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Title: A Systematic Review and Meta-Analysis of the Risk of Increasing Adiposity on Barrett's Esophagus.

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Abstract

Objectives

Esophageal adenocarcinoma and its precursor lesion, Barrett's esophagus, are increasing in incidence in Western populations. Gastro-esophageal reflux disease and high body mass index are known risk factors but it is unclear whether body mass index mediates its risk on Barrett's esophagus independently. This systematic review and meta-analysis investigated whether increasing body mass index is associated with Barrett's esophagus compared to general population and gastro-esophageal reflux disease controls.

Methods

Search strategies were conducted in MEDLINE (US National Library of Medicine, Bethesda, Maryland) (1966–2005) and EMBASE (Reed Elsevier PLC, Amsterdam, Netherlands) (1980–2005). Studies to be included were required to present 'current' body mass index data for consecutively recruited Barrett's esophagus patients and appropriate comparison arms with a minimum number of 30 subjects in each.

Results

The literature search produced 5,501 hits from which 295 papers were extracted. Only 10 studies met the criteria for inclusion. STATA was used to conduct random effects meta-analyses. Nine studies comparing the body mass index of Barrett's esophagus and gastro-esophageal reflux disease groups produced a pooled odds ratio of 0.99 per kg/m^2 (95% CI: 0.97, 1.01; $I^2=52\%$), whilst the pooled estimate of three studies comparing Barrett's esophagus with general population controls was 1.02 per kg/m^2 (95% CI: 1.01, 1.04; $I^2=0\%$).

Conclusions

Increasing adiposity is only an indirect risk factor for Barrett's esophagus through the precursor lesion of gastro-esophageal reflux disease. Hence body mass index status has no predictive value with respect to gastro-esophageal reflux disease patients and their risk of progression to Barrett's esophagus.

Abbreviations

BMI	Body Mass Index
GERD	Gastro-Esophageal Reflux Disease
GERD-HUK	GERD-histology unknown
GERD-ESO	GERD-esophagitis

Introduction

Barrett's esophagus is a metaplastic lesion usually confined to the lower region of the esophagus which substantially increases the risk of developing esophageal adenocarcinoma. Estimates of risk of progression to malignancy are approximately 0.5–1% per annum (1, 2). The strongest associated risk factor for this precancerous condition is gastro-esophageal reflux disease (GERD) (3). Frequent exposure to caustic refluxate erodes the regular squamous epithelium which may subsequently be replaced with the goblet cell-containing metaplasia termed Barrett's esophagus (4).

The increasing incidence of esophageal adenocarcinoma in Caucasian populations is well documented (5). Recent evidence also suggests that the incidence of Barrett's esophagus is following a similar pattern in these populations (6, 7). In addition, a progressive imbalance in the sex ratio throughout the progression from reflux disease, Barrett's esophagus and on to esophageal adenocarcinoma has been confirmed (8). Of relevance to these observations is the obesity pandemic (9). In England the prevalence of obesity has tripled in twenty years and continues to rise (10). Excess adiposity is a known risk factor for much morbidity, including several cancers (11). The prevalence of obesity has increased at similar rates in parts of Europe and the United States (12, 13).

Recent meta-analyses published statistically significant pooled risk estimates for overweight and obese groups for the development of GERD and esophageal adenocarcinoma (14, 15). Previous studies have not been able to investigate the risk of increasing adiposity on Barrett's esophagus due to the paucity of such data and the

failure for any to meet the eligibility criterion of having a general population control group.

The present study aimed to investigate the effect of BMI on risk of Barrett's esophagus by comparison with GERD controls as well as general population controls. Increasing BMI is already known to be a risk factor for GERD (14), which is itself a risk factor for Barrett's esophagus (3). It is unknown whether the increased risk for Barrett's esophagus associated with BMI is mediated by GERD directly or whether there is an elevated risk regardless of reflux. This study aimed to investigate these questions by conducting meta-analyses of the BMI of Barrett's esophagus patients compared with that of both GERD patients and general population controls.

