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# Long-term risk factors for developing Barrett's oesophagus in patients with gastro-oesophageal reflux disease: a longitudinal cohort study

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## ABSTRACT

**Background and aims** Several characteristics are known to affect the risk of Barrett's oesophagus (BO) in the general population, with symptomatic gastro-oesophageal reflux disease (GORD) being a critical risk factor. In this study, we examined factors that influence BO development in people living with GORD.

**Design** People living with GORD were recruited from an endoscopy unit with lifestyle, medical and prescribing history collected. Logistic regression analysis was undertaken to assess the effects of multiple parameters on the likelihood of developing BO.

**Results** 1197 participants were recruited. Most were Caucasian (n=1188, 99%), had no formal educational qualifications (n=714; 59.6%) and lived with overweight (mean body mass index >25 kg/m$^2$). Many lived in areas of least socioeconomic resource (n=568; 47.4%). 139 (11.6%) had BO at baseline. In adjusted baseline analysis (n=1197), male sex (adjusted OR, aOR 2.04 (95% CI 1.92 to 4.12), p≤0.001), increasing age (aOR 1.03 (95% CI 1.01 to 1.04), p≤0.0001) and proton pump inhibitor use (aOR 3.03 (95% CI 1.80 to 5.13), p≤0.0001) were associated with higher odds of BO. At follow-up (n=363), 22 (6.1%) participants developed BO; male sex (aOR 3.18 (95% CI 1.28 to 7.86), p=0.012), pack-years cigarettes smoked (aOR 1.04 (95% CI 1.00 to 1.08), p=0.046) and increased alcohol intake (aOR 1.02 (95% CI 1.00 to 1.04), p=0.013), were associated with increased odds of BO.

**Conclusion** Male sex, pack-years cigarettes smoked, and increasing alcohol intake, were independently associated with increased odds of developing BO over 20-year follow-up. These results align with research linking male sex and smoking with BO and extend this by implicating the potential role of alcohol in developing BO, which may require communication through public health messaging.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Gastro-oesophageal reflux disease (GORD), advanced age and male sex are established risk factors for Barrett's oesophagus (BO).

### WHAT THIS STUDY ADDS

⇒ Alcohol may also play a role in subsequent development of BO in people with GORD.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ People living with GORD should be counselled against high alcohol intake to mitigate BO risk, alongside conventional risk factors.

## INTRODUCTION

In 2018, approximately 572 034 oesophageal cancer cases were diagnosed worldwide, with an estimated 508 585 associated deaths.[1] In the UK, oesophageal cancer is the seventh most common cancer mortality cause, with a sub-20% 5-year survival.[2] Barrett's oesophagus (BO) is thought to affect close to 2% of UK adults.[3] It is a well-established risk factor for oesophageal adenocarcinoma (OAC), via a stepwise progression of cytogenetic abnormalities and is estimated to confer up to 125-fold risk of OAC relative to the general population.[4–6] Several characteristics have been linked with risk of BO in previous research.[7]

Symptomatic gastro-oesophageal reflux disease (GORD) is the strongest known risk factor.[8 9] The UK prevalence of which is estimated at 15%, representing around 10 million individuals.[10] In addition to symptomatic GORD, increasing age and male sex are established risk factors for developing BO.[11–13] Contradictory evidence exists regarding the impacts of body mass index (BMI), smoking history, and alcohol intake.[14–16] Endoscopic screening is manifestly impractical and tough to rationalise in such a large at-risk population, when the majority will never progress to BO or OAC. It is, therefore, imperative to detect characteristics of those most at risk of developing BO, enabling efficient screening with limited healthcare resources. The capability to reliably stratify individuals in the

GORD population would enable resources to be concentrated on people at highest risk of progression.

The British Society of Gastroenterologists recommends regular endoscopic surveillance of BO, with intervals depending on length of segment affected, evidence of intestinal metaplasia and presence of dysplasia.[17] Despite the well-established link between BO and OAC, data from large population-based studies suggest that malignant transformation of BO without dysplasia is less common than previously thought.[18 19] Cost–utility analyses of 5-yearly monitoring of BO without dysplasia demonstrated a high cost per quality-adjusted life-year gained, calling into question the cost-effectiveness of endoscopically monitoring BO patients with no evidence of dysplasia.[20] To augment our understanding of which patients most require enhanced surveillance, in this longitudinal study, we aimed to examine the effects of several clinical and demographic parameters on the likelihood of developing BO in a population of patients recruited from an endoscopy unit over a 2-year period, both at baseline and follow-up time points.

