Does physical activity protect against the development of gastroesophageal reflux disease, Barrett's oesophagus and oesophageal adenocarcinoma? A review of the literature with a meta-analysis

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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 reducing the risk of oesophageal adenocarcinoma. This review assesses the biological mechanisms and epidemiological evidence for the relationship between physical activity and the development of oesophageal adenocarcinoma and its precursor diseases; gastroesophageal reflux disease (GORD) and Barrett's oesophagus. **Methods:** A search of PubMed, Medline, Embase and CINAHL was conducted from their inceptions to 25th March 2017 for analytical studies that examined associations between recreational and/or occupational levels of physical activity and the risk of GORD, Barrett's oesophagus and oesophageal adenocarcinoma. Where appropriate, a meta-analysis of effects was undertaken. **Results:** Seven studies were included (2 cohort, 5 case-control). For GORD, there were 3 case-control studies with 10 200 cases among 78 034 participants, with a pooled estimated OR of 0.67 (95% CI 0.57-0.78) for high vs. low levels of recreational physical activity. In Barrett's oesophagus, there was a single case-control study, which reported no association, OR 1.19 (95% CI 0.81-1.73). For oesophageal adenocarcinoma there were 3 studies (2 prospective cohort, 1 case control) with 666 cases among 910 376 participants. The largest cohort study reported an inverse association for high vs. low levels of recreational physical activity, RR 0.68, 95% CI 0.48-0.96. The remaining 2 studies reported no associations with either occupational or combined recreational and occupational activity. Heterogeneity in the measurement of exposure (recreational, occupational and both) made a pooled estimate for oesophageal adenocarcinoma inappropriate. **Conclusion:** Although limited, there is some evidence that higher levels of recreational physical activity may reduce the risk of both GORD and oesophageal adenocarcinoma, but further large cohort studies examining the type, intensity and duration of activities that may be beneficial are needed.

Introduction

Worldwide, there is an alarmingly rapid rise in the incidence of oesophageal adenocarcinoma, which is reaching epidemic proportions.[1-4] Geographical variations, with higher incidences in more affluent countries, suggests that aspects of lifestyle may be involved in the aetiology.[1] Increasingly sedentary behaviours with reduced levels of both occupational and recreational physical activities may be a contributing factor.[5] Histological surveillance studies have demonstrated that oesophageal adenocarcinoma develops through a morphological sequence of inflammation, metaplasia, dysplasia and eventual cancer. Three distinct clinical diseases mark this progression: gastroesophageal reflux disease (GORD), Barrett's oesophagus, and oesophageal adenocarcinoma. If physical activity has a protective effect, inverse associations in published studies between increased levels and the development of all three diseases would be anticipated. The aims of this paper were to firstly, discuss the potential biological mechanisms for how physical activity may affect disease risk and secondly, to review the reported associations between physical activity GORD, Barrett's oesophagus and oesophageal adenocarcinoma.

Plausible biological mechanisms for the effect of physical activity on GORD, Barrett's oesophagus and oesophageal adenocarcinoma

Gastroesophageal reflux disease (GORD)

Reflux of stomach contents into the oesophagus is a normal physiological occurrence. However, when reflux is frequent or severe enough to cause troublesome symptoms it is defined as GORD.[6] Exercise may affect the risk of GORD in opposing ways depending on both its type and intensity. There are several mechanisms through which exercise could induce reflux, although the precise details are not fully understood. Intra-abdominal pressure is increased by activities which involve abdominal straining such as weightlifting or cycling (with a bent over posture), which may force gastric contents retrograde, beyond the lower oesophageal sphincter into the oesophagus.[7] Also, vigorous exercise, that is above 75% of VO_{2max}, has been shown to delay gastric emptying,[8] likely by decreasing splanchnic blood flow.[9] These mechanisms may account for the documented positive relationship between reflux episodes and high intensity exercise,[10] and the high prevalence of GORD in elite athletes (estimated at 60%).[7] Occupational activity may also increase the risk of GORD, particularly in heavy manual jobs, which involve bending and heavy lifting. These activities are also more likely to occur post-prandially when reflux episodes are most likely.[11] Associations between heavy manual occupations and reflux does not appear to have been studied in the

literature, but an increased risk of reflux in occupations that involve intra-abdominal straining, such as in wind instrument players[12 13] and choir or opera singers[13 14] has been reported.

