The association between physical activity and the risk of symptomatic Barrett's oesophagus: a UK prospective cohort study.

Running head: Physical activity and Barrett's oesophagus

Stephen Lam,[1,2] Leo Alexandre,[1,2] Robert Luben,[3] Andrew R. Hart.[1,2]

[1]Norfolk and Norwich University Hospital NHS Trust, Colney Lane, Norwich, NR4 7UY, UK.

[2]Norwich Medical School, University of East Anglia, Norwich, NR4 7TJ, UK.

[3]Strangeways Research Laboratory, Worts Causeway, Cambridge, CB1 8RN, UK.

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Corresponding author: Dr S.Lam (reprint author), Floor 2, Bob Champion Research and Educational Building, James Watson Road, University of East Anglia, Norwich Research Park, Norwich, NR4 7UQ. E-mail: stephen.lam@uea.ac.uk.

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Abstract

Background: Physical activity affects the functioning of the gastrointestinal system through both local and systemic effects and may play an important role in the aetiology of GORD, Barrett's oesophagus and oesophageal adenocarcinoma. We investigated, for the first time in a large prospective cohort study, associations between recreational and occupational levels of physical activity and the incidence of Barrett's oesophagus. **Methods:** EPIC–Norfolk recruited 30 445 men and women between 1993 and 1997. Occupational and recreational levels of physical activity were measured using a baseline questionnaire. The cohort was followed up until 2015 to identify symptomatic cases of Barrett's oesophagus. Cox proportional hazard regression estimated hazard ratios (HR) for physical activity and the development of disease. **Results:** Two hundred and three participants developed Barrett's oesophagus (mean age 70.6 years) the majority of whom were male (70.9%). There was an inverse association between standing occupations and disease risk (HR 0.50, 95% CI 0.31-0.82, p=0.006) when compared to sedentary jobs. Heavy manual occupations were positively associated with disease risk (HR 1.66, 95% CI 0.91-3.00), but conventional statistical significance was not reached (p=0.09). No associations were found between recreational activity and the risk of Barrett's oesophagus (HR 1.34, 95% CI 0.72-2.50, p=0.35, high vs. low levels of physical activity). **Conclusion:** Our study suggests that occupational levels of physical activity may be associated with the risk Barrett's oesophagus. However, further work is required to confirm and describe specific occupations which may be protective.

Keywords: physical activity; Barrett's oesophagus; epidemiology

Introduction

Worldwide, there is an alarmingly rapid rise in the incidence of oesophageal adenocarcinoma, which is reaching epidemic proportions [1-4]. Histological surveillance studies have demonstrated that oesophageal adenocarcinoma develops through a morphological sequence of inflammation, metaplasia, dysplasia and eventual cancer [5]. Three distinct clinical diseases mark these cellular events: gastroesophageal reflux disease (GORD), Barrett's oesophagus, and oesophageal adenocarcinoma [6]. Physical activity affects gastric emptying,[7] intra-gastric pressure,[8] systemic inflammation,[9] and the regulation of body weight [10] and may play an important role in the metaplastic-dysplastic sequence. Several epidemiological studies have examined associations between physical activity and the risk of both GORD [11-13] and oesophageal adenocarcinoma [14-16], and reported a potential protective role of recreational physical activity in the risk of both diseases. The evidence for occupational activity from these studies was inconsistent [13, 14]. To date, only one study has investigated Barrett's oesophagus and reported no association between recreational exercise and disease risk (occupational activity was not measured) [17]. Our aim was to investigate, for the first time in a prospective cohort study, the relationship between both occupational and recreational levels of physical activity and the incidence of Barrett's oesophagus.

Methods

Recruitment and measurement of exposure

The European Prospective Investigation of Cancer (EPIC-Norfolk) study [18] recruited 30 445 men and women, aged 39 to 79 years, between the years 1993 and 1997, who were identified from 35 general practices across the county of Norfolk in the United Kingdom. At baseline, participants completed a questionnaire documenting their health and lifestyle including occupational and recreational levels of physical activity. The physical activity questionnaire contained questions relating to participants' physical activities over the previous 12 months both at work and at home (appendix 1). For occupational activity, participants were asked to choose one of four categories which best described the physical demands of their job (sedentary, standing occupation, manual work or heavy manual work). In a validation study; this simple four-level occupational classification was strongly associated with objective measures of daytime energy expenditure (P_{trend} <0.001) [19]. Recreational activity was measured during both winter and summer months by asking how many hours participants typically spent per week during the last year participating in: walking, cycling, gardening, housework, do-it-yourself (DIY) and other forms of physical exercise (e.g. aerobics, swimming, jogging). A four category recreational index was derived based on the average number of hours per week that participants engaged in cycling or other recreational physical activity (0, <3.5, <7 and >7). Anthropometric measurements including height and weight were recorded at baseline health-check visits, conducted between 1993 and 1998. The EPIC-Norfolk study was approved by the Norwich District Health Authority Ethics Committee and all included participants provided written consent for involvement.