## MATERIALS AND METHODS

### Setting

The study was conducted in Tayside, a defined administrative region in the East of Scotland with around 420 000 residents. Residents' health needs are met by the National Heath Service, which is free at the point of need. The region hosts one tertiary teaching hospital, alongside several district hospitals, some general and others specialist, and multiple generalist community hospitals.

### Participants

Individuals diagnosed with GORD were recruited between November 2000 and November 2002 from an endoscopy unit at Ninewells Hospital and Medical School, in Dundee, Scotland; the largest hospital in Tayside. A proportion of participants were followed up opportunistically 20 years following index endoscopy for further evaluation as part of routine interaction with the endoscopy unit.

#### Inclusion criteria

- Patients referred for an upper gastrointestinal endoscopy who were symptomatic for GORD.
- Aged 18 years or older.

#### Exclusion criteria

- Patients who were already being followed up for BO or oesophagitis.

### Interventions

Participants received an endoscopy at baseline and follow-up time points. Whole-blood samples (7.5 mL) were obtained using a serum separation tube, and serum stored in monitored −80°C freezers until analysed (participants fasted for a minimum of 6 hours prior to sampling). Gastric aspirates were obtained from participants with no use of acid suppressive therapy in the 2 weeks prior to endoscopy, using a suction trap. Gastric antral biopsies were performed to determine helicobacter status. A questionnaire was also administered, which collected demographic and socioeconomic status, body habitus, lifestyle (including alcohol and tobacco consumption) factors, reflux activity index score (both current and worst symptoms), and self-reported use of both prescribed and over-the-counter medications. Finally, participants completed 3-day food diaries.

### Variables measurements and definitions

Oesophagitis was recorded according to the Los Angeles classification.[21] For the purpose of this study, BO was defined as an upward displacement of the squamocolumnar junction, from the oesophagus-gastric junction, with the presence of columnar lined epithelium on histological analysis. Helicobacter status was characterised into active infection, past infection and never infected, by three methods; CLO (urease detection test) on gastric antral biopsies, histopathology of gastric antral biopsies and, lastly, a quantitative ELISA was performed on serum samples for determination of IgG antibodies against *Helicobacter pylori* (DiaSorin, Hycor Biomedical, 1999, UK). For gastric aspirates, pH measurements in triplicate were made using a Corning 240 pH probe. Gastrin was measured by radioimmunoassay using antibody R98 raised to synthetic human gastrin. Daily intake of nutrients and composition of diet were calculated from food diaries using Dietplan software, using defined criteria.[22]

### Statistical analysis

Descriptive statistics were used to calculate counts and proportions. Differences between groups were assessed using the Mann-Whitney U test. For paired data, a paired t-test was performed. For comparison of categorical variables, the $\chi^2$ test was used. For these descriptive analyses, participants were categorised into three groups based on symptoms and endoscopy findings: those with non-erosive reflux disease (NERD); erosive reflux disease (ERD) and those with BO.

The primary outcome, presence of BO, was analysed as a binary outcome, therefore, logistic regression analysis was undertaken. Separate analyses were performed for the presence of BO at baseline and follow-up time points. Statistical analysis was performed with GraphPad Prism (V.3.0) and IBM Statistical Package for the Social Sciences (V.27.0).

## RESULTS

In total, 1197 individuals diagnosed with GORD were recruited. These comprised 718 (60%) participants with NERD; 344 (29%) with ERD and 135 (11%) with BO. Most participants were female (n=684; 57%) and Caucasian (n=1188, 99%), and the average age was 61 (±17) years (table 1). Close to half of all participants (n=568; 47.4%) resided in areas of least socioeconomic resource (quintiles 1–3), while none lived in areas of most

