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Epidemiologic Risk Factors in a Comparison of a Barrett Esophagus Registry (BarrettNET) and a Case–Control Population in Germany

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ABSTRACT

Endoscopic screening for Barrett's esophagus as the major precursor lesion for esophageal adenocarcinoma is mostly offered to patients with symptoms of gastroesophageal reflux disease (GERD). However, other epidemiologic risk factors might affect the development of Barrett's esophagus and esophageal adenocarcinoma. Therefore, efforts to improve the efficiency of screening to find the Barrett's esophagus population "at risk" compared with the normal population are needed. In a cross-sectional analysis, we compared 587 patients with Barrett's esophagus from the multicenter German BarrettNET registry to 1976 healthy subjects from the population-based German KORA cohort, with and without GERD symptoms. Data on demographic and lifestyle factors, including age, gender, smoking, alcohol consumption, body mass index, physical activity, and symptoms were collected in a standardized epidemiologic survey. Increased age, male gender, smoking, heavy alcohol consumption, low physical activity, low health status, and GERD symptoms were significantly associated with Barrett's esophagus. Surprisingly, among patients stratified for GERD symptoms, these associations did not change. Demographic, lifestyle, and clinical factors as well as GERD symptoms were associated with Barrett's esophagus development in Germany, suggesting that a combination of risk factors could be useful in developing individualized screening efforts for patients with Barrett's esophagus and GERD in Germany.

Introduction

The incidence of esophageal adenocarcinoma is rapidly increasing in the western populations (1, 2) and Barrett's esophagus, a metaplastic transformation of the normal squamous mucosa of the distal esophagus to columnar epithelium, represents a major precursor lesion for esophageal adenocarcinoma (3). The incidence of Barrett's esophagus has also increased over the past decades, resulting in a large number of individuals "at risk" for esophageal adenocarcinoma. Frequent and severe gastroesophageal reflux disease (GERD) symptoms are thought to be a primary risk factor for the development of Barrett's esophagus (4, 5). However, Barrett's esophagus only develops in up to 10% of patients with GERD (6), and only a fraction of patients with Barrett's esophagus develop esophageal adenocarcinoma (7), raising an economic and medical question of whom to screen by endoscopy.

GERD, Barrett's esophagus, and esophageal adenocarcinoma have been associated with similar risk factors, including white race, male gender, increasing age, and obesity (8, 9), while these results remain to be confirmed in a German cohort. Nevertheless, risk factors for Barrett's esophagus are mostly neglected in clinical management of patients with GERD and Barrett's esophagus and could help to specify appropriate screening strategies. In clinical practice, screening endoscopy is often recommended for patients with therapy (proton pump inhibitor) refractory GERD or symptoms, such as dysphagia, weight loss, and anemia (10).

Current American College of Gastroenterology guidelines (11) suggest that patients with multiple risk factors associated with Barrett's esophagus and esophageal adenocarcinoma should be screened, but the combination of risk

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factors that should trigger intervention is not defined. Most likely, a more efficient approach would be to implement a risk-adapted screening program on patients with a calculated increased risk for Barrett's esophagus and thus esophageal adenocarcinoma based on epidemiologic, lifestyle, and clinical characteristics. A first requirement would be to identify risk factors that discriminate patients with Barrett's esophagus from the general population, the motivation for this study.

Materials and Methods

Study population

The BarrettNET registry is a multicenter clinical cohort study in southern Germany that recruits patients with Barrett's esophagus who are then prospectively followed for progression to low-grade dysplasia, high-grade dysplasia, and esophageal adenocarcinoma for 10 years (12). Barrett's esophagus was identified at endoscopy and confirmed in the histopathologic diagnosis of a board-certified pathologist as intestinal metaplasia. Patients with a diagnosis of Barrett's esophagus (not dysplasia or esophageal adenocarcinoma) between 2013 and 2017 were eligible for the study and since its start, 618 patients from 20 centers have been included. For each patient 4–6 standardized biopsy samples of the distal esophagus and stomach, blood-based samples, epidemiologic survey data, as well as stool and saliva samples have been collected and a longitudinal follow-up has been performed, as described previously (12). Patients with a history of cancer ($n = 51$) were excluded.

