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REVIEW

# The association between physical activity and gastroesophageal cancer: systematic review and meta-analysis

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**Abstract** Physical activity may decrease gastroesophageal cancer risk through a reduction of oxidative stress and decreased chronic inflammation, yet few epidemiologic studies have been able to report a clear inverse association between physical activity and gastroesophageal cancer. Because no meta-analysis has investigated the relation of physical activity to gastroesophageal cancer, we conducted a comprehensive systematic review and meta-analysis according to the PRISMA guidelines based on 24 studies with a total of 15,745 cases. When we compared high versus low physical activity levels and summarized associations according to anatomic site and tumor histology, risk reductions were evident for esophageal adenocarcinoma [relative risk (RR) = 0.79, 95 % confidence interval (CI) = 0.66–0.94], gastric cardia adenocarcinoma (RR = 0.83, 95 % CI = 0.69–0.99) and gastric non-cardia adenocarcinoma (RR = 0.72, 95 % CI = 0.62–0.84). The risk reduction for esophageal squamous cell carcinoma (RR = 0.94, 95 % CI = 0.41–2.16) became statistically significant (RR = 0.66, 95 % CI = 0.46–0.96) after excluding an influential study. The test for heterogeneity by gastroesophageal cancer subtype was statistically non-significant ($p$-difference = 0.71). The RR of total gastroesophageal cancer for high versus low physical activity was 0.82 (95 % CI = 0.74–0.90). A dose–response analysis of frequency of physical activity and total gastroesophageal cancer risk revealed that the greatest risk reduction was achieved among those engaging in moderate to vigorous physical activity five times per week (RR = 0.67, 95 % CI = 0.58–0.79). Our results provide support for an inverse relation of physical activity, in particular exercise frequency, to gastroesophageal cancer risk.

**Keywords** Physical activity · Esophageal cancer · Gastric cancer · Meta-analysis

## Introduction

Gastroesophageal cancers occur at a rate of approximately one million cases of gastric cancer and half a million cases of esophageal cancer each year and they represent the fourth and sixth leading cancer sites, respectively [1]. Gastric and esophageal cancers show poor 5-year survival rates of 28 and 17 %, respectively [2]. Esophageal adenocarcinoma is one of the most rapidly growing cancers in the United States [3–5], Europe [5], and Australia [5]. The poor prognosis of gastroesophageal cancers and the rapid increase in esophageal adenocarcinomas emphasize the need to identify potential measures for the primary prevention of gastroesophageal cancers, in particular esophageal adenocarcinomas.

Recent studies concluded that smoking cessation [6, 7], alcohol avoidance [8, 9], a healthy diet [10–13], and obesity and diabetes prevention [14–16] may prevent gastroesophageal cancer. Because physical activity is closely associated with those lifestyle factors, particularly with obesity and diabetes, physical activity may plausibly be linked to decreased risk of gastroesophageal cancer. However, the epidemiologic literature regarding a protective effect of physical activity is mixed, with five [17–21]

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of twelve studies [17–28] showing an inverse association between physical activity and esophageal cancer and eight [17, 23, 24, 27, 29–32] of 21 studies [17–19, 22–27, 29–40] yielding an inverse relation to gastric cancer.

Gastroesophageal cancers show distinct etiologies according to their anatomic site and tumor histologic type [41, 42], suggesting potential differences in their relations with physical activity. However, the associations between physical activity and gastroesophageal cancers according to anatomic site and tumor histologic type have not been comprehensively quantified in a meta-analysis. We therefore conducted a systematic review and meta-analysis of physical activity in relation to gastroesophageal cancers, examining potential variation by anatomic site and tumor histology. A further goal was to perform an exploratory dose–response meta-analysis in a first attempt to produce a physical activity recommendation for the primary prevention of gastroesophageal cancers.

## Methods

### Literature search

Our systematic review and meta-analysis followed the guidelines concerning preferred reporting items for systematic reviews and meta-analyses (PRISMA) [43]. Two authors (G.B. and M.F.L.) comprehensively searched the literature using PubMed (see Supplemental Material for PubMed search options) and Web of Science to identify published non-ecologic epidemiologic studies quantifying the relation between physical activity and gastroesophageal cancer incidence or mortality. We disregarded studies of cancer survivors. Our search was complemented by a scan of the reference lists of the identified studies. We considered all human research articles published in English through mid December 2013 not classified as review, meta-analysis, editorial, comment, letter, practice guideline, or news. Articles were eligible if they reported a relative risk estimate with a corresponding 95 % confidence interval (CI) or sufficient data to calculate them and if they accounted for age and, if applicable, for sex as potential confounding factors. Our search strategy included the terms physical activity, exercise, cardiorespiratory fitness, cardiovascular fitness, lifestyle, stomach cancer, stomach carcinoma, gastric cancer, gastric carcinoma, esophageal cancer, esophageal carcinoma, cancer, risk, incidence, and mortality (see Supplemental Material for Boolean PubMed search terms). That search yielded 2,209 articles. Ineligible articles were eliminated after screening titles and abstracts (n = 2,139) or full manuscripts (n = 47). Of the 23 remaining studies [17–19, 22–27, 29, 31–40, 44–46], two [44, 45] were removed because they were updated in a subsequent analysis [33] and one mortality study [46] was excluded because incidence data [24] from the same cohort were available. Three additional studies were found by manual search in the Web of Science [20, 21, 28] and one study [30] was found in the reference lists of the identified studies. Thus, a total of 24 studies [17–40] were included in the meta-analysis.

### Data extraction

To assess potential differences in physical activity relations according to tumor histologic type and cancer anatomic site, we preferably extracted risk estimates for gastroesophageal cancer subtypes even if that meant that not all cancer cases could be considered. Specifically, we were unable to include 99 gastric cancers with an unspecified subsite from one study [23], for which no relative risks were reported. Also, we did not include the 49 gastric cardia cancers from another study [38] because risk estimates were unavailable for those cases. We extracted risk estimates for men and women separately whenever possible because men and women were considered independent samples. If studies reported on more than one physical activity domain, estimates for all domains were collected. With respect to different types of physical activity assessments, preference was given for assessments of lifelong physical activity, for assessments of vigorous physical activity, for the most comprehensive physical activity assessment, and for quantitative physical activity assessments. When there was a choice among quantitative physical activity assessments, we used frequency of physical activity because that was the most common quantitative physical activity component measured.

### Study quality score

Two previous systematic reviews on physical activity and cancer [47, 48] found that the study quality as assessed by a score proposed by Monninkhof et al. [47] affected the summary risk estimates. Thus, we employed that quality score to assess whether selection bias, misclassification, or confounding affected the summary risk estimates. In addition, we rated the degree of control for confounding by awarding points for including smoking, adiposity, and alcohol intake as major adjustment factors in the multivariate models of the underlying studies.

### Random effects meta-analysis

The odds ratios and hazard ratios presented in individual studies were interpreted as relative risk estimates ($RR_i$). These were log-transformed to $\log(RR_i)$ and their corresponding standard errors were computed as $s_i = d_i/1.96$, with $d_i$ representing the

maximum of [log(upper 95 % CI bound of $RR_i$) − log($RR_i$)] and [(log($RR_i$) − log(lower 95 % CI bound of $RR_i$)] to take into account that the log-transformed 95 % confidence interval from one study [21] was not centred at the corresponding log-transformed relative risk. We employed a random effects model using the weighted average of the log($RR_i$) expressed as $w_i = 1/(s_i^2 + t^2)$, where $s_i$ represented the standard error of log($RR_i$) and $t^2$ represented the restricted maximum likelihood estimate of the overall variance. Heterogeneity of the risk estimates was assessed using the Q- and the $I^2$-statistics [49]. Publication bias was tested using funnel plot diagnostics, Begg's test [50], and Egger's test [51].