Table 1 Demographic, helicobacter status and endoscopic findings, stratified by disease status (n=1197)

| Variable | Measure | NERD (n=718) | ERD (n=344) | BO (n=135) |
|---|---|---|---|---|
| Sex—n (%) | | | | |
| | Male | 256 (36) | 178 (52) | 79 (59) |
| | Female | 462 (64) | 166 (48) | 56 (41) |
| Age—mean (±SD) | | | | |
| | All | 56.2 (15) | 54.3 (15) | 61.2 (14) |
| | Male | 53.7 (15) | 51.8 (16) | 58 (12) |
| | Female | 57.6 (15) | 56.8 (15) | 65.7 (15) |
| Socioeconomic decile—n (%) | | | | |
| | 1 (least resource) | 68 (10) | 28 (8) | 15 (11) |
| | 2 | 156 (22) | 71 (21) | 24 (17) |
| | 3 | 115 (16) | 66 (19) | 25 (19) |
| | 4 | 111 (15) | 45 (13) | 25 (19) |
| | 5 | 46 (6) | 28 (8) | 12 (9) |
| | 6 | 222 (31) | 106 (31) | 34 (25) |
| | 7 | 0 (0) | 0 (0) | 0 (0) |
| | 8 | 0 (0) | 0 (0) | 0 (0) |
| | 9 | 0 (0) | 0 (0) | 0 (0) |
| | 10 (most resource) | 0 (0) | 0 (0) | 0 (0) |
| Ethnicity—n (%) | | | | |
| | Caucasian | 711 (99) | 343 (100) | 134 (99) |
| | Asian (subcontinent) | 5 (1) | 0 (0) | 0 (0) |
| | Asian (Far East) | 1 (0) | 0 (0) | 0 (0) |
| | African | 1 (0) | 1 (0) | 1 (1) |
| Qualifications—n (%) | | | | |
| | None | 438 (61) | 187 (54) | 89 (66) |
| | Standard grade/GCSE | 96 (13) | 55 (16) | 17 (13) |
| | CSYS/A Level | 24 (3) | 18 (5) | 3 (2) |
| | Diploma | 99 (14) | 44 (13) | 17 (13) |
| | University degree | 61 (9) | 40 (12) | 9 (6) |
| LA grade oesophagitis—n (%) | | | | |
| | A | nr | 149 (43) | nr |
| | B | nr | 113 (33) | nr |
| | C | nr | 56 (16) | nr |
| | D | nr | 26 (8) | nr |
| Helicobacter—n (%) | | | | |
| | Active | 180 (25) | 117 (34) | 54 (40) |
| | Previous | 215 (30) | 117 (34) | 25 (19) |
| | Never | 323 (45) | 110 (32) | 56 (41) |

BO, Barrett's oesophagus; CSYS, certificate of sixth year studies; ERD, erosive reflux disease; GCSE, general certificate of general education; NERD, non-erosive reflux disease; nr, not reported.

socioeconomic resource. Furthermore, over half (n=714; 59.6%) of participants had no formal educational qualifications, with only 110 (9.2%) attaining university-level education. Among participants with ERD, BO was observed among 39 (11.3%), and most participants had mild cases of oesophagitis (grade A/B), while a minority (n=351; 29.3%) had active *H. pylori* infection (table 1). There were no significant differences in *H. pylori* infection between those with NERD, ERD and BO.

91 (7.6%) participants completed the food diary. Although there were several significant differences in nutrient and dietary fat intake when stratified by

**Table 2** Lifestyle, disease symptomology and self-reported medication use, outcomes for overall cohort, and stratified by sex and disease status (n=1197)

