

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

Michael B. Cook, B.Sc., Ph.D., Darren C. Greenwood, B.Sc., M.Sc., Laura J. Hardie, B.Sc., Ph.D., Christopher P. Wild, B.Sc., Ph.D., and David Forman, B.A., Ph.D.

Centre for Epidemiology and Biostatistics, Leeds Institute for Genetics Health and Therapeutics, Faculty of Medicine and Health, University of Leeds, Leeds, England, United Kingdom

- OBJECTIVES:** Esophageal adenocarcinoma and its precursor lesion, Barrett's esophagus, are increasing in incidence in western populations. Gastroesophageal reflux disease (GERD) and high body mass index (BMI) are known risk factors, but it is unclear whether BMI mediates its risk on Barrett's esophagus independently. This systematic review and meta-analysis investigated whether increasing BMI is associated with Barrett's esophagus as compared to general population and GERD controls.
- METHODS:** Search strategies were conducted in MEDLINE (U.S. National Library of Medicine, Bethesda, MD) (1966–2005) and EMBASE (Reed Elsevier PLC, Amsterdam, The Netherlands) (1980–2005). Studies to be included were required to present "current" BMI 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. The Statistics/Data Analysis (STATA) program was used to conduct random effects meta-analyses. Nine studies comparing the BMI of the Barrett's esophagus and GERD groups produced a pooled odds ratio (OR) of 0.99 per kg/m² (95% confidence interval [CI] 0.97–1.01, $I^2 = 52\%$), while the pooled estimate of three studies comparing Barrett's esophagus with general population controls was 1.02 per kg/m² (95% CI 1.01–1.04, $I^2 = 0\%$).
- CONCLUSIONS:** Increasing adiposity is only an indirect risk factor of Barrett's esophagus through the precursor lesion of GERD. Hence, BMI status has no predictive value with respect to GERD patients and their risk of progression to Barrett's esophagus.

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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 of this precancerous condition is gastroesophageal 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 white 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 20 years and continues to rise (10). Excess adiposity is a known risk factor of 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 of any to meet the eligibility criterion of having a general population control group.

The present study is aimed to investigate the effect of body mass index (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 of GERD (14), which itself is a risk factor of 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 (U.S. National Library of Medicine, Bethesda, MD) (1966–2006), EMBASE (Reed Elsevier PLC, Amsterdam, The Netherlands) (1980–2006), and MEDLINE in Process (U.S. National Library of Medicine, Bethesda, MD) on January 20, 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 the 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 (<3 cm in length) was not excluded from the analysis as long as the study did not exclude long-segment Barrett's esophagus patients (≥ 3 cm). BMI was required to be "current;" that is, measured at study entry. Recruitment of patients had to be consecutive and 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 would 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. 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.

The 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, the BMI data were stratified using the cut points of 24.9 and 29.9 kg/m². Assuming a normal distribution, the mean of each BMI tertile was estimated for the Barrett's esophagus and comparison arms combined. A logistic regression was then undertaken of the patient group on the BMI categorical means using frequency weights. This produced an odds ratio (OR) and

standard error for each study, estimates of risk which are per 1 kg/m² increase in BMI. Thus, an assumption is made that any relationship between BMI and the risk of developing Barrett's esophagus is linear.

These risk estimates were pooled using random effects (DerSimonian–Laird) meta-analyses using I^2 as the chosen measure of heterogeneity (19). An I^2 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. 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 that 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, United Kingdom, 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, 30, 31, 32, 34, 37). Authors from eight of the initially identified studies either failed to reply, replied but could not provide 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 inclusion (*e.g.*, Barrett's esophagus group included esophageal adenocarcinoma cases). This left 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 OR of 0.99 per kg/m² (95% confidence interval [CI] 0.97–1.01) with an I^2 of 52% (Fig. 1). The OR for the GERD-ESO comparison arm was 0.99 per kg/m² (95% CI 0.96–1.01, $I^2 = 62\%$), while the estimate for those studies with a GERD-HUK arm was 1.00 per kg/m² (95% CI 0.96–1.04, $I^2 = 35\%$).