Methods

Highly sensitive search strategies were designed and executed in MEDLINE (US National Library of Medicine, Bethesda, Maryland) (1966–2006), EMBASE (Reed Elsevier PLC, Amsterdam, Netherlands) (1980–2006) and MEDLINE in Process (US National Library of Medicine, Bethesda, Maryland) on 20th January 2006 (copies are available on request).

Studies to be included could be of any design but were required to present categorical or mean BMI data for a Barrett's esophagus population and a comparison arm. The comparison arm was required to be general population, GERD with esophagitis (GERD-ESO) or GERD with histology unknown (GERD-HUK). GERD-ALL is used to refer to both of these groups combined. For studies presenting with more than one GERD comparison group GERD-ESO was used in preference over GERD-HUK to provide a more homogenous disease group. A minimum study population of 30 was required in each arm. Barrett's esophagus could be diagnosed by endoscopy or by histology. Short segment Barrett's esophagus (less than 3cm in length) was not excluded from the analysis as long as the study had not excluded long-segment Barrett's esophagus patients (more than or equal to 3cm). BMI was required to be 'current'; that is, measured at study entry. Recruitment of patients had to be consecutive and ~~have no methodological bias, which may lead to misrepresentation of BMI for the respective disease groups~~ open to all; studies from institutes with an inherent selection bias were not included (e.g. Veteran's Affairs Hospitals) nor were studies with specific age criteria or restrictions on the maximum number of GERD symptoms in a designated period. Studies with 'endoscopy negative' controls were

also not included as it is likely that many such patients will have been referred due to GERD symptomatology and inclusion of such studies may risk masking any true association between BMI and Barrett's esophagus if GERD is considered an intermediary in the causal pathway. Also a minimum study population of 30 was required in each arm. Duplicate citations were deleted using the reference management software EndNote (16). Selected references had their citations checked for any articles which may have been missed or which were absent in the databases utilized. Where required, authors were contacted with requests for additional information.

BMI data were extracted from each study and analyzed with STATA 8.2 (17) and linear trend meta-analytic statistical methodology previously described (18). Briefly, BMI data was stratified using the cut-points 24.9 and 29.9 kg/m². Assuming a normal distribution, the mean of each BMI tertile was estimated for Barrett's esophagus and comparison arms combined. A logistic regression was then undertaken of patient group on BMI categorical means using frequency weights. This produced an odds ratio and standard error for each study, estimates of risk which are per 1kg/m² increase in BMI. Thus, the assumption is made that any relationship between BMI and risk of developing Barrett's esophagus is linear.

These risk estimates were pooled using random effects (DerSimonian-Laird) meta-analyses using I² as the chosen measure of heterogeneity (19). An I² value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Random effects meta-regressions were used to investigate possible effect modifiers identified a priori (20). Effect modifiers considered were geographical location, study

population size, method of BMI data collection and year of patient recruitment.

Funnel plots were produced and Egger's test (21) was conducted to inspect potential small study bias. ~~and a~~ sensitivity analysis was also conducted whereby each study was omitted in turn.

Results

There were 5,501 hits from which 295 studies and 121 reviews were extracted. Citations in reviews were checked for any studies which may have been missed. Of the 295 studies extracted, 17 studies were identified as investigating the variable of body weight (M Gough, University of Sheffield, UK, personal communication, 2005) (22-37). Sixteen authors were contacted for further information and 10 provided it. Eight of these 10 replies enabled additional unpublished data to be incorporated in the meta-analyses (M Gough, personal communication) (24, 25, 31, 32, 34, 37, 38).

Authors from seven of the studies initially identified either failed to reply, replied but could not provide the BMI data for various reasons (e.g. lost due to a computer virus, no longer had access) or replied and sent the data only for it to be inadequate for data for inclusion (e.g. Barrett's esophagus group included esophageal adenocarcinoma cases). This, left-leaving a total of 10 studies available for meta-analyses, as shown in Table 1 ((M Gough, personal communication) (24-26, 30-32, 34, 36, 37). All of these studies either explicitly stated or are assumed, from the recruitment dates and respective regional practice guidelines, to have diagnosed Barrett's esophagus histologically (Table 1).