| Variable | Measure | NERD (n=718) | ERD (n=344) | BO (n=135) |
|---|---|---|---|---|
| Weekly units of alcohol—mean (±SD) | Overall | 6.7 (0.5) | 9.9 (0.9) | 10.3 (1.7) |
| | Among males | 12.5 (1.0) | 16.2 (1.5) | 15.4 (2.7) |
| | Among females | 3.5 (0.4) | 3.0 (0.4) | 2.3 (0.7) |
| Pack-years cigarettes smoked—mean (±SD) | Overall | 2.9 (0.2) | 2.5 (0.4) | 2.1 (0.6) |
| | Among males | 4.4 (0.5) | 3.6 (0.6) | 2.0 (0.8) |
| | Among females | 2.0 (0.2) | 1.3 (0.3) | 2.2 (0.8) |
| BMI—mean (±SD) | Overall | 26.4 (0.2) | 26.9 (0.3) | 25.9 (0.4) |
| | Among males | 26.2 (0.2) | 26.4 (0.4) | 26.0 (0.5) |
| | Among females | 26.5 (0.2) | 27.4 (0.4) | 25.8 (0.7) |
| Duration of symptoms in years—mean (±SD) | Overall | 8.6 (0.3) | 6.2 (0.5) | 8.8 (0.8) |
| | Among males | 10.3 (0.6) | 5.9 (0.6) | 9.2 (1.0) |
| | Among females | 7.7 (0.4) | 6.6 (0.7) | 8.3 (1.3) |
| Current symptoms reported—mean (±SD) | Overall | 102.4 (0.7) | 104.8 (1.1) | 96.8 (1.9) |
| | Among males | 101.6 (1.3) | 103.0 (1.5) | 95.9 (2.5) |
| | Among females | 103.4 (0.9) | 106.8 (1.6) | 98.3 (3.1) |
| Worst symptoms—mean (±SD) | Overall | 107.1 (0.9) | 102.7 (1.6) | 111.5 (2.1) |
| | Among males | 105.8 (1.6) | 100.8 (2.1) | 111.0 (2.4) |
| | Among females | 107.9 (1.2) | 104.7 (2.5) | 112.4 (3.9) |
| Duration of H2RA therapy in days—mean (±SD) | Overall | 218.5 (19.8) | 223.7 (29.9) | 186.0 (46.4) |
| | Among males | 223.5 (32.9) | 236.9 (49.5) | 231.6 (65.6) |
| | Among females | 215.7 (24.9) | 209.5 (32.1) | 121.8 (62.3) |
| Duration of PPI therapy in days—mean (±SD) | Overall | 377.2 (26.7) | 344.2 (42.9) | 668.6 (71.6) |
| | Among males | 403.5 (49.7) | 263.9 (47.5) | 742.2 (95.3) |
| | Among females | 362.7 (30.9) | 430.4 (72.5) | 564.8 (107.5) |
| Duration of alginate therapy in days—mean (±SD) | Overall | 719.9 (61.1) | 555.0 (66.4) | 536.9 (86.1) |
| | Among males | 722.7 (116.9) | 491.4 (95.8) | 410.8 (96.6) |
| | Among females | 718.4 (69.4) | 623.2 (91.6) | 709.0 (154.7) |
| Duration of antacid therapy in days—mean (±SD) | Overall | 1222.7 (90.8) | 1164.7 (117.3) | 1170.4 (145.1) |
| | Among males | 1345.0 (164.6) | 1182.3 (160.6) | 1178.6 (201.0) |
| | Among females | 1154.9 (107.7) | 1145.8 (172.1) | 1158.8 (207.1) |

BMI, body mass index; BO, Barrett's oesophagus; ERD, erosive reflux disease; H2RA, histamine-2 receptor antagonist; NERD, non-erosive reflux disease; PPI, proton pump inhibitor.

sex, there were no significant differences antioxidant and dietary fat intake when participants were stratified by NERD/ERD/BO status (online supplemental file 1). When assessed under white-light examination, 718 (60.0%) participants had normal endoscopic findings. Other endoscopic diagnoses were observed in 212 (17.7%) patients, specifically: hiatus hernia (n=184; 86.8%), duodenal ulcer (n=12; 5.7%) and gastric ulcer (n=16; 7.5%). Mean serum gastrin levels were similar across participants (online supplemental file 1). With respect to medication use (table 2), those with ERD reported the longest duration of histamine-2 receptor antagonist use, while those with BO disclosed longest use of proton pump inhibitors (men more than women, p≤0.001). Participants with NERD reported the longest duration of both alginate and antacid use.

Units of alcohol consumed per week were substantially higher in males than females (table 2). Men with NERD tended to consume less alcohol than those with ED or BO, whereas no differences among women were observed. Pack-years of cigarettes smoked varied, with those with BO tending to smoke slightly more (0.6%) relative to those with ERD (0.4%) or NERD (0.2%), but differences between these groups were not significant, including when stratified by sex (p≥0.05). BMI outcomes indicated that participants were typically overweight, with mean BMI consistently over 25 across disease and sex groupings (table 2). Those with ERD had shorter

