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DISEASES OF THE ESOPHAGUS

Original article

The association between body mass index and Barrett's esophagus: a systematic review

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SUMMARY. **Biological plausibility and evidence from case series indicate that an increased body mass index could be a risk factor for Barrett's esophagus. The aim of this study was to assemble and appraise the available evidence on the association of body mass index and Barrett's esophagus in a narrative approach. A systematic literature review identified a nested case-control study and 10 case-control studies, with sample sizes of between 129 and 953. Overall, cases were on average older than controls, more often male and white, but did not differ with regards to body mass index. An increased body mass index (≥30 and ≥35 kg/m^2) was associated with greater risk of Barrett's esophagus in four studies (odds ratio range: 2.0–4.0). These studies, however, did not adjust for symptoms suggestive of gastroesophageal reflux disease. No significant association was reported in the other six studies. To conclude, the existing evidence on the association between body mass index and risk of Barrett's esophagus relates primarily to case-control studies and is inconsistent. Gastroesophageal reflux symptoms can be a potential confounder and further research should better address this issue. Evidence from cohort studies may help shed further light on this putative association, which is of relevance to public health and cancer control.**

KEY WORDS: **Barrett's esophagus, body mass index, gastroesophageal reflux disease.**

INTRODUCTION

Patients with gastroesophageal reflux disease (GERD) may develop Barrett's esophagus (BE), a premalignant condition that can lead to the development of esophageal adenocarcinoma (OAC).[1] BE is defined as columnar-lined epithelium that can be recognized at endoscopy and is confirmed to have specialized intestinal metaplasia (SIM) by biopsy.[2,3] Depending on the length of the epithelium, it is categorized as either long-segment (LSBE) (≥3 cm) or short-segment (SSBE) (<3 cm).[4] Approximately 10% of patients with frequent GERD symptoms develop BE.[5] Of these, 0.5–1.0% per year will be diagnosed with OAC.[6]

In Western populations, a rapid increase in OAC incidence has been observed since the 1970s.[7,8] OAC has an overall poor prognosis (5-year survival is 13%[9]) and only limited treatment options exist. There is evidence that BE prevalence may follow a similar (to OAC) increasing trend.[10–13] An estimated 1.6% of the adult general population have the condition,[14] most of which however will never be detected. Only one in every 20 patients undergoing resection of OAC has BE diagnosed before resection,[15] thus, missing the chance for early intervention.

Although the association between GERD and the risk of developing BE is well established,[16–19] other accepted risk factors include older age,[20–22] male sex,[20–23] and white race.[22,24] Evidence from case series[19,25] suggests that an increased body mass index (BMI) could also be a risk factor for BE. This is an

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important research question, as body weight could potentially be modified for preventive purposes. In order to investigate this association, relevant studies were systematically assembled and critically appraised.

MATERIALS AND METHODS

Search strategy

One reviewer searched the electronic database, PubMed, for articles published between 1950, when BE was first described,[26] and March 2008 (last updated in January 2009). Key indexing terms (MeSH) describing the condition ('Barrett esophagus') and the implicated risk factor ('body mass index,' 'body weight,' and 'obesity') were used to retrieve the articles.

Identification of studies

Potentially relevant studies were identified based on inspection of the title and abstract. For those publications judged of potential relevance, using prestated eligibility criteria, a full-text copy was examined. References of identified studies were scanned to ensure that no studies were missed.

Eligibility criteria

Inclusion was limited to peer-reviewed studies in English. Only those with histological confirmation of SIM were considered. Because of the expected low number of relevant studies, no restrictions were made in terms of study design. Studies were required to have a sample relating to the general population or a specially recruited control group, i.e. GERD, reflux esophagitis, or normal endoscopy controls.

Extraction and analysis of information

One reviewer extracted data from the full-text publications once a decision was made to include the study. Data extraction was validated by a second reviewer. The methodological quality of the studies was assessed in a narrative approach, particularly focusing on study design, sample, and reported effect size.

RESULTS

From more than 1000 initial hits, 18 studies were found to be investigating the association of BMI with BE (based on title and abstract), which were extracted and fully examined. Of these, eight met the eligibility criteria stated above. A recently conducted meta-analysis[27] of 10 studies provided unpublished data for three studies that were initially excluded (due to a lack of adequate detail) but subsequently included, increasing the number of studies to 11. The meta-analysis itself was not considered in this review because it included two studies that did not meet the eligibility criteria (no histological confirmation of BE) and provided only pooled unadjusted risk estimates.