Data stratified by sex enabled sex-specific meta-analyses of the Barrett's esophagus and GERD-ALL groups to be undertaken (M. Gough, personal communication) (24, 25, 30, 31, 32, 34). The male sex random effects meta-analysis included these seven studies and provided a pooled OR of 0.99 per kg/m² (95% CI 0.96–1.03) with an overall heterogeneity of $I^2 = 50\%$. The pooled estimate for the GERD-ESO

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 <i>et al.</i> (31)	2001	USA	189	313	GERD-HUK	Categorical	SIM
Caygill <i>et al.</i> [†] (32)	2002	U.K.	101	101	GERD-ESO	Means	SIM
Gudlaugsdottir <i>et al.</i> (26)	2002	The Netherlands	34	31	GERD-ESO	Means	≥3 cm CLE or SIM
Anderson <i>et al.</i> (24)	2005	Ireland	223	229 and 258	GERD-ESO and population	Categorical	SIM
Kulig <i>et al.</i> (36)	2004	Germany, Austria, and Switzerland	702	2,660	GERD-ESO	Categorical	CLE or SIM
Solaymani-Dodaran <i>et al.</i> (25)	2004	U.K.	1,269	4,935 and 9,320	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 <i>et al.</i> (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.

comparison subgroup was 0.97 per kg/m² (95% CI 0.92–1.03, $I^2 = 70\%$), while the equivalent for the GERD-HUK comparison was 1.02 per kg/m² (95% CI 0.98–1.07, $I^2 = 0\%$). The random effects meta-analysis for women also provided no statistically significant point estimates with an OR of 0.98 per kg/m² (95% CI 0.94–1.02, $I^2 = 66\%$) for the overall analysis, 0.97 per kg/m² (95% CI 0.92–1.03, $I^2 = 70.3\%$) for the GERD-ESO comparison arm, and 0.99 per kg/m² (95% CI 0.92–1.07, $I^2 = 60.4$) for the GERD-HUK comparison group.

In addition to the statistically nonsignificant result of the Barrett's esophagus and GERD-ALL groups using logistic regression methodology, random effects meta-analyses of OR calculated by analyzing BMI as a categorical variable in the six relevant datasets were also null (overweight [BMI ≥25 and <30] 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 OR of 1.02 per kg/m² (95% CI 1.01–1.04, $I^2 = 0\%$, $P = 0.002$). 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 nonsignificant. 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 nonsignificant (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 OR against the inverse of the standard error of the log OR was produced, which did not appear to show any bias (data not shown) and this was confirmed by a statistically nonsignificant 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 I^2 value for 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 was entered into a meta-regression, it proved not to be a statistically significant source of heterogeneity ($P = 0.20$). 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 midpoint 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 that 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 that decreased from 52% to 33%. This difference was highlighted in subsequent