Alternatively, moderate levels of recreational physical activity may protect against GORD. Engagement in regular exercise helps maintain a normal body weight,[15] preventing the risk of obesity induced reflux disease;[16] where central adiposity raises intra-gastric pressure, creating a gastro-oesophageal reflux gradient and hiatus hernia formation.[17-19] It has also been postulated that regular exercise strengthens the crural diaphragm,[20] which is an important component of the anti-reflux barrier of the lower oesophageal sphincter. Finally, low or moderate intensity (30-60% of VO_{2max}) running or walking increases rather than delays gastric emptying and may therefore decrease reflux risk.[8] As the type and intensity of physical activity may influence reflux in opposing ways, measuring the precise characteristics of recreational and occupational activities is likely to be important in aetiological epidemiological investigations of GORD.

Barrett's oesophagus

Barrett's oesophagus is defined as metaplastic change of epithelium in the lower oesophagus from a squamous to columnar cell type. This transition is thought to be driven by inflammation,[21 22] where chronic exposure of oesophageal mucosa to reflux results in the release of pro-inflammatory cytokines and subsequent reactive metaplastic change.[21 22] Regular physical activity reduces inflammatory biomarker expression, and thus may prevent this inflammation-driven process.[23-26] However, further work is required to elucidate the importance of the potential anti-inflammatory mediated effect of physical activity.

Oesophageal adenocarcinoma

The epithelium of Barrett's oesophagus is biologically unstable and prone to dysplasia and neoplasia.[27] Whilst the absolute risk of progression from Barrett's oesophagus to cancer is low, at 0.2-0.7% per patient per year[28], obesity is associated with a 2-fold increased risk.[29] Body fat, in particular visceral fat, is metabolically active, releasing adipocytokines, which results in low-grade inflammation, chronic hyperinsulinemia and an increased risk of insulin-like growth factor-mediated carcinogenesis.[30] Regular levels of physical activity can not only regulate body fat levels, but also lower plasma insulin and insulin resistance over and above the effect of weight loss alone,[31] both of which are positively associated with increased cancer risk.[32] Furthermore, aerobic exercise is thought to reduce oxidative stress and improve DNA repair, which may inhibit carcinogensis.[33] Therefore, physical activity could have protective pathways which may or may not rely on modification of BMI, although more work is needed to determine the relevance and importance of these mechanisms.

Eligibility criteria, search strategy, data synthesis & statistical analysis

Original investigations with an analytical design and control group (i.e. randomised controlled trials (RCTs), cohort and case-control studies) which examined levels of physical activity (occupational and/or recreational) and the incidence of GORD, Barrett's oesophagus and oesophageal adenocarcinoma were selected. Only studies which described both the method of measuring physical activity (e.g. questionnaire) and its quantification (e.g. ≥30mins of recreational exercise/day) were included. The measurement of the disease outcome needed to be clearly stated (e.g. endoscopic and histological confirmation). Furthermore, only studies which specifically investigated oesophageal adenocarcinoma as a distinct histological subtype were included.

A literature search of PUBMED, EMBASE, MEDLINE and CINAHL (from commencement to 25th March 2017) was conducted using the terms: "exercise", "activity", physical", "occupational, "recreational", "Barrett's", "oesophagus", "oesophageal", "adenocarcinoma", "cancer", "carcinoma", "GORD", "heartburn", "reflux", "acid", "bile", "gastro-oesophageal", "oesophagitis", "oesophageal inflammation". An independent search of each disease was undertaken using both English and American (e.g. GERD, esophagus) spellings. The reference lists of all selected articles, as well as reviews, were also searched to identify other relevant papers. A total of 7 studies were included in this review (2 cohort, 5 case-control). No randomised controlled trials were identified. Data was extracted from each study (table 1). For a meta-analysis of GORD, Review Manager (RevMan) Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to calculate a summary effect using the inverse variance method, based on the ORs and upper and lower boundaries of the CIs in the included studies. Due to variations in the type, duration and intensity of recreational physical activity between studies, a random effects model was applied to estimate the mean of a distribution of effects. Only a single study in Barrett's oesophagus was identified and for oesophageal adenocarcinoma, there was significant heterogeneity in measurement of exposures (either recreational[34] or occupational activity[35] or a combination of both),[36] therefore a meta-analysis was not appropriate for these two diseases.