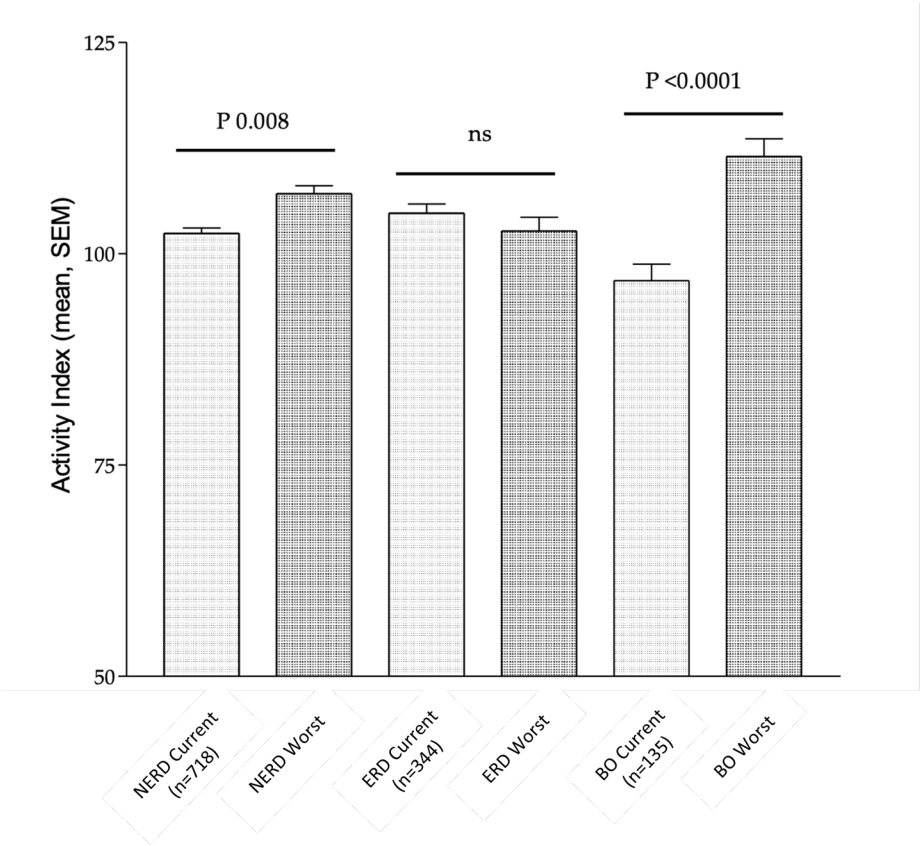


**Figure 1** GORD activity scores stratified by diagnosis, timing and severity (n=1197). BO, Barrett's oesophagus; ERD, erosive reflux disease; GORD, gastro-oesophageal reflux disease; NERD, non-erosive reflux disease.

average symptom duration (6.2 (±0.5) years) than those with NERD or BO, while men with NERD had the longest mean duration at 10.3 (±0.6) years. With respect to symptom severity, participants with NERD and BO had a significantly higher GORD activity index relative to those with ERD (figure 1), which was also the case when stratified by sex ($p \leq 0.05$).

At 20-year follow-up, of participants without BO at baseline (n=1062), 363 (34.1%) received an endoscopy. Of those, 22 (6.1%) developed BO; 15 (68.2%) were male and 7 (31.8%) were female. Regression analysis among participants at baseline (n=1197) indicated male sex, increasing age, GORD activity index, GORD symptom index and PPI use were associated with significantly higher odds of BO diagnosis. Further regression analysis among those with follow-up (n=363) indicated male sex, increased alcohol intake and higher number of pack-years cigarettes smoked were significantly associated with higher odds of subsequent development of BO (table 3).

## DISCUSSION

In this study of people with GORD recruited from a gastroenterology service in the East of Scotland, we identified multiple factors associated with developing BO at both baseline and 20-year follow-up time points. Our cohort was homogeneous in that most were Caucasian, had low educational attainment and lived in areas in low socioeconomic resource. The high prevalence of these factors introduced bias in that they were not directly evaluable in the main analyses despite being common risk factors for OAC and BO.[23] However, as these factors were so common, it would be reasonable to suppose that they were implicitly adjusted for in the analyses which allowed alternate risk factors to be identified using simpler models. Our results corroborate consensus that both male sex and advanced age are significantly associated with increased likelihood of developing BO.[17 24] Men tend to develop BO at a younger age than women, with women potentially conferred some protection by oestrogen exposure.[25–27] Smoking and alcohol exposure were associated with developing BO in our cohort, and we would suggest the gradual accumulation of genetic changes resulting from damage to oesophageal mucosa through exposure to these substances may explain their role in BO development. Existing research has suggested that people with BO are more likely to have ever smoked cigarettes relative to population controls, and therefore, have higher risk for developing it, and our work complements these findings.[28] Other existing work examining a link between alcohol consumption in a 5-year window among participants with GORD concluded no association between alcohol and developing BO exists,[29] but our results suggest longer follow-up may be required to examine this.