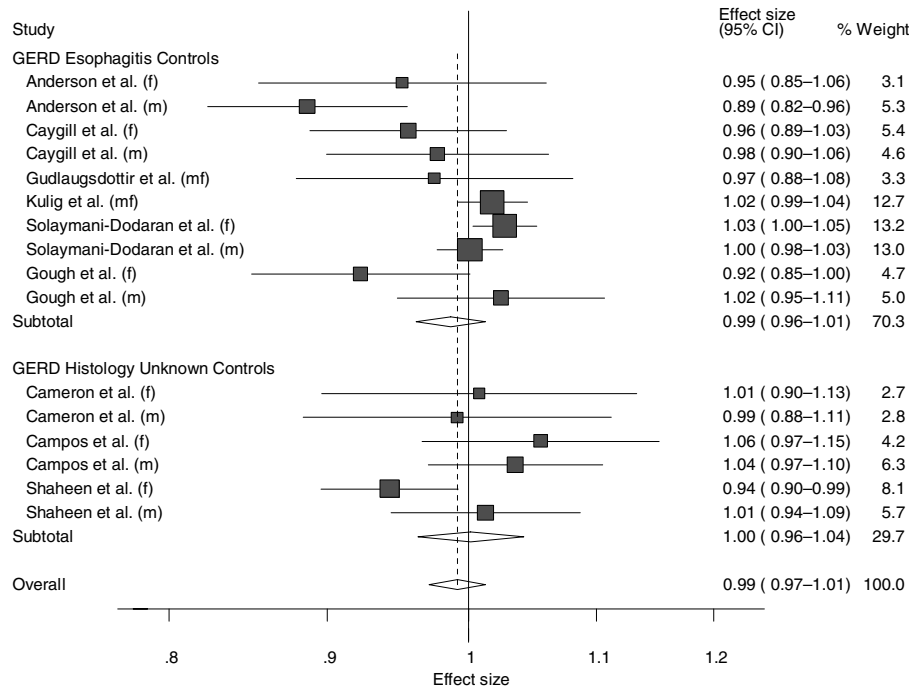


Figure 1. Forest plot of random effects meta-analysis of the risk of BMI on Barrett's esophagus compared to the GERD comparison arms. Each study's odds ratio (OR) is represented by the corresponding black square with the arms representing 95% confidence intervals. The pooled estimate subtotals are designated 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.

meta-regressions of geographical location; a comparison of the three U.S. and three U.K. studies was not statistically significant ($P = 0.9$), while there were statistically significant differences between the three U.S. studies and the Irish study ($P = 0.02$) and between the three U.K. 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 of 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 the study size by meta-regression provided no evidence to support this as a source of heterogeneity. Methods of data analysis and year of patient recruitment variables could not be investigated due to the lack of data, while it is not obvious why the only Irish study (24) included provided a protective OR for men with increasing BMI, and thus contributed significantly to the heterogeneity statistic.

The Barrett's esophagus and general population control comparison gave an OR of 1.12 per five-unit increase in

BMI. This analysis was heavily dominated by the Solaymani-Dodaran study (see Fig. 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, while additionally concluding that there 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 its progression to Barrett's esophagus. BMI is, therefore, of no value in predicting which GERD patient may be at risk of developing Barrett's esophagus, and consequently such information is of no value in making decisions about which GERD patient would benefit from endoscopic screening or surveillance.

This indirect mechanism of association could, potentially, be explanatory of the observed increases in esophageal adenocarcinoma risk in higher BMI categories (14, 15). Thus, it is proposed that increasing adiposity is only a direct risk factor of 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 in developing low-grade dysplasia from Barrett's esophagus (38). The reported OR was 1.01 per kg/m²

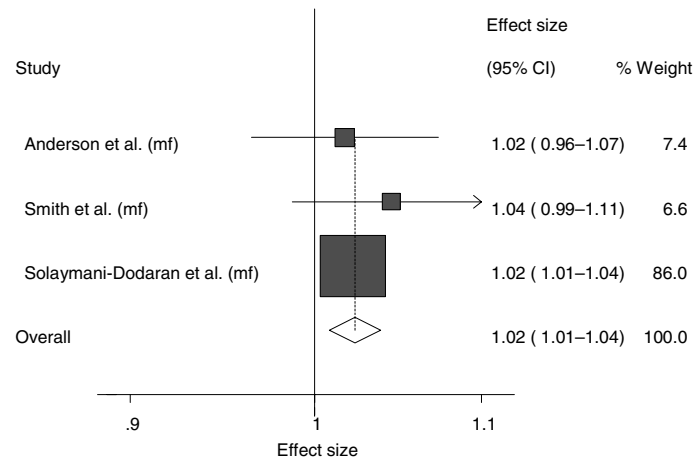


Figure 2. Forest plot of random effects meta-analysis of the risk of BMI on Barrett's esophagus compared to general population controls. Each study's odds ratio (OR) is represented by the corresponding black square with the arms representing 95% CI. The pooled estimate is designated by the diamond and is 1.02 (95% CI 1.01–1.04). Abbreviations: mf = males and females.

(95% CI 0.92–1.11, $P = 0.86$), indicating no association. Two other studies have adjusted for GERD in their investigations of esophageal adenocarcinoma and BMI as compared to population controls (39, 40). Both found evidence of BMI acting as an independent risk factor of esophageal adenocarcinoma, and this suggests that increasing adiposity has additional effects on cancer risk other than in propagating GERD. Both of these studies measured GERD on symptom questionnaires and responses for such are known to have a relatively low diagnostic sensitivity (41), 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 (42), hiatus hernia (42, 43), altered refluxate composition (44), high-fat diet (46–47), estrogens (48), *Helicobacter pylori* (49, 50), and visceral fat (42, 51). It appears unlikely that the risk is mediated wholly through any one of these; the route of association is likely to be complex and multifactorial.