Controls for this analysis were chosen from the KORA FF4 (KORA: Cooperative Health Research in the Region of Augsburg) study, which is the second follow-up of the population-based KORA S4 cohort examined between June 2013 and September 2014. A description of the primary KORA study design has been published previously (13). From the 2,279 participants of the KORA FF4 cohort, 250 patients with a history of cancer, seven participants with a history of Barrett's esophagus plus cancer, and 26 with unknown status were eliminated. Considering that both cohorts live in the same region of Germany (Southern Bavaria) 20 individuals with a history of Barrett's esophagus from the KORA cohort were included to the Barrett's esophagus cases of the BarrettNET registry. The final study sample comprised 587 Barrett's esophagus cases from the BarrettNET registry and the KORA cohort and 1,976 controls from KORA. All participants provided informed consent.

Variables for analysis

Information on sociodemographic variables, lifestyle factors, including smoking, alcohol consumption, physical activity, health, including family history, chronic diseases, and symptoms was collected by the same structured epidemiologic questionnaire from KORA (13–15) for both cohorts. Body mass index (BMI) was calculated in kg/m^2, with weight and height at the time of the KORA FF4 2013–14 survey used for the KORA controls and at first time enrollment for the BarrettNET registry case patients. GERD symptoms were defined as present for burning sensation, pain in the upper abdomen or behind the breast bone, or acid reflux, and absent otherwise. GERD symptoms were defined as frequent for 3–7 days/week and occasional for less. Alcohol consumption was categorized into heavy drinker for excess of 40 g/day and moderate drinker otherwise. Physical activity was defined as very active for regularly more than 2 hours per week, moderately active for regularly approximately 1 hour per week, little active for irregularly approximately 1 hour per week, versus not active for almost no or no physical activity. The relative state of health was self-assessed in relation to people of the same age. The status of fitness was also self-assessed.

Statistical analysis

Comparisons were made using χ^2 tests for discrete questions and the Wilcoxon test otherwise. Statistical significance for all tests was determined at the two-sided 0.05 level. Statistical analyses were conducted in *R* (www.r-project.org).

Ethical approval

The patient studies were conducted in accordance with the Declaration of Helsinki. The ethical committee of the Technical University of Munich approved the study. Written informed consent was obtained from all patients.

Results

Barrett's esophagus cases were statistically significantly more likely to be male (74.3%/587) in comparison to the population controls (48.0%/1,976), to be older (mean 63.4 vs. 59.3 years, respectively), to smoke (32.3% vs. 46.1% nonsmokers), to significantly consume alcohol (13.1% vs. 11.8% with alcohol consumption >40 g/day), and to be single or divorced (all $P < 0.01$; **Table 1**). Patients with Barrett's esophagus and controls showed no significant BMI difference (mean 27.6 kg/m^2 in Barrett vs. 27.8 kg/m^2 in controls; $P = 0.259$; **Table 1**). Patients with Barrett's esophagus were more likely to be not physically active (32.2%) compared with controls (27.5%, $P = 0.011$), and had higher rates of poor actual states of fitness (4.8% vs. 1.7%; $P < 0.001$; **Table 1**). Concomitant with these results, patients with Barrett's esophagus evaluated their state of health as worse than the general population control (15.2% vs. 7.5%; $P < 0.001$; **Table 1**).

Among the 1,976 KORA control participants, 843 (42.7%) received an upper endoscopy, with a significant majority of 545 (64.7%) due to GERD symptoms. Reasons for endoscopy and subsequent Barrett's esophagus diagnosis in the BarrettNET cohort were mostly GERD-associated symptoms such as reflux (40.6%), upper abdominal discomfort (11.4%), and dysphagia (6.3%). However, 23.7% of patients with Barrett's esophagus were diagnosed with an incidental finding without any reporting of symptoms.