### Stratified analyses

We investigated whether the summary risk estimate was affected by cancer major anatomic site (esophageal cancer, gastric cancer), histologic type (esophageal squamous cell carcinoma, esophageal adenocarcinoma), and anatomic subsite (gastric cardia adenocarcinoma, gastric non-cardia adenocarcinoma). We also examined potential differences according to study design (cohort, case–control), study quality score (tertiles), gender (men, women), study geographic region (North America, Europe, Australia, Asia), physical activity domain (recreational, occupational), timing in life of physical activity (recent past physical activity, distant past physical activity, consistent physical activity over time), physical activity assessment (assessment of energy expenditure, assessment of activity duration, assessment of activity frequency, and qualitative physical activity assessments using descriptive categories such as 'sedentary', 'light', 'moderate', or 'high' physical activity), and adjustments for smoking (yes, no), adiposity (yes, no), and alcohol intake (yes, no).

### Sensitivity analyses

In order to investigate whether our summary risk estimate was affected by the inclusion of multiple risk estimates from a given study, we conducted a sensitivity analysis that included only one risk estimate per gender from each study, choosing the risk estimate with the highest quality score and the gastroesophageal cancer endpoint with the largest number of cases. We conducted a further sensitivity analysis in which we omitted one study at a time from the analysis to examine whether results were affected by an individual study. Because studies used heterogeneous definitions of exposure and reference levels of physical activity, we investigated whether the summary risk estimate changed if the meta-analysis was restricted to studies with comparable definitions of exposure and reference categories. We also tested whether restriction to studies of gastroesophageal cancer incidence changed the summary risk estimate.

### Non-linear dose–response meta-analysis

Most studies [17, 19, 24, 29, 30, 32, 34, 38–40] based on quantitative physical activity assessments examined the association between frequency of moderate to vigorous recreational physical activity and gastroesophageal cancer risk. Five of those studies [24, 29, 32, 34, 38] provided sufficient information to be included in a non-linear dose–response meta-analysis [52].

All statistical analyses were performed in R [53] using the R-packages 'metafor' [54] and 'mvmeta' [55]. Risk estimates are reported with 95 % confidence intervals. Statistical significance was based on the 5 % significance level.

## Results

### Study characteristics

Table 1 presents the main characteristics of the nine cohort and 15 (non-nested) case–control studies of physical activity and gastroesophageal cancer included in the meta-analysis. Those studies comprised a total of 15,745 cases. Ten studies [17–19, 22–27, 29] examined more than one gastroesophageal endpoint, four studies [19, 23, 37, 39] investigated more than one physical activity domain, four studies [17, 20, 25, 31] presented results stratified by gender, one study [29] presented results stratified by geographic region, and one study [30] reported results stratified by family history of gastric cancer. Thus, the 24 studies reported 61 individual risk estimates.

All cohort studies examining recent past physical activity in relation to gastroesophageal cancer assessed the usual level of physical activity at baseline [23, 24, 26, 27, 31, 33, 37, 38], whereas case–control studies queried about physical activity performed at cancer incidence [18, 21, 22, 28, 34, 35, 39, 40], one year [32] or 2 years [29] before cancer incidence or before symptoms appeared [30]. By comparison, studies investigating distant past physical activity inquired about the level of physical activity ten or more years prior to baseline [36] (cohort study) or cancer incidence [17, 19, 20] (case–control studies).

### Main analysis

We summarized associations according to gastroesophageal cancer anatomic site and histology (Fig. 1). High levels of physical activity showed statistically significant inverse

**Table 1** Characteristics of the 9 cohort studies and 15 case–control studies on physical activity and esophageal and gastric cancer risk included in the meta-analysis grouped by study design

Cohort studies

| Authors, year, gender | Study geo-graphic region | Participants | Cases | Esophageal and gastric cancer site and type | Physical activity domain, timing in life | Relative risk (95 % CI), high versus low physical activity | Low physical activity defined by | High physical activity defined by | Adjustment factors (excluding age, sex) | Study quality score (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| *Batty et al. 2010 [33]* | | | | | | | | | | |
| Men | Europe | 6,715 | 101 | Gastric adenocarcinoma, subsite unspecified, fatal | Recreational, recent | **0.65 (0.38, 1.14)** | Not engaging in MVPA | Engaging in VPA | Forced expiratory volume in 1 s, obesity (BMI), SES (employment grade), smoking | 67 |
| *Huerta et al. 2010 [23]* | | | | | | | | | | |
| Men and women | Europe | 420,449 | 80 | Esophageal adenocarcinoma, non-fatal | Total, recent | 0.98 (0.48, 2.01) | Physically inactive | Physically active | Alcohol intake, height, energy intake, fruit intake, meat intake (red/processed), obesity (weight), SES (education), smoking | 79 |
| | | | | | Recreational, recent | 0.72 (0.36, 1.42) | No VPA | More than 2 h of VPA per week | | 78 |
| | | | | | Occupational, recent | 0.95 (0.41, 2.20) | Sedentary occupation | Manual work | | 73 |
| | | | 123 | Gastric cardia adenocarcinoma, non-fatal | Total, recent | 1.05 (0.59, 1.86) | See above | See above | | 79 |
| | | | | | Recreational, recent | 1.14 (0.68, 1.91) | See above | See above | | 78 |
| | | | | | Occupational, recent | 0.70 (0.33, 1.48) | See above | See above | | 73 |
| | | | 188 | Gastric non-cardia adenocarcinoma, non-fatal | Total, recent | **0.44 (0.26, 0.74)** | See above | See above | | 79 |
| | | | | | Recreational, recent | 0.98 (0.60, 1.60) | See above | See above | | 78 |
| | | | | | Occupational, recent | 0.82 (0.44, 1.52) | See above | See above | | 73 |
| *Inoue et al. 2008 [31]* | | | | | | | | | | |
| Men | Asia | 37,898 | 621 | Gastric adenocarcinoma, subsite unspecified, non-fatal or fatal | Total, recent | **1.04 (0.84, 1.29)** | Less than 27 METs per day | More than 36 METs per day | Alcohol intake, energy intake, history of type 2 diabetes mellitus, obesity (BMI), recreational physical activity (frequency), smoking, study center | 79 |
| Women | | 41,873 | 232 | Gastric adenocarcinoma, subsite unspecified, non-fatal or fatal | Total, recent | **0.63 (0.42, 0.94)** | | | | 79 |

**Table 1** continued

| Cohort studies | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Authors, year, gender | Study geo-graphic region | Participants | Cases | Esophageal and gastric cancer site and type | Physical activity domain, timing in life | Relative risk (95 % CI), high versus low physical activity | Low physical activity defined by | High physical activity defined by | Adjustment factors (excluding age, sex) | Study quality score (%) |
| *Leitzmann et al. 2009 [24]* | | | | | | | | | | |
| Men and women | North America | 487,732 | 149 | Esophageal squamous cell carcinoma, non-fatal | Recreational, recent | 1.05 (0.64, 1.74) | Never/rarely engaging in VPA | Engaging in VPA 5 times per week or more (for 20 min or more) | Alcohol intake, family history of cancer, fruit and vegetable intake, meat intake (red meat), marital status, obesity (BMI), race/ethnicity, SES (education), smoking | 72 |
| | | | 374 | Esophageal adenocarcinoma, non-fatal | Recreational, recent | **0.75 (0.53, 1.06)** | | | | 72 |
| | | | 313 | Gastric cardia adenocarcinoma, non-fatal | Recreational, recent | 0.83 (0.58, 1.19) | | | | 72 |
| | | | 329 | Gastric non-cardia adenocarcinoma, non-fatal | Recreational, recent | 0.62 (0.44, 0.87) | | | | 72 |
| *Paffenbarger et al. 1987 [36]* | | | | | | | | | | |
| Men | North America | 56,683 | 41 | Gastric adenocarcinoma, subsite unspecified, non-fatal or fatal | Recreational, past | **1.05 (0.50, 2.21)** | Less than 5 h of VPA per week | 5 h of VPA per week or more | Birth year | 61 |
| *Severson et al. 1989 [37]* | | | | | | | | | | |
| Men | North America | 7,925 | 172 | Gastric adenocarcinoma, subsite unspecified, non-fatal | Total, recent | **1.34 (0.92, 1.95)** | Lower tertile of daily energy-expenditure index | Upper tertile of daily energy-expenditure index | Obesity (BMI), smoking | 70 |
| | | | | | Recreational, recent | 1.45 (1.07, 1.97) | Sedentary occupation | Moderate to heavy work | | 59 |
| | | | | | Occupational, recent | 1.74 (1.08, 2.81) | Sedentary occupation | Moderate to heavy work | | 59 |
| *Sjödahl et al. 2008 [38]* | | | | | | | | | | |
| Men and women | Europe | 73,133 | 264 | Gastric non-cardia adenocarcinoma, non-fatal | Recreational, recent | **0.70 (0.50, 1.00)** | Engaging in MVPA less than once per week | Engaging in MVPA more than twice per week | Alcohol intake, obesity (BMI), salt intake, SES (job), smoking | 70 |

