] Effect of measures of abdominal obesity was reported in only 2 studies.[37,40] The median follow-up duration in cohort studies was 4.5 years (range, 2.1–7.9 years).

Participant Characteristics

The baseline characteristics of the patients included in the studies are shown in Table 2. Of all participants, 74.4% were male. Eight cohort studies reported data on 6647 male patients with baseline NDBE/LGD, of whom 555 progressed to HGD/EAC (pooled annual rate of progression, 0.02%; 95% CI, 0.01%–0.03%) and 1992 female patients with baseline NDBE/LGD with 110 progressors (pooled annual rate of progression, 0.01%; 95% CI, 0.01%–0.02%).[40–42,45,46,48,50,51] There was no significant difference in the pooled annual rate of progression between males and females ($P = .15$). The number of male and female progressors was not reported in the remaining 4 cohort studies. Nine studies reported the ethnicity of participants,[34,36,37,40,44,45,48,49,51] in which 90% were Caucasian. Smoking status was recorded in 16 studies in which more than half of the participants (53%) were smokers (current/ex-smokers).[28,34–36,38–45,48–50,52] Concurrent medication usage was recorded in 16 studies,[34–36,38–45,47–50,52] in which 33.7% of participants were statin users, 84% were PPI users, and 28% were aspirin users.

Association Between BMI and Risk of Malignant Progression of BE

Based on our meta-analyses, obesity as measured by BMI (per 5-kg/m^2 increase) was associated with a 4% increase in the risk of malignant progression in patients with BE (unadjusted OR, 1.04; 95% CI, 1.00–1.07; $I^2 = 57.23\%$; $P < .001$) (Figure 2, Supplementary Figure 1). This association persisted using adjusted risk estimates reported in individual studies, with a 6% increased risk of developing HGD and/or EAC for every 5-kg/m^2 increase in BMI

Table 1. Characteristics of Selected Studies

Study	Design	Location	Setting	Recruitment Period	Definition of BE	Patients With NDBE/LGD at Baseline With Proportion of Patients With LGD	Patients With HGD/EAC	Progression Definition	Measure of Obesity	Time Period Measured for BMI	Median FU (y)	Measure Ascertainment for BMI	Variables Adjusted for[a]	FU Period Excluded in Cohort Studies (mo)[b]
Alexandre (2017)[28]	NCC	United Kingdom	MC	2000–2013	IM, CLE, at least 3 cm	217 NDBE 100%	HGD 24, EAC 55	HGD/EAC	BMI	NR	3.9	Medical records	1, 2	6
Beales (2012)[34]	CC	United Kingdom	SC	2009–2011	IM, CLE, at least 3 cm	Control 170	EAC 85	EAC	BMI	1 y before index	NR	Self-administered questionnaire	1–3, 6, 7, 10	CC
Cooper (2014)[35]	NCC	United Kingdom	PB	1988–2006	Read code	3749	EAC 55	EAC	BMI	Closest to first coded entry of BE	4	Health Registry	1–3	12
De Jonge (2006)[36]	CC	The Netherlands	MC	2003–2005	IM, CLE >2 cm	Control 244	EAC 91	EAC	BMI	Baseline	NR	Self-administered questionnaire	1–3, 9, 10–12	CC
Di Caro (2006)[37]	CC	United Kingdom	SC	2011–2013	IM, CLE at least 3 cm	249	HGD 84	HGD/EAC	BMI, WHR	Baseline	NR	Medical records	Unadjusted	CC
Krishnamoorthi (2016)[38]	Cohort	United Kingdom	PB	1991–2010	Read code	9660	EC 103	EC	BMI	Closet to index EGD	4.8[c]	Health Registry	1–3, 5, 7, 9	12
Jung (2011)[39]	Cohort	United States	PB	1976–2006	IM, CLE	355 LGD 17%	EAC 7, HGD 12	HGD/EAC	BMI	Baseline	7.8	Medical records	Unadjusted	6
Kambhampati (2020)[40]	Cohort	United States	SC	1992–2013	IM, CLE at least 1 cm	460 LGD 4%	HGD 132, EAC 62	HGD/EAC	BMI, AO	Baseline	7.78[c]	Medical records	1, 3, 4, 7–9, 13	6
Kastelein (2011)[41]	Cohort	The Netherlands	MC	2003–2009	IM, CLE at least 2 cm	570 LGD 14%	HGD 26, EAC 12	HGD/EAC	BMI	Baseline	4.5	Self-administered questionnaire	Unadjusted	9
Klaver (2021)[42]	Cohort	The Netherlands	MC	2003–2017	IM, CLE at least 1 cm	985 LGD 7.9%	HGD 28, EAC 39,	HGD/EAC	BMI	Baseline	7.9	Self-administered questionnaire	Unadjusted	12
Masclee (2015)[43]	NCC	United Kingdom	PB	1996–2011	Read code	12,312	EAC 40	HGD/EAC	BMI	NR	NR	Medical records	Unadjusted	12
Masclee (2015)[43]	NCC	The Netherlands	PB	1996–2013	ICPC code	1383	EAC 5, HGD 12	HGD/EAC	BMI	NR	NR	Medical records	Unadjusted	12
Nguyen (2015)[44]	NCC	United States	PB	2004–2009	ICD-9 code	856	EAC 311	EAC	BMI	Index EGD	NR	Medical records	Unadjusted	NR
Nguyen (2022)[45]	Cohort	United States	SC	1990–2019	IM, CLE	608	HGD/EAC 24	HGD/EAC	BMI	Index EGD	4.1[c]	Medical records	1–4, 8	NR
O'Byrne (2020)[46]	Cohort	United Kingdom	MC	2008–2011	IM, CLE	2244 LGD 7%	HGD 87, EAC 38	HGD/EAC	BMI	Index EGD	2.7[c]	Medical records	Unadjusted	3
Oberg (2005)[47]	Cohort	Sweden	SC	1979–1999	IM, CLE at least 2 cm	140 NDBE 100%	HGD 4, EAC 3	HGD/EAC	BMI	NR	5.8	Medical records	Unadjusted	12
Parasa (2018)[48]	Cohort	United States, the Netherlands	MC	1985–2014	IM, CLE	2697 LGD 14%	HGD 106, EAC 48	HGD/EAC	BMI	NR	6	Medical records	Unadjusted	12
Pohl (2013)[49]	CC	Germany	MC	2005–2009	CLE	162 LGD 6.8%	HGD/EAC 100	HGD/EAC	BMI	At age 40 y	NR	Self-administered questionnaire	1–7, 9, 11	NR
Sikkema (2011)[50]	Cohort	The Netherlands	MC	2003–2004	IM, CLE at least 2 cm	713 LGD 16%	HGD/EAC 26	HGD/EAC	BMI	Baseline	2.1[c]	Self-administered questionnaire	1,2	6

Table 1. Continued

Study	Design	Location	Setting	Recruitment Period	Definition of BE	Patients With NDBE/LGD at Baseline With Proportion of Patients With LGD	Patients With HGD/EAC	Progression Definition	Measure of Obesity	Time Period Measured for BMI	Median FU (y)	Measure Ascertainment for BMI	Variables Adjusted for[a]	FU Period Excluded in Cohort Studies (mo)[b]
Thota (2016)[51]	Cohort	United States	SC	2000–2012	IM, CLE	363 LGD 28.1%	HGD–28, EAC 15	HGD/EAC	BMI	Baseline	2.6[c]	Medical records	Unadjusted	6
Timmer (2016)[52]	Cohort	The Netherlands	MC	2002–2013	IM, CLE at least 1 cm	428 NDBE 100%	HGD 9, EAC 13	HGD/EAC	BMI	Baseline	3.6	NR	Unadjusted	6

AC, abdominal circumference; BMI, body mass index; CC, case-control; CLE, columnar-lined esophagus; EAC, esophageal adenocarcinoma; EC, esophageal carcinoma; EGD, esophagogastroduodenoscopy; FU, follow-up; HGD, high-grade dysplasia; ICD-9, International Classification of Diseases–Ninth Revision; ICPC, International Classification of Primary Care; IM, intestinal metaplasia; LGD, low-grade dysplasia; NCC, nested case-control; NDBE, nondysplastic Barrett's esophagus; NR, not reported; PB, population based; SC, single center; WHR, waist-to-hip ratio.

[a]1 = age; 2 = gender; 3 = smoking; 4 = length of Barrett's; 5 = proton pump inhibitor; 6 = aspirin; 7 = statin; 8 = baseline LGD; 9 = reflux; 10 = alcohol intake; 11 = fruit and vegetable intake; 12 = educational attainment; 13 = family history of EC.

[b]Deferred outcome ascertainment after diagnosis of BE to avoid prevalent neoplasia.

[c]Mean reported when median not available.

(adjusted OR, 1.06; 95% CI, 1.02–1.10; $I^2 = 0.01\%$; $P < .001$) (Figure 3, Supplementary Figure 2). Moderate heterogeneity was observed in the overall unadjusted analysis ($I^2 = 57.23\%$). This was primarily seen in the magnitude of the effect and not in the direction of the effect and was partially explained by differences in study design (see Subgroup Analysis).

Association Between Abdominal Obesity and Risk of Malignant Progression of BE

Only 2 studies assessed the role of abdominal obesity (AO) on the risk of malignant progression.[37,40] One study used WHR as a measure of AO,[37] while the other did not specify the measure used to define AO.[40] A case-control study conducted by di Caro et al[37] demonstrated that AO as measured by WHR was significantly associated with an increased risk of malignant progression in patients with BE (OR, 2.44; 95% CI, 1.2–4.9; $P = .01$). There were insufficient studies for meta-analyses that examined the effect of AO on malignant progression of BE.

Subgroup Analysis

We performed subgroup analyses based on study design, study location, baseline dysplasia status, outcome, study quality, definition of BE, follow-up duration, period excluded until the diagnosis of HGD/EAC, and exposure ascertainment. Significant heterogeneity was explained at least in part by study design in unadjusted analysis (OR of case-control studies vs cohort: 1.08 [95% CI, 1.03–1.14; $I^2 = 0$; 4 studies] vs 1.02 [95% CI, 0.98–1.06; $I^2 = 56.18\%$; 16 studies]; $P_{\text{interaction}} = .08$) (Table 3, Supplementary Figure 3). The association remained consistent across other subgroups (Table 3, Supplementary Figures 4–11). Similarly, consistent associations were observed across all subgroups in adjusted analysis (Table 3, Supplementary Figures 12–21).The results of the post hoc analysis suggested that there is no significant association between study-level proportion of men and the risk of malignant progression in both unadjusted and adjusted analyses (unadjusted OR vs adjusted OR [per % increase in men]: 0.999 [95% CI, 0.997–1.002; $P = .75$] vs 0.999 [95% CI, 0.995–1.004; $P = .91$]).

Study Quality and Small-Study Effects

Study quality, as assessed using the modified Newcastle-Ottawa scale, is summarized in Supplementary Table 5. The included studies scored between 4 and 8 (maximum 10). One scored 4 (low quality), 14 scored between 5 and 7 (moderate quality), and 5 scored 8 (high quality). No studies were excluded from meta-analysis as a consequence of quality assessment. There was no evidence of small-study effects, such as publication bias, based on visual inspection of funnel

Table 2. Baseline Characteristics of Patients in the Included Studies

Study	Age (y)	Male (%)	Caucasian (%)	Smoking (%)	Statin at Baseline (%)	Aspirin at Baseline (%)	PPI Use at Baseline (%)
Alexandre (2017)[28]	67.9 ± 10.3	86.1	NR	55.8	22.8	24.7	67.1
Beales (2012)[34]	67.3 ± 12.0	80	100	59.4	35.3	27.1	NR
Cooper (2014)[35]	63 (52–72)	63	NR	55	30	32	97
De Jonge (2006)[36]	62 ± 11.7	67	99	74	NR	NR	93
Di Caro (2016)[37]	52.03 ± 16.44	41.1	97.20	NR	NR	NR	NR
Krishnamoorthi (2016)[38]	63 ± 13.5	62.6	NR	51.91	27.62	NR	84.65
Jung (2011)[39]	63 ± 14	72	NR	62	NR	NR	NR
Kambhampati (2020)[40]	67.01 ± 12.99	64	91	49	38	30	93
Kastelein (2011)[41]	60.4	72	NR	66	37	28	NR
Klaver (2021)[42]	57 ± 11	74	NR	63.7	NR	NR	89.5
Masclee (United Kingdom) (2015)[43]	70.2 ± 9.0	91	NR	51	36	26.4	86.9
Masclee (the Netherlands) (2015)[43]	66.4 ± 8.8	70	NR	49.5	16.3	6.2	51.7
Nguyen (2015)[44]	64.5 ± 9.1	100	83.70	13.4	54	1.3	80.4
Nguyen (2022)[45]	61.6 ± 8.6	95.9	79.90	74.3	NR	NR	69.4
O'Byrne (2020)[46]	60 (50–69)	68.7	NR	NR	NR	NR	NR
Oberg (2005)[47]	57.3 (47.6–67.5)	74.3	NR	NR	NR	NR	60.7
Parasa (2018)[48]	55.4 ± 20.1	84.1	87.60	54.1	58.2	NR	96.5
Pohl (2012)[49]	63.4 ± 11.4	72	100	64	31	51	78
Sikkema (2011)[50]	60.5 (20–86)	74	NR	65	NR	14	90
Thota (2016)[51]	60.6 ± 13.0	75.7	94.70	NR	NR	NR	NR
Timmer (2016)[52]	60 (51–67)	81	NR	69	NR	NR	99

Values are mean ± SD or median (interquartile range), unless otherwise indicated.
NR, not reported; PPI, proton pump inhibitor.

plots or with Egger's regression test ($P = .57$) (Supplementary Figure 22). Meta-regression was performed to assess the effect of study quality on the association between BMI and malignant progression of BE. The association was not statistically significant in both unadjusted and adjusted analyses (unadjusted OR vs adjusted OR [per 1-unit increase in study quality]: 1.01 [95% CI, 0.98–1.04; $P = .52$] vs 0.99 [95% CI, 0.94–1.05; $P = .7$]).

Discussion

Our systematic review suggests there is some evidence of a dose-response relationship between obesity as measured by BMI on the malignant progression of BE. Adjusted and unadjusted analyses demonstrate a 6% and 4% relative increase, respectively, in risk of progression for every 5 kg/m^2 increase in BMI. Associations were most pronounced in case-control studies that relied on self-reported BMI, and the effect of obesity on the malignant progression of BE seemed to be consistent across all other subgroups.

To the best of our knowledge, our study is the largest and most comprehensive assessment of the literature on the association between obesity and risk of malignant progression of BE. Our results are compatible with the findings from the previous meta-analysis by Krishnamoorthi et al,[54] which in addition to BMI, investigated a host of demographic, clinical, and endoscopic predictors for malignant progression. This study reported a 4% increase in the risk of malignant progression for each unit increase in BMI based on adjusted estimates; however, it did not reach statistical significance (OR, 1.04; 95% CI, 0.93–1.17; $I^2 = 53\%$; 6 studies; 14,532 participants with 275 progressors). We did not include 1 prospective study by Hardikar et al[55] included in the previous analysis, as the baseline population included patients with HGD, which therefore did not meet our eligibility criteria. Our meta-analysis

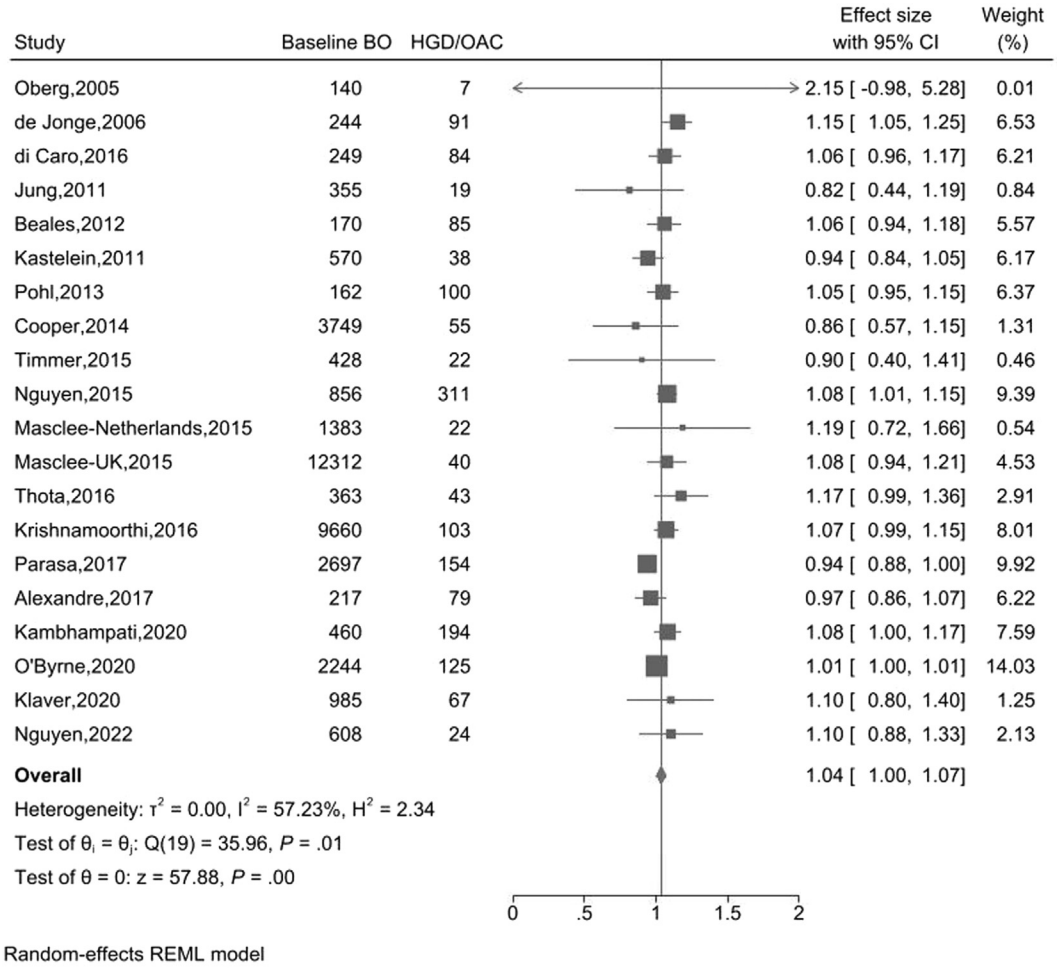

Figure 2. Unadjusted meta-analysis assessing the risk of EAC and/or HGD in patients with baseline BE (purely NDBE), a mixture of nondysplastic and LGD or BE based on diagnostic codes) per 5-kg/m^2 increase in BMI.