Study designs

Table 1 contains some characteristics of the studies included. Aside from two more recent studies, all were published post-2004 – eight of which were conducted in the USA,[29–34,36,38] one in Australia,[37] one in Ireland,[28] and one in Sweden.[35] Ten were case-control studies,[28–30,32–38] and one was a nested case-control study.[31] Five studies compared BE cases with population controls free of the condition and with no history of OAC or other malignancies.[28,31,32,35,37] Two of these additionally recruited a second group consisting of GERD controls[31] and normal endoscopy controls.[35] The remaining studies compared BE cases with GERD controls,[30,34,36] normal endoscopy controls,[38] or both normal endoscopy and reflux esophagitis controls.[29,33]

Laboratory pathology reports, data from a health services organization, and endoscopy records were used to identify cases and controls. Population controls (matched by age, sex, and residential area) were drawn from general practices,[28] a health services organization,[31] population registries,[32,37] and hospital endoscopy services.[35] Four studies included only newly diagnosed BE cases,[31,32,35,37] one enrolled prevalent cases under endoscopic surveillance,[29] and six made no apparent distinction between incident and prevalent case status.[28,30,33,34,36,38] All except for one study[28] included both cases with SSBE and LSBE.

Data on weight and height were retrieved from patient records in three studies,[29,33,38] ascertained by the use of questionnaires in four studies,[30,34,35,37] and taken during interviews (either at the study participant's home or in the study setting) in four studies.[28,31,32,36] In addition to BMI at diagnosis, Anderson *et al.*[28] assessed BMI 5 years ago and at age 21. Most studies were conducted in hospital settings, generally at gastroenterology clinics. Two were set in Veterans Affairs Medical Centers.[33,38]

Study participants

In total, the reviewed studies comprised 5080 participants (Table 2). Sample sizes ranged from 129 to 953. The lowest number of cases was 21 and the greatest was 320. Overall, cases were – on average – older than controls and more often male, but did not substantially differ with regards to mean BMI. Among the

Table 1 Designs of the included studies ($n = 11$)

Author(s)	Year	Country	Study design	Setting	
				Cases	Controls
Anderson *et al.*[28]	2007	Ireland	Population-based case-control study	Laboratory pathology reports	General practices
Cameron[29]	1999	USA	Case-control study with reflux esophagitis/normal endoscopy controls	Hospital gastroenterology division	Hospital gastroenterology division
Campos *et al.*[30]	2001	USA	Case-control study with GERD controls	University tertiary referral center	University tertiary referral center
Corley *et al.*[31]	2007	USA	Population-based nested case-control study with GERD controls	Integrated health services delivery organization	Integrated health services delivery organization
Edelstein *et al.*[32]	2007	USA	Population-based case-control study	Community gastroenterology clinics	Population registry
El-Serag *et al.*[33]	2005	USA	Case-control study with reflux esophagitis/normal endoscopy controls	Veterans Affairs Medical Center	Veterans Affairs Medical Center
Gerson *et al.*[34]	2007	USA	Case-control study with GERD controls	Hospital gastroenterology division	Hospital gastroenterology division
Johansson *et al.*[35]	2007	Sweden	Population-based case-control study with normal endoscopy controls	Hospital endoscopy services	Hospital endoscopy services
Shaheen *et al.*[36]	2005	USA	Case-control study with GERD controls	Gastroenterology clinic	Gastroenterology clinic
Smith *et al.*[37]	2005	Australia	Population-based case-control study	Two private and one public pathology laboratory	Population registry
Stein *et al.*[38]	2005	USA	Case-control study with normal endoscopy controls	Veterans Affairs Medical Center	Veterans Affairs Medical Center

GERD, gastroesophageal reflux disease.

four studies that reported information about ethnic group,[31–34] there were slightly more white participants among cases compared with controls.

Six studies reported on participation rates.[28,31,32,35,37,38] Comparatively high proportions of eligible cases and controls (between 69% and 93%) participated in three studies.[32,37,38] By contrast, less than 50% of cases and less than 40% of controls participated in the study by Corley *et al.*[31] Participation was slightly higher with the difference between cases and controls being less pronounced in another study.[35] Anderson *et al.*[28] interviewed four out of five eligible cases, but only two out of five eligible controls.

Effect sizes

Key findings are summarized in Table 3. No effect size was reported in one study[34] for which gender-specific odds ratios (OR) and 95% confidence intervals (CI) were calculated (based on the information provided in the publication). A statistically significant positive association was observed in four studies,[31–33,38] although the remaining six studies found no significant association.[28–30,34–37] None of the studies with significant results adjusted for GERD symptoms.