**Table 1** continued

Cohort studies

| Authors, year, gender | Study geo-graphic region | Participants | Cases | Esophageal and gastric cancer site and type | Physical activity domain, timing in life | Relative risk (95 % CI), high versus low physical activity | Low physical activity defined by | High physical activity defined by | Adjustment factors (excluding age, sex) | Study quality score (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| *Wannamethee et al. 2001 [26]* | | | | | | | | | | |
| Men | Europe | 7,588 | 65 | Esophageal cancer, type unspecified, non-fatal or fatal | Recreational, recent | **0.46 (0.11, 1.90)** | No or moderate PA | High PA | Alcohol intake, obesity (BMI), SES (job), smoking | 74 |
| | | | 59 | Gastric adenocarcinoma, subsite unspecified, non-fatal or fatal | Recreational, recent | 0.60 (0.14, 2.47) | | | | 74 |
| *Yun et al. 2008 [27]* | | | | | | | | | | |
| Men | Asia | 444,963 | 293 | Esophageal cancer, type unspecified, non-fatal | Recreational, recent | 0.84 (0.66, 1.06) | Combination of MVPA frequency and duration: MVPA less than 4 times per week and less than 30 min per session | Combination of MVPA frequency and duration: MVPA at least 2 times per week for at least 30 min per session or, alternatively, at least 5 times per week for less than 30 min per session | Alcohol intake, fruit and vegetable intake (healthy dietary pattern), history of diabetes (fasting glucose level), obesity (BMI), SES (employment), smoking | 67 |
| | | | 3,633 | Gastric adenocarcinoma, subsite unspecified, non-fatal | Recreational, recent | **0.91 (0.86, 0.98)** | | | | 67 |

**Table 1** continued

Case–control studies

| Authors, year, gender | Study geographic region | Controls | Cases | Esophageal and gastric cancer site and type | Physical activity domain, timing in life | Relative risk (95 % CI), high versus low physical activity | Low physical activity defined by | High physical activity defined by | Adjustment factors (excluding age, sex) | Study quality score (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| *Boccia et al. 2005 [34]* | | | | | | | | | | |
| Men and women | Europe | 255 | 74 | Gastric adenocarcinoma, subsite unspecified, non-fatal | Recreational, recent | **0.97 (0.45, 2.09)** | Never engaging in physical activity | Engaging in physical activity 5 or more times per week | – | 49 |
| *Brownson et al. 1991 [22]* | | | | | | | | | | |
| Men | North America | 16,910 | 237 | Esophageal cancer, type unspecified, non-fatal | Occupational, recent | 1.43 (0.71, 3.33) | Low PA | High PA | Smoking | 45 |
| | | 16,789 | 358 | Gastric adenocarcinoma, subsite unspecified, non-fatal | Occupational, recent | **0.71 (0.45, 1.11)** | | | | 45 |
| *Campbell et al. 2007, non-Ontario sample [29]* | | | | | | | | | | |
| Men and women | North America | 3100 | 636 | Gastric adenocarcinoma, subsite unspecified, non-fatal | Recreational, recent | **0.67 (0.53, 0.86)** | Lowest VPA quartile | Highest VPA quartile | Meat intake (Western dietary pattern), obesity (BMI), SES (education), smoking | 53 |
| *Campbell et al. 2007, Ontario sample [29]* | | | | | | | | | | |
| Men and women | North America | 1,387 | 144 | Gastric cardia adenocarcinoma, non-fatal | Recreational, consistent | 0.60 (0.34, 1.07) | Lowest lifetime VPA quartile | Highest lifetime VPA quartile | Meat intake (Western dietary pattern), obesity (BMI), SES (education), smoking | 68 |
| | | | 401 | Gastric non-cardia adenocarcinoma, non-fatal | Recreational, consistent | **0.73 (0.50, 1.07)** | | | | 68 |

**Table 1** continued

| Case–control studies | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Authors, year, gender | Study geo-graphic region | Controls | Cases | Esophageal and gastric cancer site and type | Physical activity domain, timing in life | Relative risk (95 % CI), high versus low physical activity | Low physical activity defined by | High physical activity defined by | Adjustment factors (excluding age, sex) | Study quality score (%) |
| *Dar et al. 2013 [28]* | | | | | | | | | | |
| Men and women | Asia | 1,663 | 703 | Esophageal squamous cell carcinoma, non-fatal | Occupational, recent | **5.65 (3.49, 9.12)** | Sedentary | Very active | Alcohol intake, fruit and vegetable intake, place of residence, race/ethnicity, religion, SES (education), smoking (cigarettes, hookah, bidi), tobacco chewing (nass, gutka) | 61 |
| *Dosemeci et al. 1993 [35]* | | | | | | | | | | |
| Men | Europe | 2,127 | 224 | Gastric adenocarcinoma, subsite unspecified, non-fatal | Occupational, recent | **0.91 (0.59, 1.67)** | Energy expenditure < 8 kJ/min | Energy expenditure > 12 kJ/min | Smoking, SES (occupation) | 47 |
| *Etemadi et al. 2012 [20]* | | | | | | | | | | |
| Men | Middle East | 278 | 150 | Esophageal squamous cell carcinoma, non-fatal | Occupational, past | **0.53 (0.26, 1.11)** | Sedentary | Very active | Age of first adult tooth loss, family history of esophageal cancer, obesity (BMI at age 15 years), opium use, SES (education), smoking, use of piped water | 49 |
| Women | | 293 | 150 | | | **0.30 (0.12, 0.77)** | | | | 49 |
| *Huang et al. 2004, family history of gastric cancer [30]* | | | | | | | | | | |
| Men and women | Asia | 6,310 | 464 | Gastric adenocarcinoma, subsite unspecified, non-fatal | Recreational, recent | **0.71 (0.57, 0.89)** | Less than 3 times per month of physical activity | 3 times per month or more of physical activity | – | 45 |
| *Huang et al. 2004, no family history of gastric cancer [30]* | | | | | | | | | | |
| Men and women | Asia | 44,396 | 1,524 | Gastric adenocarcinoma, subsite unspecified, non-fatal | Recreational, recent | **0.79 (0.70, 0.89)** | Less than 3 times per month of physical activity | 3 times per month or more of physical activity | – | 45 |