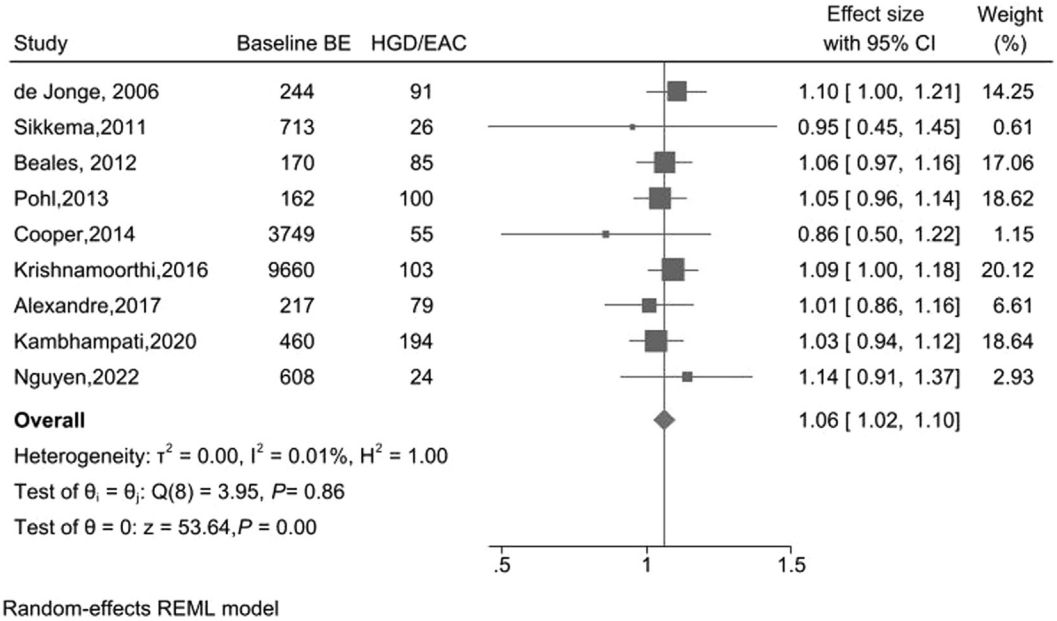

Figure 3. Adjusted meta-analysis assessing the risk of esophageal adenocarcinoma(EAC) and/or high-grade dysplasia (HGD) in patients with baseline BE (purely NDBE, a mixture of nondysplastic and LGD or BE based on diagnostic codes) per 5-kg/m^2 increase in body mass index (BMI).

Table 3. Subgroup Analyses

Groups	Category	Studies	Odds Ratio (95% CI)	Heterogeneity Within Groups (I^2) (%)	Heterogeneity Between Groups (P for interaction)
Unadjusted analysis					
Study design	Case-control	4	1.08 (1.03–1.14)	0	.080
	Cohort	16	1.02 (0.98–1.06)	56.18	
Study setting	Hospital based	14	1.03 (0.99–1.08)	63.50	.290
	Population based	6	1.07 (1.02–1.11)	0	
Baseline dysplasia	Nondysplastic	3	0.96 (0.86–1.07)	0	.160
	At most LGD	12	1.04 (0.99–1.08)	67.13	
	Unknown	5	1.07 (1.02–1.12)	0.01	
Study outcome	HGD/EAC	18	1.04 (1.00–1.08)	59.77	.790
	EC	2	1.01 (0.83–1.20)	46.68	
Study quality	Higher (Newcastle-Ottawa scale score ≥7)	10	1.03 (1.00–1.06)	26.03	.750
	Lower (Newcastle-Ottawa scale score <7)	10	1.04 (0.97–1.12)	62.03	
Exposure ascertainment	Medical records	14	1.03 (0.99–1.07)	56.98	.620
	Self-report	5	1.06 (0.98–1.13)	52.19	
Definition of BE	Length specified (at least 1 cm)	10	1.03 (0.98–1.08)	62.90	.610
	Length not specified	10	1.05 (0.99–1.11)	36.59	
Study follow-up period	Follow-up <3 y	2	1.06 (0.91–1.22)	68.87	.10
	Follow-up more than 3 y	13	1.01 (0.96–1.06)	37.31	
	Not reported	5	1.08 (1.04–1.12)	0.02	
Period excluded until the diagnosis of HGD/cancer in cohort studies	12 mo	7	1.02 (0.94–1.10)	44.59	.12
	3 mo	1	1.01 (1.00–1.01)	NA	
	6 mo	5	1.04 (0.94–1.13)	40.76	
	9 mo	1	0.94 (0.84–1.05)	NA	
	Not reported	2	1.08 (1.02–1.15)	0.00	
Adjusted analysis					
Study design	Case-control	3	1.07 (1.01–1.12)	0	.72
	Cohort	6	1.05 (1.00–1.11)	0	
Study setting	Hospital based	7	1.06 (1.01–1.1)	0.01	.89
	Population based	2	1.04 (0.86–1.23)	33.54	
Baseline dysplasia	Nondysplastic	1	1.01 (0.86–1.16)	NA	.8
	At most LGD	6	1.06 (1.02–1.11)	0	
	Unknown	2	1.04 (0.86–1.23)	33.54	
Study outcome	HGD/EAC	8	1.05 (1.01–1.10)	0	.45
	EC	1	1.09 (1.00–1.18)	NA	
Study quality	Higher (Newcastle-Ottawa scale score ≥7)	8	1.05 (1.01–1.10)	0.02	.37
	Lower (Newcastle-Ottawa scale score <7)	1	1.10 (1.00–1.21)	NA	
Exposure ascertainment	Medical records	5	1.06 (1.00–1.11)	0.01	.78
	Self-report	4	1.07 (1.01–1.12)	0.01	
Definition of BE	Length specified (at least 1 cm)	3	1.06 (1.00–1.12)	0.02	.93
	Length not specified	6	1.06 (1.01–1.11)	0.01	
Study follow-up period	Follow up <3 y	1	0.95 (0.45–1.45)	NA	.86
	Follow up more than 3 y	5	1.06 (1.00–1.11)	0.01	
	Not reported	3	1.07 (1.01–1.12)	0.00	
Period excluded until the diagnosis of HGD/cancer in cohort studies	12 mo	2	1.04 (0.86–1.23)	33.54	.64
	6 mo	3	1.02 (0.95–1.10)	0.00	
	Not reported	1	1.14 (0.91–1.37)	NA	
Concurrent medication use	Adjusted for	4	1.06 (1.01–1.10)	0.02	.83
	Not adjusted for	5	1.07 (0.99–1.15)	0	

BMI, body mass index; BE, Barrett's esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; EC, esophageal carcinoma; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NA, not applicable.

included a further 14 studies. Our meta-analysis also adds to the previous meta-analysis in that we investigated several potential important sources of heterogeneity, and investigated both linear and nonlinear associations. Previous research has demonstrated a strong association between BMI and BE, with the risk increasing by 12% per kg/m^2 increase in BMI (OR, 1.12; 95% CI, 1.00–1.25).[56] A meta-analysis of prospective cohort studies demonstrated a strong dose-response relationship between BMI (per 5-kg/m^2 increase) and EAC in both men and women (relative risk in men vs women: 1.52 [95% CI, 1.33–1.74; $I^2 = 24\%$; $P < .0001$; 5 studies] vs 1.51 [95% CI, 1.31–1.74; $I^2 = 0\%$; $P < .0001$; 3 studies]).[20] These effects are much stronger than those observed in our study. This may suggest that obesity (as determined by BMI) may play a more important role in the etiology of BE than in malignant progression.

Interestingly, some studies suggest that the pattern of fat distribution plays a more important role than general obesity in esophageal carcinogenesis.[16,21] There were only 2 studies identified from the literature search that explored the effect of abdominal obesity on the malignant progression of BE.[37,40] It was demonstrated in both studies that AO is significantly associated with malignant progression of BE. A meta-analysis by Singh et al[16] reported that central obesity, independent of BMI, was strongly and consistently associated with the development of esophageal inflammation, metaplasia and neoplasia.

Although the exact mechanisms by which obesity promotes esophageal carcinogenesis is not fully understood, several possible mechanisms may explain this association. The most obvious pathologic link is via GERD, with the mechanical effect of visceral obesity promoting the GERD directly, and hence the sequence of Barrett's dysplasia–cancer indirectly.[18,57] It has been demonstrated in experimental studies that gastric acid and bile acid drive malignant changes in esophageal epithelium through stimulation of proliferation, inhibition of apoptosis, and generation of free radicals.[58,59]

In addition, the role of systematic inflammatory and metabolic pathways has been implicated in obesity-induced carcinogenesis.[57] Visceral adipose tissue has been recognized as a complex metabolically active tissue, which secretes cytokines such as tumor necrosis factor α, interferon β, and interleukins (ILs) such as IL-1 and IL–6.[59,60] Furthermore, adiposity is associated with increased production of adipocytokines such as leptin and reduced secretion of adiponectin, which may play a pivotal role in cancer progression through promotion of cell proliferation and angiogenesis.[61,62] Whereas relative adiponectin deficiency may exacerbate the preneoplastic signaling of these growth factors,[62] another potential mechanism that can explain the association is the state of insulin resistance induced by obesity associated chronic inflammation.[57] This drives an increased plasma levels of insulin and insulin growth factors, which in turn leads to activation of insulin growth factor receptors, resulting in signaling pathways that stimulate carcinogenesis.[63]

Our systematic review has a number of strengths. The study protocol was preregistered. We used a robust and contemporaneous search strategy with well-defined inclusion criteria. Study quality was rigorously assessed. Additionally, studies were selected from a range of locations including Europe and the United States, and as such the results are broadly generalizable to Western populations. We also performed a detailed subgroup analysis, allowing better assessment of the magnitude of associations based on important study and patient characteristics. Adjusted and unadjusted risk estimates were evaluated and enabled analysis of the potential influence of measured confounders on the summary estimate. Use of aspirin, PPIs, and statins did not appear to confound the association between obesity and malignant progression (assuming that they exert a chemopreventive effect), as suggested by a post hoc analysis that demonstrated effect sizes were similar between studies that did and did not adjust for the use of these medications. Pooled annual rates of malignant progression in cohort studies were broadly consistent with the literature, supporting generalizability of this research.[64]

There are some limitations in our study. First, our meta-analysis included both cohort (including nested case-control designs) and case-control studies. There is a possibility of reverse causation bias, and the strength of the association between obesity and risk of malignant progression may be underestimated. This is particularly pertinent in case-control studies, in which weight was recorded close to cancer diagnosis. However, it is unlikely that reverse causation bias would explain the positive association seen with the dose-response relationship. Second, we considered whether recall bias might explain the observed associations, a limitation applicable to case-control studies. The results of subgroup analyses demonstrated the association was more pronounced in case-control studies compared with cohort studies in unadjusted analyses. Interestingly, 3 out of 4 case-control studies included in the analyses relied on self-reported BMI. Recall bias could operate if cases systematically overestimated their weight (and/or underestimated their height) or controls systematically underestimated their weight (and/or overestimated their height). However, each of these scenarios seems unlikely. Subgroup analyses comparing the method ascertainment of BMI (self-reported vs based on medical records) demonstrated no significant differences in either for unadjusted or adjusted effect sizes. Furthermore, in adjusted analyses, effect sizes were similar in both case-control and cohort studies. Third, despite our efforts to mitigate the possible influence of confounding factors on the summary estimate, the presence of residual confounding factors which were not routinely adjusted for in most studies cannot be excluded. Fourth, baseline histopathology data were not available in some

studies. This limited the authors' and our ability to assess the grade of dysplasia at baseline. This is applicable to population-based studies reliant on diagnostic codes for BE. However, the majority of patients would be expected to be nondysplastic at a population level.[46] Fifth, similarly, it is not possible to verify whether all patients with BE included in population-based studies using diagnostic codes were strictly defined by the presence of columnar-lined esophagus of at least 1 cm as recommended by the guidelines. However, the results of a post hoc subgroup analysis revealed no significant difference in overall effect sizes between studies that strictly used the definition of BE as recommended by the guidelines and those that did not specify the length of BE or used diagnostic codes. Sixth, there were limited published data available that assessed the association between measures of abdominal obesity (such as abdominal circumference and WHR) and malignant progression of BE. Most studies included in the meta-analysis used BMI as a measure of obesity and only 2 studies incorporated other measures of obesity such as abdominal obesity. Although BMI is widely used in large scale studies, it is a crude form of measurement of body composition and cannot differentiate between lean and fat mass. Seventh, although we acknowledge the potential role of the differences in hormonal profile and fat distribution between males and females, we could not directly estimate the effect of BMI on the malignant progression of BE through stratification by sex. This is because BMI values were not provided separately for men and women in all included studies. Eighth, similar BMI categories (eg, World Health Organization classification of obesity) were used in most studies, which limited assessment of nonlinear associations and inferences from extremes in BMI.

The findings of this review have implications for clinical practice and future research. Our study has highlighted the paucity of research on the impact of measures of visceral obesity on the malignant progression of BE. Future high-quality observational studies that incorporate anthropometric measures of AO and sophisticated body composition parameters will help elucidate the relationship between obesity and malignant progression of BE. High-quality cohort studies that examine the linear and nonlinear associations between measures of obesity and malignant progression of BE are also required. Additionally, future studies that examine the role of diet, lifestyle, and bariatric interventions in modulating the risk of EAC in obese patients with BE are required. Furthermore, there is a need for the development and validation of simple risk prediction models which incorporate BMI or measures of central obesity alongside other recognized risk factors, to allow targeted surveillance of higher-risk groups.

In conclusion, this research provides some evidence obesity as measured by BMI is associated with malignant progression of BE with a dose-response relationship. The association remained broadly consistent across subgroup analyses. The findings from our study are consistent with mechanistic evidence, which suggests the carcinogenic effect of obesity. The research has implications for risk stratification of patients with BE and supports future mechanistic and interventional research in the role of obesity in malignant progression.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2024.07.041.

References

1. Pennathur A, Gibson MK, Jobe BA, et al. Esophageal carcinoma. Lancet 2013;381:400–412.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7–30.
3. Solaymani-Dodaran M, Logan RF, West J, et al. Risk of oesophageal cancer in Barrett's oesophagus and gastro-oesophageal reflux. Gut 2004;53:1070–1074.
4. Solaymani-Dodaran M, Card TR, West J. Cause-specific mortality of people with Barrett's esophagus compared with the general population: a population-based cohort study. Gastroenterology 2013;144:1375–1383, 1383.e1.
5. Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. Gut 2002;51:130–131.
6. Flejou JF. Barrett's oesophagus: from metaplasia to dysplasia and cancer. Gut 2005;54:i6–i12.
7. Montgomery E, Goldblum JR, Greenson JK, et al. Dysplasia as a predictive marker for invasive carcinoma in Barrett esophagus: a follow-up study based on 138 cases from a diagnostic variability study. Hum Pathol 2001;32:379–388.
8. 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.
9. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association technical review on the management of Barrett's esophagus. Gastroenterology 2011;140:e18–e52; quiz e13.
10. Shaheen NJ, Falk GW, Iyer PG, et al. Diagnosis and Management of Barrett's Esophagus: An Updated ACG Guideline. Am J Gastroenterol 2022;117:559–587.
11. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst 2011;103:1049–1057.
12. 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.
13. 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 2020;396:333–344.
14. Corley D, Kubo A. Body mass index and gastroesophageal reflux disease: a systematic review and meta-analysis. Am J Gastroenterol 2006;101:2619–2628.
15. Turati F, Tramacere I, La Vecchia C, et al. A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. Ann Oncol 2013;24:609–617.