With regard to differentiating participants by disease state: whether NERD represents a significantly different

Table 3 Adjusted regressions for Barrett's oesophagus diagnosis at baseline and follow-up time points

| Factor | aOR (95% CI) | P value |
|---|---|---|
| **Baseline (n=1197)** | | |
| Sex (male) | 2.04 (1.92 to 4.12) | <0.001 |
| Age | 1.03 (1.01 to 1.04) | <0.0001 |
| Body mass index | 0.97 (0.94 to 1.01) | 0.174 |
| Alcohol intake | 1.01 (1.00 to 1.02) | 0.067 |
| Pack-years cigarettes smoked | 0.98 (0.95 to 1.01) | 0.242 |
| GORD Activity Index | 0.97 (0.96 to 0.99) | <0.0001 |
| GORD Worst Symptom Index | 1.02 (1.01 to 1.03) | <0.0001 |
| Duration of symptoms | 1.01 (0.99 to 1.03) | 0.247 |
| Antacid use | 1.06 (0.73 to 1.53) | 0.769 |
| Alginate use | 1.31 (0.88 to 1.94) | 0.182 |
| H2RA use | 0.82 (0.57 to 1.17) | 0.280 |
| PPI use | 3.03 (1.80 to 5.13) | <0.0001 |
| **Follow-up (n=363)** | | |
| Sex (male) | 3.18 (1.28 to 7.86) | 0.012 |
| Age | 0.99 (0.96 to 1.02) | 0.353 |
| Body mass index | 0.99 (0.91 to 1.09) | 0.877 |
| Alcohol intake | 1.02 (1.00 to 1.04) | 0.013 |
| Pack-years cigarettes smoked | 1.04 (1.00 to 1.08) | 0.046 |
| Duration of symptoms | 0.99 (0.95 to 1.04) | 0.782 |
| Antacid use | 1.79 (0.69 to 4.60) | 0.230 |
| Alginate use | 0.76 (0.32 to 1.80) | 0.537 |
| H2RA use | 1.70 (0.69 to 4.20) | 0.251 |
| PPI use | 1.50 (0.55 to 4.09) | 0.431 |

All participants were diagnosed with GORD, and therefore, the follow-up analysis it is implicitly adjusted for this.
aOR, adjusted OR; GORD, gastro-oesophageal reflux disease; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

disease entity to that of ERD remains contentious; it is plausible that they represent varying severity on the same disease spectrum.[30–35] We found women were more likely to be living with NERD relative to men, while as the severity of mucosal erosive burden increased, men appeared to predominate. This dichotomy suggests NERD does not appear to have the same pathophysiological determinants as ERD and BO. GORD activity index (both current and worst) was significantly associated with higher odds of BO at baseline, which aligns well with the significant effect observed for increased PPI use (ie, those with worsening symptomology are more likely to be in receipt of PPIs). Existing research has identified associations between increased reflux symptoms and developing long-segment BO, with some suggesting using GORD disease symptomology as a prescreening tool for BO.[36 37] Our results are consistent with these findings, and we would suggest screening based on GORD symptomology as a potentially useful approach to BO surveillance.

Few studies have assessed micronutrient intake in the context of BO, though it has been suggested vitamin C and beta-carotene confer protection.[38–40] We examined nutrient intake and found men had significantly higher intakes of certain nutrients which may be explained by beer consumption which, as noted, was subsequently linked to increased odds of BO. Examining the direct impacts of specific nutrients on subsequent development of BO was not within the scope of this work, but could be a potential avenue of future research, which could further aid in harmonising and scaling surveillance programmes perhaps using existing bloods samples within laboratories for other aetiological investigations. Separately, we found men in our cohort had significantly higher intake of dietary fat, monounsaturated fat, and cholesterol, relative to women, which may somewhat explain the sex differences in the regression analyses as high intake of dietary fat, especially monounsaturated fat, has been associated with many forms of malignancy including OAC.[41 42]

Overall, only a small proportion of patients in follow-up developed BO. However, given that most BO is asymptomatic,[43] the proportion diagnosed may not reflect to true prevalence in our cohort. Two-thirds of our participants did not attend for follow-up endoscopy, which may have been driven by a lack of symptoms, alongside other well-known reasons for participant attrition, such as how the study fits with personal beliefs, preferences, capabilities or life circumstances.[44] Indeed, our prevalence at follow-up (6.1%) was lower than global estimates of BO among people living with GORD (14%).[45] Consequently, we would position our findings as tentative, and acknowledge that new strategies may be required to retain people at risk of BO in long-term follow-up for surveillance.