**Table 1** continued

Case–control studies

| Authors, year, gender | Study geo-graphic region | Controls | Cases | Esophageal and gastric cancer site and type | Physical activity domain, timing in life | Relative risk (95 % CI), high versus low physical activity | Low physical activity defined by | High physical activity defined by | Adjustment factors (excluding age, sex) | Study quality score (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| *Ibiebele et al. 2012 [18]* | | | | | | | | | | |
| Men and women | Australia | 1,507 | 245 | Esophageal squamous cell carcinoma, non-fatal | Recreational, recent | 0.65 (0.47, 0.91) | Low PA | High PA | – | 49 |
| | | | 299 | Esophageal adenocarcinoma, non-fatal | Recreational, recent | 0.81 (0.58, 1.12) | | | | 49 |
| | | | 336 | Esophago-gastric junction adenocarcinoma, non-fatal | Recreational, recent | **0.92 (0.67, 1.26)** | | | | 49 |
| *Jessri et al. 2011 [21]* | | | | | | | | | | |
| Men and women | Middle East | 96 | 47 | Esophageal squamous cell carcinoma, non-fatal | Total, recent | **0.93 (0.25, 0.96)** | Low PA | High PA | Energy intake, history of gastroesophageal reflux, medication, obesity (BMI), SES (education), smoking | 49 |
| *Lam et al. 2004 [17]* | | | | | | | | | | |
| Men | Asia | 3,918 | 235 | Esophageal cancer, type unspecified, fatal | Recreational, past | 0.57 (0.41, 0.80) | Engaging in MVPA less than once per month | Engaging in MVPA at least once per month | Alcohol intake, occupational physical activity, SES (education), smoking | 60 |
| | | | 369 | Gastric adenocarcinoma, subsite unspecified, fatal | Recreational, past | **0.76 (0.60, 0.96)** | | | | 60 |
| Women | | 9,136 | 54 | Esophageal cancer, type unspecified, fatal | Recreational, past | 0.52 (0.28, 0.97) | | | | 60 |
| | | | 200 | Gastric adenocarcinoma, subsite unspecified, fatal | Recreational, past | **0.57 (0.41, 0.78)** | | | | 60 |

**Table 1** continued

Case–control studies

| Authors, year, gender | Study geo-graphic region | Controls | Cases | Esophageal and gastric cancer site and type | Physical activity domain, timing in life | Relative risk (95 % CI), high versus low physical activity | Low physical activity defined by | High physical activity defined by | Adjustment factors (excluding age, sex) | Study quality score (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| *Parent et al. 2011 [19]* | | | | | | | | | | |
| Men | North America | 533 | 99 | Esophageal cancer, type unspecified, non-fatal | Total, consistent | 0.54 (0.31, 0.93) | Less than 1.5 METs at work independent of leisure time PA or 1.5–3.9 METs at work and less than once per week engaged in leisure time MVPA | Energy expenditure of 4 METs per day or more at work independent of leisure time PA or 1.6–3.9 METs per day at work and at least once per week engaged in leisure time MVPA | Alcohol intake, beta-carotene intake, coffee intake (in models of esophageal cancer only), obesity (BMI), proxy respondent, race/ethnicity, recreational/occupational activity (mutual adjustment), SES (socio-economic status, education), smoking, tea intake (in models of esophageal cancer only) | 73 |
| | | | | | Recreational, past | 0.54 (0.30, 0.97) | MVPA less than once per week | MVPA at least once per week | | 70 |
| | | | | | Occupational, consistent | 0.66 (0.23, 1.88) | 1.5 METs or less of energy expenditure | Energy expenditure of 4 METs or more | | 69 |
| | | | 251 | Gastric adenocarcinoma, subsite unspecified, non-fatal | Total, consistent | **0.93 (0.67, 1.31)** | See above | See above | | 73 |
| | | | | | Recreational, past | 1.09 (0.76, 1.54) | See above | See above | | 70 |
| | | | | | Occupational, consistent | 0.68 (0.35, 1.32) | See above | See above | | 69 |
| *Suwanrungruang et al. 2008 [39]* | | | | | | | | | | |
| Men and women | Asia | 202 | 101 | Gastric adenocarcinoma, subsite unspecified, non-fatal | Recreational, recent | **0.70 (0.33, 1.33)** | Exercising less than 3 times per week | Exercising 3 times or more per week | – | 49 |
| | | | | | Occupational, recent | 0.52 (0.23, 1.17) | Sedentary occupation | Heavy work | | 42 |

**Table 1** continued

Case–control studies

| Authors, year, gender | Study geo-graphic region | Controls | Cases | Esophageal and gastric cancer site and type | Physical activity domain, timing in life | Relative risk (95 % CI), high versus low physical activity | Low physical activity defined by | High physical activity defined by | Adjustment factors (excluding age, sex) | Study quality score (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| *Vigen et al. 2006 [25]* | | | | | | | | | | |
| Men | North America | 988 | 192 | Esophageal adenocarcinoma, non-fatal | Occupational, consistent | 0.77 (0.54, 1.08) | Lifetime occupational PA averaged over years worked prior to age 65 years less than median | Lifetime occupational PA averaged over years worked prior to age 65 years equal to or greater than median | Birth place, obesity (BMI), race/ethnicity, SES (education), smoking status | 58 |
| | | | 221 | Gastric cardia adenocarcinoma, non-fatal | Occupational, consistent | 0.81 (0.58, 1.11) | | | | 58 |
| | | | 235 | Gastric non-cardia adenocarcinoma, non-fatal | Occupational, consistent | **0.77 (0.55, 1.07)** | | | | 58 |
| Women | | 342 | 20 | Esophageal adenocarcinoma, non-fatal | Occupational, consistent | 0.35 (0.04, 3.15) | | | | 58 |
| | | | 43 | Gastric cardia adenocarcinoma, non-fatal | Occupational, consistent | 0.30 (0.07, 1.40) | | | | 58 |
| | | | 154 | Gastric non-cardia adenocarcinoma, non-fatal | Occupational, consistent | **1.07 (0.59, 1.91)** | | | | 58 |
| *Watabe et al. 1998 [40]* | | | | | | | | | | |
| Men and women | Asia | 484 | 242 | Gastric adenocarcinoma, subsite unspecified, non-fatal | Recreational, recent | **0.94 (0.68, 1.32)** | Engaging in MVPA less than once per week | Engaging in MVPA at least once per week | Place of residence | 48 |
| *Wen et al. 2010 [32]* | | | | | | | | | | |
| Men and women | Asia | 600 | 300 | Gastric adenocarcinoma, subsite unspecified, non-fatal | Recreational, recent | **0.69 (0.51, 0.99)** | Not engaging in MVPA | Engaging in MVPA at least 4 times per week | Alcohol intake, family history of cancer, fruit and vegetable intake, obesity (BMI), smoking | 58 |

The bold risk estimates (N = 30) represent those risk estimates included in the rigorous sub-analysis allowing just one estimate per study and gender

*RR* relative risk, *CI* confidence interval, *PA* physical activity, *MVPA* moderate to vigorous physical activity, *VPA* vigorous physical activity, *MET* metabolic equivalent of task, *BMI* body mass index, *SES* socio-economic status

relations to gastric non-cardia adenocarcinoma (RR = 0.72, 95 % CI = 0.62–0.84), gastric cardia adenocarcinoma (RR = 0.83, 95 % CI = 0.69–0.99), and esophageal adenocarcinoma (RR = 0.79, 95 % CI = 0.66–0.94). No statistically significant association was observed for esophageal squamous cell carcinoma (RR = 0.94, 95 % CI = 0.41–2.16). No overall differences in the relations of physical activity to esophageal squamous cell carcinoma, esophageal adenocarcinoma, gastric cardia adenocarcinoma, and gastric non-cardia adenocarcinoma were observed ($p$-difference = 0.71). Similarly, comparing the relation of physical activity to esophageal adenocarcinoma with that to esophageal squamous cell carcinoma ($p$-difference = 0.61) and comparing the relation of physical activity to gastric non-cardia adenocarcinoma with that to gastric cardia adenocarcinoma ($p$-difference = 0.26) revealed no statistically significant differences.

Combining all 61 risk estimates in a random effects model, we observed a statistically significant 18 % reduction in gastroesophageal cancer risk when comparing high versus low levels of physical activity (RR = 0.82, 95 % CI = 0.74–0.90). A funnel plot (supplementary Figure S1), Begg's test ($p = 0.95$), and Egger's test ($p = 0.19$) suggested no publication bias. The funnel plot, though, identified one extreme risk estimate [28]. We detected statistically significant heterogeneity between studies ($I^2 = 76$ %, $p$-heterogeneity $< 0.001$).