Compared with the KORA population control, patients with Barrett's esophagus reported significantly more GERD

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Table 1. Comparison of epidemiologic risk factors in patients with Barrett's esophagus ($n = 587$) and population-based controls ($n = 1,976$).

Characteristics	Barrett cohort *n* (%)	Population-based control *n* (%)	*P*
Total	587	1,976	
Gender			
Male	436 (74.3)	948 (48.0)	<0.001
Female	151 (25.7)	1,028 (52.0)	
Age (years)			
Mean (SD)	63.4 (12.5)	59.3 (12.2)	<0.001
Range	23–93	38–88	
Smoking			
Regular smoker	89 (15.2)	274 (13.9)	<0.001
Irregular smoker	28 (4.8)	43 (2.2)	
Ex-smoker	251 (42.8)	748 (37.9)	
Nonsmoker	190 (32.3)	911 (46.1)	
Missing	29 (4.9)		
Alcohol consumption			
<40 g/day	386 (65.8)	1,742 (88.2)	0.006
>40 g/day	77 (13.1)	233 (11.8)	
Missing	124 (21.1)	1 (0.05)	
Marital status			
Married	386 (65.7)	1,451 (73.4)	<0.001
Single	85 (14.5)	193 (9.8)	
Divorced	60 (10.2)	166 (8.4)	
Widowed	35 (6.0)	166 (8.4)	
Missing	21 (3.6)		
BMI (kg/m^2)			
Mean BMI (SD)	27.6 (5.4)	27.8 (5.1)	0.259
Range	16.7–70.6	16.6–62.2	
Missing	25	2	
Physical activity			
Very active	146 (24.9)	514 (26)	0.011
Moderately active	152 (25.9)	634 (32.1)	
Little active	67 (11.4)	284 (14.4)	
Not active	189 (32.2)	544 (27.5)	
Missing	33 (5.6)		
Actual state of fitness			
Very good	56 (9.5)	251 (12.7)	<0.001
Good	352 (60.0)	1,357 (68.7)	
Intermediate	130 (22.1)	334 (16.9)	
Poor	28 (4.8)	34 (1.7)	
Missing	21 (3.6)		
Relative state of health			
Better	177 (30.1)	903 (45.7)	<0.001
Equal	213 (36.3)	889 (45)	
Worse	89 (15.2)	148 (7.5)	
Unknown	87 (14.8)	36 (1.8)	
Missing	21 (3.6)		
GERD symptoms			
Yes	359 (61.2)	985 (49.8)	<0.001
No	199 (33.9)	990 (50.1)	
Missing	29 (4.9)	1 (0.1)	
GERD frequency among those answering yes to symptoms			
Frequently	177 (49.3)	224 (22.7)	<0.001
Occasionally	155 (43.2)	761 (77.3)	
Unknown	27 (7.5)		
Reasons for Barrett's esophagus diagnosis			
Dysphagia	37 (6.3)		
Reflux	238 (40.6)		
Upper abdominal discomfort	67 (11.4)		
Incidental finding	139 (23.7)		
Other	39 (6.6)		
Missing	67 (11.4)		
Chronic diseases			
Diabetes	64 (10.9)	169 (8.6)	0.097
Hypertension	288 (49.1)	957 (48.4)	0.824
Hypercholesterolemia	274 (46.7)	966 (48.9)	0.372
Neurodermatitis	27 (4.6)	133 (6.7)	0.076
Asthma	52 (8.9)	165 (8.4)	0.761
Hay fever	92 (15.7)	374 (18.9)	0.083

Note: *P* values are from Wilcoxon and χ^2 tests.

symptoms (61.2% vs. 49.8%), and among those that did report symptoms, stated more often to have them frequently (49.3% vs. 22.7%; **Table 1**; both $P < 0.001$). Chronic diseases, including diabetes, hypertension, and hypercholesterinemia, were not associated with Barrett's esophagus (all $P > 0.05$; **Table 1**).

