Physical activity and risks of proximal and distal colon cancers: A systematic review and meta-analysis

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ABSTRACT

Background: Although there is convincing epidemiological evidence that physical activity is associated with a reduced risk of colon cancer, it is unclear whether physical activity is differentially associated with the risks of proximal colon and distal colon cancers. We conducted a systematic review and meta-analysis to investigate this issue.

Methods: MEDLINE and EMBASE were searched for English-language cohort and case–control studies that examined associations between physical activity and the risks of proximal colon and distal colon cancers. A random-effects meta-analysis was conducted to estimate the summary relative risks (RRs) for the associations between physical activity and the risks of the two cancers. All statistical tests were two-sided.

Results: A total of 21 studies met the inclusion criteria. The summary relative risk of the main results from these studies indicated that the risk of proximal colon cancer was 27% lower among the most physically active people compared with the least active people (RR = 0.73, 95% confidence interval [CI] = 0.66 to 0.81). An almost identical result was found for distal colon cancer (RR = 0.74, 95% CI = 0.68 to 0.80).

Conclusion: The results of this systematic review and meta-analysis suggest that physical activity is associated with a reduced risk of both proximal colon and distal colon cancers, and that the magnitude of the association does not differ by subsite. Given this finding, future research on physical activity and colon cancer should focus on other aspects of the association that remain unclear, such as whether sedentary behavior and non-aerobic physical activity are associated with the risk of colon cancer.

INTRODUCTION

The association between physical activity and the risk of colon cancer is well established, and the majority of studies have found that the most physically active individuals have a statistically significantly lower risk of colon cancer compared with the least active (1,2). A 2009 meta-analysis estimated this risk reduction to be approximately 24% for both males and females (3). Despite the extensive research that has been conducted on this topic, several features of the association between physical activity and risk of colon cancer remain unclear (4).

For example, it remains unclear whether physical activity is differentially associated with the risks of proximal colon and distal colon cancers. It has been proposed that cancers of the proximal and distal colon may be two distinct cancer types with different genetic and environmental risk factors (5). There are embryologic, morphological, physiological, and biochemical differences between the proximal colon and the distal colon, and morphological, molecular, and genetic differences between cancers that arise in the proximal colon and the distal colon (5). There are also epidemiological differences between cancers at these two anatomical sites: Proximal colon cancers are more common in older people and females, whereas distal colon cancers are more common in younger people and males, and while the incidence of proximal colon cancer in Western countries has increased, the incidence of distal colon cancer has decreased (5).

Examining whether physical activity is differentially associated with proximal colon and distal colon cancers is important for several reasons. Identification of a differential association between physical activity and colon cancer risk by subsite may lead to a better understanding of the etiology of colon cancer. There may also be implications for future research in this area. If physical activity is more strongly associated with the risk of distal colon cancer, the association between physical activity and the risk of colon cancer may

attenuate as colorectal cancer screening programs become more widespread (1). This attenuation would reflect the fact that adenomas—the known precursors to carcinomas—are more likely to be removed during flexible sigmoidoscopy and colonoscopy procedures when they are located in the distal colon vs the proximal colon (6, 7) and that colonoscopy has been shown to be associated with a greater risk reduction for advanced neoplasms in the distal colorectum than those in the proximal colorectum (8). However, the results of studies that have examined the associations between physical activity and the risk of proximal colon and distal colon cancers have been inconsistent, and it remains unclear whether the association between physical activity and colon cancer differs by subsite (9). We conducted a systematic review and meta-analysis to investigate this issue.

METHODS

Eligibility Criteria and Search Strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (10). We searched MEDLINE (from 1946 to January 16, 2012) and EMBASE (from 1947 to January 16, 2012) for cohort and case–control studies published in English that investigated the association between physical activity and the risks of incident proximal colon and distal colon cancers in humans. For the purpose of this study, "right colon," "right-sided colon," and "proximal colon" were considered to be analogous terms, as were "left colon," "left-sided colon," and "distal colon."

To be included in this analysis, a study must have 1) classified colon cancer into no more than two outcomes (ie, proximal colon cancer and distal colon cancer), and 2) defined the proximal colon as including at least the cecum, the ascending colon, and the transverse colon, but no anatomical sites distal to the splenic flexure, and the distal colon as including at least the descending and sigmoid colons, but not the rectosigmoid junction or the rectum, and

no anatomical sites proximal to the splenic flexure. We also included studies that investigated the association between physical activity and the risk of cancer at specific anatomical sites within the colon (ie, cecum, ascending colon, and so on) and reported sufficient information to allow us to combine the results from these anatomical sites and calculate an effect size for our specified definitions of proximal colon and distal colon.

The following search strategy was used: (exercise OR physical activity OR walking OR motor activity) AND (colon OR colorectal OR rectum OR rectal OR bowel) AND (cancer OR neoplasm OR carcinoma). We also manually searched the reference lists of all included original studies, as well as those of several recent review articles (1–3). After eliminating duplicate studies, all articles obtained from the searches of the databases and reference lists were screened by one author (TB) to identify those that investigated the association between physical activity and the risk of colon cancer or colorectal cancer. Two authors (TB and TK) then independently read the full text of all remaining articles to determine whether the study met the eligibility criteria outlined above. Differences were resolved by discussion.

Data Extraction

Data were extracted by one author (TB) using a data extraction form and entered into a database. A second author (TK) independently checked these data, and all differences were resolved by discussion. For each study, we extracted the effect estimate (reported as a relative risk [RR] or odds ratio) and its associated 95% confidence interval (CI) for the association of physical activity with the risks of proximal colon and distal colon cancers. If a study combined two or more physical activity domains (such as recreational, household, and occupational) into a single measure of physical activity, the effect estimate for the combined measure result was used for the primary meta-analysis. If a study reported the effect

estimates for two or more domains of physical activity but did not combine them, we used the result for recreational physical activity for the primary meta-analysis because recreational physical activity is the most commonly measured domain in observational studies of physical activity and cancer, and it has been suggested that it is the main modifiable aspect of energy expenditure (11). Recreational physical activity was measured in all of the studies that reported effect estimates from two or more domains of physical activity. If a study reported the effect of physical activity at multiple periods or ages and over the lifetime, we used the lifetime result. For all studies, we used the result that compared the most active group with the least active group. The effect size and 95% confidence intervals were inverted for studies in which the most active group was used as the reference group.

Other extracted data included the study type (ie, case–control or cohort); the sex of the participants; the country in which the study took place; the study definitions of proximal colon and distal colon; the total number of colon cancers; the numbers of proximal colon cancers and distal colon cancers; and whether the study reported information about the validity and/or reliability of the questionnaire used to measure physical activity. We also noted the physical activity domain(s) on which the main result was based; the definitions of the highest and lowest categories of physical activity that were used for the main result; any confounders that were controlled for in the analysis; any other variable whose confounding effect was assessed but was not included in the final model; whether dose–response analyses were conducted; and, if applicable, the results of the dose–response analyses. Finally, if a study reported effect estimates for any physical activity domain other than that used for the primary meta-analysis, we extracted the effect estimates that compared the most active group with the least active group.

If a study reported insufficient data to include in the meta-analysis (ie, no risk estimates and/or 95% confidence intervals), we contacted the corresponding author via email

and asked if it was possible to supply the missing data. If a study did not provide definitions of the proximal and distal colon, we searched the literature for another publication from the same cohort or case–control study that did report the definitions.

Assessment of Risk of Bias in Individual Studies

We used a three-item checklist to categorize studies as having either a lower risk of bias or a higher risk of bias. The first item concerned the study setting: cohort studies and population-based case–control studies were considered to have a lower risk of bias, whereas case–control studies that were hospital-based or cancer registry–based were considered to have a higher risk of bias. The second item concerned the validity and/or reliability of the instrument used to measure physical activity. Studies that reported that the instrument used to measure physical activity was valid and/or reliable or was similar to another questionnaire with known validity and/or reliability were considered to have a lower risk of bias. Studies that did not report this information were considered to have a higher risk of bias. The third item concerned whether a study matched on, controlled for, or considered the confounding effects of (ie, did not include these variables in the final model but reported that adjusting for them did not affect the results) age and obesity (eg, body mass index, body weight, or waist circumference) because we considered these variables to be the main potential confounders of the association between physical activity and proximal colon and distal colon cancers. Studies that matched on, controlled for, or considered the confounding effects of both of these variables were considered to have a lower risk of bias compared with those that did not. Studies that were categorized as having a lower risk of bias according to all three criteria were classified as having a lower risk of bias, whereas those that met zero, one, or two criteria were classified as having a higher risk of bias.

Statistical Analysis

We used random-effects meta-analyses to estimate the summary relative risks for the associations between physical activity and the risks of proximal colon and distal colon cancers. We combined the case–control and cohort studies in the primary meta-analysis because odds ratios and rate ratios provide similar estimates of risk when the outcome is rare (12). If a study reported results for males and females separately, both risk estimates were included in the primary analysis. Heterogeneity was assessed using the I^2 and Q statistics, and meta-regression was used to examine whether there was a statistically significant difference between the summary effect sizes for the association between physical activity and the risks of proximal and distal colon cancers. Publication bias was assessed by visual inspection of funnel plots, as well as statistically with the use of the Egger test (13). In sensitivity analyses, we assessed the impact of any possible publication bias by using the trim-and-fill method (14).

We also examined whether smaller studies were more likely than larger studies to find that physical activity had different associations with the risks of proximal colon and distal colon cancers. For each study, we calculated the ratio of the risk ratios (and 95% confidence interval), which compared the association between physical activity and the risk of proximal colon cancer with the association between physical activity and the risk of distal colon cancer; as stated above, if the same study reported risk estimates for males and females, both results were used. The ratio of risk ratios (RRRs) and associated 95% confidence intervals and standard errors were calculated using the formula outlined by Altman and Bland (15). A forest plot of the ratio of risk ratios, with studies sorted by standard error, was visually inspected to examine whether study size influenced the likelihood of a study finding that physical activity had differential associations with the risks of proximal colon and distal colon cancers.

Subgroup Analyses

Four prespecified subgroup analyses were conducted: by sex (males vs females); by study type (cohort vs case–control); by risk of bias (lower vs higher risk of bias); and by physical activity domain (occupational, recreational, household, or two or more of these domains combined). We also conducted one post hoc subgroup analysis by the definition of the proximal colon and the distal colon used in the study. For this analysis, studies that included the splenic flexure as part of the proximal colon were classified as having used definition 1, studies that included the splenic flexure as part of the distal colon were classified as having used definition 2, and studies that did not include the splenic flexure in their definition of the proximal colon or the distal colon were classified as having used definition 3. Meta-regression analysis was used to calculate ratios of risk estimates to test for statistically significant effect modification by sex, study type, risk of bias, definition of proximal colon and distal colon, and physical activity domain. In each subgroup category, meta-regression analysis was used to examine whether there was a statistically significant difference between the summary effect sizes for the associations between physical activity and proximal colon cancer and distal colon cancer.