Physical activity and the development of GORD

Results

The search terms identified 1 426 potentially relevant articles, which were screened by title; with inclusion of 66. After removal of duplicates, 6 were included by abstract. Of these, 3 were excluded by full paper review according to the inclusion criteria. One paper was identified from the reference lists, but later excluded after full review. In total, 3 papers were included and the

characteristics of the studies are shown in table 1. All 3 were case-control studies with a total of 10 200 symptomatic cases of GORD identified among 78 034 participants. The largest case-control study was of 43 363 men and women aged ≥20 years from a single county in Norway. In this study, physical activity levels were measured with a questionnaire and divided into 4 categories according to the number of 30 min recreational exercise sessions engaged in per week (none, <1/week, 1-3/week and >3/week). GORD was defined as self-reported 'severe and recurrent heartburn or regurgitation during the previous 12 months'. The authors reported an OR of 0.50 (95% CI 0.40-0.70) for 30mins/week vs none and development of GORD,[20] but less benefit with exercise levels above this, OR 0.70 (95% CI 0.60-0.90) for >90mins vs. none. The second largest study was of 27 717 monozygotic twins aged 42-104 years recruited from the Swedish Twin Registry. Both recreational and occupational activities were measured by questionnaire and divided into 4 categories. The highest recreational physical activity category was defined as 'much', the lowest as 'almost no'. GORD symptoms were assessed by questionnaire. The authors reported an OR of 0.60 (95% CI 0.47-0.77) for men (highest vs. lowest levels of recreational physical activity and GORD symptoms) and 0.56 (95% CI 0.41-0.75) for women, with a dose depended trend, p=0.002 and p=0.001, respectively.[37] No associations were found for high vs. low levels of occupational activity for either men, OR 1.23 (95% CI 0.99-1.53), or women, OR 1.16 (95% CI 0.78-1.72). The smallest study was of 6 954 German men and women aged 18-79 years recruited by national survey. Only sports activities were measured and categorised as none, ≤2hrs/week and >2hrs/week. GORD was established by self-reported questionnaire on symptoms of heartburn or regurgitation. The authors reported an OR of 0.75 (95% CI 0.60-0.93) for sports activity of >2hrs/week vs. no sports.[38] All studies adjusted for known confounders (age, gender), but also for unestablished risk factors (e.g. education, coffee consumption and intake of salt, dietary fibre and bread). All adjusted for BMI, and by doing so they assumed that physical activity has an independent effect that does not rely on a reciprocal change in BMI. None conducted an unadjusted BMI analysis to assess the effect of physical activity via the regulation or reduction of BMI (the BMI mediated effect). In a meta-analysis, the estimated mean effects of the 3 studies gave an OR of 0.67 (95% CI 0.57-0.78) for the highest vs lowest levels of physical active and the risk of GORD (figure 1). Statistical heterogeneity was low (I^2 = 39%).

Risk of bias and interpretation of the results

The findings from the meta-analysis suggests that higher levels of physical activity may reduce the risk of GORD by 1/3. However, there are several potential sources of bias which should be considered when interpreting the result. None of the studies used a validated questionnaire to measure physical activity, which may represent a source of measurement error, reducing associations towards the null. Furthermore, the specific types of physical activities (e.g.

