Leisure-time physical activity and gastric cancer risk: a pooled study within the Stomach cancer Pooling (StoP) Project

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Abstract

Background Physical activity (PA) has been recognized as a protective factor against several types of cancer, though robust evidence related to Gastric Cancer (GC) are lacking. This study aimed to establish whether leisure-time PA can prevent GC using data from a large pooled analysis of case-control studies within the Stomach cancer Pooling (StoP) Project.

Methods Five case-control studies from StoP project collected data on PA, for a total of 2,415 cases and 9,722 controls. Subjects were classified into three leisure-time PA categories, either none/low, intermediate or high, based on study-specific tertiles. We used a two-stage approach. Firstly, we applied multivariable logistic regression models to obtain study-specific odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Afterwards, we used a random-effect models for estimating pooled effect estimates. Heterogeneity across studies was assessed using Q and I 2 statistics. We performed stratified analyses according to demographic, lifestyle and clinical covariates.

Results The pooled ORs for GC risk were 0.90 (95% CI: 0.72, 1.13) for intermediate, and 0.72 (95% CI: 0.57, 0.91) for high levels of leisure-time PA. There was no evidence of significant heterogeneity in outcome estimates (I 2 = 49.7%; p=0.094 for intermediate; I 2 = 42.9%, p=0.135 for high levels of exposure). GC risk estimates did not differ across strata of selected covariates.

Conclusions Our study is the largest pooled analysis that provides insights about protective effects of high levels of recreational PA on GC risk. Although our results should be confirmed from large cohort studies, the implications have relevant public health significance.

Background

Gastric cancer (GC) is one of the most common cancers worldwide, particularly in less developed countries, with a wide difference of the incidence rate between males and females (1,2). In most countries, the relative 5-year survival rate is low, around 30%. In the last few decades, a decline of the incidence rates was observed, mainly because of the recognition of risk factors such as dietary and environmental factors, and H. Pylori infection (3,4). Despite this decline, the trend in incidence of cardia GC remained stable or increased in the Western countries (5,6) .

Physical activity (PA) is a complex, multidimensional behavior that represents one of the most important modifiable determinants of all-cause mortality and non-communicable diseases (7). In particular, recreational PA largely incorporates various activities undertaken during leisure time (i.e. walking and hiking, jogging, cycling, swimming etc.) and represents a potentially modifiable component of energy expenditure (7,8). Insufficient levels of PA cause around 3.2 million deaths each year, while 2010 figures show that lack of PA contributed to 69.3 million disability-adjusted life years globally (2.8% of the total) (9). Among plausible biological pathways responsible for the beneficial effects of PA, the literature highlights the following: insulin resistance, growth factors, adipocytokines, steroid hormones, and immune function (10–12).

PA has been intensively studied in relation to several types of cancer, and recent estimates indicate that between 9 and 19% of the incidence of cancer in Europe could be attributed to physical inactivity (13,14). There is substantial epidemiologic evidence linking inadequate levels of PA with an increased incidence and mortality from colorectal, breast and endometrial cancers (12,15,16). Despite these known benefits, recent WHO estimates conducted on a global level in 2010 indicate that 23% of adults remain insufficiently active (men 20% and women 27%) (17).

To date, the World Cancer Research Fund has published a series of systematic reviews, showing a lack of firm evidence for the association between PA and GC risk (18). Several meta-analyses evaluated the effect of different domains of PA on GC risk across diverse settings, with risk reductions ranging from 13 to 21% among the most physically active people (19–22). However, the majority of the included studies did not provide adequate data for conducting subgroup analyses nor did they take in consideration important potential confounders, which may have influenced the results (socio-economic status, dietary habits etc.). The objective of this study was to explore the association between leisure-time PA and GC risk through a pooled analysis of case-control studies within the International “Stomach cancer Pooling Project” (StoP) (23), and to further assess this relationship in strata of selected covariates.