For the Barrett's esophagus and GERD-ALL groups a random effects meta-analysis produced an odds ratio of 0.99 per kg/m² (95% CI: 0.97, 1.01) with an I² of 52% (Figure 1). The odds ratio for the GERD-ESO comparison arm was 0.99 per kg/m² (95% CI: 0.96, 1.01; I²=62%) whilst the estimate for those studies with a GERD-HUK arm was 1.00 per kg/m² (95% CI: 0.96, 1.04; I²=35%).

Data stratified by sex enabled sex-specific meta-analyses of Barrett's esophagus and GERD-ALL groups to be undertaken (M Gough, personal communication) (24, 25, 31, 32, 34, 38). The male sex random effects meta-analysis included these seven studies and provided a pooled odds ratio of 0.99 per kg/m² (95% CI: 0.96, 1.03) with an overall heterogeneity of I²=50%. The pooled estimate for the GERD-ESO comparison subgroup was 0.97 per kg/m² (95% CI: 0.92, 1.03; I²=70%) whilst the equivalent for the GERD-HUK comparison was 1.02 per kg/m² (95% CI: 0.98, 1.07; I²=0%). The random effects meta-analysis for females also provided no statistically significant point estimates with an odds ratio of 0.98 per kg/m² (95% CI: 0.94, 1.02; I²=66%) for the overall analysis, 0.97 per kg/m² (95% CI: 0.92, 1.03; I²=70.3%) for the GERD-ESO comparison arm and 0.99 per kg/m² (95% CI: 0.92, 1.07; I²=60.4) for the GERD-HUK comparison group.

In addition to the statistically non-significant result of the Barrett's esophagus and GERD-ALL groups using the logistic regression methodology, random effects meta-analyses of odds ratios calculated by analyzing BMI as a categorical variable in the six relevant datasets~~derived by cross-tabulations of the six categorical datasets~~ were also null (overweight (BMI=25) OR=0.97 per kg/m²; 95% CI: 0.78, 1.20) (obese (BMI=30) OR=1.06 per kg/m²; 95% CI: 0.91, 1.24).

In the Barrett's esophagus and general population control comparison, shown in Figure 2, the random effects meta-analysis gave a pooled odds ratio of 1.02 per kg/m² (95% CI: 1.01, 1.04; I²=0%; p=0.002). When stratified by sex there was no difference between both the male (OR=1.02; 95% CI: 0.98, 1.08; p=0.32) and female (OR=1.03; 95% CI: 0.996, 1.08; p=0.07) point estimates, although both became statistically non-

significant. A sensitivity analysis was conducted due to the relative study sizes. When the largest study was omitted the point estimate increased slightly but became statistically non-significant (OR=1.03 per kg/m²; 95% CI: 0.99, 1.07). Additional subgroup analyses were not undertaken for the Barrett's esophagus and general population control analysis due to the inclusion of only three studies.

To investigate possible small study bias in the Barrett's esophagus and GERD-ALL analysis a funnel plot of the log odds ratio against the inverse of the standard error of the log odds ratio was produced and did not appear to show any bias (data not shown) and this was confirmed by a statistically non-significant Egger's test (p=0.08).

A random effects sensitivity analysis was conducted whereby each study was excluded in turn to give an indication of how much influence each individual study had on the pooled estimate. No single study significantly altered the pooled estimate for the Barrett's esophagus and GERD-ALL analysis (data not shown).

The I² value for the Barrett's esophagus and GERD-ALL meta-analysis was 52% while the subgroup values for comparison to the GERD-ESO group and the GERD-HUK group were 62% and 35% respectively. The full dataset was utilized for investigation of heterogeneity by meta-regression. When study population size was dichotomized by the median and entered into meta-regression it proved not to be statistically significant source of heterogeneity (p=0.202). The method of BMI data collection (clinical measurement or self-reported) could not be investigated due to only one dataset confirming clinical measurement as its method (34). The remaining studies either did not report their method of data collection or were self-reported. A

meta-regression on the mid-point of patient recruitment year could also not be undertaken as this was unknown for four of the nine studies.