cycling, swimming, running) were not analysed in any of the studies. Instead, all activities were grouped together and categorised according to duration (e.g. 'physical activity of at least 30mins' or 'sports ≤2hrs/week'). This may suffice to explore the cardiometabolic benefits of physical activity, but in the context of reflux disease; where specific activities or intensities might increase risk, such categorisation may confound associations. Not accounting for occupational activity is a further potential source of error as it is likely to be an important confounder, particularly in the case of heavy manual work, which may involve intra-abdominal straining. However, only one of the studies undertook a separate analysis of both occupational and recreational activities,[37] where the risk of GORD did appear to be increased in strenuous occupations, OR 1.23 (95% CI 0.99-1.53 - most physically strenuous vs. sedentary), although conventional statistical significance was not demonstrated, $p_{\text{trend}} = 0.549$. Use of a validated questionnaire to measure GORD was used in two studies[20 37], but no studies, by the nature of their retrospective designs, were able to measure exposure prior to disease onset. This may be a significant source of measurement bias (if cases reduced their exercise levels due to reflux symptoms and exercise was measured during the symptomatic period), again, the effect would be to reduce the effect sizes. Finally, the study of monozygotic same sex twins represents a select sub-population, and although participants were specifically chosen by the authors to examine the genetic influences of GORD), the generalisability of these findings is limited.

Authors' summary: There is limited observational evidence that engaging in any recreational physical activity may reduce the risk of GORD by up to 1/3. However, to clarify such associations, a large and well-designed prospective cohort study, where exposure is accurately measured prior to disease onset, is required.

Physical activity and the development of Barrett's oesophagus

Results

Sixty seven potentially relevant articles were screened by title and 10 were suitable for abstract review. After removal of duplicates and screening by abstract, only 1 remained, which was included by full paper review. This was a case-control investigation of 307 cases of Barrett's oesophagus and 1724 controls. The participants were US war veterans (men and women) aged 40-80 years recruited by 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 asks about the previous 7 days recreational exercise. Cases were confirmed both endoscopically and histologically. 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).[39] The statistical model used in the study adjusted for age, sex, race, GORD symptoms, *Helicobacter pylori* infection status (which may reduce risk if positive), BMI and high waist to hip ratio (WHR).

Risk of bias and interpretation of the results

Although IPAQ is a validated physical activity questionnaire, its use in this study population (to measure lifelong physical activity exposure) may introduce significant measurement error. War veterans are likely to have engaged in high levels of physical activity during their military service, which would not be reflected in their previous 7 days post-retirement activities as measured by IPAQ. Measurement bias is also likely to occur in the 106 surveillance cases of Barrett's disease who may have changed their physical activity levels due to symptoms. Therefore, physical activity would have been measured during the symptomatic period, or after disease onset. The authors adjusted for GORD and BMI/WHR which lie along the presumed causal pathway (figure 2). If we assume that the protective effect of exercise is largely by regulation of weight and reduction of reflux risk (a reasonable assumption) then controlling on these variables is likely to reduce any association between physical activity and Barrett's oesophagus towards the null. Collinearity between BMI and WHR is also likely to be high, yet the authors adjusted for both in the same model. Finally, the study sample (US war veterans) is unlikely to be representative of the general population. Overall, the findings of this study are difficult to interpret and definitive conclusions about physical activity and Barrett's oesophagus risk are unable to be made based on its evidence.

Authors' summary: There is insufficient evidence to define the association between physical activity and Barrett's oesophagus. Evidence from large and well-designed prospective cohort studies are needed, which use an accurate and validated measure of physical activity prior to disease onset.

Physical activity and the development of oesophageal adenocarcinoma

Results

Five hundred and seventy three potentially relevant articles were screened by title with inclusion of 49. After removal of duplicates, 17 were included by abstract. Of these, 14 were excluded by full paper review according to the inclusion criteria. Two papers were included by reference lists but later excluded after full review. In total, 3 papers were included in this review (2 large prospective cohort studies[34 36] and one case-control study)[35] and the characteristics are shown in table 1. A total of 666 cases of oesophageal adenocarcinoma were identified among 989 046 participants. The largest prospective cohort study investigated men and