Methods

Studies and participants

All the studies participating in the StoP consortium (23) were conducted in accordance with applicable laws, regulations and guidelines for protection of human subjects, and the StoP Project received ethical approval from the University of Milan Review Board (reference no. 19/15 of 01/04/2015). Overall, ten out of over 30 studies included in the latest release (number 2.1) of the StoP dataset collected data on leisure-time PA (24–33). However, five studies were not considered for the present investigation, mainly because available PA variables were characterized by a large amount of missing data or were qualitative in their nature (29–33). Studies with large percentage of missing values on PA were not included (34). Five studies were ultimately included in the pooled analysis: Italy (28), Canada (27), Russia (26), USA (25), and Spain (24).

Exposure assessment and data standardization

The questionnaires administered to study subjects usually include demographic and lifestyle data on PA, cigarette smoking, alcohol use, dietary habits, and family history of cancer. Additional data from the study cases were obtained from cancer registries or hospital medical records. All data were collected and standardized according to a pre-specified format at the data-pooling center.

The main characteristics of PA variables are outlined in **Table 1**. Studies reported (25–28) the duration (number of hours) of leisure-time PA over a certain interval of time (a week period). In particular, Italian and US centers (25,28) had pre-specified criteria with cut-off points in their questionnaires, while Canada, Russia and Spain (24,26,27) reported continuous values. Only the Canadian center incorporated data on the PA intensity (moderate or vigorous) (27). The period for study-specific PA variables ranged from one year to 5 years.

Since the variables related to leisure-time PA as well as period of referral showed certain levels of variation across the centers, we designed PA exposure category based on study-specific tertiles that were created using control populations. Study subjects were assigned to one of three PA categories, either none/low, intermediate or high (most commonly expressed as number of hours engaging in recreational PA across a week period). None and low levels of exposure were combined together due to the nature of individual study questionnaires and were considered as a reference category.

Statistical analysis

Descriptive analyses were conducted to describe the study population in terms of demographic characteristics, selected lifestyle habits, GC characteristics (subsite and histotype) and *H. pylori* infection. The relationship between PA and GC was evaluated using a two-stage approach (35). Firstly, multivariable logistic regression models were applied to obtain study-specific odds ratios (ORs) and the corresponding 95% Confidence Intervals (CIs). These models were adjusted for sex, age, *H. Pylori,* smoking, alcohol consumption, BMI, social class, occupational PA, cancer history, and dietary habits (Additional file 1). In the second phase, a random-effect model was applied in order to estimate summary (pooled) effect measures. Heterogeneity across studies was assessed with the Q and I^2 statistics measures (36).

In order to investigate the effects of leisure-time PA across strata of selected covariates, we performed stratified analyses according to: sex, age (≤55, 56-65, >65), BMI (normal weight, overweight, obese), social class (study-specific low, intermediate, high), smoking status (never, former, current smoker), alcohol drinking status (never, ever), vegetables and fruit intake (study-specific low, intermediate, high), occupational PA (study-specific low, intermediate, high), cancer history among first degree relatives (yes, no), GC subsite (cardia, non-cardia), GC histotype (intestinal, diffuse, undifferentiated) and *H. Pylori* status (positive, negative). Heterogeneity tests were performed across all the strata estimates. Lastly, we performed a test for linear trend across the three levels of PA variable (37).

All statistical tests were two-sides and a p-value < 0.05 was considered as statistically significant. Statistical analyses were carried out using STATA software, version 12.

Results

The main characteristics of the 2,415 cases and 9,722 controls included in the present analysis are reported in **Table 2**. Two-thirds (65%) of GC cases were men. Cases were fairly older than controls and more commonly belonged to lower social classes (41.7% in cases vs 38.3% in controls). Majority of study subjects showed none or low levels of PA (47.8 % among cases and 43% among controls). The proportion of current smokers was similar across cases (18.8%) and controls (20%), while cases were more likely to consume high levels of alcoholic beverages than controls (15.2% vs 6.8%, respectively). Furthermore, the percentage of obese subjects was slightly higher among cases in respect to controls (16.2% vs 15.8%, respectively). Considering information on cases of GC, the vast majority were non-cardia site (46.2%). Regarding information on *H. Pylori* status, the data were available for two study centers (24,26).