16. Singh S, Sharma AN, Murad MH, et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2013;11:1399–1412.e7.
17. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med 2005;143:199–211.
18. Lagergren J. Influence of obesity on the risk of esophageal disorders. Nat Rev Gastroenterol Hepatol 2011;8:340–347.
19. Kubo A, Cook MB, Shaheen NJ, et al. Sex-specific associations between body mass index, waist circumference and the risk of Barrett's oesophagus: a pooled analysis from the international BEACON consortium. Gut 2013;62:1684–1691.
20. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371:569–578.
21. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. Cancer Epidemiol Biomarkers Prev 2008;17:352–358.
22. Steffen A, Huerta JM, Weiderpass E, et al. General and abdominal obesity and risk of esophageal and gastric adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2015;137:646–657.
23. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
24. Wells GA, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed August 8, 2023.
25. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135:1301–1309.
26. Orsini NBR, Greenland S. Generalized Least Squares for Trend Estimation of Summarized Dose–response Data. Stata J 2006;6:40–57.
27. Yates M, Cheong E, Luben R, et al. Body mass index, smoking, and alcohol and risks of Barrett's esophagus and esophageal adenocarcinoma: a UK prospective cohort study. Dig Dis Sci 2014;59:1552–1559.
28. Alexandre L, Royston C, Caygill C, et al. PWE-130 Statin use and risk of malignant progression in patients with nondysplastic barrett's oesophagus: a nested case-control study. Gut 2017;66:A192–A193.
29. Hamling J, Lee P, Weitkunat R, et al. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 2008;27:954–970.
30. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence–inconsistency. J Clin Epidemiol 2011;64:1294–1302.
31. Kanwal F, White D. "Systematic Reviews and Meta-analyses" in Clinical Gastroenterology and Hepatology. Clin Gastroenterol Hepatol 2012;10:1184–1186.
32. Richardson M, Garner P, Donegan S. Interpretation of subgroup analyses in systematic reviews: A tutorial. Clinical Epidemiology and Global Health 2019;7:192–198.
33. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634.
34. Beales IL, Vardi I, Dearman L. Regular statin and aspirin use in patients with Barrett's oesophagus is associated with a reduced incidence of oesophageal adenocarcinoma. Eur J Gastroenterol Hepatol 2012;24:917–923.
35. Cooper S, Menon S, Nightingale P, et al. Risk factors for the development of oesophageal adenocarcinoma in Barrett's oesophagus: a UK primary care retrospective nested case-control study. United European Gastroenterol J 2014;2:91–98.
36. de Jonge PJ, Steyerberg EW, Kuipers EJ, et al. Risk factors for the development of esophageal adenocarcinoma in Barrett's esophagus. Am J Gastroenterol 2006;101:1421–1429.
37. Di Caro S, Cheung WH, Fini L, et al. Role of body composition and metabolic profile in Barrett's oesophagus and progression to cancer. Eur J Gastroenterol Hepatol 2016;28:251–260.
38. Krishnamoorthi R, Borah B, Heien H, et al. Rates and predictors of progression to esophageal carcinoma in a large population-based Barrett's esophagus cohort. Gastrointest Endosc 2016;84:40–46.e7.
39. Jung KW, Talley NJ, Romero Y, et al. Epidemiology and natural history of intestinal metaplasia of the gastroesophageal junction and Barrett's esophagus: a population-based study. Am J Gastroenterol 2011;106:1447–1455, quiz 1456.
40. Kambhampati S, Tieu AH, Luber B, et al. Risk Factors for Progression of Barrett's Esophagus to High Grade Dysplasia and Esophageal Adenocarcinoma. Sci Rep 2020;10:4899.
41. Kastelein F, Spaander MC, Biermann K, et al. Nonsteroidal anti-inflammatory drugs and statins have chemopreventative effects in patients with Barrett's esophagus. Gastroenterology 2011;141:2000–2008; quiz e13-e14.
42. Klaver E, Bureo Gonzalez A, Mostafavi N, et al. Barrett's esophagus surveillance in a prospective Dutch multi-center community-based cohort of 985 patients demonstrates low risk of neoplastic progression. United European Gastroenterol J 2021;9:929–937.
43. Masclee GM, Coloma PM, Spaander MC, et al. NSAIDs, statins, low-dose aspirin and PPIs, and the risk of oesophageal adenocarcinoma among patients with Barrett's oesophagus: a population-based case-control study. BMJ Open 2015;5:e006640.
44. Nguyen T, Duan Z, Naik AD, et al. Statin use reduces risk of esophageal adenocarcinoma in US veterans with Barrett's esophagus: a nested case-control study. Gastroenterology 2015;149:1392–1398.
45. Nguyen TH, Thrift AP, Ketwaroo GA, et al. External validation of a model determining risk of neoplastic progression of Barrett's esophagus in a cohort of U.S. veterans. Gastrointest Endosc 2022;95:1113–1122.
46. O'Byrne LM, Witherspoon J, Verhage RJJ, et al. Barrett's Registry Collaboration of academic centers in Ireland reveals high progression rate of low-grade dysplasia and low risk from nondysplastic Barrett's esophagus: report of the RIBBON network. Dis Esophagus 2020;33:doaa009.
47. Oberg S, Wenner J, Johansson J, et al. Barrett esophagus: risk factors for progression to dysplasia and adenocarcinoma. Ann Surg 2005;242:49–54.
48. Parasa S, Vennalaganti S, Gaddam S, et al. Development and Validation of a Model to Determine Risk of Progression of Barrett's Esophagus to Neoplasia. Gastroenterology 2018;154:1282–1289.e2.
49. Pohl H, Wrobel K, Bojarski C, et al. Risk factors in the development of esophageal adenocarcinoma. Am J Gastroenterol 2013;108:200–207.
50. Sikkema M, Looman CW, Steyerberg EW, et al. Predictors for neoplastic progression in patients with Barrett's Esophagus: a

prospective cohort study. Am J Gastroenterol 2011; 106:1231–1238.
51. Thota PN, Arora Z, Benjamin T, et al. Influence of body mass index on the prevalence and progression of dysplasia in Barrett's esophagus: a retrospective analysis. Scand J Gastroenterol 2016;51:1288–1293.
52. Timmer MR, Martinez P, Lau CT, et al. Derivation of genetic biomarkers for cancer risk stratification in Barrett's oesophagus: a prospective cohort study. Gut 2016;65:1602–1610.
53. Alexandre L. The potential role of statins in the treatment and prevention of oesophageal adenocarcinoma, 2017. Available at: https://ueaeprints.uea.ac.uk/id/eprint/65124. Accessed October 10, 2023.
54. Krishnamoorthi R, Singh S, Ragunathan K, et al. Factors Associated With Progression of Barrett's Esophagus: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2018;16:1046–1055.e8.
55. Hardikar S, Onstad L, Blount PL, et al. The role of tobacco, alcohol, and obesity in neoplastic progression to esophageal adenocarcinoma: a prospective study of Barrett's esophagus. PLoS One 2013;8:e52192.
56. Thrift AP, Shaheen NJ, Gammon MD, et al. Obesity and risk of esophageal adenocarcinoma and Barrett's esophagus: a Mendelian randomization study. J Natl Cancer Inst 2014;106:dju252.
57. Alexandre L, Long E, Beales IL. Pathophysiological mechanisms linking obesity and esophageal adenocarcinoma. World J Gastrointest Pathophysiol 2014;5:534–549.
58. Beales IL, Ogunwobi OO. Leptin synergistically enhances the anti-apoptotic and growth-promoting effects of acid in OE33 oesophageal adenocarcinoma cells in culture. Mol Cell Endocrinol 2007;274:60–68.
59. Dvorak K, Chavarria M, Payne CM, et al. Activation of the interleukin–6/STAT3 antiapoptotic pathway in esophageal cells by bile acids and low pH: relevance to barrett's esophagus. Clin Cancer Res 2007;13:5305–5313.
60. Doyle SL, Donohoe CL, Lysaght J, et al. Visceral obesity, metabolic syndrome, insulin resistance and cancer. Proc Nutr Soc 2012;71:181–189.
61. Howard JM, Beddy P, Ennis D, et al. Associations between leptin and adiponectin receptor upregulation, visceral obesity and tumour stage in oesophageal and junctional adenocarcinoma. Br J Surg 2010;97:1020–1027.
62. Beales ILP, Garcia-Morales C, Ogunwobi OO, et al. Adiponectin inhibits leptin-induced oncogenic signalling in oesophageal cancer cells by activation of PTP1B. Mol Cell Endocrinol 2014; 382:150–158.
63. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. Annu Rev Med 2010; 61:301–316.
64. Desai TK, Krishnan K, Samala N, et al. The incidence of oesophageal adenocarcinoma in nondysplastic Barrett's oesophagus: a meta-analysis. Gut 2012;61:970–976.

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Supplementary References

e1. Allen JE, Desai M, Roumans CAM, et al. Low risk of progression of Barrett's esophagus to neoplasia in women. J Clin Gastroenterology 2021;55:321–326.

e2. Anaparthy R, Gaddam S, Kanakadandi V, et al. Association between length of Barrett's esophagus and risk of high-grade dysplasia or adenocarcinoma in patients without dysplasia. Clin Gastroenterol Hepatology 2013;11:1430–1436.

e3. Akiyama T, Inamori M, Akimoto K, et al. Risk factors for the progression of endoscopic Barrett's epithelium in Japan: a multivariate analysis based on the Prague C & M Criteria. Dig Dis Sci 2009;54:1702–1707.

e4. Bani-Hani KE, Bani-Hani BK, Martin IG. Characteristics of patients with columnar-lined Barrett's esophagus and risk factors for progression to esophageal adenocarcinoma. World J Gastroenterol 2005;11:6807–6814.

e5. Bird-Lieberman EL, Dunn JM, Coleman HG, et al. Population-based study reveals new risk-stratification biomarker panel for Barrett's esophagus. Gastroenterology 2012;143:927–935.e3.

e6. Brown CS, Lapin B, Goldstein JL, et al. Predicting progression in Barrett's Esophagus: development and validation of the Barrett's Esophagus Assessment of Risk Score (BEAR Score). Ann Surg 2018;267:716–720.

e7. Coleman HG, Bhat S, Johnston BT, et al. Tobacco smoking increases the risk of high-grade dysplasia and cancer among patients with Barrett's esophagus. Gastroenterology 2012; 142:233–240.

e8. Dong LM, Kristal AR, Peters U, et al. Dietary supplement use and risk of neoplastic progression in esophageal adenocarcinoma: a prospective study. Nutr Cancer 2008;60:39–48.

e9. Duggan C, Onstad L, Hardikar S, et al. Association between markers of obesity and progression from Barrett's esophagus to esophageal adenocarcinoma. Clin Gastroenterol Hepatol 2013;11:934–943.

e10. Duits LC, Lao-Sirieix P, Wolf WA, et al. A biomarker panel predicts progression of Barrett's esophagus to esophageal adenocarcinoma. Dis Esophagus 2019;32:doy102.

e11. Duits LC, Klaver E, Bureo Gonzalez A, et al. The Amsterdam ReBus progressor cohort: identification of 165 Barrett's surveillance patients who progressed to early neoplasia and 723 nonprogressor patients. Dis Esophagus 2019;32:doy037.

e12. El-Serag HB, Aguirre TV, Davis S, et al. Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. Am J Gastroenterol 2004;99:1877–1883.

e13. Gatenby PA, Ramus JR, Caygill CP, et al. Aspirin is not chemoprotective for Barrett's adenocarcinoma of the oesophagus in multicentre cohort. Eur J Cancer Prev 2009; 18:381–384.

e14. Gatenby P, Caygill C, Wall C, et al. Lifetime risk of esophageal adenocarcinoma in patients with Barrett's esophagus. World J Gastroenterol 2014;20:9611–9617.

e15. Gatenby P, Bhattacharjee S, Wall C, et al. Risk stratification for malignant progression in Barrett's esophagus: Gender, age, duration and year of surveillance. World J Gastroenterol 2016;22:10592–10600.

e16. Hardikar S, Onstad L, Blount PL, et al. The role of tobacco, alcohol, and obesity in neoplastic progression to esophageal adenocarcinoma: a prospective study of Barrett's esophagus. PLoS One 2013;8:e52192.

e17. Hillman LC, Chiragakis L, Shadbolt B, et al. Effect of proton pump inhibitors on markers of risk for high-grade dysplasia and oesophageal cancer in Barrett's oesophagus. Aliment Pharmacol Ther 2008;27:321–326.

e18. Hillman LC, Chiragakis L, Shadbolt B, et al. Proton-pump inhibitor therapy and the development of dysplasia in patients with Barrett's oesophagus. Med J Aust 2004;180:387–391.

e19. Holmberg D, Ness-Jensen E, Mattsson F, et al. Clinical prediction model for tumor progression in Barrett's esophagus. Surg Endosc 2019;33:2901–2908.

e20. Hvid-Jensen F, Pedersen L, Funch-Jensen P, et al. Proton pump inhibitor use may not prevent high-grade dysplasia and oesophageal adenocarcinoma in Barrett's oesophagus: a nationwide study of 9883 patients. Aliment Pharmacol Ther 2014;39:984–991.

e21. 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.

e22. Iyer PG, Codipilly DC, Chandar AK, et al. Prediction of progression in Barrett's esophagus using a tissue systems pathology test: a pooled analysis of international multicenter studies. Clin Gastroenterol Hepatol 2022;20:2772–2779.e8.

e23. Kantor ED, Onstad L, Blount PL, et al. Use of statin medications and risk of esophageal adenocarcinoma in persons with Barrett's esophagus. Cancer Epidemiol Biomarkers Prev 2012;21:456–461.

e24. Katz D. The development of dysplasia and adenocarcinoma during endoscopic surveillance of Barrett's esophagus. Am J Gastroenterol 1998;93:536–541.

e25. Kunzmann AT, Thrift AP, Johnston BT, et al. External validation of a model to determine risk of progression of Barrett's oesophagus to neoplasia. Aliment Pharmacol Ther 2019; 49:1274–1281.

e26. Lastraioli E, Lottini T, Iorio J, et al. hERG1 behaves as biomarker of progression to adenocarcinoma in Barrett's esophagus and can be exploited for a novel endoscopic surveillance. Oncotarget 2016;7:59535–59547.

e27. Monardo A, McCullough J. Incidence of dysplasia in obese vs nonobese patients with nondysplastic Barrett esophagus. Ochsner J 2019;19:347–352.

e28. Murray L, Sedo A, Scott M, et al. TP53 and progression from Barrett's metaplasia to oesophageal adenocarcinoma in a UK population cohort. Gut 2006;55:1390–1397.

e29. Nelsen EM, Kirihara Y, Takahashi N, et al. Distribution of body fat and its influence on esophageal inflammation and dysplasia in patients with Barrett's esophagus. Clin Gastroenterol Hepatol 2012;10:728–734, quiz e61–e62.

e30. Nguyen DM, El-Serag HB, Henderson L, et al. Medication usage and the risk of neoplasia in patients with Barrett's esophagus. Clin Gastroenterol Hepatol 2009;7:1299–1304.

e31. Nguyen DM, Schwartz J, Richardson P, et al. Oral bisphosphonate prescriptions and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. Dig Dis Sci 2010;55:3404–3407.

e32. Nguyen DM, Richardson P, El-Serag HB. Medications (NSAIDs, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. Gastroenterology 2010;138:2260–2266.

e33. Peleg N, Schmilovitz-Weiss H, Shamah S, et al. Neutrophil to lymphocyte ratio and risk of neoplastic progression in patients with Barrett's esophagus. Endoscopy 2021;53:774–781.

e34. Peleg N, Ringel Y, Shamah S, et al. Development and validation of a prediction model for histologic progression in

patients with nondysplastic Barrett's esophagus. Dig Endosc 2023;35:718–725.

e35. 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.

e36. Redston M, Noffsinger A, Kim A, et al. Abnormal TP53 predicts risk of progression in patients with Barrett's esophagus regardless of a diagnosis of dysplasia. Gastroenterology 2022;162:468–481.

e37. Rubenstein JH, Raghunathan T, Doan C, et al. Validation of tools for predicting incident adenocarcinoma of the esophagus or esophagogastric junction. Am J Gastroenterol 2021; 116:949–957.

e38. Vaughan TL, Dong LM, Blount PL, et al. Non-steroidal anti-inflammatory drugs and risk of neoplastic progression in Barrett's oesophagus: a prospective study. Lancet Oncol 2005;6:945–952.

e39. Van Olphen SH, Ten Kate FJC, Doukas M, et al. Value of cyclin A immunohistochemistry for cancer risk stratification in Barrett esophagus surveillance: a multicenter case-control study. Medicine 2016;95:e5402.

e40. Thrift AP, Kendall BJ, Pandeya N, et al. A clinical risk prediction model for Barrett esophagus. Cancer Prev Res 2012; 5:1115–1123.

e41. Van Olphen S, Biermann K, Spaander MCW, et al. SOX2 as a novel marker to predict neoplastic progression in Barrett's esophagus. Am J Gastroenterol 2015;110:1420–1428.

e42. Tan MC, El-Serag HB, Yu X, et al. Acid suppression medications reduce risk of oesophageal adenocarcinoma in Barrett's oesophagus: a nested case-control study in US male veterans. Aliment Pharmacol Ther 2018;48:469–477.

e43. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's oesophagus patients: results from a large population-based study. J Natl Cancer Inst 2011;103:1049–1057.

e44. Sato F, Jin Z, Schulmann K, et al. Three-tiered risk stratification model to predict progression in Barrett's oesophagus using epigenetic and clinical features. PLos One 2008;3:e1890.

e45. Dong J, Buas MF, Gharahkhani P, et al. Determining risk of Barrett's esophagus and esophageal adenocarcinoma based on epidemiologic factors and genetic variants. Gastroenterology 2018;154:1273–1281.e3.

e46. Alexandre L, Royston C, Caygill C, et al. PWE-130 Statin use and risk of malignant progression in patients with nondysplastic barrett's oesophagus: a nested case-control study. Gut 2017;66:A192–A193.

e47. Beales IL, Vardi I, Dearman L. Regular statin and aspirin use in patients with Barrett's oesophagus is associated with a reduced incidence of oesophageal adenocarcinoma. Eur J Gastroenterol Hepatol 2012;24:917–923.

e48. Cooper S, Menon S, Nightingale P, et al. Risk factors for the development of oesophageal adenocarcinoma in Barrett's oesophagus: a UK primary care retrospective nested case-control study. United European Gastroenterol J 2014;2:91–98.