In a gender-stratified analysis, male patients with Barrett's esophagus ($n = 436$) were significantly older, had significantly more GERD symptoms, and were more likely to smoke compared with the male population–based controls ($n = 948$; **Table 2**). Moreover, they showed a significantly higher rates of poor fitness and lower rates of good state of health (**Table 2**). Female patients with Barrett's esophagus ($n = 151$) were significantly older and had significantly more GERD symptoms, but did not show a significant difference in smoking compared with the female population–based controls ($n = 1,028$; **Table 3**). Barrett's esophagus females also showed significantly higher rates of poor fitness and lower rates of good state of health than female controls (**Table 3**). To prevent a bias effect between gender, age, and further lifestyle risk factors through a significant difference in gender and age between Barrett's esophagus cases and controls, we performed a gender–age-matched analysis. In a gender–age-matched analysis we could confirm our previous results with significantly more smokers, individuals with single or divorced status, more GERD symptoms, a poor state of fitness, and a poor state of health among patients with Barrett's esophagus ($n = 587$) compared with controls ($n = 587$; Supplementary Table S1).

As GERD is still considered to be the primary decision factor for initiating endoscopic screening and a main risk factor for Barrett's esophagus and esophageal adenocarcinoma development, we next compared patients with Barrett's esophagus with GERD to population controls with GERD (**Table 4**). In the KORA cohort, 545 people reported reflux, had upper endoscopy, and no diagnosis of Barrett's esophagus and were therefore considered as a GERD control group. These were compared in a subanalysis to 359 patients with Barrett's esophagus which reported GERD symptoms.

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Table 2. Comparison of epidemiologic risk factors in male patients with Barrett's esophagus ($n = 436$) and male population–based controls ($n = 948$).

Characteristics	Barrett cohort *n* (%)	Population-based control *n* (%)	*P*
Total	436	948	
Age (years)			
Mean (SD)	63.1 (12.3)	60 (12.3)	<0.001
Range	23–93	38–87	
GERD symptoms			
Yes	260 (59.6)	474 (50)	0.004
No	157 (36)	473 (49.9)	
Missing	19 (4.4)	1 (0.1)	
GERD frequency among those answering yes to symptoms			
Frequently	123 (47.3)	89 (18.8)	0.004
Occasionally	122 (46.9)	385 (81.2)	
Missing	15 (5.8)		
Reasons for Barrett's esophagus diagnosis			
Dysphagia	24 (5.5)		
Reflux	186 (42.7)		
Upper abdominal discomfort	47 (10.8)		
Incidental finding	106 (24.3)		
Other	28 (6.4)		
Missing	45 (10.3)		
Smoking			
Regular smoker	70 (16.1)	148 (15.6)	<0.001
Irregular smoker	20 (4.6)	18 (1.9)	
Ex-Smoker	205 (47)	419 (44.2)	
Nonsmoker	123 (28.2)	363 (38.3)	
Missing	18 (4.1)		
Alcohol consumption			
<40 g/day	270 (61.9)	756 (79.7)	0.613
>40 g/day	75 (17.2)	192 (20.3)	
Missing	91 (20.9)		
BMI (kg/m^2)			
Mean BMI (SD)	27.8 (4.8)	27.3 (4.6)	0.028
Range	18.5–70.0	16.8–62.2	
Missing	17	2	
Marital status			
Married	304 (69.7)	745 (78.6)	0.005
Single	66 (15.2)	94 (9.9)	
Divorced	41 (9.4)	72 (7.6)	
Widowed	11 (2.5)	37 (3.9)	
Missing	14 (3.2)		
Physical activity			
Very active	113 (25.9)	260 (27.4)	0.243
Moderately active	108 (24.8)	271 (28.6)	
Little active	51 (11.7)	135 (14.2)	
Not active	146 (33.5)	282 (29.8)	
Missing	18 (4.1)		
Actual state of fitness			
Very good	43 (9.9)	119 (12.5)	0.002
Good	285 (65.4)	687 (72.5)	
Intermediate	81 (18.6)	128 (13.5)	
Poor	15 (3.4)	14 (1.5)	
Missing	12 (2.7)		
Relative state of health			
Better	145 (33.2)	495 (52.2)	<0.001
Equal	66 (15.1)	59 (6.2)	
Worse	152 (34.9)	376 (39.7)	
Unknown	60 (13.8)	18 (1.9)	
Missing	13 (3)		