The pooled ORs of different levels of leisure-time PA are reported in **Figure 1**. The overall pooled OR was 0.90 (95% CI: 0.72, 1.13) for subjects with an intermediate level of PA versus none/low levels, and 0.72 (95% CI: 0.57, 0.91) for high levels of PA. There was no evidence of a significant trend in risk estimates and no significant heterogeneity for either intermediate (I^2 = 49.7%; p=0.094) or high levels of exposure (I^2 = 42.9%, p=0.135) (Fig 1).

The results show the absence of a meaningful effect modification from the variables considered, although we reported a noticeable stronger effect among non-cardia tumor site (OR=0.59; 95% CI: 0.42, 0.84 for high levels of PA, and OR=0.77; 95% CI: 0.60, 0.98 for intermediate levels of PA).

When evaluating studies with available information on *H.Pylori* status, our results indicated a lack of statistically significant association both for high and intermediate levels of PA (Table 3).

Discussion

Our study evaluated the association between leisure-time PA and GC risk by pooling data from five case-control studies of the StoP consortium, totaling to 2,415 cases and 9,722 controls. The overall pooled estimates report a 28% reduced risk of GC among individuals practicing high levels of leisure-time PA (OR = 0.72; 95% CI: 0.57, 0.91). We also reported a protective effect of intermediate and high levels of PA among non-cardia GC cases with a trend in outcome estimates (OR = 0.77; 95% CI: 0.60, 0.98 for intermediate PA and OR = 0.59; 95% CI: 0.42, 0.84 for high PA).

Our study findings are in line with the most recent meta-analyses on the effects of PA on GC, where authors reported a protective effect of PA on GC development (19–22). In the most recent meta-analysis(22) including 10 cohort and 12 case–control studies, results showed a 19% reduced risk for GC among the persons in the highest category of any PA compared to the lowest (22). However, when restricting the analysis to data on recreational PA and including nine case control studies (3045 cases and 21,128 controls) and seven cohort studies (4814 cases), the meta-analysis reported non-significant effect estimates (pooled OR for case-control studies = 0.86, 95% CI (0.69–1.07); pooled risk ratio (RR) for cohort studies = 0.92, 95% CI (0.74–1.15)). Significant protective effects, however, were reported from two cohort studies including non-cardia GC cases (pooled RR = 0.62; 95% CI: 0.52–0.75) (22). Additional pooled analyses of 12 US and EU cohorts with around 1.44 million participants showed a protective, but non-significant, association among 1428 non-cardia GC cases (hazard ratio (HR) = 0.93, 95% CI: 0.73, 1.19) when comparing high versus low levels of leisure-time PA (14). In accordance with these findings, our analysis suggests a reduced GC risk among individuals with non-cardia GC engaging both in intermediate and high levels of PA levels compared to none/low levels. The biological mechanisms by which PA affects cancer development cover mostly indirect beneficial effects of PA on adiposity: lowering the levels of circulating adipokines, improving insulin resistance and blood insulin levels, but also lowering the production of sex hormones and inflammatory cytokines (7,12,38). There are several factors that can influence PA effects and they may or may not be PA related (i.e. type, duration, intensity of activity, but also age, sex, adiposity etc.) (38,39). The literature regarding modifying effects of sex and BMI is quite conflicting. Some studies showed a stronger inverse association among women due to negative effects of estrogen levels on the growth of gastric tumors (40). On the other hand, recent review reported only 1% weaker association in men compared to women and 10% weaker association as BMI increases with near significant findings (21). Another study showed the effects of PA on gastroesophageal cancer risk change only slightly when meta-analyzing studies that adjusted for adiposity (40). Our study showed a lack of significant heterogeneity in the stratified analyses by sex and weight. It is worth noting that all of the models in the present analysis were sex and BMI adjusted, which may suggest that observed effects of PA on GC are not entirely influenced through its effects on weight (20,41).