These results indicate that BMI, *per se*, is unlikely to explain the large male-to-female sex ratio of Barrett's esophagus and esophageal adenocarcinoma (8), especially given that levels of overweight and obesity are more prevalent in women. However, anthropometric measures may be able to account for these differences in risk (29, 42, 51, 52), and future studies should be encouraged to investigate such exposures.

The meta-analysis undertaken has several limitations. First, the accuracy of the BMI measurement and its reliability as a measure of adiposity are known to be imperfect, although this measure is still more applicable to epidemiologic 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 early 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 precancerous condition, it is likely that this measurement is less susceptible to reporting bias than in the case of studies of cancer.

Third, we assume that all Barrett's esophagus 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 Barrett's esophagus patients report reflux symptoms (24, 26, 37). It is conceivable that the remaining 20% may not have GERD. Conversely, Barrett's esophagus is known to cause desensitization of the esophagus (53), and coupled with the fact that GERD is the most potent and consistent risk factor of Barrett's esophagus (3, 54), it is therefore likely that the majority of Barrett's esophagus patients have GERD and this provides confidence to our conclusions.

A final weakness of this meta-analysis is that all OR 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 OR 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 what it presents by increasing the risk of GERD alone. The large body of evidence on 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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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. enr.d.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. brachyoesophag\$.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.

5. (gastro-oesophageal adj2 reflux).tw.
6. gord.tw.
7. gerd.tw.
8. erd.tw.
9. enr.d.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. brachyoesophag\$.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

STUDY HIGHLIGHTS

What Is Current Knowledge

- The natural history of esophageal adenocarcinoma is conventionally regarded as progressing from gastroesophageal reflux to Barrett's esophagus to dysplasia and then esophageal adenocarcinoma.
- Increasing body mass index is associated with gastroesophageal reflux and esophageal adenocarcinoma when compared to population-based controls.

What Is New Here

- Increasing body mass index is not associated with Barrett's esophagus when compared to gastroesophageal reflux disease controls but is associated with Barrett's esophagus when compared to population-based controls.
- Increasing body mass index increases the risk of Barrett's esophagus indirectly through increasing the risk of gastroesophageal reflux.
- Therefore, body mass index is unlikely to be indicative as to which gastroesophageal reflux disease patients may progress to Barrett's esophagus and, possibly, esophageal adenocarcinoma.

Reprint requests and correspondence: David Forman, Centre for Epidemiology and Biostatistics, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Arthington House, Cookridge Hospital, Leeds, LS16 6QB, United Kingdom.

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REFERENCES

1. Jankowski JA, Provenzale D, Moayyedi P. Esophageal adenocarcinoma arising from Barrett's metaplasia has regional variations in the west. *Gastroenterology* 2002;122:588–90.
2. Shaheen NJ, Crosby MA, Bozymski EM, et al. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology* 2000;119:333–8.
3. Conio M, Filiberti R, Bianchi S, et al. Risk factors for Barrett's esophagus: A case-control study. *Int J Cancer* 2002;97:225–9.
4. Wild CP, Hardie LJ. Reflux, Barrett's oesophagus, and adenocarcinoma: Burning questions. *Nat Rev Cancer* 2003;3:676–84.
5. Vizcaino AP, Moreno V, Lambert R, et al. Time trends in incidence of both major histologic types of esophageal carcinomas in selected countries, 1973–1995. *Int J Cancer* 2002;99:860–8.
6. van Soest EM, Dieleman JP, Siersema PD, et al. Increasing incidence of Barrett's oesophagus in the general population. *Gut* 2005;54:1062–6.
7. Irani S, Parkman H, Krevsky B, et al. A decade (1991–2000) of increasing incidence of endoscopic and histologic Barrett's esophagus (BE) at a single academic medical center. *Am J Gastroenterol* 2003;98:S16.