In the Barrett's esophagus and GERD-ALL analysis one dataset, from Ireland, provided an estimate which was considerably lower than all others (24). When this dataset was temporarily excluded from the meta-analysis the I^2 for the GERD-ESO comparison group was reduced to 36%; this was also reflected in the GERD-ALL I^2 value which decreased from 52% to 33%. This difference was highlighted in subsequent meta-regressions of geographical location; a comparison of the three US and the three UK studies was not statistically significant ($p=0.9$) whilst there were statistical significant differences between the three US studies and the Irish study ($p=0.02$) and between the three UK studies and the Irish study ($p=0.02$).

Discussion

The systematic review and meta-analysis presented provides evidence that increasing BMI does not present an increased risk for Barrett's esophagus above what would be expected from GERD alone. Point estimates calculated for the Barrett's esophagus and GERD-ALL meta-analysis, and those detailed for the subgroup and sex specific analyses, were not statistically significant.

There was a 'moderate' amount of heterogeneity with an I^2 value of 52% for the Barrett's esophagus and GERD-ALL analysis (19). An investigation of study size by meta-regression provided no evidence to support this as a source of heterogeneity. Method of data analysis and year of patient recruitment variables could not be investigated due to lack of data whilst it is not obvious why the only Irish study (24) included provided a protective odds ratio for males with increasing BMI and thus contributed significantly to the heterogeneity statistic.

The Barrett's esophagus and general population control comparison gave an odds ratio of 1.12 per five unit increase of BMI. This analysis was heavily dominated by the Solaymani-Dodaran study (see Figure 2) (25). When excluded in a sensitivity analysis, the point estimate increased slightly but was no longer statistically significant.

A previous meta-analysis of esophagitis and esophageal adenocarcinoma is suggestive to a hypothesis that increasing adiposity is a risk factor for the development of Barrett's esophagus (14). Our results support such a hypothesis whilst additionally

concluding that it is an increased risk of GERD, caused by increasing BMI, which underlies this association; once GERD occurs it would seem that there is no additional effect of BMI on progression to Barrett's esophagus. BMI is, therefore, of no value in predicting which GERD patients may be at risk of developing Barrett's esophagus and consequently such information is of no value in making decisions about which GERD patients would benefit from endoscopic screening or surveillance.

This indirect mechanism of association could, potentially, be explanatory of observed increases in esophageal adenocarcinoma risk in higher BMIs categories. (14, 15) Thus, it is proposed that increasing adiposity is only a direct risk factor for GERD and that this association acts as an intermediary in the etiology of Barrett's esophagus and, possibly, esophageal adenocarcinoma. There is a lack of data on BMI comparisons between patients with this cancer and GERD or Barrett's control groups. One cohort study has investigated the risk of BMI for developing low grade dysplasia from BO (39). The reported OR was 1.01 per kg/m^2 (95% CI: 0.92, 1.11; $p=0.862$) indicating no association. Two other studies have adjusted for GERD in their investigations of esophageal adenocarcinoma and BMI compared to population controls (40, 41). Both found evidence for BMI acting as an independent risk factor for esophageal adenocarcinoma and this suggests that increasing adiposity has additional effects on cancer risk other than propagating GERD. Both of these studies measured GERD on symptom questionnaires and responses from such are known to have a relatively low diagnostic sensitivity (42), thus further investigation into this association and its potential mechanisms is warranted.

The mechanistic explanation of why increasing adiposity should increase the likelihood of GERD remains enigmatic. Several hypotheses have been forwarded to explain the association including a decrease in pressure of the lower esophageal sphincter (43), hiatus hernia (43, 44), altered refluxate composition (45), high fat diet (46-48), estrogens (49), *Helicobacter pylori* (50, 51) and visceral fat (43, 52). It appears unlikely that the risk is mediated wholly through any one of these; the route of association is likely to be complex and multi-factorial.