All statistical tests were two-sided, and a *P* value less than .05 was considered statistically significant. All analyses were conducted with Stata software (version 11.2; StataCorp, College Station, TX), using the metan, metareg, metafunnel, metabias, and metatrim commands (16).

RESULTS

Study Selection

A total of 2588 articles were identified in the literature search (Figure 1). Two additional articles were identified in a manual search of reference lists. After eliminating the duplicate studies, a total of 1763 unique articles remained. After excluding articles that were not relevant to this review, as well as correspondence, editorials, and review articles, a total of 101 articles that investigated the association between physical activity and the risk of colon cancer or colorectal cancer remained. After reviewing the full text of these articles, we excluded 49 articles that did not include analyses of colorectal subsites and another 11 articles because there was another article from the same parent study with either longer follow-up or a more complete measure of physical activity [although one of these studies (17) was included in the subgroup meta-analysis of occupational physical activity]. We excluded six studies because they did not meet the required definition of proximal colon and distal colon; another 10 studies that reported results for specific anatomical sites within the colon were excluded because it was not possible to combine the results from these anatomical sites to calculate an effect size for our definitions of proximal colon and distal colon. Three studies that did not provide a definition of proximal colon and distal colon (18–20) were retained because we were able to obtain a definition from other publications based on the same cohort or case–control study. This left 25 articles, of which five (21–25) did not report sufficient data to include in the meta-analysis. We contacted the authors of these five studies and were able to obtain the requested data for one study (21). This left a total of 21 studies that were included in the primary meta-analysis (9,18–21,26–41).

Study Characteristics

The main characteristics of the 21 studies included in the primary meta-analysis are displayed in Table 1, and additional study characteristics are reported in Supplementary Table 1 (available online). More than 9512 people with proximal colon cancer and 8171 people with distal colon cancer participated in the studies included in the meta-analysis [three studies (29,34,38) did not report the number of cancers by subsite]. Twelve studies (19,21,26,27,29,30,32,33,35–37,39) were cohort studies and nine (9,18,20,28,31,34,38,40,41) were case–control studies. Eleven studies (19,26–29,33–37,39) used definition 1 to classify anatomical sites as proximal colon or distal colon, six studies (9,18,21,30,32,38) used definition 2, and four studies (20,31,40,41) used definition 3. Eight studies were conducted in Europe [one (27) in multiple European countries, three (28,32,36) in Sweden, and one each in Finland (21), France (18), Norway (37), and Switzerland (34)], nine (19,26,29,30,35,38–41) were conducted in the United States, three (20,31,33) were conducted in Japan, and one (9) was conducted in Australia. Five studies (21,29,32,40,41) involved males only, three (19,35,39) involved females only, five (18,21,27,34,37) involved both males and females but did not report sex-specific results, and eight (9,20,28,30,31,33, 36,38) involved both males and females and did report sex-specific results. A total of 29 sets of results were included in the primary analysis [13 sets of results for males (9,20,21,28–33,36,38,40,41), 11 sets of results for females (9,19,20,29–31,33,35,36,38,39), and five sets of results for both sexes combined (18,26,27,34,37)]. The main results of four studies (34,36,40,41) were based on occupational activity, those of nine studies (9,21,26,29–31,35,37,39) were based on recreational activity, three studies (18,28,33) were based on recreational and occupational activity combined, one study (38) was based on recreational and household activity combined, three studies (21,27,32) were based on recreational, occupational, and household

activity combined, and one study (20) was based on recreational, occupational, and transport-related activity combined.

The subgroup meta-analyses of physical activity domains included 10 studies (17,20,21,27,30,32,34,36,40,41) that reported results for occupational activity, 11 studies (9,20,21,26,27,29,30,32,35,37,39) that reported results for recreational activity, two studies (27,32) that reported results for household activity, and eight studies (18–20,27,28,32,33,38) that reported results from a combination of two or more domains.

Risk of Bias. Four (31,34,40,41) of the 21 studies were neither a cohort or a population-based case–control study. Eleven studies (9,19,20,27,29,30,32,33,37–39) reported that the questionnaire used to measure physical activity was valid and/or reliable or similar to other valid and/or reliable questionnaires. Sixteen studies (9,19–21,26–30,32–35,37–39) matched on, adjusted for, or considered the confounding effects of both age and obesity. Eleven studies [eight cohort (19,27,29,30,32,33,37,39), three case–control (9,20,38)] were categorized as having a lower risk of bias according to all three criteria and were classified as having a lower risk of bias, whereas 10 studies [four cohort (21,26,35,36), six case–control (18,28,31,34,40,41)] met zero, one, or two criteria and were classified as having a higher risk of bias.

Dose–Response Analyses. A total of 18 dose–response analyses (six in males, eight in females, and four in males and females combined) were conducted in the 13 studies that examined whether there was a dose–response relationship between physical activity and proximal colon and distal colon cancers (9,20,21,26–28,30,32–36,39). Seven analyses of physical activity and the risk of proximal colon cancer (three in males, one in females, and three in male and females combined) found a statistically significant ($P < .05$) dose–response relationship (26,27,30,33,34,36), and four analyses of physical activity and the risk of distal

colon cancer (one in males, one in females, and two in males and females combined) found a statistically significant dose–response relationship (28,34,36,39).

Meta-Analyses

Primary Meta-Analysis. The summary relative risk of the main results from the 21 studies indicated that the risk of proximal colon cancer was 27% lower among the most physically active people compared with the least active people (RR = 0.73, 95% CI = 0.66 to 0.81) (Figure 2). There was low heterogeneity (I^2 = 31.3%; P = .057). An almost identical result was found for distal colon cancer (RR = 0.74, 95% CI = 0.68 to 0.80), again with low heterogeneity (I^2 = 0.0%; P = .473). There was essentially no difference between the summary risk estimates for the associations between physical activity and proximal colon cancers and distal colon cancers (ratio of risk estimates = 0.98, 95% CI = 0.87 to 1.11) (Table 2).

Publication Bias and Small-Study Effects. There was some evidence of publication bias in the primary meta-analysis**.** Visual inspection of the funnel plots revealed a small degree of asymmetry, primarily due to one to two studies, in both the proximal colon cancer and distal colon cancer results (Figure 3). The P values from the Egger tests were .053 for the proximal colon cancer studies and .344 for distal colon cancer studies. Using the trim-and-fill method to assess the impact of any potential publication bias, we found that four potentially missing studies would be needed to obtain funnel plot symmetry for the proximal colon cancer results and three potentially missing studies would be needed to obtain funnel plot symmetry for the distal colon cancer results (Figure 3). However, inclusion of these potentially missing studies in the meta-analyses did not substantially change the summary relative risk estimates (proximal colon cancer: 0.77 (95% CI = 0.68 to 0.87); distal colon cancer: 0.75 (95% CI = 0.69 to 0.82).

To examine whether study size influenced the likelihood of a study finding that physical activity had differential associations with the risks of proximal colon and distal colon cancers, for each of the 29 sets of results in the primary meta-analysis, we calculated a ratio of the risk ratios (and 95% confidence interval), which compared the association between physical activity and the risk of proximal colon cancer with the association between physical activity and the risk of distal colon cancer. These ratios of risk ratios, sorted by standard error, are graphically represented in a forest plot (Figure 4). Visual inspection of this forest plot indicated that the ratios with larger standard error were generally farther from the null than those with less standard error, suggesting that smaller studies (ie, studies with larger standard error) were more likely than larger studies to find that physical activity has differential associations with proximal colon and distal colon cancers.

Subgroup Meta-Analyses. The results of the subgroup random-effects meta-analyses revealed no meaningful or statistically significant differences between the risk estimates for proximal colon and distal colon cancers (Table 2). Subgroup analyses also showed no statistically significant differences between the results for males and females, between studies with a higher risk of bias and those with a lower risk of bias, among studies with different definitions of proximal colon and distal colon, or among studies with results based on different physical activity domains. However, risk estimates from case–control studies were, on average, statistically significantly lower than those from cohort studies (ratio of risk estimates = 0.86, 95% CI = 0.76 to 0.98). Forest plots for meta-analyses of all subgroups (ie, study design, sex, risk of bias, definition of proximal colon and distal colon, physical activity domain) are presented in Supplementary Figures 1–5 (available online).

DISCUSSION

The results of this systematic review and meta-analysis suggest that the association between physical activity and the risk of colon cancer does not differ by anatomical subsite. The summary risk estimates from the 21 studies indicate that the risks of both proximal colon cancer and distal colon cancer are approximately 25% lower among the most physically active people compared with the least active people. There was no strong evidence that the results differed between males and females, between studies with a higher or lower risk of bias, between studies with different definitions of proximal colon and distal colon, or between physical activity domains. However, the risk estimates from case–control studies were, on average, farther from the null than those from cohort studies, which may reflect the influence of selection and recall biases in case–control studies (3). Sensitivity analyses suggested that any publication bias that was present had minimal effect on the summary relative risks.

Although the results of this meta-analysis suggest that physical activity has similar associations with the risks of proximal colon and distal colon cancers, many of the individual studies included in our meta-analysis reported results that suggested otherwise. However, the results of these studies are inconsistent: while some studies have found that physical activity may be associated with a greater risk reduction for proximal colon cancer than for distal colon cancer, others have found the opposite, or no difference. It has been suggested that these inconsistent results may be due to methodological differences among the studies (21). For example, several different definitions of proximal colon and distal colon were used in the studies included in this meta-analysis. However, our subgroup analyses revealed no meaningful differences among the results from studies that used different definitions of proximal colon and distal colon.

Another methodological difference involves the measurement of physical activity, which was measured during various periods, at different intensities, and in different domains. The timing, intensity, and domain of physical activity may influence its association with the risk of colon cancer (4), and there is interest in how these components influence health outcomes (42). Although too few studies reported the timing and intensity of physical activity to investigate to investigate these variables separately in this meta-analysis, it was possible to examine separate physical activity domains. The results of these physical activity domain-specific meta-analyses revealed no statistically significant differences among studies with results based on different physical activity domains and indicated that physical activity in any domain is associated with a reduced risk of colon cancer.