## Stratified analyses

The relation of physical activity to gastroesophageal cancer was statistically significantly inverse in case–control studies (RR = 0.77, 95 % CI = 0.67–0.89), whereas it was statistically non-significant in cohort studies (RR = 0.89, 95 % CI = 0.78–1.01; $p$-difference = 0.18, Fig. 2).

A direct comparison between women and men revealed a stronger inverse association between physical activity and gastroesophageal cancer in women (RR = 0.60, 95 % CI = 0.48–0.73) than men (RR = 0.87, 95 % CI = 0.77–0.98; $p$-difference = 0.01) (Fig. 3), but modelling the effect of gender did not materially attenuate between-study heterogeneity ($I^2 = 72$ %, $p$-heterogeneity $< 0.001$). In contrast, no statistically significant differences in relations were observed for study quality score, study geographic region, physical activity domain, timing in life of physical activity, physical activity assessment, and adjustments for smoking, adiposity, or alcohol intake (all $p$-difference $> 0.05$) (Table 2).

In sub-analyses of total esophageal cancer (supplementary Table S1), the relations of distant past physical activity (RR = 0.53, 95 % CI = 0.42–0.67) and consistent physical activity over time (RR = 0.68, 95 % CI = 0.51–0.91) were statistically significant inverse, while that of recent past physical activity was not (RR = 1.01, 95 % CI = 0.70–1.47; $p$-difference = 0.04).

Sub-analyses examining the relation of physical activity to total gastric cancer (supplementary Table S2) revealed that the inverse association was statistically significant in case–control studies (RR = 0.77, 95 % CI = 0.72–0.82) but not in cohort studies (RR = 0.90, 95 % CI = 0.76–1.06; $p$-difference = 0.04). Similarly, the inverse association of physical activity to gastric cancer was statistically non-significant in men (RR = 0.95, 95 % CI = 0.84–1.08) but it was statistically significant in women (RR = 0.64, 95 % CI = 0.50–0.84; $p$-difference = 0.02).

## Sensitivity analyses

In a sensitivity analysis, we generated a summary risk estimate that included only one risk estimate per study and gender, using the risk estimate with the highest quality score for the gastroesophageal cancer endpoint with the largest number of cases. The 30 selected risk estimates are printed in bold in Table 1. We found no difference between that summary risk estimate (RR = 0.82, 95 % CI = 0.70–0.95) and our summary risk estimate from the main analysis (RR = 0.82, 95 % CI = 0.74–0.90; $p$-difference = 0.96).

We tested for influential studies by removing one study at a time from the meta-analysis and observed no material differences in the summary risk estimates for total gastroesophageal cancer, for total esophageal cancer or for total gastric cancer. Similarly, we observed no material changes in the modifying effects of study design and gender on the physical activity and gastroesophageal cancer relation. After excluding the study by Dar et al. [28] from the main analysis, the previously observed between-study heterogeneity was substantially attenuated ($I^2 = 51$ %, $p$-heterogeneity $< 0.001$) and the inverse association between physical activity and esophageal squamous cell carcinoma became statistically significant (RR = 0.66, 95 % CI = 0.46–0.96). After additionally including terms for study design and gender in the model, the heterogeneity between studies was no longer apparent ($I^2 = 0$ %, $p$-heterogeneity = 0.08).

We identified four studies [23, 24, 32, 34] of recreational physical activity and gastroesophageal cancer whose exposure and reference levels could be considered comparable. Those studies compared participants engaging in 2 h per week or more of recreational physical activity with those not regularly engaging in recreational physical activity. The summary risk estimate combining those studies (RR = 0.79, 95 % CI = 0.69–0.91) did not statistically significantly differ from the risk estimate that was based on all studies of recreational physical activity (RR = 0.78, 95 % CI = 0.72–0.85; $p$-difference = 0.97) or from the risk estimate from our main analysis (RR = 0.82, 95 % CI = 0.74–0.90; $p$-difference = 0.80).

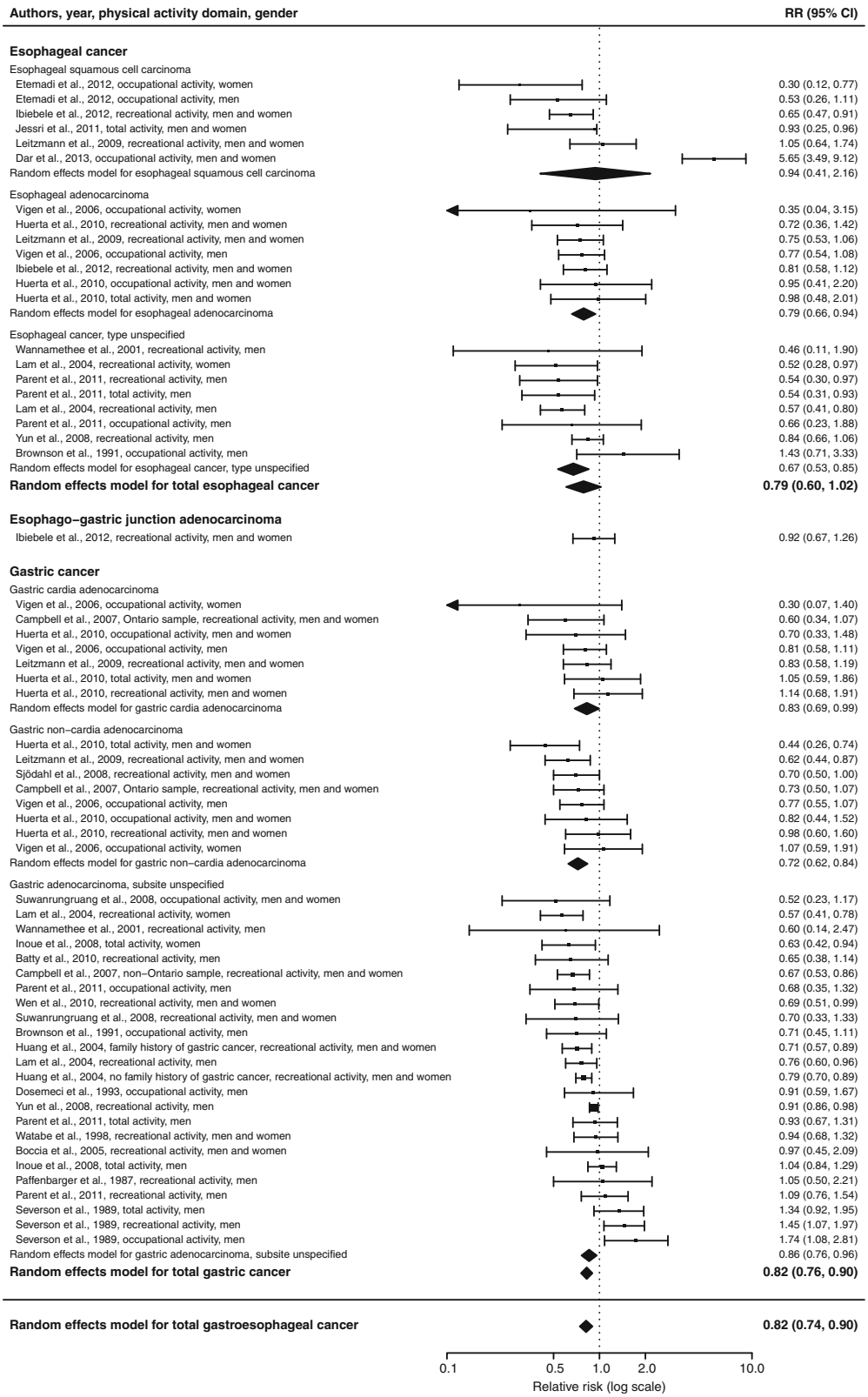


**Fig. 1** Forest plot of a random effects meta-analysis including 61 risk estimates of gastroesophageal cancer for a high versus low level of physical activity, grouped by anatomic site and histologic type. *RR* relative risk, *CI* confidence interval