(Continued on the following column)

Table 2. Comparison of epidemiologic risk factors in male patients with Barrett's esophagus ($n = 436$) and male population–based controls ($n = 948$). (Cont'd)

Characteristics	Barrett cohort *n* (%)	Population-based control *n* (%)	*P*
Chronic diseases			
Diabetes	46 (10.6)	94 (9.9)	0.789
Hypertension	212 (48.6)	484 (51.1)	0.434
Hypercholesterolemia	204 (46.8)	479 (50.5)	0.217
Neurodermatitis	15 (3.4)	49 (5.2)	0.199
Asthma	33 (7.6)	68 (7.2)	0.879
Hay fever	67 (15.4)	169 (17.8)	0.292

Note: *P* values are from Wilcoxon and χ^2 tests.

In contrast to the previous comparison, patients with Barrett's esophagus with GERD were not significantly older than population controls with GERD symptoms, while as previously, a higher proportion was male (**Table 4**). GERD sufferers with Barrett's esophagus had more frequent symptoms than those without Barrett's esophagus, were more likely to be active smokers, and also drink heavily (**Table 4**). Patients with Barrett's esophagus with GERD showed a slightly lower BMI than controls with GERD (**Table 4**). Patients with Barrett's esophagus with GERD were more likely not physically active and had lower relative health than controls with GERD (**Table 4**).

Discussion

There has been considerable interest in identifying populations at risk for esophageal adenocarcinoma, as for the past 4 decades its incidence has continuously risen, with the annual incidence increasing 8-fold (16). The increase in incidence has occurred despite the development of antiacid treatment and endoscopic screening. As Barrett's esophagus is assumed to be a precursor lesion in the development of esophageal adenocarcinoma, screening to identify subjects with Barrett's esophagus may be one effective strategy to prevent progression to cancer. Nevertheless, controversy persists concerning endoscopic screening and surveillance, as no study has validated a decrease in morbidity and mortality from esophageal adenocarcinoma due to Barrett's esophagus screening. This may be because more than 80% of patients with Barrett's esophagus remain undiagnosed (17). It is all the more necessary to identify patients at risk for Barrett's esophagus to prevent unnecessary overdiagnosis of healthy patients on the one hand and to detect patients with Barrett's esophagus on the other hand, at a stage where the disease can easily be treated with chemoprevention or ablation therapy.

In search for demographic, lifestyle, and clinical risk factors for Barrett's esophagus in Germany, we performed a cross-sectional analysis in a multicenter study sample consisting of 587 patients with Barrett's esophagus and 1,976 population controls. Overall, 50% of the general population reported

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Table 3. Comparison of epidemiologic risk factors in female patients with Barrett's esophagus ($n = 151$) and female population–based controls ($n = 1,028$).