Corley *et al.*[31] adjusted for age, sex, ethnicity, and smoking and found that individuals with a BMI of $\geq$35 had an increased odds of BE (OR = 2.0, 95% CI: 1.1–3.7) as compared with the reference group (GERD controls with a BMI <25). A BMI of $\geq$30 was associated with a 2.6-fold increase in BE risk when compared with population controls in a study by Edelstein *et al.*[32] Stein *et al.*[38] obtained a comparable effect size associated with both a BMI of 25–30 (OR = 2.4) and >30 (OR = 2.5). Participants with a BMI of >30 in the study by El-Serag *et al.*[33] were at a fourfold increased risk with each additional unit of BMI, increasing the risk by 12%. This effect was similar after controlling for subcutaneous adipose tissue; however, it was attenuated and became non-significant after controlling for visceral adipose tissue.

DISCUSSION

A nested case-control study and 10 case-control studies were eligible for this review. No further studies, in particular no cohort studies, were identified. The results are inconsistent with some studies indicating that a BMI of $\geq$30 ('obese') and $\geq$35 ('morbid obesity') is associated with an increased BE risk (regardless of control group type), although others failed to detect such an association.

A major threat to the validity of case-control studies stems from the potential lack of representa-

Table 2 Study samples by age, sex, race, and BMI ($n = 11$)

	Study sample		Age (mean)		Male (%)		White (%)		BMI (mean)	
Author(s)	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Anderson *et al.*[28]	224	260	62.4	63.0	82.6	84.6	–	–	27	27
Cameron[29]†	64	103	68.3	59.0	79.7	55.3	–	–	–	–
Campos *et al.*[30]†	174	328	52	52	78.7	62.8	–	–	27.2	26.9
Corley *et al.*[31]‡	320	317	–	–	73.1	67.5	86.6	84.5	29.5	29.5
		316§				69.0§		80.1§		28.9§
Edelstein *et al.*[32]††	193	211	–	–	61.1	63.0	89.1	91.0	–	–
El-Serag *et al.*[33]	36	93	64	63.0	100	96.8	83.3	66.7	27	24
Gerson *et al.*[34]	165	586	58.5	54.5	90.3	68.9	80.0	73.4	28.0	27.8
Johansson *et al.*[35]	21	160	60.3	61.8	28.6	33.8	–	–	26.5	25.7
		498††		51.4††		43.0††				25.2††
Shaheen *et al.*[36]†	62	121	55.9	49.1	76	48	–	–	27.8	27.9
Smith *et al.*[37]	117	261	56	63	64.1	65.9	–	–	–	–
Stein *et al.*[38]	65	385	61.1	59.9	100	100	90.8	82.0	29.8	28.0

†Data are presented as obtained from the original publication, but may differ from unpublished data used in the meta-analysis by Cook *et al.*[27] ‡Most cases (59.7%) and controls (64.0% of population controls and 59.2% of GERD controls) were in the age stratum 60–79 years. §GERD controls (versus population controls). ††Most cases (31.1%) were in the age stratum 60–80 years and most controls (30.3%) in the age stratum 50–59 years. †††Normal endoscopy controls (versus population controls). BMI, body mass index; GERD, gastroesophageal reflux disease.

tiveness of both cases and controls. Many individuals with BE are asymptomatic[39] and therefore unlikely to be referred for endoscopy. Thus, selected cases might have only been representative of a subsection of all BE cases in the population – those with a more symptomatic presentation. Similarly, if obese individuals were underrepresented among the cases because they are less likely to undergo endoscopy, then this could have attenuated a potential association between BMI and BE. Lastly, observed associations would have been artificially diminished if selected controls had a higher BMI than those eligible but not selected. Nested case-control studies are less susceptible to these biases, because cases are drawn from the same known population as controls to which they are compared. In this respect, nested case-control studies have better validity. However, only one of the reviewed studies used a nested-case control design. Only six studies reported on participation rates, two of which evaluated nonparticipation bias. The low participation in some of the studies might have introduced selection bias. Corley *et al.*[31] and Johansson *et al.*[35] conducted subsequent analyses without finding any marked difference between participating and nonparticipating subjects. Finally, studies conducted in specific settings, such as Veterans Affairs Medical Centers, may have included unrepresentative cases.