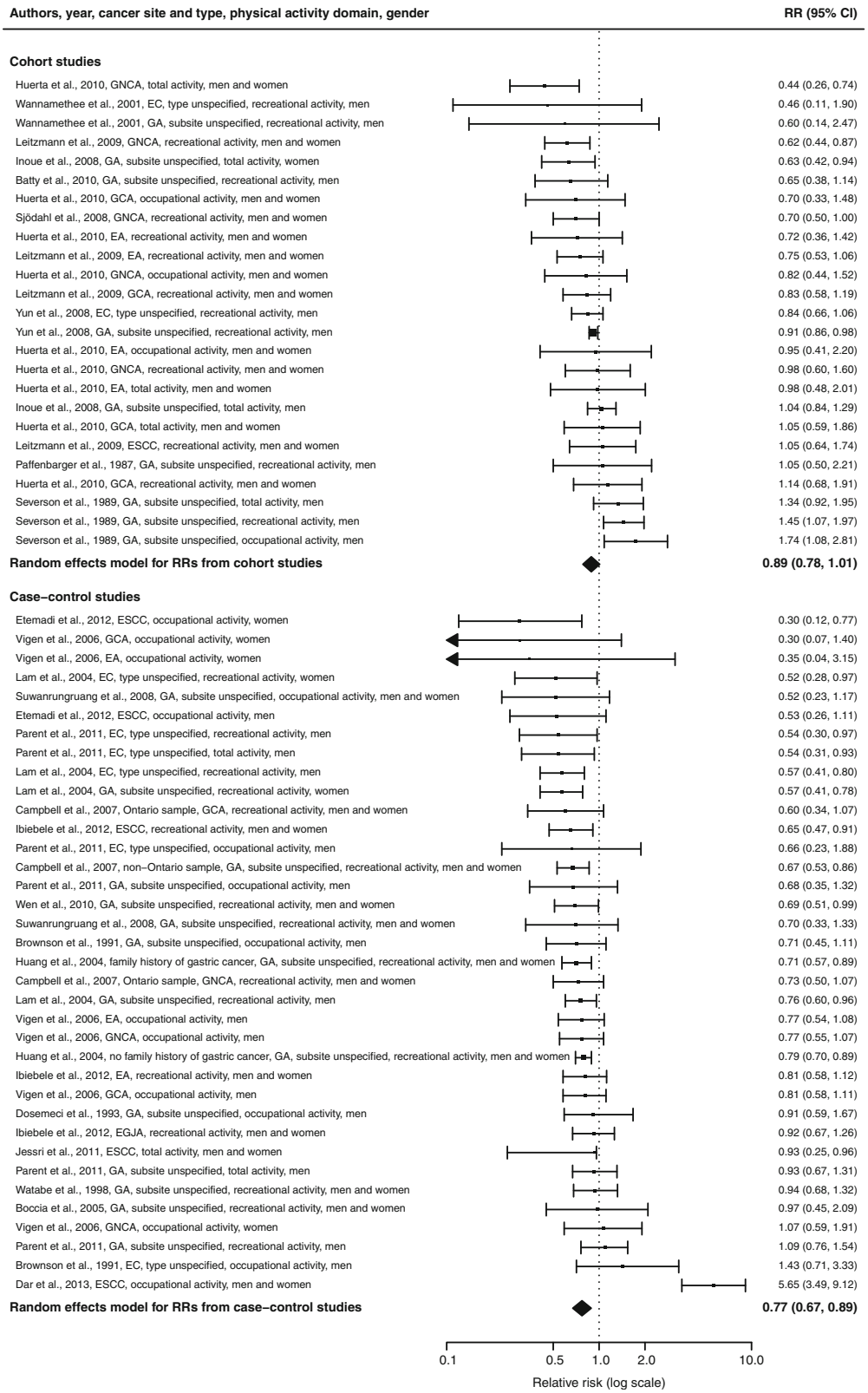


**Fig. 2** Forest plot of a random effects meta-analysis including 61 risk estimates of total gastroesophageal cancer for a high versus low level of physical activity, grouped by study design. *RR* relative risk, *CI* confidence interval, *ESCC* esophageal squamous cell carcinoma, *EA* esophageal adenocarcinoma, *EC* esophageal cancer, *GCA* gastric cardia adenocarcinoma, *GNCA* gastric non-cardia adenocarcinoma, *GA* gastric adenocarcinoma

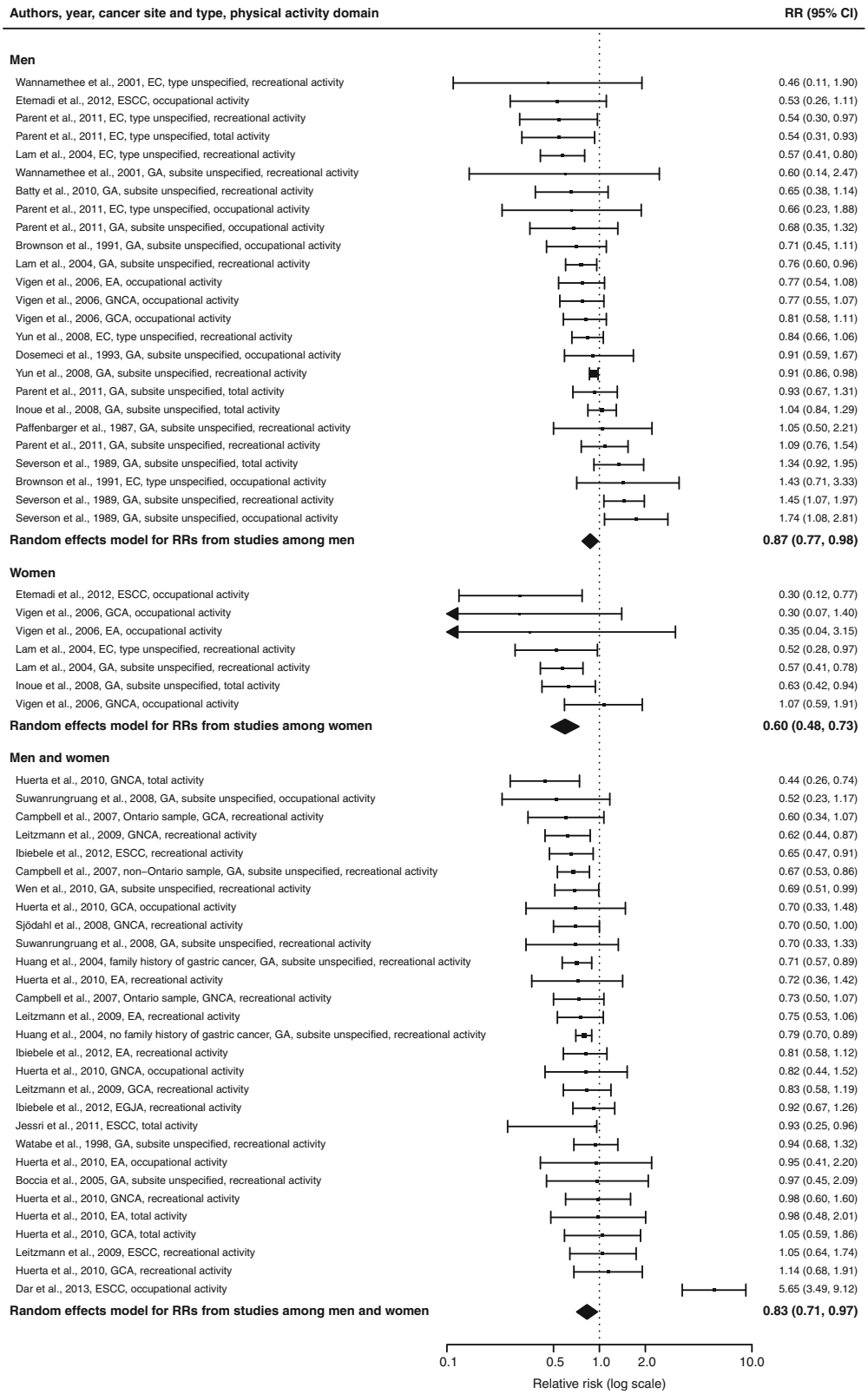


**Fig. 3** Forest plot of a random effects meta-analysis including 61 risk estimates of total gastroesophageal cancer for a high versus low level of physical activity, grouped by gender. *RR* relative risk, *CI* confidence interval, *ESCC* esophageal squamous cell carcinoma, *EA* esophageal adenocarcinoma, *EC* esophageal cancer, *GCA* gastric cardia adenocarcinoma, *GNCA* gastric non-cardia adenocarcinoma, *GA* gastric adenocarcinoma