## CONCLUSIONS

In this study, we found multiple factors associated with BO at both baseline and 20-year follow-up, which broadly align with similar research and may have implications for targeted screening programmes among people living with GORD in the UK. Beyond factors known to impact development of BO, we have identified a potential association between alcohol intake and subsequent BO diagnosis. Alcohol is classified as a group one carcinogen by the World Health Organization, and the increasing consensus is that no level of alcohol consumption is safe for health.[46–48] Communicating this message to people living with GORD may be a useful strategy to mitigate risk of subsequent development of BO, although we acknowledge that, given the modest association, the impact of any public health messaging on overall prevalence of BO will be modest.

## Limitations

This study has several limitations. First, and foremost, is the limited sample with follow-up endoscopy and subsequent non-representative prevalence of BO at this time point. This may have led to model misspecification and/or other biases in the estimates and association testing among participants in our study. Furthermore—and perhaps a cause of the low proportion with follow-up—BO may occur in the context of a reduction in reflux symptoms, so affected patients may not have presented to the health service for follow-up and subsequently some participants living with BO may have been omitted from the analysis, further biasing our estimates. Second, our sample was recruited from a specialist health centre in a region in the East of Scotland; almost all participants were Caucasian, living with overweight, residing in areas of least socioeconomic resource and had low educational attainment. These are frequently described risk factors for OAC and BO.[23] Consequently, our cohort is unlikely to be representative of the UK population living in large urban conurbations, or indeed European countries more broadly. This limits the generalisability of our findings. Finally, the longitudinal nature makes it difficult to separate the reciprocal impact of our measured exposures and the outcome of developing BO, due to the myriad (potentially unreported) factors participants may have been exposed to between index and follow-up endoscopy. Subsequently, we acknowledge the potential role that unmeasured confounders may have contributed to the analyses and recognise the constraints this places on validity of the results.

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**Contributors** Conceptualisation: JFD. Methodology: JCo and JFD. Software: not applicable. Validation: JCo. Formal analysis: JCo. Investigation: JCo. Resources: not applicable. Data curation: JCo and JFD. Writing–original draft: CJB, JCa and JCo. Writing–review and editing: all authors. Visualisation: JCa and JCo. Supervision: JFD. Project administration: JCo. Funding acquisition: JFD. Also, JFD is the guarantor for this work and, as such, takes responsibility for its integrity and accuracy. All authors have approved the final version of this manuscript.

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**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by East of Scotland NHS research ethics committee (ref: 186/00). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request. Consideration will be given to sharing the data underpinning this study on receipt of a proportionate and methodologically sound data access request. Such requests should be sent, in the first instance, to the corresponding author.



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**SUPPLEMENTARY FILE 1**

## Title

Evaluating the Development of Barrett's Oesophagus in the Context of Gastro-oesophageal Reflux Disease: A longitudinal cohort study.

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**Dietary comparisons**

Men had significantly higher intake of thiamine (*p*=<0.05), copper (*p*=<0.05), selenium (*p*=<0.001), carotene (*p*=<0.05) and zinc (*p*=<0.005), relative to women. Men also had significantly greater dietary fat (83.45 [72.6-89.2]) to 63.1 [57.1-67.6], *p*=<0.001), monounsaturated fat (25.2 [21.1-27.1] to 18.5 [17.1-20.7], *p*=<0.005), and cholesterol intake (270.5 [253.5-330.9] to 189.0 [170.7-230.9], *p*=<0.001). There was no significant difference in polyunsaturated fat intake (8.7 [8.2-11.1] to 8.5 [7.21-9.8], *p*=>0.05). For both antioxidant and dietary fat intake no significant differences were observed when stratified by NERD/ERD/BO status (*p*=>0.05).

**Intragastric pH, serum gastrin**

Among those who had their intragastric pH measured (n=571; 47.7%), 101 (17.7%) had an intragastric pH over seven, potentially related to PPI use. Intragastric pH did not vary significantly by sex (*p*=>0.05). Mean serum gastrin levels were similar across participants with NERD (64.3 [±21.6] ng/L), ERD (66.6 [±31.2] ng/L), and BO (70.9 [±34.1] ng/L).