The present evidence base has certain limitations. A major drawback of case-control studies is that they provide weak evidence about the temporal association between exposure and outcome. Considering that individuals who develop BE may be 40 years of age[40] and those diagnosed with the condition may be 60 years of age and over,[12] more than 20 years could pass between the initiation and manifestation of BE. Only one of the reviewed studies[28] attempted to address this lead time by collecting information on self-reported BMI at age 21, which was found to be associated with an increased but nonsignificant BE risk. Yet, study participants were – on average – 63 years old and the potential for recall bias was high. This problem could be obviated by examining the association in the context of established cohort studies with long-term follow-up. It is also acknowledged that case-control studies with a small number of cases relative to controls may lack statistical power. Yet, independent of such considerations, it was decided to include all studies that met the eligibility criteria as we focused on methodological aspects.

The use of incident cases in case-control studies is preferable to the use of prevalent cases. Recruiting cases right after they are diagnosed minimizes recall bias and potential problems that could result from knowledge of 'case status' among prevalent patients; being diagnosed with BE might cause change of behavior and influence risk factor profiles. The accuracy of the exposure measurement is subject to interviewer bias in studies that used interviews to assess BMI. Blinding interviewers, like in the study by Corley *et al.*,[31] generally provides some protection against measurement error. Perhaps, because BE itself is not a life-threatening condition, it is rather unlikely that the interviewer's knowledge of the case status could have induced bias in significant ways. Nevertheless, the reliability of BMI as an obesity indicator is imperfect because variations in body proportions are not accounted for. Evidence suggested that visceral adipose tissue confounded the association between BMI and BE; this was also true for waist circumference in the study by Corley *et al.*,[31] but not for waist-to-hip ratio in the study by Edelstein *et al.*[32] Indicators of body fat accumulation merit further

Table 3 Effect sizes and model adjustments ($n = 11$)

Author(s)	Data format (BMI)	Effect size		Model adjustment
		BMI	OR (95% CI)	
Anderson *et al.*[28]	Ordinal	Current		Age
		<25.8	1.0	Sex
		25.8–29.0	0.6 (0.4–1.0)	Smoking status (never/ex/ current)
		>29.0	0.8 (0.4–1.3)	Alcohol intake (grams per week)
		5 years ago		Education (years full-time)
		<25.0	1.0	Job type (manual/non manual)
		25.0–28.1	0.8 (0.5–1.4)	GERD symptoms (ever/never)
		>28.1	0.9 (0.5–1.4)	
		Age 21		
		<22.1	1.0	
		22.1–24.1	1.2 (0.7–2.0)	
		>24.1	1.0 (0.6–1.8)	
Cameron[29]	Continuous	Male		Sex
		Per 1 kg/m^2	1.0 (0.9–1.1)	
		Female		
		Per 1 kg/m^2	1.0 (0.9–1.1)	
Campos *et al.*[30]	Continuous	Male		Sex
		Per 1 kg/m^2	1.0 (1.0–1.1)	
		Female		
		Per 1 kg/m^2	1.1 (1.0–1.2)	
Corley *et al.*[31]	Ordinal, continuous	Population controls		Age
		<25.0	1.0	Sex
		25.0–27.4	1.2 (0.7–1.9)	Ethnicity
		27.5–29.9	1.2 (0.7–2.0)	Smoking
		30.0–34.9	1.1 (0.7–1.7)	
		≥35.0	1.3 (0.7–2.1)	
		Per 1 kg/m^2	1.0 (1.0–1.0)	
	Ordinal, continuous	GERD controls		Age
		<25.0	1.0	Sex
		25.0–27.4	1.2 (0.1–2.0)	Ethnicity
		27.5–29.9	0.8 (0.5–1.3)	Smoking
		30.0–34.9	1.1 (0.7–1.7)	
		≥35.0	2.0 (1.1–3.7)	
		Per 1 kg/m^2	1.0 (1.0–1.1)	
Edelstein *et al.*[32]	Ordinal	<25.0	1.0	Age (categorical)
		25.0–29.9	1.6 (0.9–2.8)	Sex
		≥30.0	2.6 (1.5–4.4)	Cigarette use (ever/never)
El-Serag *et al.*[33]	Ordinal, continuous	<25.0	1.0	–
		25.0–30.0	1.7 (0.7–4.2)	
		>30.0	4.0 (1.4–11.1)	
		Per 1 kg/m^2	1.1 (1.0–1.2)	
	Continuous	Per 1 kg/m^2	1.1 (1.0–1.3)	Subcutaneous adipose tissue
		Per 1 kg/m^2	1.0 (0.9–1.2)	Visceral adipose tissue
Gerson *et al.*[34]	Ordinal	Male		Sex
		<18.5	1.0	
		18.5–24.9	1.4 (0.1–14.7)	
		25.0–29.9	0.8 (0.1–7.1)	
		≥30.0	0.7 (0.1–10.8)	
		Female		
		<18.5	1.0	
		18.5–24.9	1.1 (0.4–2.7)	
		25.0–29.9	0.8 (0.3–1.8)	
		≥30.0	0.9 (0.4–2.2)	
Johansson *et al.*[35]	Ordinal	Population controls		Age (continuous)
		<23.6	1.0	Sex
		23.6–26.6	1.9 (0.5–7.4)	Reflux symptoms (yes/no)
		>26.6	1.2 (0.3–4.5)	*Helicobacter pylori* infection (present/absent)
		Normal endoscopy controls		Smoking (ever/never)
		<23.6	1.0	Alcohol consumption (user/abstainer)
		23.6–26.6	0.9 (0.3–2.9)	
		>26.6	1.1 (0.3–3.3)	
Shaheen *et al.*[36]	Continuous	Male		Sex
		Per 1 kg/m^2	1.0 (0.9–1.1)	
		Female		
		Per 1 kg/m^2	0.9 (0.9–1.0)	
Smith *et al.*[37]	Ordinal	Maximum		Age
		18.5–24.9	1.0	Sex
		25.0–29.9	1.0 (0.5–1.7)	Age
		≥30.0	1.7 (0.9–3.2)	Sex
		Maximum		Frequency of GERD symptoms
		18.5–24.9	1.0	BMI (continuous)
		25.0–29.9	0.9 (0.5–1.8)	Pack-years smoked (continuous)
		≥30.0	1.5 (0.7–3.1)	NSAID use
Stein *et al.*[38]	Ordinal	<25.0	1.0	Age (categorical)
		25.0–30.0	2.4 (1.1–5.3)	Race (white/non-white)
		>30.0	2.5 (1.1–5.4)	