8. Cook MB, Wild CP, Forman D. A systematic review and meta-analysis of the sex ratio for Barrett's esophagus, erosive reflux disease, and nonerosive reflux disease. *Am J Epidemiol* 2005;162:1050-61.
9. James PT. Obesity: The worldwide epidemic. *Clin Dermatol* 2004;22:276-80.
10. The National Audit Office, The Audit Commission, The Healthcare Commission. Tackling child obesity: First steps. London. Her Majesty's Stationary Office, 2006.
11. International Agency for Research on Cancer. Handbooks of cancer prevention. Weight control and physical activity. Lyon: International Agency for Research on Cancer, 2002.
12. Seidell JC. Prevalence and time trends of obesity in Europe. *J Endocrinol Invest* 2002;25:816-22.
13. Flegal KM. Epidemiologic aspects of overweight and obesity in the United States. *Physiol Behav* 2005;86:599-602.
14. 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.
15. Kubo A, Corley DA. Body mass index and adenocarcinomas of the esophagus or gastric cardia: A systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006;15:872-8.
16. The EndNote Team. EndNote 7. Berkeley, CA: Thomson ISI ResearchSoft, 2003.
17. StataCorp. Stata statistical software: Release 8.2. College Station, TX: StataCorp LP, 2004.
18. Chene G, Thompson SG. Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form. *Am J Epidemiol* 1996;144:610-21.
19. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
20. Sharp SJ. Meta-analysis regression. *Stata Tech Bull* 1998;(42):16-22.
21. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
22. Banki F, Demeester SR, Mason RJ, et al. Barrett's esophagus in females: A comparative analysis of risk factors in females and males. *Am J Gastroenterol* 2005;100:560-7.
23. Reed PI, Caygill CPJ, Watson A, et al. The United Kingdom Barrett's esophagus registry (UKBOR): The first six years. *Gastroenterol Pol* 2003;10:299-304.
24. Anderson LA, Murphy SJ, Johnston BT, et al. Obesity and smoking in patients with Barrett's esophagus, esophageal adenocarcinoma, and esophageal adenocarcinoma: Results from the Finbar study. *Gastroenterology* 2005;128:A49.
25. Solaymani-Dodaran M, Logan RF, West J, et al. Risk of esophageal cancer in Barrett's oesophagus and gastroesophageal reflux. *Gut* 2004;53:1070-4.
26. Gudlaugsdottir S, Verschuren W, Dees J, et al. Hypertension is frequently present in patients with reflux esophagitis or Barrett's esophagus but not in those with nonulcer dyspepsia. *Eur J Intern Med* 2002;13:369-75.
27. Rajendra S, Kutty K, Karim N. Ethnic differences in the prevalence of endoscopic esophagitis and Barrett's esophagus: The long and short of it all. *Dig Dis Sci* 2004;49:237-42.
28. Chak A, Lee T, Kinnard MF, et al. Familial aggregation of Barrett's oesophagus, oesophageal adenocarcinoma, and oesophagogastric junctional adenocarcinoma in Caucasian adults. *Gut* 2002;51:323-8.
29. Vaughan TL, Kristal AR, Blount PL, et al. Nonsteroidal anti-inflammatory drug use, body mass index, and anthropometry in relation to genetic and flow cytometric abnormalities in Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev* 2002;11:745-52.
30. Cameron AJ. Barrett's esophagus: Prevalence and size of hiatal hernia. *Am J Gastroenterol* 1999;94:2054-9.
31. Campos GM, DeMeester SR, Peters JH, et al. Predictive factors of Barrett esophagus: Multivariate analysis of 502 patients with gastroesophageal reflux disease. *Arch Surg* 2001;136:1267-73.
32. Caygill CP, Johnston DA, Lopez M, et al. Lifestyle factors and Barrett's esophagus. *Am J Gastroenterol* 2002;97:1328-31.
33. Moe GL, Kristal AR, Levine DS, et al. Waist-to-hip ratio, weight gain, and dietary and serum selenium are associated with DNA content flow cytometry in Barrett's esophagus. *Nutr Cancer* 2000;36:7-13.
34. Shaheen N. Body fat distribution predicts the presence of Barrett's esophagus: A case-control study. *Gastroenterology* 2005;128:A231.
35. Casson AG, Veugeliers PJ, Fitzgerald AL, et al. Dietary and lifestyle risk factors in the etiology of gastroesophageal reflux disease, Barrett esophagus, and esophageal adenocarcinoma. *Can J Gastroenterol* 2005;19:3.
36. Kulig M, Nocon M, Vieth M, et al. Risk factors of gastroesophageal reflux disease: Methodology and first epidemiological results of the ProGERD study. *J Clin Epidemiol* 2004;57:580-9.
37. Smith KJ, O'Brien SM, Smithers BM, et al. Interactions among smoking, obesity, and symptoms of acid reflux in Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev* 2005;14:2481-6.
38. Oberg S, Wenner J, Johansson J, et al. Barrett esophagus: Risk factors for progression to dysplasia and adenocarcinoma. *Ann Surg* 2005;242:49-54.
39. Chow WH, Blot WJ, Vaughan TL, et al. Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst* 1998;90:150-5.
40. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. *Ann Intern Med* 1999;130:883-90.
41. Klauser AG, Schindlbeck NE, Muller-Lissner SA. Symptoms in gastroesophageal reflux disease. *Lancet* 1990;335:205-8.
42. Pandolfino JE, El-Serag HB, Zhang Q, et al. Obesity: A challenge to esophagogastric junction integrity. *Gastroenterology* 2006;130:639-49.
43. Wilson LJ, Ma W, Hirschowitz BI. Association of obesity with hiatal hernia and esophagitis. *Am J Gastroenterol* 1999;94:2840-4.
44. Wisen O, Rossner S, Johansson C. Impaired pancreaticobiliary response to vagal stimulation and to cholecystokinin in human obesity. *Metabolism* 1988;37:436-41.
45. Nebel OT, Castell DO. Lower esophageal sphincter pressure changes after food ingestion. *Gastroenterology* 1972;63:778-83.
46. Holloway RH, Kocyan P, Dent J. Provocation of transient lower esophageal sphincter relaxations by meals in patients with symptomatic gastroesophageal reflux. *Dig Dis Sci* 1991;36:1034-9.
47. Becker DJ, Sinclair J, Castell DO, et al. A comparison of high- and low-fat meals on postprandial esophageal acid exposure. *Am J Gastroenterol* 1989;84:782-6.
48. Nilsson M, Lagergren J. The relation between body mass and gastroesophageal reflux. *Best Pract Res Clin Gastroenterol* 2004;18:1117-23.
49. Loffeld RJ. *Helicobacter pylori*, obesity, and gastroesophageal reflux disease: Is there a relation? A personal view. *Neth J Med* 2005;63:344-7.
50. Suzuki M, Suzuki H, Masaoka T, et al. *Helicobacter pylori* eradication treatment modulates epithelial cell prolifer-