e49. de Jonge PJ, Steyerberg EW, Kuipers EJ, et al. Risk factors for the development of esophageal adenocarcinoma in Barrett's esophagus. Am J Gastroenterol 2006;101:1421–1429.

e50. Di Caro S, Cheung WH, Fini L, et al. Role of body composition and metabolic profile in Barrett's oesophagus and progression to cancer. Eur J Gastroenterol Hepatol 2016;28:251–260.

e51. Krishnamoorthi R, Borah B, Heien H, et al. Rates and predictors of progression to esophageal carcinoma in a large population-based Barrett's esophagus cohort. Gastrointest Endosc 2016;84:40–46.e7.

e52. Jung KW, Talley NJ, Romero Y, et al. Epidemiology and natural history of intestinal metaplasia of the gastroesophageal junction and Barrett's esophagus: a population-based study. Am J Gastroenterol 2011;106:1447–1455, quiz 1456.

e53. Kambhampati S, Tieu AH, Luber B, et al. Risk Factors for Progression of Barrett's Esophagus to High Grade Dysplasia and Esophageal Adenocarcinoma. Sci Rep 2020;10:4899.

e54. Kastelein F, Spaander MC, Biermann K, et al. Nonsteroidal anti-inflammatory drugs and statins have chemopreventative effects in patients with Barrett's esophagus. Gastroenterology 2011;141:2000–2008; quiz e13-e14.

e55. Klaver E, Bureo Gonzalez A, Mostafavi N, et al. Barrett's esophagus surveillance in a prospective Dutch multi-center community-based cohort of 985 patients demonstrates low risk of neoplastic progression. United European Gastroenterol J 2021;9:929–937.

e56. Masclee GM, Coloma PM, Spaander MC, et al. NSAIDs, statins, low-dose aspirin and PPIs, and the risk of oesophageal adenocarcinoma among patients with Barrett's oesophagus: a population-based case-control study. BMJ Open 2015;5: e006640.

e57. Nguyen T, Duan Z, Naik AD, et al. Statin use reduces risk of esophageal adenocarcinoma in US veterans with Barrett's esophagus: a nested case-control study. Gastroenterology 2015;149:1392–1398.

e58. Nguyen TH, Thrift AP, Ketwaroo GA, et al. External validation of a model determining risk of neoplastic progression of Barrett's esophagus in a cohort of U.S. veterans. Gastrointest Endosc 2022;95:1113–1122.

e59. O'Byrne LM, Witherspoon J, Verhage RJJ, et al. Barrett's Registry Collaboration of academic centers in Ireland reveals high progression rate of low-grade dysplasia and low risk from nondysplastic Barrett's esophagus: report of the RIBBON network. Dis Esophagus 2020;33:doaa009.

e60. Oberg S, Wenner J, Johansson J, et al. Barrett esophagus: risk factors for progression to dysplasia and adenocarcinoma. Ann Surg 2005;242:49–54.

e61. Parasa S, Vennalaganti S, Gaddam S, et al. Development and Validation of a Model to Determine Risk of Progression of Barrett's Esophagus to Neoplasia. Gastroenterology 2018; 154:1282–1289.e2.

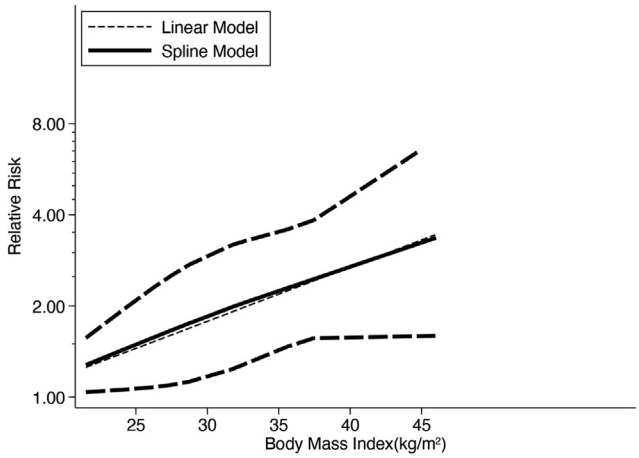
e62. Pohl H, Wrobel K, Bojarski C, et al. Risk factors in the development of esophageal adenocarcinoma. Am J Gastroenterol 2013;108:200–207.

e63. Sikkema M, Looman CW, Steyerberg EW, et al. Predictors for neoplastic progression in patients with Barrett's Esophagus: a prospective cohort study. Am J Gastroenterol 2011; 106:1231–1238.

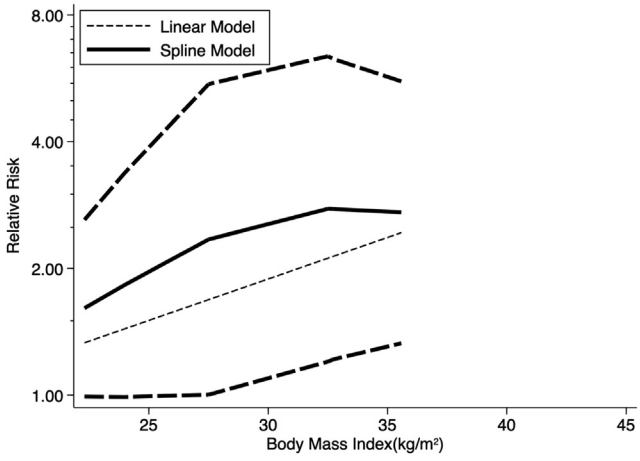
e64. Thota PN, Arora Z, Benjamin T, et al. Influence of body mass index on the prevalence and progression of dysplasia in Barrett's esophagus: a retrospective analysis. Scand J Gastroenterol 2016;51:1288–1293.

e65. Timmer MR, Martinez P, Lau CT, et al. Derivation of genetic biomarkers for cancer risk stratification in Barrett's oesophagus: a prospective cohort study. Gut 2016;65:1602–1610.

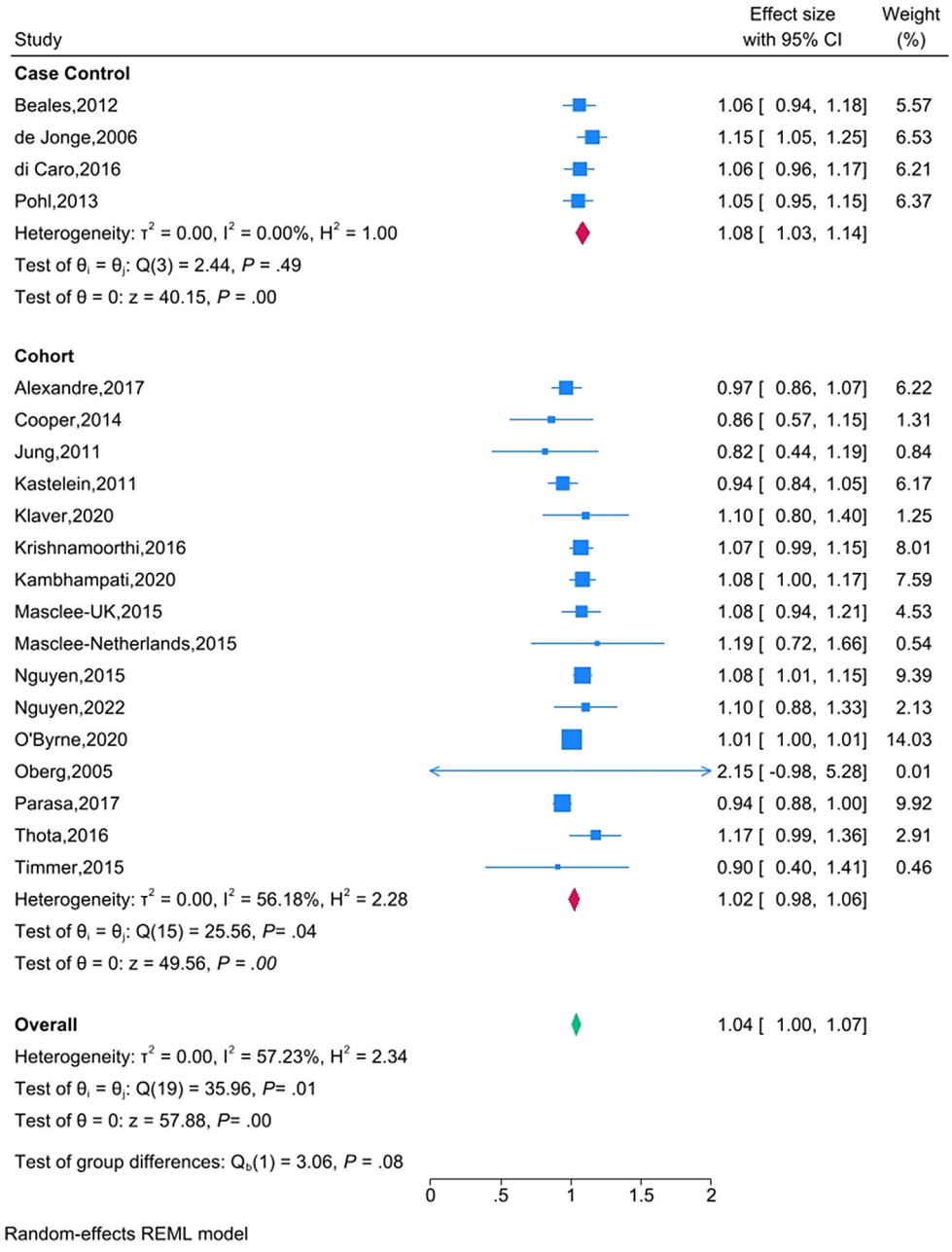
e66. Textor J, Van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. Int J Epidemiol 2016;45: 1887–1894.



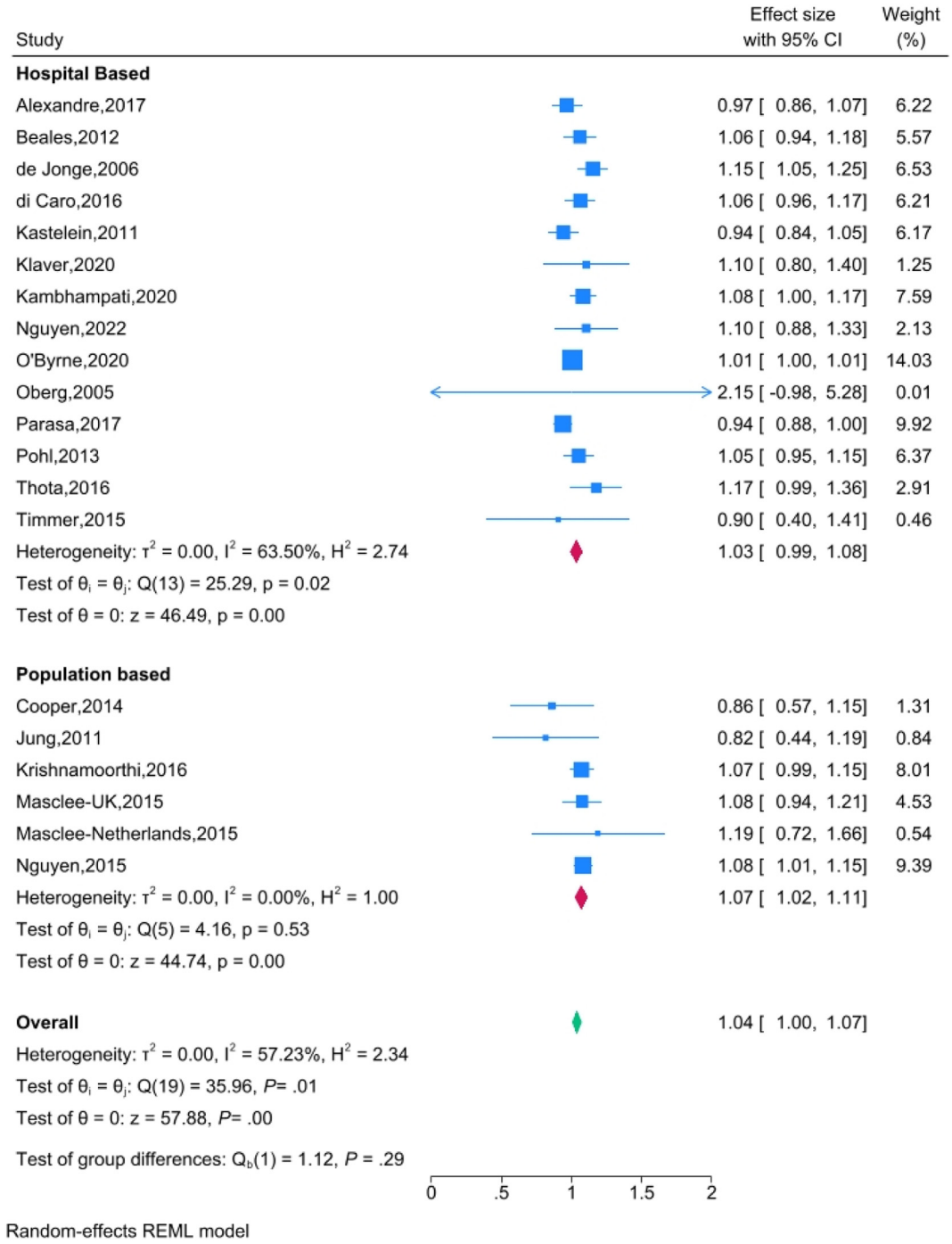
Supplementary Figure 1. Cubic spline model to assess the possible nonlinear relationship between obesity and risk of malignant progression of Barrett's esophagus (unadjusted). Number of contributing studies = 20.



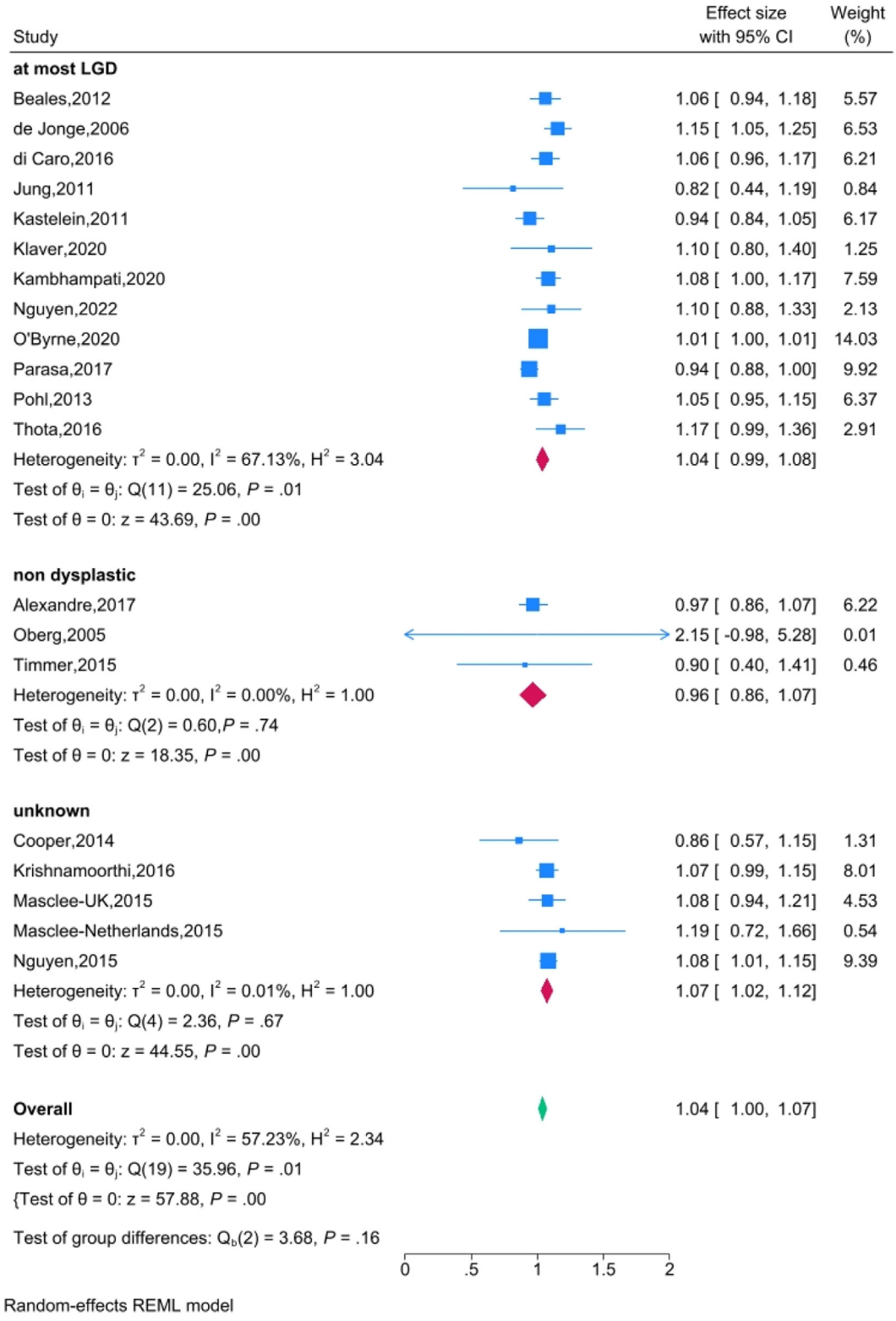
Supplementary Figure 2. Cubic spline model to assess the possible nonlinear relationship between obesity and risk of malignant progression of Barrett's esophagus (adjusted). Number of contributing studies = 9.