Both alcohol and smoking are known to increase the risk of GC. Heavy drinkers are associated with approximately 50% increased risk of GC, while smokers of more than 20 cigarettes per day have around 30% greater risk for developing the disease (42,43). Although significant risk reductions were observed among ever drinkers, former and current smokers in our analyses, we did not observe significant effect modification due to alcohol and smoking when comparing high to none/low levels of PA. One recent analyses exploring the associations between exercise, smoking and mortality from various causes may complement our findings. O'Donovan et al. (44) followed 106,341 individuals and suggested that physical exercise may reduce the risk of overall cancer mortality by around 30% both in current and ex-smokers. In contrast, a meta-regression of studies on GC suggested that tobacco smoking may reduce the positive effect of PA on GC, particularly among individuals practicing sufficient levels of PA (21). The present study and conflicting previous literature imply that the complex interlink between behavioral risk factors and PA and their mutual effects on cancer development is yet to be disentangled (7).

Our results implicate no substantial differences in the risk estimates according to occupational PA strata. These findings are somewhat expected, since previous research reported no evidence of the effect of occupational PA on GC risk (45,46). The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort observed no increase in risk of GC among sedentary occupations in comparison to manual or standing occupations (47). Individuals of lower socio-economic positions and employed in manual occupations tend to engage in less leisure-time PA (48). However, a causal relationship between job position and health outcomes is far more complex and prone to influence of various factors including socioeconomic indicators such as education and wealth (49). EPIC data reported a reduction in GC risk among populations of higher educational level. In a nested case-control study from this cohort, these effects were largely attenuated after adjusting for a known risk factor - H. Pylori (50). In that sense, adjustments for social class position in our statistical models are of particular importance in the present research.

The limitations of our study are mainly due to the fact that data regarding recreational PA were collected by study-specific questionnaires with different definitions and classifications. In order to make the available information comparable, we defined three levels of PA intensity based on study specific tertiles (44). This might have led to information misclassification of the exposure. In addition, data on PA was collected at different time points prior to GC diagnosis, i.e. from one year up to 5 years and this might have contributed to non-differential misclassification of PA exposure. Another limitation is the lack of information on H. Pylori infection that was available only in two study centers (24,26). Besides adjusting for H. Pylori status in study specific regression models, we have also provided a stratified analysis including only individuals with available information.

Our study has some important strengths. First of all, it represents the solely pooled analyses of case-control studies that was able to adjust the results for the most important confounding factors of GC. These adjustments are extremely important when evaluating the complex relationship between PA and cancer, especially when taking into account that cancer development is a multifactorial and site-specific process and that PA may act through multiple biological pathways. Secondly, our analyses included a substantial number of GC cases enabling us to evaluate the outcomes across the strata of different behavioral risk factors and clinical features.

Conclusions

This study represents the first pooled analysis of observational studies exploring the association between leisure-time PA and risk of GC. We provide positive insights about the preventive role of high amounts of leisure-time PA on GC development. Future studies should develop and implement standardized data collection procedures that could facilitate further evaluations of the role of PA in cancer prevention.

Abbreviations

GC - Gastric cancer

PA - Physical activity

StoP - Stomach cancer Pooling Project

OR - Odds ratios

CIs - 95% Confidence Intervals

HR - hazard ratio

RR - Risk ratio

EPIC - The European Prospective Investigation into Cancer and Nutrition

Declarations

Ethics approval and consent to participate

StoP Project received ethical approval from the University of Milan Review Board (reference no. 19/15 of 01/04/2015).

Consent for publication

Not applicable.