Follow-up and identification of cases

After recruitment, the cohort was followed up to June 2015 to identify participants subsequently diagnosed with Barrett's oesophagus detected due to reflux symptoms. Cases were identified by linking the EPIC database with the Norfolk and Norwich Hospital histology database, with all potential cases verified by review of the medical notes. To be included, cases had to meet the diagnostic criteria as defined by the British Society of Gastroenterology [20], i.e., required both endoscopic characteristics of Barrett's oesophagus of ≥1cm with histological confirmation of metaplasia. Potential cases were reviewed to exclude participants with prevalent Barrett's oesophagus at recruitment. To ensure the physical activity levels were more likely to represent pre-symptomatic levels, symptomatic Barrett's oesophagus cases were excluded if diagnosed within 1 year of recruitment into EPIC.

<u>Statistical analysis</u>

Participants were followed up from study entry until the earliest date of: first diagnosis, death, or last data collection date (June 2015). Comparative analyses between cases and controls were undertaken using Student t-tests for continuous, and X^2 tests for categorical variables. In multivariable analyses, Cox proportional hazard regression models estimated hazards ratios (HRs), with 95% confidence intervals (CI), for associations between both recreational and occupational physical activity. The fully adjusted model contained the covariates: age, gender, smoking category (never, ex-smoker, current smoker) and alcohol intake (units/week). As it is unclear whether body mass index (BMI) lies along the causal pathway, that is; whether the effect of physical activity is by regulation of BMI, we presented both BMI unadjusted and adjusted analyses.

Results

Of 30 445 individuals aged between 39 and 79 years in EPIC-Norfolk, 24 110 (79.2%) had a record of physical activity, attended a base-line health check, had no previous cancer diagnosis, subsequent diagnosis of oesophageal adenocarcinomas or diagnosis of Barrett's oesophagus within the first year of recruitment (figure 1). Follow-up ended a mean of 17.6 years (SD 4.5) after cohort entry, totalling 424 336 person years. During the maximum follow-up of 22 years, 203 of 24 110 individuals (0.84%) developed reflux symptoms which led to referral for gastroscopy and diagnosis of Barrett's oesophagus. The mean age at diagnosis was 70.6 years (± SD 9.3), and 70.9% were male. The median time of diagnosis after study enrolment was 12 years (interquartile range (IQR), 8 to 17 years). The subtypes of metaplasia were documented as: intestinal (69.5%, n=141), gastric (9.9%, n=20), mosaic (9.9%, n=20), and non-specified in 10.8% (n=22). Dysplasia was present in 5% of cases. A hiatal hernia was present in 72% of participants.

In the descriptive analyses, cases of Barrett's oesophagus, compared to controls, were more likely to be male and older at the time of recruitment (table 1). They were also more likely to have formerly smoked and be overweight, with higher levels of alcohol consumption. Finally, a greater percentage of cases had either sedentary or heavy manual occupations. In the adjusted Cox model for physical activity and the risk of Barrett's oesophagus, there was a suggestion of a U-shaped association between levels of occupational activity and disease risk (table 2); with a decreased risk in participants with a standing vs sedentary occupation (HR 0.50, 95% CI 0.31-0.82, p=0.006) and an increased risk with heavy manual jobs, although conventional statistical significant was not reached (HR 1.66, 95% CI 0.91-3.00, p=0.09). The effect sizes were not attenuated by adjustment for BMI. No associations were found for levels of recreational activity in either models adjusted, or unadjusted, for BMI. In a sub-analysis of only the cases with intestinal metaplasia (n=141) the results remained similar to the findings for all types of metaplasia. In a model adjusted for: age, sex, smoking and levels of recreational activity the results for standing vs. sedentary occupations estimated a HR of 0.55, 95% CI 0.31-0.99, p=0.046. For heavy manual vs. sedentary occupations the HR was 1.78, 95% CI 0.87-3.61, p=0.11.