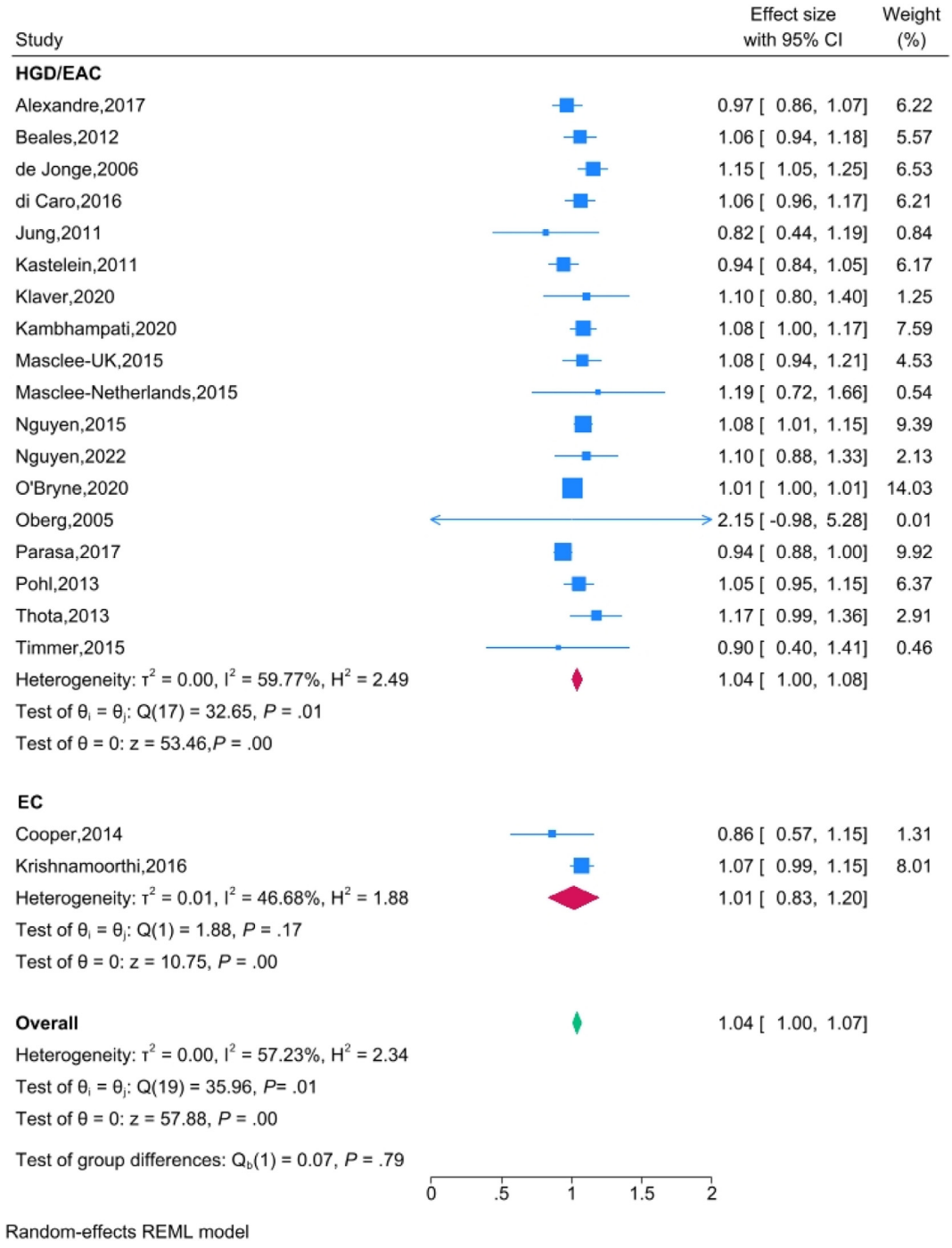
Supplementary Figure 3. Subgroup analysis based on study design (unadjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



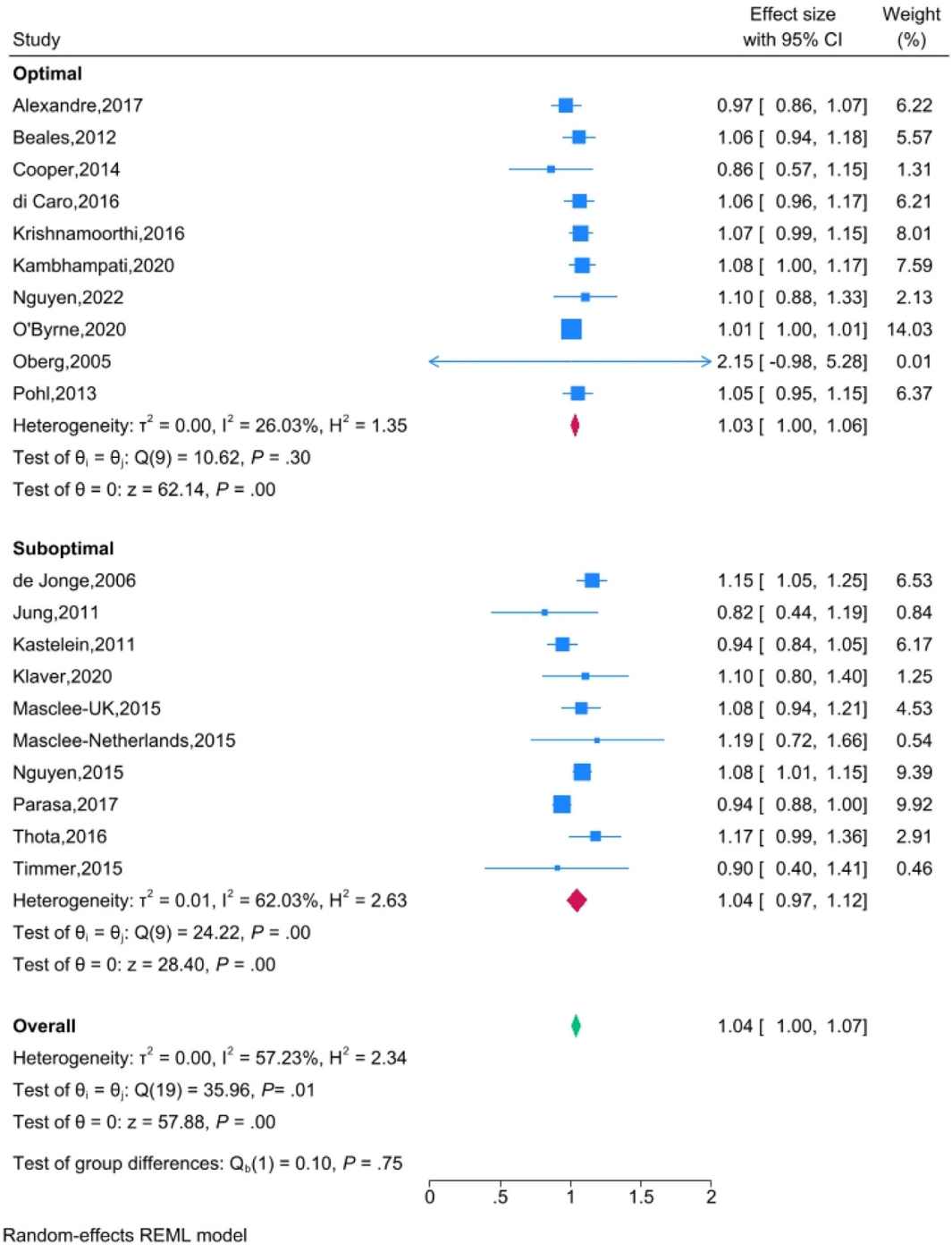
Supplementary Figure 4. Subgroup analysis based on study setting (unadjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



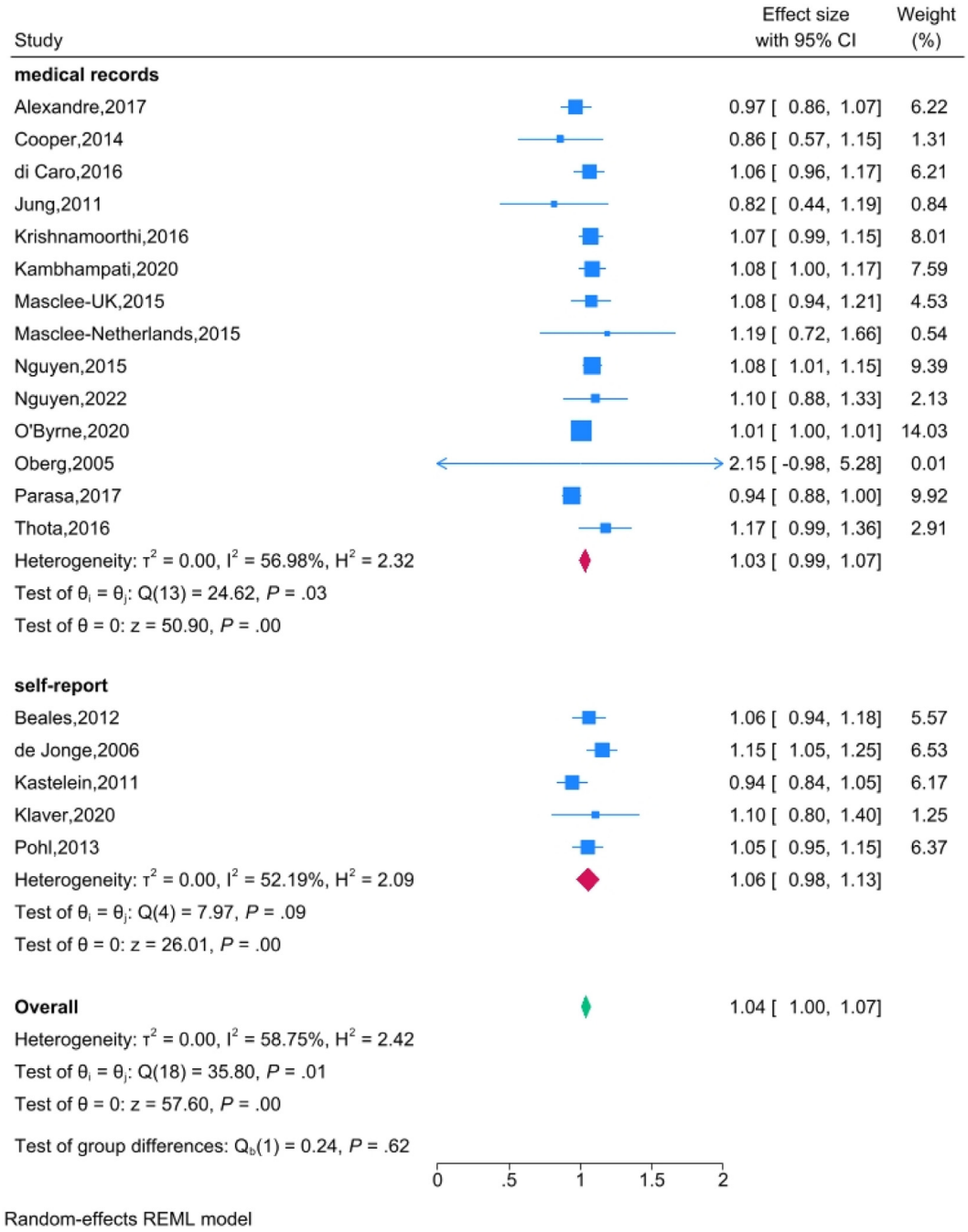
Supplementary Figure 5. Subgroup analysis based on baseline dysplastic status (unadjusted analysis). CI, confidence interval; LGD, low-grade dysplasia; REML, restricted maximum likelihood.



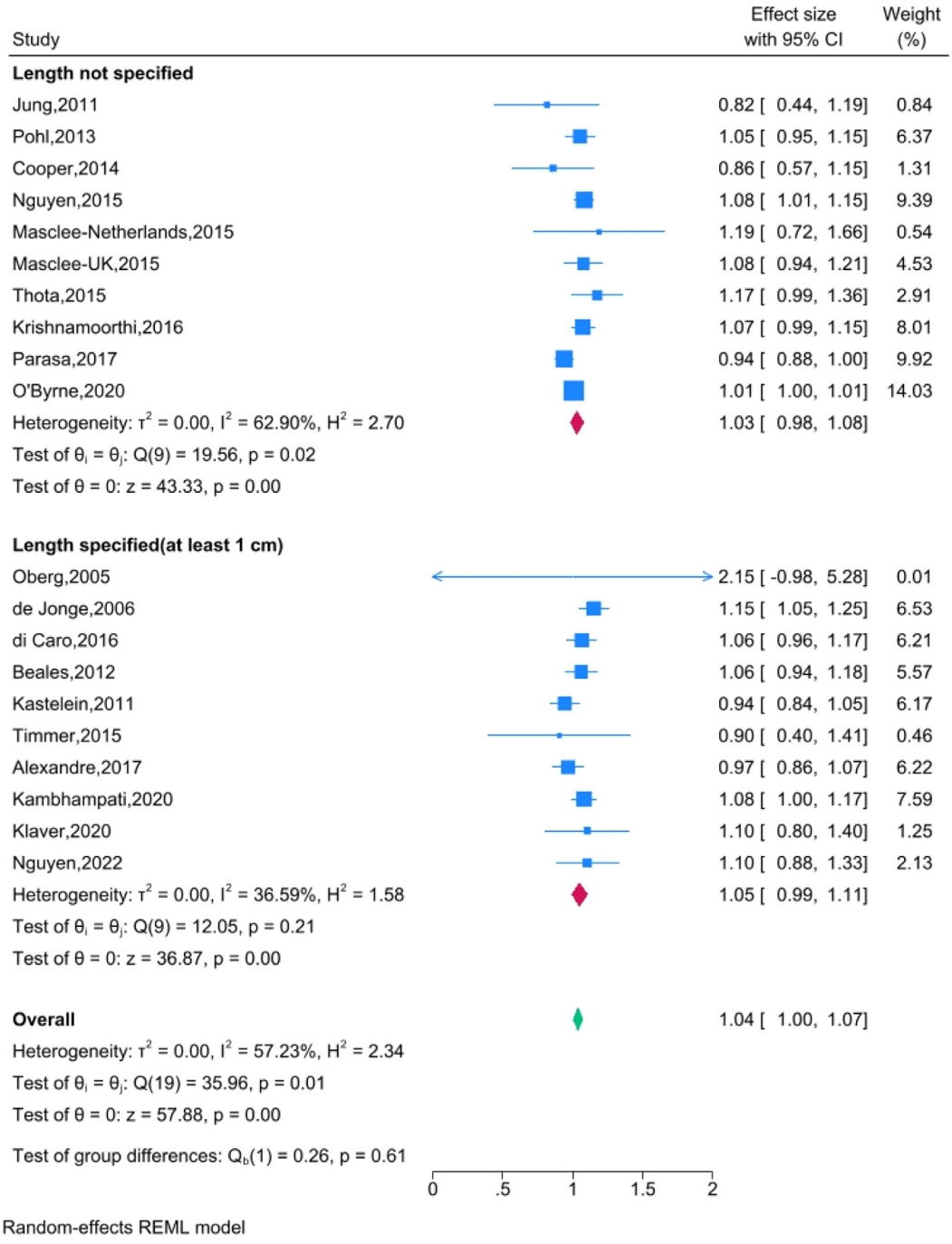
Supplementary Figure 6. Subgroup analysis based on study outcome (unadjusted analysis). CI, confidence interval; EAC, esophageal adenocarcinoma; EC, esophageal carcinoma; HGD, high-grade dysplasia; REML, restricted maximum likelihood.