Availability of data and material

This study brought together existing data obtained upon request and subject to licence restrictions from a number of different sources. Full details of how these datasets were obtained are available in the documentation available at 10.1097/CEJ.0000000000000017

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SJ, LG, PR and SB were involved in the conception of the work. SJ and GL performed the analysis. All the authors were involved in data acquisition. PR, BS, PC, RM, NE, LVC, MTAJ, and FTG were involved in the interpretation of the data. SJ, LG, PR and SB were responsible for drafting the work. All the authors were involved in substantial revision and making improvements to the work as well as approval of the submitted version.

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Tables

Table 1. Study specific definitions for PA and derived tertiles. Stomach cancer pooling (StoP) Project consortium.

Study center	Study-specific definition	Study-specific tertiles
Italy	Sport, leisure, activities, bycicle rides at various ages (12,15-19,30-39,50-59).	None/Low: <2 hours per week Intermediate: 2-7 hours per week High: >7 hours per week
Canada	Number of hours per week spent doing both moderate and strenuous activities (walking, jogging, gardening, home exercises, golf, racquet sports, bowling, swimming, skiing or skating, bicycling, social dancing and other) averaged over seasons and related to 2 years before the interview.	None/Low: = 0 hours per week Intermediate: >0 & ≤ 2.93 hours per week High: > 2.93 hours per week
Russia	Walking and sport activities (hours per week) during summer/winter seasons and referring to 1 year preceding the disease (cases and hospital controls) and 1 year prior to the interview for visitor controls.	None/Low: ≤ 0.33 hours per week Intermediate: > 0.33 & ≤ 0.7 hours per week High: > 0.7 hours per week
USA	Frequency of certain activities (active sports, physical exercise, jogging-running, swimming/long walks, gardening/fishing/hunting, other activities)	None/Low: few times a year or rarely/never engaging in any kind of rPA Intermediate: 1 hour per week or few times per month of any kind of rPA High: >1 hour per week of any kind of rPA
Spain	PA defined as activities that took place outside working hours, including walking, doing some sport, going to the gym, etc. in the last 5 years and for a period of at least 6 months (excluding 1 year prior to diagnosis)	None/Low: 0 Intermediate: >0 & ≤ 5.6 h/week High: > 5.7 h/week

Table 2. Distribution of 2,415 cases of stomach cancer and 9,722 controls according to selected covariates. Stomach cancer pooling (StoP) Project consortium.

	Cases		Controls		chi^2 test
	N	%	N	%	p value
Total	2,415		9,722		
Study Center					
Italy	219	9.1	519	5.3	
Canada	1,182	48.9	5,039	51.8	
Russia	442	18.3	602	6.2	
USA	131	5.4	131	1.3	
Spain	441	18.3	3,431	35.3	
Physical activity [a]					
None/Low	1,155	47.8	4,180	43.0	p<0.001
Medium	594	24.6	2,433	25.0	
High	666	27.6	3,109	32.0	
Sex					
Male	1,570	65.0	5,058	52.0	p<0.001
Female	845	35.0	4,664	48.0	
Age					
<=55	558	23.1	3,246	33.4	p<0.001
(55-65]	697	28.9	2,574	26.5	
>65	1,160	48.0	3,902	40.1	
Social class					
Low	1,006	41.7	3,721	38.3	p<0.001
Medium	938	38.8	3,380	34.8	
High	432	17.9	2,530	26.0	
Missing	39	1.6	91	0.9	
BMI [b]					
underweight	68	2.8	174	1.8	p=0.012
normal weight	973	40.3	3,875	39.9	
overweight	867	35.9	3,593	37.0	
obese	391	16.2	1,538	15.8	
Missing	116	4.8	542	5.6	
Tobacco smoking					
Never	857	35.5	4,032	41.5	p=0.001
Former	904	37.4	3,471	35.7	
Current	454	18.8	1,951	20.1	
Missing	200	8.3	268	2.8	
Alcohol consumption					
Never	494	20.5	2,102	21.6	p<0.001
Low	695	28.8	3,781	38.9	
Intermediate	552	22.9	1,881	19.3	
High	368	15.2	663	6.8	
Missing	306	12.7	1,295	13.3	
Vegetables and fruit intake					
Low	630	26.1	2,871	29.5	p<0.001
Medium	786	32.5	3,041	31.3	
High	884	36.6	3,145	32.3	
Missing	115	4.8	665	6.8	
Occupational PA [c]					
Low	348	14.4	1,588	16.3	p<0.001
Medium	460	19.0	2,000	20.6	
High	234	9.7	650	6.7	
Missing	1,373	56.9	5,484	56.4	
History of stomach cancer					
No	1,028	42.6	4,326	44.5	p<0.001
Yes	184	7.6	319	3.3	
Missing	1,203	49.8	5,077	52.2	
H. Pylori status [d]					
Negative	202	8.4	484	5.0	p<0.001
Positive	427	17.7	2,127	21.9	
Missing	1,786	74.0	7,111	73.1	
Histotype					
Intestinal	435	18.0	nc	nc	nc
Diffuse	328	13.6	nc	nc	
Mixed	1,394	57.7	nc	nc	
Missing	258	10.7	nc	nc	