Characteristics	Barrett cohort *n* (%)	Population-based control *n* (%)	*P*
Total	151	1,028	
Age (years)			
Mean (SD)	64.4 (12.9)	59.0 (12.0)	<0.001
Range	27–93	38–88	
GERD symptoms			
Yes	99 (65.6)	511 (49.7)	<0.001
No	42 (27.8)	517 (50.3)	
Missing	10 (6.6)		
GERD frequency among those answering yes to symptoms			
Frequently	54 (54.6)	135 (26.4)	<0.001
Occasionally	33 (33.3)	376 (73.6)	
Missing	12 (12.1)		
Reasons for Barrett's esophagus diagnosis			
Dysphagia	13 (8.6)		
Reflux	52 (34.4)		
Upper abdominal discomfort	20 (13.2)		
Incidental finding	33 (21.9)		
Other	11 (7.3)		
Missing	22 (14.6)		
Smoking			
Regular smoker	19 (12.6)	126 (12.3)	0.133
Irregular smoker	8 (5.3)	25 (2.4)	
Ex-smoker	46 (30.4)	329 (32)	
Nonsmoker	67 (44.4)	548 (53.3)	
Missing	11 (7.3)		
Alcohol consumption			
<40 g/day	112 (74.2)	986 (95.9)	0.748
>40 g/day	6 (4.0)	41 (4)	
Missing	33 (21.8)	1 (0.1)	
BMI (kg/m^2)			
Mean BMI (SD)	26.9 (6.6)	27.4 (5.5)	0.103
Range	16.7–70.6	16.6–48.8	
Missing	8		
Marital status			
Married	82 (54.3)	706 (68.7)	0.047
Single	19 (12.6)	99 (9.6)	
Divorced	19 (12.6)	94 (9.1)	
Widowed	24 (15.9)	129 (12.6)	
Missing	7 (4.6)		
Physical activity			
Very active	33 (21.9)	254 (24.7)	0.446
Moderately active	44 (29.1)	363 (35.3)	
Little active	16 (10.6)	149 (14.5)	
Not active	43 (28.5)	262 (25.5)	
Missing	15 (9.9)		
Actual state of fitness			
Very good	9 (6.0)	132 (12.8)	<0.001
Good	75 (49.7)	670 (65.2)	
Intermediate	53 (35.1)	206 (20)	
Poor	5 (3.3)	20 (2)	
Missing	9 (5.9)		
Relative state of health			
Better	32 (21.2)	408 (39.7)	<0.001
Equal	31 (20.5)	89 (8.6)	
Worse	53 (35.1)	513 (49.9)	
Unknown	27 (17.9)	18 (1.8)	
Missing	8 (5.3)		
Chronic diseases			
Diabetes	18 (11.9)	71 (6.9)	0.044
Hypertension	76 (50.3)	473 (46)	0.365
Hypercholesterolemia	70 (46.4)	487 (47.4)	0.884
Neurodermatitis	12 (7.9)	84 (8.2)	1
Asthma	19 (12.6)	97 (9.4)	0.286
Hay fever	25 (16.6)	205 (19.9)	0.384

Note: *P* values are from Wilcoxon and χ^2 tests.

GERD symptoms and Barrett's esophagus was present in 2.6%. The reported prevalence is consistent with the Barrett's esophagus prevalence of 1.6% in the general Swedish population (18).

We analyzed demographic, lifestyle, and health factors, along with GERD symptoms for association with Barrett's esophagus. Consistent with the literature, we confirmed known demographic risk factors for Barrett's esophagus, including older age and male gender, in a German population (19–21). Moreover, we observed a significantly higher percentage of likely male singles among patients with Barrett's esophagus, which might point to family status–dependent lifestyle conditions as a confounding factor for the development of Barrett's esophagus. In a gender–age-matched analysis, the identified lifestyle risk factors for Barrett's esophagus did not significantly change the results of the comparison of patients with Barrett's esophagus and the controls in this study, indicating that lifestyle factors are increasing Barrett's esophagus risk independently from epidemiologic risk factors.