It is also possible that the differential associations of physical activity with the risks of colon cancer at anatomical subsites were due to chance, given that many of the included studies had small numbers of participants with proximal colon and distal colon cancers (43). We assessed this possibility by investigating whether smaller studies were more likely than larger studies to find that physical activity had differential associations with the risks of proximal colon and distal colon cancers and found that was indeed the case (Figure 2). This finding suggests that at least some of the inconsistent results of the included studies may be due to imprecise estimates of risk caused by low statistical power.

A number of biological reasons have been put forth to explain why physical activity may have differential associations with the risks of proximal colon and distal colon cancers. Some have suggested that physical activity may increase gut motility more extensively in the proximal colon than in the distal colon (27,33,44). However, it has also been argued that by increasing gastrointestinal transit time and decreasing constipation, physical activity would have a greater impact on the risk of distal colon cancer, because the distal colon has a stronger storage function than the proximal colon (20,28). It has been proposed that the

effect of physical activity on metabolic hormone levels and growth factors may influence the risk of proximal colon cancer more than the risk of distal colon cancer (33). Finally, the associations between physical activity and obesity (decreased risk) and vitamin D (increased levels) have been suggested as reasons for a greater risk reduction for distal colon cancer than for proximal colon cancer (9).

This study has some limitations. Although we found low statistical heterogeneity in the primary meta-analysis and in the subgroup analyses, as with most meta-analyses of observational studies, the included studies were conducted on different population groups, and the measurement and categorization of the exposure (physical activity) was highly heterogeneous. As such, the results of this meta-analysis should only be interpreted as showing that the research conducted to date indicates that the most active individuals have a 25% lower risk of colon cancer compared with the least active, and that the risk reduction is virtually identical for cancers of the proximal colon and distal colon. Our results do not provide any information about the duration, frequency, intensity, or timing of physical activity required to optimally reduce the risk of colon cancer.

Another limitation is our exclusion of four studies that investigated associations between physical activity and the risks of proximal colon and distal colon cancers but did not report sufficient data to include in the meta-analysis and for which we were unable to obtain the information from the authors. Three of these studies (22,24,25) reported that physical activity had similar associations with the risks of proximal colon and distal colon cancers, and the fourth study (23) reported identical risk estimates (but no confidence intervals) for the association between lifetime recreational physical activity and the risks of proximal colon and distal colon cancers. It is therefore unlikely that inclusion of these studies would have substantially changed the results of this meta-analysis. There are also many published studies that have investigated the association between physical activity and the risk of colon cancer

that were not included in this meta-analysis because they did not report separate results for proximal colon and distal colon cancers. Nonetheless, our results are very similar to those of a recent meta-analysis that estimated the association between physical activity and the risk colon cancer but did not look at subsite-specific colon cancer (3), suggesting that the studies included in this meta-analysis are a representative sample of the published studies that have investigated the association between physical activity and the risk of colon cancer. That meta-analysis (3), which included 17 of the 21 studies in this meta-analysis, found a summary risk estimate of 0.76 for colon cancer, compared with our summary relative risks of 0.73 for proximal colon cancer and 0.74 for distal colon cancer.

In conclusion, the results of this systematic review and meta-analysis indicate that there is strong and consistent evidence that physical activity is associated with reduced risks of both proximal colon and distal colon cancers and that the association between physical activity and risk of colon cancer does not differ by subsite. This finding suggests that future research on physical activity and colon cancer should focus on other aspects of the association that remain unclear, such as whether sedentary behavior and non-aerobic physical activity (eg, resistance training) are associated with the risk of colon cancer, whether the intensity of physical activity influences the association between physical activity and the risk of colon cancer, and whether obesity, diet, and/or ethnicity modify the association between physical activity and the risk of colon cancer (3,4).

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Table 1. Main characteristics of the studies included in the primary meta-analysis of studies that have investigated associations between physical activity and the risks of proximal colon cancer (PCC) and distal colon cancer (DCC)*

First Author, Year, Country (reference)	Sex	Study setting	Number of cancers	Physical activity domain in main result (in subgroup analyses)	Physical activity measurement mode, validity reported, and reliability reported	Confounding effect of age and obesity considered?	Main Result RR or OR (95% CI)	Dose–response *P*
COHORT STUDIES								
Giovanucci, 1995, United States (29)	Males	Health professionals	CC: 203 PCC: NR DCC: NR	REC	Self-administered, Yes, Yes	Age: Yes Obesity: Yes	PCC: 0.75 (0.36 to 1.55) DCC: 0.50 (0.25 to 1.00)	NR
Colbert, 2001, Finland (21)	Males	Participants in a randomized controlled trial	CC: 152 PCC: 69 DCC: 81	REC (OCC)	Self-administered, No, No	Age: Yes Obesity: Yes	PCC: 0.73 (0.47 to 1.14) DCC: 0.94 (0.58 to 1.53)	NR
Chao, 2004, United States (26)	Both, combined	Population	CC: 940 PCC: 505 DCC: 339	REC	Self-administered, No, No	Age: Yes Obesity: Yes	PCC: 0.63 (0.45 to 0.88) DCC: 0.82 (0.55 to 1.24)	PCC: .008 DCC: .15
Calton, 2006, United States (19)	Females	Breast Cancer Screening Project	CC: 243 PCC: 103 DCC: 68	REC, OCC, HH	Self-administered, Yes, No	Age: Yes Obesity: Yes	PCC: 0.87 (0.46 to 1.62) DCC: 1.36 (0.75 to 2.46)	PCC: .84 DCC: .34
Friedenreich, 2006, Europe (27)	Both, combined	Population	CC: 1094 PCC: 429 DCC: 491	REC, OCC, HH (All examined separately)	Self-administered or interview, Yes, Yes	Age: Yes Obesity: Yes	PCC: 0.65 (0.43 to 1.00) DCC: 0.96 (0.64 to 1.45)	PCC: .004 DCC: .83
Larsson, 2006, Sweden (32)	Males	Population	CC: 309 PCC: 133 DCC: 138	REC, OCC, HH (All examined separately)	Self-administered, Yes, No	Age: Yes Obesity: Yes	PCC: 0.71 (0.39 to 1.29) DCC: 0.70 (0.38 to 1.27)	PCC: .32 DCC: .47
Lee, 2007, Japan (33)	Both, separate	Population	CC: 337 PCC: 154 DCC: 166	REC, OCC	Self-administered, Yes, No	Age: Yes Obesity: Yes	Females: PCC: 0.55 (0.24 to 1.26) DCC: 1.37 (0.66 to 2.85) Males: PCC: 0.29 (0.14 to 0.60) DCC: 0.89 (0.53 to 1.51)	Females: PCC: .151 DCC: .401 Males: PCC: <.001 DCC: .685
Mai, 2007, United States (35)	Females	Teachers	CC: 395 PCC: 272 DCC: 107	REC	Self-administered, No, No	Age: Yes Obesity: Yes	PCC: 0.77 (0.54 to 1.08) DCC: 0.63 (0.37 to 1.09)	PCC: .24 DCC: .49
Wolin, 2007,	Females	Nurses	CC: 547	REC	Self-administered,	Age: Yes	PCC: 0.97 (0.68 to 1.38)	PCC: .77

United States (39)			PCC: 302 DCC: 245		Yes, Yes	Obesity: Yes	DCC: 0.54 (0.34 to 0.84)	DCC: .004
Howard,2008, United States (30)	Both, separate	Population (Retirees)	CC: 3410 PCC: 1860 DCC: 1360	REC (OCC)	Self-administered, Yes, Yes	Age: Yes Obesity: Yes	Females: PCC: 0.91 (0.70 to 1.17) DCC: 0.82 (0.58 to 1.14) Males: PCC: 0.83 (0.68 to 1.02) DCC: 0.83 (0.67 to 1.03)	Females: PCC: .969 DCC: .336 Males: PCC: .033 DCC: .285
Moradi, 2008, Sweden (36)	Both, separate	Census records	CC: 7900 PCC: 3720 DCC: 3074	OCC	Job title–based, No, No	Age: Yes Obesity: No	Females: PCC: 0.71 (0.50 to 0.91) DCC: 0.83 (0.59 to 1.25) Males: PCC: 0.83 (0.67 to 1.00) DCC: 0.71 (0.59 to 0.83)	Females: PCC: .029 DCC: >.05 Males: PCC: .004 DCC: <.001
Nilsen, 2008, Norway (37)	Both, combined	Population	CC: 736 PCC: 391 DCC: 264	REC	Self-administered, Yes, No	Age: Yes Obesity: Yes	PCC: 0.81 (0.59 to 1.10) DCC: 0.56 (0.37 to 0.83)	NR
CASE–CONTROL STUDIES								
Vena, 1985, United States (41)	Males	Hospital	CC: 210 PCC: 70 DCC: 98	OCC	Job title–based, No, No	Age: No Obesity: No	PCC: 0.39 (0.21 to 0.71) DCC: 0.72 (0.44 to 1.16)	NR
Brownson, 1989, United States (40)	Males	Cancer registry	CC: 1993 PCC: 779 DCC: 939	OCC	Job title–based, No, No	Age: No Obesity: No	PCC: 0.60 (0.39 to 0.94) DCC: 0.83 (0.57 to 1.21)	NR
Gerhardsson, 1990, Sweden (28)	Both, separate	Population	CC: 452 PCC: 181 DCC: 147	REC, OCC	Self-administered, No, No	Age: Yes Obesity: Yes	Females: PCC: 0.71 (0.20 to 2.50) DCC: 0.24 (0.07 to 0.83) Males: PCC: 1.25 (0.33 to 5.00) DCC: 0.30 (0.09 to 1.00)	Combined: PCC: .863 DCC: .002
Inoue, 1995, Japan (31)	Both, separate	Hospital	CC: 432 PCC: 42 DCC: 61	REC	Self-administered, No, No	Age: Yes Obesity: No	Females: PCC: 0.50 (0.20 to 1.50) DCC: 1.00 (0.50 to 2.00) Males: PCC: 0.70 (0.40 to 1.50) DCC: 0.70 (0.40 to 1.30)	NR
Slattery, 1995, United States (38)	Both, separate	Population	CC: 1993 PCC: NR	REC, HH	Interview, No, Yes	Age: Yes Obesity: Yes	Females: PCC: 0.63 (0.44 to 0.89)	NR