women aged 50-71 years recruited from the general population by postal questionnaire in the US.[31] Only recreational physical activity was measured (by questionnaire) and categorised into 5 levels based on the number of sessions lasting ≥20mins/week (0, <1, 1-2, 3-4, ≥5). Disease outcome was confirmed using cancer registry data. The authors reported a RR of 0.68 (95% CI 0.48-0.96) for recreational physical activity of ≥5/week vs. none, with a dose dependent trend (p=0.007). There was attenuation of the effect size when BMI was added to the model; OR=0.75 (95% CI 0.53-1.06). The second largest cohort study identified men and women aged 25-70 years from 9 European countries recruited by postal questionnaire. [33] Exposure was measured using a questionnaire for both recreational and occupational physical activities, which was combined into a 4-level physical activity index: inactive, moderately inactive, moderately active and active. Confirmation of cases was largely confirmed by a panel of pathologists, but also from cancer registry data. This study reported a HR of 0.98 (95% CI 0.48-2.01) for the highest levels of occupational and recreational physical activity vs the lowest. Finally, the case-control study was of US men and women aged between 30-74 years identified from a cancer surveillance programme. [35] Only occupational physical active was measured and based on job title. Case confirmation was by using cancer surveillance data. The authors reported an OR of 0.67 (95% CI 0.38-1.19, p_{trend} =0.07), for the highest vs lowest physically active occupation. All 3 studies adjusted for known confounders (age, gender, smoking status), but also adjusted for unconfirmed potential risk factors (e.g. education, fruit and vegetable intake). All 3 adjusted for BMI, but only one included results of the multivariable model excluding BMI. [31]

Risk of bias and interpretation of the results

The US prospective study is the largest investigation of physical activity and oesophageal adenocarcinoma (374 cases), but whilst it specifically measured leisure time activity, the specific types of exercise were not defined.[34] Furthermore, occupational activity was not measured or adjusted for as a potential confounder. Nonetheless, the estimated RR of 0.68 (95% CI 0.48-0.96) (unadjusted for BMI) likely represents the least biased estimate of effect size in the literature for recreational physical activity and the risk of oesophageal adenocarcinoma. The European cohort study used a validated questionnaire to measure physical activity, but both recreational and occupational activities were combined to produce a physical activity index from inactive to active. Therefore, all groups contained a heterogeneous population of people in terms of the types of physical activity they engaged in. The reported HR for the active vs. inactive category of 0.98 (95% CI 0.48-2.01) may represent the dilution of any potential protective effect of recreational exercise by the hazardous effect of heavy manual work. The number of cases (n=80) was also relatively small resulting in

imprecision. The case-control study[35] measured physical activity identified by job title from which an index was created based on the levels of activity associated with each job (from sedentary to highly active). Jobs with high levels of exertion may involve bending and lifting which could increase the risk of reflux disease, particularly if done post-prandially. This is not accounted for in the study, but rather all high energy expenditure jobs are categorised together without distinction. Furthermore, recreational exercise was not measured and therefore could not be included in the statistical modelling.

Authors' summary: There is a limited evidence from a large prospective cohort study that recreational physical activity of at least 100mins every week vs. no activity may reduce the risk of oesophageal adenocarcinoma by up to 32%.

Overall summary and future research directions

This review shows there is some evidence, although limited, that increasing levels of recreational physical activity may be associated with a reduced risk of GORD and oesophageal cancer. However, the type, duration and intensity of recreational exercise that may be protective is poorly defined. Whilst we did not identify any other previous reviews on physical activity and risk of GORD and Barrett's oesophagus, there have been several reviews for oesophageal adenocacinoma.[40-43] All estimated a pooled risk reduction for the highest vs. lowest levels of physical activity of between 21-52%.[40-43] However, pooling of observational data from different study designs is methodologically questionable,[44] particularly when some examined different exposures (occupational or recreational activity). Case-control studies also have inherent selection and recall biases which may give erroneous findings. The only review to investigate one type of activity (recreational) and pool data only from prospect cohorts studies reported a HR of 0.58 (95% CI 0.37-0.89) for high vs. low levels of physical activity and the risk of oesophageal adenocarcinoma.[40] The authors also included a BMI adjusted HR estimate of 0.62 (95% CI 0.40-0.97), suggesting that physical activity has a mostly non-BMI mediated effect. However, pooling of data from different cohort studies, particularly where the measurements of physical activity differ introduces potential error.