Discussion

To the best of our knowledge, this is the first prospective cohort study investigating associations between levels of physical activity and the development of Barrett' oesophagus. Although there were no associations with recreational activity, we found a possible U-shaped association between levels of occupational activity and disease risk. There are biologically plausible mechanisms by which such an association could exist. Low to moderate levels of physical activity in standing occupations, which involve frequent walking, may protect against GORD by helping to maintain a normal body weight,[10] thus preventing obesity induced reflux disease [21] (central adiposity increasing intra-gastric pressure, creating a gastro-oesophageal reflux gradient and hiatus hernia formation) [22-24]. Low intensity exercise such as walking also increases gastric emptying and may therefore decrease reflux episodes [7]. Finally, regular physical activity reduces inflammatory biomarker expression, and thus may prevent the inflammation-driven metaplastic process involved in the aetiology of Barrett's oeosphagus [9, 25-27]. Alternatively, heavy manual occupations may involve both bending and heavy lifting, increasing intra-abdominal pressure and forcing gastric contents retrograde, beyond the lower oesophageal sphincter into the oesophagus [8]. Activity at work is also likely to occur post-prandially, when reflux episodes are most likely [28]. Associations between heavy manual occupations and reflux do not appear to have been studied previously in the literature. However, an increased risk of reflux in occupations that involve intra-abdominal straining, such as in wind instrument players [29, 30] and choir or opera singers [30, 31] has been reported.

Our findings of no association between recreational physical activity and the risk of Barrett's oesophagus is consistent with the only other epidemiological study (a case-control investigation of 307 cases of Barrett's oesophagus and 1724 controls). This study was in US war veterans (men and women) aged 40-80 years enrolled in a screening and surveillance endoscopy programme in Texas, USA. One hundred and six (35%) of the cases were known to have Barrett's oesophagus prior to recruitment. The exposure was measured using the International Physical Activity Questionnaire (IPAQ), which measures the previous 7 days recreational exercise. The authors reported no association between the highest vs. lowest levels of physical activity and odds of Barrett's oesophagus (OR = 1.19, 95% CI 0.82-1.73) [17]. Limitations of this study included the potential for measurement error by using a 7 day measure of physical activity in symptomatic individuals and the limited generalisability of war veterans. A further potential limitation was adjustment for GORD, BMI and waist-to-hip ratio (WHR), which lie along the presumed causal pathway. If we assume that the protective effect of exercise is largely by regulation of weight and reduction of reflux risk then controlling on these variables is likely to reduce any association between physical activity and Barrett's oesophagus towards the null.

The strengths of our study include; its prospective design, which minimised both selection and recall biases; adjustment in the analyses for potential confounders; confirmation of all incident cases of Barrett's oesophagus by medical note review; and a long follow-up period of up to 22 years. Follow-up bias was minimised by studying a cohort that was geographically stable, with 94.6% of participants still living in the county of Norfolk 20 years after recruitment. As this is a large population based-study, the findings are reasonably generalisable, with inclusion of both men and women from: rural, suburban and inner city areas. However, exclusion of participants from larger UK urban areas such as London and Manchester may limit the UK-wide generalisability of our findings. Nonetheless, our case numbers are similar to larger UK cohorts. Cohort data derived from primary care databases in the UK reported 12 312 Barretts oesophagus cases among 6 885 420 people (0.18%) aged ≥18 years [32], compared to the 0.84% found in our study. The higher figure in our study likely reflects an older population (aged 39-79 years). A final strength of the study was the measurement of both occupational and recreational activity, allowing an estimate of the differential effects of both. A study limitation was that we could not identify participants with asymptomatic Barrett's oesophagus in the cohort. Including only symptomatic disease, diagnosed by oesophagogastroduodenoscopy (OGD), may identify as little as 55% of all cases within a population [33]. Nevertheless, it would be expected that misclassification of asymptomatic Barrett's oesophagus cases (as non-cases) would be non-differentially distributed between physical activity categories and therefore draw associations to the null. The only way to identify all cases of Barrett's oesophagus within a population would be by screening with gastroscopy, which is unfeasible in large studies. A further potential limitation was the use of a questionnaire measure of physical activity, rather than an objective physiological variable. Questionnaires are a pragmatic necessity of measuring physical activity in large population studies and although measurement error could arise it would again reduce the magnitude of the effect size of any association, rather than incorrectly inflate it.