			DCC: NR				DCC: 0.62 (0.44 to 0.88) Males: PCC: 0.56 (0.40 to 0.78) DCC: 0.65 (0.47 to 0.90)	
Levi, 1999, Switzerland (34)	Both, combined	Hospital	CC: 119 PCC: NR DCC: NR	OCC	Interview, No, No	Age: Yes Obesity: Yes	PCC: 0.28 (0.11 to 0.67) DCC: 0.53 (0.24 to 1.16)	PCC: .01 DCC: .01
Boutron-Ruault, 2001, France (18)	Both, combined	Population	CC: 106 PCC: 43 DCC: 63	REC, OCC	Self-administered, No, No	Age: Yes Obesity: No	PCC: 0.09 (0.01 to 0.70) DCC: 0.50 (0.20 to 1.00)	NR
Isomura, 2006, Japan (20)	Both, separate	Population	CC: 438 PCC: 175 DCC: 262	REC, HH, COM (OCC)	Self-administered, No, Yes	Age: Yes Obesity: Yes	Females: PCC: 1.60 (0.70 to 3.60) DCC: 0.60 (0.30 to 1.10) Males: PCC: 0.90 (0.50 to 1.70) DCC: 0.70 (0.40 to 1.10)	Females: PCC: .41 DCC: .12 Males: PCC: .69 DCC: .19
Boyle, 2011, Australia (9)	Both, separate	Population	CC: 552 PCC: 284 DCC: 268	REC (OCC†)	Self-administered, No, Yes	Age: Yes Obesity: Yes	Females: PCC: 0.90 (0.52 to 1.54) DCC: 0.84 (0.47 to 1.50) Males: PCC: 1.11 (0.68 to 1.83) DCC: 0.66 (0.41 to 1.07)	Females: PCC: .794 DCC: .713 Males: PCC: .577 DCC: .227

*CC = colon cancer; COM = commuting (transport-related) physical activity; HH = household physical activity; NR = not reported; OCC = occupational physical activity; REC = recreational physical activity.

†Result from occupational physical activity domain from Boyle et al. (17).

Table 2. Summary of results from the primary random-effects meta-analysis and the subgroup random-effects meta-analyses*

Meta-analysis	Proximal colon cancer			Distal colon cancer			Meta-Regression	
	RR (95% CI)	I^2, %	*P*	RR (95% CI)	I^2, %	*P*	Ratio of RRs (95% CI)†	Within-group ratio of results (95% CI)
Primary meta-analysis	0.73 (0.66 to 0.81)	31.3	.057	0.74 (0.68 to 0.80)	0.0	.473	0.98 (0.87 to 1.11)	–
Subgroup meta-analyses								
Study design								
Cohort studies	0.78 (0.72 to 0.86)	2.6	.423	0.78 (0.70 to 0.87)	15.4	.281	0.98 (0.86 to 1.13)	1.00 (reference)
Case–control studies	0.67 (0.54 to 0.85)	43.5	.041	0.67 (0.59 to 0.77)	0.0	.789	1.01 (0.80 to 1.29)	0.86 (0.76 to 0.98)
Sex								
Males	0.71 (0.60 to 0.83)	40.7	.063	0.74 (0.67 to 0.82)	0.0	.828	1.00 (0.84 to 1.19)	1.00 (reference)
Females	0.81 (0.71 to 0.92)	0.0	.516	0.76 (0.63 to 0.92)	33.9	.128	0.94 (0.74 to 1.18)	1.06 (0.92 to 1.21)
Risk of bias								
Lower risk of bias	0.78 (0.68 to 0.89)	33.4	.095	0.74 (0.66 to 0.84)	14.9	.282	0.95 (0.79 to 1.14)	1.00 (reference)
Higher risk of bias	0.67 (0.57 to 0.79)	25.7	.184	0.73 (0.65 to 0.82)	0.0	.603	1.04 (0.87 to 1.24)	0.94 (0.87 to 1.06)
Definition of proximal and distal colon‡								
Definition 1	0.73 (0.64 to 0.84)	24.8	.186	0.73 (0.62 to 0.86)	37.6	.076	0.98 (0.80 to 1.19)	1.00 (reference)
Definition 2	0.77 (0.65 to 0.91)	39.9	.102	0.75 (0.66 to 0.85)	0.0	.725	0.96 (0.78 to 1.18)	1.04 (0.91 to 1.18)
Definition 3	0.68 (0.48 to 0.97)	43.5	.115	0.75 (0.61 to 0.93)	0.0	.908	1.14 (0.77 to 1.67)	0.97 (0.79 to 1.19)
Physical Activity domain								
≥2 domains	0.66 (0.53 to 0.83)	33.5	.122	0.74 (0.60 to 0.90)	35.8	.104	1.13 (0.83 to 1.54)	1.00 (reference)
Recreational	0.84 (0.76 to 0.92)	0.0	.766	0.74 (0.66 to 0.83)	10.9	.334	0.89 (0.77 to 1.04)	1.14 (0.98 to 1.33)
Occupational	0.72 (0.61 to 0.85)	41.9	.056	0.75 (0.63 to 0.88)	45.6	.037	1.03 (0.80 to 1.34)	1.05 (0.89 to 1.24)
Household§	0.65 (0.46 to 0.93)	29.6	.233	0.97 (0.75 to 1.25)	0.0	.587	1.44 (0.63 to 3.29)	–

*RR = relative risk; CI = confidence interval; – = not applicable.

†Reference is relative risk of proximal colon cancer

‡Definition 1 = splenic flexure included as part of the proximal colon; Definition 2 = splenic flexure included as part of the distal colon; Definition 3 = splenic flexure not included in definition of the proximal colon or the distal colon

§Omitted from within-group meta-regression due to collinearity.