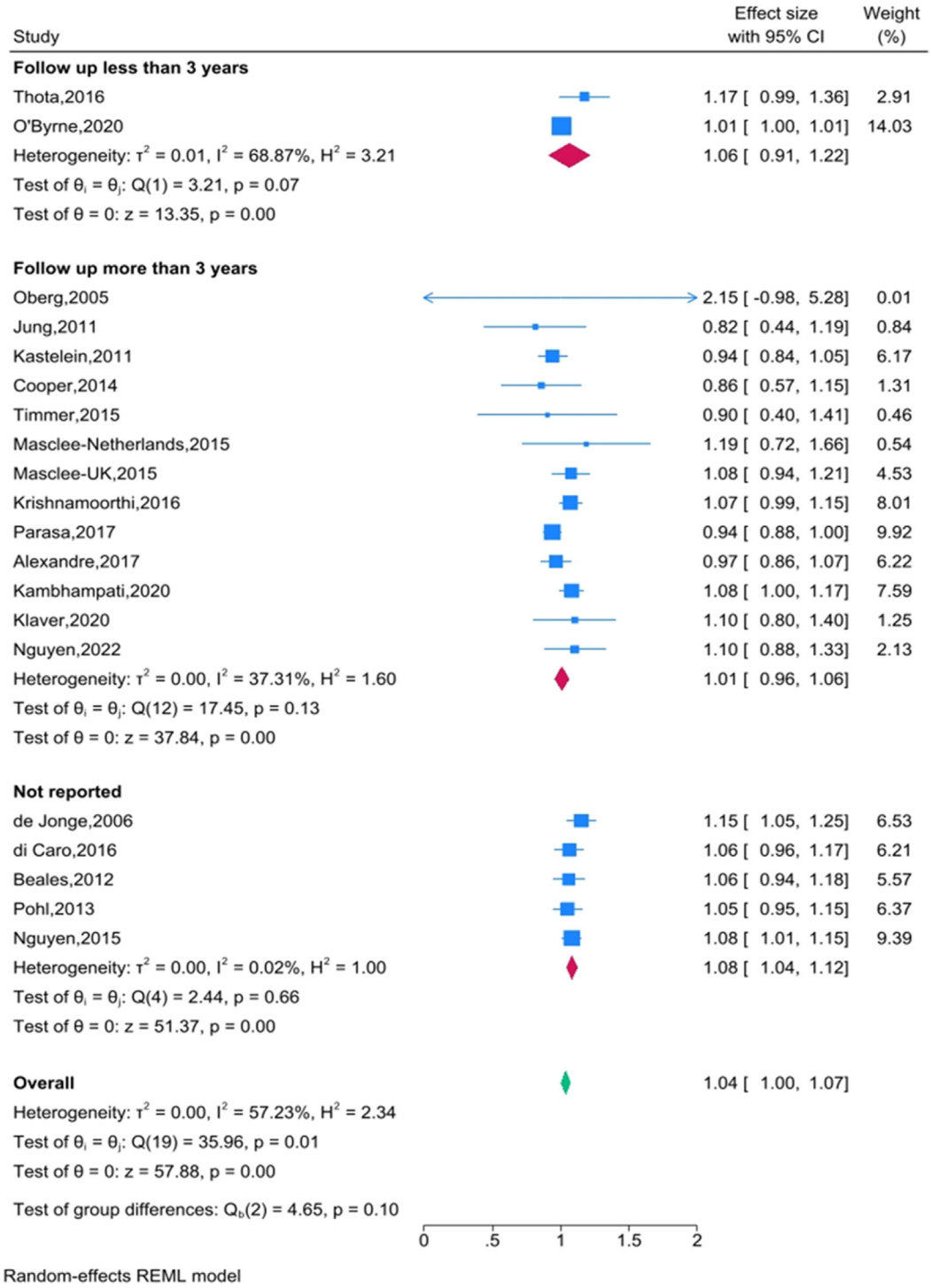
Supplementary Figure 7. Subgroup analysis based on study quality (unadjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



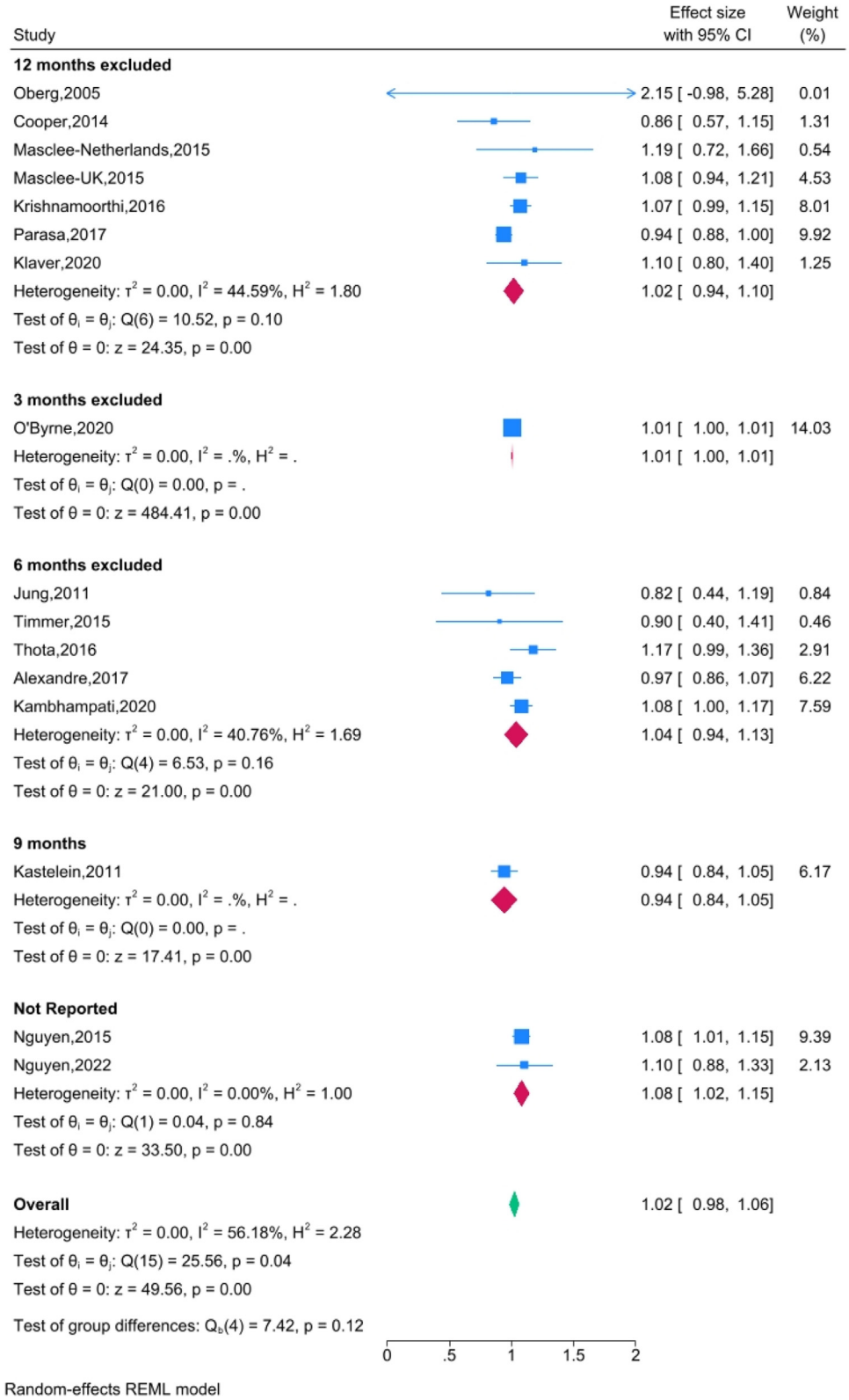
Supplementary Figure 8. Subgroup analysis based on exposure assessment (unadjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



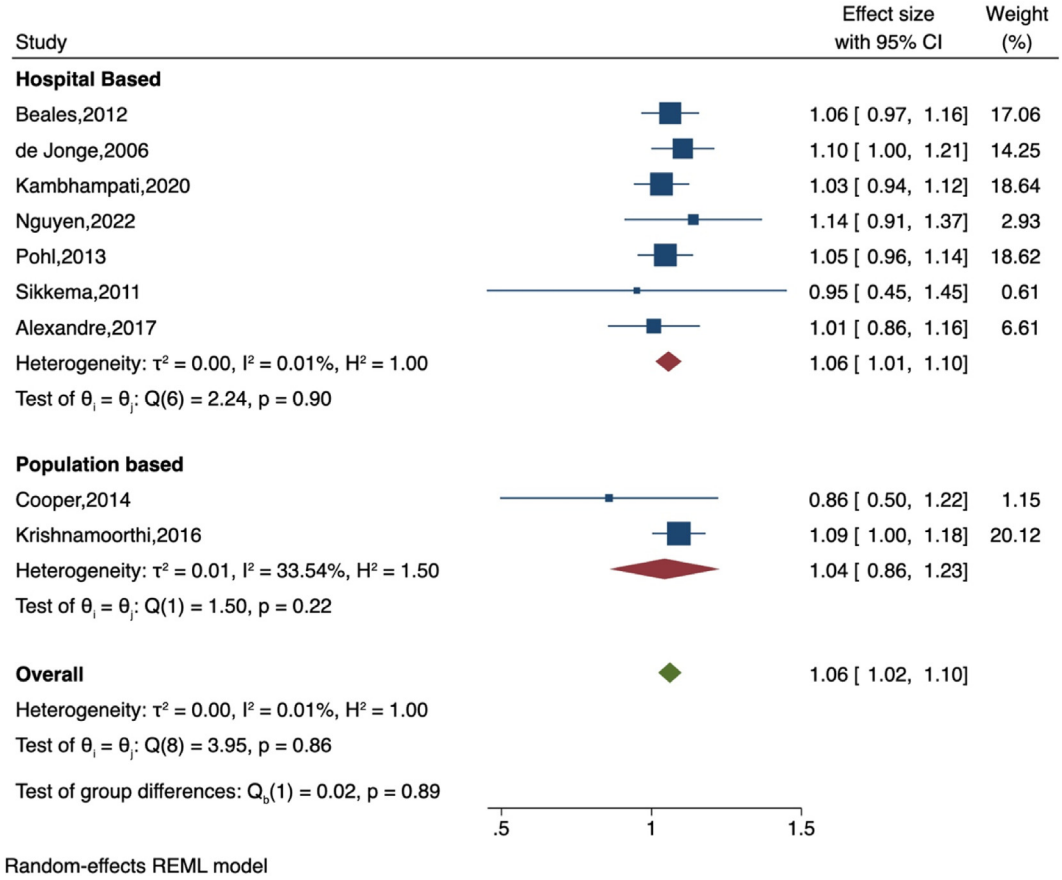
Supplementary Figure 9. Subgroup analysis based on definition of Barrett's esophagus (unadjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



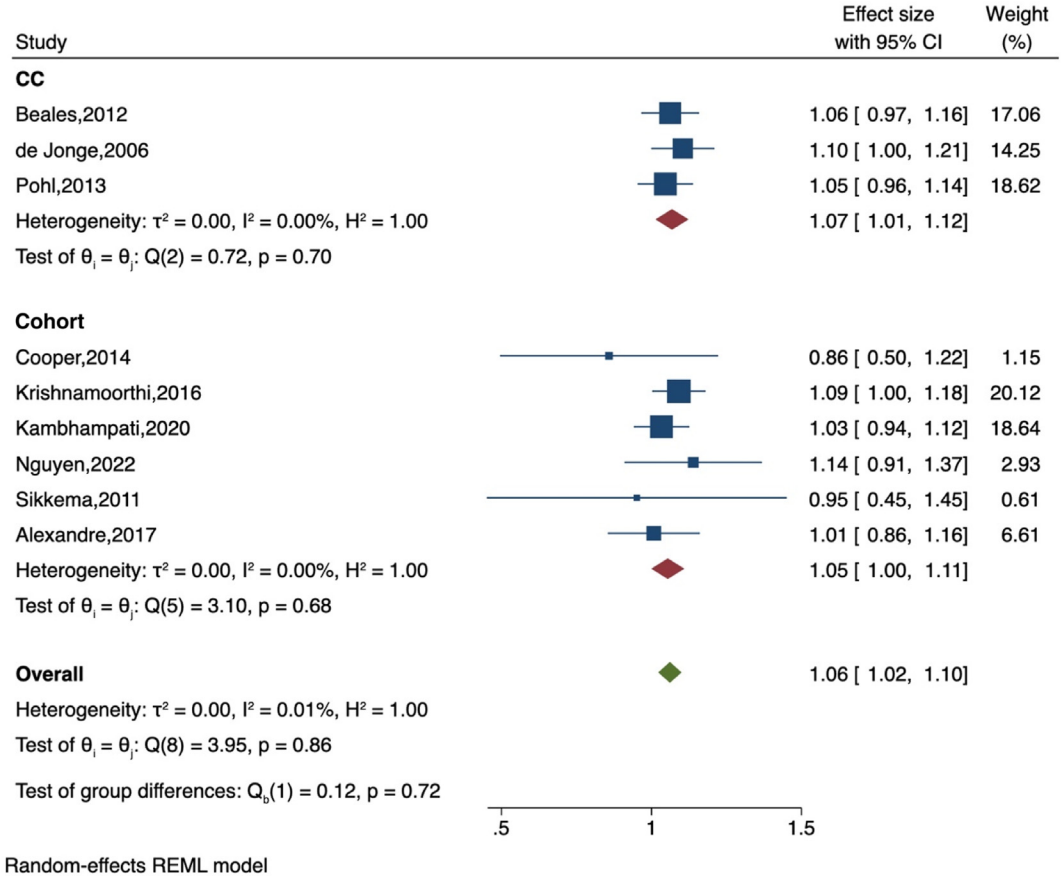
Supplementary Figure 10. Subgroup analysis based on study follow-up period (unadjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



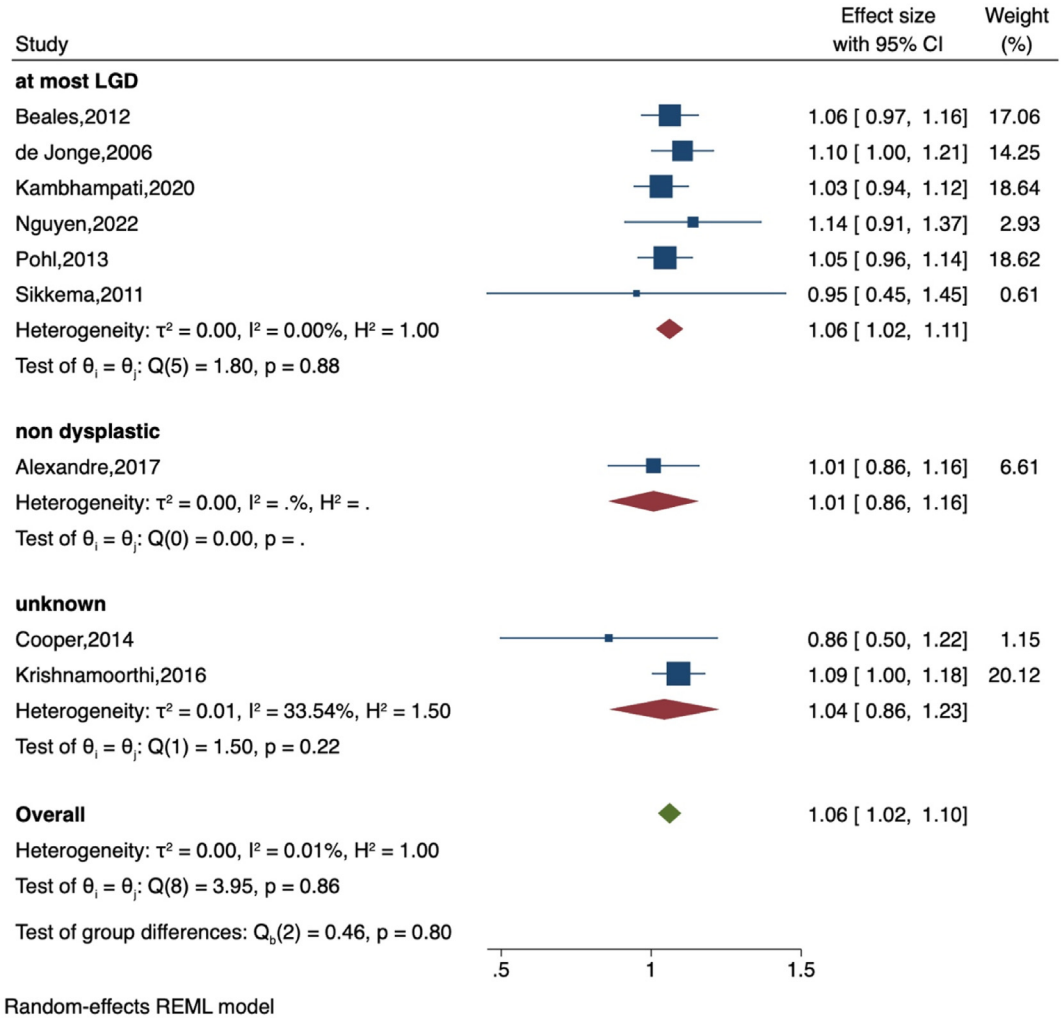
Supplementary Figure 11. Subgroup analysis based on the period excluded until the diagnosis of high-grade dysplasia/cancer (unadjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



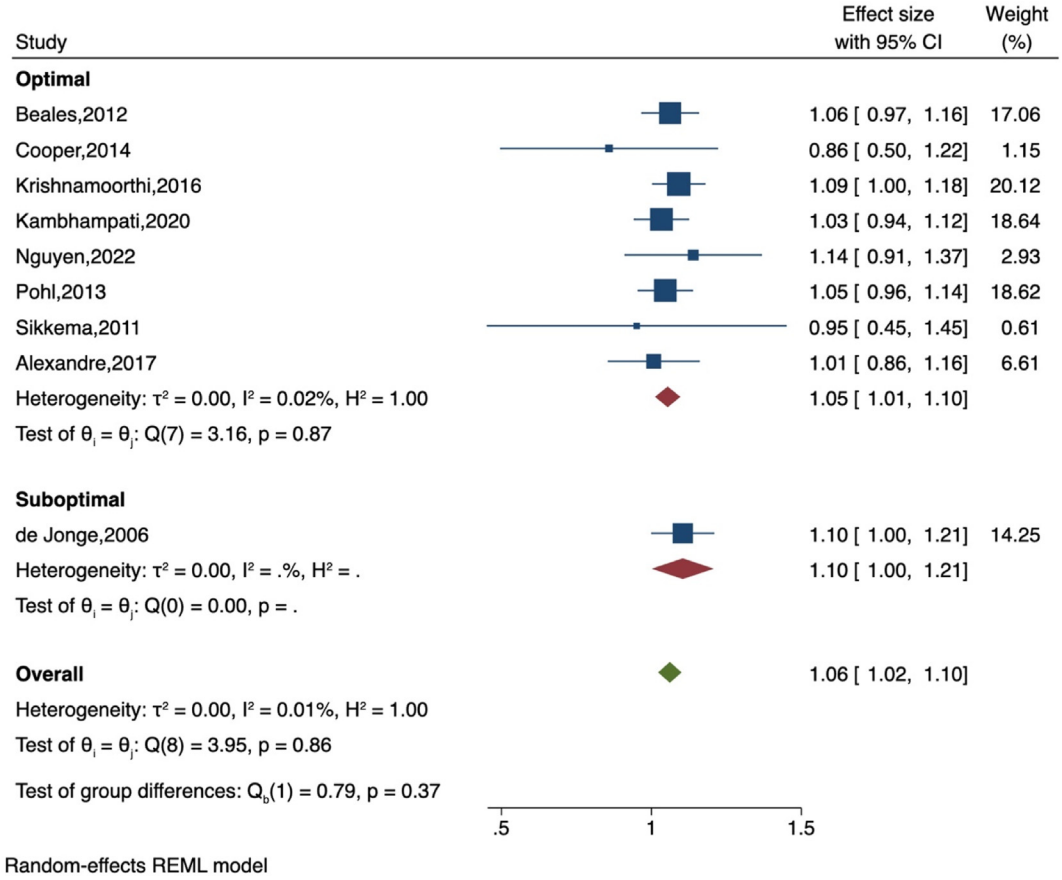
Supplementary Figure 12. Subgroup analyses based on study setting (adjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