The meta-analysis undertaken has several limitations. Firstly, the accuracy of BMI measurement and its reliability as a measure of adiposity are known to be imperfect, although this measure is still more applicable to epidemiological studies than other methodologies such as computed tomography, which is expensive and impractical for large populations.

Second, the timing of the BMI measurement was denoted as 'current' in all studies. This is not ideal as it is not truly representative of the situation earlier in the disease process. It is, however, the only time-point for which BMI is consistently recorded for Barrett's esophagus patients in a research field which already exhibits a paucity of adiposity data. Given that Barrett's esophagus is a pre-cancerous condition, it is likely that this measurement is less susceptible to reporting bias than in the case of studies of cancer.

Thirdly, we assume that all BO patients also have GERD. Although for two of the included studies this is true (31, 36), three other studies included in this meta-analysis indicate only approximately 80% of BO patients report reflux symptoms (24, 26, 37).

It is conceivable that the remaining 20% may not have GERD. Conversely BO is known to cause de-sensitization of the esophagus (53) and, coupled with the fact that GERD is the most potent and consistent risk factor for BO (3, 54), it is therefore likely that the majority of BO patients have GERD and this provides confidence to our conclusions.

A final weakness of this meta-analysis is that all odds ratios are unadjusted. Exposures including smoking, alcohol, diet and medication may be hypothesized as effect modifiers but data on these variables have rarely been published on Barrett's esophagus patients, hence their omission from the analysis. In addition there was no study which provided unadjusted and adjusted odds ratios which may have allowed artificial adjustment of study point estimates (55).

This meta-analysis indicates that increasing adiposity presents no additional risk for Barrett's esophagus above that which it presents by increasing risk of GERD alone. The large body of evidence of the associated risk between obesity and GERD, when compared to general population controls, is conclusive. In summary, the causality of the association between obesity and esophageal adenocarcinoma requires further investigation, although it may be postulated that the effect is indirect via the known associations with GERD.

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1) What is current knowledge

- Increasing body mass index is a risk factor for gastro-esophageal reflux disease
- Increasing body mass index is a risk factor for esophageal adenocarcinoma
- Gastro-esophageal reflux disease is the main risk factor for Barrett's esophagus

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2) What is new here

- In gastro-esophageal reflux disease patients increasing body mass index does not alter the risk of Barrett's esophagus
- Increasing body mass index is an indirect risk factor for Barrett's esophagus mediated through gastro-esophageal reflux

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Table 1. Studies Included in the Meta-Analyses

Authors Year of Publication	Country	Patients (N)	Comparison Arm (N)	Comparison Group(s)	Data format	Barrett's Esophagus Definition	
Cameron 1999	USA 61	103 GERD-HUK*	Categorical	SIM			
Campos et al. (31)	2001	USA	189	313	GERD-HUK	Categorical	SIM
Caygill et al. [†] (32)	2002	U.K.	101	101	GERD-ESO	Means	SIM
Gudlaugsdottir et al. (26)	2002	The Netherlands	34	31	GERD-ESO	Means	≥3 cm CLE or SIM
Anderson et al.	2005	Ireland	223	229 and 258	GERD-ESO	Categorical	SIM

(24)					and population		
Kulig et al. (36)	2004	Germany, Austria, and Switzerland	702	2660	GERD-ESO	Categorical	CLE or SIM
Solaymani- Dodaran et al. (25)	2004	U.K.	1269	4935 and 9320	GERD-ESO and population	Categorical	SIM [‡]
Gough§	2005	U.K.	150	151	GERD-ESO	Categorical	SIM
Shaheen (34)	2005	USA	169	302	GERD-HUK	Means	SIM
Smith et al. (37)	2005	Australia	115	259	Population	Categorical	SIM

*As well as the GERD patients, this comparison group may also include some patients presenting for endoscopy with no GERD symptoms.