GERD symptoms are likely associated with the development of esophageal adenocarcinoma (9, 22, 23), and up to date, remain the most common indication for upper endoscopy for further triage screening for Barrett's esophagus and esophageal adenocarcinoma (24). Consistent with these findings, we observed that GERD symptoms were more likely in patients with Barrett's esophagus than in the population controls. However more than 90% of esophageal adenocarcinoma present *de novo* (17, 25), suggesting that the strong emphasis on screening patients with GERD might be an insufficient strategy. Moreover, population-based studies indicate that only 40% of Barrett's esophagus report GERD symptoms (18) and about 40% of esophageal adenocarcinoma occur in people without chronic symptoms of GERD (23), pointing out the necessity of combining different risk factors to optimize screening strategies. In our study, a considerable percentage (33.9%) of Barrett's esophagus cases had no GERD and in 23.7% of the patients, Barrett's esophagus was an incidental finding during upper endoscopy for other reasons. In addition, a subanalysis of the cohorts revealed that stratification for GERD symptoms did not change the association of risk factors for Barrett's esophagus nor altered its significance. The identified risk factors:

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Table 4. Comparison of epidemiologic risk factors in patients with Barrett's esophagus with GERD ($n = 359$) and population-based controls with GERD ($n = 545$).

Characteristics	Barrett with GERD *n* (%)	Population-based control with GERD *n* (%)	*P*
Total	359	545	
Gender			
Male	260 (72.4)	241 (44.2)	<0.001
Female	99 (27.6)	304 (55.8)	
Age (years)			
Mean (SD)	61.7 (12.7)	63.3 (11.6)	0.345
Range	22–93	38–86	
Smoking			
Regular smoker	68 (19.0)	65 (11.9)	<0.001
Irregular smoker	18 (5.0)	9 (1.7)	
Ex-smoker	153 (42.6)	228 (41.8)	
Nonsmoker	115 (32.0)	243 (44.6)	
Missing	5 (1.4)		
Alcohol consumption			
<40 g/day	245 (68.2)	493 (90.5)	0.007
>40 g/day	47 (13.1)	52 (9.5)	
Missing	67 (18.7)		
BMI (kg/m^2)			
Mean BMI (SD)	27.5 (5.4)	28.6 (5.0)	<0.001
Range	17.8–70.6	17.9–48.8	
Missing	4	1	
Physical activity			
Very active	96 (26.7)	125 (22.9)	0.002
Moderately active	87 (24.2)	184 (33.8)	
Little active	43 (12.0)	89 (16.3)	
Not active	126 (35.1)	147 (27.0)	
Missing	7 (2.0)		
Actual state of fitness			
Very good	24 (6.7)	31 (5.7)	0.165
Good	211 (58.8)	350 (64.2)	
Intermediate	102 (28.4)	150 (27.5)	
Poor	18 (5.0)	14 (2.6)	
Missing	4 (1.1)		
Relative state of health			
Better	93 (25.9)	237 (43.5)	<0.001
Equal	83 (23.1)	240 (44.0)	
Worse	118 (32.9)	60 (11.0)	
Unknown	62 (17.3)	8 (1.5)	
Missing	3 (0.8)		
GERD frequency			
Frequently	177 (49.3)	170 (31.2)	<0.001
Occasionally	155 (43.2)	375 (68.8)	
Missing	27 (7.5)		

Note: *P* values are from Wilcoxon and χ^2 tests.

gender, age, existence and frequency of GERD, smoking, alcohol consumption, physical activity, and state of health need to be confirmed in a novel prospective study, screening healthy patients equitably for Barrett's esophagus onset, to create a risk score for screening strategies (26).

Our data are consistent with prior studies, which showed that any history of smoking was significantly associated with Barrett's esophagus (27–29). Similar patterns of association have been observed between smoking and esophageal adenocarcinoma and Barrett's esophagus progression to esophageal adenocarcinoma (26, 29, 30). A high BMI has long been recognized as a risk factor for GERD, Barrett's esophagus, and esophageal adenocarcinoma (31–33). However, our study showed no association between a higher BMI and the diagnosis of Barrett's esophagus, in correlation with our recent findings from the mouse model that Western diet is not only inducing obesity but also changing the gut microbiota and induces an accelerated inflammatory condition in the esophagus (34). Recently, the waist to hip ratio has been found to be more strongly associated with the risks of Barrett's esophagus and esophageal adenocarcinoma than BMI (35). However, waist and hip measurements were not assessed in this study. Results from studies analyzing the association between alcohol consumption and the risk of Barrett's esophagus have been inconsistent, with some studies reporting a positive association with moderate to heavy alcohol consumption (18, 36, 37) and others reporting no association (38, 39). In this study, we observed an increased risk for Barrett's esophagus among heavy drinkers, although there was no consistent dose–response relationship as moderate drinkers were less frequent among Barrett's esophagus subjects than in the population control.