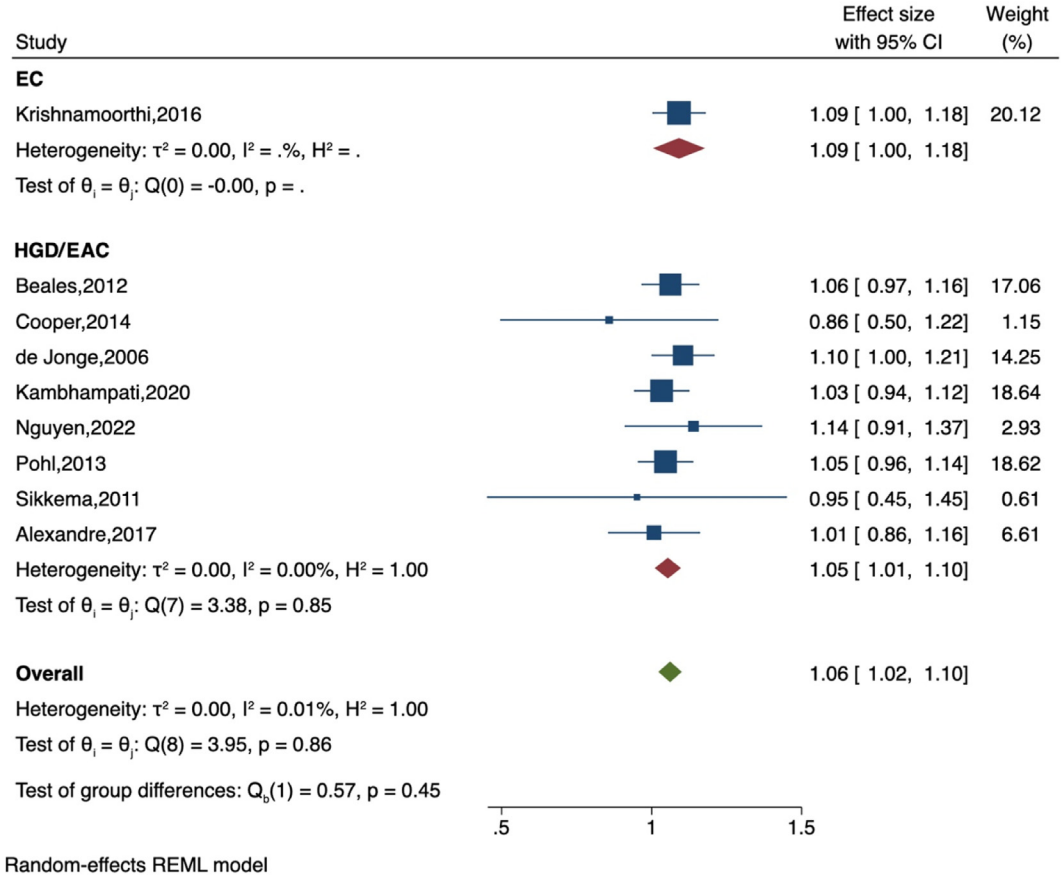
Supplementary Figure 13. Subgroup analyses based on study design (adjusted analysis). CC, case-control; CI, confidence interval; REML, restricted maximum likelihood.



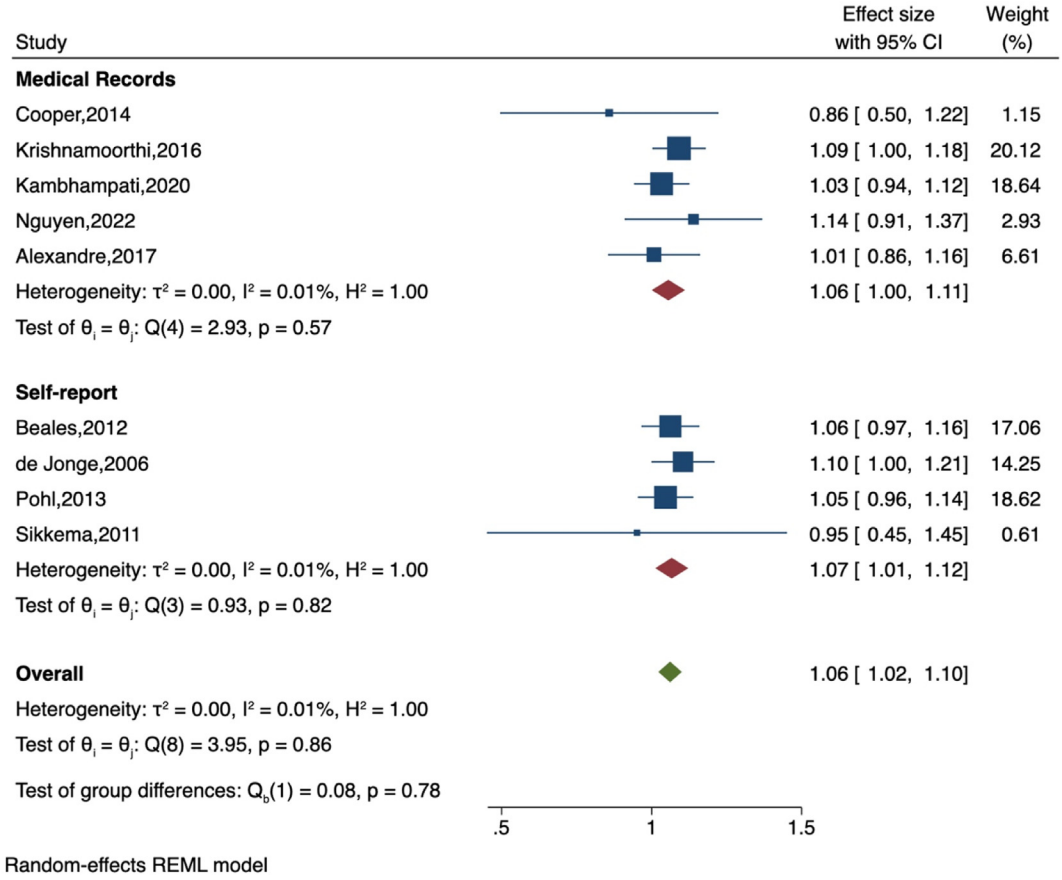
Supplementary Figure 14. Subgroup analyses based on baseline dysplastic status (adjusted analysis). CI, confidence interval; LGD, low-grade dysplasia; REML, restricted maximum likelihood.



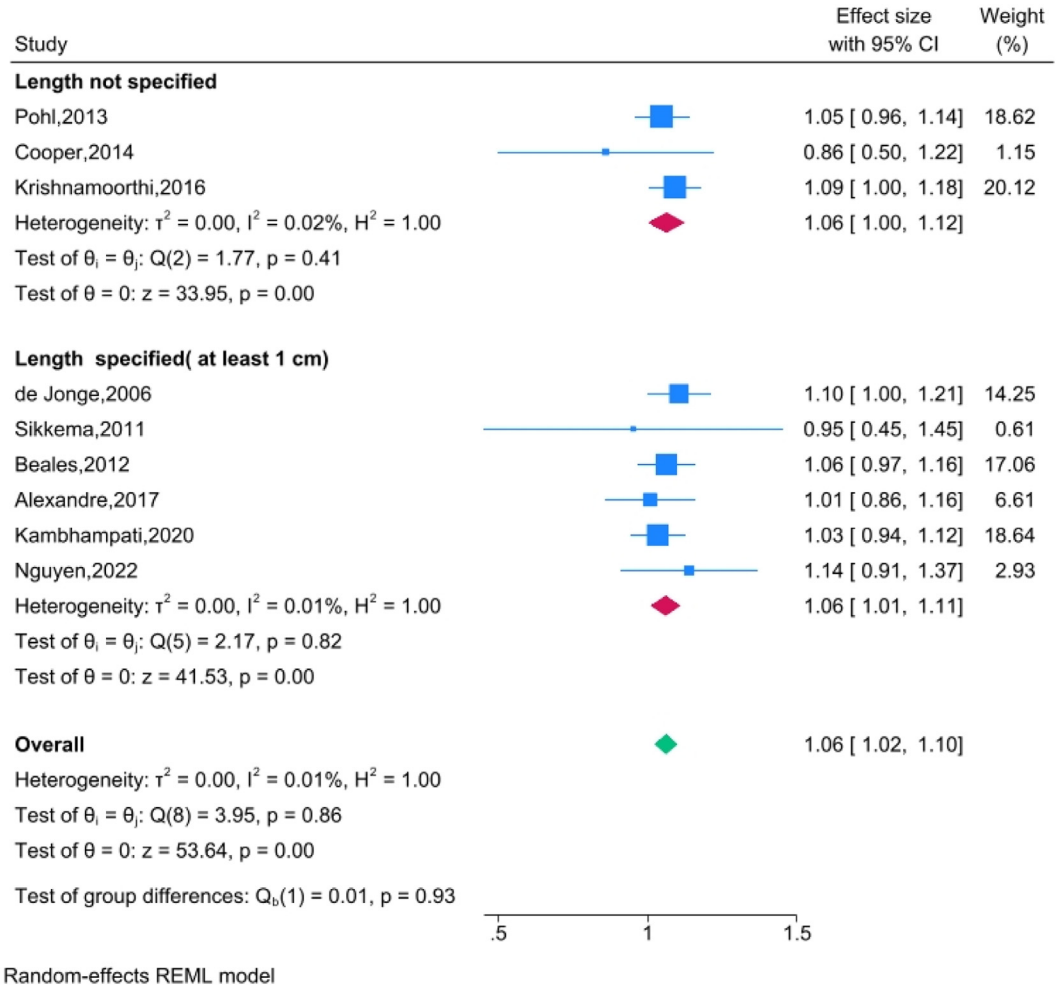
Supplementary Figure 15. Subgroup analyses based on study quality (adjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



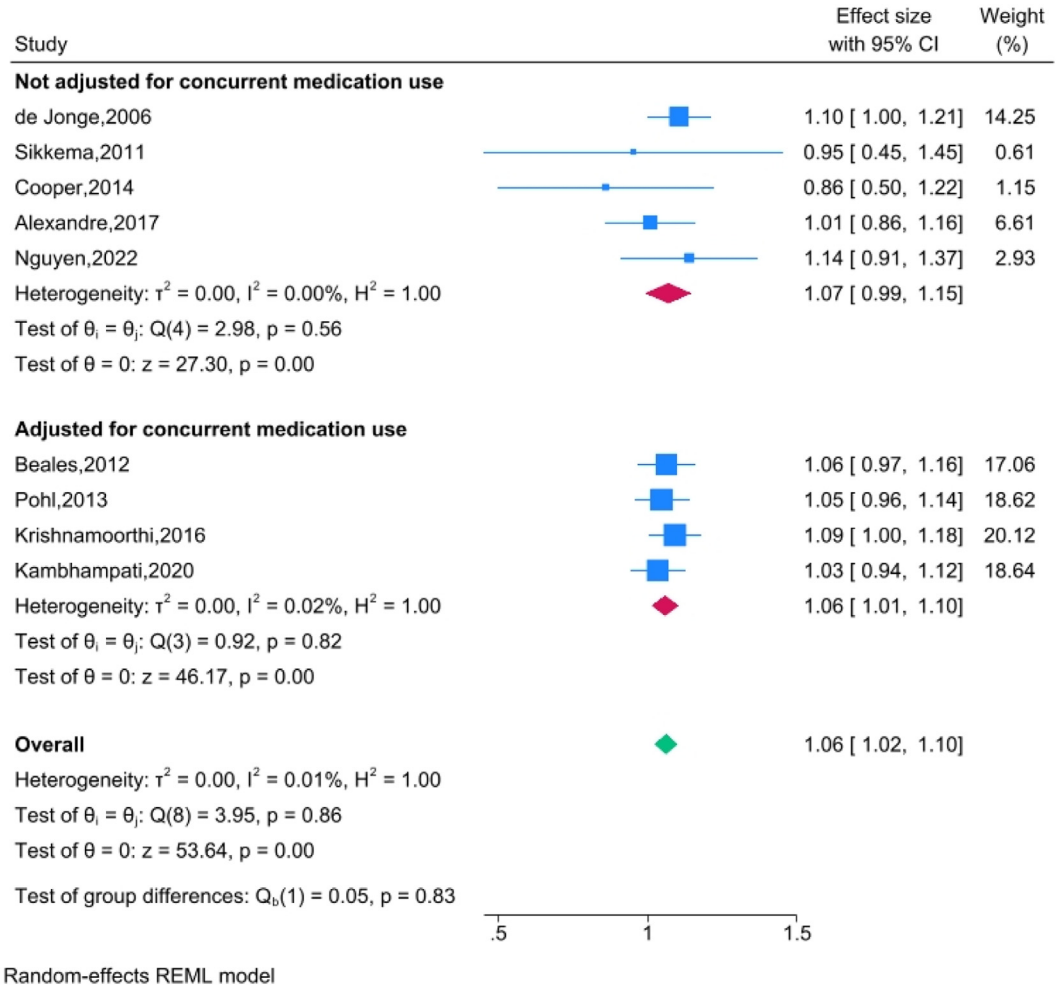
Supplementary Figure 16. Subgroup analyses based on study outcome (adjusted analysis). CI, confidence interval; EAC, esophageal adenocarcinoma; EC, esophageal carcinoma; REML, restricted maximum likelihood.



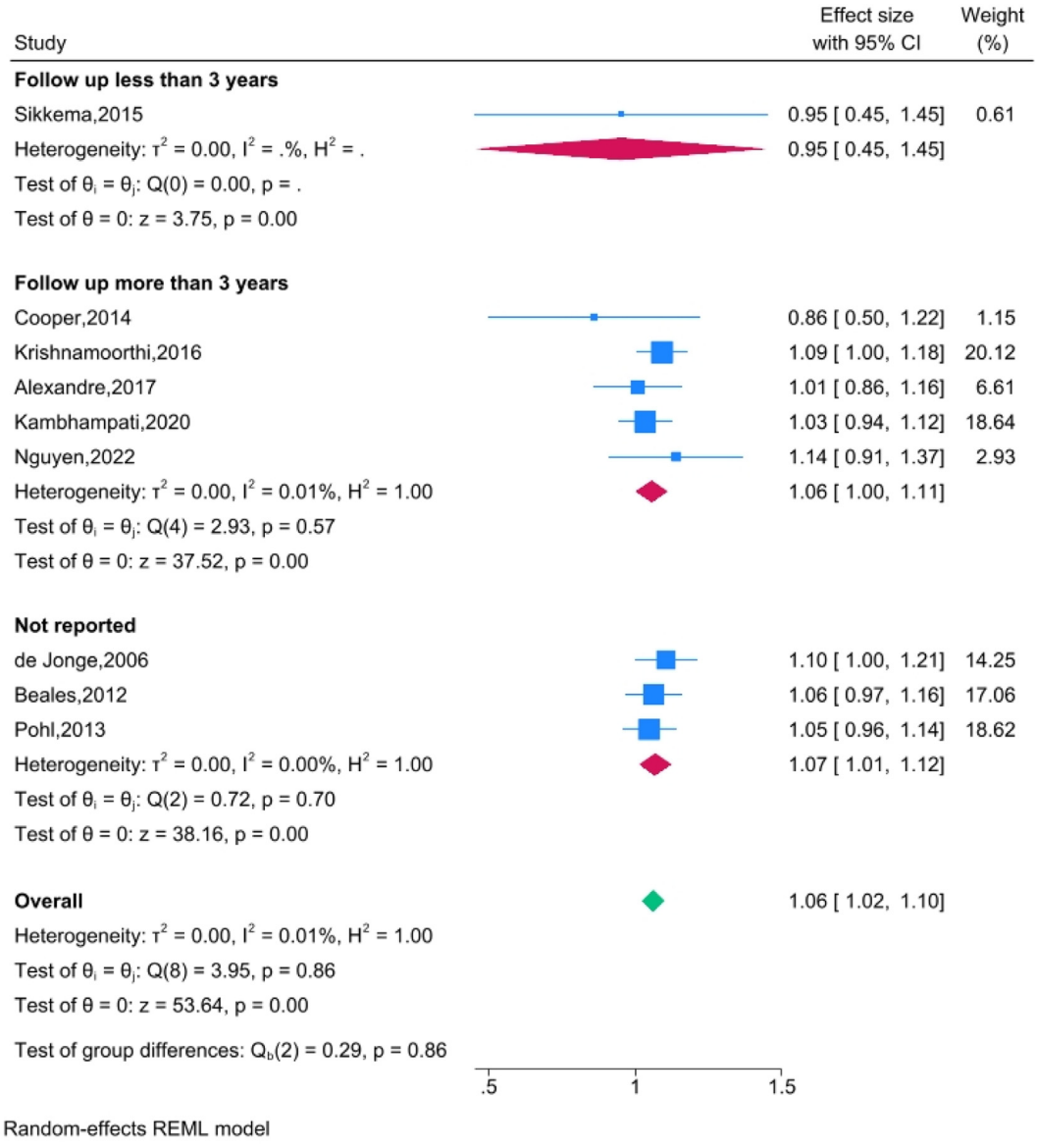
Supplementary Figure 17. Subgroup analyses based on exposure ascertainment (adjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