- eration and tissue content of hepatocyte growth factor in the gastric mucosa. *Aliment Pharmacol Ther* 2004;20:158–64.
51. El-Serag HB, Kvavil P, Hacken-Bitar J, et al. Abdominal obesity and the risk of Barrett's esophagus. *Am J Gastroenterol* 2005;100:2151–6.
 52. Edelstein ZR, Vaughan TL. Obesity and central adiposity and risk for Barrett's esophagus. *Am J Epidemiol* 2006;163:S90.
 53. Byrne PJ, Mulligan ED, O'Riordan J, et al. Impaired visceral sensitivity to acid reflux in patients with Barrett's esophagus: The role of esophageal motility. *Dis Esophagus* 2003;16:199–203.
 54. Eisen GM, Sandler RS, Murray S, et al. The relationship between gastroesophageal reflux disease and its complications with Barrett's esophagus. *Am J Gastroenterol* 1997;92:27–31.
 55. Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev* 1987;9:1–30.

CONFLICT OF INTEREST

Guarantor of the article: David Forman, Ph.D.

Specific author contributions: Michael B. Cook: study design, data analysis, manuscript contributor, and reviewer; Darren C. Greenwood: statistical direction, manuscript contributor, and reviewer; Laura J. Hardie: study design, manuscript contributor, and reviewer; Christopher P. Wild: study design, manuscript contributor, and reviewer; and David Forman: study concept, study design, manuscript contributor, and reviewer.

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