**Table 2** Random effects summary estimates of total gastroesophageal cancer risk for a high versus low level of physical activity by selected study characteristics

| Stratification criterion | Number of included RRs | RR[a] (95 % CI) | *p*-difference[b] |
|---|---|---|---|
| Total gastroesophageal cancer risk | 61 | 0.82 (0.74, 0.90) | |
| *Cancer major anatomic site* | | | |
| Esophageal cancer | 21 | 0.79 (0.60, 1.02) | |
| Esophago-gastric junction adenocarcinoma | 1 | 0.92 (0.67, 1.26) | |
| Gastric cancer | 39 | 0.82 (0.76, 0.90) | 0.92[c] |
| *Cancer anatomic subsite and histologic type* | | | |
| Esophageal squamous cell carcinoma | 6 | 0.94 (0.41, 2.16) | |
| Esophageal adenocarcinoma | 7 | 0.79 (0.66, 0.94) | 0.61[d] |
| Esophageal cancer, type unspecified | 8 | 0.67 (0.53, 0.85) | |
| Esophago-gastric junction adenocarcinoma | 1 | 0.92 (0.67, 1.26) | |
| Gastric cardia adenocarcinoma | 7 | 0.83 (0.69, 0.99) | |
| Gastric non-cardia adenocarcinoma | 8 | 0.72 (0.62, 0.84) | 0.26[e] |
| Gastric adenocarcinoma, subsite unspecified | 24 | 0.86 (0.76, 0.96) | |
| *Study design* | | | |
| Cohort | 25 | 0.89 (0.78, 1.01) | |
| Case–control | 36 | 0.77 (0.67, 0.89) | 0.18 |
| *Study quality score*[f] | | | |
| Upper tertile of quality score | 19 | 0.81 (0.71, 0.92) | |
| Intermediate tertile of quality score | 19 | 0.90 (0.70, 1.16) | |
| Lower tertile of quality score | 23 | 0.77 (0.72, 0.82) | 0.32 |
| *Gender* | | | |
| Men | 25 | 0.87 (0.77, 0.98) | |
| Women | 7 | 0.60 (0.48, 0.73) | 0.01[g] |
| Men and women | 29 | 0.83 (0.71, 0.97) | |
| *Study geographic region* | | | |
| North America | 25 | 0.85 (0.75, 0.97) | |
| Europe | 15 | 0.80 (0.68, 0.93) | |
| Australia | 3 | 0.79 (0.64, 0.96) | |
| Middle East | 3 | 0.48 (0.29, 0.81) | |
| Asia | 15 | 0.82 (0.63, 1.08) | 0.58 |
| *Physical activity domain* | | | |
| Total activity | 9 | 0.84 (0.65, 1.08) | |
| Recreational activity | 33 | 0.78 (0.72, 0.85) | |
| Occupational activity | 19 | 0.86 (0.64, 1.16) | 0.19[h] |
| *Timing in life of physical activity* | | | |
| Recent past physical activity | 40 | 0.88 (0.78, 1.00) | |
| Distant past physical activity | 9 | 0.66 (0.53, 0.82) | |
| Consistent physical activity over time | 12 | 0.77 (0.67, 0.88) | 0.06 |
| *Physical activity assessment* | | | |
| Assessment of energy expenditure | 10 | 0.91 (0.86, 0.96) | |
| Assessment of activity duration | 4 | 0.98 (0.74, 1.32) | |
| Assessment of activity frequency | 19 | 0.74 (0.69, 0.80) | |
| Qualitative physical activity assessment | 28 | 0.85 (0.68, 1.05) | 0.33 |
| *Adjustment for smoking* | | | |
| Adjusted for smoking | 51 | 0.82 (0.73, 0.92) | |
| Not adjusted for smoking | 10 | 0.79 (0.72, 0.86) | 0.78 |
| *Adjustment for adiposity* | | | |
| Adjusted for adiposity | 43 | 0.82 (0.74, 0.90) | |
| Not adjusted for adiposity | 18 | 0.85 (0.67, 1.08) | 0.67 |
| *Adjustment for alcohol intake* | | | |
| Adjusted for alcohol intake | 32 | 0.81 (0.69, 0.94) | |
| Not adjusted for alcohol intake | 29 | 0.83 (0.74, 0.93) | 0.87 |

*RR* relative risk, *CI* confidence interval, *MVPA* moderate to vigorous physical activity

[a] RR comparing highest versus lowest physical activity level

[b] The *p*-difference values were obtained using meta-regression comparing the model including the stratification variable as explanatory variable with the null model not including any explanatory variables

[c] Comparing risk estimates of total esophageal cancer with risk estimates of total gastric cancer disregarding risk estimates of esophago-gastric junction adenocarcinoma

[d] Comparing risk estimates of esophageal squamous cell carcinoma with risk estimates of esophageal adenocarcinoma and disregarding risk estimates of esophageal cancers with unspecified histologic type

[e] Comparing risk estimates of gastric cardia adenocarcinoma with risk estimates of gastric non-cardia adenocarcinoma and disregarding risk estimates of gastric adenocarcinoma with unspecified anatomic subsite

[f] The quality score ranged from 42 to 79 percentage points (out of 100 percentage points), with lower and upper tertile cut-offs of 58 percentage points and 70 percentage points, respectively

[g] Comparing risk estimates of men with risk estimates of women and disregarding risk estimates of men and women combined

[h] Comparing risk estimates of recreational activity with risk estimates of occupational activity and disregarding risk estimates of total activity

When we excluded two studies on gastroesophageal cancer mortality [17, 33] and three studies using fatal and non-fatal gastroesophageal cancers as a combined endpoint [26, 31, 36], we obtained a summary risk estimate of RR = 0.83 (95 % CI = 0.77–0.89), which was comparable to that of the main analysis (*p*-difference = 0.62).

## Dose–response meta-analysis

We conducted a random-effects dose–response meta-analysis to further explore the relation between frequency of moderate

to vigorous physical activity and gastroesophageal cancer (Fig. 4). The best fitting dose–response model was given by

$$RR = \exp(a_1 dose^2 + a_2 dose^3),$$

where $a_1 = -0.051$, $a_2 = 0.007$, $var(a_1) = 1 \times 10^{-4}$, $cov(a_1, a_2) = -2 \times 10^{-5}$, and $var(a_2) = 3 \times 10^{-6}$, and no heterogeneity between studies was observed ($I^2 = 8$ %, $p$-heterogeneity = 0.36). The J-shaped dose–response relation indicated that a maximal reduction in gastroesophageal cancer risk of 33 % was attained by engaging in moderate to vigorous physical activity at a frequency of five times per week (RR = 0.67, 95 % CI = 0.58–0.79) as compared to not engaging in moderate or vigorous physical activity.