An important point to consider when investigating associations between physical activity and the risk of GORD, Barrett's oesophagus and oesophageal adenocarcinoma is the complex interplay which likely occurs between levels of physical activity, diet and BMI. People who engage in higher levels of recreational physical activity would be expected to eat a healthier diet and avoid high levels of alcohol consumption. These factors may therefore confound any associations with physical activity and disease risk. However, although dietary modification is often recommended to control symptoms of GORD,[45] it is currently unknown from the literature

whether specific dietary components are involved in the aetiology.[46] A comprehensive review of published epidemiological studies (case-series, cross-sectional and case-control studies) did not support the role of diet (including fatty foods, chocolate, fruit and vegetables) in the development of symptoms of GORD.[46] However, in the absence of prospective cohort data, where diet is measured prior to disease onset, conclusions could be subject to recall bias. For Barrett's oesophagus and oesophageal adenocarcinoma, a review has suggested that a diet low in fruit and vegetable intake may represent a modest risk factor for both diseases.[47] This is based on evidence from case-control studies that an increased intake of fruit, [48] plant based fibre [49 50] and vegetables [51] was inversely associated with disease risk. However, spurious over-estimation of the effect sizes due to recall bias may explain these findings, which are derived from retrospective investigations. Alcohol does not seem to have an important role in the aetiology of all three disease states. Large case-control studies found no associations between alcohol intake and the risk of GORD.[20 37] Consistent with these findings, a review of population-based case-control studies found no overall effect of alcohol consumption on Barrett's oesophagus or oesophageal adenocarcinoma risk, although the methological weaknesses of case-control studies in terms of selection and information biases was noted.[52] Large prospective cohort studies are required to examine dietary intake prior to disease onset, which would reduce the effects of reverse causation bias (i.e., patients are more likely to avoid foods which they feel exacerbate their symptoms or eat foods which alleviate them). As there are no consistent associations documented between any specific dietary factors and the risk of GORD, Barrett's oesophagus or oesophageal adenocarcinoma, we suggest it is currently reasonable not to include dietary intake in statistical modelling. However, emerging data in the future from prospective studies may show this is required. For BMI, the epidemiological evidence does support a positive correlation between being overweight and disease risk. Meta-analyses have estimated that obesity (BMI>30kg/m^2), compared to a normal weight, is a positive risk factor for GORD (OR 1.94, 95% CI 1.47-2.57)[53], Barrett's oesophagus (OR 1.70, 95% CI 1.36-212)[54] and oesophageal adenocarcinoma (2.78, 95% CI 1.85-4.16).[53] BMI is therefore an established risk factor, and should be measured and analysed when considering physical activity and the risk of all three disease states. An approach to this would be to provide both BMI adjusted and unadjusted values when estimating the effect size of physical activity on disease risk, as this would clarify whether the effect of physical activity is mediated through BMI.

In conclusion, this review is the first to examine the association between physical activity and the risk of GORD, Barrett's oesophagus and oesophageal adenocarcinoma. All three disease states were included in his review as consistent associations (in a disease which occurs in sequence) would provide supportive evidence for causality. The evidence from biological and

epidemiological studies does suggest a potential protective effect of moderate levels of recreational physical activity on the risk of GORD and oesophageal adenocarcinoma, but there is insufficient data for an assessment of Barrett's oesophagus. An inverse association between increased recreational activity with both GORD and oesophageal adenocarcinoma does provide some credibility for a causal association, but the evidence should be interpreted with caution as it is mainly derived from case-control investigations. The association between physical activity and risk of oesophageal adenocarcinoma is likely to be non-linear, where both low and very high levels of recreational activity may increase risk, but moderate levels decrease risk (figure 3). However, the potentially hazardous effect of high intensity recreational exercise, or heavy manual occupations; particularly those that raise intra-gastric pressure, has not been fully investigated in epidemiological studies. In fact, only one of the studies in this review considered a possible differential effect of occupational and recreational activities, which suggested that vigorous work may indeed increase GORD risk.[37] However, further large prospective studies are required investigating the type, duration and intensity of recreational and occupational physical activity that may be protective or hazardous. If these find consistent inverse associations with the development of GORD, Barret's oesophagus and oesophageal adenocarcinoma, physical activity may offer a public health intervention to reduce the rising epidemic of oesophageal adenocarcinoma.

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Table and Figure Legends

Table 1. Characteristics of the included studies

Figure 1. Forest plot for the association between high vs. low levels of recreational physical activity and the risk of GORD. PA=physical activity.