Subsite				
Cardia	593	24.6	nc	nc
Non-Cradia	1,115	46.2	nc	nc
Missing	707	29.3	nc	nc

nc: non computable

[a] details regarding the classification of PA variable available in table 2;

[b] underweight (below 18.5); Normal or Healthy Weight (18.5–24.9); Overweight (25.0–29.9); Obese (30.0 and above);

[c] available for three centers (Italy, Russia and Spain)

[d] available for two centers (Russia and Spain).

Table 3. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for gastric cancer according to physical activity levels in strata of selected covariates (sex, age, socioeconomic status, BMI, cigarette smoking, alcohol drinking, vegetables and fruit intake, occupational PA, cancer site, and cancer histotype). Stomach cancer Pooling (StoP) Project consortium.

	Physical activity levels									
	Low		Intermediate				High			
	Ca : Co	OR[a]	Ca : Co	OR (95 % CI)	I^2(%)	p[b]	Ca : Co	OR (95 % CI)	I^2(%)	p[b]
Overall	1155/4180	1.00	594/2433	0.90 (0.72, 1.13)	49.7		666/3109	0.72 (0.57, 0.91)	42.9	
Gender										
Male	762/2080	1.00	361/1180	0.88 (0.63, 1.23)	58.6	0.492	447/1798	0.65 (0.53, 0.79)	10.5	0.304
Female	393/2100	1.00	233/1253	1.01 (0.82, 1.24)	0		219/1311	0.82 (0.55, 1.22)	46.3	
Age (years)										
≤ 55	257/1451	1.00	159/875	1.06 (0.82, 1.36)	0	0.52	142/920	0.75 (0.57, 0.99)	0	0.961
>55 & ≤ 65	315/1046	1.00	180/682	0.90 (0.65, 1.24)	20.7		202/846	0.80 (0.50, 1.30)	50.6	
> 65	583/1683	1.00	255/876	0.81 (0.51, 1.27)	67.1		322/1343	0.72 (0.39, 1.32)	79.6	
Social class										
Low	531/1641	1.00	231/938	0.81 (0.58, 1.15)	35.7	0.824	244/1142	0.66 (0.53, 0.81)	0	0.47
Intermediate	390/1351	1.00	260/896	0.91 (0.73, 1.13)	0		288/1133	0.78 (0.63, 0.97)	0	
High	207/1137	1.00	95/575	0.83 (0.58, 1.20)	8.5		130/818	0.65 (0.49, 0.87)	0	
BMI										
Normal weight	452/1603	1.00	246/960	0.87 (0.71, 1.08)	0	0.934	275/1312	0.66 (0.48, 0.92)	26.5	0.933
Overweight	428/1527	1.00	196/893	0.83 (0.52, 1.34)	64.8		243/1173	0.70 (0.56, 0.86)	0	
Obese	203/707	1.00	91/402	0.80 (0.53, 1.21)	10.5		97/429	0.72 (0.51, 1.01)	0	
Cigarette smoking status										
Never	372/1748	1.00	235/1048	0.96 (0.76, 1.20)	0	0.896	250/1236	0.86 (0.63, 1.19)	29.5	0.267
Former	436/1391	1.00	197/828	0.87 (0.61, 1.26)	33.9		271/1252	0.63 (0.52, 0.77)	0	