[‡]The data from one study (31) provided only mean weights, by sex, for the Barrett's esophagus and reflux esophagitis groups, as height had not been measured. These data were converted into mean BMIs using average U.K. national heights for men and women (30).

‡This study cannot verify method of diagnosis, but is assumed to be representative of SIM; in consideration of the dates of the study and the current U.K. practice guidelines, the majority of such patients are assumed to have undergone histologic diagnosis.

§M. Gough, The University of Sheffield, United Kingdom, personal communication, 2005.

CLE = columnar-lined epithelium; GERD-HUK = gastroesophageal reflux disease histology unknown; GERD-ESO = gastroesophageal reflux disease with esophagitis;

SIM = specialized intestinal metaplasia.

Figure 1. Forest plot of random effects meta-analysis of the risk of BMI on Barrett’s esophagus compared to the GERD comparison arms.

Each study’s odds ratio (OR) is represented by the corresponding black square with the arms representing 95% confidence intervals. The pooled estimate subtotals are designated by the diamonds, which follow each subgroup; these are 0.99 per kg/m² (95% CI 0.96–1.01) and 1.00 per kg/m² (95% CI 0.96–1.04), respectively, while the last diamond is the overall pooled estimate, which is 0.99 (95% CI 0.97–1.01).

Abbreviations: f=females; m=males; mf=males and females.

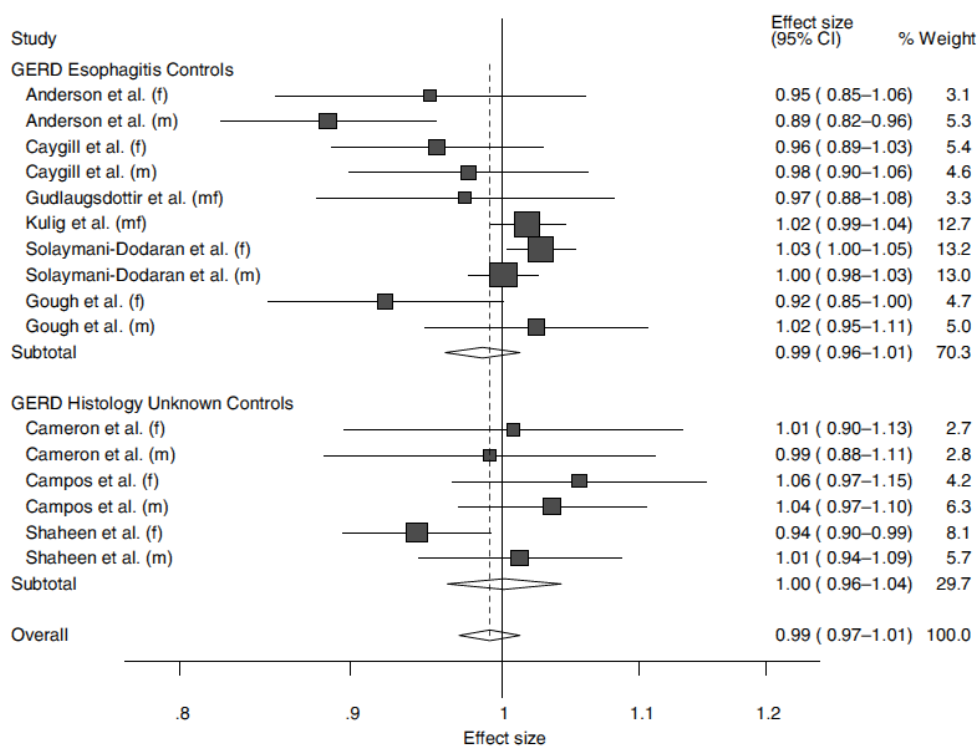
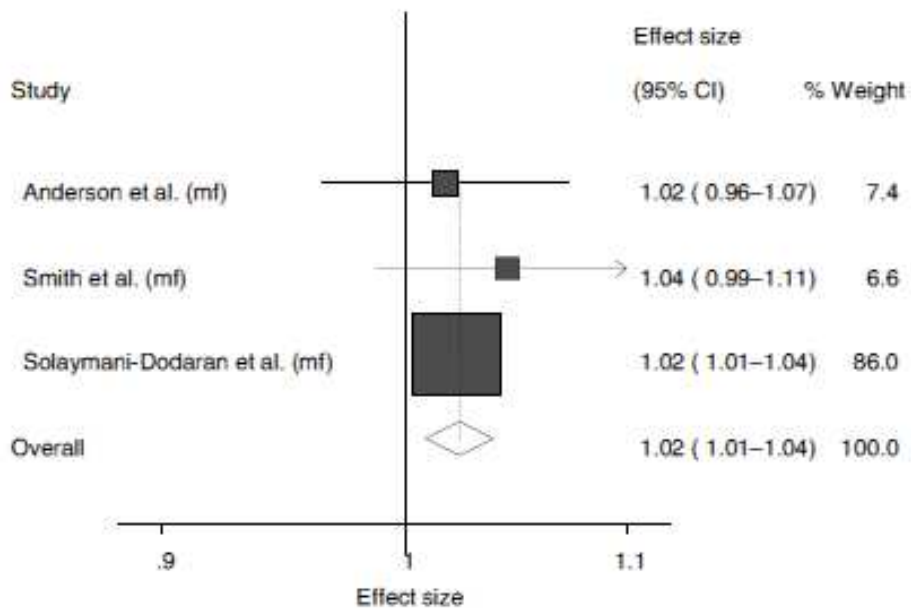