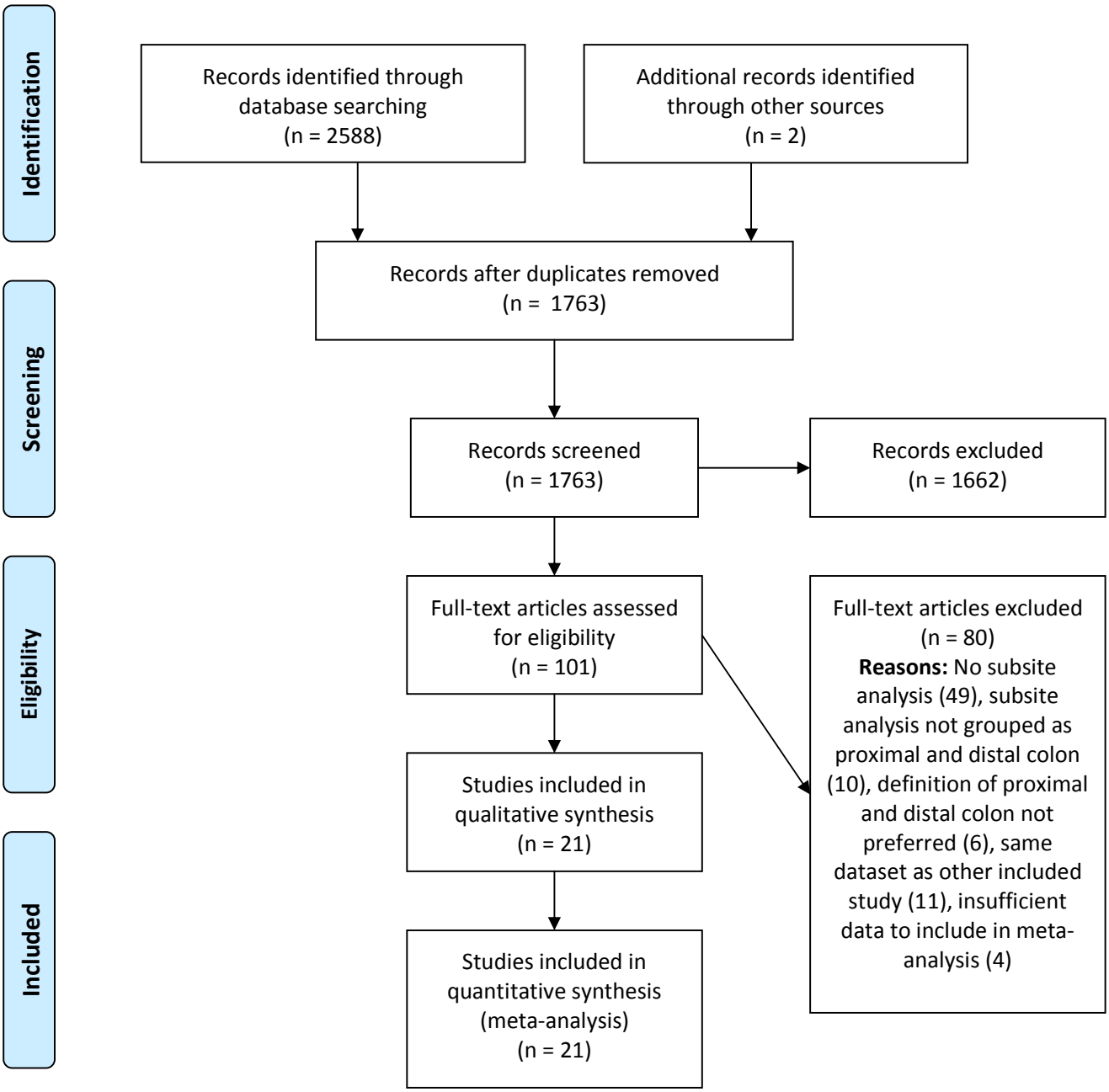
FIGURE LEGENDS

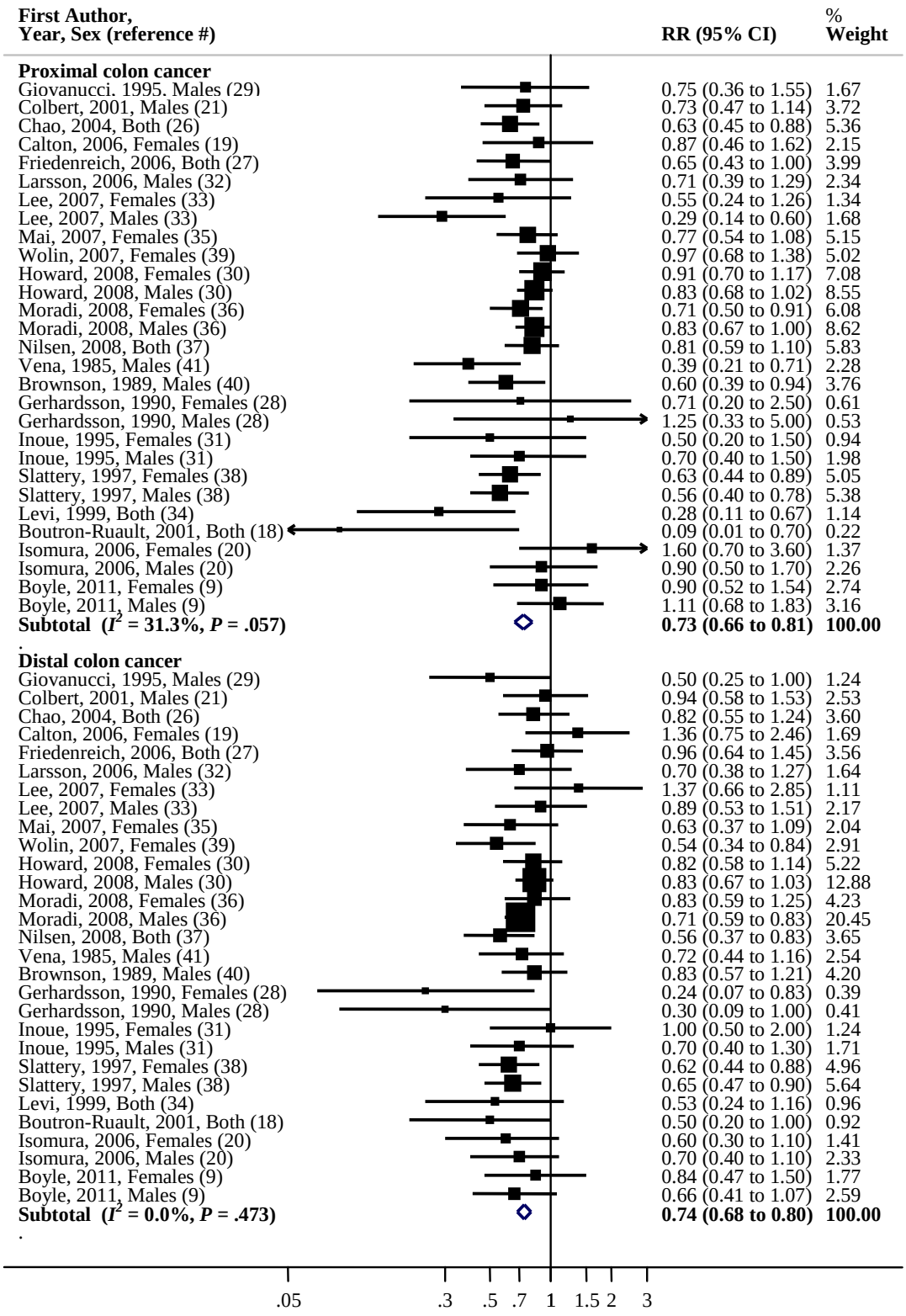
Figure 1. Flow chart of study selection

Figure 2. Random-effects meta-analysis of the main result of studies that investigated the associations between physical activity and the risks of proximal colon and distal colon cancers. The **black squares** and **horizontal lines** represent the effect estimate and 95% confidence interval of each study. The **relative size** of the black square represents the weight that the study contributed to the summary relative risk. The **diamonds** represent the summary relative risk and associated 95% confidence intervals. RR = relative risk; CI = confidence interval.

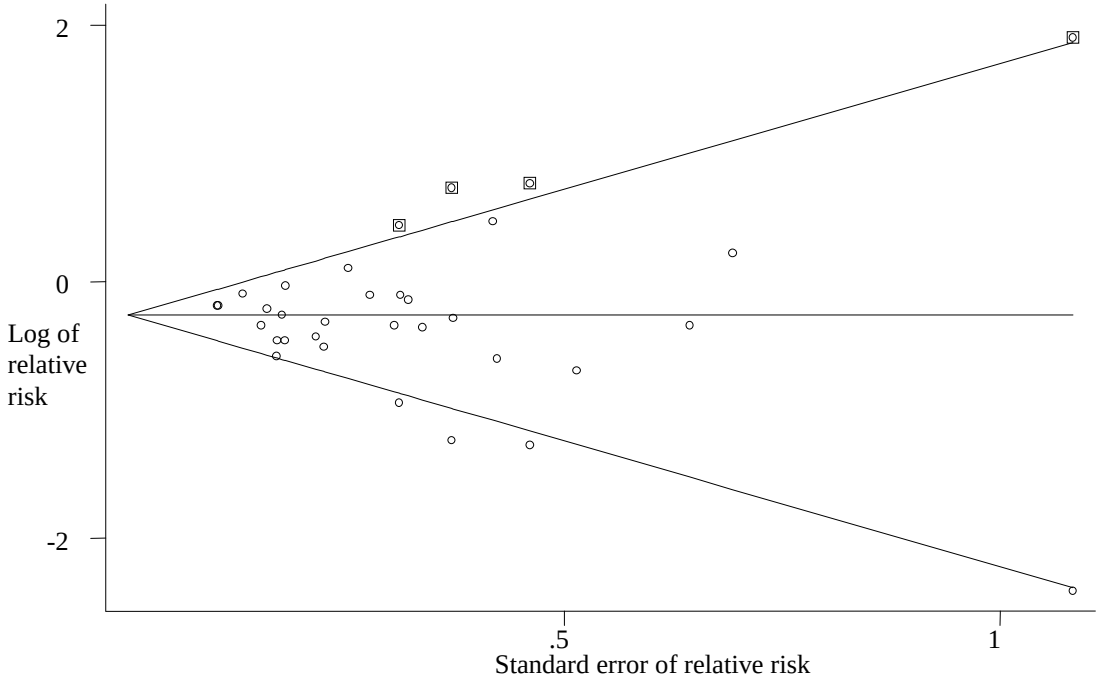
Figure 3. Filled funnel plot of risk estimates from studies that investigated the associations between physical activity and the risks of proximal colon cancer (**A**) and distal colon cancer (**B**). The **circles alone** are real studies and the **circles enclosed in boxes** are "filled" studies. The **horizontal lines** represent the summary effect estimates, and the **diagonal lines** represent pseudo- 95% confidence interval limits.

Figure 4. Forest plot of ratios of risk ratios (RRRs) for associations between physical activity and risks of proximal colon cancer (PCC) and distal colon cancer (DCC) in each study (sorted by the standard error of the RRR). CI = confidence interval. The **black diamonds** and **horizontal lines** represent the ratios of risk ratio and 95% confidence interval for each study.

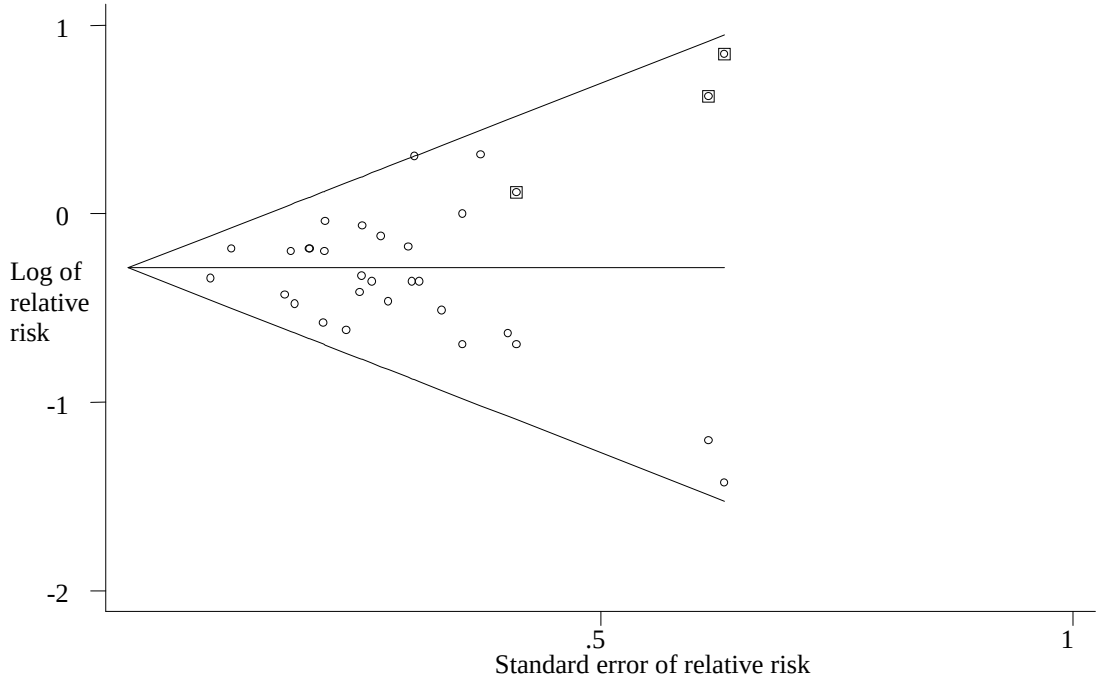

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 2588)
Additional records identified through other sources (n = 2)
Records after duplicates removed (n = 1763)
Records screened (n = 1763)
Records excluded (n = 1662)
Full-text articles assessed for eligibility (n = 101)
Full-text articles excluded (n = 80)
Reasons: No subsite analysis (49), subsite analysis not grouped as proximal and distal colon (10), definition of proximal and distal colon not preferred (6), same dataset as other included study (11), insufficient data to include in meta-analysis (4)
Studies included in qualitative synthesis (n = 21)
Studies included in quantitative synthesis (meta-analysis) (n = 21)