BMI, body mass index; CI, confidence interval; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

investigation as they may be associated with the condition.

The potential for misclassification of the outcome was small. Only studies with histological confirmation of SIM were included. However, it is possible that cases in at least some of the studies could have had metaplastic changes of the junctional/stomach cardia epithelium, and not of the esophagus per se, either because such cases may not have been excluded by design or because of potential (endoscopic biopsy) sampling error. Three of the studies specifically excluded such cases from the BE case definition.[34,37,38] The exploration of the association between obesity and metaplasia of the gastroesophageal junction/stomach cardia by further studies will be useful. It is unlikely that endoscopy controls were misclassified, but population controls could have been sampled together with undiagnosed cases from the general population. This would have made cases and controls more alike and biased the findings towards null. However, the potential residual error is small given the rareness of the condition. Of greater concern is the use of the ICD-9 code 530.2 ('ulcer of esophagus') in studies using routine data to identify cases and non-cases, as this code can also be used for conditions other than BE. A recent investigation into its validity[41] found that the positive predictive value for BE diagnosis was less than 50%. To what extent this could have led to misclassification is difficult to interpret. Only Corley *et al.*[31] explicitly use this method of case identification. However, records were additionally reviewed by a physician, which limits the potential for bias.

Studies in support of the association of a high BMI and an increased BE risk were adjusted for a maximum of four variables, including age, sex, and race. None of the 'positive' studies, however, adjusted for GERD symptoms – probably the most important risk factor for BE and a potential confounder. A meta-analysis[42] has shown that a BMI of >30 is associated with a twofold increased risk of GERD symptoms. Findings from Smith *et al.*[37] suggested that the BE risk associated with a BMI of $\geq$30 is still increased (OR = 1.5) but no longer significant (95% CI: 0.7–3.1) after adjustment for GERD symptoms. It may be that the aforementioned significant estimates could have been attenuated or lost significance if GERD symptoms had been taken into account.

To conclude, the evidence from one nested case-control study and three case-controls studies was suggestive of a significant positive association between high levels of BMI and risk of BE. Other case-control studies did not report a significant association. The evidence is constrained by the fact that GERD symptoms were not adjusted for in the statistical analyses. This lack of adjustment, however, does not invalidate the potential public health importance of a positive association between BMI and BE. It is plausible that obesity contributes to the risk of BE through increasing the risk of GERD. Further research should aim to address this question through analysis of cohort study datasets. Quantitative synthesis of the relevant studies may be of help, although the small number of relevant studies and the apparent heterogeneity in methodologies employed limits its value.

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