Current	232/920	1.00	120/497	0.91 (0.68, 1.24)	0		102/534	0.65 (0.46, 0.90)	0	
Alcohol drinking status										
Never	213/893	1.00	139/584	0.91 (0.69, 1.20)	0	0.838	142/625	0.69 (0.35, 1.34)	56.5	0.939
Ever	791/2669	1.00	376/1523	0.87 (0.63, 1.21)	63.9		448/2133	0.71 (0.53, 0.96)	51.7	
	Physical activity levels									
	Low		Intermediate				High			
	Ca : Co	OR[a]	Ca : Co	OR (95 % CI)	I^2(%)	p	Ca : Co	OR (95 % CI)	I^2(%)	p
Vegetables and fruit intake										
Low	347/1339	1.00	150/783	0.84 (0.65, 1.07)	0	0.866	133/749	0.65 (0.40, 1.05)	36.4	0.859
Intermediate	358/1234	1.00	197/782	0.90 (0.52, 1.55)	70.4		231/1025	0.72 (0.46, 1.13)	49.2	
High	382/1235	1.00	219/733	0.92 (0.73, 1.16)	0		283/1177	0.76 (0.57, 1.01)	19.6	
Occupational PA[c]										
Low	170/770	1.00	114/433	1.21 (0.75, 1.97)	48.5	0.46	64/385	0.87 (0.35, 2.16)	72.4	0.863
Intermediate	228/844	1.00	113/498	0.86 (0.61, 1.21)	0		119/658	0.73 (0.44, 1.22)	36.3	
High	105/290	1.00	61/158	0.82 (0.48, 1.37)	0		68/202	0.65 (0.37, 1.14)	0	
Anatomical type										
Cardia	251/4180	1.00	133/2433	0.87 (0.65, 1.17)	10.7	0.531	209/3109	0.84 (0.68, 1.05)	0	0.097
Non Cardia	579/4180	1.00	263/2433	0.77 (0.60, 0.98)	31.6		273/3109	0.59 (0.42, 0.84)	56.4	
Histological type										
Intestinal	171/4180	1.00	99/2433	0.99 (0.62, 1.56)	41.2	0.339	165/3109	1.27 (0.77, 2.09)	56.7	0.115
Diffuse	147/4180	1.00	95/2433	1.15 (0.83, 1.59)	0		86/3109	0.82 (0.48, 1.41)	40.6	
Mixed	691/4180	1.00	344/2433	0.86 (0.69, 1.07)	13.3		359/3109	0.68 (0.50, 0.93)	21	
H. Pylori status [d]										
Negative	69/189	1.00	56/150	0.87 (0.54, 1.43)	0	0.862	77/145	1.14 (0.70, 1.88)	0	0.258
Positive	195/872	1.00	118/530	0.94 (0.46, 1.93)	79.7		114/725	0.71 (0.37, 1.36)	75.2	
Gastric Cancer History [e]										
No	473/1927	1.00	269/1080	1.04 (0.79, 1.38)	30.5	0.578	286/1319	0.74 (0.58, 0.95)	0	0.922
Yes	78/123	1.00	51/92	0.67 (0.15, 3.07)	78.5		55/104	0.68 (0.13, 3.65)	71	

[a] Pooled ORs were computed using random-effects models using the non/low category as reference. Study-specific ORs were adjusted for covariates outlined in Additional file 1. [b] p for heterogeneity . [c] available for three centers (Italy, Spain and Russia). [d] available for two centers (Russia and Spain). [e] Information for cancer history was not available for Canadian center.