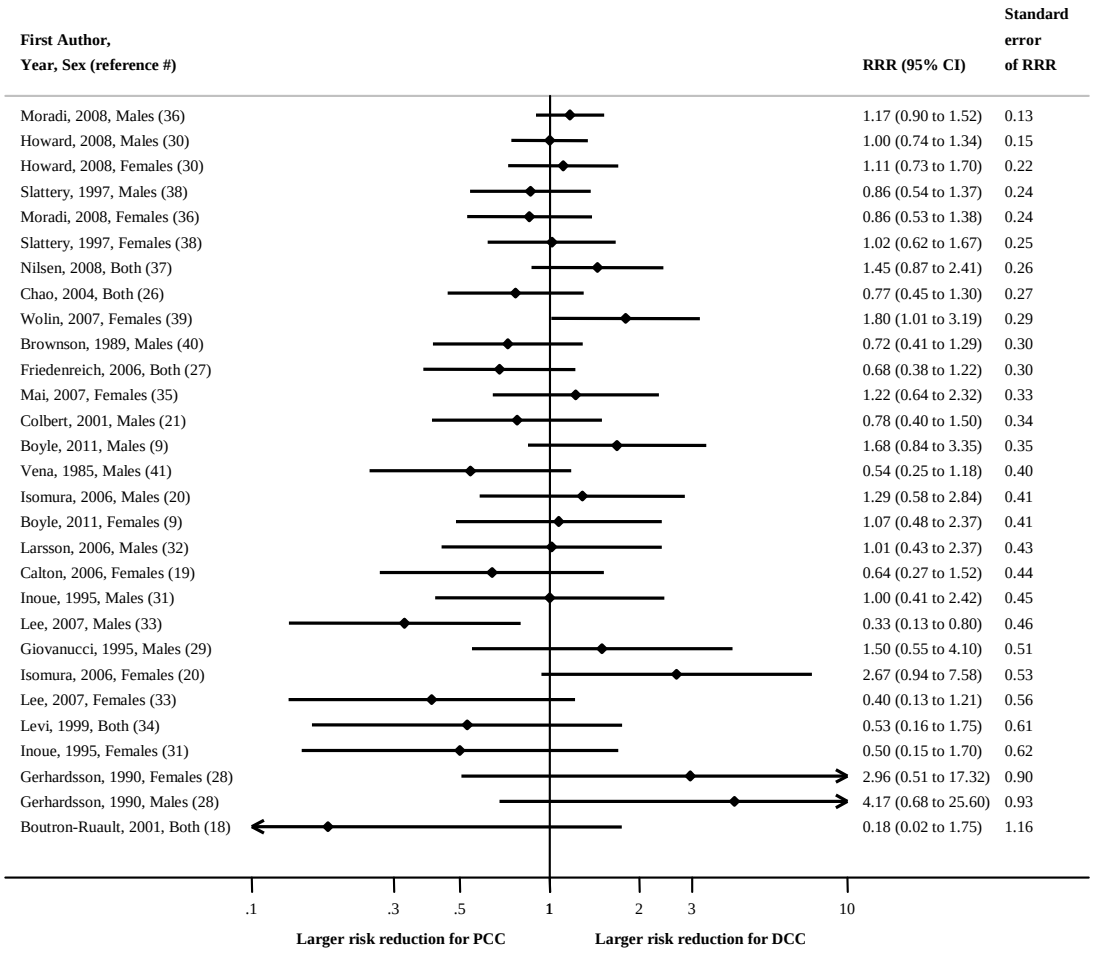

First Author,
Year, Sex (reference #)
RR (95% CI)
% Weight
Proximal colon cancer
Giovanucci, 1995, Males (29) 0.75 (0.36 to 1.55) 1.67
Colbert, 2001, Males (21) 0.73 (0.47 to 1.14) 3.72
Chao, 2004, Both (26) 0.63 (0.45 to 0.88) 5.36
Calton, 2006, Females (19) 0.87 (0.46 to 1.62) 2.15
Friedenreich, 2006, Both (27) 0.65 (0.43 to 1.00) 3.99
Larsson, 2006, Males (32) 0.71 (0.39 to 1.29) 2.34
Lee, 2007, Females (33) 0.55 (0.24 to 1.26) 1.34
Lee, 2007, Males (33) 0.29 (0.14 to 0.60) 1.68
Mai, 2007, Females (35) 0.77 (0.54 to 1.08) 5.15
Wolin, 2007, Females (39) 0.97 (0.68 to 1.38) 5.02
Howard, 2008, Females (30) 0.91 (0.70 to 1.17) 7.08
Howard, 2008, Males (30) 0.83 (0.68 to 1.02) 8.55
Moradi, 2008, Females (36) 0.71 (0.50 to 0.91) 6.08
Moradi, 2008, Males (36) 0.83 (0.67 to 1.00) 8.62
Nilsen, 2008, Both (37) 0.81 (0.59 to 1.10) 5.83
Vena, 1985, Males (41) 0.39 (0.21 to 0.71) 2.28
Brownson, 1989, Males (40) 0.60 (0.39 to 0.94) 3.76
Gerhardsson, 1990, Females (28) 0.71 (0.20 to 2.50) 0.61
Gerhardsson, 1990, Males (28) 1.25 (0.33 to 5.00) 0.53
Inoue, 1995, Females (31) 0.50 (0.20 to 1.50) 0.94
Inoue, 1995, Males (31) 0.70 (0.40 to 1.50) 1.98
Slattery, 1997, Females (38) 0.63 (0.44 to 0.89) 5.05
Slattery, 1997, Males (38) 0.56 (0.40 to 0.78) 5.38
Levi, 1999, Both (34) 0.28 (0.11 to 0.67) 1.14
Boutron-Ruault, 2001, Both (18) 0.09 (0.01 to 0.70) 0.22
Isomura, 2006, Females (20) 1.60 (0.70 to 3.60) 1.37
Isomura, 2006, Males (20) 0.90 (0.50 to 1.70) 2.26
Boyle, 2011, Females (9) 0.90 (0.52 to 1.54) 2.74
Boyle, 2011, Males (9) 1.11 (0.68 to 1.83) 3.16
Subtotal (I^2 = 31.3%, P = .057) 0.73 (0.66 to 0.81) 100.00
Distal colon cancer
Giovanucci, 1995, Males (29) 0.50 (0.25 to 1.00) 1.24
Colbert, 2001, Males (21) 0.94 (0.58 to 1.53) 2.53
Chao, 2004, Both (26) 0.82 (0.55 to 1.24) 3.60
Calton, 2006, Females (19) 1.36 (0.75 to 2.46) 1.69
Friedenreich, 2006, Both (27) 0.96 (0.64 to 1.45) 3.56
Larsson, 2006, Males (32) 0.70 (0.38 to 1.27) 1.64
Lee, 2007, Females (33) 1.37 (0.66 to 2.85) 1.11
Lee, 2007, Males (33) 0.89 (0.53 to 1.51) 2.17
Mai, 2007, Females (35) 0.63 (0.37 to 1.09) 2.04
Wolin, 2007, Females (39) 0.54 (0.34 to 0.84) 2.91
Howard, 2008, Females (30) 0.82 (0.58 to 1.14) 5.22
Howard, 2008, Males (30) 0.83 (0.67 to 1.03) 12.88
Moradi, 2008, Females (36) 0.83 (0.59 to 1.25) 4.23
Moradi, 2008, Males (36) 0.71 (0.59 to 0.83) 20.45
Nilsen, 2008, Both (37) 0.56 (0.37 to 0.83) 3.65
Vena, 1985, Males (41) 0.72 (0.44 to 1.16) 2.54
Brownson, 1989, Males (40) 0.83 (0.57 to 1.21) 4.20
Gerhardsson, 1990, Females (28) 0.24 (0.07 to 0.83) 0.39
Gerhardsson, 1990, Males (28) 0.30 (0.09 to 1.00) 0.41
Inoue, 1995, Females (31) 1.00 (0.50 to 2.00) 1.24
Inoue, 1995, Males (31) 0.70 (0.40 to 1.30) 1.71
Slattery, 1997, Females (38) 0.62 (0.44 to 0.88) 4.96
Slattery, 1997, Males (38) 0.65 (0.47 to 0.90) 5.64
Levi, 1999, Both (34) 0.53 (0.24 to 1.16) 0.96
Boutron-Ruault, 2001, Both (18) 0.50 (0.20 to 1.00) 0.92
Isomura, 2006, Females (20) 0.60 (0.30 to 1.10) 1.41
Isomura, 2006, Males (20) 0.70 (0.40 to 1.10) 2.33
Boyle, 2011, Females (9) 0.84 (0.47 to 1.50) 1.77
Boyle, 2011, Males (9) 0.66 (0.41 to 1.07) 2.59
Subtotal (I^2 = 0.0%, P = .473) 0.74 (0.68 to 0.80) 100.00
.05
.3
.5
.7
1
1.5
2
3