In summary, our study was the first to examine the associations between both occupational and recreational levels of physical activity and the risk of Barrett's oesophagus. We have shown that whilst differing levels of recreational exercise were not associated with disease risk, occupational physical activity may be either protective (as in standing occupations), or possibly hazardous (as in heavy manual occupations). The public health importance of Barrett's oesophagus lies in its association with oesophageal adenocarcinoma [34]. If further work is able to confirm specific occupations which may be hazardous then occupational physical activity would form an important component of the aetiological model for Barrett's oesophagus and oesophageal cancer.

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Table and Figure Legends

Table 1. Characteristics of cases and controls (values are number of patients (%) unless otherwise stated).

Table 2. Multivariable Hazard Ratios (HRs) for physical activity and the risk of symptomatic Barrett's oesophagus.

Figure 1. Study flow diagram

Appendix 1. Physical activity questionnaire

Table 1. Characteristics of cases and controls (values are number of patients (%) unless otherwise stated).

Variable	Barrett's oesophagus (n=203)	Controls (n=23 907)	P-value
Age at recruitment (mean, years & SD)	60.3 (±8.6)	59.0 (±9.3)	0.05
Gender (male)	144 (70.9)	10 978 (45.9)	<0.001
Cigarette smoking			
Never	66 (32.5)	10 938 (45.8)	<0.001
Former	109 (53.7)	9 985 (41.8)	0.001
Current	26 (12.8)	2 781 (11.6)	0.60
Missing data	2 (1.0)	203 (0.8)	0.83
WHO BMI category (kg/m^2)			
Underweight (<18.5)	0	115 (0.5)	0.32
Normal weight (18.5 to <25)	65 (32.3)	9 293 (38.9)	0.05
Overweight (25 to <30)	107 (52.7)	10 826 (45.3)	0.03
Class I obesity (30 to <35)	25 (12.3)	2 935 (12.3)	0.98
Class II obesity (35 to <40)	4 (2.0)	532 (2.2)	0.81
Class III obesity (≥40)	2 (1.0)	206 (0.9)	0.85
Alcohol			
(mean units/week & SD)	9.83 (11.4)	7.2 (9.5)	0.001
Missing data	n=2 (1.0)	n=244 (1.0)	
Occupational activity			
Sedentary	57 (28.1)	6 362 (26.6)	0.64
Standing	24 (11.8)	6 002 (25.1)	<0.001
Manual	39 (19.2)	4 161 (17.4)	0.50
Heavy manual	14 (6.9)	575 (2.4)	<0.001
Unemployed	69 (34.0)	6 807 (28.5)	0.08
Recreational activity			
None	116 (57.1)	12 651(52.9)	0.23
<3.5 hours/week	49 (24.1)	7 201 (30.1)	0.06
3.5 to <7 hours/week	22 (10.8)	2 591 (10.8)	1.00
>7 hours/week	16 (7.9)	1 464 (6.1)	0.30

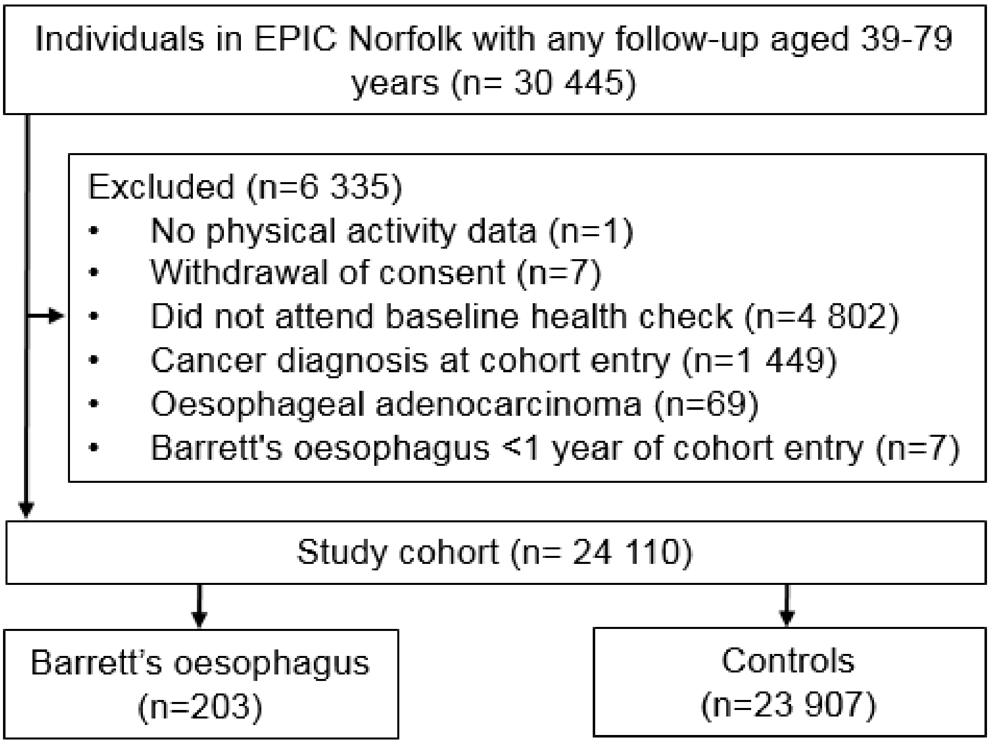
Comparative P-values for continuous variables were derived using Student t-tests, whereas, for categorical variables, X^2 tests were used.