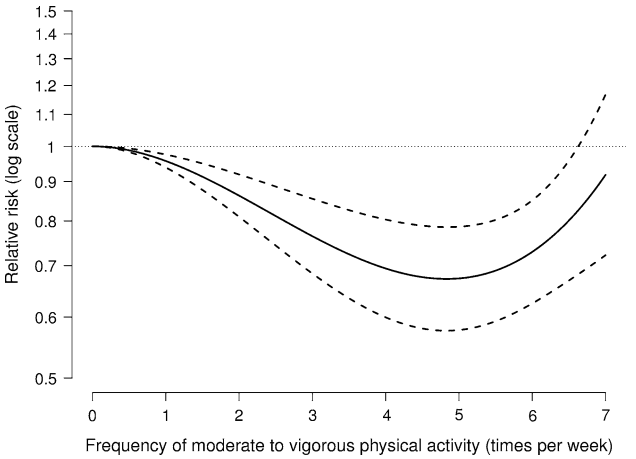


**Fig. 4** Dose-response analysis of frequency of moderate to vigorous physical activity in relation to total gastroesophageal cancer

## Discussion

We conducted a random effects meta-analysis of physical activity in relation to gastroesophageal cancer and found that high versus low physical activity was associated with risk decreases of 17–28 % for esophageal adenocarcinoma, gastric cardia adenocarcinoma, and gastric non-cardia adenocarcinoma, whereas no relation was detected for esophageal squamous cell carcinoma. However, apparent differences in risk across tumor subtypes were not statistically significant. When combining gastroesophageal cancer subsites, we observed a statistically significant 18 % reduction in total gastroesophageal cancer risk with high versus low levels of physical activity. Our dose–response meta-analysis showed that the greatest risk reduction of 33 % was achieved by engaging in moderate to vigorous activity at a frequency of five times per week.

We initially observed substantial between-study heterogeneity, which was no longer apparent after removing an influential study [28] and additionally including terms for study design and gender in the model. The authors of that influential, large hospital-based case–control study from Kashmir, India [28] compared high versus low levels of occupational physical activity and reported an odds ratio of 5.65 (95 % CI = 3.49–9.12) for esophageal squamous cell carcinoma but speculated about the possibility of residual confounding by socioeconomic status. After excluding that study [28], we found that physical activity was related to a substantial risk reduction of 34 % for esophageal squamous cell carcinoma.

Numerous biologic mechanisms potentially mediate the observed inverse association between physical activity and gastroesophageal cancer. For example, chronic inflammatory processes, such as *Helicobacter pylori* infection [56], gastroesophageal reflux [57], Barrett's esophagus [58], obesity [14] and type 2 diabetes mellitus [15, 16] support gastroesophageal carcinogenesis, while factors that reduce chronic inflammation, such as regular aspirin use [59, 60] and dietary fiber intake [10, 11] are associated with reduced gastroesophageal cancer risk. In a similar vein, physical activity may inhibit gastroesophageal carcinogenesis by reducing chronic inflammation [61] and alleviating metabolic disorders associated both with chronic inflammation and gastroesophageal cancer, such as insulin resistance [62] and elevated insulin-like growth factor 1 levels [63, 64]. Physical activity may also prevent gastroesophageal carcinogenesis by decreasing oxidative stress [65] and improving DNA repair [66].

The observed consistency in risk reduction with physical activity across gastroesophageal cancer subtypes suggests that physical activity represents a shared protective factor for these cancers. That gastroesophageal cancers show common risk factors despite distinct etiologies is supported by observations of quite similar risk increases across gastroesophageal cancer subtypes of 7–16 % for each increment of 10 pack-years of smoking [67] and risk decreases of about 35–45 % for regular aspirin use [59, 60] and intakes of dietary fiber [10, 11]. Also, exposure to alcohol intake [8, 9, 68] and pickled foods [69, 70] has been positively related to all gastroesophageal cancer subtypes.

We examined whether obesity mediated the inverse relation of physical activity to risk of gastroesophageal cancer by comparing risk estimates that were adjusted for adiposity with those that were not. We noted that the inverse association between physical activity and gastroesophageal cancer was only modestly attenuated when the meta-analysis was restricted to datasets that were adjusted for adiposity. This suggests that the biologic mechanisms by which physical activity decreases risk for gastroesophageal cancer are only partly mediated through its effects on weight control. That the etiologic pathways linking increased physical activity to decreased risk of gastroesophageal cancer are distinct from those associated with weight control is supported by widely divergent

associations between obesity and gastroesophageal cancer histologic types. Notably, obesity shows an approximate 30–50 % reduced risk for esophageal squamous cell carcinoma [71], whereas it exhibits a substantial increased risk for esophageal and gastric cardia adenocarcinomas in the order of 100 % [14].

The inverse association between physical activity and gastroesophageal cancer was more pronounced in case–control studies than cohort studies. Possible explanations for this particular constellation of findings are preferential selection of physically active controls, physical activity under-reporting among cases, or superior physical activity assessment in case–control studies than cohort studies. The gastroesophageal cancer risk reduction of 11 % with high versus low physical activity obtained from cohort studies likely represents the more conservative risk estimate than the 23 % risk reduction generated by case–control studies.

We observed a stronger inverse association between physical activity and gastroesophageal cancer in women than men. The modifying effect of gender was statistically significant for total gastroesophageal cancer and for total gastric cancer but not for total esophageal cancer, for which case numbers were limited. Apart from chance, one possible explanation for this finding is inhibitory effects of estrogen on gastroesophageal cancer growth [72, 73]. Support for a protective role of circulating estrogen levels also comes from observational studies showing an inverse association between hormone replacement therapy and gastroesophageal cancer [74].

We noted that distant past physical activity and consistent physical activity over time showed stronger inverse relations with total esophageal cancer than recent past physical activity. Other than chance, one possible explanation for this observation is that distant past or long-term consistent physical activity may better capture the relation of physical activity to gastroesophageal cancer, if one exists. Future studies should confirm whether distant past or consistent physical activity has greater potential for esophageal cancer prevention than recent past physical activity.

One potential limitation of the present meta-analysis is that a causal relation for the observed inverse association between physical activity and gastroesophageal cancer could not be established because no intervention study was available for inclusion. In addition, the investigation of the relation of physical activity to gastroesophageal cancer by anatomic subsite and histologic type was limited because only nine [18, 20, 21, 23–25, 28, 29, 38] of the 24 studies provided relevant data on cancer anatomic subsite and histologic type. Information on esophageal squamous cell carcinoma was provided by only five studies [18, 20, 21, 24, 28], which may partly explain the observed statistically non-significant inverse association with physical activity in the main analysis. Furthermore, we lacked sufficient information to assess whether the relation of physical activity to gastric cancer was modified by *H. pylori* infection status. One previous study [23] found no effect modification of the association between physical activity and gastric cancer by *H. pylori* infection status.

This first meta-analysis of physical activity and gastroesophageal cancer also has a number of important strengths. We included a large number of studies, which yielded a substantial number of cases and enabled us to evaluate different subtypes of gastroesophageal cancers according to anatomic site and tumor histologic type. We used standardized criteria for identifying pertinent studies and abstracting key information. Our meta-analysis differs from a previous meta-analysis of physical activity and gastric cancer [75] in that we (1) included five additional gastric cancer studies with 1,054 additional cases of gastric cancer [17, 33, 36, 39, 40]; (2) examined physical activity in relation to esophageal cancer and assessed differences according to gastroesophageal cancer histologic types; (3) generated a quantitative physical activity recommendation for the primary prevention of gastroesophageal cancers based on an exploratory dose–response meta-analysis; (4) used random effects meta-regression to identify and remove the sources of between-study heterogeneity in the published data; (5) explored for potential differences between studies of gastroesophageal cancer incidence and those of gastroesophageal cancer mortality; and (6) summarized risk estimates using comparable exposure and reference categories in a sensitivity analysis, thereby confirming the robustness of our primary findings.

In conclusion, our comprehensive meta-analysis provides support for an inverse relation of physical activity to risk of gastroesophageal cancer. We estimate that high versus low physical activity decreases the risk of gastroesophageal cancer by approximately 18 %. Our dose–response meta-analysis suggests that engaging in any amount of moderate to vigorous physical activity is beneficial and that a frequency of five times per week of physical activity is associated with a risk reduction of 33 %. Future research is required to discern which specific types and durations of physical activity are needed for gastroesophageal cancer risk reduction. High-quality epidemiologic studies that employ standardized physical activity assessments and uniform definitions of high versus low physical activity levels are warranted.

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