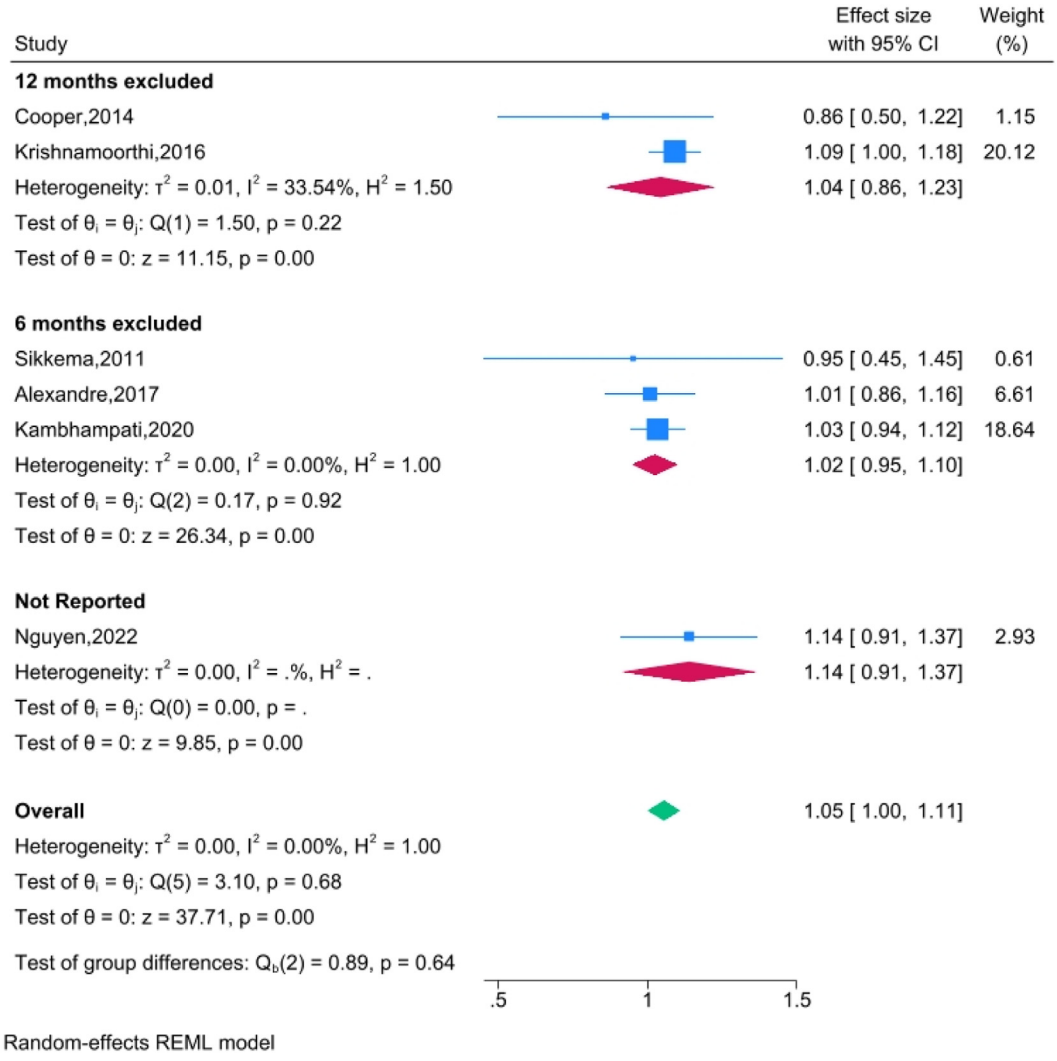
Supplementary Figure 18. Subgroup analyses based on definition of Barrett's esophagus (adjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



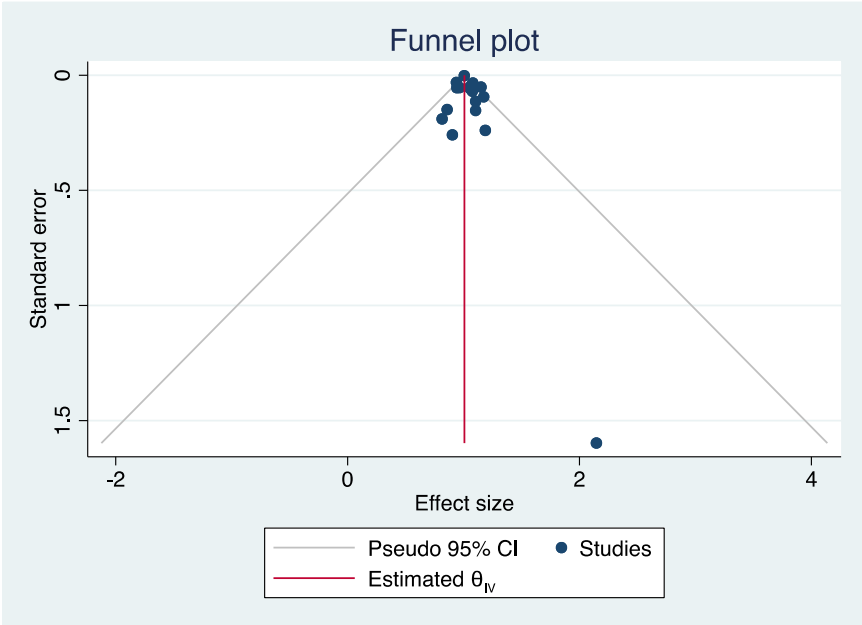
Supplementary Figure 19. Subgroup analyses based on adjustment of concurrent medication usage (adjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



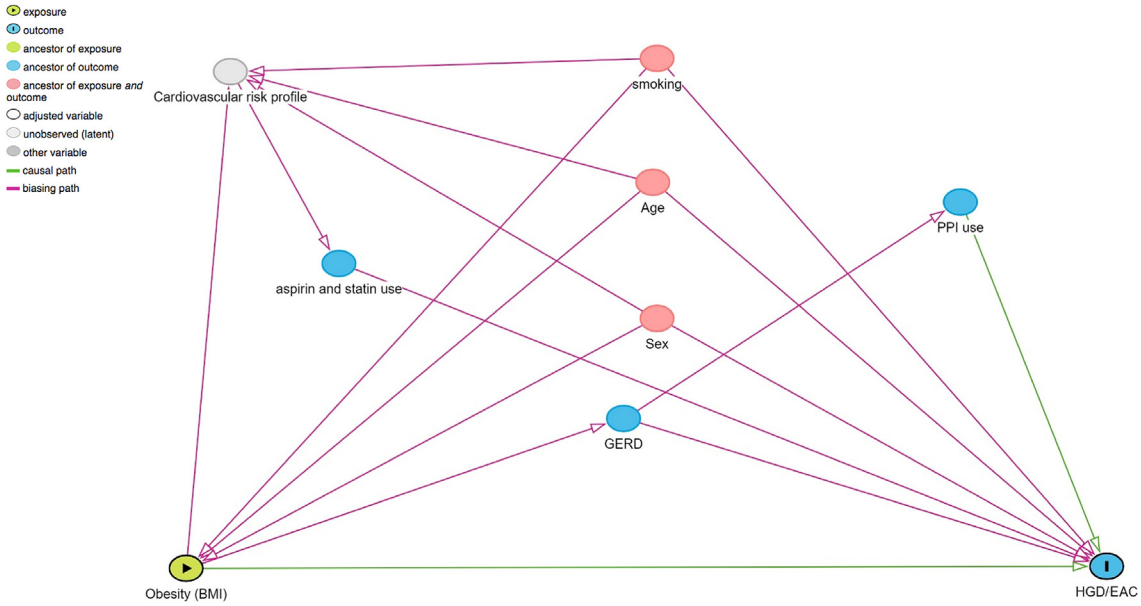
Supplementary Figure 20. Subgroup analysis based on study follow-up period (adjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



Supplementary Figure 21. Subgroup analysis based on the period excluded until the diagnosis of high-grade dysplasia/cancer (adjusted analysis). CI, confidence interval; REML, restricted maximum likelihood.



Supplementary Figure 22. Funnel plot to assess publication bias. Egger's regression test: $P = .57$. CI, confidence interval.



Supplementary Figure 23. Directed acyclic graph: the assumed causal relationships between obesity and malignant progression of Barrett's esophagus. Given that gastroesophageal reflux disease (GERD) and proton pump inhibitor (PPI) use are included in the causal pathway, studies that adjusted for these variables might have led to an underestimation of effect sizes. Furthermore, if PPIs are prescribed as part of the routine care for symptoms of undiagnosed high-grade dysplasia (HGD)/esophageal adenocarcinoma (EAC) reverse causation may operate. Under this circumstance, adjustment for PPI use would open a biasing pathway as PPI use would become a collider. Diagram generated using DAGitty.[e66]

Supplementary Table 1. Search Strategy

Ovid MEDLINE(R) ALL (from 1946) and Embase (from 1974) were searched via OvidSP. The most recent database search was in March 2024.

1. ((barret$ or columnar) adj1 (esophag$ or oesophag$ or metaplasia)).ab,hw,kw,ti.
2. ((columnar adj1 lined) and (esophag$ or oesophag$)).ab,hw,kw,ti.
3. Barrett Esophagus/
4. or/1–3c
5. (dysplasia or cancer or carcinoma or adenocarcinoma or neoplas$ or malignan$ or progression or progressor$).ab,hw,kw,ti.
6. (observational or epidemiologic$ or case-control or cohort$ or cross-section$ or retrospective or prospective$).ab,hw,kw,ti.
7. and/4–6
8. (overweight or obese or adiposity or body mass index or BMI or waist or WHR).ab,hw,kw,ti.
9. (genetic or biomarker or risk factor or smoking or drug or proton pump or PPI or statin or aspirin).ab,hw,kw,ti.
10. or/8–9
11. 7 and 10
12. (conference abstract or editorial or erratum or note or news).st,mp. or (case report or expert review or case series or consensus).ti. or (letter or review).pt.
13. 11 not 12
14. Remove duplicates from 13

BMI, body mass index; PPI, proton pump inhibitor; WHR, waist-to-hip ratio.

Supplementary Table 2. Adapted Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies

Selection
1) Is the case definition adequate?
   a) yes, with independent validation (HGD or EAC confirmed on histology)
   b) yes, for example, record linkage (eg, confirmed in cancer registry)
   c) self-report
   d) no description
2) Representativeness of the cases
   a) consecutive or obviously representative series of cases with a prior history of Barrett's esophagus
   b) No previous history of Barrett's esophagus
   c) potential for selection biases or not stated
3) Selection of controls
   a) community controls
   b) hospital controls
   c) no description
4) Definition of controls
   a) no history of disease (endpoint)
   b) no description of source

Comparability
1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for sex
   a) study controls for age
   b) study controls for smoking

Exposure
1) Ascertainment of exposure
   a) secure record (eg, prior record in medical notes or primary/secondary care dataset [recorded at least 3 y before the outcome of interest])
   b) structured interview blind to case/control status
   c) interview not blinded to case/control status
   d) written self-report or medical record only
   e) no description
2) Same method of ascertainment for cases and controls
   a) yes
   b) no
3) Nonresponse rate
   a) same rate for both groups
   b) nonrespondents described
   c) rate different and no designation

EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia.

Supplementary Table 3. Adapted Newcastle-Ottawa Quality Assessment Scale for Cohort Studies

Selection
1) Representativeness of the exposed cohort
   a) truly representative of the average Barrett's population in the community
   b) somewhat representative of the average Barrett's population in the community
   c) selected group of users (eg nurses, volunteers, veterans)
   d) no description of the derivation of the cohort
2) Selection of the nonexposed 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 nonexposed cohort
3) Ascertainment of exposure
   a) secure record (eg, prior record in medical notes or primary/secondary care dataset)
   b) structured interview
   c) written self-report
   d) no description
   e) secure record but period of exposure not long enough for the outcome of interest (ie, <3 y) or uncertain exposure period
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 sex
   a) study controls for age
   b) study controls for smoking

Outcome
1) Assessment of outcome
   a) with independent validation (HGD or EAC confirmed on histology)
   b) record linkage (eg, confirmed in cancer registry)
   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—3 y)
   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 (<10%)
   c) follow-up rate <90% or differential loss to follow-up between BMI categories
   d) no statement

BMI, body mass index; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia.

Supplementary Table 4. Studies Selected for Full Text Review That Did Not Meet Eligibility

Study	Reason Excluded
MEDLINE and Embase Search	
Allen (2021)[e1]	Inclusion criteria 4 not met
Anaparthy (2023)[e2]	Inclusion criteria 4 not met
Akiyama (2009)[e3]	Inclusion criteria 3 not met
Bani-Hani (2005)[e4]	Inclusion criteria 4 not met
Bird-Lieberman (2012)[e5]	Inclusion criteria 4 not met
Brown (2018)[e6]	Inclusion criteria 3 not met
Coleman (2012)[e7]	Inclusion criteria 3 and 4 not met
Dong (2007)[e8]	Inclusion criteria 2 and 4 not met
Duggan (2013)[e9]	Inclusion criteria 2 and 4 not met
Duits (2019)[e10]	Inclusion criteria 4 not met
Duits (2019)[e11]	Inclusion criteria 4 not met
El-Serag (2004)[e12]	Inclusion criteria 4 not met
Gatenby (2009)[e13]	Inclusion criteria 3 and 4 not met
Gatenby (2014)[e14]	Inclusion criteria 4 not met
Gatenby (2016)[e15]	Inclusion criteria 4 not met
Hardikar (2013)[e16]	Inclusion criteria 2 not met
Hillman (2008)[e17]	Inclusion criteria 4 not met
Hillman (2004)[e18]	Inclusion criteria 4 not met
Holmberg (2019)[e19]	Inclusion criteria 4 not met
Hvid-Jensen (2014)[e20]	Inclusion criteria 4 not met
Hvid-Jensen (2011)[e21]	Inclusion criteria 4 not met
Iyer (2022)[e22]	Inclusion criteria 4 not met
Kantor (2012)[e23]	Inclusion criteria 2 not met
Katz (1998)[e24]	Inclusion criteria 4 not met
Kunzmann (2019)[e25]	Inclusion criteria 4 not met
Lastraioli (2016)[e26]	Inclusion criteria 4 not met
Monardo (2019)[e27]	Inclusion criteria 4 not met
Murray (2006)[e28]	Inclusion criteria 4 not met
Nelson (2012)[e29]	Inclusion criteria 3 (4 not met
Nguyen (2009)[e30]	Inclusion criteria 4 not met
Nguyen (2010)[e31]	Inclusion criteria 4 not met
Nguyen (2010)[e32]	Inclusion criteria 4 not met
Peleg (2021)[e33]	Inclusion criteria 4 not met
Peleg (2023)[e34]	Inclusion criteria 4 not met
Peters (2019)[e35]	Inclusion criteria 4 not met
Redston (2022)[e36]	Inclusion criteria 4 not met
Rubenstein (2021)[e37]	Inclusion criteria 4 not met
Vaughan (2005)[e38]	Inclusion criteria 4 not met
van Olphen (2016)[e39]	Inclusion criteria 4 not met
Thrift (2012)[e40]	Inclusion criteria 2 not met
van Olphen (2015)[e41]	Inclusion criteria 4 not met
Tan (2018)[e42]	Inclusion criteria 1–4 met, met but overlapping population with more contemporaneous cohort
Citation searching	
Bhat (2011)[e43]	Inclusion criteria 4 not met
Sato (2008)[e44]	Inclusion criteria 4 not met
Dong (2018)[e45]	Inclusion criteria 2 not met

Supplementary Table 5. Study-Level Risk of Bias

Study	Location	Selection	Comparability	Exposure/ Outcome	Total	Quality
Alexandre (2017)[e46]	United Kingdom	3	2	2	7	M
Beale (2012)[e47]	United Kingdom	2	3	2	7	M
Cooper (2014)[e48]	United Kingdom	3	3	2	8	H
de Jonge (2006)[e49]	The Netherlands	2	3	1	6	M
di Caro (2016)[e50]	United Kingdom	3	2	2	7	M
Krishnamoorthi (2016)[e51]	United Kingdom	3	3	2	8	H
Jung (2011)[e52]	United States	4	0	2	6	M
Kambhampati (2020)[e53]	United States	4	2	2	8	H
Kastelein (2011)[e54]	The Netherlands	3	0	2	5	M
Klaver (2020)[e55]	The Netherlands	3	0	2	5	M
Masclee (2015)[e56]	United Kingdom, The Netherlands	3	3	0	6	M
Nguyen (2015)[e57]	United States	3	1	1	5	M
Nguyen (2022)[e58]	United States	3	3	2	8	H
O'Byrne (2020)[e59]	United Kingdom	3	2	2	7	M
Oberg (2005)[e60]	Sweden	3	3	2	8	H
Parasa (2018)[e61]	United States, The Netherlands	3	0	2	5	M
Pohl (2013)[e62]	Germany	3	3	1	7	M
Sikkema (2011)[e63]	The Netherlands	3	2	2	7	M
Thota (2016)[e64]	United States	4	0	1	5	M
Timmer (2015)[e65]	The Netherlands	3	0	1	4	L

Abbreviations: H, high; L, low; M, moderate.