Figure 2. Forest plot of random effects meta-analysis of the risk of BMI on Barrett's esophagus compared to general population controls.

Each study's odds ratio (OR) is represented by the corresponding black square with the arms representing 95% CI. The pooled estimate is designated by the diamond and is 1.02 (95% CI 1.01–1.04). Abbreviations: mf=males and females.



APPENDIX

Search Strategy 1

1. exp obesity/
2. obes\$.tw.
3. exp body mass index/
4. (body adj2 mass adj2 index\$.tw.
5. bmi.tw.
6. exp body weight/
7. overweight\$.tw.
8. (body adj5 fat).tw.
9. over-weight.tw.
10. exp adipose tissue/
11. adipose tissue.tw.
12. physical\$ inactiv\$.tw.
13. exp energy intake/
14. exp caloric intake/
15. energ\$ intake.tw.
16. calor\$ intake.tw.
17. exp energy expenditure/
18. exp energy metabolism/
19. energy balance.tw.
20. energy expend\$.tw.
21. energy metabol\$.tw.

22. exp anthropometry/
23. anthropom\$.tw.
24. (quetelet\$ adj index\$).tw.
25. exp body composition/
26. body weight.tw.
27. body size.tw.
28. fat\$ distribut\$.tw.
29. (waist adj3 hip adj3 ratio).tw.
30. (waist adj3 circumference\$).tw.
31. (hip adj3 circumference\$).tw.
32. or/1-31
33. exp gastroesophageal reflux/
34. (gastroesophageal adj2 reflux).tw.
35. (gastro?esophageal adj2 reflux).tw.
36. (gastro-esophageal adj2 reflux).tw.
37. (gastro-oesophageal adj2 reflux).tw.
38. gord.tw.
39. gerd.tw.
40. erd.tw.
41. enrd.tw.
42. erosive reflux.tw.
43. non-erosive reflux.tw.
44. non erosive reflux.tw.
45. endoscopy-negative reflux.tw.
46. endoscopy negative reflux.tw.