Table 2. Multivariable Hazard Ratios (HRs) for physical activity and the risk of symptomatic Barrett's oesophagus.

	HR (95% CI), P-value	
Type of physical activity	**Not BMI adjusted**	**BMI adjusted**
Occupational[a]		
Sedentary	Reference (1.00)	Reference (1.00)
Standing	0.50 (0.31-0.82), p=0.006	0.51 (0.31-0.83). p=0.006
Manual	0.91 (0.61-1.34), p=0.67	0.93 (0.61-1.40), p=0.71
Heavy manual	1.66 (0.91-3.00), p=0.09	1.66 (0.92-3.02), p=0.09
Recreational[b]		
None/week	Reference (1.00)	Reference (1.00)
<3.5 hours/week	0.84 (0.56-1.30), p=0.43	0.85 (0.56-1.30), p=0.46
3.5 to <7 hours/week	0.98 (0.56-1.72), p=0.94	0.99 (0.57-1.75), p=0.98
>7 hours/week	1.34 (0.72-2.50), p=0.35	1.36 (0.73-2.51), p=0.33

Multivariable models were adjusted for: age, gender, smoking status and alcohol consumption +/- BMI. [a]Additional adjustment for recreational activity. [b]Additional adjustment for occupational activity.

Figure 2. Study flow diagram



Appendix 1. Physical activity questionnaire

1. We would like to know the type and amount of physical activity involved in your work. Please tick what best corresponds to your present activities from the following four possibilities

   - Sedentary occupation___________________________

   You spend most of your time sitting (such as in an office)

   - *or* Standing occupation_________________________

   You spend most of your time standing or walking. However, your work does not require intense physical effort (e.g. shop assistant, hairdresser, guard, etc.)

   - *or* Physical work______________________________

   This involves some physical effort including handling of heavy objects and use of tools (e.g. plumber, cleaner, nurse, sports instructor, electrician, carpenter, etc.)

   - *or* Heavy manual work_________________________

   This involves very vigorous physical activity including handling of very heavy objects (e.g. docker, miner, bricklayer, construction worker, etc.)

2. In a typical week during the past 12 months, how many hours did you spend on each of the following activities? (Put '0' if none).

   - Walking, including walking to work, shopping and leisure

   In summer ____________ hours per week
   In winter ____________ hours per week

   - Cycling, including cycling to work and during leisure time

   In summer ____________ hours per week
   In winter ____________ hours per week

   - Gardening

   In summer ____________ hours per week
   In winter ____________ hours per week

   - Housework such as cleaning, washing, cooking and childcare

   ____________ hours per week

   - Do-it-yourself

   ____________ hours per week

   - Other physical exercise such as keep fit, aerobics, swimming, jogging

   In summer ____________ hours per week
   In winter ____________ hours per week

3. In a typical week during the past year did you practice any of these activities vigorously enough to cause sweating or faster heartbeat?
   Yes______ No______ Don't know______
   If yes, for how many hours per week in total did you practise such vigorous physical activity? (Put '0' if none)
   ____________ hours per week

4. In a typical day during the last 12 months, how many floors of stairs did you climb up? (Put '0' if none)
   ____________ floors per day