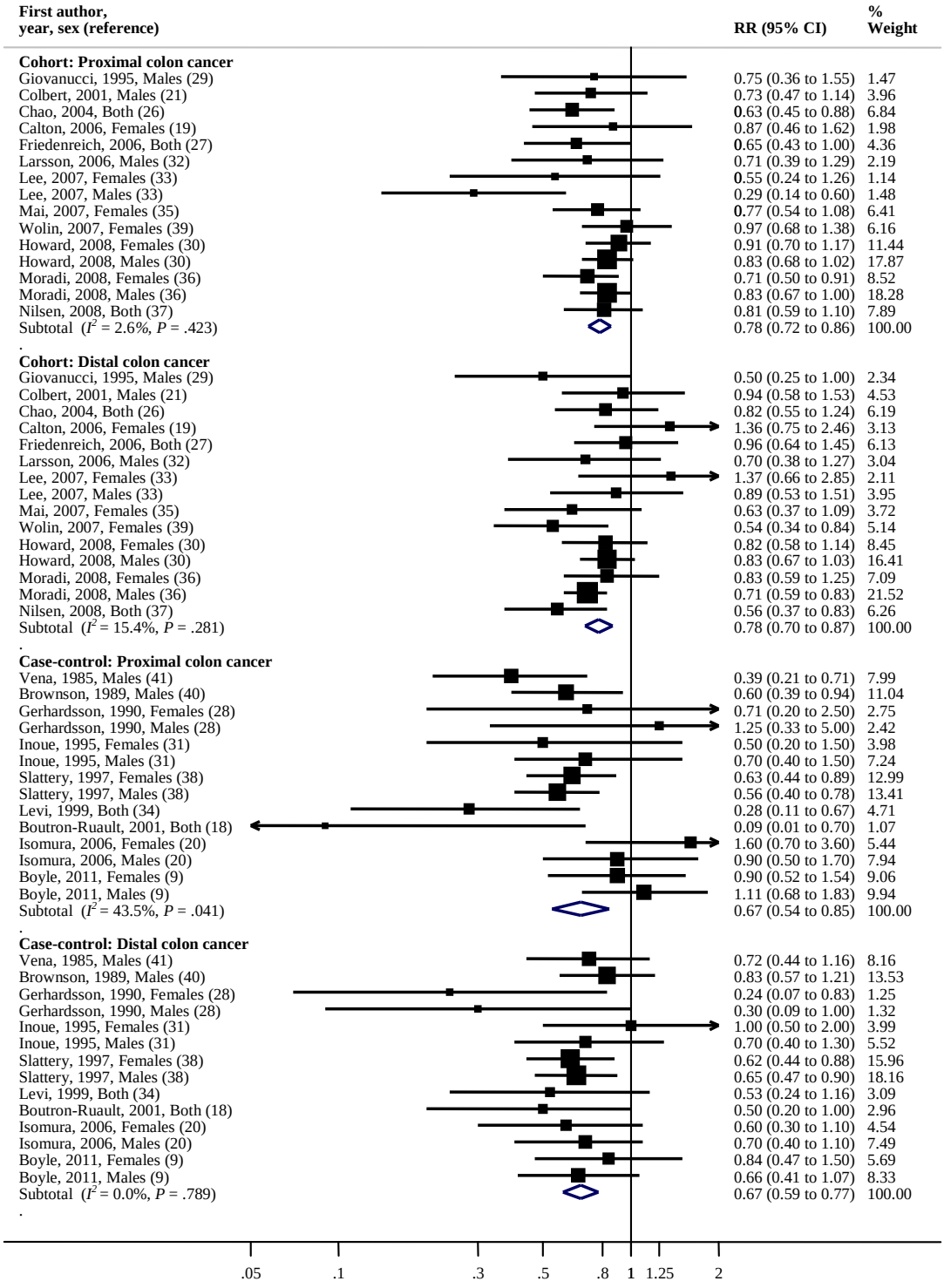
A. Proximal colon cancer



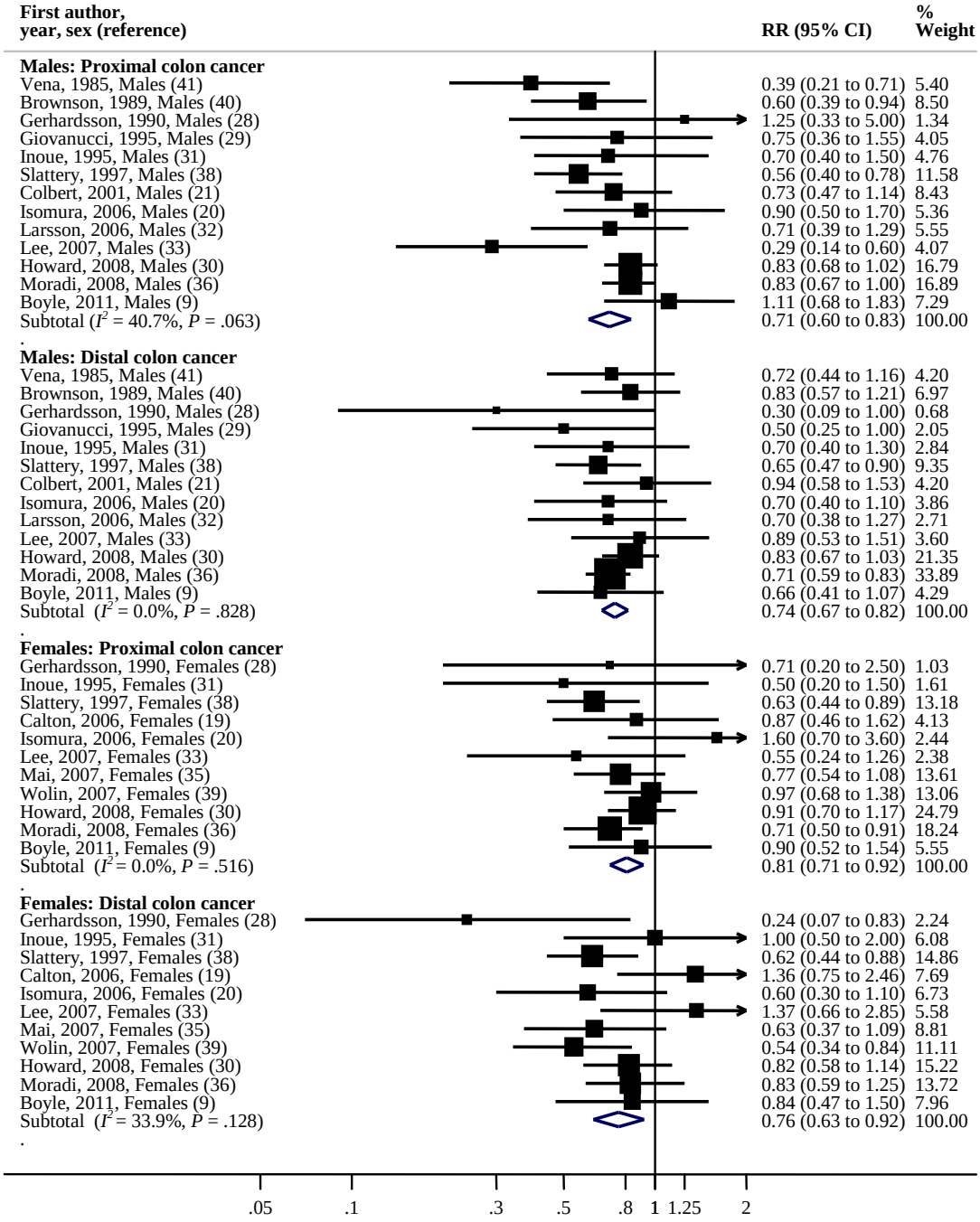
B. Distal colon cancer



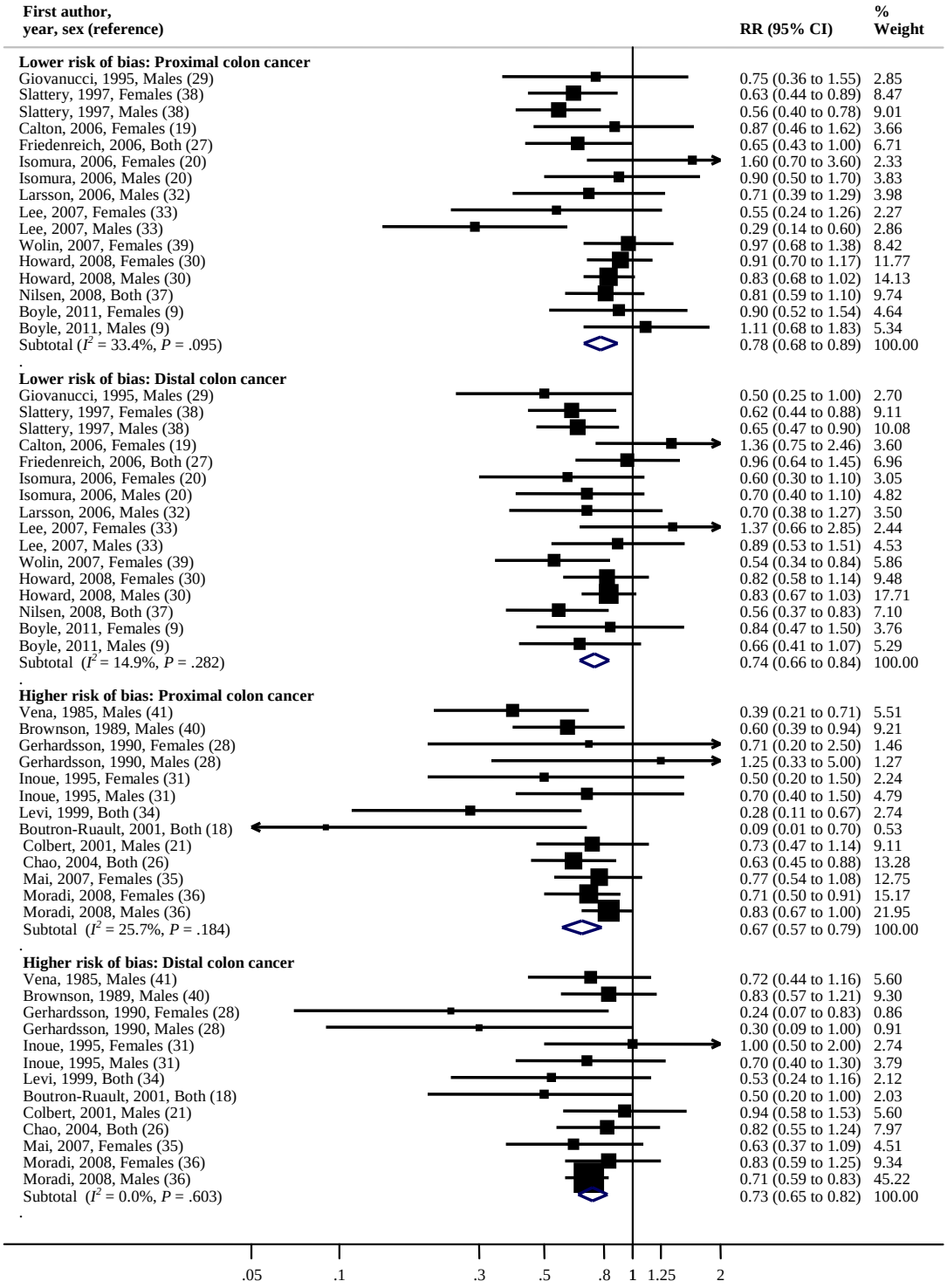

First Author,
Year, Sex (reference #)
RRR (95% CI)
Standard error of RRR
Moradi, 2008, Males (36) 1.17 (0.90 to 1.52) 0.13
Howard, 2008, Males (30) 1.00 (0.74 to 1.34) 0.15
Howard, 2008, Females (30) 1.11 (0.73 to 1.70) 0.22
Slattery, 1997, Males (38) 0.86 (0.54 to 1.37) 0.24
Moradi, 2008, Females (36) 0.86 (0.53 to 1.38) 0.24
Slattery, 1997, Females (38) 1.02 (0.62 to 1.67) 0.25
Nilsen, 2008, Both (37) 1.45 (0.87 to 2.41) 0.26
Chao, 2004, Both (26) 0.77 (0.45 to 1.30) 0.27
Wolin, 2007, Females (39) 1.80 (1.01 to 3.19) 0.29
Brownson, 1989, Males (40) 0.72 (0.41 to 1.29) 0.30
Friedenreich, 2006, Both (27) 0.68 (0.38 to 1.22) 0.30
Mai, 2007, Females (35) 1.22 (0.64 to 2.32) 0.33
Colbert, 2001, Males (21) 0.78 (0.40 to 1.50) 0.34
Boyle, 2011, Males (9) 1.68 (0.84 to 3.35) 0.35
Vena, 1985, Males (41) 0.54 (0.25 to 1.18) 0.40
Isomura, 2006, Males (20) 1.29 (0.58 to 2.84) 0.41
Boyle, 2011, Females (9) 1.07 (0.48 to 2.37) 0.41
Larsson, 2006, Males (32) 1.01 (0.43 to 2.37) 0.43
Calton, 2006, Females (19) 0.64 (0.27 to 1.52) 0.44
Inoue, 1995, Males (31) 1.00 (0.41 to 2.42) 0.45
Lee, 2007, Males (33) 0.33 (0.13 to 0.80) 0.46
Giovanucci, 1995, Males (29) 1.50 (0.55 to 4.10) 0.51
Isomura, 2006, Females (20) 2.67 (0.94 to 7.58) 0.53
Lee, 2007, Females (33) 0.40 (0.13 to 1.21) 0.56
Levi, 1999, Both (34) 0.53 (0.16 to 1.75) 0.61
Inoue, 1995, Females (31) 0.50 (0.15 to 1.70) 0.62
Gerhardsson, 1990, Females (28) 2.96 (0.51 to 17.32) 0.90
Gerhardsson, 1990, Males (28) 4.17 (0.68 to 25.60) 0.93
Boutron-Ruault, 2001, Both (18) 0.18 (0.02 to 1.75) 1.16
.1
.3
.5
1
2
3
10
Larger risk reduction for PCC
Larger risk reduction for DCC