Figures

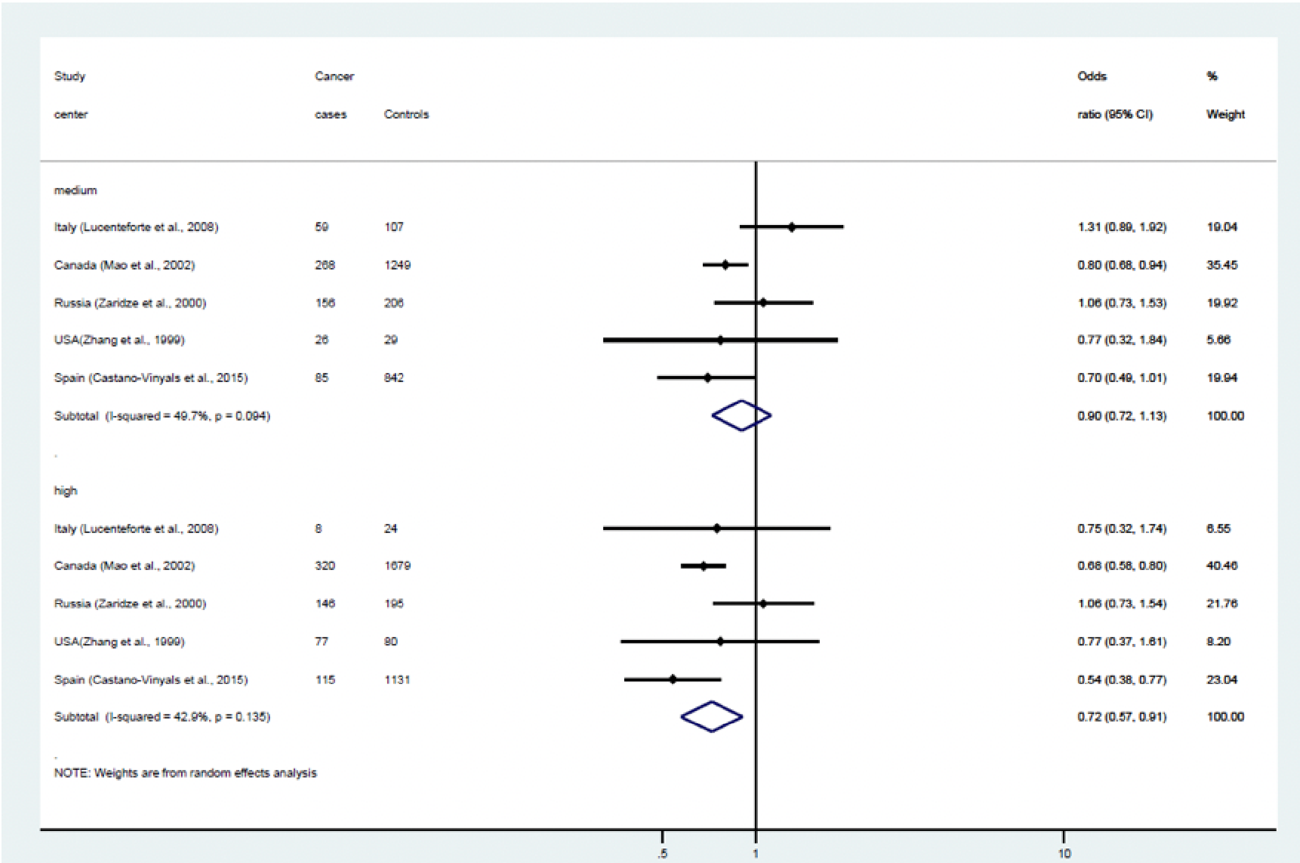

Figure 1

Study-specific and adjusted pooled odds ratios (ORs) and corresponding 95% confidence intervals of GC risk for intermediate and high PA levels. The combined estimate is based on a random-effects model

Supplementary Files

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