47. negative-endoscopy reflux.tw.
48. negative endoscopy reflux.tw.
49. exp esophagitis/
50. esophagitis.tw.
51. oesophagitis.tw.
52. (reflux\$ adj3 disease\$.tw.
53. heartburn.tw.
54. indigestion.tw.
55. or/33-54
56. exp barrett esophagus/
57. (barret\$ adj3 esophagus).tw.
58. (barret\$ adj3 oesophagus).tw.
59. (metaplas\$ adj5 epitheli\$.tw.
60. (columnar adj5 line\$.tw.
61. (columnar adj5 metaplas\$.tw.
62. (intest\$ adj5 metaplas\$.tw.
63. brachyesophag\$.tw.
64. brachyoesophag\$.tw.
65. brachy-esophag\$.tw.
66. brachy-oesophag\$.tw.
67. endobrachy\$.tw.
68. or/56-67
69. exp esophageal neoplasms/
70. (esophag\$ adj250 neoplas\$.tw.
71. (oesophag\$ adj250 neoplas\$.tw.

72. (esophag\$ adj250 cancer\$).tw.
73. (esophag\$ adj250 carcin\$).tw.
74. (oesophag\$ adj250 carcin\$).tw.
75. (esophag\$ adj250 tumo\$).tw.
76. (oesophag\$ adj250 tumo\$).tw.
77. (esophag\$ adj250 metasta\$).tw.
78. (oesophag\$ adj250 metasta\$).tw.
79. (esophag\$ adj250 malig\$).tw.
80. (oesophag\$ adj250 malig\$).tw.
81. (adenocarcinoma\$ adj250 esophag\$).tw.
82. (adenocarcinoma\$ adj250 oesophag\$).tw.
83. or/69-82
84. 32 and 55
85. 32 and 68
86. 32 and 83
87. 84 or 85 or 86
88. limit 87 to human

Search Strategy 2

1. exp gastroesophageal reflux/
2. (gastroesophageal adj2 reflux).tw.
3. (gastro?esophageal adj2 reflux).tw.
4. (gastro-esophageal adj2 reflux).tw.
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5. (gastro-oesophageal adj2 reflux).tw.
6. gord.tw.
7. gerd.tw.
8. erd.tw.
9. enrd.tw.
10. erosive reflux.tw.
11. non-erosive reflux.tw.
12. non erosive reflux.tw.
13. endoscopy-negative reflux.tw.
14. endoscopy negative reflux.tw.
15. negative-endoscopy reflux.tw.
16. negative endoscopy reflux.tw.
17. exp esophagitis/
18. esophagitis.tw.
19. oesophagitis.tw.
20. (reflux\$ adj3 disease\$).tw.
21. heartburn.tw.
22. indigestion.tw.

23. or/1-22

24. exp barrett esophagus/

25. (barret\$ adj3 esophagus).tw.

26. (barret\$ adj3 oesophagus).tw.

27. (metaplas\$ adj5 epitheli\$).tw.

28. (columnar adj5 line\$).tw.

29. (columnar adj5 metaplas\$).tw.

30. (intest\$ adj5 metaplas\$).tw.

31. brachyesophag\$.tw.

32. brachyoesophag\$.tw.

33. brachy-esophag\$.tw.

34. brachy-oesophag\$.tw.

35. endobrachy\$.tw.

36. or/24-35

37. exp esophageal neoplasms/

38. (esophag\$ adj250 neoplas\$).tw.

39. (oesophag\$ adj250 neoplas\$).tw.

40. (esophag\$ adj250 cancer\$).tw.

41. (esophag\$ adj250 carcin\$).tw.

42. (oesophag\$ adj250 carcin\$).tw.

43. (esophag\$ adj250 tumo\$).tw.

44. (oesophag\$ adj250 tumo\$).tw.

45. (esophag\$ adj250 metasta\$).tw.

46. (oesophag\$ adj250 metasta\$).tw.

47. (esophag\$ adj250 malig\$).tw.

48. (oesophag\$ adj250 malig\$).tw.
49. (adenocarcinoma\$ adj250 esophag\$).tw.
50. (adenocarcinoma\$ adj250 oesophag\$).tw.
51. or/37-50
52. (risk\$ adj2 factor\$).ti.
53. exp Risk factors/
54. 52 or 53
55. 23 and 54
56. 36 and 54
57. 51 and 54
58. or/55-57
59. limit 58 to human