Figure 2. A simplified diagram of the proposed casual pathway of physical activity in the aetiology of GORD, Barrett’s oesophagus and oesophageal adenocarcinoma. The blackline represents a potential independent pathway which does not rely on modification of BMI (e.g. by decreasing inflammation or improving insulin sensitivity).

Figure 3. A graph of the proposed U-shaped association between levels of physical activity and the risk of GORD, Barrett’s oesophagus and oesophageal adenocarcinoma, where moderate levels are protective, but high levels are hazardous.

Table 1.

First author and year of publication	Study type	Study sample	Validated physical activity questionnaire?	Quantification of physical activity	Outcome measure	Validated outcome measure?	Cases of GORD (n)	Adjusted variables in statistical model	Effect size (95% CIs)
GORD									
Nilsson, 2004 [20]	Case-control	Men and women aged ≥20 years from a single county in Norway recruited by postal questionnaire (n=43 363)	No	Recreational physical activity of at least 30mins duration. Categorised as never, <1/week, 1-3/week and >3/week	Self-reported questionnaire of severe and recurrent heartburn or regurgitation during the past 12 months	Yes	3 153	Age, gender, BMI, smoking and intake of coffee, salt, dietary fibre and bread	OR for highest vs lowest level of physical activity =0.70 (0.60-0.90)
Zheng, 2007 [37]	Case-control	Monozygotic same sex twins aged between 42-104 years recruited from the Swedish Twin Registry by postal questionnaire (n=27 717)	No	Ordinal scale from 1-4 for both occupational and recreational physical activity separately. Occupational = sedentary, walking, lifting, strenuous. Recreational = almost no, little, medium and much	Questionnaire delivered by telephone interview	Yes	4 083	Age, BMI, smoking, coffee intake and education	OR for highest vs. lowest recreational physical activity in men = 0.6 (0.47-0.77). In women = 0.56 (0.41-0.75). OR for highest vs. lowest occupational physical activity in men= 1.23 (0.99-1.53). In women= 1.16 (0.78-1.72)
Nocon, 2006 [38]	Case-control	Men and women aged 18-79 years in Germany recruited by national survey (n=6 954)	No	Recreational sports only. Categorised as none, ≤2hrs/week or >2 hrs/week	Self-reported heartburn or acid regurgitation. Categorised as no, mild, moderate and severe	No	2 964	Age, gender, BMI, smoking, alcohol and 12 nutritional factors	OR for highest vs lowest level of sport =0.75 (0.6-0.93)
Barrett's oesophagus									
Hilal, 2015 [39]	Case-control	Men and women aged 40-80 years in Texas USA attending a Veteran Affairs Medical Centre for an elective endoscopy (n=2 172)	Yes	Recreational levels of physical activity categorised as low, moderate or high. Moderate is defined as 150mins moderate or <75 mins vigorous exercise/week. Low =<moderate. High=>moderate	Endoscopic and histological appearance consistent with Barrett's oesophagus	Yes	323	Age, gender, race, GORD symptoms, *H.pylori* infection status, BMI and high WHR	OR for highest vs lowest level of physical activity =1.19 (0.82-1.73)
Oesophageal adenocarcinoma									
Leitzmann, 2009 [34]	Prospective cohort	American men and women aged between 50-71 years. Recruited from the general population by a postal questionnaire (n=487 732)	No	5 categories according to the number of moderate recreational physical activity sessions lasting ≥20 minutes (0,<1,1-2,3-4,≥5	Cancer registry	n/a	374	Age, gender, race, smoking, alcohol, education, marital status, family history of cancer, intake of fruit, vegetables and red meat (+/- BMI)	RR for highest vs. lowest physical activity category=0.68 (0.48-0.96) (unadjusted for BMI)
Huerta, 2010 [36]	Prospective cohort	Men and women from 9 European countries aged 25-70 years. Recruited from general population by postal questionnaire (n=420 449)	Yes	A validated physical activity index of four ordinal categories combining both occupational and recreational levels of physical activity (inactive, mod inactive, mod active, active)	Confirmed by a panel of pathologists (69%), pathology reports (15%) and cancer registry (16%)	n/a	80	Age, gender, height, weight, education, smoking, alcohol, energy intake, fruit, red meat and processed meat intake	HR for highest vs. lowest category = 0.98 (0.48-2.01)
Vigen, 2005 [35]	Case-control	American men and women aged 30-74 years identified by a cancer surveillance programme. Controls were matched based on gender, race, date of birth and residence (n=2 195)	No	A Total Activity Index calculated by multiplying the number of years worked in a sedentary (0), moderate (1) or highly active (2) job over a lifetime	Cancer surveillance programme data	n/a	212	Age, gender, race, smoking status, education, birthplace and BMI	OR for highest vs lowest category = 0.67 (0.38-1.19)

Figure 1.