Earlier epidemiologic studies suggest a protective effect of moderate levels of physical activity on the risk of GERD (40, 41) and esophageal adenocarcinoma (42, 43). Up to date there is insufficient evidence to elucidate the association between physical activity and Barrett's esophagus (44). Our data indicate an association between a low level of physical activity and the development of Barrett's esophagus. Evidence from large long-term prospective cohort studies is needed to further verify this association. Patients with Barrett's esophagus not only have an increased risk for esophageal adenocarcinoma but also a reduced quality of life (45). In concordance with these data we observed a reduced state of fitness and of relative state of health among patients with Barrett's esophagus compared with the general population control.

Strengths of this study include its large sample size of both Barrett's esophagus cases and population controls, which evaluated multiple demographic, lifestyle, heath, and clinical risk factors with validated questionnaires. The histologic diagnosis of Barrett's esophagus was confirmed by board-certified gastrointestinal pathologists. The KORA cohort is based on the general population of southern Germany, increasing the generalizability of results.

Limitations of this study are that it is a retrospective case–control study with Barrett's esophagus cases drawn from a separate clinical referral center and controls from a general screening cohort not specific to Barrett's esophagus. Therefore, cases and controls have been subject to different ascertainment and are subject to selection bias. Only 43% of the KORA cohort underwent upper endoscopy, compared with 100% in the Barrett's esophagus cohort. Hence, results from this retrospective study require prospective validation. Patients with Barrett's esophagus enrolled in the BarrettNet registry receive a regular follow-up including a reassessment of the epidemiologic survey data and biopsy sampling of the distal esophagus and stomach.

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In the future, we will perform a prospective analysis of genetic factors and our identified risk factors with the endpoint esophageal adenocarcinoma development in our Barrett's esophagus cohort (12). A multivariate risk score including lifestyle, epidemiologic, and genetic factors for Barrett's esophagus development and progression to esophageal adenocarcinoma might lead to a more targeted screening and surveillance strategy in patients with Barrett's esophagus.

In conclusion, this is the first study to analyze demographic, lifestyle, and clinical factors in a large German population identifying significant associations between age, male gender, high income, nicotine, heavy alcohol consumption, GERD symptoms, reduced physical activity, low fitness level, poor health status, and the development of Barrett's esophagus.

In cardiovascular disease (46) and more recently in other cancer entities such as breast and colorectal cancer (47–49) demographic, lifestyle, and clinical factors have been integrated into screening selection. For esophageal adenocarcinoma prevention there is need for evidence-based strategies, including effective means of risk stratification for endoscopic Barrett's esophagus screening among patients with GERD. Given the high prevalence of GERD symptoms in the general population and low prevalence of Barrett's esophagus in these patients, targeted screening for early detection and treatment on the one hand and cost-effective approaches on the other are warranted. Integration of identified risk factors into clinical assessment could help identify more high-risk patients for cancer prevention and avoid overtreatment for low-risk patients.

Disclosure of Potential Conflicts of Interest

None, these are third party funding for the study.

Authors' Contributions

Conception and design: M. Schmidt, D.P. Ankerst, A.S. Quante, M. Quante

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Wiethaler, J. Slotta-Huspenina, K.-F. Becker, J. Horstmann, B. Linkohr

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D.P. Ankerst, Y. Chen, M. Quante

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Epidemiologic Risk Factors in a Comparison of a Barrett Esophagus Registry (BarrettNET) and a Case–Control Population in Germany

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