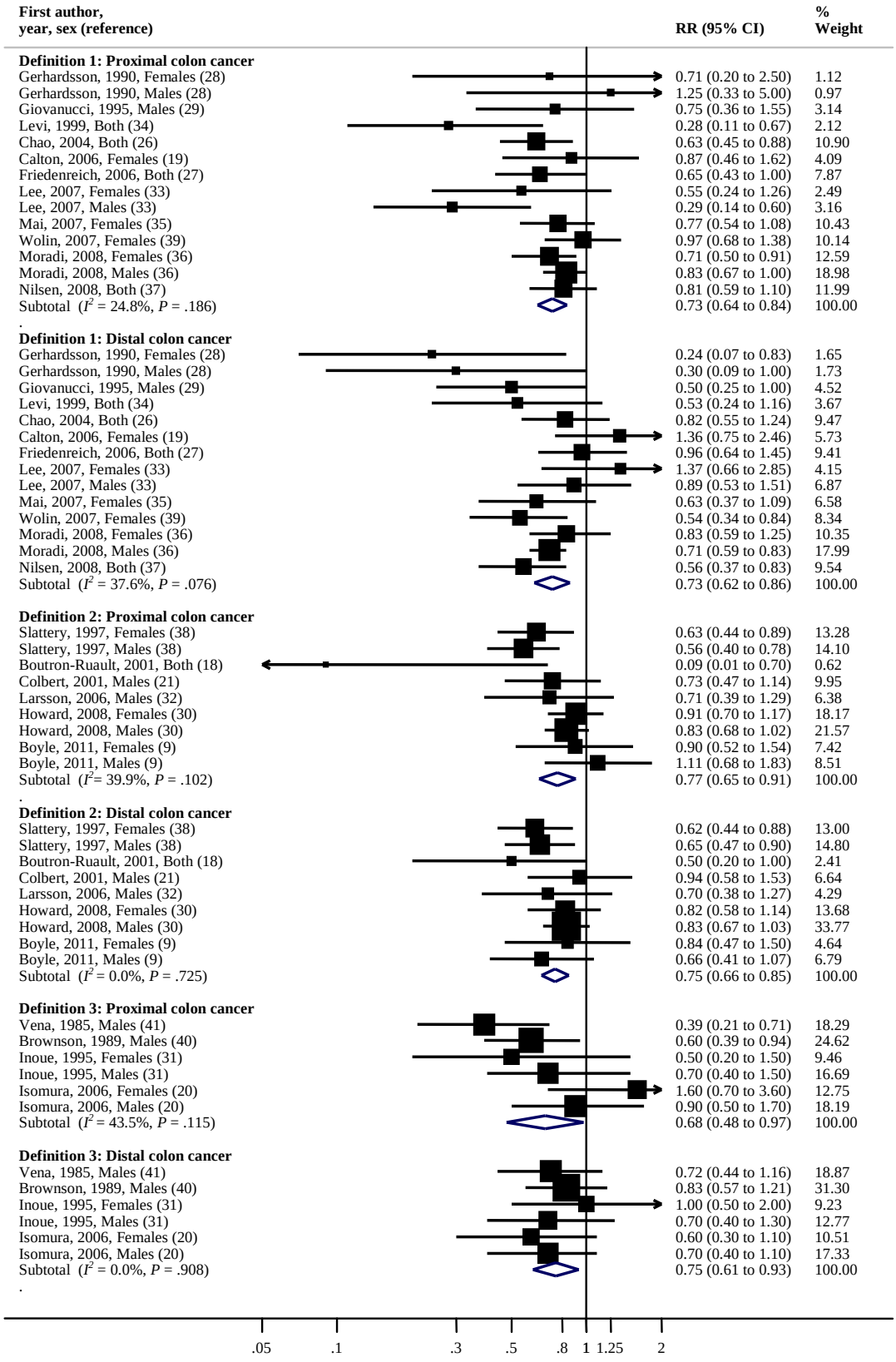
Supplementary Figure 1. Random-effects meta-analyses of cohort studies and case–control studies that investigated associations between physical activity and the risks of proximal colon and distal colon cancers. The **black squares** and **horizontal lines** represent the effect estimate and 95% confidence interval of each study. The **relative size** of the black square represents the weight that the study contributed to the summary relative risk. The **diamonds** represent the summary relative risk and associated 95% confidence intervals. RR = relative risk; CI = confidence interval.



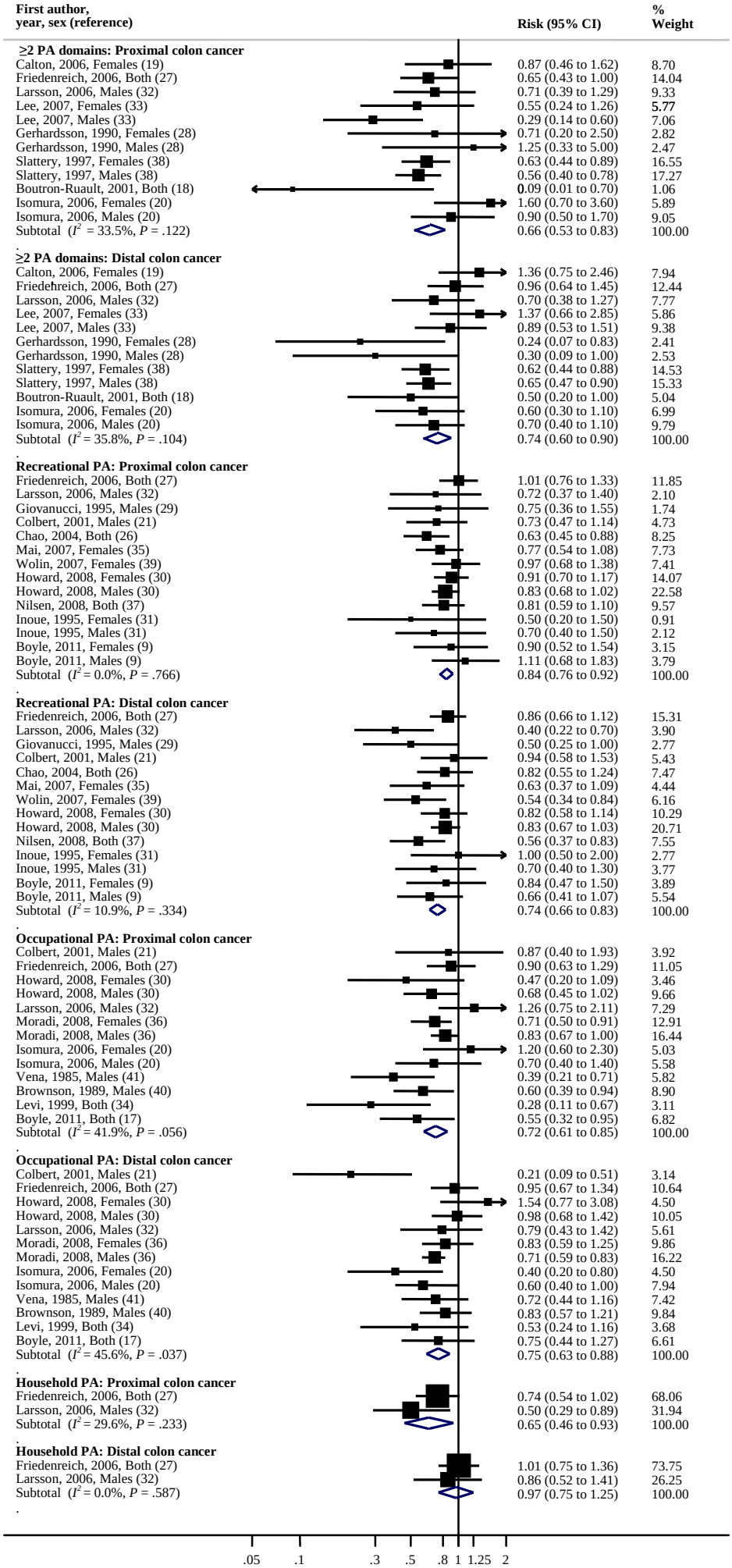
Supplementary Figure 2. Random-effects meta-analyses of studies that investigated associations between physical activity and the risks of proximal colon and distal colon cancers among males and females. **The black squares** and **horizontal lines** represent the effect estimate and 95% confidence interval of each study. The **relative size** of the black square represents the weight that the study contributed to the summary relative risk. The **diamonds** represent the summary relative risk and associated 95% confidence intervals. RR = relative risk; CI = confidence interval.



Supplementary Figure 3. Random-effects meta-analyses of studies with a lower risk of bias and studies with a higher risk of bias that investigated associations between physical activity and the risks of proximal colon and distal colon cancers. The **black squares** and **horizontal lines** represent the effect estimate and 95% confidence interval of each study. The **relative size** of the black square represents the weight that the study contributed to the summary relative risk. The **diamonds** represent the summary relative risks and associated 95% confidence intervals. RR = relative risk; CI = confidence interval.



Supplementary Figure 4. Random-effects meta-analyses of studies that used definition 1, definition 2, and definition 3 for the proximal colon and the distal colon to investigate associations between physical activity and the risks of proximal colon and distal colon cancers. The **black squares** and **horizontal lines** represent the effect estimate and 95% confidence interval of each study. The **relative size** of the black square represents the weight that the study contributed to the summary relative risk. The **diamonds** represent the summary relative risks and associated 95% confidence intervals. RR = relative risk; CI = confidence interval.



Supplementary Figure 5. Random-effects meta-analyses of studies that investigated associations between physical activity (PA) and the risks of proximal colon and distal colon cancers based on physical activity performed in two or more domains, recreational physical activity, occupational physical activity, and household physical activity. The **black squares** and **horizontal lines** represent the effect estimate and 95% confidence interval of each study. The **relative size** of the black square represents the weight that the study contributed to the summary relative risk. The **diamonds** represent the summary relative risk and associated 95% confidence intervals. RR = relative risk; CI = confidence interval.