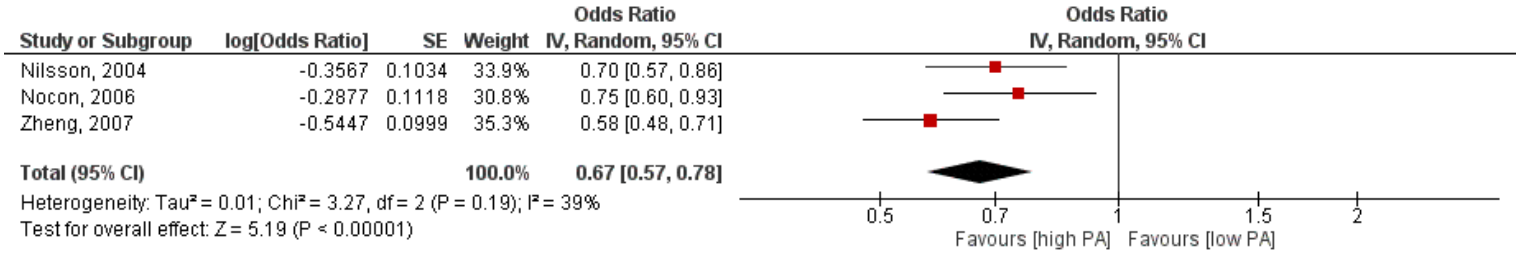
Study or Subgroup
log[Odds Ratio]
SE
Weight
Odds Ratio
IV, Random, 95% CI
Nilsson, 2004 -0.3567 0.1034 33.9% 0.70 [0.57, 0.86]
Nocon, 2006 -0.2877 0.1118 30.8% 0.75 [0.60, 0.93]
Zheng, 2007 -0.5447 0.0999 35.3% 0.58 [0.48, 0.71]
Total (95% CI) 100.0% 0.67 [0.57, 0.78]
Heterogeneity: Tau² = 0.01; Chi² = 3.27, df = 2 (P = 0.19); I² = 39%
Test for overall effect: Z = 5.19 (P < 0.00001)
Odds Ratio
IV, Random, 95% CI
0.5
0.7
1
1.5
2
Favours [high PA]
Favours [low PA]

Figure 2.

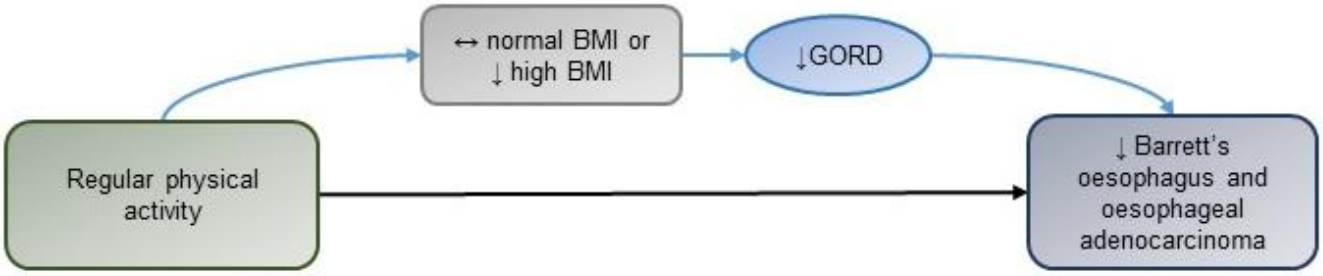
↔ normal BMI or
↓ high BMI
↓GORD
Regular physical activity
↓ Barrett's oesophagus and oesophageal adenocarcinoma

Figure 3.